NEW FUNCTIONALISATION CHEMISTRY OF 2- AND 4-PYRIDONES AND RELATED HETEROCYCLES

by

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Doctoral Thesis

Submitted in partial fulfilment of the requirements

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Table of contents

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Abbreviations

cat.	Catalyst
CDI	1,1'-Carbonyldiimidazole
CNS	Central Nervous System
CTP	Camptothecin
°C	Degree(s) Celsius
DCM	Dichloromethane
DNA	Deoxyribonucleic acid
DEAD	diethyl azodicarboxylate
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPE	Diphenyl ether
eq.	Equivalent(s)
FVP	flash vacuum pyrolysis
g	Gram(s)
h	Hour(s)
HCV	Hepatitis C virus
HRMS	High-resolution Mass Spectrometry
KHMDS	Potassium bis(trimethylsilyl)amide
HWE	Horner-Wadsworth-Emmons reaction
HPP	High-pressure pyrolysis
IR	Infrared spectroscopy
K-10	Montmorillonite K-10.
LDA	Lithium diisopropylamide
MHz	Mega Hertz
mL	Millilitre(s)
mg	Milligram(s)
min	Minute(s)
mmol	Millimole(s)
m.p	Melting point
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
n-BuLi	n-butyllithium
PCC	Pyridinium chlorochromate
ppm	Parts per million
PPA	Polyphosphoric acid
PMA	Phosphomolybdic acid
PSP	Pneumatic spray pyrolysis
***p*-TSA**	*p*-Toluenesulfonic acid
RCM	Ring-closing metathesis
r.t	Room temperature
s	Second(s)
TEA	Trimethylamine
THF	Tetrahydrofuran

Abstract

New methodology for the synthesis of several 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones has been developed from commercially available 2-aminopyridines and β-oxo esters catalysed by Montmorillonite under solvent-free conditions in good yields. This methodology was expanded for the synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivatives from 2-aminopyrimidine and different β-keto esters.

The new methodology for the synthesis of *N*-alkylated 6-methyl 2-pyridones and *N*-alkylated 2-methyl 4-pyridones, from commercially available starting materials was developed. For the synthesis of *N*-alkylated 6-methyl 2-pyridones, 2-methoxy-6-methyl pyridine and a number of different alkylating reagents have been employed as starting materials. For the synthesis of *N*-alkylated 2-methyl 4-pyridones, 4-chloro 2-methyl pyridine was used successfully to make the desired pyridone in 3 steps.

Selective mono-metallation at the 6-methyl substituent of *N*-alkylated 6-methyl 2-pyridones and *N*-alkylated 2-methyl 4-pyridones with n-BuLi/KHMDS at -78 °C proceeded smoothly, and the reactivity of the lithiated intermediates towards a wide range of electrophile (diketones, aldehydes, alkylating reagents) was studied.

A straightforward synthesis of desirable 4*H*-quinolizin-4-one scaffolds by condensation of *N*-benzyl 6-methyl 2-pyridones with dicarbonyl compounds, and the formation of the desired quinolizinone after the condensation step was achieved. An unexpected quinolizinone bearing a fused β-lactam ring was isolated and its structure confirmed by single crystal X-ray diffraction analysis.

Introduction

The pharmaceutical industry is interested in heterocyclic motifs, because over 60% of the top retailing drugs contain at least one heterocyclic nucleus as part of the overall compound scaffold.[1,2] In addition, the agrochemical industry is interested in this important class of compounds, since heterocycles can display activity as herbicides or pesticides.[3,4,5] Many heterocyclic compounds have shown good properties as new bioactive agents. [1,3,6] Heteroaromatic scaffolds are associated with desirable physicochemical properties, and provide good building blocks for a new biological targets.[7]

New studies are looking for novel ring systems, in order to improve properties over existing frameworks, for example: to improve metabolic stability, solubility, or lower log P.[1] Another interesting area is the development of novel synthetic routes to introduce new substituents, which will allow a change in the reactivity in the compound to improve these properties. The introduction of new substituents will change the shape conformation, or electronic properties of the molecule affording a new range of biological effects.

Furthermore, bacteria have started to show resistance to a broad range of the known antibacterial agents. Consequently, the development of new heterocyclic derivatives is still required by the pharmaceutical industry.

Among the heterocyclic compounds, those containing a Nitrogen atom at the ring junction are of great interest, since these compounds have a wide range of biological and pharmaceutical applications.[6]

The following ring systems (**Figure 1**), 4*H*-quinolizin-4-one **1**, 2*H*-quinolizin-2-one **2**, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **3** and 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one **4,** have shown highly important biological activities.[8-9] These moieties are important targets, and there have been several studies looking at the cheapest and mildest appropriate synthetic conditions in order to decrease the cost of production and to allow easy synthesis in industrial processes.

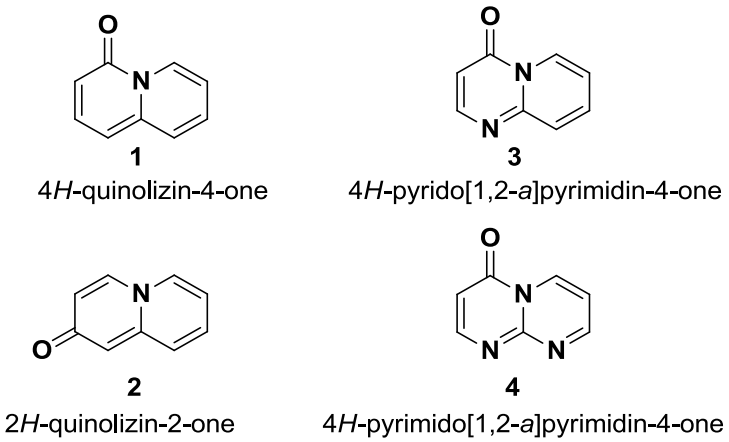


Figure 1: Bicyclic compounds containing a N atom at the ring junction.

Some of the properties and characteristics of heteroaromatic rings are explained next, together with reasons for selecting them as good building blocks for drug development: i) their structure and associated physicochemical properties often lead to efficient binding to a biological target with selectivity, ii) heteroaromatic derivatives are often readily available via common synthetic transformations, iii) there are no complications due to stereochemistry.[1]

Part of our studies was focused at the following monocyclic motifs (**Figure 2**). These scaffolds started as an essential building block of the desirable quinolizinones. However, 2- and 4-pyridones are important structures. They are found in many natural compounds and also they have shown several biological activities. For example, (-)-cytisine,[10] which is a potent α4β2 subtype selective partial agonist at nicotinic acetylcholine receptors, or the antibiotic ciprofloxacin.[11] Furthermore, they can be used as precursors for more complex biological compounds. For these reasons, 2- and 4-pyridones became as an essential part of this study.

Figure 2: 2- and 4-pyridone scaffolds.

This report firstly summarizes the more relevant biological activities of each scaffold and secondly it explains some of the previous methods of synthesis for each ring system (**1** to **6**).

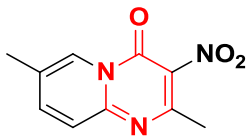
1- Pyridopyrimidine derivatives.

1.1- Biological activities.

The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one scaffold **3** has been of great interest in the pharmaceutical industry because of its various biological properties.[12] Also, this scaffold consisting of two fused heterocyclic rings usually meets the criteria of the "rule of five" for orally active drugs with good bioavailability.[13,14]

Several 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives have diverse biological activities such as analgesic, anti-inflammatory, and anti-allergenic properties.[15]

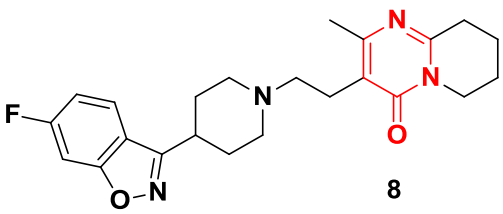
M.S. Youssouf *et al*. have studied the immunopharmacological profile of one particular derivative, 2, 7- dimethyl-3-nitro-4*H*-pyrido[1,2-*a*] pyrimidin-4-one **7** (**Figure 3**), in both *in vitro* and *in vivo* models, representing various features of Type I allergy. It showed a promising profile as an anti-asthmatic agent.[16]



7

Figure 3: 2, 7-dimethyl-3-nitro-4-*H*-pyrido[1,2-a]pyrimidin-4-one.

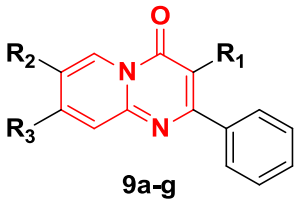
Risperidone **8**,[17] a derivative of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, was explored and used as a potent antipsychotic agent due to its significant dopamine D2 and serotonin 5HT2 blocking activities, and was one of the drugs most widely prescribed worldwide in 2007 (**Figure 4**).[5]



8

Figure 4: Risperidone.

A series of pyrido[1,2-*a*]pyrimidin-4-ones **9a-g** have been identified as new agonists enhancing the transcriptional functions of ERRα (**Figure 5**). The nuclear estrogen-related receptor α (ERRα) plays a central role in the regulation of expression of the genes. Consequently, the compounds improved glucose and fatty acid uptake in C2C12 muscle cells.[18]

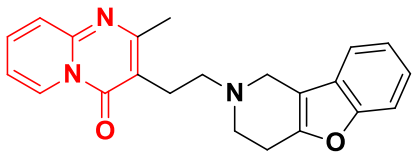


9a-g

a. $R_1 = C_2H_5$, R_2 = H, R_3 = H
b. $R_1 = CH_3$, R_2 = H, R_3 = H
c. $R_1 = CH_3$, R_2 = H, R_3 = H
d. R_1 = t-Bu, R_2 = H, R_3 = H
e. R_1 = i-Pr CH_3, R_2 = H, R_3 = H
f. $R_1 = C_2H_5$, R_2 = H, $R_3 = CH_3$
g. $R_1 = C_2H_5$, R_2 = H, $R_3 = C_2H_5$

Figure 5: Compounds 9a-g agonize the transcriptional function of ERRα at 10 µM.

Two more examples that demonstrate the importance of this privileged scaffold are shown in **Figure 6**, Lusaperidone **10**[19] which is an antidepressant and SSR69071 **11**[20] which is a human leukocite elastase inhibitor. Besides the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one scaffold is found as part of many fused heterocyclic compounds which show anti-malarial,[21] anti-cancer[22] and anti-oxidant activities.[23]



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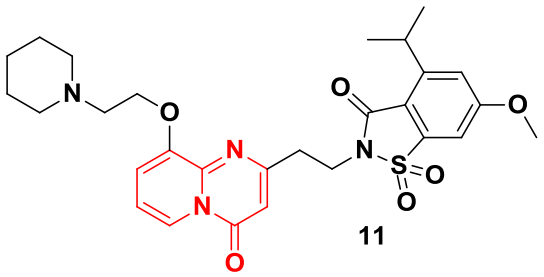
Lusaperidone



11

SSR69071

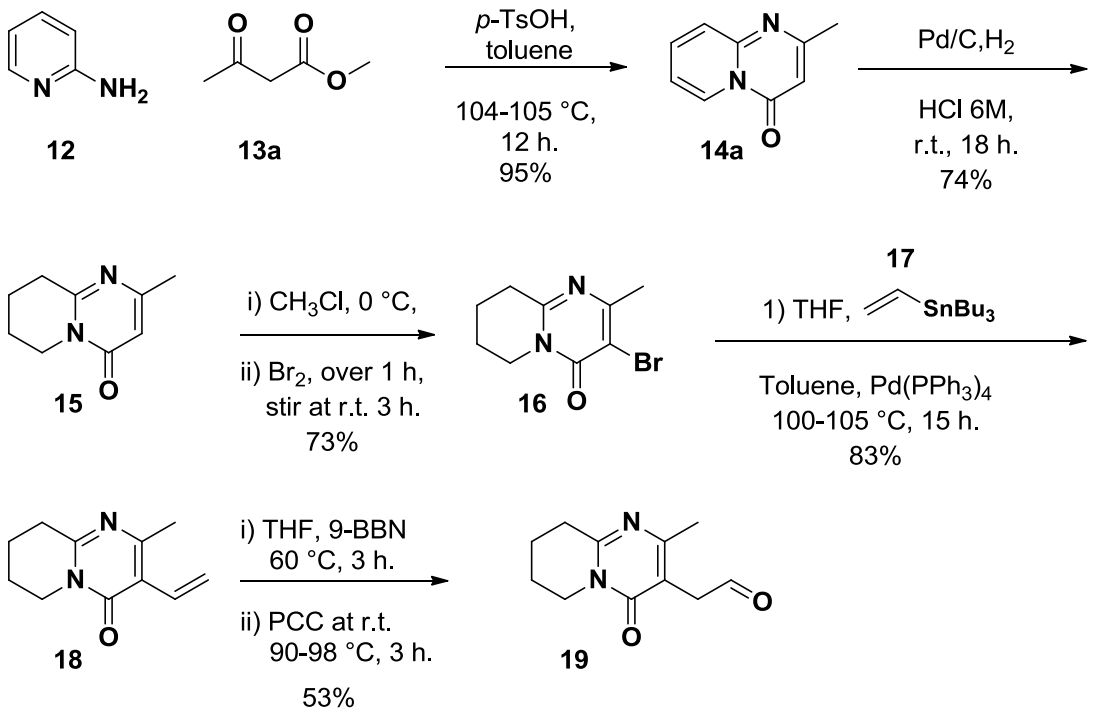
Figure 6: Lusaperidone and SSR69071 structures.

1.2- Previous synthesis of pyrido[1,2-a]pyrimidines.

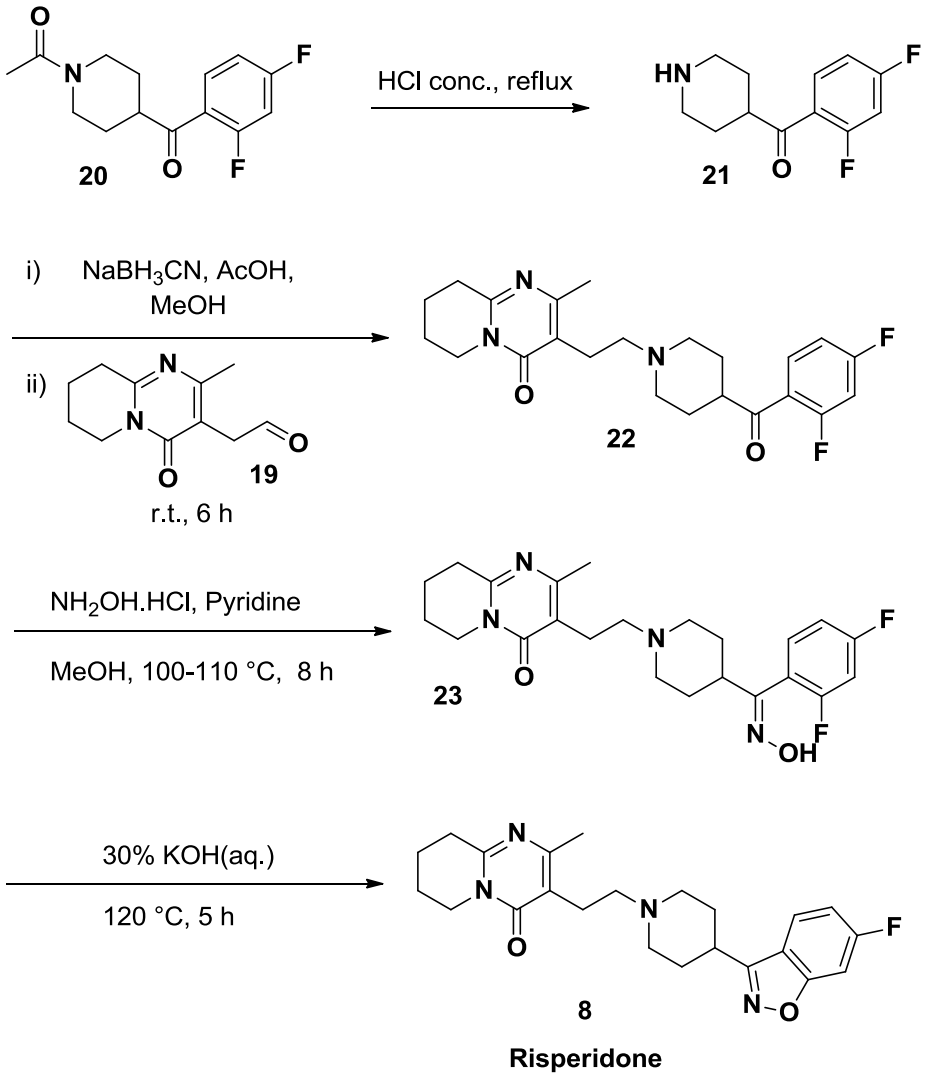
There are a number of different ways available to synthesize the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one moiety, and since this scaffold shows important pharmaceutical properties, there have been a lot of synthetic studies undertaken. Some authors have reported the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives using 2-aminopyridines and β-keto esters as starting materials under different reaction conditions. Also there are others synthetic routes using different starting materials to synthesize this interesting scaffold, as described in the following pages.

In 2005 Kim *et al.*[24] reported the synthesis of risperidone **8**. This paper describes the synthesis of risperidone beginning from readily available 2-aminopyridine **12** and 1-(4-(2,4-(2,4-difluorobenzoyl)piperidin-1-yl)ethanone compound **20** in **Scheme 1** and **Scheme 2** respectively. The first step of this synthesis of 4-methyl-2-oxo-(2H)-pyrido[1,2-*a*]pyrimidines **14a** was by cyclocondensation of 2-aminopyridine **12** and ethyl acetoacetate **13a** catalysed by p-TsOH in toluene at 104-105 °C over 12 h, to afford 95 % yield (**Scheme 1**).[24]

The pyridopyrimidone **14a** was then reduced and brominated to give **16** and an aldehyde group added via Stille coupling and hydroboration-oxidation forming **19**. This was then coupled to the amine **21** by reductive amination before the benisoxazole of **8** was formed by cyclisation of oxime **23**.



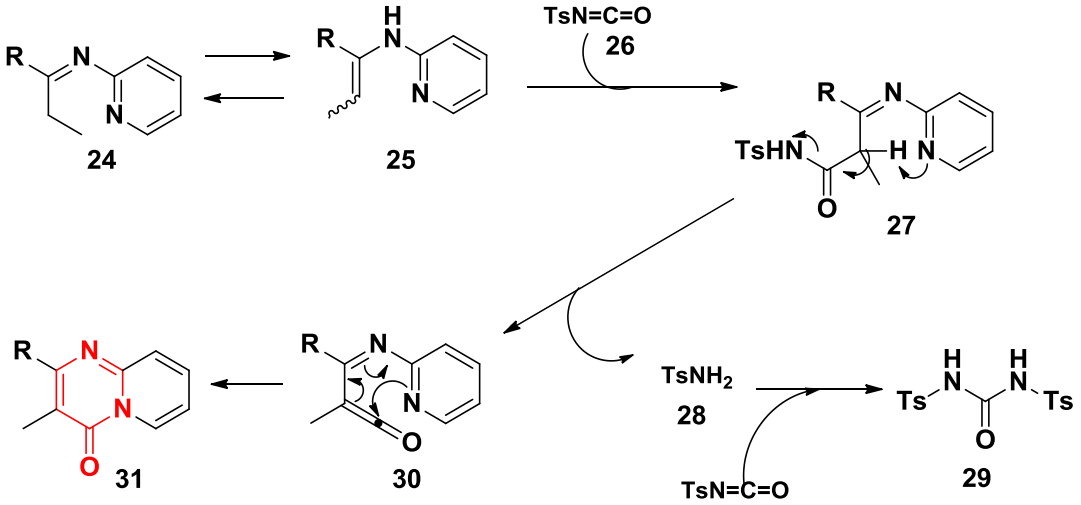
Scheme 1: Synthesis of compound 19.



Scheme 2: Synthesis of Risperidone.

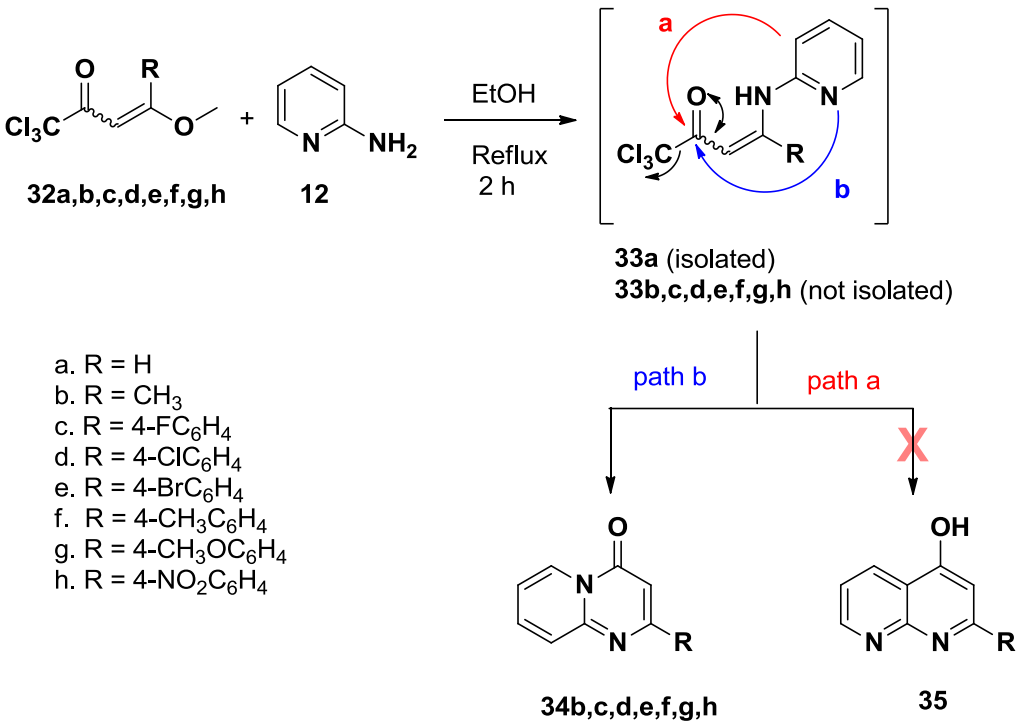
Yoichiro Kuninobu and co-workers[25] reported, in 2006, that 4*H*-pyrido[1,2-*a*]pyrimidines-4-one derivatives could be synthesized, using the reaction of ketimines bearing a pyridyl or a picolyl group on a nitrogen atom of the imine moiety with tosylisocyanate in toluene at 80-135 °C over 10 to 60 min to afford compound **31** in good yield (**Scheme 3**).

The proposed mechanism is shown in **Scheme 3.** The imine **24** is in equilibrium with the corresponding enamine **25**; addition of an isocyanate **26** to the enamine afforded imine **27**. In order to synthesize compound **31**, intermediate **27** would lose 4-toluensulfonamide, possibly helped internally by the pyridine, generating compound **30** which would undergo an intramolecular cyclisation in order to generate product **31**.



Scheme 3: Synthesis of 4-*H*-pyrido[1,2-*a*]pyrimidines-4-one derivates, from ketimines bearing a pyridyl or a picolyl group.

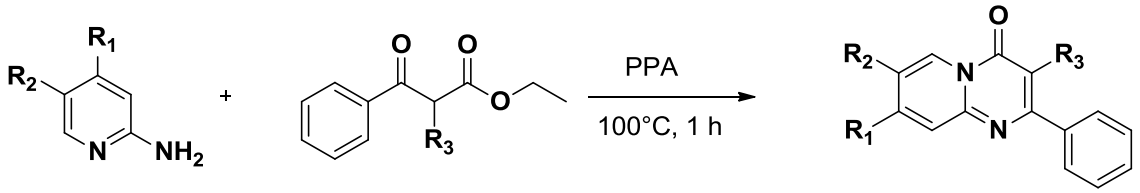
Bonacorso *et al.*[26] reported, in 2006, a new efficient approach for the synthesis of 2-alkyl(aryl) substituted 4*H*-pyrido[1,2-*a*]pyrimidines-4-ones **34b-h** (**Scheme 4**). The synthesis was carried out from β-alkoxyvinyl tri-chloromethyl ketones **32a-h** with 2-aminopyrimidine **12** under mild conditions; the reaction delivered the products in low to good yield (45-80%).



Scheme 4: Synthesis of 2-alkyl(aryl) substituted 4*H*-pyrido[1,2-*a*]pyrimidines-4-ones.

In 2011 Peng *et al.*[18] reported the synthesis of 3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **9a-g** (**Scheme 5**). The synthesis of these scaffolds was by direct condensation/cyclization of 2-aminopyridines **36a-d** with substituted β-keto esters **37a-c** in PPA (polyphosphoric acid) at 100 °C.

After 1 h, the mixture was cooled in an ice bath and neutralized with 5% aqueous sodium hydroxide. The solid precipitate was collected by filtration, and washed with water. The crude products were purified by recrystallization from ethanol. The authors did not report any yield data.



36a. $R_1 = C_2H_5$, R_2 = H.
36b. $R_1 = CH_3$, R_2 = H.
36c. R_1 = *i*-Pr CH_3, R_2 = H.
36d. R_1 = *t*-Bu, R_2 = H.

37a. R_3 = H
37b. $R_3 = CH_3$
37c. $R_3 = C_2H_5$

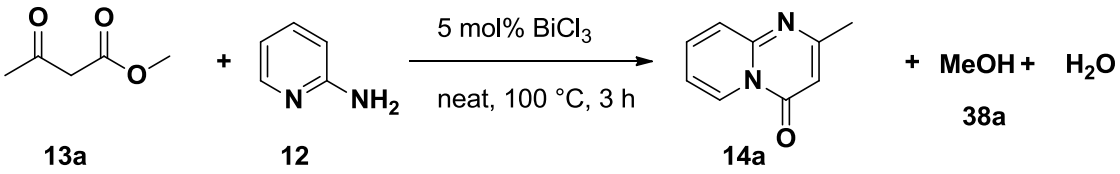
9a. $R_1 = C_2H_5$, R_2 = H, R_3 = H
9b. $R_1 = CH_3$, R_2 = H, R_3 = H
9c. R_1 = *i*-Pr CH_3, R_2 = H, R_3 = H
9d. R_1 = *t*-Bu, R_2 = H, R_3 = H
9e. $R_1 = CH_3$, R_2 = H, R_3 = H
9f. $R_1 = C_2H_5$, R_2 = H, $R_3 = CH_3$
9g. $R_1 = C_2H_5$, R_2 = H, $R_3 = C_2H_5$

Scheme 5: Synthesis 3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives 9a-g.

The use of 2-aminopyridines and β-oxo esters is the traditional methodology for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. In these previous methodologies, corrosive acids were used such as polyphosphoric acid (PPA), p-toluenesulphonic acid and also high temperatures (150-250 °C) were required.[24,18,27]

Recently, in 2015, Roslan and co-workers[13] reported the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones from the commercially available 2-aminopyridines and β-oxo esters catalyzed by bismuth compounds. The novelty of this strategy is that the reaction was catalyzed by a non-corrosive Brønsted acid such as $BiCl_3$ or $Bi(OTf)_3$.

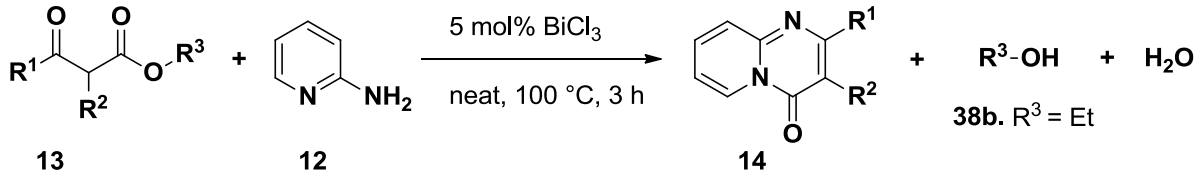
They optimized the reaction conditions for 2-aminopyridine **12** and methyl acetoacetate **13a**. Firstly they used as a catalyst $Bi(OTf)_3$, and several solvents were tested, such as dioxane, $MeNO_2$, H_2O, toluene and the reaction worked in moderate to good yields. The best result was obtained when the reaction was performed solvent free, when the product was obtained in 100% yield.

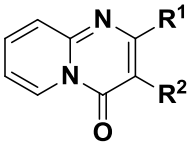


Scheme 6: The optimized conditions for the synthesis of 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (14a).

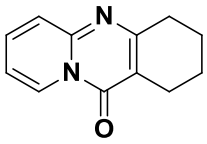
They tried without any catalyst; however the reaction did not work. Also, they screened other Lewis acids such as $InCl_3$ and $ZnCl_2$, however only traces of the product were obtained. The conclusion was that the bismuth(III) salt was necessary to obtain the product. Furthermore, other bismuth(III) salts were also used such as $BiCl_3$ and Bi(OAc). $BiCl_3$ was found to be as good as $Bi(OTf)_3$. $BiCl_3$ was chosen as the catalyst for the following synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives, because it is cheaper than $Bi(OTf)_3$.

The optimized conditions for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **14a-i** were 2-aminopyrimidine **12** (0.5 mmol), β-oxo ester (1 mmol) and $BiCl_3$ (0.025 mmol) neat at 100 °C for 3 h.





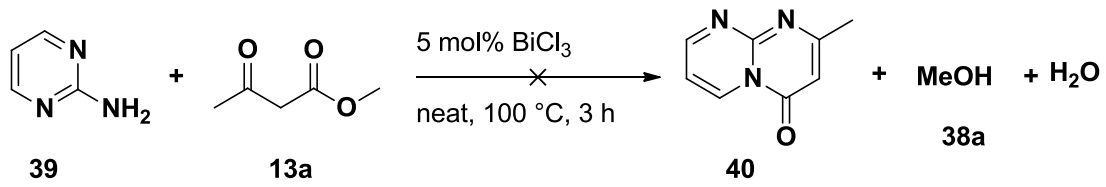
14a. $R^1 = CH_3$, $R^2 = H$; 100%
14b. $R^1 = i$Pr, $R^2 = H$; 91%
14c. $R^1 = n$Pr, $R^2 = H$; 96%
14d. $R^1 = Ph$, $R^2 = H$; 85%
14e. $R^1 = CO_2Et$, $R^2 = H$; 96%
14f. $R^1 = CH_3$, $R^2 = CH_3$; 99%
14g. $R^1 = CH_3$, $R^2 = Ph$; 94%
14h. $R^1 = CH_3$, $R^2 = Bn$; 98%



14i. 97%

Scheme 7: Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones using $BiCl_3$ as catalyst.

They also employed this procedure when 2-aminopyrimidine **39** was used as starting material, however, the reaction failed to give **40**. A reason could be that the nucleophilicity of the NH_2 group may be reduced due to the additional nitrogen atom on the pyrimidine ring.



Scheme 8: Attempted synthesis of 2-methyl-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one using $BiCl_3$ as catalyst.

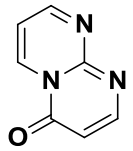
They developed an efficient and green new methodology for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones using $BiCl_3$ as catalyst. The starting materials are commercially available and cheap and $BiCl_3$ is a mild, moisture and air stable Lewis acid. It is easy to handle and is not carcinogenic. Furthermore, the reaction proceeds under mild conditions, (no solvent and no inert atmosphere were required) and in excellent yields. In addition, the co-products formed were only alcohol and water.

2- Pyrimidopyrimidine derivatives.

Pyrimidopyrimidines are bicyclic pyrimidine derivatives containing two fused pyrimidine rings or two fused pyridine and pyrimidine rings.

Numerous pyrimidine and pyrimidopyrimidine derivatives show interesting pharmaceutical properties. It is known that pyrimidine rings containing sulfonamides form part of the antibacterial agents group. The pyrimidopyrimidine derivatives have shown other interesting pharmaceutical properties such as antiviral, anti-HIV, antiallergic, and antitumoral activities. Also, derivatives of aminopyrimidines with diverse substituents on the pyrimidine ring show biological activities.[9]

Pyrimido[1,2-*a*]pyrimidines (**Figure 7**) derivative group is a less studied group of bicyclic pyrimidine heterocycles. There are not a high number of methods for the synthesis of this group in the literature. One of the reasons could be because of the lack of a widely applicable method for their synthesis.[9]



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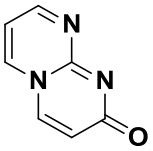
4*H*-pyrimido[1,2-*a*]pyrimidin-4-one



41

2*H*-pyrimido[1,2-*a*]pyrimidin-2-one

Figure 7: Isomers of pyrimido[1,2-*a*]pyrimidinone.

2.1- Biological activities.

In both medicinal chemistry and the agrochemical industry it is common to use phosphorylated azaheterocycles.[4] These versatile scaffolds are also important intermediates in organic synthesis. Some examples are: 2-pyridylthionophosphonate **42** which is an important constituent of various preparations of pesticides, 2-pyridylphosphonate **43** is an agonist of cyclic adenosine monophosphate-dependent protein kinase (i.e., it is potential blood platelet aggregation inhibitor, smooth muscle relaxant, and inflammation inhibitor) and compound **44** which is a potent and selective AMPA/kainate antagonist with neuroprotective properties.[4]

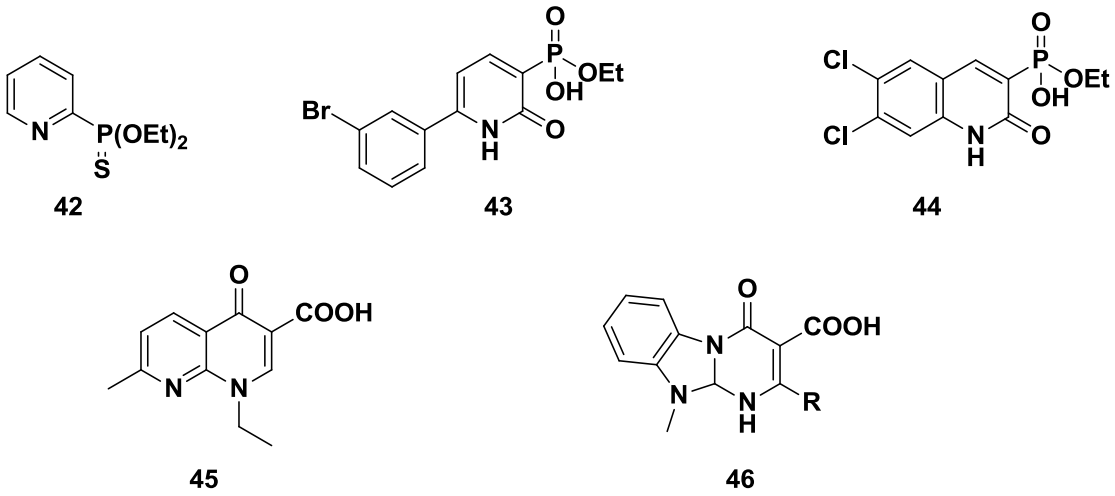


Figure 8: The importance of phosphorus group and the fused heterocycles as biological active molecules.

On the other hand compound **45** is a derivative of nalidixic acid which is a well-known antibacterial agent[28] and 4-oxopyrimidobenzimidazole-3-carboxylic acid **46**, is a central nervous system depressant and anti-inflammatory agent.[29] Both of them are carboxy-substituted azaheterocycles with interesting biological properties. For this reason the synthesis of phosphorus analogous of these carboxylic acids is under study.

These new scaffolds are the combination of two interesting parts; one part is the phosphorus group, which has shown biological properties. The other part is a fusion of two or more heterocycles forming a new single moiety, which also possesses biological properties.[4]

For these reasons; the following compounds could be an interesting profile for new drugs development.

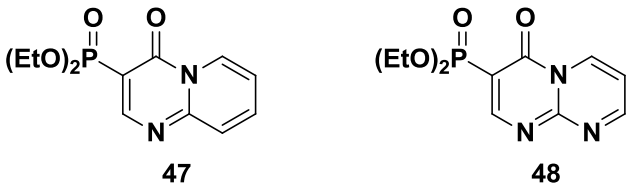


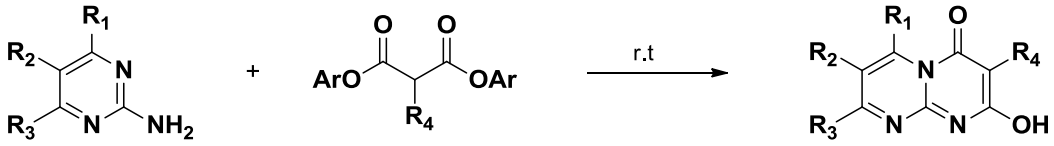
Figure 9: New phosphorylated azaheterocyclic compounds.

Moreover, the compounds could be also interesting synthetic intermediates for further reactions.

2.2- Previous synthesis of pyrimido[1,2-a]pyrimidines.

One of the most interesting routes to the synthesis of pyrimido[1,2-*a*]pyrimidines was reported by Güllü and co-workers in 2010.[9] They reported the reaction of 2-aminopyrimidine with active malonates. The active malonates used are highly reactive, with good leaving groups, namely bis(2,4,6-trichlorophenyl) or bis(pentachlorophenyl). The reactions were carried out in an inert solvent, and a tertiary amine was employed as catalyst.

Table 1: Reaction of 2-aminopyrimidines with bis(2,4,6-trichlorophenyl) malonates.



49 **50** **51a-d**

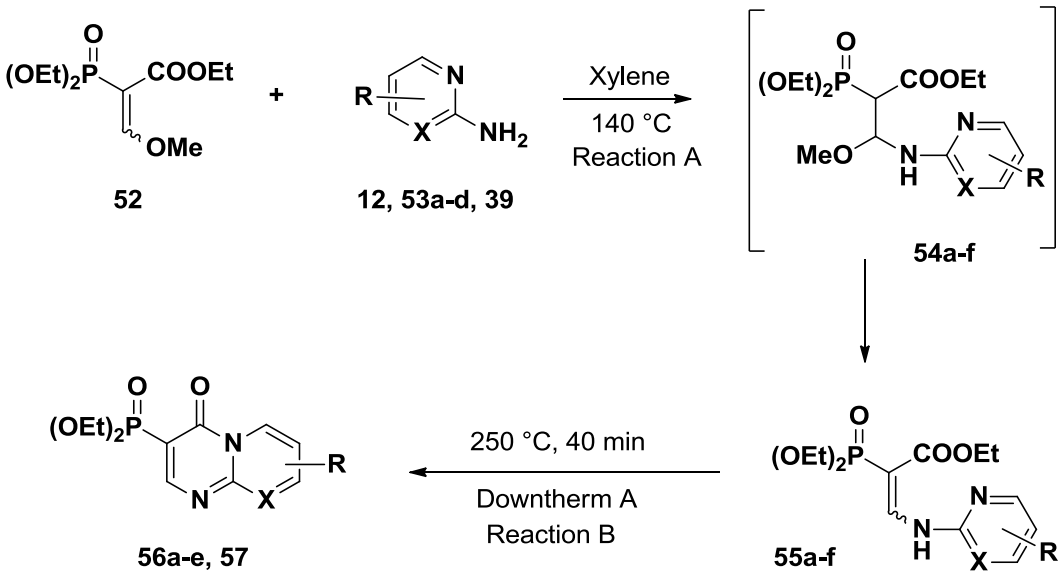
Ar= 2,4,6-$C_6H_2Cl_3$

Entry	R_1	R_2	R_3	R_4	Solvent	Time (h)	Product	Yield %
1	H	H	CH_3	H	$CHCl_3$	6	**51a**	84
2	H	H	H	H	Acetone	2	**51b**	75
3	CH_3	H	OCH_3	H	$CHCl_3$	8	**51c**	78
4	CH_3	H	OCH_3	butyl	Et_2O	24	**51d**	86

A study of several substituted-pyrimidines **49** with bis(2,4,6-trichlorophenyl) **50** at room temperatures in different solvents and different time of reactions, gave the results shown above in **Table 1**. The reaction worked in good yields, and this methodology gave a straightforward synthesis of several 2-hydroxy-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivatives bearing 4 different substituents.

Modranka and Janecki reported in 2011[4] the synthesis of diverse phosphorylated ortho-fused azaheterocycles, by the reaction of pyridopyrimidone and pyrimidopyrimidone scaffolds as part of the phosphorylated ortho-fused azaheterocycles compounds:

Table 2: Synthesis of 2-diethoxyphosphoryl-3-aminoacrylates (reaction A) and intermolecular cyclization of acrylates (reaction B).



Entry	Amine	Product[e]	Yield %	Product	Yield %
1	**12.** R=H; X=C	**55a**[a]	86%	**56a.**[c] R=H; X=C	75%
2	**53a.** R=3-Me; X=C	**55b**[a]	84%	**56b.**[c] R=3-Me; X=C	84%
3	**53b.** R=4-Me; X=C	**55c**[a]	90%	**56c.**[c] R=4-Me; X=C	67%
4	**53c.** R=5-Me X=C	**55d**[a]	83%	**56d.**[c] R=5-Me X=C	68%
5	**53d.** R=6-Me; X=C	**55e**[a]	81%	**56e.**[d] R=6-Me; X=C	14%
6	**39.** R=H; X=N	**55f**[b]	72%	**57.**[d] R=H; X=N	73%

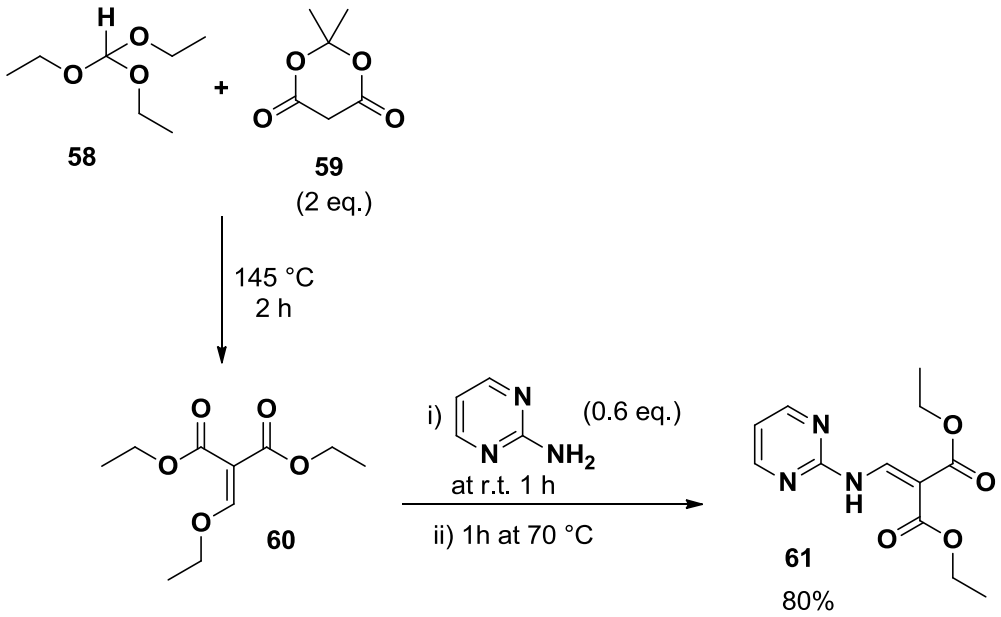
[a]Reaction A time: 16h. [b]Reaction A time: 8 h. [c]Reaction B time: 40 h. [d]Reaction B time 60 h. [e]E/Z Ratio (30:70).

A mixture of 2-diethoxyphosphoryl-3-methoxyacrylate **54** with several heteroaromatic amines (**12**, **53a-d** and **39**) was heated in xylene over 8-16 h. Depending on the heteroaromatic amine (**Table 2**), this led to a mixture of E and Z isomers of ethyl 2-diethoxyphosphoryl-3-aminoacrylates **55a-f** in a (30:70) ratio in most of the cases, in mostly excellent yields. Subsequently, the optimal conditions for the intramolecular cyclization were applied to the ethyl-2-diethoxyphosphoryl-3-aminoacrylates intermediates **55a-f**. The reactions underwent fully regioselective intramolecular N-cyclization, followed by deprotonation to give pyridopyrimidones **56a-e** and pyrimidopyrimidone **57**.

An efficient two-step synthesis of a variety of phosphorylated pyridopyrimidinones and pyrimidopyrimidone via intramolecular N-cyclization has been described.

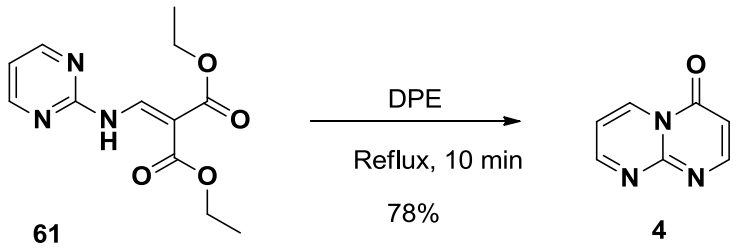
Recently, in 2015, Lengyel *et al.*[30] developed the synthesis of pyridopyrimidones by the Gould-Jacobs reactions in a three-mode pyrolysis reactor. They demonstrated the capabilities of the pyrolysis instrument for the synthesis of heterocyclic systems that require the reaction to cross a high activation barrier.

Firstly the synthesis of the key intermediate was required (**Scheme 9**).



Scheme 9: Synthesis of the precursor, compound 61.

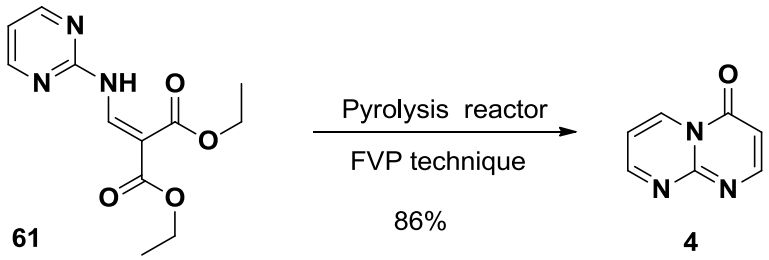
Having the key intermediate precursors **61** in hand, they synthesized the compound **4** under two different methodologies: i) firstly under conventional batch conditions:



Scheme 10: Synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one under conventional batch conditions.

After they obtained the 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one using conventional conditions, they studied different conditions for the synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in the modules of the pyrolysis reactor. The three modules of the pyrolysis reactor are: i) a flash vacuum pyrolysis (FVP) module that applies high vacuum (10^{-3} mbar), allowing the starting material to pass through the reactor chamber which is heated up to 1000 °C; (ii) a pneumatic spray pyrolysis (PSP) module that can inject non-volatile reactants to the heated reactor zone; and (iii) a high-pressure pyrolysis (HPP) continuous-flow module that operates from atmospheric to 400 bar pressure and between room temperature and 600 °C.

Among the three modules, the FVP module was the more effective for this thermal cyclisation. For the synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one **4**, in the FVP reactor the following parameters were used: T_f (furnace temperature) = 450 °C; T_i (inlet temperature) = 140 °C; P (pressure) = 5 x 10^{-1} mbar; t (pyrolysis time) = 20 min; tube dimensions (30 cm × 2 cm) (**Scheme 11**).



Scheme 11: Synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one using FVP technique.

The product **4** was collected successfully from the tube as orange crystals in 86% yield.

The advantage of this technique is that the flash pyrolysis method is the shortest reaction time and gave better results. Also this technique delivered the product pure; no work-up was needed and the reaction was performed under solvent-free conditions.

3- Pyridone derivatives.

2-Pyridone **5** and 4-pyridone **6** derivatives are interesting and important scaffolds among the N-alkylated heterocycles; these structural motifs are an essential core in natural products and medicinal targets. Moreover, they often serve as synthetic precursors for nitrogen-containing six-membered ring compounds.

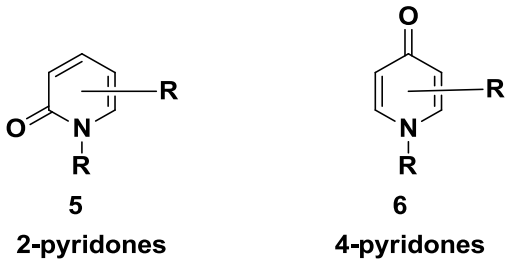


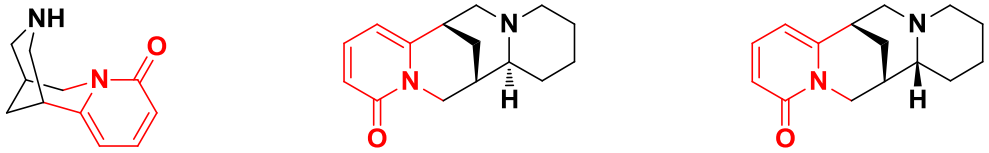
Figure 10: 2- and 4-pyridone scaffold.

The **Figure 10** shows the general core of N-alkylated 2-and 4-pyridone scaffolds.

3.1- Biological activities.

The presence of N-alkylated-2-pyridone scaffold in several natural products such as (-)-cytisine **62**,[10] (-)-anagyrine **63**,[31] and (-)-thermopsine **64**,[10] makes this core a remarkable scaffold. It represents an important group of natural products, and also it represents a numerous groups of pharmacologically active structures containing 2-pyridone as an essential core (**Figure 11**).

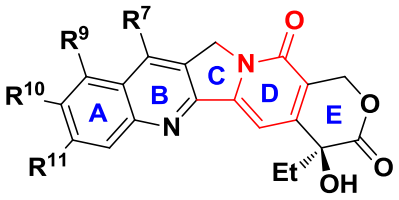
An example of a natural product and a precursor of a pharmacologically active structure is (-)-cytisine[10] **62**, which is present in several plants of the leguminosae family (Cytisus, Sophora, Ulex, Baptisia).[32] It is a potent α4β2 subtype selective partial agonist at nicotinic acetylcholine receptors.[10,33] The cytosine analogues have been studied for the treatment of various CNS disorders and for assisting smoking cessation.[33]



(-)-cytisine **62** (-)-anagyrine **63** (-)-thermopsine **64**

Figure 11: (-)-Cytisine, (-)-anargyrine, (-)-thermopsine structure.

20(*S*)-Camptothecin (CTP) **65a** is a natural product, which belongs to the Lupin alkaloid family, It was isolated for the first time from the chinese tree *Camptotheca* by Wall and co-workers in 1966.[34]



65a R^7-R^{11}= H.

Camptothecin

Figure 12: 20(*S*)-Camptothecin structure.

This compound (**Figure 12**) has attracted much attention because has shown impressive activity against leukemia and wide range of solid tumors.[35]

Although this natural product showed good biological activity, in clinical trials it showed poor water solubility, and this is an obstacle to the supply of this treatment in patients. Also, CTP showed severe toxicities such as myelosuppresion, vomiting, and diarrhea; therefore the use of CTP was ceased in clinical trials. The investigation of new CTP derivatives was required and moreover the research aim was to design water-soluble camptothecin derivatives that maintained the antitumor activity.

Later on, based on this natural product, the following family of topoisomerase poisons **65b** and **65c** were synthesized by Huber Josien *et al*. in 1998. The solubility of these derivatives was improved and furthermore these compounds are shown some of the most promising agents for the treatment of solid tumours by chemotherapy (**Figure 13)**.[36]

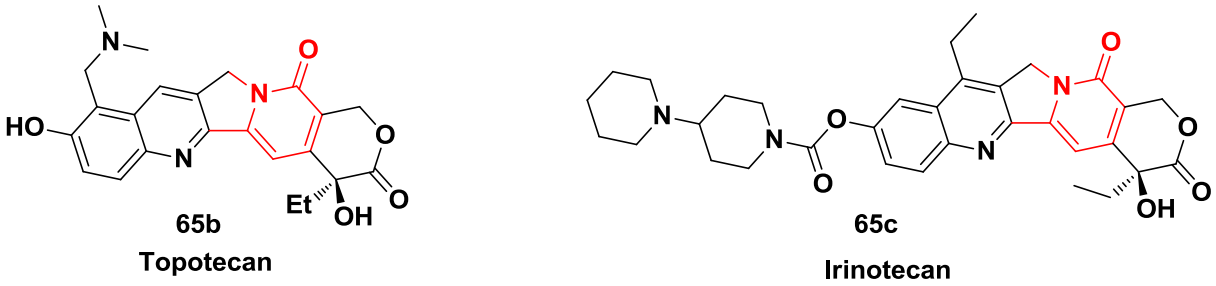


Figure 13: Topotecan and Irinotecan structure.

Other examples showing the importance of N-alkylated-2-pyridones in pharmaceutical and medicinal chemistry are: Ricinine **66** as a simple bioactive molecule and aurodox **68** as an example of a more complex compound. Funiculisin **67**, isolated from *Penicillium funiculosum*, is a 2-pyridone derivative which bears substituents at C-3 and C-5 (**Figure 14**).[37]

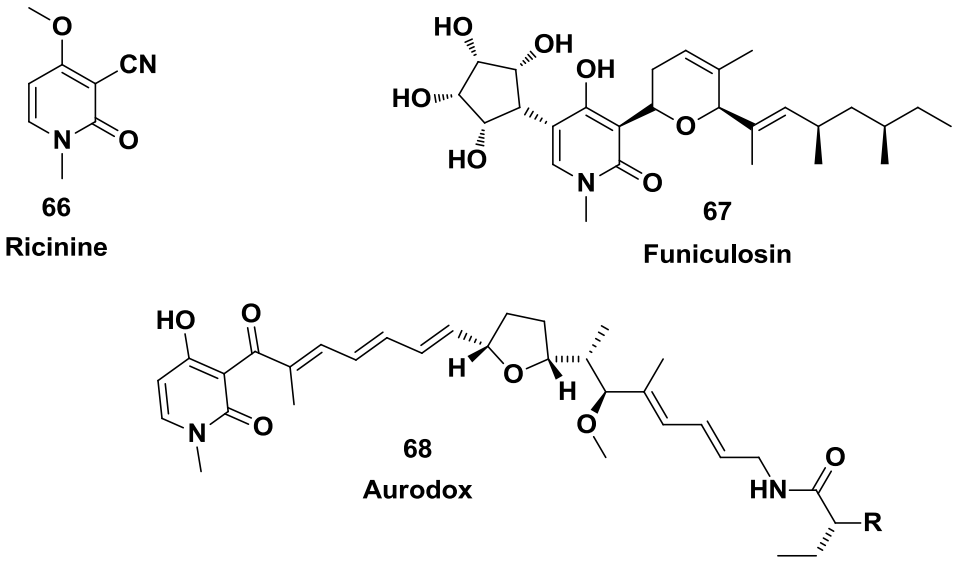
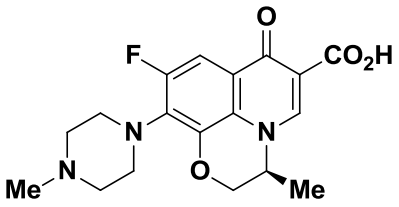


Figure 14: Ricine, Funiculosin and Aurodox structure.[37]

An example of a 4-pyridone derivative of a pharmaceutical compound and natural product is levofloxacin **69** (**Figure 15**).[38]



69

Figure 15: Levofloxacin compound.

Among all natural products or pharmaceutical compounds that have been described before, either the 2-pyridone or 4-pyridone rings are an essential part of the scaffold, hence the pursuit of a large number of pathways to synthesize 2- and 4-pyridone scaffolds are wanted. There is especial interest in the development of new reactions to functionalize these special scaffolds, in order to form the skeleton for the synthesis more complex molecules.

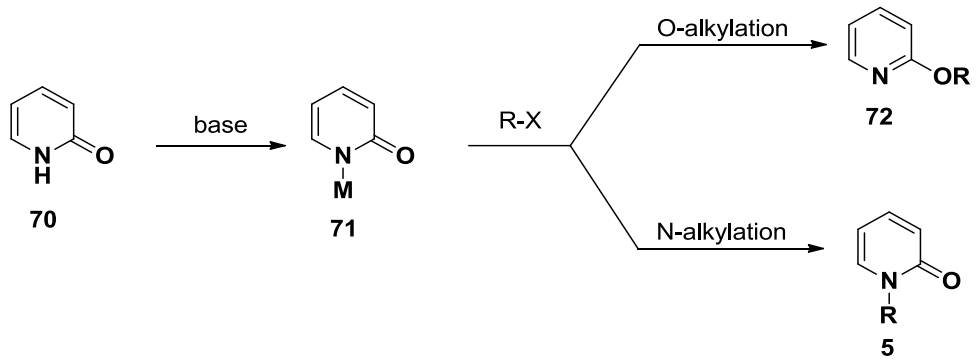
3.2- Previous synthesis of 2-pyridones.

There are several pathways to synthesize 2-pyridones. However, in this report we are focusing in the synthesis of N-alkyl 2-pyridones from 2-pyridones (section 3.2.1) and from 2-alkoxypyridines (section 3.2.2).

3.2.1- Synthesis of N-alkyl 2-pyridones from 2-pyridones.

2-Alkoxypyridines **72** and N-alkyl-2-pyridones **5** are valuable synthetic intermediates. A common synthetic method to synthesize N-alkyl-2-pyridones **5** is using 2-pyridone as starting material. The reason to study this in depth was due to the ambident nucleophilic character of 2-oxopyridines.[39]

One of the problems has been to control the N-alkylation vs O-alkylation of 2-pyridone derivatives, for example 2-pyridone **70**.[39,40] The synthesis of N-alkylated products is difficult to achieve without forming mixtures of N- and O-alkylated products. A general procedure to obtain N-alkylation involves treating a metal salt of the 2-pyridone **71** with an alkyl halide (**Scheme 12**).[41,42]



Scheme 12: N-alkylation *vs* O alkylation product.[39]

There are some variables that need to be taken into account in controlling the regioselectivity between N- and O- alkylation. Increasing the size of the alkyl halide favours O-alkylation, due to the steric hindrance in the transition state leading to the N-alkylated product as the minor product. In previous investigations, the use of a silver salt in non-polar solvent was frequently used as a good procedure to obtain the O-alkylation product. Although, the O-alkylation was achieved using silver salts, they are expensive,[42] which is the main reason to continue working in the development of cheaper synthetic routes.

These are the four important variables to consider in order to favouring one or the other isomers:

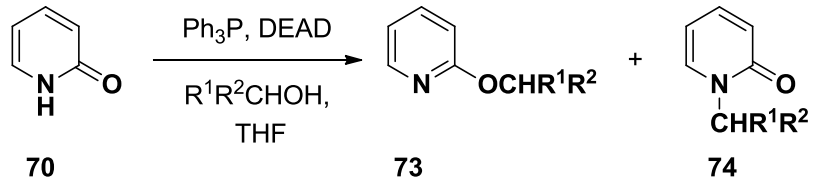
- The nature of the metal.
- The structure of the alkyl halide.
- The substituents on the pyridone ring.
- The solvent.

Depending on these, it is possible to control N-alkylation vs O-alkylation. In general, the N-alkylated product had been performed using sodium salts.[41,42,43] However, the continuous development of new methodologies to perform a selective N-alkylation of 2-pyridones was needed, due to the competition of O-alkylation and N-alkylation and therefore the formation of mixtures of both products.

In 1994 Daniel L. Comins and Gao Jianjua reported a study of "N- vs O-alkylation in the Mitsunobu reaction of 2-pyridone". The authors chose to investigate the Mitsunobu reaction, because it operates under mild conditions. The 2-pyridone is a good candidate for this reaction, the essential requirement is to use a nucleophile (HA) with a pK_a less than 13, and the pK_a of 2-pyridone is 11.62.[39]

In this reaction, standard reagents were used: 2-pyridone (1 mmol), PhP_3 (1.5 eq.) and diethyl azodicarboxylate (1.5 eq.) in THF (20 mL) at RT, and the other reagents used in the reactions are summarised in the following **Table 3**:

Table 3 : Mitsunobu reaction of 2-Pyridone with alcohols (R^1R^2CHOH).



70 **73** **74**

Entry	R^1	R^2	73 (%)	74 (%)	73:74
1	Ph	H	**73a** (20)	**74a** (67)	1:4
2	$PhCH_2$	H	**73b** (88)	-	10:1
3	$PhCH_2$	CH_3	**73c** (63)	**74c** (0)	1:0
4	Ph	CH_3	**73d** (60)	**74d** (0)	1:0
5	$PhCHCH_3$	H	**73e** (89)	**74e** (0)	1:0
6	2-Naphth	H	**73f** (15)	**74f** (54)	1:3.5

They reported the alkylation of 2-pyridones which does not required the presence of a strong base, and as electrophiles, 1° or 2° alcohols were used. Under these conditions, it was possible to control N- and O-alkylation and to achieve O-alkylation as a major product.

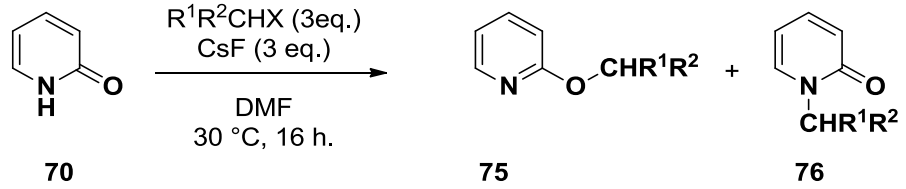
This procedure gave an alternative to O-alkylate 2-pyridones avoiding the use of expensive silver salts. However, only in entries 3, 4 and 5, was a selective O-alkylation achieved. In the other reactions a mixture of N and O-alkylated product was obtained and in some cases, such as entries 1 and 6, the N-alkylated product was the major product.

In 1995, Sato *et al.*[43] reported that the selectivity for the N or O-alkylation of 2-pyridone, under mild conditions, depended on the alkyl halide.

The alkylation of 2-pyridones was performed under standard mild conditions (**Table 4**), and primary and secondary alkyl halides were studied.

The highest N-alkylation selectivity was found with primary alkyl halides, such as benzyl and allyl halides; furthermore the alkyl chlorides have better selectivity (entries 1 and 3) than the corresponding bromides and iodides (entries 2, 4 and 5). On the other hand a selective O-alkylation was obtained when secondary halides were used (entries 9, 10 and 11) (**Table 4**).

Table 4: CsF-Promoted alkylation of 2-pyridone.

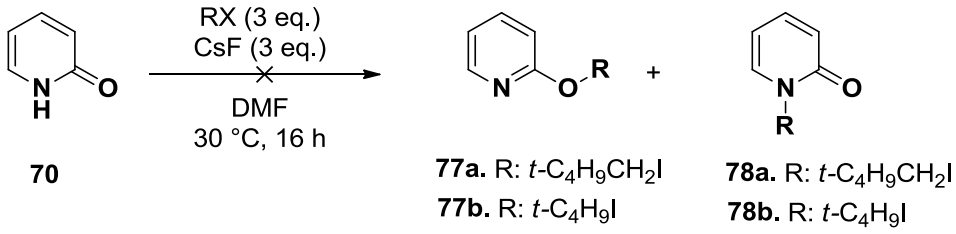


70 **75** **76**

Entry	R^1	R^2	X	75 (%)[b]	76 (%)[b]	75:76
1	Ph	H	Cl	**75a** (7)	**76a** (93)	7:93
2	Ph	H	Br	**75a** (10)	**77a** (68)	13:87
3	CH_2=CH	H	Cl	**75g** (8)	**76g** (85)	9:91
4	CH_2=CH	H	Br	**75g** (7)	**76g** (55)	11:89
5	CH_2=CH	H	I	**75g** (9)	**76g** (58)	13:87
6	CH_3	H	Br	**75h** (29)	**76h** (71)	29:71
7	CH_3	H	I	**75h** (40)	**76h** (60)	40:60
8	CH_3	H	OMs	**75h** (32)	**76h** (41)	44:56
9	CH_3	CH_3	Br	**75i** (72)	**76i** (28)	72:28
10	CH_3	CH_3	I	**75i** (55)	**77i** (7)	89:11
11	CH_3	CH_3	OMs	**75i** (41)	**76i** (9)	82:18

[b] **Determinated by GLC.**

For bulky alkyl halides (**Scheme 13**) no N-alkylation or O-alkylation product was obtained.



70

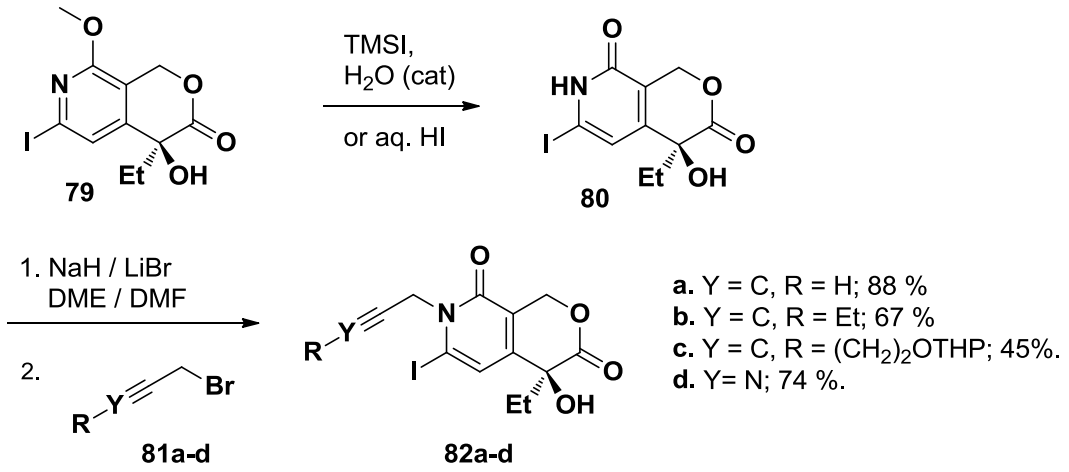
77a. R: t-$C_4H_9CH_2I$
77b. R: t-C_4H_9I

78a. R: t-$C_4H_9CH_2I$
78b. R: t-C_4H_9I

Scheme 13: Attempt to CsF-promote alkylation of bulky haliders of 2-pyridone.

In 1998, Curran *et al.*[36] reported the synthesis of 20(*S*)-Camptothecin family. As a part of this total synthesis, they synthesized the following pyridones **82a-d**. One of the concerns in the N-alkylation reaction was the ambident behaviour of the pyridone anion.

Even though they overcame this problem using NaH and LiBr dissolved in a mixture of DMF and DME and the desirable pyridone was produced in 88% yield, a small quantity of the unwanted O-alkylpyridine was still formed and needed to be separated (**Scheme 14**).[44]



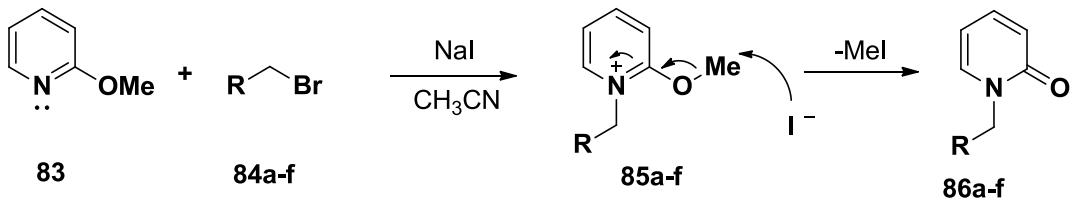
Scheme 14 : Synthesis of N-substituted-2-pyridones.

The O and N-alkylation of 2-pyridone has been studied intensely, to try to control the ambident behaviour of the 2-pyridone anion. The O and N alkylation has been controlled to some extent with the use of CsF, or using the conditions reported by Curran et *al.,* however, small amounts of unwanted O-alkylated product were always formed.

The following authors used as starting material 2-alkoxypyridines, trying to avoid the O and N-alkylation competition.

3.2.2- Synthesis of N-alkyl 2-pyridones from 2-alkoxypyridines.

Bowman and Bridge reported in 1999 a facile and selective one-pot conversion of α–methoxypyridines to N-alkylpyridones (**Scheme 15**).[44] The reaction was performed in acetonitrile as solvent and the use of NaI was needed to activate the halide, in order to speed up alkylation by conversion of the bromide into the iodide *in situ*.



84 and 85:

a. R = benzyl **b.** R = allyl **86a.** R = benzyl **86g.** R =allyl
c. R = 2-bromobenzyl **d.** R = 2-iodobenzyl **86j.** R = 2-bromobenzyl **86k.** R = 2-iodobenzyl
e. R = cinnamyl **f.** R = CH_2CO_2Me **86l.** R = cinnamyl **86m.** R = CH_2CO_2Me

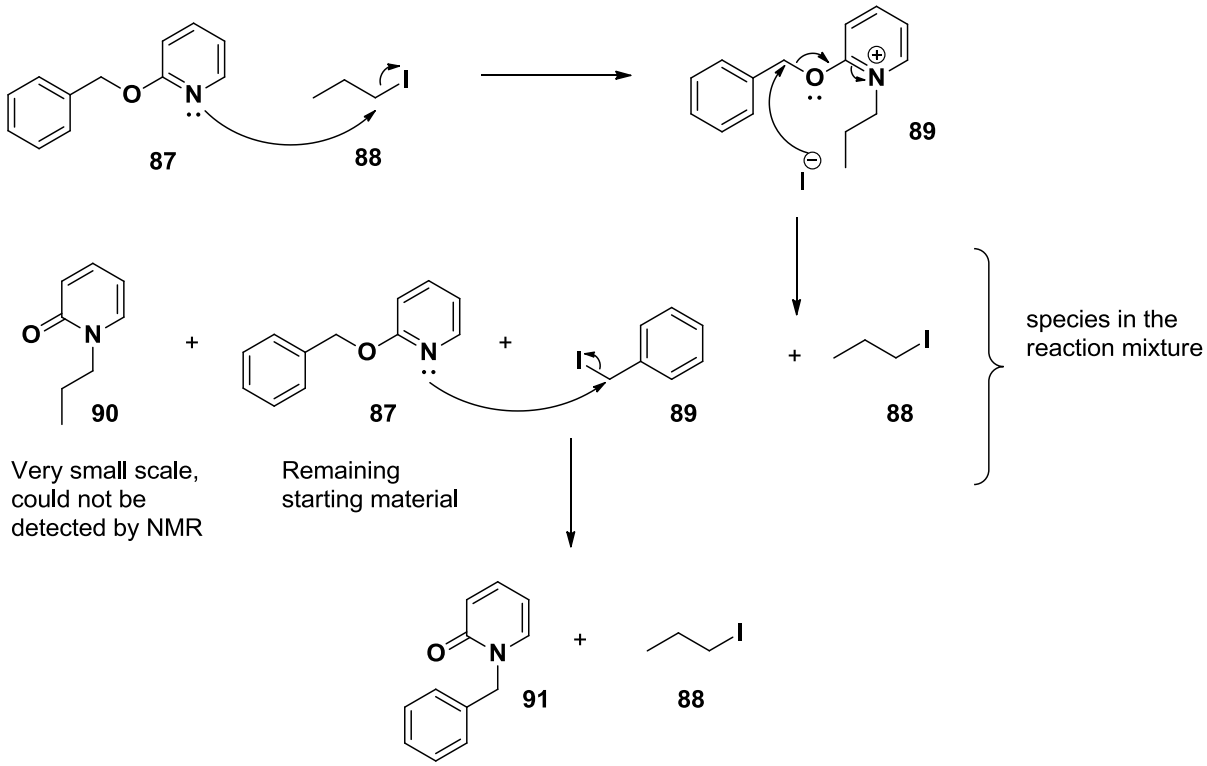
Scheme 15 : Selective synthesis of N-alkylpyridones.

The mechanism is described in **Scheme 15** where an initial alkylation, to generate the pyridinium salt, was required in order to initiate C-O cleavage. The reaction worked in good yields and no O-alkyl products were detected, however the pyridone products required some purification.[44]

The benefit of this methodology is the conversion step of α-methoxypyridine to the corresponding pyridone using TMSI reported by Curran *et al.*[36] was not needed. One drawback of this reaction pathway however was the reaction did not work with a range of unactivated halides, such as ethyl 4-bromobutanoate, 4-bromobutanonitrile or 2-bromo-1-(bromoethyl)benzene. Also we need to take into account the fact that Bowman's methodology was only applied to unsubstituted 2-alkoxypyridines.

In 2002, Ruda and co-workers reported a similar approach for the regioselective solid-phase synthesis of N-alkylated 2-pyridones.[45]

Ruda's group studied a model solution-phase reaction of the N-alkylation of substituted 2-alkoxypyridines with alkyl halides. This strategy was studied as a solution of the problems shown in the following scheme:



Scheme 16: Attempt to synthesize N-alkylate of 2-benzyloxipyridine with propyl iodide.

The study of the effect of the alkoxy group on the 2-alkoxypyridine was essential in this reaction, since, the alkoxy group was the source of new alkyl halide reagent which was generated *in situ* as a by-product.

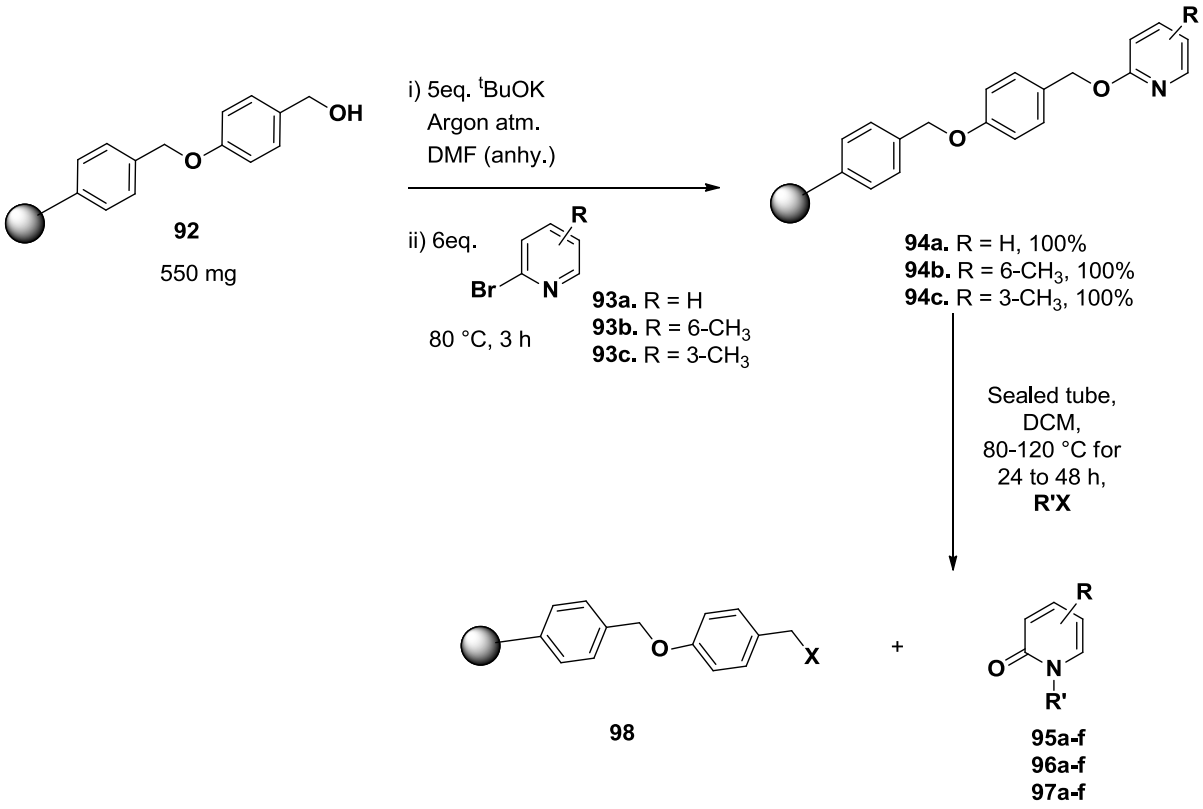
When the alkylating reagent formed *in situ* (benzyl iodide) was more reactive than the selected alkylating reagent (1-iodopropane), the former reacted faster with the remaining 2-alkoxypiridone, generating the N-benzyl-2-pyridone **91** as a major product (**Scheme 16**).

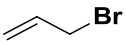
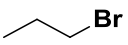
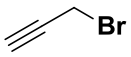
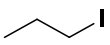
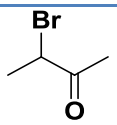
This problem was solved in an interesting way. By linking the benzyloxy group to a solid support, it was possible to avoid the formation of the free alkylating reagent. The by-product was also linked to the solid support, avoiding side reactions (**Table 5**).

The Wang resins were exposed to *t*-BuOK, the resultant products were subsequently reacted with 2-halopyridines **93a-c** and via aromatic nucleophilic substitution, the intermediate resins **94a-c** were obtained. The coupled products were N-alkylated with several alkylating reagents. Once the coupled products were alkylated, the reaction to form the pyridone compounds **95a-f**, **96a-f** and **97a-f** occurred, and no O-alkylated products were isolated (**Table 5**).

Using this methodology, competition reactions between the alkylating reagents added to the reaction mixture and the alkylating reagents formed *in situ*, were avoided. Another advantage of this methodology was the use of several substituted 2-alkoxypyridone was possible, also including 6-substituted 2-alkoxypyridones. The drawbacks of this methodology were: the impossibility to attach pyridines bearing acidic protons. Unalkylated pyridone was also formed; presumably, traces of water in the reaction mixture caused cleavage of unalkylated pyridine from the resin. The yields were generally moderate (19-86%), (**Table 5**).

Table 5: Coupling 2-halopyridines to the Wang resin and the synthesis of 2-pyridones on solid phase.



R'X	$PhCH_2Br$						
Resin	**95a**	**95b**	**95c**[b]	**95d**[b]	**95e**[b]	**95d**	**95f**
94a	58%[a]	79%[a]				19%[a]	17%[a]
Resin	**96a**	**96b**	**96c** 85%[a]	**96d**[c]	**96e**	**96d** [c]	**96f**
94b	24%[e](1:2)[d]	78%[a]			27%[e](1:2)[d]		33%[e](1:3:1)[d]
Resin	**97a**	**97b**[c]	**97c**	**97d**[c]	**97e**	**97d**	**97f**
94c	62%[a]		17%[e](1:2)[d]		51%[a]	35%[a]	81%[a]

[a] Overall isolated yield (loading +cleavage). Loading yields appear to be 100% on the basis of 1H MAS NMR. [b] Not attempted. [c] Product could only be detected by ES-MS. [d] Alkylated product versus unalkylated product. [e] Yield of the N-alkylated product.

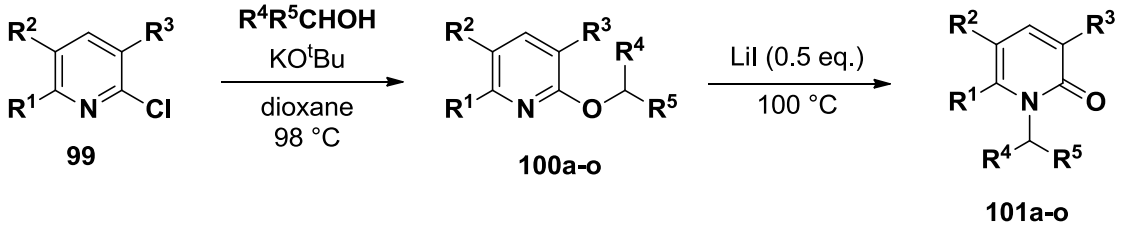
In 2008, Lanni and co-workers[46] reported the conversion of O-alkylated pyridines to the corresponding N-alkylated pyridones in good to excellent yields. Using this methodology a wide range of substituted benzyl groups could be used for O- to N-alkyl migration.

In order to start the study, the synthesis of O-alkylated pyridines **100a-o** was required (**Table 6**). The 2-chloropyridine derivatives **99** were exposed to potassium tert-butoxide in dioxane at 98 °C and the corresponding alcohol was added to the mixture, after the necessary purification step, the reaction leading to the required O-alkylated product.

In the screening to synthesize N-alkyl-2-pyridones, the following variables were studied: solvents (acetonitrile, neat reaction); additives (CF_3COOH, BF_3OEt_2 or LiI) and temperatures (from rt to 200 °C). After the screening, the best conditions were LiI (0.5 eq.) and conventional heating at 100 °C and no solvent, due to the reaction having a better yield when the concentration of pyridine was increased. Good yields were obtained after 8 h, and slightly better yields were obtained after 26 h (**Table 6**).

Table 6 shown, the reaction conditions worked in good to excellent yield for benzyl groups, which bears substituents in *ortho*, meta and *para* position (entries 1-10). On the other hand, a methyl group at 2-position on the pyridine ring had a negative effect in the O- to N migration, 1 eq. of LiI was needed and the yield dropped to 57 %, (entry 12). Pyridine **100n** bearing a substituent on the benzylic position gave the desirable pyridone in even lower yield 34% (entry 13). Furthermore, an extra methylene on the chain in the alkyl derivative was even more problematic (entry 14). The reaction did not work and only starting material was recovered. The migration could fail due to the less electrophile nature of the oxygen-bound carbon. In this development, the study the O-to N-alkyl migration for 6-substituted pyridines was not developed.

Table 6 : Synthesis of 2-alkoxypyridines.



Entry	R^1	R^2	R^3	R^4	R^5	Product (%)[a,b]	Product (%)[c,d]
1	H	H	H	H	C_6H_5	**100a** (77)	**101a** (94)
2	H	H	H	H	4-$CH_3C_6H_4$	**100b** (92)	**101b** (99)
3	H	H	H	H	4-$CH_3OC_6H_4$	**100c** (89)	**101c** (88)
4	H	H	H	H	4-ClC_6H_4	**100d** (93)	**101d** (90)
5	H	H	H	H	3-$CH_3C_6H_4$	**100e** (91)	**101e** (91)
6	H	H	H	H	3-$CH_3OC_6H_4$	**100f** (97)	**101f** (96)
7	H	H	H	H	3-ClC_6H_4	**100g** (94)	**101g** (93)
8	H	H	H	H	2-$CH_3C_6H_4$	**100h** (84)	**101h** (97)
9	H	H	H	H	2-$CH_3OC_6H_4$	**100i** (87)	**101i** (85)
10	H	H	H	H	2-ClC_6H_4	**100j** (97)	**101j** (75)
11	H	CH_3	H	H	C_6H_5	**100k** (78)	**101k** (93)
12	H	H	CH_3	H	C_6H_5	**100l** (98)	**101l** (57)[f]
13	H	H	H	CH_3	C_6H_5	**100m** (89)	**101m** (34)
14	H	H	H	H	$CH_2C_6H_5$	**100n** (58)	**101n** (NR)
15	H	H	H	H	3-pyridyl	**100o** (92)	**101o** (NP)

[a] Conditions: 2-chloropyridine or a substituted analogue (1.0 eq.), RR'OH (1.5eq.), KO^{t}Bu (1.5 eq.), 1.4-dioxane (0.22M), 98 °C, 18 h. [b]Isolated yields. [c] Conditions: substrate (1.0 eq.), LiI (0.5 eq.), 100 °C. [d] Isolated yield. [e] Mean values from duplicate experiments (±3%). [f] 1.0 eq. of LiI used. [g] NR = no reaction, starting material recovered. [h] NP = no product, a number of unidentified byproducts were observed in addition to recovered starting material.

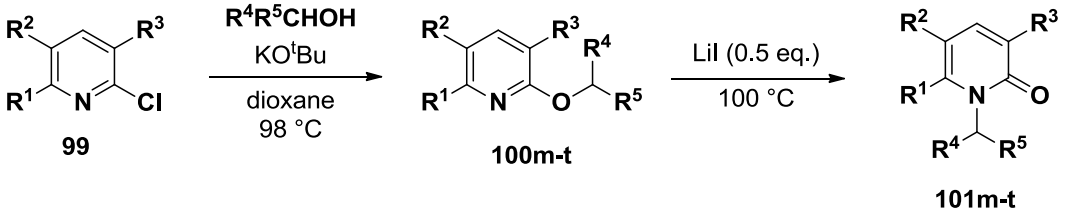
Control reactions showed that the migration of requires LiI and heat to occur. However, the advantage of this methodology is that a substoichiometric amount of LiI was used in all the reactions, apart from entry 12 where 1 eq of LiI was needed to effect the reaction. This method allows the O- to N- migration of a wide range of substituted benzyl groups in high yields.

Later on, in 2012, Tasker, Lanni and co-workers continued the study of the synthesis of 2-pyridones via O- to N-alkyl migration of 2-benzyloxy, 2-allyloxy and 2-propargyloxypyridines.[47] The study started with the synthesis of the essential 2-alkyloxypyridines, following the synthetic route reported by Lanni and co-workers in 2008.[46]

An extension of the previous paper, they studied the O-to N-alkyl migration for 6-substituted pyridines and the synthesis of 2-pyridones via O- to N-alkyl migration of other substituted benzyl groups.

The required alcohols (benzyl, allyl, and propargyl alcohol), were treated with potassium tert-butoxide in dioxane, the 2-chloropyridine was added to the mixture to obtain the desired 2-alkoxypyridine derivative.

Table 7 : Synthesis of N-alkyl-2-pyridone derivatives from 2-chloro-pyridines.



Entry	R^1	R^2	R^3	R^4	R^5	Product	Yield (%)[a,b]
1	H	H	CH_3	H	C_6H_5	**101m**	57[c,d,e]
2	CH_3	H	H	H	C_6H_5	**101p**	59[d]
3	H	H	H	H	2,6-$Cl_2C_6H_4$	**101q**	85[c,e]
4	H	H	H	H	2-naphthyl	**101r**	95[c]
5	H	H	H	H	4-$CF_3C_6H_5$	**101s**	84[d]
6	H	H	H	H	4-CNC_6H_5	**101t**	60[d]

[a]Conditions: substrate (1.0 eq.), LiI (0.5 eq.), 100 °C, 8 h. [b]Isolated yield. Mean values from duplicate experiments (±3%). [c]Reference [46]. [d]Reaction duration = 26 h. [e]1.0 eq. of LiI used.

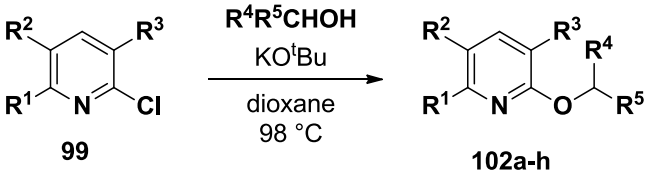
The synthesis of several N-benzyl pyridones is summarised in **Table 7**. The reaction took place under the optimized conditions: LiI (0.5 eq.), neat reaction, conventional heating, from 8 h to 26 h depending on the ring substitution. For the compounds with electron-withdrawing groups on the aryl group, 26 h were needed to take the reaction to completion. The 3-methyl-substituted pyridine needed 1 eq. of LiI and 26 h at 100 °C to afford the 2-pyridone **101m** (entry 1), and the 6-methyl-substituted pyridine needed 26 h to afford the corresponding pyridone **101p**.

The main advantage of this reaction is this 6-methyl pyridine (entry 2) has been found by others authors to be unreactive in other O to N-alkyl migration methods, and using this methodology, the 6-methyl pyridone **101p** was synthesized in 59% yield.

Furthermore, the optimized conditions were evaluated on heterocycle analogues, some of them with an extra heteroatom in the scaffold such as dibenzylpyridazine, pyrimidine and quinolone. However the migration was less successful: higher quantities of LiI and a longer time were needed to obtain the products.

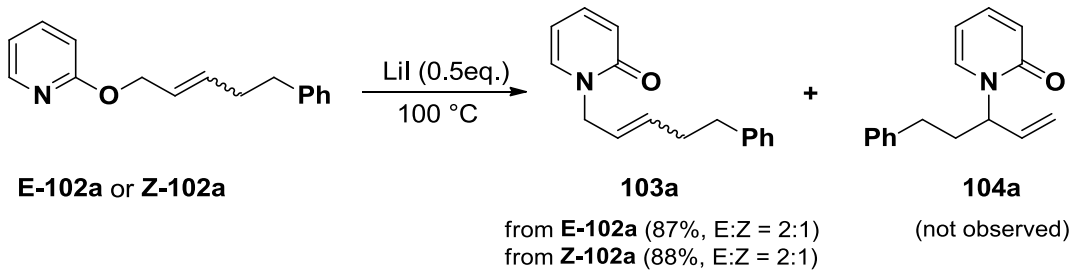
In a continuation of the study, in **Table 8** are shown the synthesis of new 2-allyloxypyridines and 2-propargyloxypyridines. Under the following standard conditions, the synthesis of 2-alkoxypyridines worked in good yields.

Table 8 : Formation of 2 allyloxy- and 2-propargyloxypyridines.



Entry	R^5	R^4	R^3	R^2	R^1	product	Yield(%)a,b
1	(E)-CH=CH$(CH_2)_2$Ph	H	H	H	H	**E-102a**	77
2	(Z)-CH=CH$(CH_2)_2$Ph	H	H	H	H	**Z-102a**	85
3	C≡C$(CH_2)_4CH_3$	H	H	H	H	**102b**	95
4	C≡C$(CH_2)_2$Ph	H	H	H	H	**102c**	90
5	C≡CCy	H	H	H	H	**102d**	94
6	C≡CPh	H	H	H	H	**102e**	58
7	C≡C$(CH_2)_4CH_3$	H	Me	H	H	**102f**	91
8	C≡C$(CH_2)_4CH_3$	H	H	Me	H	**102g**	60
9	C≡C$(CH_2)_4CH_3$	H	H	H	Me	**102h**	75

Having the 2-allyloxypyridine and 2-propargyloxypyridines in hand, they evaluated the standard conditions for promoting O to N alkyl migration. The migration worked successfully, (**Scheme 17**, and **Table 9**). However, the ideal amount of LiI was optimized for each substrate, and most of the time, longer reaction times were needed to obtain the product.



E-102a or **Z-102a** | **103a** | **104a**

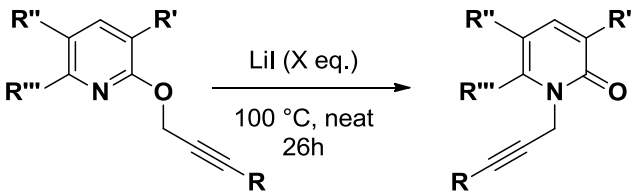
from **E-102a** (87%, E:Z = 2:1)
from **Z-102a** (88%, E:Z = 2:1)

(not observed)

Scheme 17 : Migration of allyl group in allyloxypiridines.

The O- to N-alkyl migration of 2-propargyloxypyridine derivatives is shown in **Table 9**. The migration occurred more slowly than for the corresponding benzyl substituted analogues (26 h vs 8 h) and in most all the cases the amount of LiI had to be increased. The amount of LiI was optimised for each substrate.

Table 9 : Formation of N-propargyl 2-pyridones.



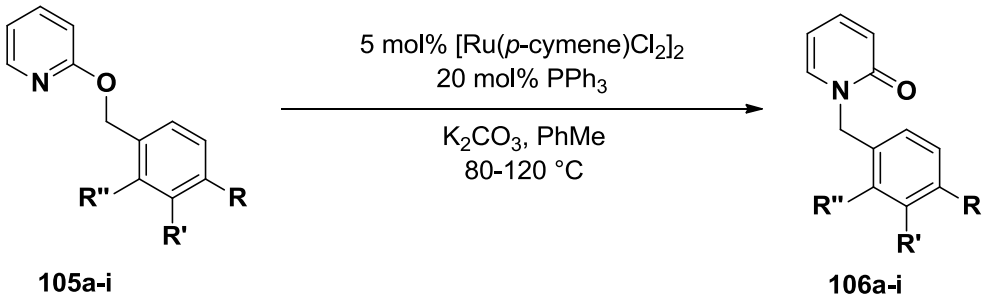
102b-h | **103b-h**

Entry	R	R’	R’’	R’’’	LiI (eq.)	Product	Yield (%)
1	Pentyl	H	H	H	05	**103b**	81
2	CH_2CH_2Ph	H	H	H	0.8	**103c**	85
3	Cy	H	H	H	1.2	**103d**	77
4	Ph	H	H	H	2.0	**103e**	66
5	Pentyl	Me	H	H	0.5	**103f**	NP
6	Pentyl	H	Me	H	1.0	**103g**	64
7	Pentyl	H	H	Me	0.5	**103h**	15

The reaction worked in moderate yields, and the 2-alkoxypyridones bearing substituent at position 3, the migration did not occur. The reason could be that the additional substituent interferes with coordination of lithium to the heteroatoms and thus impedes the migration.

In 2011 Charles *et al.* developed a Ru-catalyzed O- to N-alkyl migratory rearrangement reaction. The first part of Charles and co-workers' work was an optimization study of the promotion of O- to N-migration, with different transitions metals such as: Pd, Ni, Fe or Rh; were unsuccessful in promoting the O- to N-migration. Until they found the excellent catalyst ($[Ru(arene)Cl_2]_2/PPh_3$). The study showed that the reaction needs a weak inorganic base K_2CO_3, since using a strong base or organic base such as NaO^tBu or NEt_3 caused the reaction to fail.

The optimal reaction conditions are shown in **Scheme 18**.



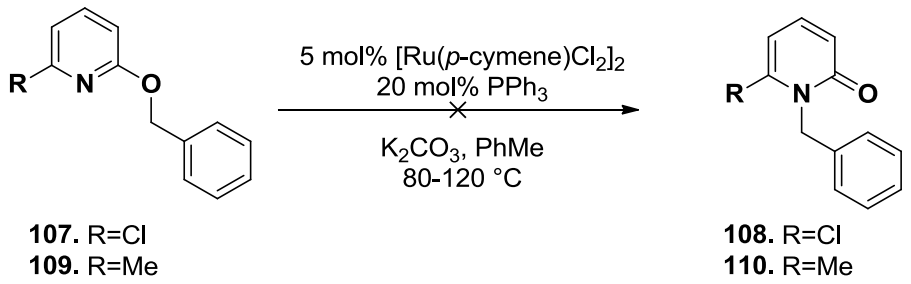
105a-i **106a-i**

a. R = R' = R'' = H; 91%
b. R = Me, R' = R'' = H; 76%
c. R = ^{t}Bu, R' = R'' = H; 99%
d. R = Ph, R' = R'' = H; 99%
e. R = H, R' = Cl, R'' = H; 95%
f.R = Cl, R' = R'' = H; 89%
g. R = F, R' = R'' = H; 88%
h. R = R' = H, R'' = Br; 66%
i. R = H, R' = OBn, R'' = H; 88%

Scheme 18: O-to N-Migratory rearrangement of substituted-2-benzoxypyridines.

The O- to N-alkylation migration in 2-substituted benzoxypyridines worked successfully when the phenyl group bore different substituents such as electron-neutral, electron-deficient, or electron-donating groups in the ortho, metha or para positions. However, in the reactions involving ortho substituents, higher temperatures were required (**Scheme 18**).

The optimized conditions were studied for pyridine derivatives bearing different substituents in all possible positions, (positions 3, 4, 5 and 6 were studied). For pyridine derivatives bearing electron-donating and electron-deficient substituents in positions 3, 4 and 5 the reactions worked in good yields. However the reaction with 6-substituted pyridines bearing electron-withdrawing **107** and electron-donating **109** groups did not work due to steric effects (**Scheme 19**).



107. R=Cl
109. R=Me

108. R=Cl
110. R=Me

Scheme 19 : O-to N-Migratory rearrangement of 2-benzoxy-6-substituted-pyridines.

In addition, the general strategy for O-to N-alkyl migratory rearragement also worked for pyridines bearing large aryl- and heteroaryl substituents such as naphthyl, benzodioxolyl, furyl and benzofuryl at the 2-position.

This methodology was challenging since ethereal C-O bonds are typically inert. Normally it is difficult to do a direct insertion into electron-rich bonds. They reported a new methodology for sp^3 ethereal C-O activation in 2-alkoxypyridines and several other O-alkylated N-containing heterocycles such as 3-alkoxypyridazines.

Overall, the synthesis of N-pyridones has been reviewed, and there are several methods for synthesising O-alkyl pyridines and N-alkyl pyridones. The problem of competition of O and N alkylation has been minimised.

The literature presents many examples of the synthesis of O-alkyl pyridones as a mean of synthesizing N-alkyl-2-pyridones. However, in some cases of pyridines bearing a substituent at position 6, the reaction did not take place.

In our research, we are interested in the synthesis of N-alkyl 6-methyl-2-pyridone as a starting material to synthesize quinolizinone derivatives. Base on Bowman's work, we aimed to develop a new strategy for the synthesis of N-alkyl 6-methyl-2-pyridone using 2-methoxy-6-methylpyridine as the starting material.

3.3- Pyridone as building blocks in synthesis.

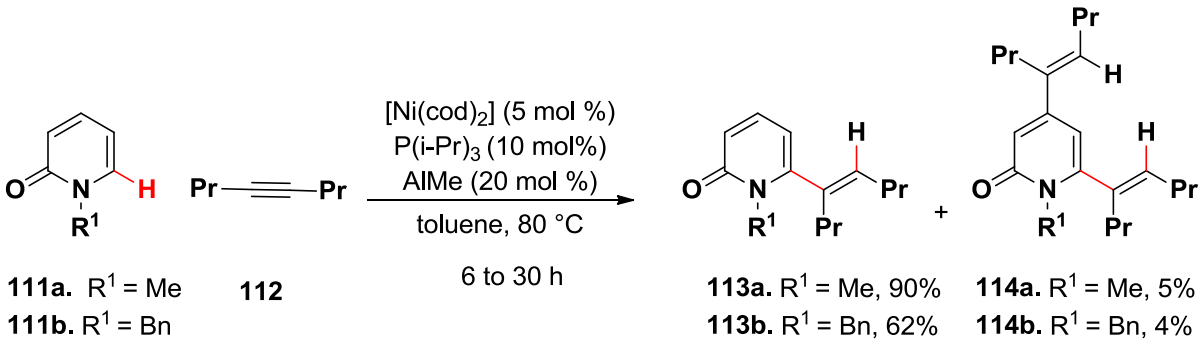
3.3.1- Functionalization of 2- and 4-pyridone ring.

The brief summary of biological activities highlighted the importance of 2- and 4-pyridone cores as constituents of natural products and pharmaceutical compounds. Also, these scaffolds are very important as precursors of new, complex pharmaceutical targets, since the pharmaceutical industry is in a continuous development of new compounds.

In the following pages different pathways for the functionalization at position 6 are described.

Nakao[48] in 2009 reported the C(6)-H alkenylation and alkylation of pyridone derivatives using Ni/$AlMe_3$ catalysis. They reported the inter- and intramolecular insertion of an unsaturated bond into the C(6)-H. The insertion could be activated by Ni(0) upon coordination to a Lewis acid.

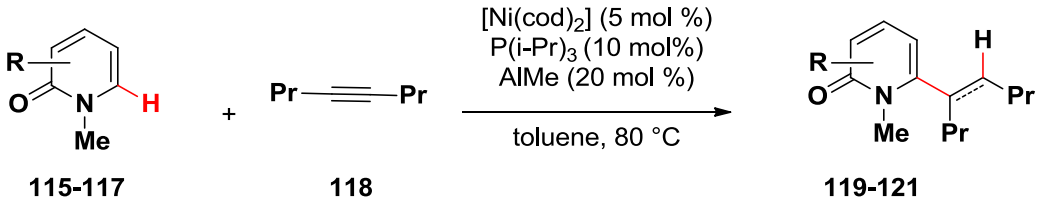
After the screening of ligands and Lewis acids, the optimum combination was used for non-substituted pyridines (**Scheme 20**) and for methyl-substituted pyridines (**Table 10**).



Scheme 20: C(6)-H alkenylation of N-benzyl and N-methyl 2-pyridones.

For pyridone **111a** the product **113a** was obtained in 6 h, however for the synthesis of product **113b** a longer time was required (30 h). And a small amount of 4,6-dialkylated product was formed in both examples.

Table 10: C(6)-H alkenylation of N-methyl-substituted-pyridones.



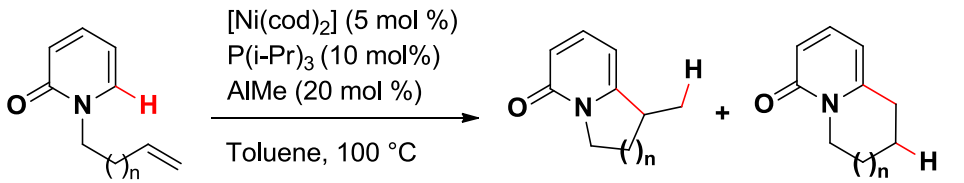
115-117 **118** **119-121**

Entry	Pyridone	Time	Product (yield %)
1	**115.** R = 3-Me	16	**119** R = 3-Me (62%)
2	**116.** R = 4-Me	6	**120** R = 4-Me (88%)
3	**117.** R = 5-Me	44	**121** R = 5-Me (29%)*

*The 4,6-dialkylated product was obtained in 1%.

A methyl group at position 3 and 4 did not affect the reaction, (entry 1 and entry 2), however a methyl group at position 5 resulted in a lower yield (entry 3), and the reason could be due to steric repulsions (**Table 10**).

The intramolecular reaction worked in good yields, using the standard conditions but a higher temperature (100 °C) was needed. The intramolecular addition to alkenes proceeds normally in an exo-trig fashion to give bicyclic products **124a,b** and **125a,b**.



122a (n=1)
123b (n=2)

75%, **124a:125a** (n =1) = 89:11 (6h)
72%, **124b:125b** (n=2) = >95:5 (4h)

Scheme 21: Intramolecular insertion of unsaturated bond into the C(6)-H.

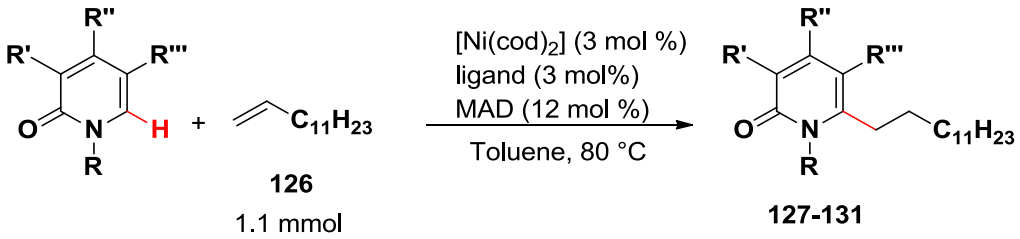
The regio- and stereo-selective alkenylation and alkylation of pyridones was demonstrated. Later on, in 2012, Tamura, Nakao and co-workers continued the study of the C(6)-H insertion with unactivated alkenes (linear alkenes **126**),[38] using the optimal conditions reported in 2009.[48]

Using 1-methyl-2-pyridones (0.5 mmol) as a starting material and 1-tridecene (0.55 mmol) as the unactivated alkene, the optimised conditions reported in the previous paper[48] [Ni(cod)2] (5 mol %); $P(i\text{-}Pr)_3$ (10 mol%); AlMe (20 mol %); toluene, 80 °C worked in low yield.

Screening for the best conditions showed that 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr) was the optimal ligand and (2,6-tBu_2-4-Me-$C_6H_2O)_2AlMe$ (MAD) the best Lewis acid.

The reaction was performed on double the scale using the effective combination of ligand and Lewis acid (IPr and MAD). The reaction yielded the product **150** in 92% yield, and as a by-product, a small amount of the 4,6-dialkylation product was also obtained. However, the alkylation proceeded mainly at position 6 (**Table 11**).

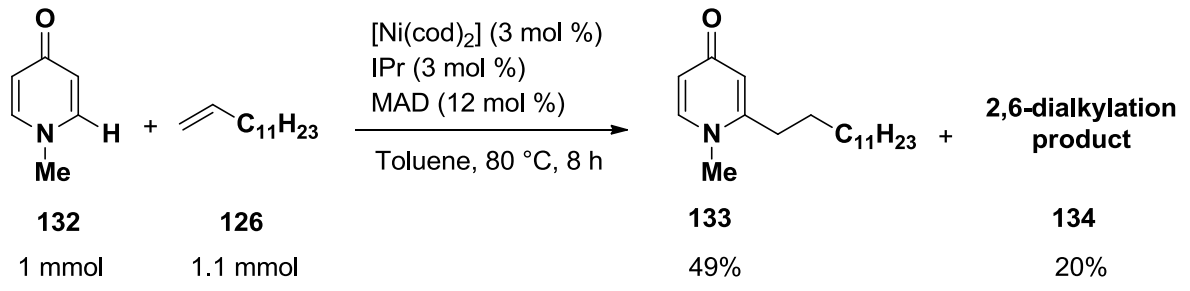
Table 11: The study of the C(6)-H insertion with lineal alkenes.



Entry	Pyridone	R	R'	R''	R'''	Time (h)	Product (%)
1	111a	Me	H	H	H	15	**127** (92%)*
2	111b	Bn	H	H	H	10	**128** (64%)*
3	115	Me	Me	H	H	9	**129** (82%)
4	116	Me	H	Me	H	8	**130** (94%)
5	117	Me	H	H	Me	9	**131** (62%)*

*Dialkylation product was also obtained (entry1: 2%; entry 2: 16%; entry 5: 13%)

In order to complete their study, 1-methyl-4-pyridone was also alkylated directly at the C2-position (**Scheme** 22).

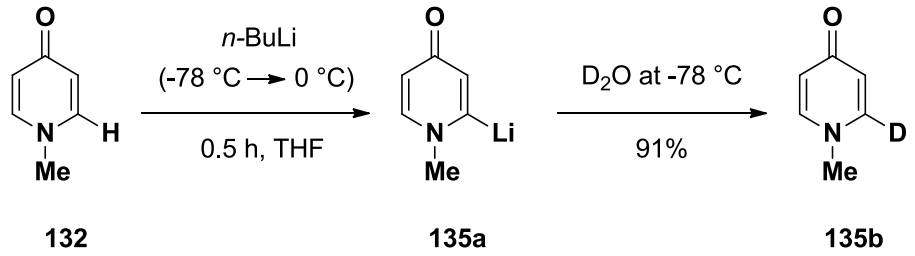


Scheme 22 : C-2-Alkylation of 1-methyl-4-pyridones.

They also reported the unprecedented C(6)-selective functionalization of pyridone. Through these two papers, both regio- and stereoselective alkylation reactions with active and unactivated alkenes were developed, using nickel/Lewis acid catalysis. Depending on the alkene, the ligand and the catalyst were optimized for each reaction. The drawback was that the 4,6-dialkylation product was obtained as a by-product in small yield.

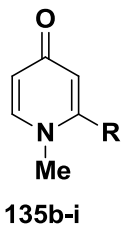
Focusing on the functionalization of 4-pyridone, Patel and Joule in 1985, were the first research group to study the lithiation of 4-pyridone.[49]

They exposed the 1-methyl-4-pyridone **132** to 1 eq. of n-butyllithium (*n*-BuLi) at -78 °C and allowed the mixture to warm up to 0 °C over 30 min to afford the 2-lithiated species. The reaction was quenched with D_2O at -78 °C, and the 2-deuteriated 4-pyridone **135b** was recovered in 91% yield (**Scheme 23**).



Scheme 23: 2-Deuterated 4-pyridone.

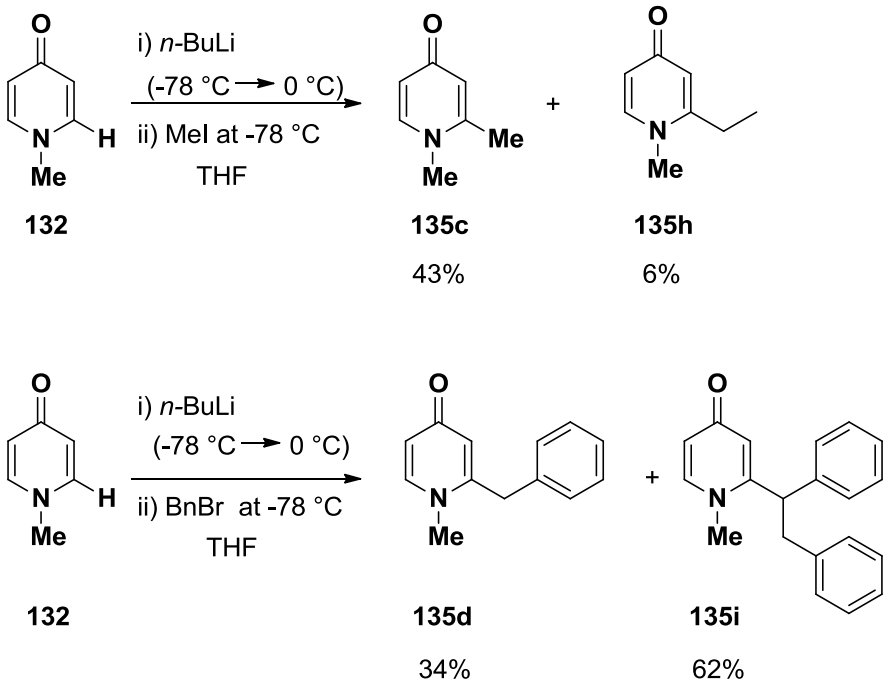
Following the condition described above, the 2-lithiopyridone **135a** was treated in THF at -78 °C to 0 °C with a range of alkylating and acylating agents during 2 to 3 h. Lithiation at the C-2 position led to the following series of 2-substituted 4-pyridones (**Scheme 24**).



b. D, 91%
c. Me, 43%
d. CH_2Ph, 34%
e. CH(OH)Ph, 78%
f. COPh, 48%
h. Et, 6%
i. $CH(Ph)CH_2Ph$, 62 %

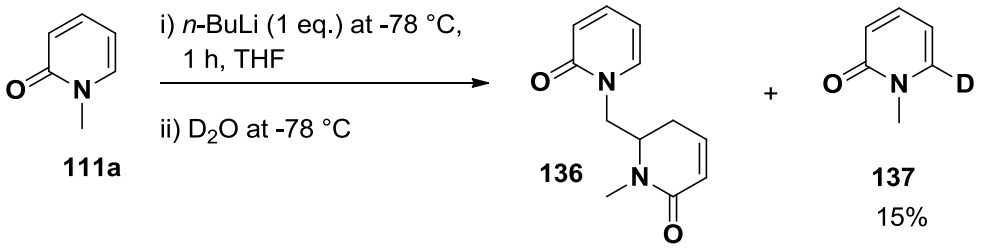
Scheme 24: C-2-Lithiation of 1-methyl-4-pyridone.

The reaction occurred smoothly at the C-2 position in most of the cases, however there were some problems, for example, in the synthesis of compound **135c** (the methylation). Compound **135h** was obtained as a by-product, and in the synthesis of compound **135d** (the benzylation), the reaction underwent a second alkylation in the benzyl chain leading compound **135i** as the mayor product.



Scheme 25: By-product of the methylation and benzylation reactions.

The same conditions were applied to the N-methyl-2-pyridone, however, the lithiation did not occur at the C6 position, it reacted instead at the methyl group (which must have deprotonated more rapidly than the C6 position) and reacted with the unreactive pyridone forming a dimer **136**, (**Scheme 26**).



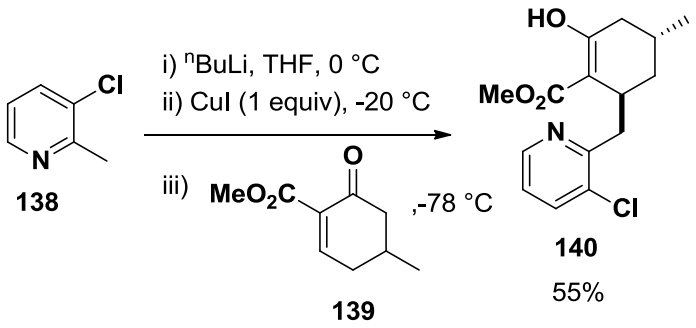
Scheme 26: Dimer formation in the lithiation of N-methyl-2-pyridone.

These results opened a new chapter in this study, selective metallation of 2-picoline and N-substututed-6-methyl-2-pyridones and N-substututed-2-methyl-4-pyridones.

3.3.2- Metallation of 2-picoline.

In 2010 two research groups were focused on the study of the conjugate addition of lithiated methyl pyridones to enones as part of a total synthesis of three alkaloid derivatives.

In February DeLorbe *et al.*[50] reported the total synthesis of the *Lycopodium* alkaloid lycopladine A. As an essential part of this synthesis, a novel strategy involving the 1,4-addition of lithiated methyl pyridines to cyclic enones was presented as shown below (**Scheme 27**).



Scheme 27: 1,4-addition of lithiated methyl pyridine (179) to cyclic enone (180).

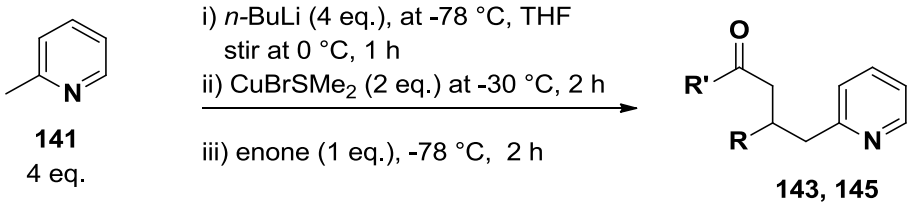
In previous publications, it had been found that 1,2-addition was a significant side reaction. In order to confirm this affirmation, some reactions of **139** with organocopper derivatives of **138** were performed, and they yielded, in approximately (1:1) ratio, both 1,4- and 1,2 addition products. In DeLorbe and co-workers' paper it is reported how they achieved the 1,4-addition product as the major product.

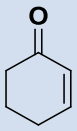
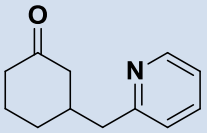
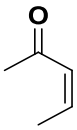
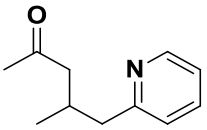
There are important variables which favour the 1,4 addition: Firstly, the use of CuI salt to generate the organocopper reagent and performing the reaction at low temperature (-30 °C). Secondly the yield of 1,4-addition product is higher when THF was used as the solvent instead of Et_2O.

Two months later, Taber and co-workers[51] reported the study of conjugate addition of lithiated methyl pyridines to cyclic and acyclic enones, (**Table 12**) as part of the synthesis of (±)-senepodine G and (±)-cermizine C.

A search of the literature showed that 1,4-conjugate addition of metallated 2-picolines to α,β-unsaturated esters worked successfully. However, the conjugated addition with enones did not work efficiently and moreover the 1,2-addition product was obtained as main product. In these previous studies, the required organocopper reagent was made at 0 °C.[52] That could be the reason for the low reactivity, as at this temperature (0 °C) the organocopper reagent could be decomposed. Taber *et al*. modified the procedure and they prepared the cuprate reagent at -30 °C instead at 0 °C. In their study, firstly they chose 2-picoline and cyclohexanone as model substrates and extensively screened the following two parameters: several copper salts (CuCN, $CuCN_2LiCl$, CuI and $CuBrSMe_2$) and different temperatures of the addition of the cyclohexanone (-20 and -78°C). After the screening the best result was obtained when a more soluble salt, $CuBrSMe_2$ was used, and the addition of the enone was a lower temperature. The ratio up to 7:1 (1,4- : 1,2-product) and obtaining compound **143** in 79%. Furthermore, the optimised conditions were applied to acyclic enones and the reactions proceeded efficiently (**Table 12**).

Table 12: Conjugate addition of Lithiated Pyridone to enones.



Entry	Enone	Product (%)*
1	 **142**	 **143** 79%
2	 **144**	 **145** 45%

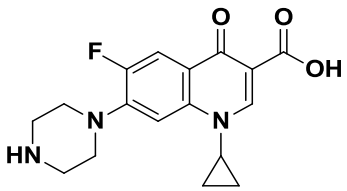
*Yields are for pure isolated conjugate additions products. The corresponding 1,2-adducts were observed but were not characterized.

They developed a general synthetic method for the conjugate addition of lithiated methyl pyridines to cyclic and acyclic enones.

4- Quinolizinone derivatives.

4.1- Biological activities.

The quinolone family, in particular fluoroquinolones, has been one of the most important classes of broad-spectrum antibacterial agents. For example, Ciprofloxacin (**Figure 16**) is the most potent of the fluoroquinolone derivatives against Gram-negative bacteria.[28] It is used for the treatment of bacterial infections of the respiratory and urinary tracts, skin and soft tissues.[53]



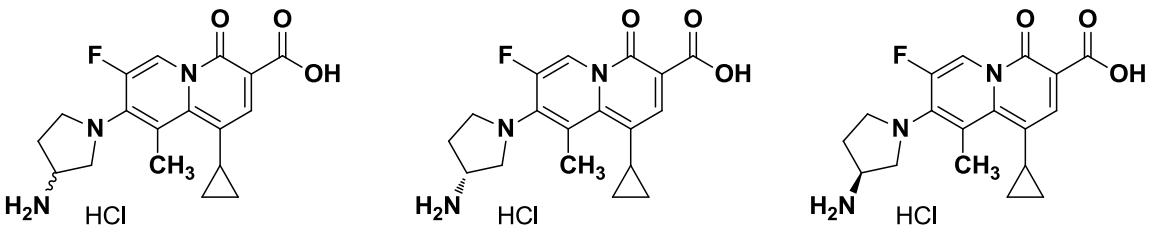
146

Figure 16: Ciprofloxacin.

The fluoroquinolones are effective against gram-negative infections; however they have only limited activity against gram-positive bacteria.[54] Also, due to the increasing frequency of bacterial resistance to quinolones, it was and still is, necessary to develop new analogues compounds to overcome antibiotic resistance.

Looking for new classes of antibacterial agents, the quinolizin-4-ones were developed as the new antibacterial agents. The structure differs from the quinolone scaffold by the relocation of the nitrogen atom to the ring junction.

Abbott laboratories developed the following quinolizin-4-one family (**Figure 17**).



147a 147b 147c

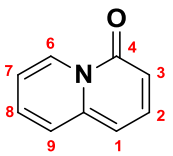
Figure 17: Quinolizin-4-ones synthesized at Aboott laboratories.[54,55]

The quinolizin-4-one and the quinolones have been shown to be inhibitors of bacterial DNA gyrase.[56] ABT-719 **147c** is a representative quinolizin-4-one which exhibits potent broad spectrum *in vitro* activity (**Figure 17**).

It has been found that ABT-719 **147c** was more potent than ciprofloxacin against the *E. faecalis* strain. Also, ABT-719 **147c** has abroad spectrum activity against a wide array of Gram-positive and Gram-negative bacteria and anaerobic bacteria.[55]

This highlighted that further research in this area is needed, due to the increasing resistance of many particular pathogens against antibacterial and antimicrobial compounds. This interesting new scaffold (4*H*-quinolizin-4-one) has been studied in more detail.

The 4*H*-quinolizin-4-one **1** is an interesting scaffold to study.[57] There have been a number of studies reporting the biological activities of their related, partially or fully-saturated systems. Partially or fully-saturated 4*H*-quinolizin-4-one derivatives have shown significant biological activities as ligands for a variety of receptors targets, including Alzheimer´s disease,[58] Type 2 diabetes,[59] and HIV.[60,61]



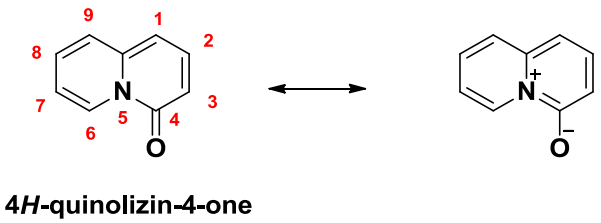
1

4*H*-quinolizin-4-one Structure

* Charge sepaprated aromatic structure-polar.
* Attractive physicochemical attributes (low log P, etc.).
* Prevalent within synthetic bioactive compounds.
* No general synthetic routes.

Figure 18 : 4*H*-quinolizin-4-one scaffold.[1]

Herein we are interested in the quinolizinone scaffold; looking at the structure in **Figure 19** the scaffolds are predicted to have favourable physico-chemical properties as a result of their polar and nearly zwitterionic character.[3]



4*H*-quinolizin-4-one

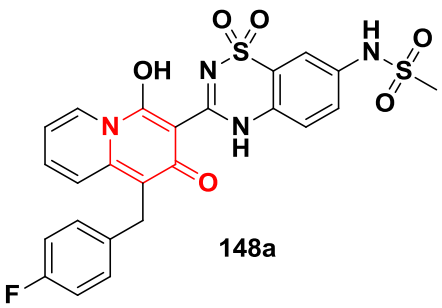
Figure 19: The 4-H-quinolizinone system and its dipolar canonical form.[3]

Hepatitis C is a disease affecting the liver, caused by the hepatitis virus.[62] Currently, about 3% of the world's population has been infected with HCV (Hepatitis C virus) and the disease may progress to chronic liver disease in about 60-80% of patients, 20% of whom develop cirrhosis.

There are five different genotypes of HCV and, thus far, there is no universally effective therapy for all HCV genotypes. For this reason, it is important to know which genotype is affecting each patient, because the treatment is different for every genotype.

For example, genotype 2 and 3 HCV need treatment for 24 weeks, whilst genotype 1 and 4 HCV require prolonged treatment for 48 weeks. This is the reason why patients of genotype 1 have difficulty in tolerating the treatment, due to the long duration and side effects produced, such as flu-like symptoms, depression, gastrointestinal symptoms, fatigue, pulmonary effects, and others.

Taking into account these limitations, Wang *et al*.[8] were interested in the discovery and development of novel compounds that target the viral and host proteins, such as a series of quinolizinone benzothiadiazines, which exhibit potent inhibition of HCV NS5B polymerase. The most active compound in the replicon system was compound **148a** (**Figure 20**).



148a

Figure 20: Most active compound in replicon system.

The following compound also exhibited excellent replicon activity.

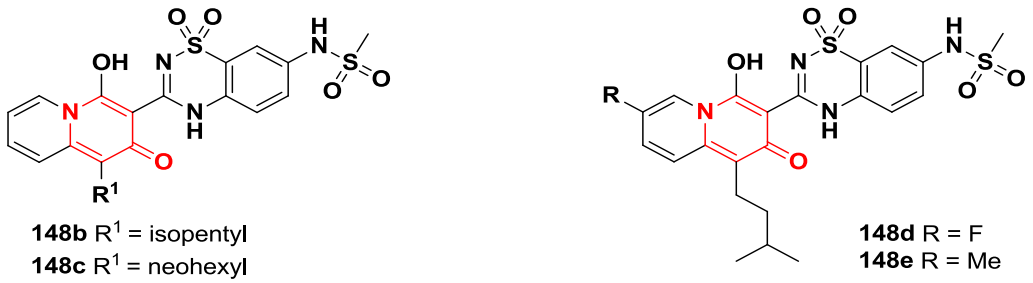


Figure 21: These four derivatives 203b-d show excellent replicon activity.

Wang *et al.* studied the anti-HCV activity of all these compounds **148a-e**, (**Figure 20** and **Figure 21**) and found they inhibited HCV NS5B polymerase. Wang *and* co-workers therefore perceived the quinolizinone ring to be a promising scaffold for the development anti-HCV activity.

Quinolizinone derivatives can be also used for other applications beyond the pharmaceutical area, Rosas-Sanchez and co-workers synthesized interesting photoluminiscencent compounds, based on quinolizinones (**149**-**152**), which exhibited fluorescence. These compounds are yellow in colour and display bright yellow/green fluorescence in solution. This property makes them potential precursors for optical applications (**Figure 22**).

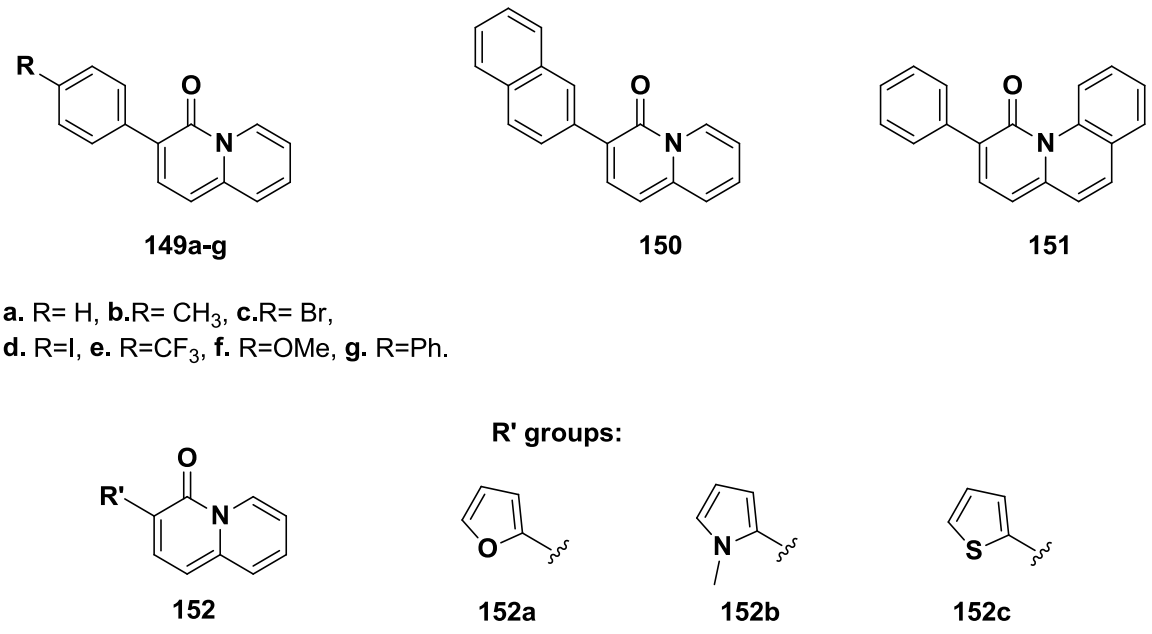
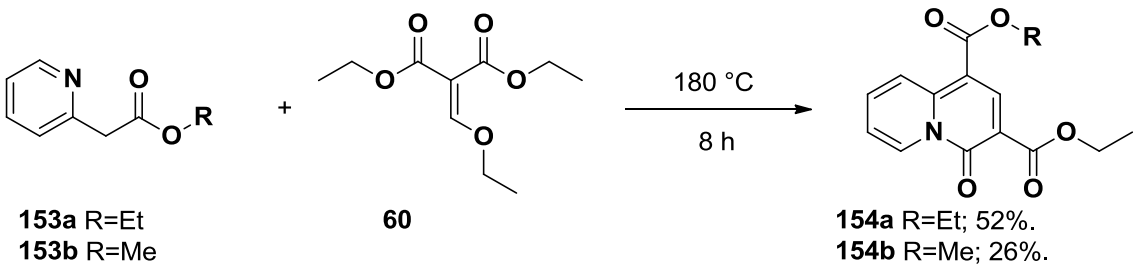


Figure 22: Quinolizinone derivatives as potential precursors for optical applications.

4.2- Previous synthesis of quinolizinone.

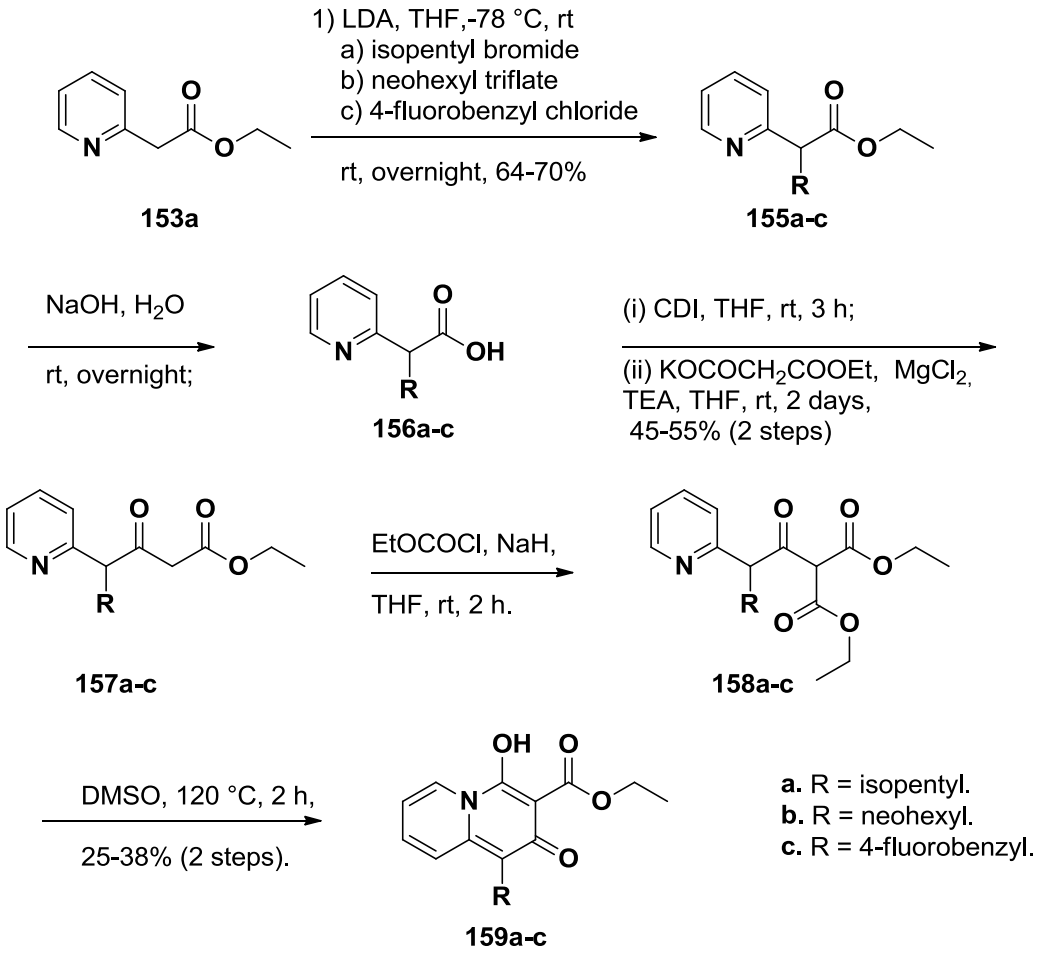
In 1951 Boekelheide *et al*. reported the synthesis of quinolizone derivatives from ethyl or methyl 2-pyridylacetate **153a** or **153b** as starting material.[63] The cyclocondensation of ethyl 2-pyridylacetate **153a** with diethyl ethoxymethylenemalonate **60**, at 180 °C was studied and afforded a 52% yield of **154a** after 8 h (**Scheme 28**). The same procedure was followed with methyl 2-pyridylacetate **153b** and diethyl ethoxymethylenemalonate **60** to afford compound **154b** in 26% yield (**Scheme 28**).



Scheme 28: Synthesis of quinolizinone derivatives.

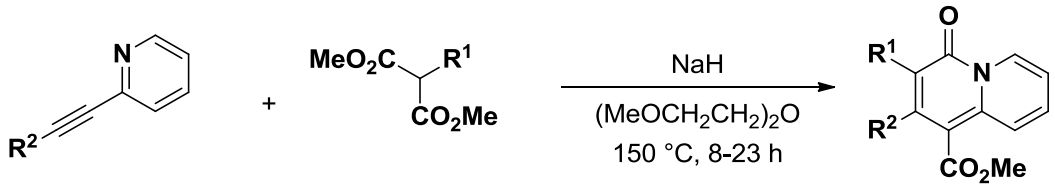
In 2009 Wang *et al*.[8] reported the synthesis of compounds **159a-c** which are quinolizinone derivatives. In this synthesis, also starting from ethyl pyridylacetate.

The 1-substituted quinolizinones **159a-c** were obtained by cyclization under thermal conditions in 25-38% yield. The products **159a-c** were synthesized in six steps in 25-38 % yield, as shown in **Scheme 29**.



Scheme 29 : Synthesis of quinolizinone precursors to HCV NS5B inhibitors.

In 2009, Makoto *et al.*[64] reported the synthesis of 4*H*-quinolizin-4-ones **162a-d** by the reaction of 2-alkynylpyridines **160a-c** with several malonic esters **161a-d** in moderate to good yields (36-77%), (**Scheme 30**).



160a. R^2= Ph
160b. R^2= n-Bu
160c. R^2=H

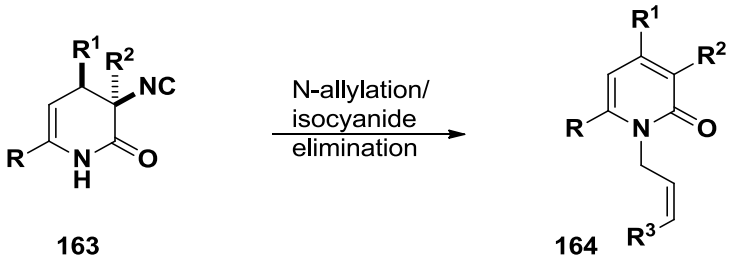
161a. R^1= Me
161b. R^1= Me
161c. R^1=4-$MeOC_6H_4$
161d. R^1= 2-Pyridyl

162a. R^1= Me, R^2= Ph, 38%
162b. R^1= Me, R^2= n-Bu, 36%
162c. R^1=4-$MeOC_6H_4$, R^2=H, 77%
162d. R^1= 2-Pyridyl, R^2=H, 43%

Scheme 30: Synthesis of 3,4,5,6-tetrasubstituted-2-pyridones 162a-d using addition of active methane compounds 161a-d to alkynyl imines 160a-c.

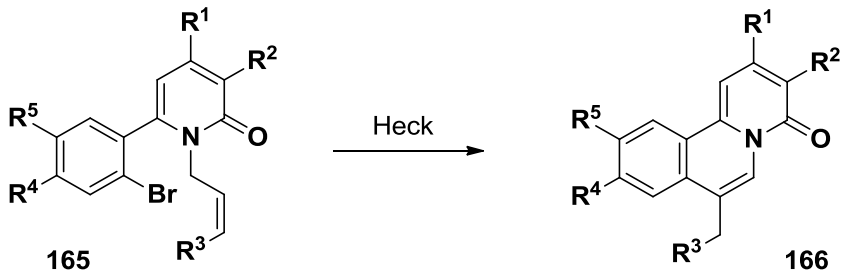
In 2012, E. Ruijter *et al.*[65] reported a straightforward synthesis of benzo[a]quinolizine scaffolds **166**, using highly substituted 3,4-dihydropyridones **163** as starting material. The reaction pathway involved a subsequent allylation and intramolecular Heck-type cyclisation. The authors reported a three-step sequence to generate a library of benzo[a]quinolizin-4-ones **166** derivatives, several examples of diversely substituted benzo[a]quinolizines and various heterocyclic compounds.

3,4-Dihydropyridones **163** were deprotonated by NaH followed by the N-alkylation. In this process, when an excess of NaH was present, the isocyano group of the 3,4-dihydropyridone derivatives underwent facile elimination to give the corresponding 2-pyridones **164** (**Scheme 31**).



Scheme 31 : N-allylation followed by isocyanide elimination to afford 2-pyridone 164.

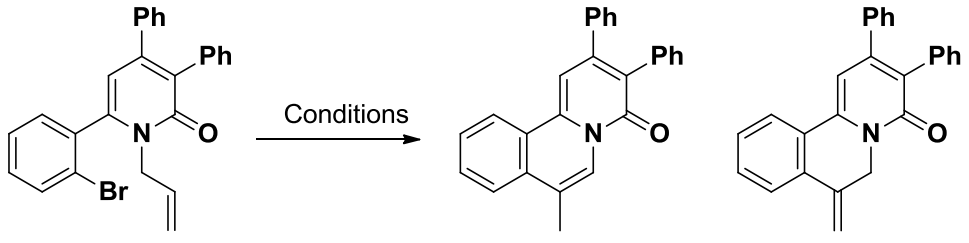
When compound **164** bore an O-bromophenyl substituent as the R substituent, compound **165** became an interesting candidate for the synthesis of benzo[a]quinolizin-4-ones **166** via intramolecular Heck-type reaction (**Scheme 32**).



Scheme 32 : Heck reaction for the construction of benzo[α]quinolizines 166.

The intramolecular Heck-type cross-coupling reaction of **165** was also the next step in the synthesis of another tricyclic system. E. Ruijter *et al.* hypothesized that the intramolecular cyclisation of compound **165a** proceeds via a 6-*exo*-trig route to afford the exocyclic form **166a**. The endocyclic product **166a** was obtained by isomerisation of the exocyclic product **167a** (**Table 13**).[65]

Table 13: Intramolecular Heck reaction.



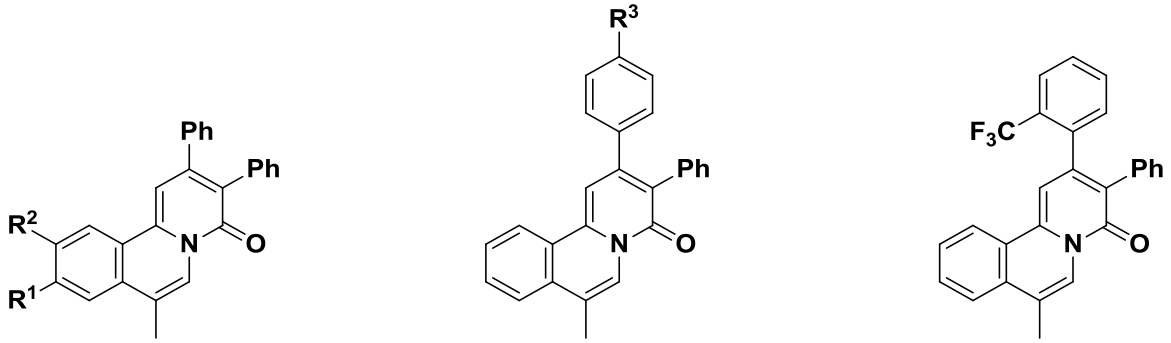
165a **166a** **167a**

Entry[a]	Catalyst	Base	Yield (%)[b]	Ratio 166a:167a [c]
1	$Pd(OAc)_2$ +PPh_3	Et_3N	82	92:8
2	$PdCl_2$ +PPh_3	Et_3N	79	59:41
3	$Pd(PPh_3)_4$	Et_3N	75	54:46
4[d]	$Pd(OAc)_2$ +PPh_3	Et_3N	84	78:22
5	$Pd(OAc)_2$ +PPh_3	Cs_2CO_3	90	100:0
6	$Pd(OAc)_2$	Et_3N	86	100:0
7[e]	$Pd(OAc)_2$ +PPh_3	Et_3N	<20	n.d.

[a] Conditions: 5 mol-% Pd, 10 mol-% L, 20eq. Base, DMF, 120°C, 16h. [b] Isolate yield. [c] Determined by ^{1}H NMR spectroscopy. [d] NMP used as solvent. [e] 1mol-% Pd, 2 mol % L.

Table 13 shows the cyclisation of compound **165a** was achieved in high conversions in all the tested conditions to afford the desired tricyclic system. However the degree of isomerisation varied depending on the palladium source. Entries 5 and 6, show the best conditions for the cyclisation reaction. The most effective and practical method was obtained in entry 6, the "ligandless" protocol using $Pd(OAc)_2$ as the palladium source in combination with Et_3N as a base.

Using the optimized conditions (**Table 13**, entry 6) for the intramolecular Heck reaction, compounds **166a**-**g** were synthesized in moderate to very good yields (30-94%). Some examples are shown in **Figure 23**. Moderate yields were observed for compounds bearing a highly electron rich **166g** or electron deficient **166e**, **166f** aryl group at the 4-position of the pyridone ring (37%-58%), and the remaining benzo[a]quinolizines were typically obtained in good to excellent yields.



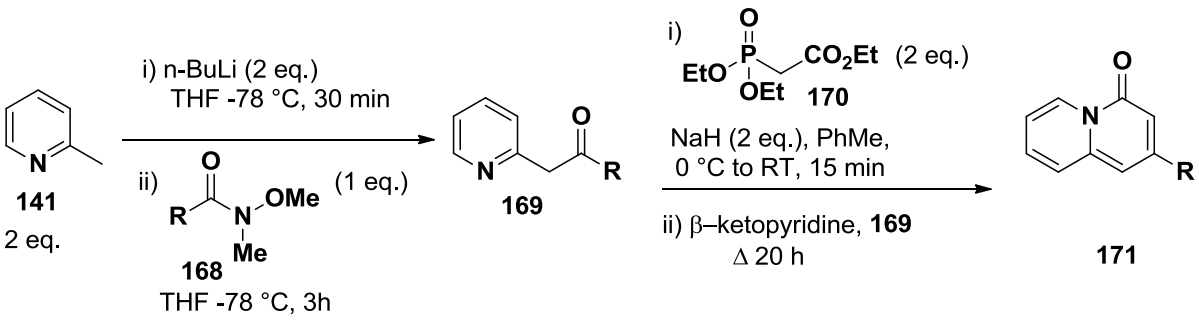
166a. R^1 = H, R^4 = H, 88%
166b. R^1 = OMe, R^4 = OMe, 41%
166c. R^1 = Cl, R^4 = H, 71%
166d. R^1 = Me, R^4 = H, 94%

166e. R^3 = NMe_2, 37%
166f. R^3 = NO_2, 50%

166g 58%

Figure 23 : Synthesis of polycyclic compounds 166a-166g by intramolecular Heck reaction. Reagent and conditions: $Pd(OAc)_2$ (5 mol%), Et_3N (2.0 eq.), DMF, 120°C, 16 h.

In March 2013 Calum *et al.* reported the synthesis of functionalised 4*H*-quinolizin-4-ones via tandem Horner-Wadsworth-Emmons olefination/cyclisation.[1] This pathway enabled effective synthesis of 2-substituted 4*H*-quinolizin-2-ones **171** which proceeded in good to excellent yields (**Scheme 33**).

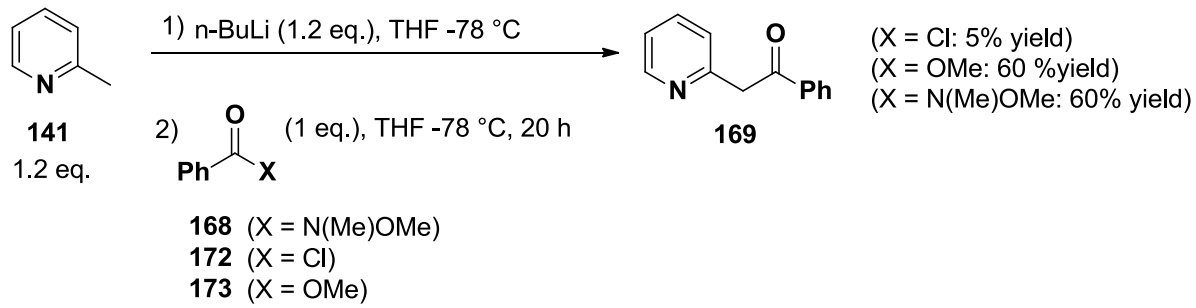


Scheme 33 : Synthesis of quinolizinone derivatives via tandem Horner-Wadsworth-Emmons/Cyclisation strategy.

A suitable β-carbonyl pyridine **169** was used as the starting material, and the pyridone ring was annulated via a tandem Horner-Wadsworth-Emmons olefination/cyclisation event with the cyclisation taking place under thermal conditions.

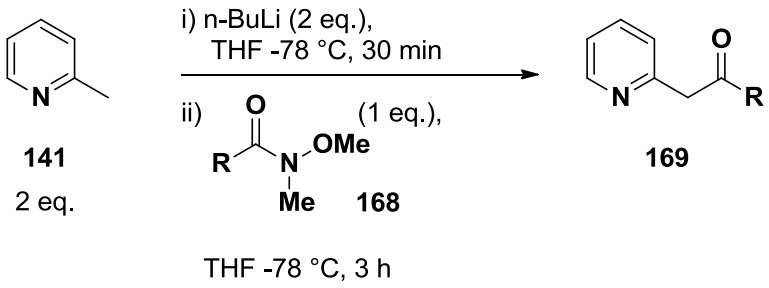
The first step in the synthesis of 4*H*-quinolizin-2-ones **171**, was the synthesis of β-ketopyridines **169** (**Scheme 34**). Calum *et al.* developed a convenient method of preparing these compounds, via direct acylation of the 2-picoline anion, derived from the deprotonation of the methyl group using organolithium reagents (e.g., LDA, *n*-BuLi).

Acyl chlorides, esters and Weinreb amides were chosen as three potential acylating reagents. One part of their study was to evaluate the reactivity of different acylating agents, (**Scheme 34**).



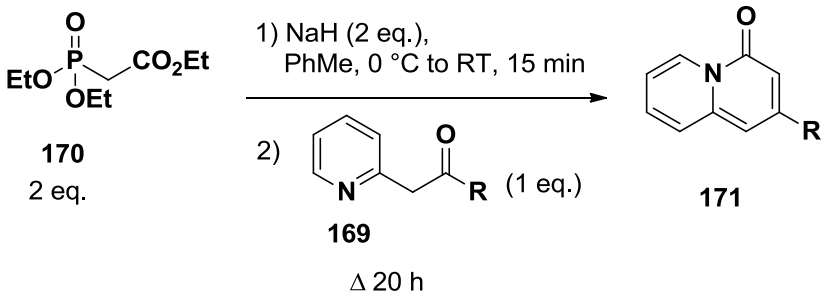
Scheme 34 : Evaluation of potential acylating agents.

In the preliminary reactions, esters **173** were found to perform equally as well as Weinreb amides **168**. However, acyl chlorides **172** were unsuited to the desired transformation, since the product was obtained in just 5 % yield. After several reactions, the optimization study demonstrated that the yields for ester-base acylation were consistently lower than those achieved using the corresponding Weinreb amide. The acylation reaction operated effectively for both alkyl and aryl Weinreb amides bearing a range of functionality, in generally high yields (80-97%), with only two exceptions: 4-nitro-substituted aryl groups generated a complex mixture of undesired products, presumably through a reaction pathway enabled by the NO_2 functionality and the 4-OTBS-phenyl-substituted derivative, which was isolated in moderate yield (55%). The optimised conditions for the synthesis of β-ketopyridines **169** are shown in **Scheme 35**.



Scheme 35 : The optimised conditions for the synthesis of β-ketopyridines.

The next step in the synthesis of 4*H*-quinolizin-4-ones, was the pivotal tandem HWE/ cyclisation process. The best results were obtained when 1 eq. of β-ketopyridine **169** was exposed to a mixture of 2 eq. of triethylphosphonoacetate **170** and 2 eq. of NaH in toluene at 0 °C, followed by heating to under reflux for 20 h. This delivered a collection of 4*H*-quinolizin-2-ones **171** in generally good yields (**Scheme 36**).

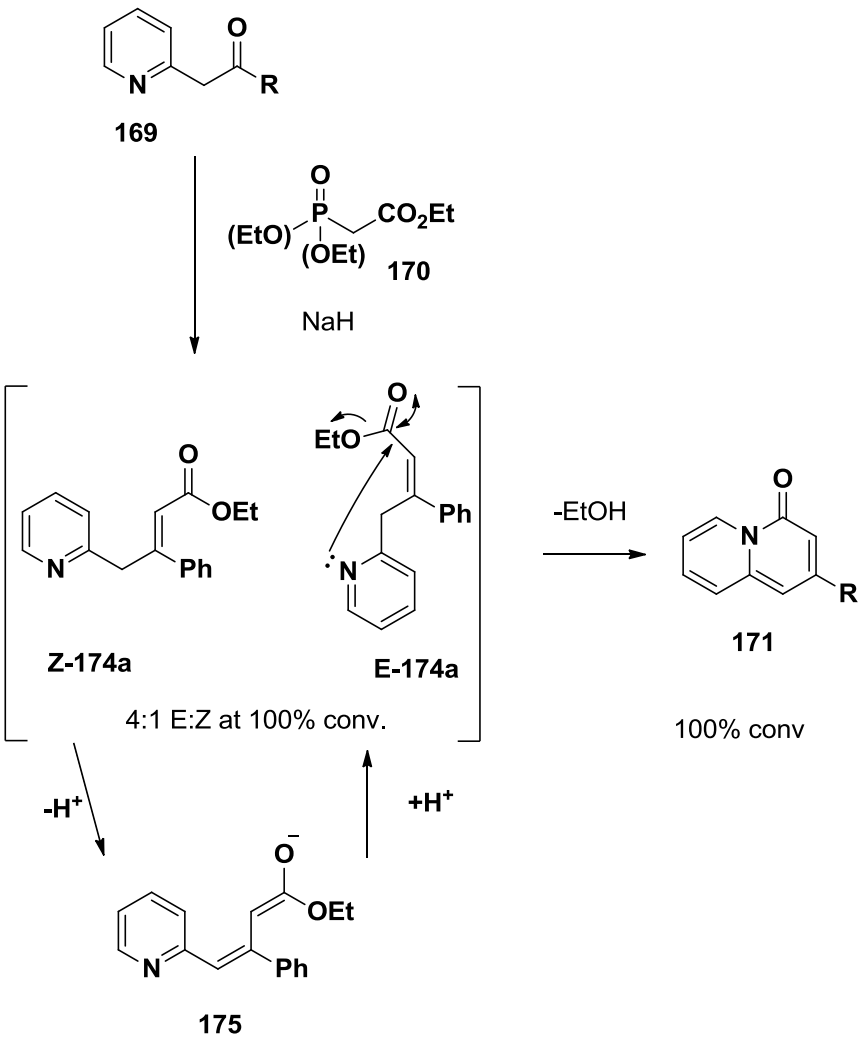


Scheme 36: Tandem synthesis of 4*H*-quinolizin-4-one.

This pathway proceeds via HWE olefination of the carbonyl unit followed by straightforward intramolecular N-acylation of the pyridine, proton loss, and electronic reorganisation to provide the annulated product **171**. Generally high yields of 4*H*-quinolizin-4-one products **171** were obtained, and the assumption was that only the E-olefin **E-174a** would be able to be converted to the annulated product due to the special configuration. An aliquot of the reaction prior to reflux step was analysed in order to confirm this hypothesis.

The E/Z selectivity of the olefination is rather modest at only 4:1 E/Z ratio. However, 100 % conversion of 4*H*-quinolizin-2-ones was observed. This fact suggests that the Z isomer **Z-174a** must be converted to the E isomer **E-174a** prior to cyclisation. Calum *et al.* suggested that the reaction proceeds through the enolate **175**, which allows for olefin isomerisation and subsequent cyclisation to **171** (**Scheme 37**).

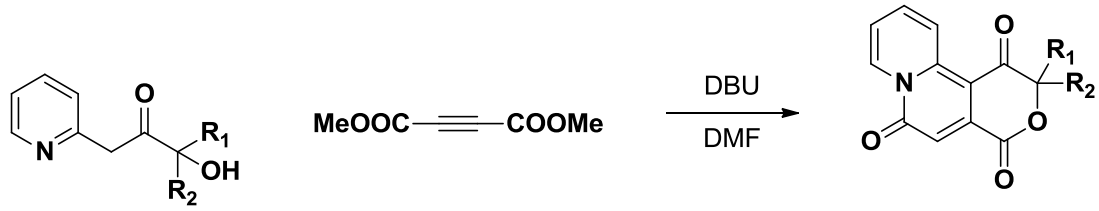
The proposed mechanism for the tandem reaction is shown in **Scheme 37**.



Scheme 37: Proposed mechanism for the tandem reaction.

In 2014 Haitao *et al*. reported the synthesis of the pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-trione derivative **178**. This interesting tricycle scaffold is a fusion between 4*H*-quinolizin-4-one and 2H-pyran-2,5(6H)dione. Both compounds are important bioactive motifs. Haitao and co-workers have been develop a novel straightforward construction of pyrano[4,3-*a*]quinolizine-1,4,6(2H)-trione derivatives via a base-promoted cascade annulation reaction of tertiary α-hydroxyketones **176** and dimethyl but-2-ynedioate **177**.[66]

They developed a new reaction using a variety of tertiary α-hydroxyketones **176** bearing different R^1 and R^2 substituents on the alkyl group adjacent to the hydroxyl group with dimethyl but-2-ynedioate as the other starting material. Under the optimal conditions showed in (**Scheme 38**) a library of pyrano[4,3-*a*]quinolizine-1,4,6(2H)-trione derivatives **178** and **180** was synthesized.

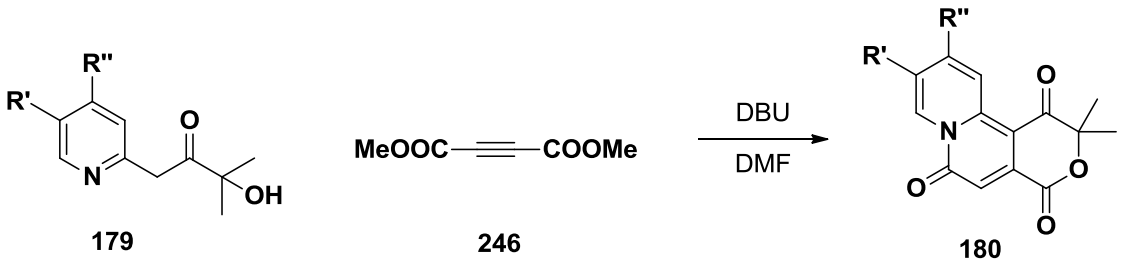


176 177 178a-e

a. R_1= Me; R_2= Me; 83%.
b. R_1= Et; R_2= Me; 86%.
c. R_1= Et; R_2= Et; 80%.
d. R_1= Me; R_2= Ph; 89%.
e. R_1= Me; R_2= n-$(CH_2)_5CH_3$; 90%.

Scheme 38: Synthesis of pyrano[4,3-a]quinolizine-1,4,6(2H)-trione derivatives.

This strategy showed a good tolerance toward a wide range of functional groups: electron-donating groups (Me and OMe) and electron-withdrawing substituents (F, Cl, Br, CN, COMe, CF_3 and CO_2Et) at positions 4- and 5-of the pyridyl ring. Excellent yields were obtained with the non-substituted pyridyl ring. The better yields were from compounds bearing strong electron donating groups rather than those bearing weak electron-withdrawing or electron-donating groups. The 4,5 disubstituted pyridyl yielded the product in low yield.



179 246 180

180a. R' = Me, 69%
180b. R' = OMe, 59%
180c. R' = F, 83%
180d. R' = Cl, 70%
180f. R' = Br, 40%
180g. R' = CN, 75%
180h. R' = CO_2Me, 93%
180i. R' = CF_3, 94%
180j. R''=Me, 86%
180k. R'' = Cl, 88%
180l. R'' = CO_2Et, 94%
180m. R' = NO_2, R'' = CH_3, 22%

Scheme 39: Synthesis of pyrano[4,3-*a*]quinolizine-1,4,6(2H)-trione derivatives from 4- and 5-substituted pyridyl derivatives.

The continuous development of these kinds of scaffolds and their further biological testing for potential new drug development is very attractive for the pharmaceutical industry.

Other interesting methodology to assembly heterocyclic compounds is the RCM (Ring-closing metathesis) strategy. This strategy has been shown to be a powerful methodology for assembling bicyclic heterocyclic systems containing a nitrogen atom at the ring conjunction. In the following scheme the different type of heterocycles formed via RCM methodology.

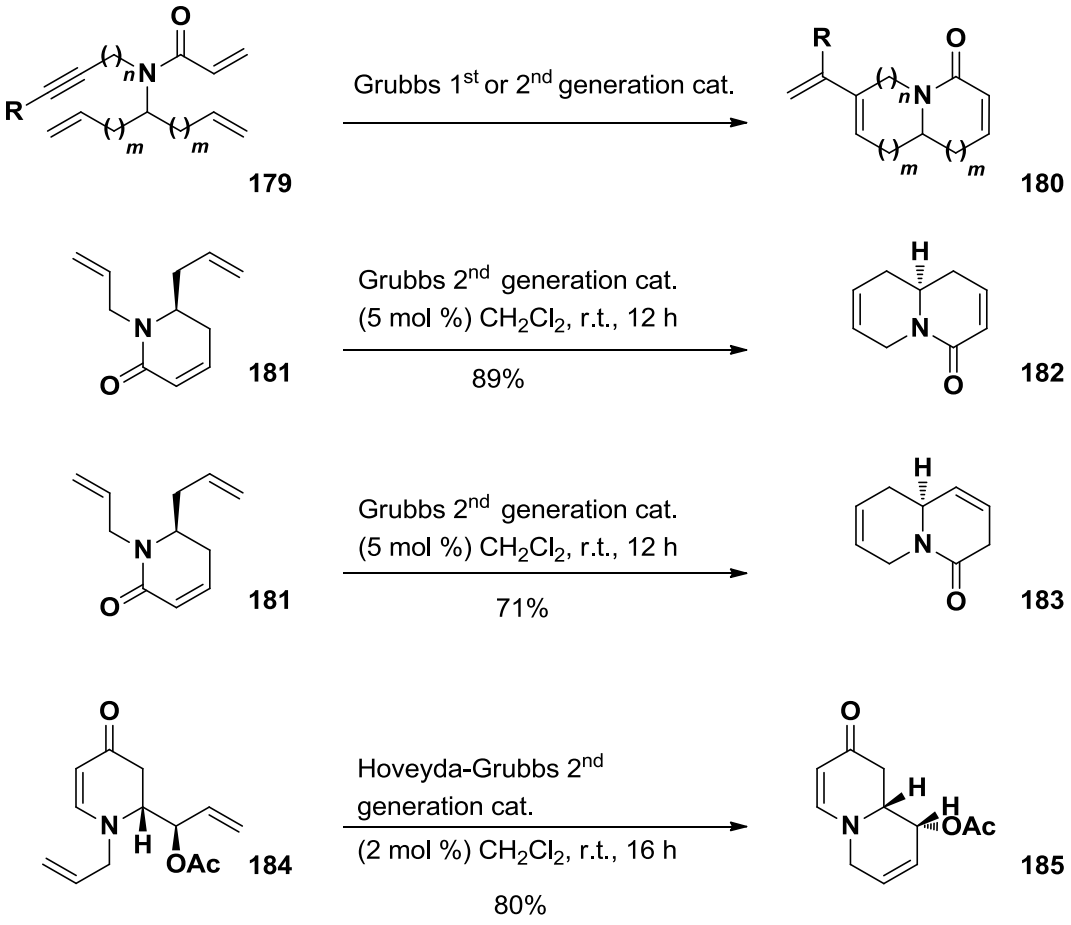
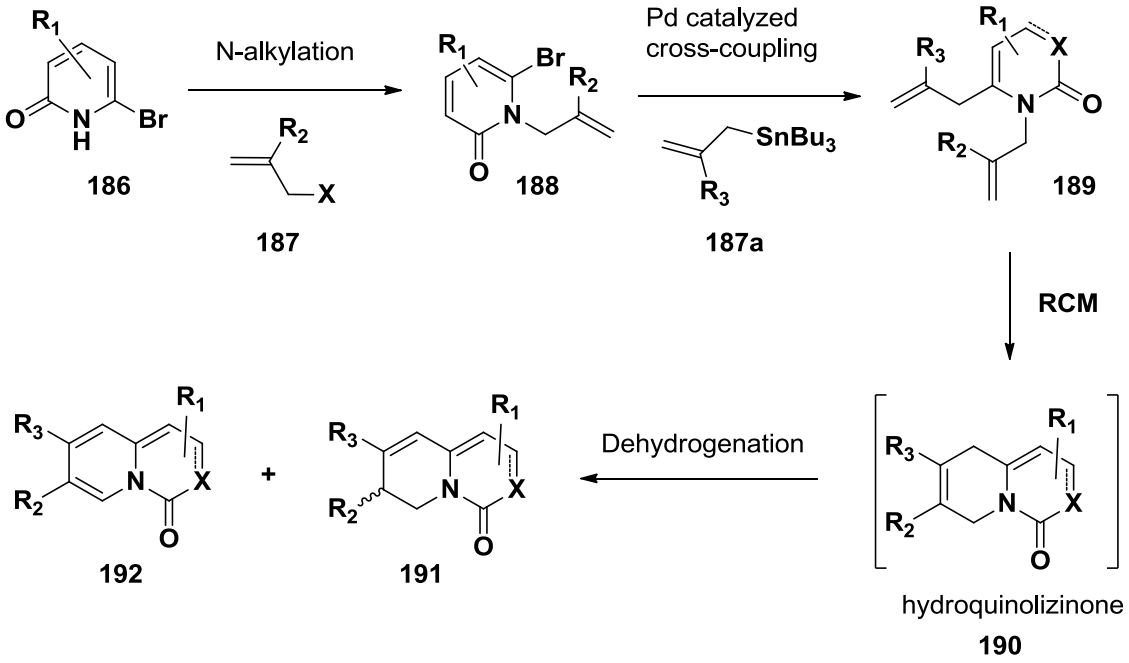


Figure 24: Synthesis of 6,6-fused bicyclic ring system via RCM strategy.[67,68,69]

However the quinolizinone system has not been synthesized using this methodology so far. Recently, Alanine *et al*. reported the synthesis of 4*H*-quinolizinones via Ring Closing Metathesis.[3] Their work started with the N-alkylation of the readily available 2-pyridone **186**, followed by Pd-catalysed cross coupling to synthesize the essential precursor for the RCM strategy **189**. The RCM reaction rendered another interesting substrate; the hydroquinolizinone **190** and the desirable quinolizinone **192** was obtained after the final dehydrogenation step. The general synthesis and the conditions are summarised in **Table 14**.

Table 14 : Synthesis of quinolizinones via Ring Closing Metathesis strategy.



Entry	R_1	R_2	R_3	Product	Ratio[d] (192:190)	Yield[e] %
1	H	H	H	192a[a]	4:1	68
2	H	H	CH_3	192b[b]	3:2	33
3	H	CH_3	CH_3	192c[c]	10:0	75
4	H	CH_3	H	192d[b]	3:1	62
5	H	Ph	H	192e[b]	10:1	72
6	H	Ph	CH_3	192f[c]	4:1	36
7	H	CO_2Me	H	192g[b]	3:1	40
8	H	CO_2Me	CH_3	192h[c]	3:3:4[f]	25

RCM and dehydrogenation steps:

[a] Condition A: Grubbs 2nd generation catalyst (5 mol-%), CH_2Cl_2 (substrate concentration 0.1 M), r.t., 2h.

[b] Conditions B: Grubbs 2nd generation catalyst (5 mol-%), CH_2Cl_2 (substrate concentration 0.1 M), 50 °C, 2h.

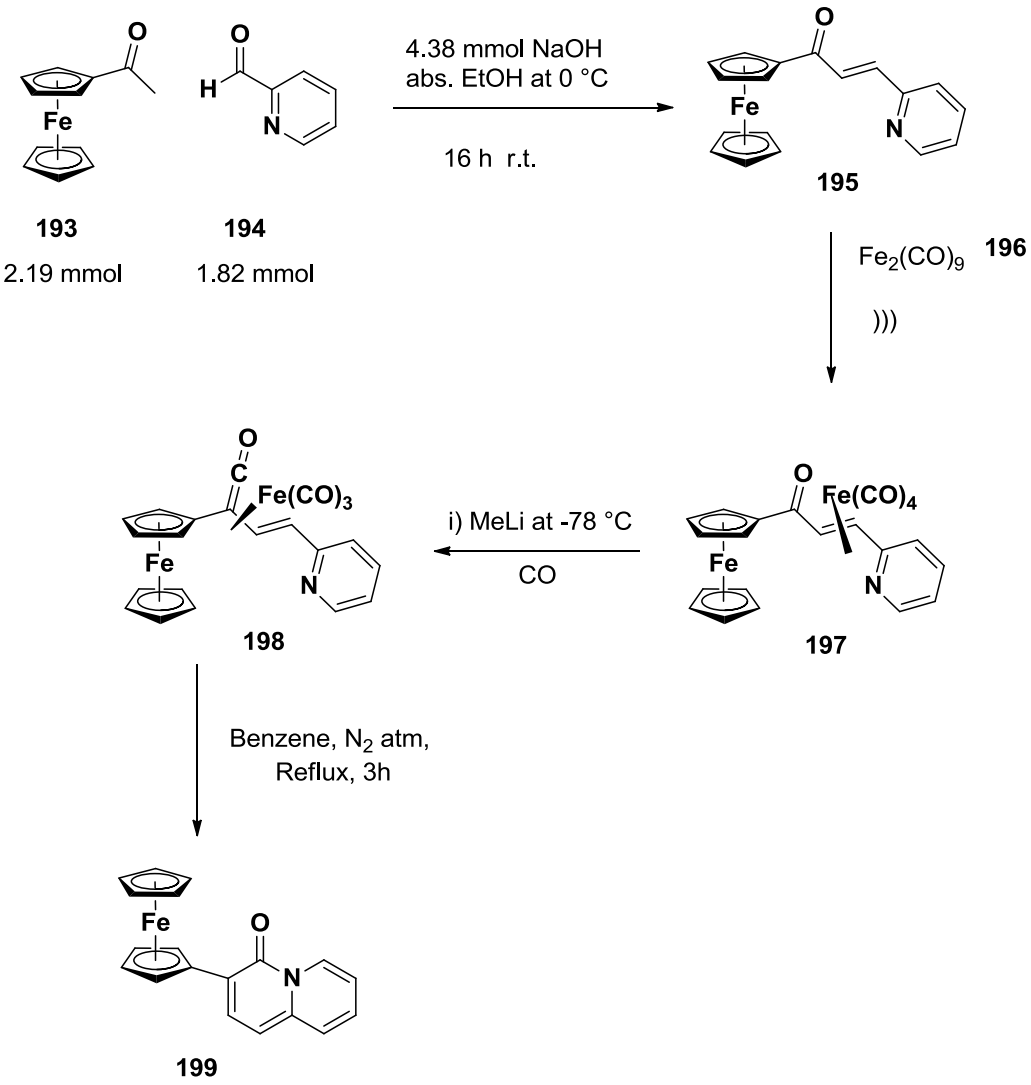
[c] Grubbs 2nd generation catalyst portionwise (3 X 5 mol-%), CH_2Cl_2 (substrate concentration 0.1 M), 50 °C, 2h.

[d] Ratio determined by ^{1}H NMR analysis of crude product mixture.

[e] Isolated yield of pure material. [f] Ratio of 14h/15h/12h.

A new strategy has been developed for the synthesis of wanted 4*H*-quinolizin-4-ones bearing a wide range of substituents.

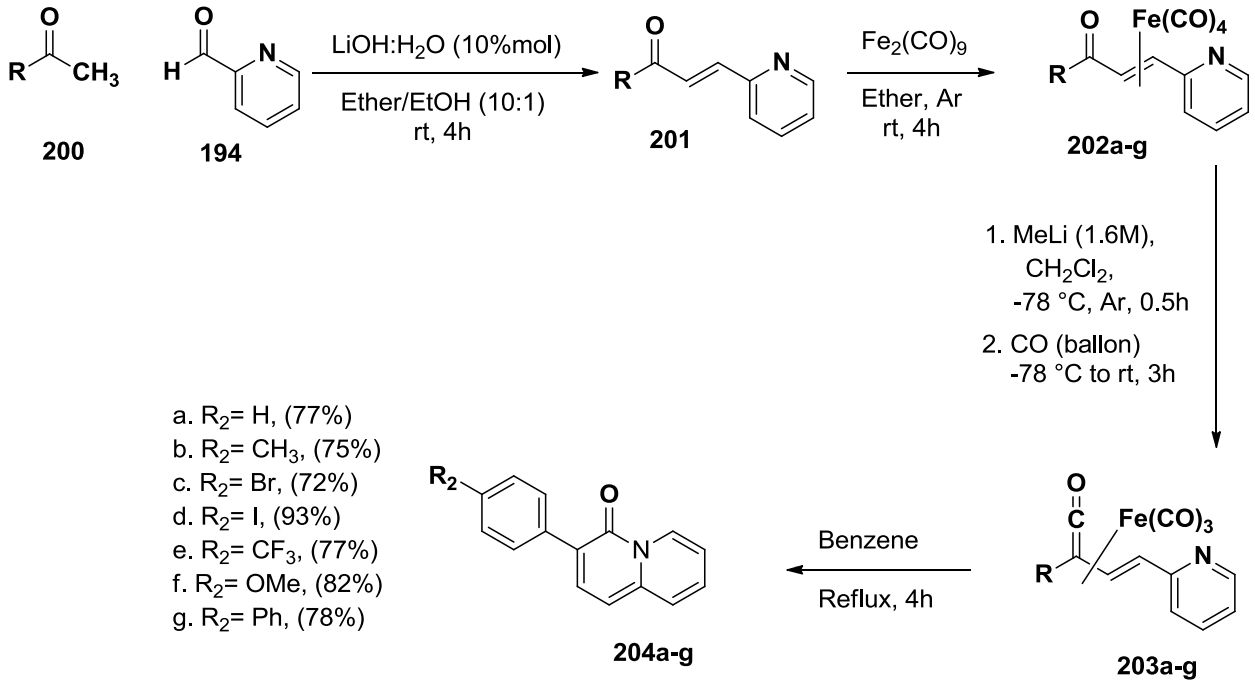
In 2011 Rosas-Sánchez and coworkers[6] reported the synthesis of 3-ferrocenyl-4*H*-quinolizin-4-one **199**, using acetylferrocene **193** and $Fe_2(CO)_9$ **196** in order to synthesize (η^4-ferrocenylvinylketene)$Fe(CO)_3$ complex **197**, and a subsequent thermal cyclization reaction furnished the 3-ferrocenyl-4*H*-quinolizin-4-one **199** (**Scheme 40**).



Scheme 40: Synthesis of 3-ferrocenyl-4*H*-quinolizin-4-one.[70]

As an extension of this paper in 2014 they reported an efficient route to synthesize 3-substituted 4*H*-quinolizin-4-ones, using a (η^4-vinylketene)Fe(0) **203** complex as key intermediate.

They heated the (η^4-vinylketene)$Fe(CO)_3$ **203** complexes to synthesize a library of 3-substituted 4*H*-quinolizin-4-ones.



Scheme 41: Synthetic route of 4*H*-quinolizi-4-one derivatives using isolable and stable tricarbonyl(η-vinylketene)iron(0) complex 203.[6]

α,β-Unsaturated ketones **201a-g** were synthesized via aldol-type condensation reaction, and then were exposed to $Fe_2(CO_3)_9$, to obtain the necessary (η^2-PyCHCHCOR)-$Fe(CO)_4$ complex **202a-g** for the carbonylation reaction. (η^4-vinylketene)-$Fe(CO)_3$ complex **203a-g** was obtained under carbonylation conditions. The majority of the complexes were purified and isolated in moderate to good yields. The quinolizinone derivatives **204a-g** were obtained in good yields (**Scheme 41**).

The literature presents many examples of the synthesis of 4*H*-quinolizin-4-one scaffolds using ethyl or methyl pyridylacetate, 2-picoline or 3,4-dihydropyridones. In our research, we are interested in a straightforward synthesis of desirable 4*H*-quinolizin-4-one scaffolds by condensation of *N*-benzyl 6-methyl 2-pyridones with dicarbonyl compounds, and the formation of the desired quinolizinone after the condensation step.

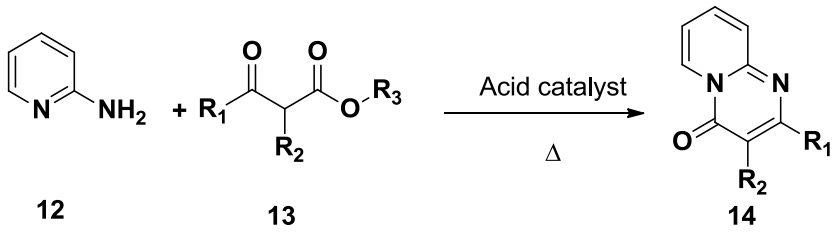
Result and discussion

1- Synthesis of Pyridopyrimidine derivatives.

The pyridopyrimidine ring system has been one of most studied in the literature due to its wide ranging biological activities. In particular, the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one ring has been found as part of the core of many fused heterocyclic compounds. It is a significant scaffold for the synthesis of more complex molecules and is thus an important synthetic intermediate.

The thermal cyclocondensation of 2-aminopyrimidine **12** with different β-keto esters **13** has been one of the most reported pathways for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.[24,18,13]

A drawback of this route is that corrosive acids are involved in the reaction, such as polyphosphoric acid, sulfuric acid, p-toluenesulfonic acid (p-TsOH) or phosphoryl chlorides (**Scheme 42**). [24,13,71,72]

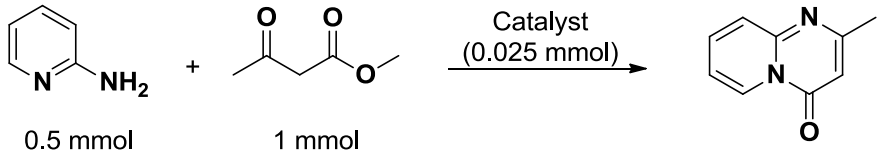


Scheme 42: Traditional methodology to assembly 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

This reaction (**Scheme 42**) is still an effective means for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives. This is the reason why in our study, we wanted to improve on the traditional methodology, to assemble 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **14** from commercially available 2-aminopyridine **12** and β-keto esters **13** under thermal conditions. We wanted to design a more environmentally friendly pathway, replacing the corrosive acids with milder reagents.

Recently, Roslan *et al.*[13] and our research group envisioned the same general idea for the improvement of the traditional methodology, to replace the corrosive reagents for mild, available and cheap Lewis acids. They decided to study bismuth salts as catalysts. They replaced the corrosive Brønsted acid for $Bi(OTf)_3$ or $BiCl_3$. The results of their optimized study are shown in the following table:

Table 15: Optimization parametres for Bi(III)-catalized synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives.



0.5 mmol **12** + 1 mmol **13a** → **14a**

Entry	Solvent	Catalyst	Temp (°C)	Time (h)	Yield (%)[a]
1	Dioxane	$Bi(OTf)_3$	100	8	37
2	$MeNO_2$	$Bi(OTf)_3$	100	8	38
3	H_2O	$Bi(OTf)_3$	100	8	41
4	Toluene	$Bi(OTf)_3$	100	8	88
5	-	$Bi(OTf)_3$	100	8	100
6	-	-	100	8	Traces
7	-	$Bi(OAc)_3$	100	8	21
8	-	$BiCl_3$	100	8	100
9	-	$InCl_3$	100	5	Traces
10	-	$ZnCl_2$	100	5	0
11	-	$BiCl_3$	100	5	99
12	-	$BiCl_3$	100	3	97
13	-	$BiCl_3$	100	1	85
14	-	$BiCl_3$	80	3	75
15	-	$BiCl_3$	50	3	52

[a]Yield determinated by GC analysis.

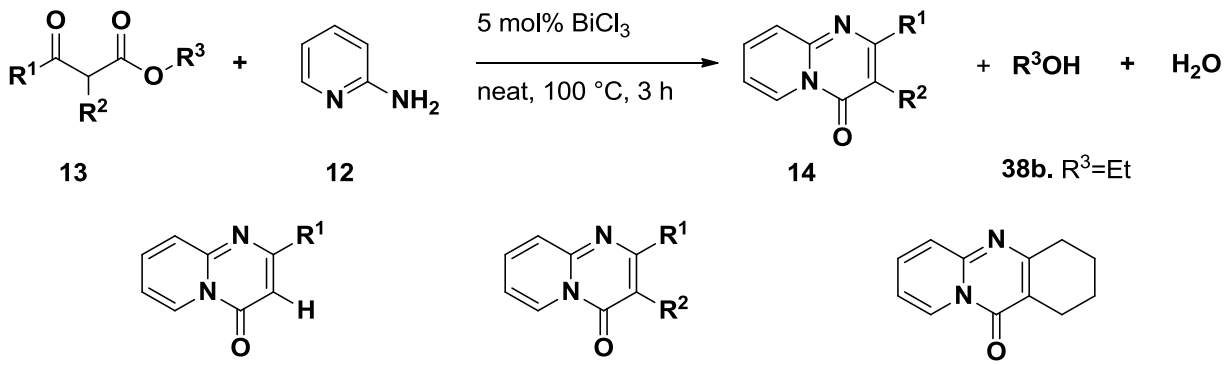
They investigated different solvents (entries 1-4), obtaining the best yield in entry 4, however the highest yield was obtained when the reaction was performed under solvent free conditions (entry 5); here the product was synthetized in 100% yield. They tried to perform the reaction without catalyst (entry 6), however the reaction did not work efficiently and only traces of product were formed. Other Lewis acids, such as $InCl_3$ and $ZnCl_2$ were also used. However, the reaction catalyzed by $InCl_3$ (entry 9) only yielded traces of product, and for the reaction catalyzed by $ZnCl_2$, cyclization was not achieved (entry 10).

In addition, other bismuth(III) salts were also tried (entries 7 and 8) and $BiCl_3$ was found to be as effective as $Bi(OTf)_3$. Hence, $BiCl_3$ was chosen as the catalyst for the following synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives, because $BiCl_3$ is cheaper than $Bi(OTf)_3$.

$BiCl_3$ is a mild, moisture and air-stable Lewis acid. Although bismuth is a heavy metal, this element is not toxic or carcinogenic.

They also wanted to optimize other parameters, and shorter reaction times and lower temperatures were studied. They were able to decrease the reactions times from 8 h to 3 h, obtaining the same good yields. On the other hand, when they tried to decrease the temperature from 100 °C to 80 °C in entry 14 and to 50 °C in entry 15, the yield dropped from 97% to 75% and 52% respectively. As a result of the temperature screening, the optimum temperature was found to be 100 °C.

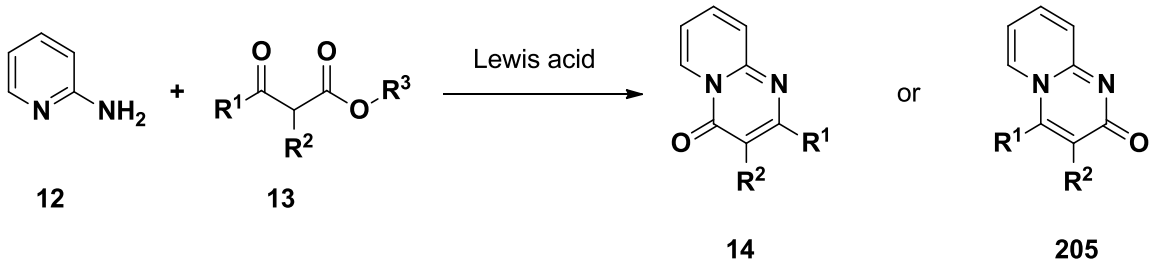
After the screening of different times and temperatures, for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **14a-i** the optimized conditions were 2-aminopyrimidine **12** (0.5 mmol), β-oxo ester (1 mmol) and $BiCl_3$ (0.025 mmol) neat at 100 °C for 3 h. The following compounds were synthesized (**Scheme 43**).



Scheme 43: Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones using $BiCl_3$ as catalyst.

The work described in Roslan and co-workers' paper was conducted simultaneously with our project which is described in the following pages. We had a similar idea to Roslan *et al*. In our study we wanted to find simple, convenient and mild conditions for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. As Roslan and co-workers reported in their paper, we also wanted to replace the corrosive acid for a mild Lewis acid, or to obtain the product using only the two starting material under thermal conditions, avoiding the use of any extra reagent.

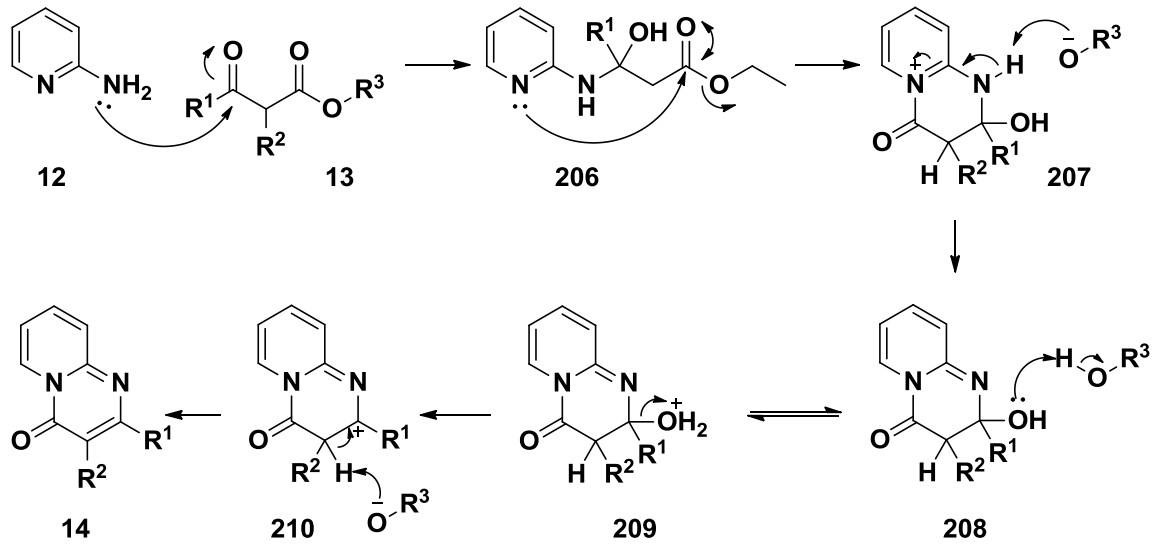
In the literature the isomer most reported is the 4-oxo isomer **14** (**Scheme 42**). The fact that the reaction of 2-aminopyridine and a β-keto ester could deliver two possible isomers **14** and **205** depends on the site of the first nucleophilic attack and this also needs to be taken into account (**Scheme 44**).



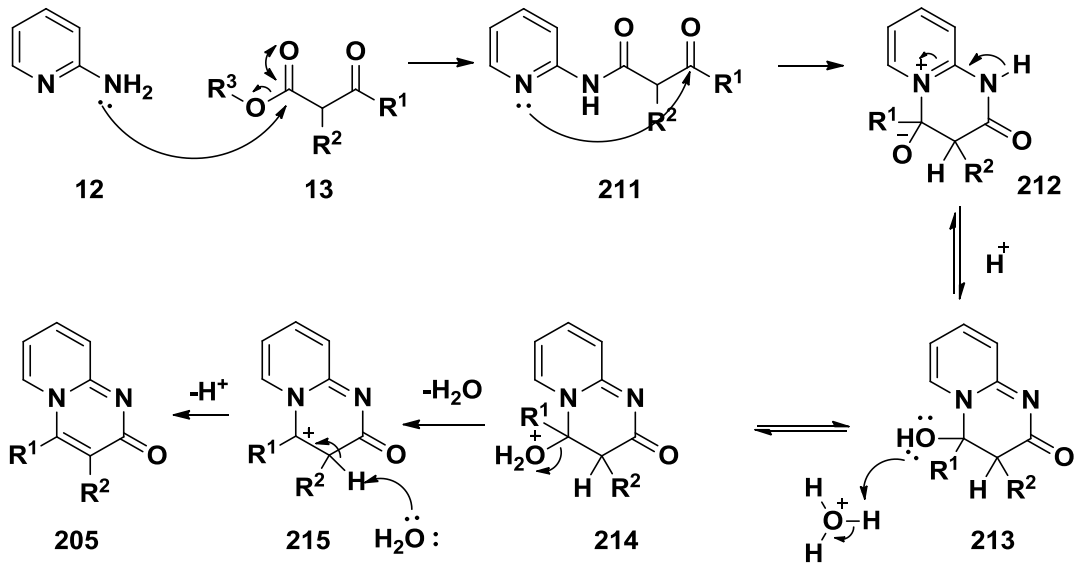
Scheme 44: Two possible isomers from the condensation reaction of 2-aminopyridine and β-keto esters.

Therefore, we looked into the literature for the synthesis of the two isomers and found many papers which report the synthesis of 4-oxo-isomer; however there are few papers reporting the synthesis of the 2-oxo isomer.

The two possible mechanisms for the formation of 2-oxo **205** and 4-oxo **14** isomer starting from 2-aminopyridine and β-ester are shown in the following schemes:

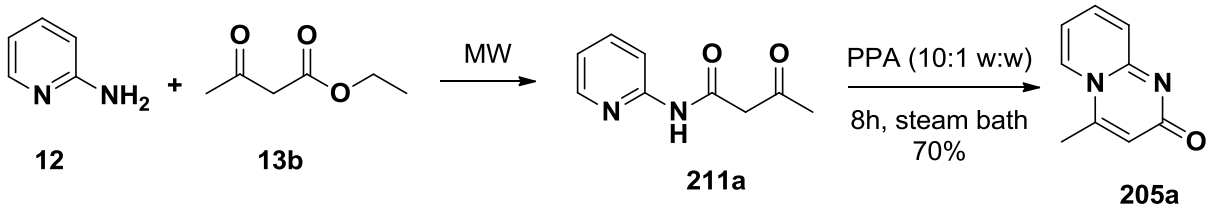


Scheme 45: Proposed mechanism for formation of 2-alkyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.



Scheme 46: Proposed mechanism for formation of 4-alkyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones.

Suris and co-workers were aware of the same problem: the possibility of the synthesis of two different isomers and they carried out a study entitled "An unequivocal synthesis of 4-methyl-2-oxo-(2*H*)-pyrido[1,2-*a*]pyrimidine **205a**", which reported the following reaction (**Scheme 47**).[71]



Scheme 47: An unequivocal synthesis of 4-methyl-2-oxo- (2*H*)-pyrido[1,2-*a*]pyrimidine. [71,73]

Suri *et al.* published three papers for the synthesis of the 2- and 4-oxo isomer. The first one reported the first step of the total synthesis of 4-methyl-2-oxo-(2*H*)-pyrido[1,2-*a*]pyrimidine **205a,** the acetoacetylation of 2-aminopyridine **12** with ethyl acetoacetate **13b** under microwave irradiation to afford compound **211a** (**Scheme 47**).[73]

The second paper reported the unequivocal synthesis of 4-methyl-2-oxo-(2*H*)-pyrido[1,2-*a*]pyrimidine **205a.** Describing the cyclisation of compound **211a** under thermal conditions using PPA as the catalyst.[71]

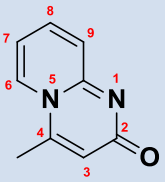
They claimed to be the first research group to report the synthesis of 4-methyl-2-oxo-(2*H*)-pyrido[1,2*a*]pyrimidines by the reaction between β-oxoesters and 2-aminopyridines.

They explained that they had problems in the synthesis of these two isomers, because both isomers have very similar ^{1}H and ^{13}C NMR data. A number of research groups had claimed the synthesis of the 2-oxo-isomer and later on these products were determined to be the 4-oxo-isomer. One of the cases discussed in Suris' paper is the work of Antaki[74] who in 1958 reported the synthesis of 2-oxo-(2*H*)-pyrido[1,2-*a*]-pyrimidines by the reaction of 2-amino-4-methyl pyridines with ethyl ethoxymethylenecyanoacetate. However, the products were later determined to be the 4-oxo-isomer.

The third paper reported by Suri *et al.* was called "Unequivocal total assignment of ^{13}C and ^{1}H NMR spectra of some pyrido[1,2-*a*]pyrimidine derivatives", and in the paper the similarity of the NMR data of both isomers **14** and **205** was discussed.[75]

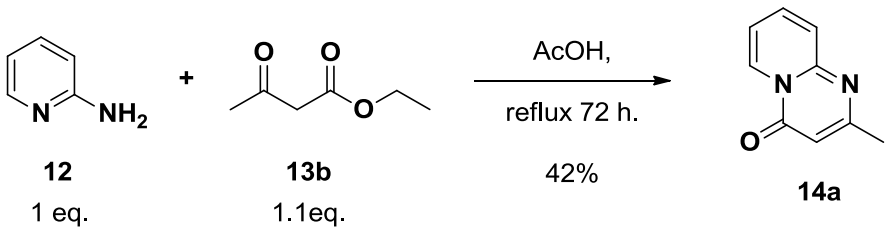
In this paper they reported a comparison of the ^{1}H and ^{13}C NMR data for the following two isomers (**Table 16**). The synthesis of the 2-oxo isomer has been described (**Scheme 47**), and for the synthesis of the 4-oxo isomer, the data used that reported by Suri and co-workers in previous work in 1993.

Table 16: Comparison of ^{1}H NMR data for 4-methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one by Suri et al.[75]

Compound	Data	Compound	Data
 **205a**	2.47 (s, 3H, C4-CH_3)	 **14a**	2.47 (s, 3H, C2-CH_3)
	6.35 (s, 1H, H-3)		6.35 (s, 1H, H-3)
	7.13 (dt, 1H, *J* = 7.12, 1.28 Hz, H-7)		7.13 (dd, 1H, *J* = 7.12, 7.12 Hz, H-7)
	7.60 (bd, 1H, *J* = 7.12 Hz, H-9)		7.59 (d, 1H, *J* = 7.12 Hz, H-9)
	7.74 (m, 1H, H-8)		7.74 (m, 1H, H-8)
	9.03 (bd, 1H, *J* = 7.12 Hz, H-6)		9.04 (d, 1H, *J* = 7.12 Hz, H-6)

To try to help to clarify the issue we carried out a similar study to Suri *and co-workers.* We synthesized the same two isomers, in order to understand the reaction better, and to obtain spectroscopic and X-ray diffraction data.

Firstly, we synthesized the 4-oxo-isomer (2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **14a**), following the procedure reported by Shifeng *et al.* in 2008.[76]



Scheme 48: Synthesis of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one 14a.[76]

The reaction was carried out in acetic acid as catalyst and solvent, affording 2-methyl-4-oxo-(4*H*)-pyrido[1,2-*a*]pyrimidine **14a**. The compound was fully characterised by ^{1}H and ^{13}C NMR spectroscopy, and the structure (as a mono-acetic acid solvate) was confirmed by X-ray crystallography unambiguously to be the 4-oxo isomer. This confirmed that this approach led to the 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one isomer **14a**.

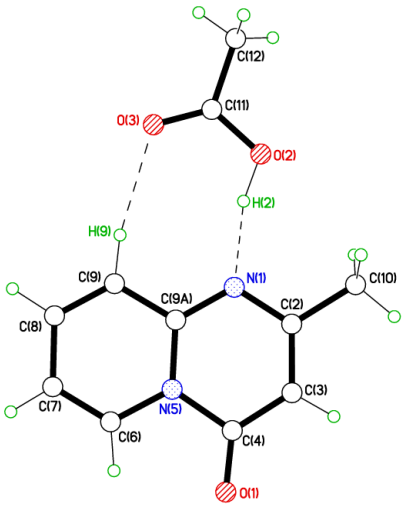
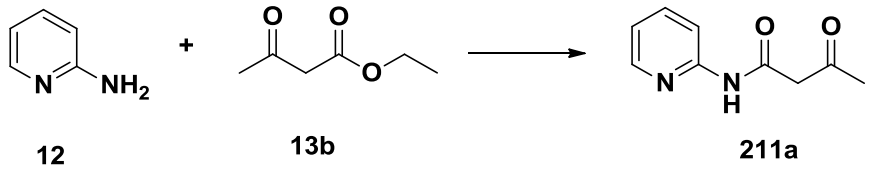


Figure 25: X-ray crystallography structure of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

Secondly, we followed Suri's synthesis pathway, pre-forming the amide link. However for the synthesis of compound **205** (**Scheme 47**) we modified the procedure, and instead of carrying out the reaction with microwave assistance, we performed the reaction under conventional heating.

The N-acetoacetylation of 2-aminopyridine **12** by ethyl acetoacetate **13b** under thermal conditions was carried out using the conditions described in (**Table 17**).

Table 17 : N- acetoacetylation of 2-aminopyridine from ethyl acetoacetate.

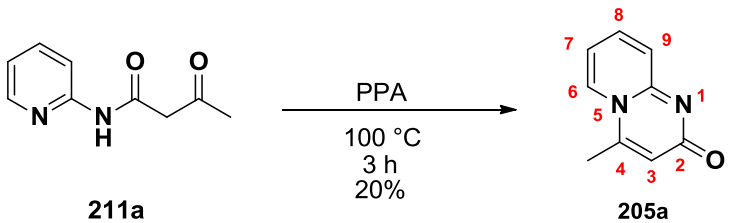


12 13b 211a

Entry	2-aminopyridine (mmol)	Ethylacetoacetate (mmol)	T ° C	Solvent (ml)	Time (h)	Product (Yield %)
1	2.5	2.5	Reflux	Xylene (20ml)	24	-
2	5	5	91	Xylene (3ml)	24	-
3	2.5	2.5	170	No solvent	2	**211a** (60%)
4	3	9	110	No solvent	5	**211a** (62%)

The reaction was carried out in xylene due to its high boiling point (entry 1 and entry 2). The first reaction was performed using 2.5 mmol in 20 ml of solvent, but unfortunately the reaction gave only the starting material back. For this reason, in entry 2, the quantities of reagents were increased to 5 mmol and the volume of solvent was decreased to 3 mL of xylene to increase the reaction mixture concentration, but the reaction was still unsuccessful. The NMR spectrum showed only starting material signals. Taking advantage of one of the reagents (ethyl acetoacetate) being a liquid and with a boiling point of 181 °C, the next reaction was carried under solvent-free conditions, and was heated at 170 °C over 2 h obtaining the desired product **211a** in 60% yield (entry 3). The optimal conditions achieved are given in entry 4: reagent ratio was 1:3 equivalents (2-aminopyrimidine: ethyl acetoacetate), heated at 110 °C over 5 h to afford the product **211a** in 62% yield.

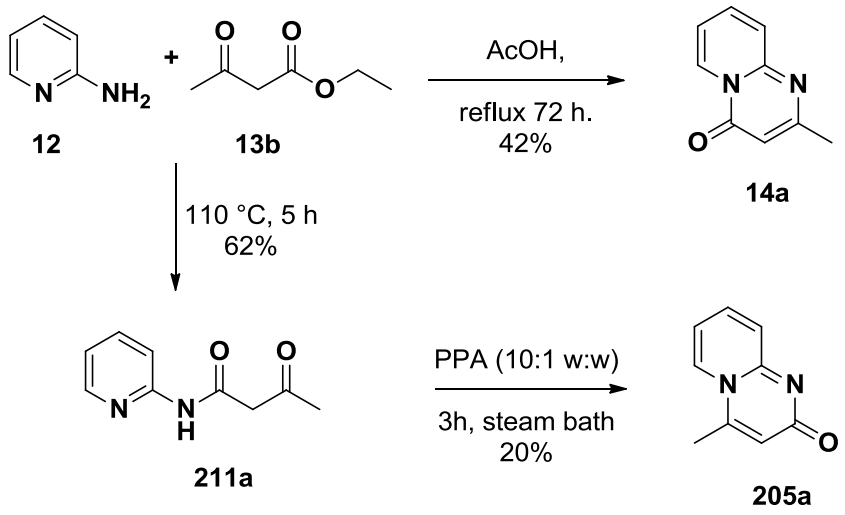
Having the N-acetoacetylated pyridine in hand, the following step was to effect the cyclisation of **211a** to afford the 4-oxo-isomer, compound **205a**. We followed the procedure reported by Suri *et al.:* Cyclisation of N-(1,3-dioxobutyl)-2-aminopyrimidine under thermal condition catalysed by polyphosphoric acid (PPA).[71] Thus we obtained the 4-oxo isomer.



211a 205a

Scheme 49: Synthesis of 4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one.

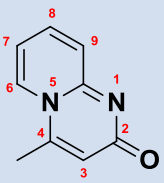
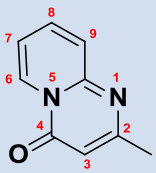
Following the reaction pathway reported by Suri only the synthesis of the 2-oxo isomer **205a** was possible (assuming the amide remains intact during the second step). We thus could confirm Suri's conclusions, and the chemical shift data for both isomers are very similar, as shown in **Table 18**.



Scheme 50: Synthesis pathways for the synthesis of 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

In the following table is the comparison of the ^{1}H NMR data of 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, that we synthesized.

Table 18: ^{1}H NMR data for 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

Compound	Data	Compound	Data
 **205a**	2.51 (s, C4-CH_3)	 **14a**	2.48 (s, 3H, C2-CH_3)
	6.37 (s, 1H, H-3)		6.36 (s, 1H, H-3)
	7.12 - 7.19 (t, *J*= 6.8 Hz, 1H, H-7)		7.12 (td, *J*=6.8, 1.2 Hz, 1H-7)
	7.68 (d, *J*=8.8 Hz, 1H, H-9)		7.60 (bd, *J*=8.8 Hz, H-9)
	7.77 (ddd, *J*=8.8, 6.8, 1.5 Hz, 1H, H-8)		7.73 (ddd, *J*=8.8, 6.8, 1.6 Hz, 1H-8).
	9.07 (d, *J*=6.8 Hz, 1H H-6)		9.04 (d, *J*=6.8 Hz, H-6

As can be seen in **Table 18** the ^{1}H NMR data are very similar, as are that actual spectra (**Figure 26**). There is only important difference, the doublet at 7.60 in the first spectrum is sharper than the one for compound where **205a** the doublet is broad. Also the J values are lightly different between both spectra; however nothing in the spectra clarified which one is which.

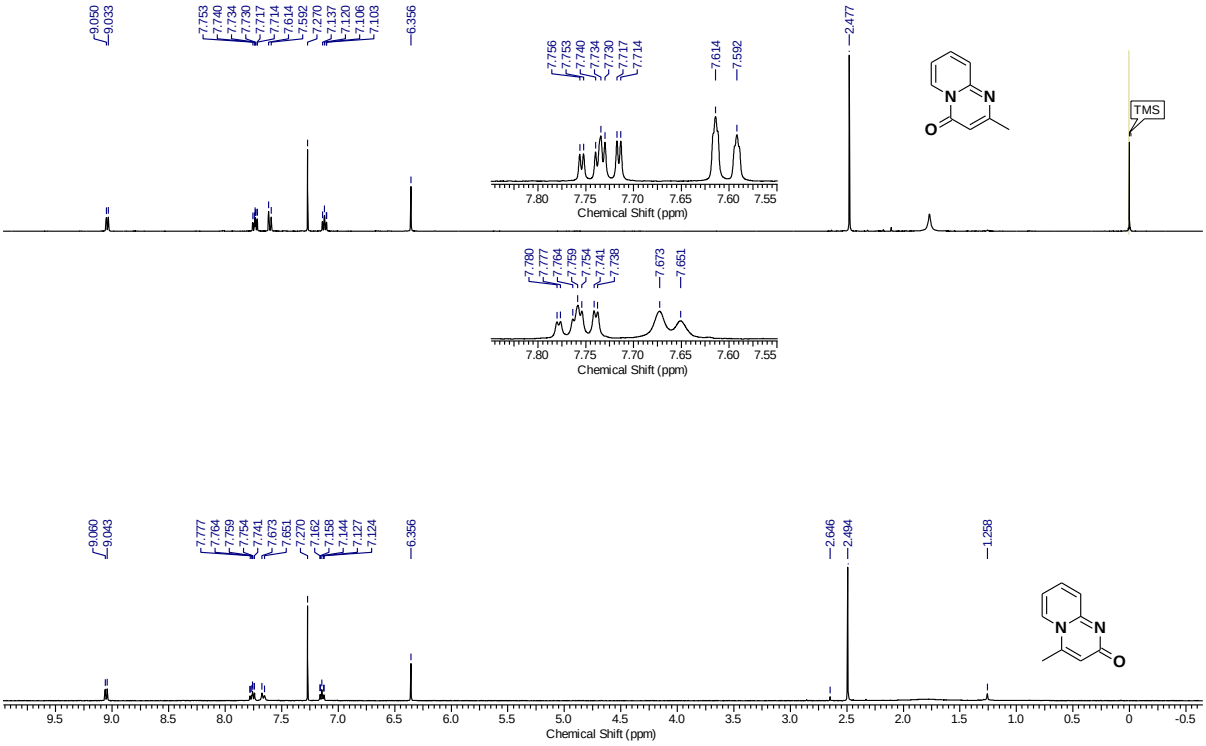
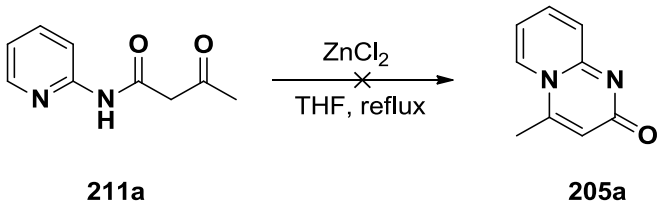


Figure 26: Comparision of 2 and 4-oxo isomer spectra.

Taking this information into account, we wanted to introduce a new procedure for the synthesis of these two isomers using Lewis acids. We needed to further study the ^{1}H NMR data because we wanted to be sure that we reported the correct product (isomer). The study showed that the synthesis of the two isomers is possible depending on the pathway that we decided to follow.

Having the N-acetoacetylated amine **211a** in hand, firstly we looked for mild conditions for the cyclisation step to afford the pyridopyrymidine **205a**. We decide to study the reaction catalyzed by a Lewis acid ($ZnCl_2$).

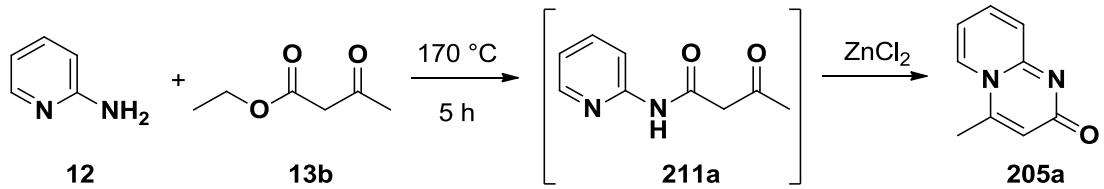
N-acetoacetylated product and $ZnCl_2$ were dissolved in THF and stirred under reflux, **Scheme 51**. The reaction was not successful and only starting material was recovered. It is possible that THF competed for the zinc catalyst preventing activation of the carbonyl group by the Lewis acid.



Scheme 51 : Attempted synthesis of 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one.

In the next reaction we started with 2-aminopyridine **12** and ethyl acetoacetate **13b**, and the reaction mixture was stirred over 5 h, neat and then $ZnCl_2$ was added to the reaction mixture, with stirring for a further 30 min. An emulsion was formed after the $ZnCl_2$ was added. The reaction mixture was worked-up, adding the same quantities of water and ethyl acetate, and it was left overnight to obtain two separate layers, so this procedure was difficult to work with.

Table 19: Synthesis of 4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one catalysed by $ZnCl_2$.

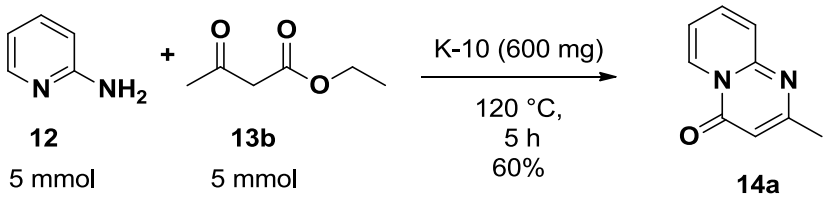


Entry	Catalyst	T (°C)	Time (h)	Yield (%) [a]
1	$ZnCl_2$ (1 eq)	170	6	5
2	$ZnCl_2$ (1 eq)	170	6	50

[a] Reaction conditions: 2-amino pyridine and the ethyl acetoacetate staring over 5.30 h and the ZnC_{l2} was added to reaction mixture, the reaction was stopped after 30 min to afford compound 205a.

Isomer **205a** was obtained in low yield (entry 1) due to the difficulty in the work-up step, leading to a decreased yield for the reaction. The reaction was reproducible and the yield was improved to 50%, however, the work-up step was always problematic due to the emulsion that was formed. In order to solve this problem, other conditions were tested. We looked for other Lewis acid which might give an easier work-up and therefore, a higher yield. Montmorillonite clay was chosen as an ideal Lewis acid, due to its properties, inexpensive, strong acidity and non-corrosivity.[77] It is used under mild reaction conditions and can be recovered from the reaction mixture by simple filtration.

The synthesis of the 4-oxopyrido[1,2-*a*]pyrimidine moiety **14** was carried out by direct condensation/ cyclization of 2-aminopyridine with substituted β-keto esters catalysed by the clay mineral montmorillonite (K-10)[77] under solvent-free conditions. It was concluded that the method was an effective, clean process and easy to work-up. Also a higher yield was obtained 60% (**Scheme 52**).



Scheme 52: Synthesis of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one 14a.

The montmorillonite (K-10) was added at the same time than the pyridine **12** and the ester **13b**. The product yield was calculated from the NMR spectrum of the crude product (**Scheme 52**).

In (**Figure 27**) is summarized the four reactions conducted: reactions 1 and 2 are the method following the previous literature procedures. For reaction 1, we obtained confirmation of the synthesis of the 4-oxo isomer from its X-ray crystal structure. For reaction 2, we had followed an unequivocal synthesis for the 2-oxo isomer. Reaction 3 is the reaction catalysed by montmorillonite, which was added at the beginning of the reaction. The final reaction (reaction 4), involved stirring the 2-aminopyridine and the β-ketoester at 170 °C for 5 h, and then adding the $ZnCl_2$ to the reaction mixture.

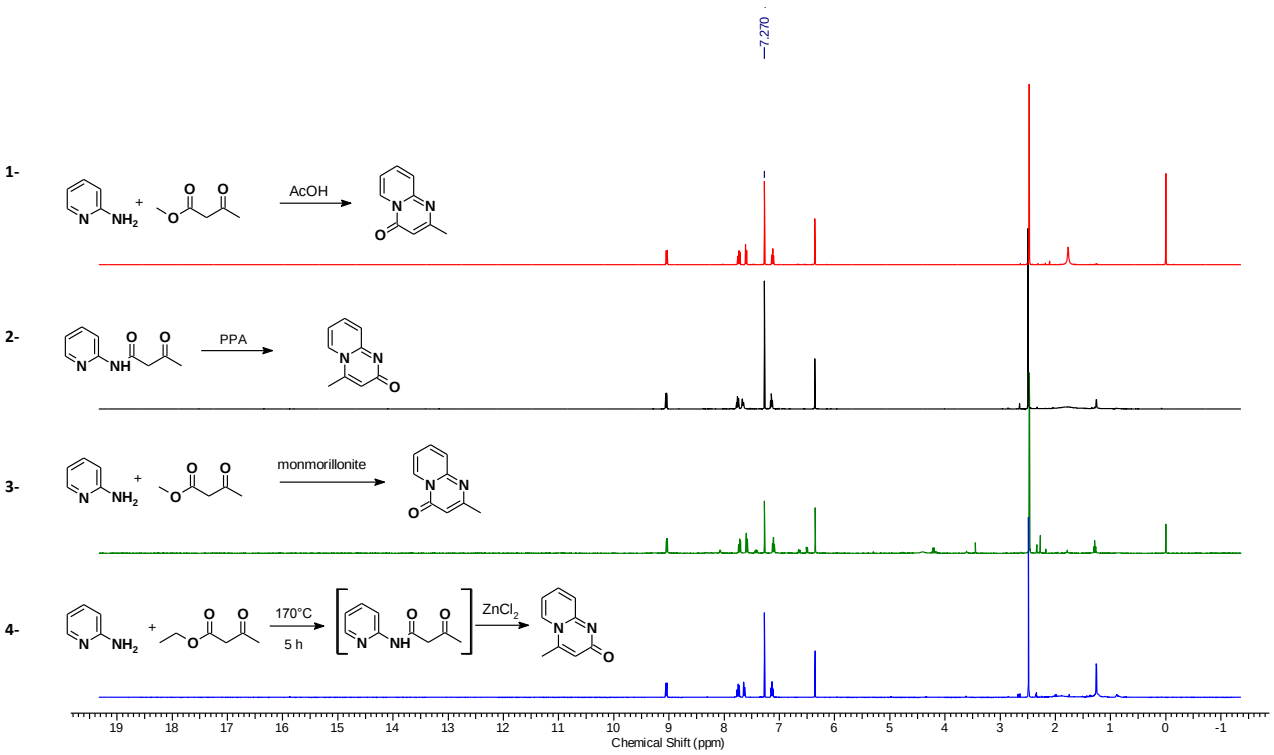


Figure 27: Comparison of the four spectra.

Below is an expansion of **Figure 27**, where it is possible to see that although there are small differences between all spectra (and a minor impurity in entry 3), spectra 1 and 3 are effectively the same, and likewise spectra 2 and 4 are the same.

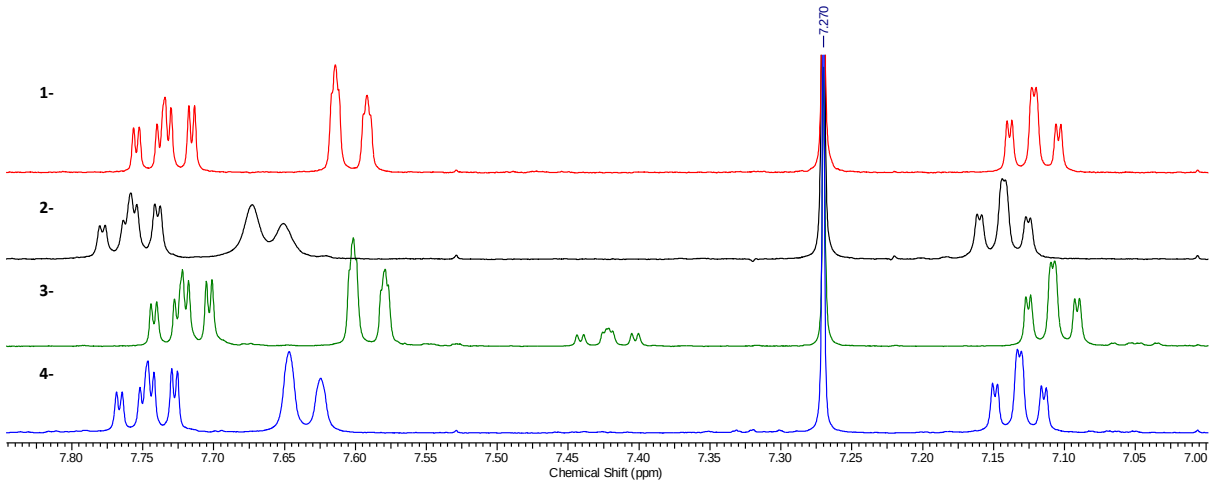


Figure 28: Zoom of Figure 27.

Following this comparison, between spectra we can conclude that the ^{1}H NMR spectra for the four reactions show 1 and 3 are the same, and 2 and 4 are also the same (despite small changes in chemical shift which could be due to concentration or temperature).

This means that the product from reactions 1 and 3 is the 2-methyl-4-oxo isomer **14a** as drawn, which was confirmed by X-ray diffraction analysis.

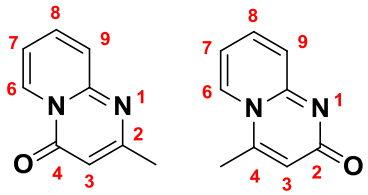


Figure 29: 2-methyl-4-oxo isomer (14a) and 4-methyl-2-oxo isomer (205a).

The product of reactions 2 and 4 must therefore be the 4-methyl-2-oxo isomer **205a**, which was confirmed by the unequivocal synthesis pathway reported by Suri *et al*.

We tried to further substantiate these results by nOe experiments with the product of reaction 4, believed to be the 2-oxo isomer. The methyl group was therefore irradiated leading to enhancement of the singlet at 6.33 (which is H-3) as expected (and this enhancement would be observed in both isomers). A weak enhancement of the doublet at 7.6 was also observed, but no enhancement of the doublet at 9.0 was seen. This was surprising as enhancement of H-6 was expected, as this proton, adjacent to the bridgehead nitrogen, has previously been assigned at δ 9.0.

This suggests the doublet at 7.6 could be due H-6, although the weakness of the enhancement is of concern. In the 2-methyl-4-oxo isomer, the methyl group appears so far away from H-9, that no nOe effect would be expected.

The nOe study did not help to further substantiate the structure of the product of reaction 4 (which we still believe to be the 4-methyl-2-oxo compound). Further nOe studies on both isomers as well as C-6 and C-9 substituted analogues would be required to gain a full understanding.

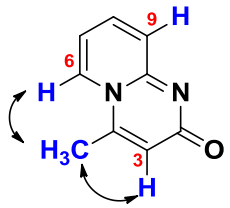


Figure 30: nOe coupling of 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (205a).

In conclusion, all the data confirmed that the compound was the 2-oxo isomer. However, the nOe experiment conducted was inconclusive.

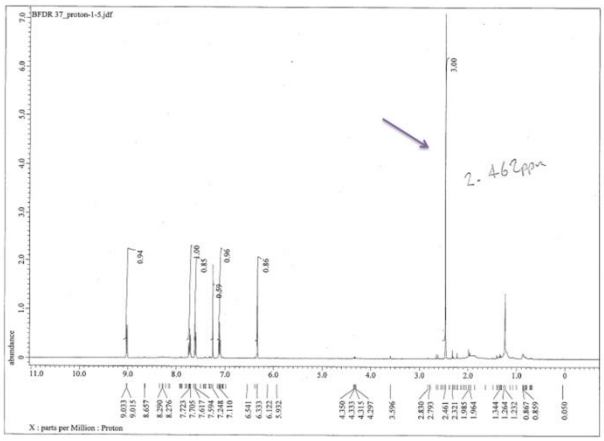


Figure 31: ^{1}H NMR spectrum of 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (205a).

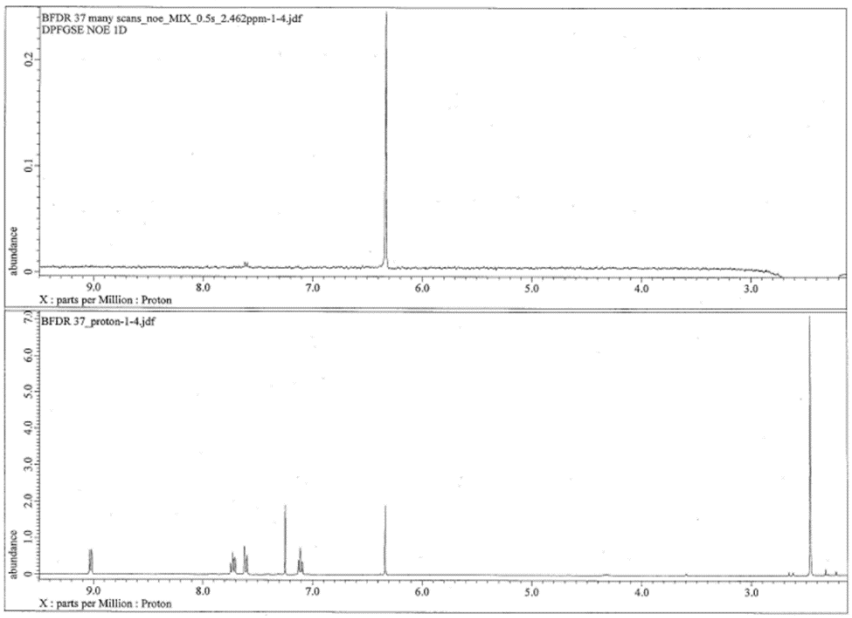


Figure 32: Spectrum of the nOe study of 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (205a), irradiation at 2.46 ppm (CH_3).

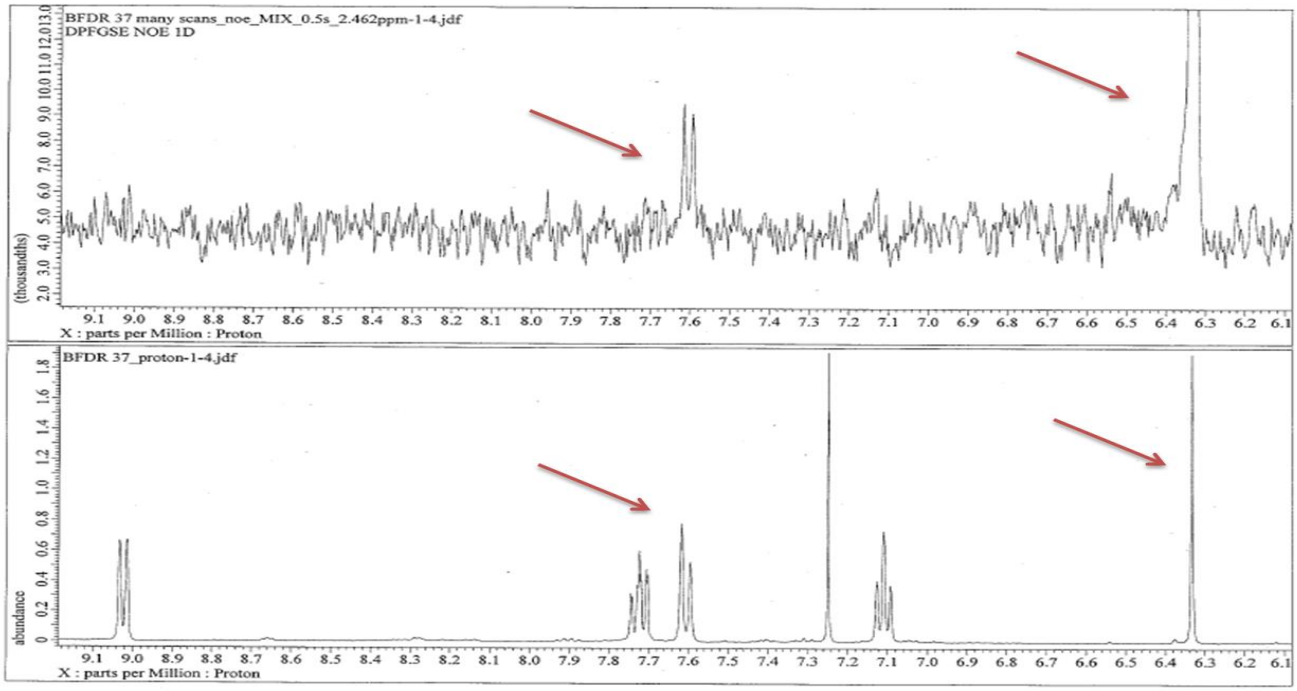
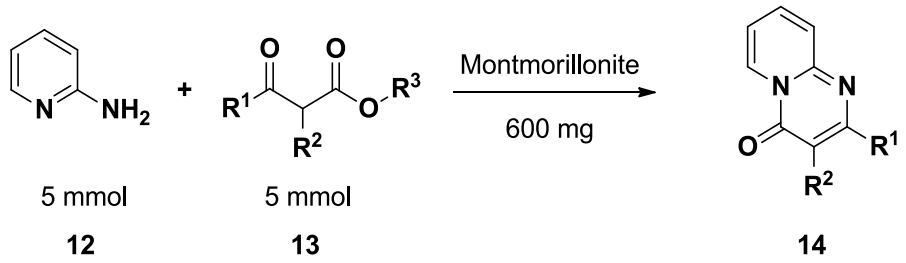
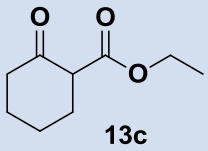
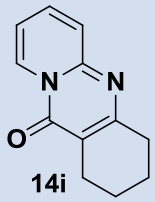
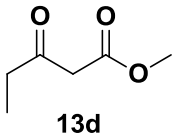
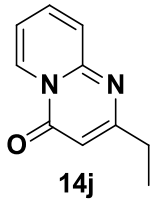
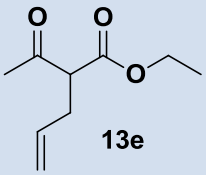
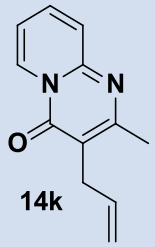


Figure 33: Expansion of Figure 32.

We wanted to expand the chemistry, so the optimal reaction conditions (110 -120 °C, solvent free and montmorillonite as the Lewis acid) were used with the following β-keto esters, obtaining clean reactions, easy work-up and good NMR spectra in most cases (**Table 20**).

Table 20: Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives.



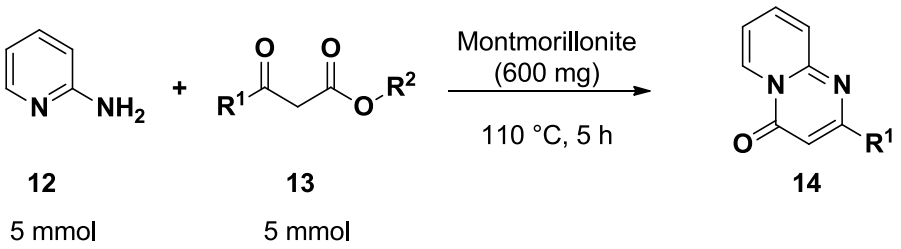
Entry	β-ketoester	Temperature (°C)	Time (h)	Product	Yield (%)
1	 13c	120	7	 14i	80
2	 13d	100	7	 14j	60
3	 13e	120	5	 14k	66

In these reactions (**Table 20**), the Lewis acid (montmorillonite) was added at the same time as the 2-aminopyridine and the β-ester and the reaction was stirred at 100-120 °C to afford the 4-oxo isomers. The cyclic product was formed, because the NMR spectra showed an aromatic proton at 9 ppm.

The problem of this method so far was the NMR chemical shifts for the 2-oxo- and 4-oxo- isomers were found to be very similar as indicated by Suri [1] and co-workers, and that care was required in assigning the structures of these types of compound.

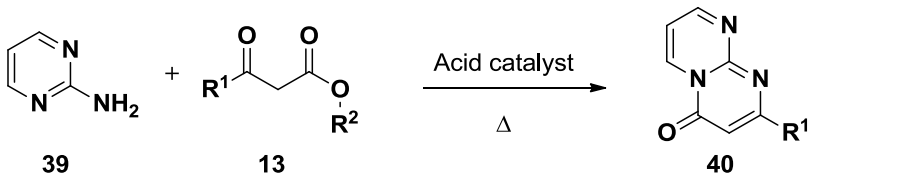
2- Synthesis of pyrimidopyrimidine derivatives.

After finding that the synthesis of pyridopyrimidines could be achieved under mild thermal conditions, using a protic acid catalyst or Lewis acid, we wanted to then synthesize pyrimidopyrimidine derivatives **40** from commercially available 2-aminopyrimidine **39** with different β-keto esters **13.**



Scheme 53: Optimal conditions for the synthesis of pyridopyrimidines from 2-aminopyridine with different β-keto esters.

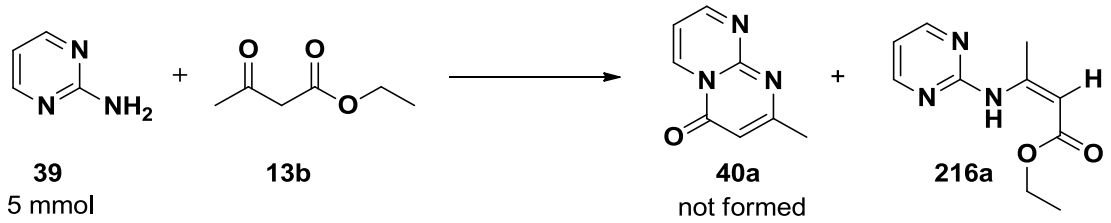
The same conditions that were studied for the synthesis pyridopyrimidine derivatives in the previous section (synthesis of pyridopyrimidine derivatives) were used for the synthesis of pyrimidopyrimidines **40a** and **40b** from the readily available starting material, 2-aminopyrimidine **39** and two different β-keto esters **13b** and **13d** (**Scheme 54**).



Scheme 54: Proposed pathway for the synthesis of pyrimidopyrimidines from 2-aminopyrimidine and two different β-keto esters.

The study started with the synthesis of pyrimidopyrimidine from 2-aminopyrimidine **39** and ethyl acetoacetate **13b**, the reaction was catalysed by montmorillonite (**Table 21**, entry 1). Also, small amount of DCM was added to the reaction mixture in order to obtain a homogeneous mixture before heating the reaction at 100 °C. Once the reaction mixture reached this temperature, the DCM was boiled off, so the reaction was performed solvent free. ii) The reaction was cooled down and was stirred at room temperature overnight. The crude product showed signals of the mono addition compound **216a** instead the expected heterocyclic compound.

Table 21: Attempted synthesis of 2-methyl-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one.



39
5 mmol

13b

40a
not formed

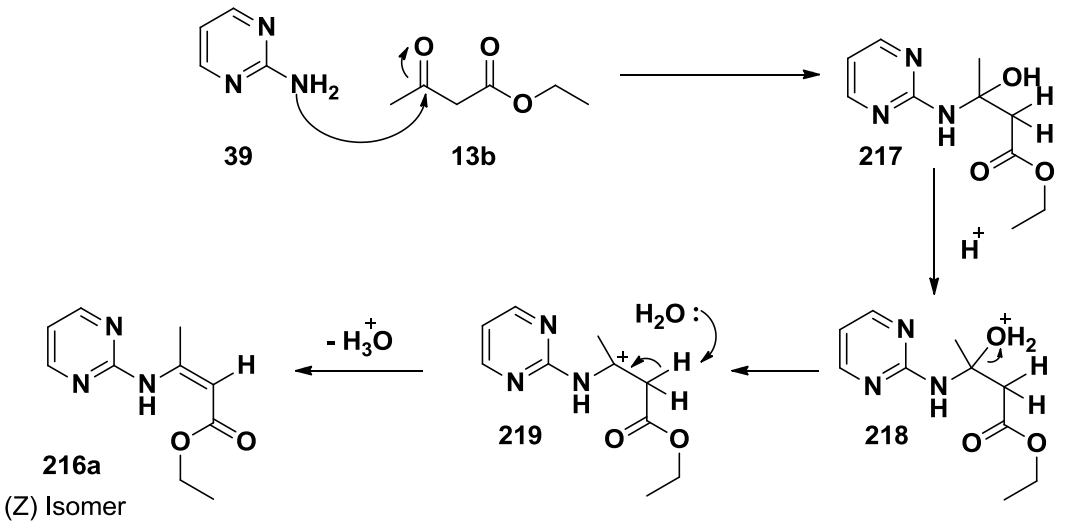
216a

Entry	2-amino pyrimidine	β-ketoester 13b	Catalyst (mg / eq.)	Solvent	T °C	Time	Product
1	1	1	Montmorillonite[a]	DCM*	100 r.t	7.30h 12h	(**39:216a**) (0.39:0.61)
2	1	1	Neat	-	175	3h	decomposed
3	1	1		AcOH	Reflux	24	**216a** (9%)
4	1	2	Montmorillonite[a]	-	110	24	**216a** (20%)

[a]**Monmorillonite (600 mg) / 2-aminopyrimidine (5 mmol).**

In entry 2, **Table 21** the reaction was performed as a neat reaction, but the reaction generated a complex mixture, not product was isolated. In entry 3, the reaction was performed in acetic acid as solvent and catalyst; the compound **216a** was synthesized. Also, when the reaction was carried out with two equivalents of ethyl acetoacetate (using the ethyl acetoacetate as a solvent) and montmorillonite as catalyst, the reaction resulted in formation of enamine **216a** in 20% yield (entry 4, **Table 21**).

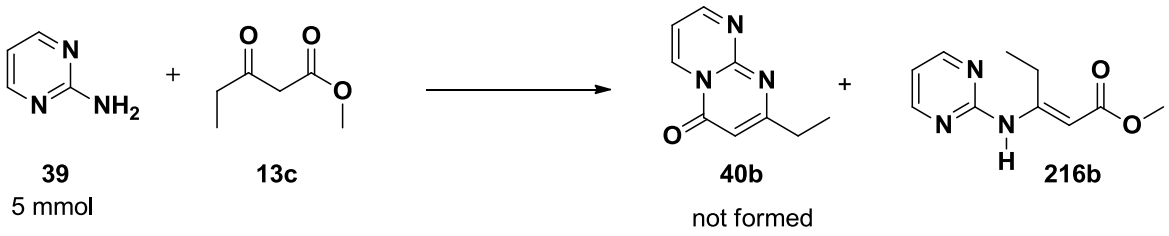
The conclusion of this screening was that the reactivity of 2-aminopyrimidine is lower than the 2-aminopyridine, delivering the mono-addition product **216a**, and before the second nucleophilic attack at the carbonyl group a dehydration occurred, delivering the (Z)-enamine product **216a,** (**Scheme 55**).



Scheme 55: Proposed mechanisme for the enamine 216a formation.

A similar screening was performed for 2-aminopyrimidine and methyl propionylacetate, and surprisingly, the reactivity of methyl propionyl acetate was different from the ethyl acetoacetate, as shown in **Table 22**.

Table 22: Attempt to synthesise 2-ethyl-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one 216b.



Entry	2-amino Pyrimidine (eq)	β-ketoester (13c) (eq)	Catalyst (mg / eq)	Solvent	T °C	Time (h)	Product (Yield)
1	1	1	Montmorillonite[a]	DCM[b]	120	24	-
2	1	3	Montmorillonite[a]	-	110	24	-
3	1	3	-	AcOH	Reflux	24	-
4	1	3	Montmorillonite[a]	Xylene	110	5	**216b** (10%)

[a]**Monmorillonite (600 mg) / 2-aminopyrimidine (5 mmol).**

[b]**DCM was added in order to mix all the reagent, as soon as the reaction was heat it up, the DCM was boiled off.**

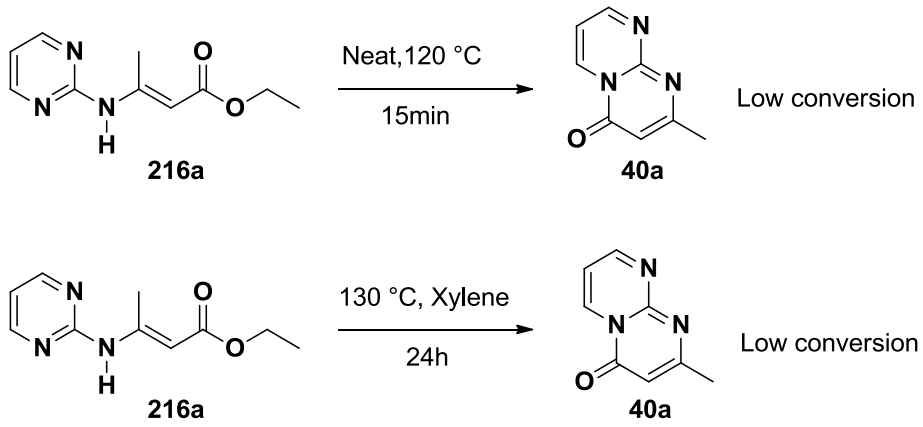
In entry 1, (**Table 22**) the reaction was performed using montmorillonite as catalyst. Again a small quantity of DCM was used in order to ensure a homogeneous mixture formed before the reaction was heated at 120°C for 24 h. Even though the reaction was heated for 24 h, the reaction gave back starting material. In entry 2, the amount of ester was increased to 3 eq. hoping that the reaction would form product. However, the reaction was again unsuccessful.

After the experiments using 2-aminopyrimidine **39** and the β-ketoesters: ethyl acetoacetate **13b** (entry 2, **Table 21**) and methyl propionylacetate **13c** (entries 1 and 2, **Table 22**) under solvent free conditions, we arrived at the following conclusion. The 2-aminopyrimidine was subliming during the reaction, and the β-ketoester was likely to be reacting with itself to afford polymeric or complex products, leading to the NMR spectrum showing only 2-aminopyrimidine signals.

In entry 3, the reaction was performed in acetic acid as the solvent and catalyst. However, the reaction was not successful and the NMR spectrum showed only starting material.

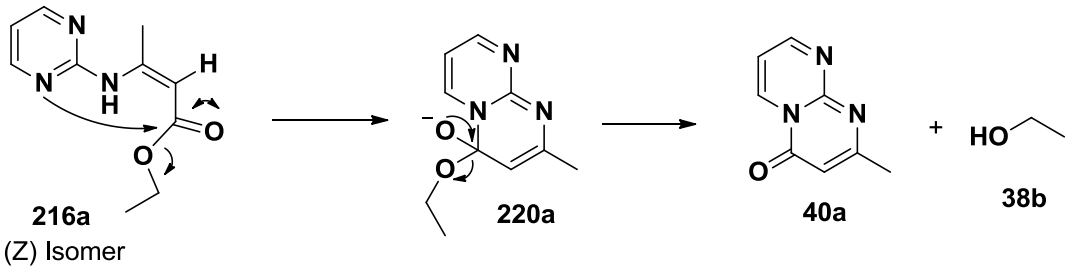
The reaction did not work under acidic conditions, so we tried again with montmorillonite, but we needed to solve the problem of the ester reacting with itself, therefore xylene was chosen as a solvent, due to its high boiling point. In entry 4, the reaction was performed in xylene at 110 °C using montmorillonite as a catalyst, over 5 h. These conditions delivered the enamine **216b** in 66% yield.

After isolation of compound **216a**, the following reactions were conducted to cyclise the enamine **216a** to form compound **40a,** using the conditions shown in **Scheme 56**. The yield of the reaction was very low, and the ^{1}H NMR spectrum signals were very weak. However, the product was confirmed by GS-MS and the ^{1}H NMR spectrum showed new aromatic signals at 9.32 ppm, 9.08ppm and 7.17 ppm. The symmetry of the pyrimidine ring was lost, giving three different signals for the aromatic protons, also the lack of the ester signals confirmed the cyclisation of the enamine.



Scheme 56 : Synthesis of 2-methyl-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one under thermal conditions.

The reactivity found for 2-aminopyridine was much better than for 2-aminopyrimidine, possibly due to the second nitrogen in the aromatic ring removing electron density from the amino substituent, lowering its nucleophilicity.



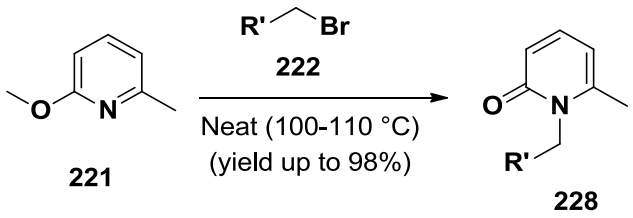
Scheme 57: Proposed mechanism for the synthesis of 2-methyl-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one.

The mechanism of nucleophilic attack in the N-acylation step involved attack at C-3, and the product **290a** was afforded after dehydration of the presumed aminal intermediate. However, the double bond of enamine caused a serious problem in the cyclisation step, because there was limited free rotation in the molecule and the probability to cyclise was low.

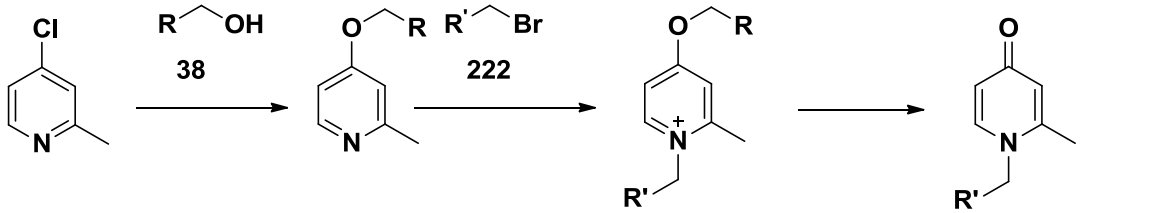
3- Study of 2-pyridones and 4-pyridone derivatives.

Six-membered ring scaffolds containing nitrogen are known to be prominent in medicinal chemistry (e.g. pyridines, pyridones, quinolizinones).[11] Here we focus on 2- and 4-pyridones, as they have been found in different antibacterial agents such as pilicidines, and curlide (ciprofloxacin).[11,54]

Herein I report the synthesis of 2-pyridones and 4-pyridone derivatives, from commercially available starting materials, and their subsequent metallation reactions. In the synthesis of N-alkylated 6-methyl 2-pyridones we used 2-methoxy-6-methylpyridine **221** and a number of different alkylating reagents (**Scheme 58**). We employed a 6-methyl substituted pyridine so that we could investigate deprotonation of the methyl group for subsequent ring-forming reactions. For the synthesis of N-alkylated 2-methyl 4-pyridones, 4-chloro-2-methyl pyridine **223** was used as starting material, and the desired pyridone was achieved after 3 steps (**Scheme 59**).



Scheme 58: Synthesis of N-alkylated-6-methyl 2-pyridones.

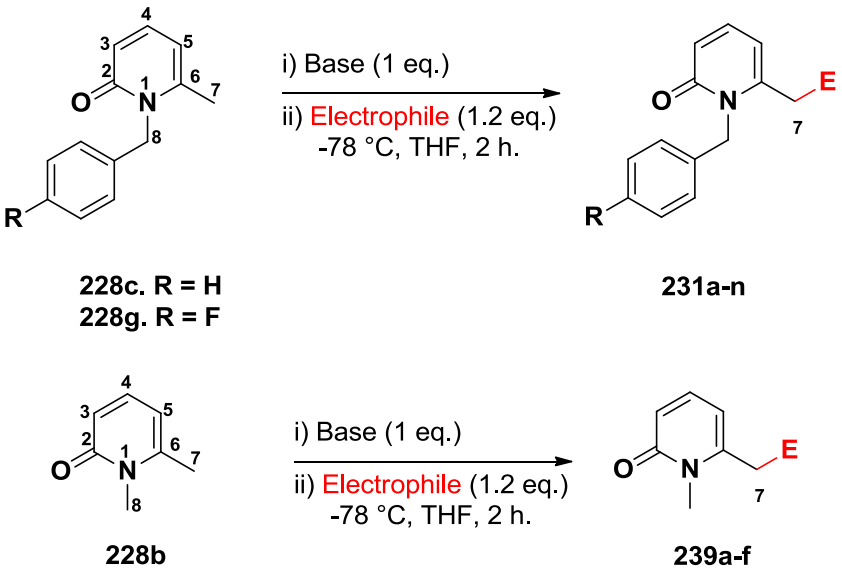


Scheme 59: Synthesis route to N-alkyl 2-pyridone and N-alkyl 4-pyridone.

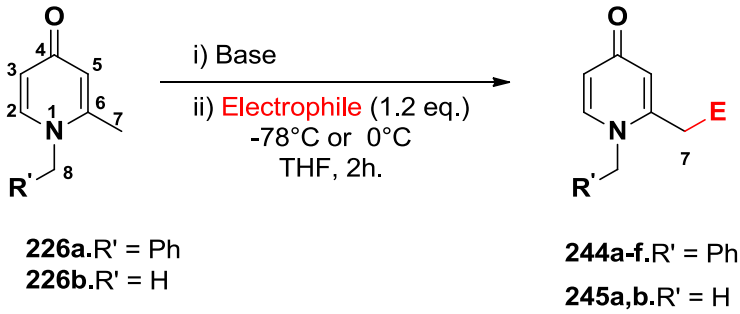
The ring functionalization of 2- and 4-pyridone and analoguous pyridines such as 2-picoline, have been studied intensively in the past years. Furthermore, the metallation at the methyl position of 2-picoline has been studied as an efficient means for the preparation of complex molecules, and therefore, has been study intensively. There are studies in this field dating back to 1974.

Our group has been interested in the regioselective methyl lithiation and subsequent electrophilic quenching of N-alkyl-6-methyl-2-pyridone and N-alkyl-2-methyl 4-pyridone. There are only a few papers which report the metallation and functionalization of N-alkyl-6-methyl-2-pyridone and N-alkyl-6-methyl-2-pyridone, at the methyl position. To the best of our knowledge, there is only one paper which describes the metallation of 1,6-dimethyl 2-pyridone, which was reported by Sammes and co-workers.[78]

The metallation at the methyl position of 2- and 4- pyridone has not been reported in detail, and it requires a thorough investigation. This scaffold represents an interesting synthetic intermediate for the synthesis of larger and more complex molecules, and for this reason we present the selective mono-metallation at the 6-methyl position of 1-substituted-6-methyl-2-pyridone and 1-substituted-2-methyl-4-pyridone with n-BuLi/KHMDS at -78 °C at 6-methyl position and the reactivity of such synthetic intermediates towards a wide range of electrophiles (diketones, aldehydes, alkylating reagents), (**Scheme 60** and **Scheme 61**).



Scheme 60: Synthesis of 1-substituted-6-methyl-2-pyridones 231a-n and 239a-f by regioselective metallation at methyl position.



226a.R' = Ph
226b.R' = H

244a-f.R' = Ph
245a,b.R' = H

Scheme 61: Synthesis of 1-substituted-2-methyl-4-pyridone (244a-d, and 245a,b).

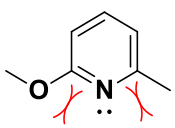
As shown in **Scheme 60** and **Scheme 61**, firstly the synthesis of 2- and 4-pyridone precursors was required. The second part of the study was the metallation at the methyl position of 2-pyridone and 4-pyridone.

During the following pages the synthesis of 1-substituted-6-methyl-2-pyridone and 1-substituted-2-methyl-4-pyridone and the subsequent metallation at the 6-methyl position and at the 2-methyl position, respectively, will be discussed in detail.

3.1- Study of 2-pyridone derivatives.

3.1.1- Synthesis of N-alkylated 2-pyridones.

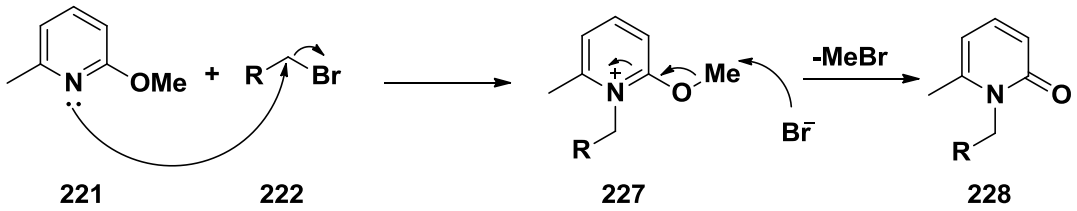
Our synthesis pathway was based on Bowman's work.[44] We decided to study the synthesis of N-alkylated 2-pyridones from 2-methoxy-6-methylpyridine and a number of different alkylating reagents. Using 2-methoxy-6-methylpyridine **221** as the starting material, we needed to take into account the fact that the starting material has an extra methyl group at position 6, therefore the reactivity of the nitrogen atom could be different since this position could be less accessible and because of this, less reactive.



221

Figure 34: 2-Methoxy-6-methylpyridine.

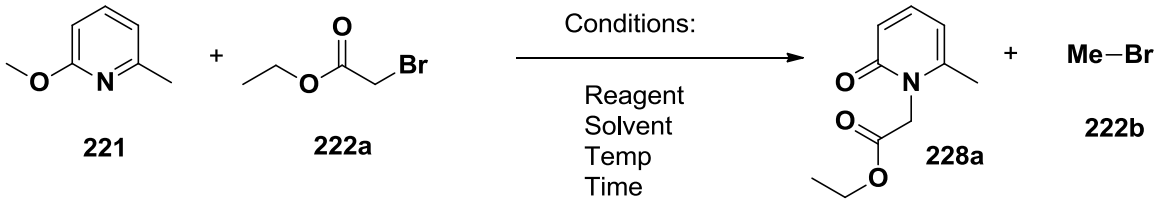
The 2-methoxy-6-methylpyridine **221** bears a methoxy group on position 2, which during the reaction conditions underwent dealkylation to the pyridone derivative, losing a methyl group in the process and forming one molecule of methyl bromide which evaporated during the reaction due to its low boiling point (**Scheme 62**). Bearing all this information in mind, we started screening different solvents, temperatures and reaction times.



Scheme 62: Proposed mechanism of the synthesis of N-substituted-6methyl-2-pyridones.

As a first example, ethyl bromoacetate was chosen as good alkylating reagent, to afford ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a**.

Table 23: Screening for the synthesis of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate.



Entry	2-methoxy-6-methylpyridine	Ethyl-2-bromoacetate	Reagent	Solvent	Temp	Time	Product (%)
1	1	2.5	-	EtOAc	Reflux	48 h	-*
2	1	2.5	$AgNO_3$ (1.5 eq)	Butanone	Reflux	24 h	30%
3	1	3	NaI (3 eq)	Butanone	Reflux	24 h	40%
4	1	3	-	Neat	150 °C	48 h	30%
5	1	1	-	Neat	120 °C	48 h	40%
6	1	1	-	Neat	100-110 °C	48 h	70%
7	1	1	-	Neat	100 °C	72 h	77%

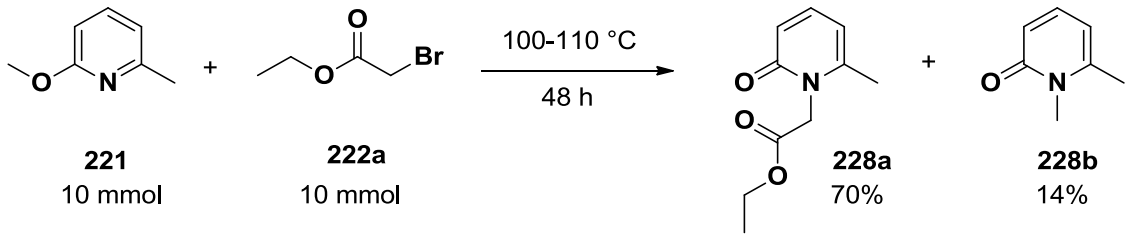
*Analysis of the crude product.

In entry 1, the reaction was performed in ethyl acetate; and gave only recovered starting material. In the following reactions (entries 2 and 3) reagents to speed up the reaction were added, $AgNO_3$ and NaI respectively. $AgNO_3$ was used to make the alkyl halide more electrophilic (entry 2), and the desired pyridone was afforded in 30% yield. In entry 3, NaI was used to activate the halide, by conversion of the bromide into the iodide *in situ* and the reaction worked in 40% yield (**Table 23**).

Using 2-methoxy-6-methylpyridine as the starting material in the synthesis of N-substituted 2-pyridones, the ambident character problem of 2-pyridone anion was avoided. In trying to remove the need for an extra reagent, in entry 4, the reaction was performed solvent free, and only 2-methoxy-6-methylpyridine and ethyl-2-bromoacetate (3 eq.) were used. These conditions were possible due to both reagents being liquids and having high boiling points. The same yield as in entry 2 was obtained, the reaction working in 30% yield, however some by-product was formed. In entry 5, we decreased the temperature from 150 to 120 °C, in order to avoid the by-product formation, and also the quantity of ethyl-2-bromoacetate, resulting in a yield of 40%. Decreasing the temperature further, and increasing the reactions times, improved yields again entries 6 and 7; the product was obtained in 70 and 77% yields respectively.

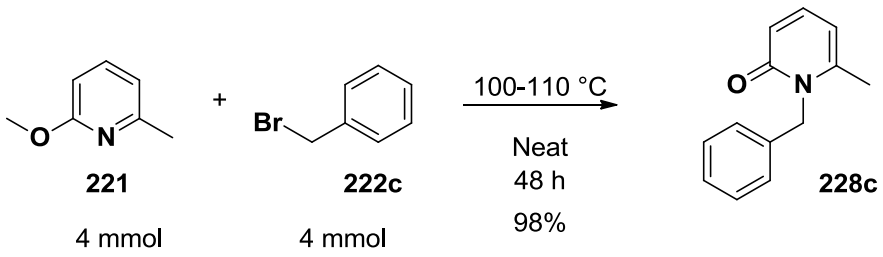
The advantage of the conditions in entry 6 and 7 was that the reaction was performed solvent free, and no extra reagent was needed, so the reaction conditions are more environmental friendly than those in entries 2 and 3, where butanone was used as a solvent and an extra reagent was needed to speed up the reaction.

Having the optimized conditions in hand, the reaction was scaled up to 10 mmol, and the ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** was isolated in 70% yield, and also 1,6-dimethyl 2-pyridine **228b** was formed as a by-product in 14 % yield (**Scheme 63**).



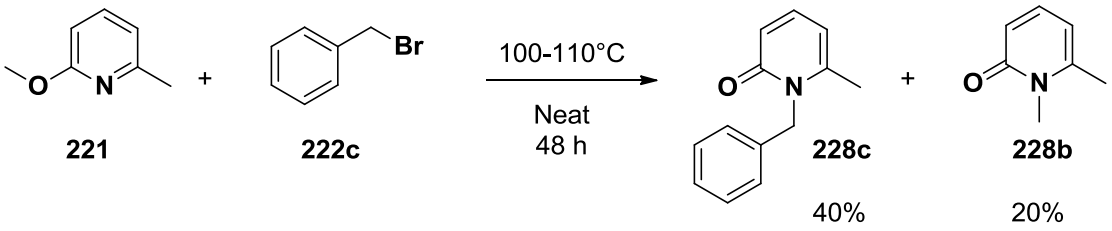
Scheme 63: Scale up the synthesis of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate at 10 mmol scale.

Continuing on the synthesis of other pyridones, benzyl bromide was chosen as the next alkylating reagent, and the reaction was performed on a 4 mmol scale. Pyridone **228c** was obtained in excellent yield 98% (**Scheme 64**).



Scheme 64 : Synthesis of pyridone 228c.

Performing the reaction on a large scale (24 mmol), 1,6-dimethyl 2-pyridone **228b** was also isolated as a by-product in 20% yield (**Scheme 65**).

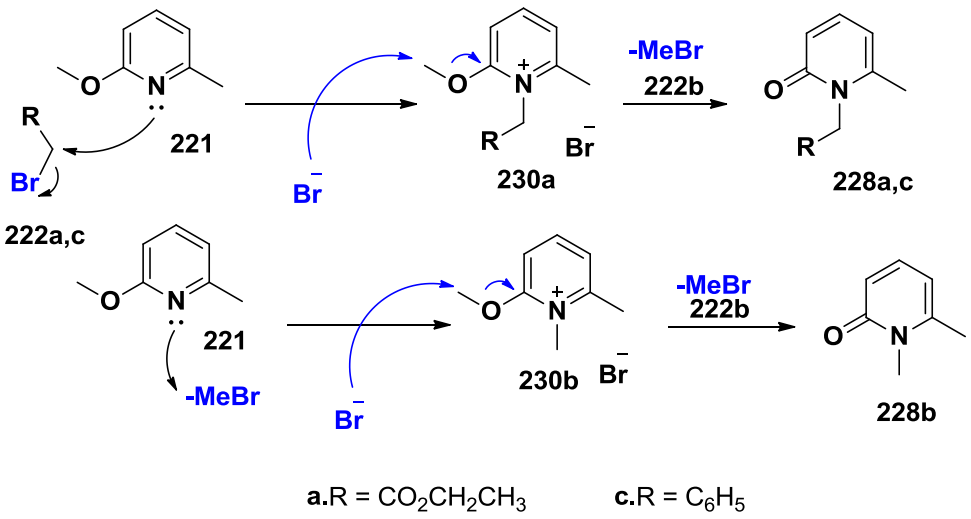


Scheme 65: Synthesis of pyridone 228b and 228c at 24 mmol scale.

The formation of 1,6-dimethyl 2-pyridone **228b** as a by-product was a constant problem. It was an unexpected result initially. Nevertheless, an explanation was given in Ruda and co-workers' work.[45] The aim of their work was to study the way to avoid the formation of these by-products.

In contrast of Ruda's work, we were very interested in 1,6-dimethyl pyridone **228b**, because we could use this potentially versatile scaffold for further applications. We wanted to find a good procedure for the synthesis of 1,6-dimethyl-2-pyridone **228b**.

In the following scheme a proposed mechanism of the formation of 1,6-dimethylpyridine is given.

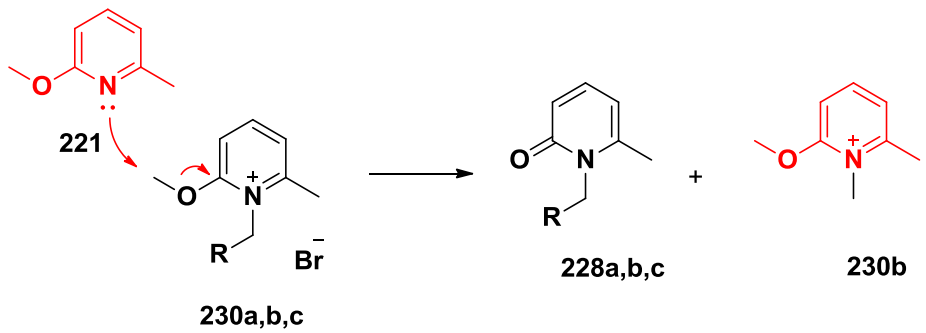


a.R = $CO_2CH_2CH_3$ **c.**R = C_6H_5

Scheme 66: A proposed mechanism of the synthesis of 1,6-dimethylpyridin-2(1H)-one.

In the synthesis of N-alkylated pyridones, an alkoxypyridine (2-methoxy-6-methylpyridine) **221** is the starting material. The nitrogen of the alkoxypyridine **221** attacks the halide and produces a pyridinium salt **230a**. Then the bromide anion subsequently displaces the methyl group to afford the N-alkyl pyridone **228a** or **228c,** depending on the alkylating reagent **222a** or **222c**, and generating one molecule of methyl bromide **222b**. The methyl bromide formed *in situ*, it is a potential alkylating reagent and can also N-alkylate the remaining unreacted alkoxypyridine **221** leading to a mixture of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** and 1,6-dimethyl pyridone **228b** or benzyl pyridine **228c** and 1,6-dimethyl pyridone **228b** correspondingly (**Scheme 66**).

Also, it could be possible that the nitrogen of the alkoxypyridine **221** displaces the methyl group to afford the N-alkyl pyridone **228a**, **228b** or **228c**, and generated another pyridinium salt **230b** (**Scheme 67**).



a.R = $CO_2CH_2CH_3$, **b.** R = H, **c.**R = C_6H_5

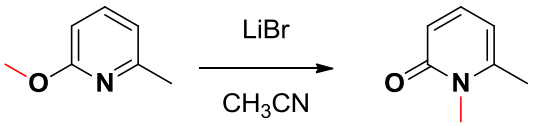
Scheme 67: Proposed mechanism of the synthesis of 1,6-dimethylpyridin-2(1H)-one, being the alkoxypyridine (221) which displace the methyl group.

To continue the study of the synthesis of 1,6-dimethyl 2-pyridone we tried to synthesize the 1,6-dimethyll pyridone via three different methods:

Following the work of Tasker, who developed an efficient and inexpensive LiI-promoted O-to N-alkyl migration of 2-benzyloxy-, 2-allyloxy-, and 2-propargyloxypyridines,[79] we used similar conditions.

We tried to promote O- to N-methyl migration of 2-methoxy-6-methylpyridines using lithium bromide to cleave the C-O bond of the alkoxypyridine follow by methyl migration (**Table 24**).[79] In these reaction conditions (entries 1 and 2) acetonitrile was used as a solvent in order to dissolve de LiBr and to obtain a homogeneous mixture. In entry 1, the reaction mixture was heating under reflux but reaction was not successful, for this reason in entry 2 the reaction was heating in the microwave at 150 °C. However, the methyl migration did not occur. In conclusion, we thought that it could be necessary to alkylate the pyridine before the bromide ion was able to cleave the C-O bond n (**Table 24**).

Table 24: Synthesis of 1,6-dimethylpyridine-one via LiI-promoted O-to N-alkyl migration.

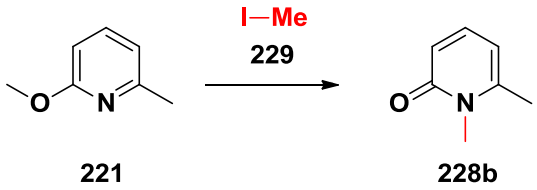


221 **228b**

Entry	Pyridine	LiBr (mmol)	Heating	Temp	Time	221:228b
1	1eq	1eq	Conventional	Reflux	20 hours.	1:0
2	1eq	1eq	MW	150 °C	33 min	1:0

We tried to alkylate the pyridone using methyl iodide in a catalytic amount, supposing the pyridine could be alkylated and afterwards the iodide anion might cleave the C-O bond. Therefore, the reaction could be initiated, and may have delivered the 1,6-dimethyl pyridone. We designed the following two reaction conditions:

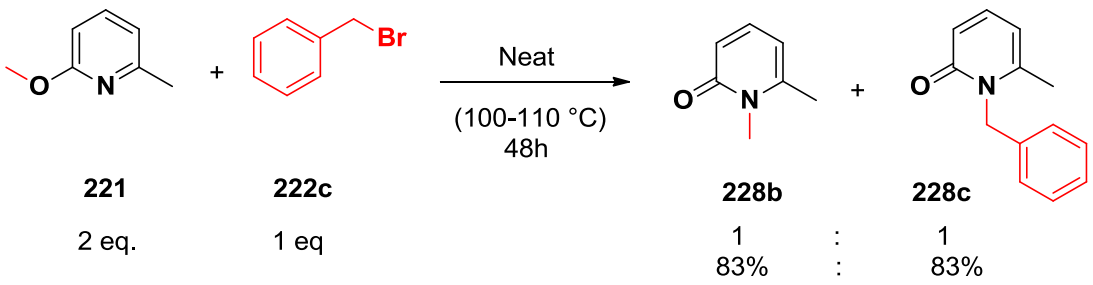
Table 25: Synthesis of 1,6-dimethylpyridine-one via methyl alkylation.



Entry	MeI	Solvent	Temp	Time	221:228b
1	10%	neat	100 °C	24h	1:0
2	10%	neat	30 °C	24h	1:0

The first reaction was performed at 100 °C, solvent free, 24 hours, however the reaction did not work and all the starting material was recovered. One explanation could be the low boiling point of methyl iodide (42-43 °C). The MeI **229** could boil off at this temperature before the lone pair on the pyridine nitrogen was able to attack the MeI **229**. As a result of this, the second reaction was performed at 30 °C, however this reaction also did not work. The information obtained in the last reaction demonstrated that the reaction could not be effected with a catalytic amount of alkyl halide at ambient temperature. The alkylation of 2-methoxy-6-methylpyridine with methyl iodide had to be conducted at 100 °C.

As shown in the following **Scheme 68**, the inconvenience of the low boiling point of the MeBr was overcome by using benzyl bromide.



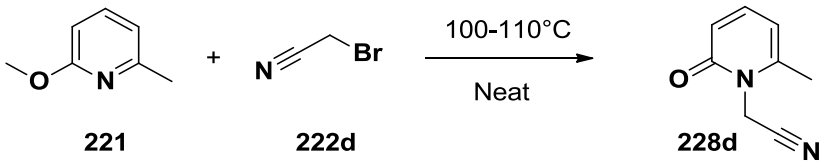
Scheme 68: Synthesis of 1,6-dimethyl-2-pyridone in 83% yield.

1,6-Dimethylpyridin-2(1H)-one **228b** proved to be more difficult to synthesize than 1-benzyl-6-methylpyridin-2(1H)-one **228c** via the N-alkylation reaction under standard conditions (2-methoxy-6-methylpyridine (1 eq.), alkylating reagent (1 eq.), 100-110 °C, 48 h). However, we were able to synthesize 1,6-dimethylpyridin-2(1H)-one **228b** in a good yield. On increasing the quantity of (2-methoxy-6-methylpyridine to 2 eq., and using only 1 eq. of benzyl bromide, at 100-110 °C, over 48 h)

1,6-dimethylpyridin-2(1H)-one **228b** and 1-benzyl-6-methylpyridin-2(1H)-one **228c** were obtained in a (1:1) mixture and in excellent yields 83 % and 83 % respectively, which could be separated fairly easily by flash chromatography.

After these excellent results, we continued with the synthesis of a range of pyridones. The following reaction was carried out under the different conditions (**Table 26**):

Table 26: Synthesis of 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetonitrile.



221 222d 228d

Entry	temperature	time	Product (%)
1	100-110 °C	48 h	48 %
2	100-110 °C (2 h) and at rt (48 h)	50 h	80 %

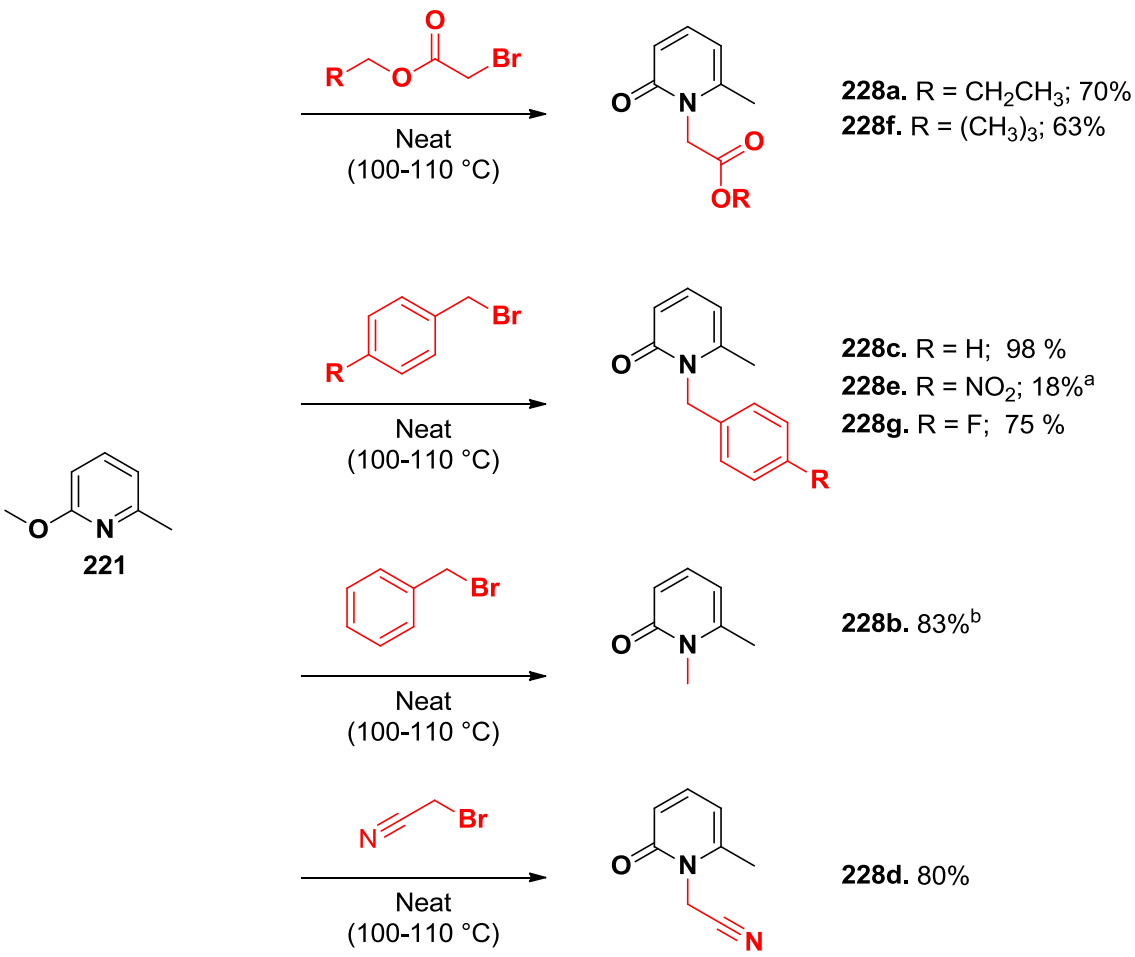
The synthesis of pyridone **228d** was performed under standard conditions (neat reaction, 100-110 °C, 48 h) in entry 1. However in entry 2, after 2 h the reaction mixture became black. Although the reactions normally darkened to a brown colour, this indicated decomposition, so we decided to stop the heating and the reaction mixture was stirred for 48 h at room temperature. The yield increased to 80%.

For the synthesis of 6-methyl-1-(4-nitrobenzyl)pyridin-2(1H)-one **228e**; 4-nitrobenzyl bromide was used as the alkylating agent. The reaction was performed in toluene as a solvent because 4-nitrobenzyl bromide is a solid reagent, and so the neat conditions could not be used. The reaction gave the product in a very low yield, only 18%.

For the remaining pyridones, the standard conditions were 2-methoxy-6-methylpyridine (1 eq.), alkylating reagent (1 eq.), 100-110 °C, 48 h. The two following pyridones were obtained: tert-butyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228f** in 63% yield, and 1-(4-fluorobenzyl)-6-methylpyridin-2(1H)-one **228g** in 75% yield.

To conclude, under our standard conditions the alkylating reagent did not need to be activated with NaI. Non-activated halides could be used, and the reaction could be performed in a solvent free environment, with only one exception, when 4-nitrobenzyl bromide was used as an alkylating agent. Here the reaction was performed in toluene as a solvent.

In the following scheme there is a summary of the pyridones synthesized using our new conditions.



[a]In toluene. [b]2 eq of **221**

Scheme 69: Library of N-alkylated-2-pyridones.

The synthesis of 2-pyridones derivatives (**Scheme 69**) via direct alkylation of 2-methoxy-6-methylpyridine **221** represents a new alternative for the synthesis of 2-pyridone derivatives. The reaction could be performed in the absence of solvent and no catalyst was needed, and the reaction could be effected in good to excellent yields. Furthermore, using 2-methoxy-6-methylpyridine **221** as the starting material, the competition between N and O-alkylation was avoided. As a drawback of this pathway, MeBr **222b** was formed as by-product, one part of MeBr boiled off during the reaction time and did not react with the unreacted pyridine. However, some molecules of MeBr could react with the unreacted pyridine and when the reaction was scale up to 10 mmol, the 1,6-dimethyl-2-pyridone **228b** appeared as a by-product. On other hand, this by-product could be separated easily by flash chromatography in all the reaction mixtures.

3.1.2- Study of metallation of N-benzyl-6-methyl-2-pyridones.

With the 2-pyridone derivatives **228a-g** in hand, our study of the synthesis of new N-alkyl-6-(monosubstituted-methyl)-2-pyridinones focused initially on pyridone **228b** and **228c** as starting materials.

Our study started with the investigation of the selective methyl lithiation (position 7) of 1-benzyl-6-methyl-2-pyridone **228c** (**Figure 35**).

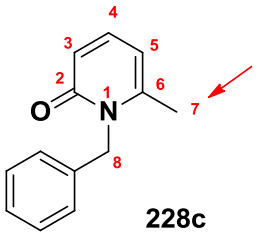
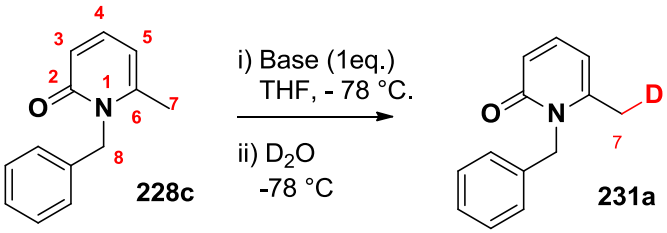


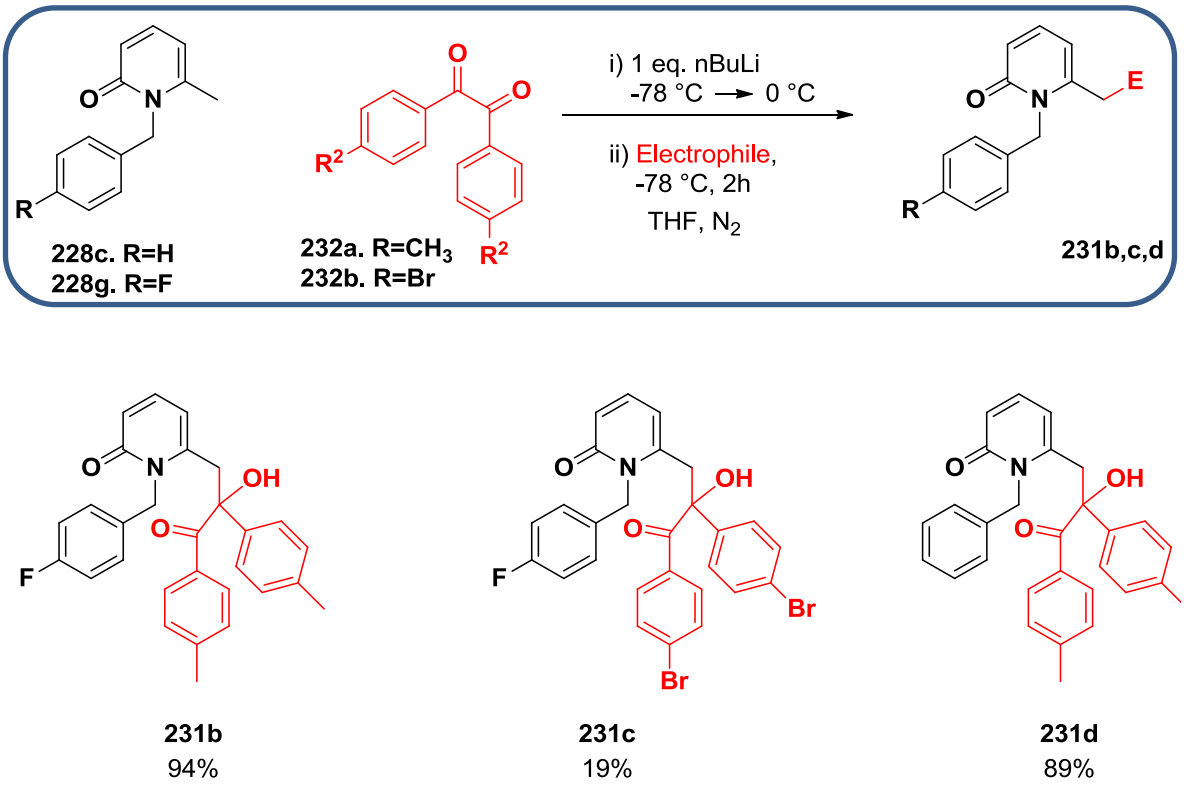
Figure 35: 1-benzyl-6-methyl-2-pyridone structure.

A study of reactivity was undertaken and 1-benzyl-6-methyl-2-pyridone **228c** was treated with n-butyllithium (n-BuLi) in tetrahydrofuran (THF) at -78 °C , the reaction mixture being warmed up to 0°C, and cooled down to -78°C again. This process resulted in an intense blue solution shown to contain the 6-methyl-lithiated species by quenching with D_2O at -78 °C. This led to recovery of only the mono-deuterated pyridone **231a** (>98%) at C-7 position. The location of the label was easily established by ^{1}H NMR and ^{13}C NMR spectroscopic analysis.



Scheme 70 : Deuterium study.

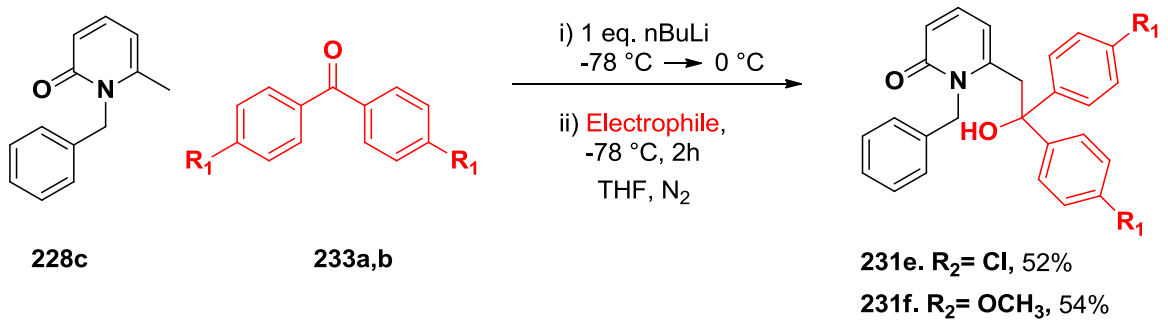
The methyl lithiated 1-benzyl-6-methylpyridin-2(1H)-one **228c** was then reacted with a variety of electrophiles, starting with diketones under the following standard conditions:



Scheme 71: Using diketone as electrophiles.

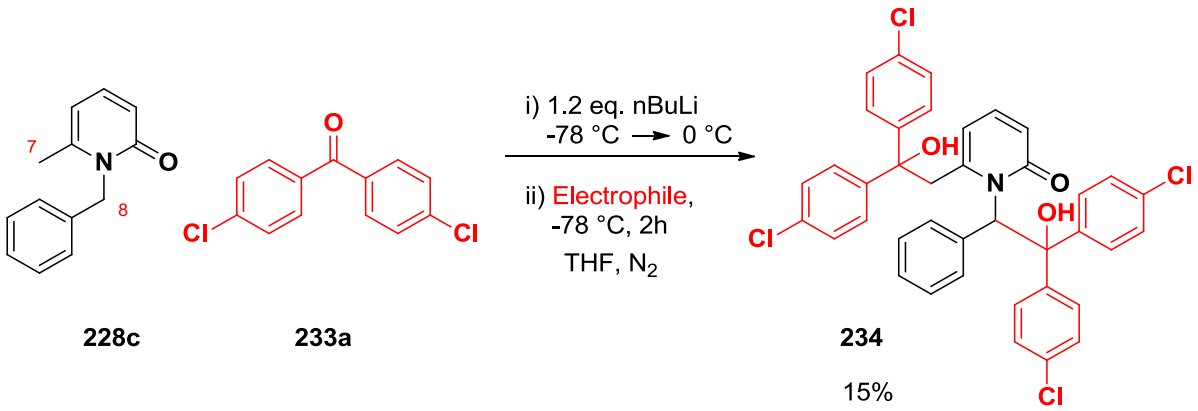
Scheme 71 shows the optimized conditions for several diketones, which are highly reactive electrophiles. Only, pyridone **231c** was obtained in a poor yield (19 %), because the electrophile 4,4-dibromobenzil **232b** was insoluble in THF.

The product of methyl lithiation of 1-benzyl-6-methylpyridin-2(1H)-one **228c,** was also reacted with a range of mono-carbonyl electrophiles. The reactions worked in good yields with again, alkylation occurring on the methyl substituent, obtaining compound **231e** and **231f** (**Scheme 72**).



Scheme 72: Reactivity of 1-benzyl-6-methyl-2-pyridones with ketones.

However, careful control of methyl lithiation of 1-benzyl-6-methylpyridin-2(1H)-one was needed in this part of the study. The stoichiometry of the base to the pyridone was very important, since an excess of base yielded an undesired product, the doubly alkylated pyridone **234** as shown in **Scheme 73**.



228c **233a** **234**

15%

Scheme 73 : Synthesis of the dialkylated product 234.

Using 1.2 eq. of base (an excess of base), the reaction generated the dialkylated product **234** in 15% yield along with a complex mixture of unidentifiable compounds. So, we needed to answer the following questions: did we have a double alkylation because the electrophile was less reactive than the diketone, and was there a competition between position 7 and 8, or did we have a double alkylation due to the excess of base?

In order to answer these questions, we set up a reaction where the amount of base and the electrophile was lower than that of the pyridone, so no double alkylation would be obtained. Only the mono-alkylated pyridone **231e** (alkylation at methyl position) and the unreacted pyridone **228c** were obtained. The product **231e** and the starting material ran very close on a TLC plate, so they were very difficult to separate, so we reported the mixture of compounds, and the ratio was 1:1. In conclusion, the more acidic protons are those in the methyl group (position 7).

Trying to confirm that an excess of base (2 eq.) was the source of the dialkylation product **234a,** a reaction with 2 eq. of base was performed. As soon as we added more than 1 eq. of base, position 8 was also deprotonated and the electrophile was added to both positions.

The comparison of the NMR spectra of products **231e**, **234** and the starting material are shown in **Figure 36**:

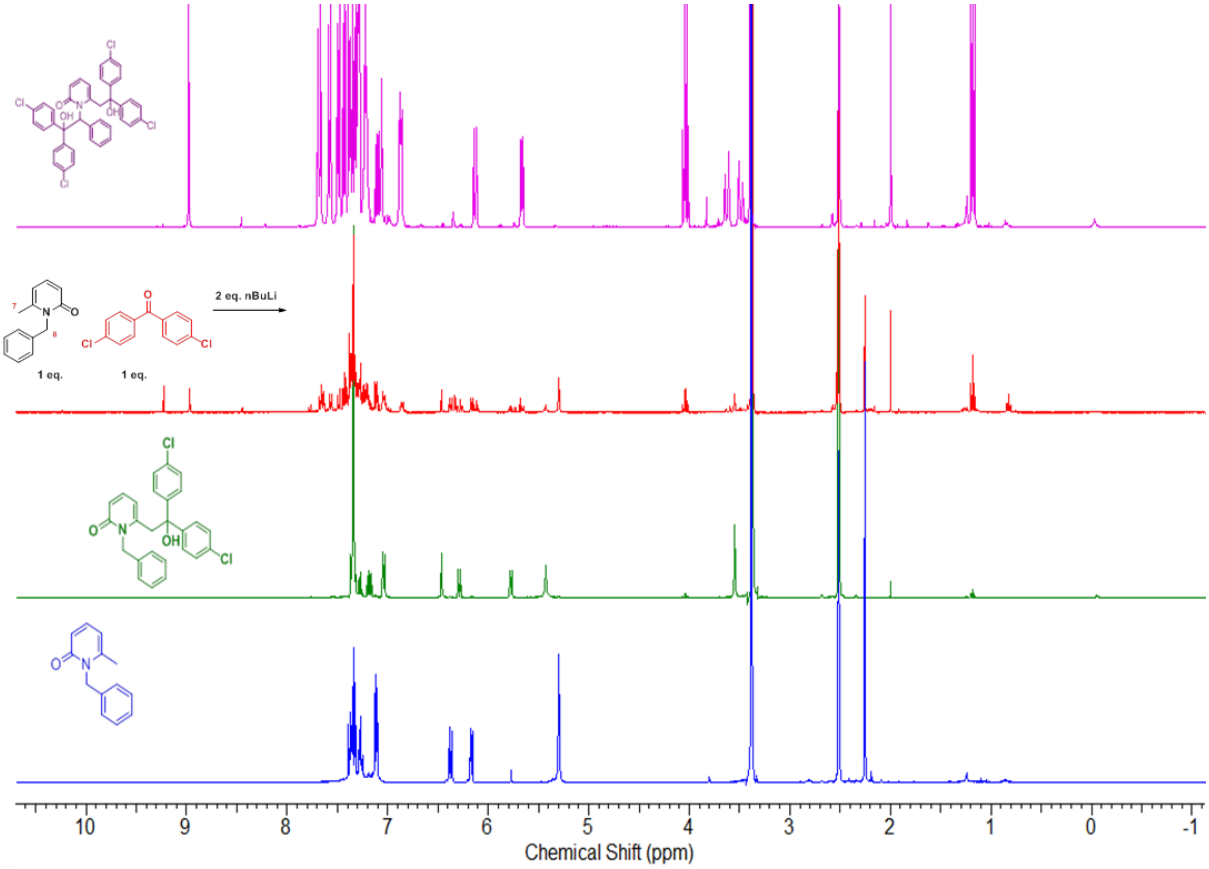


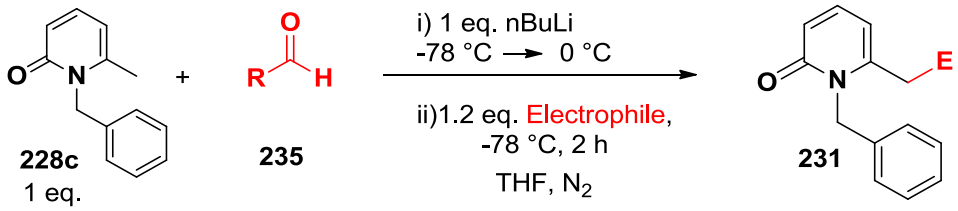
Figure 36: The comparison of NMR spectrum from reaction using 2 eq. of base with starting material and mono alkylate product 231e and the dialkylated product 234.

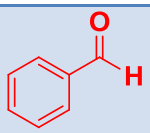
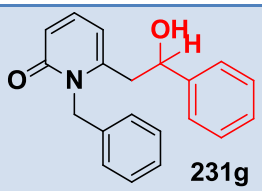
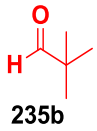
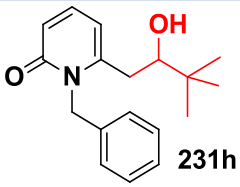
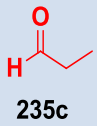
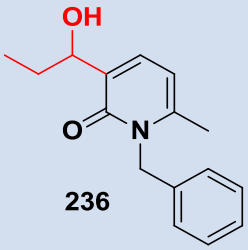
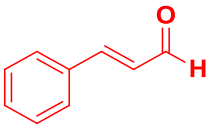
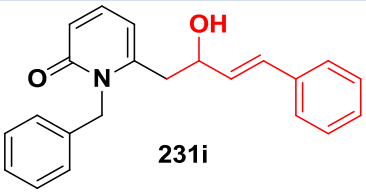
In the NMR spectra shown above, when 2 eq. of n-BuLi were added to 1eq. of pyridone the reaction yielded in a complex mixture. Looking at the spectra, it is possible to distinguish the signals of a mixture of 3 different compounds (**231e**, **234** and **unknown compound**) and unreacted pyridone.

The reactions showed that careful control over the amount of base was needed, since an excess of base led to the unwanted dialkylated product. The standard conditions for further reactions with ketones were: 1 eq. of pyridone, 1 eq. of n-BuLi and 1.2 eq. of electrophile.

The next type of carbonyl compounds investigated were aldehydes, the first being benzaldehyde. The reaction was performed under the standard conditions developed for the diketones and ketones, giving compound **231g** in a good 85% yield. (Entry 1, **Table 27**).

Table 27:Methyl lithiation of 1-benzyl-6-methyl-2-pyridone.



Entry	Electrophile	Temperature	Compound	Yield
1	 235a	-78 °C	 231g	85%
2	 235b	-78 °C	 231h	80%
3	 235c	-78 °C	 236	26%
4	 235d	-78 °C	 231i	33%

In entry 2, pivaldehyde was next used as an electrophile, and the reaction again worked in excellent yield, the new pyridone **231h** was isolated pure in 80 % yield.

On the contrary, an interesting result was found, when propianaldehyde, as shown in entry 3, was used as the electrophile. This electrophile was different from the previous ones, since it bears an acidic proton in the α-position to the carbonyl. The metalated pyridone reacted in a different way. The pyridone anion has several resonance structures as shown in **Figure 37**. The most reactive position is 6-methyl position (position 7, Figure 37). However, there is the possibility of alkylating the 3- or 5- positions of the ring, or to obtain O-alkylation.

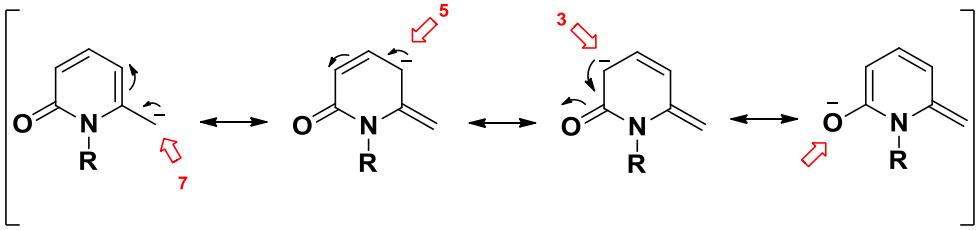
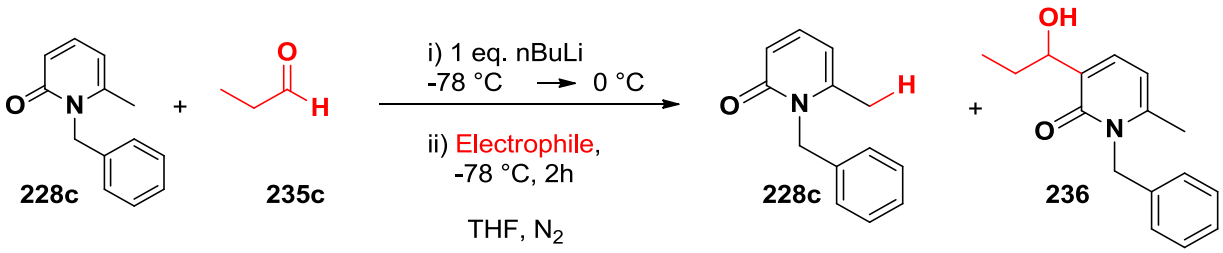


Figure 37: Resonance structures of the anion of N-alkylated-6-methyl 2-pyridones.

Using propionaldehyde as the electrophile, the pyridone anion appeared to behave mainly as a base and the major compound recovered was the starting 1-benzyl-6-methyl-2-pyridone, presumably formed by deprotonation of the α-position of the aldehyde. Some of the anion did react as a nucleophile however, and 26% of the pyridone **236** with alkylation at position **3** was obtained. It is not clear why this aldehyde behaved differently and gave ring alkylation. Further investigation with other aliphatic aldehydes would be desirable.



Scheme 74: Alkylation at position 3 instead of position 7 of 1-benzyl-6-methylpyridin-2(1H)-one.

The compound structure was confirmed by an nOe study. The spectra are shown in the following figures.

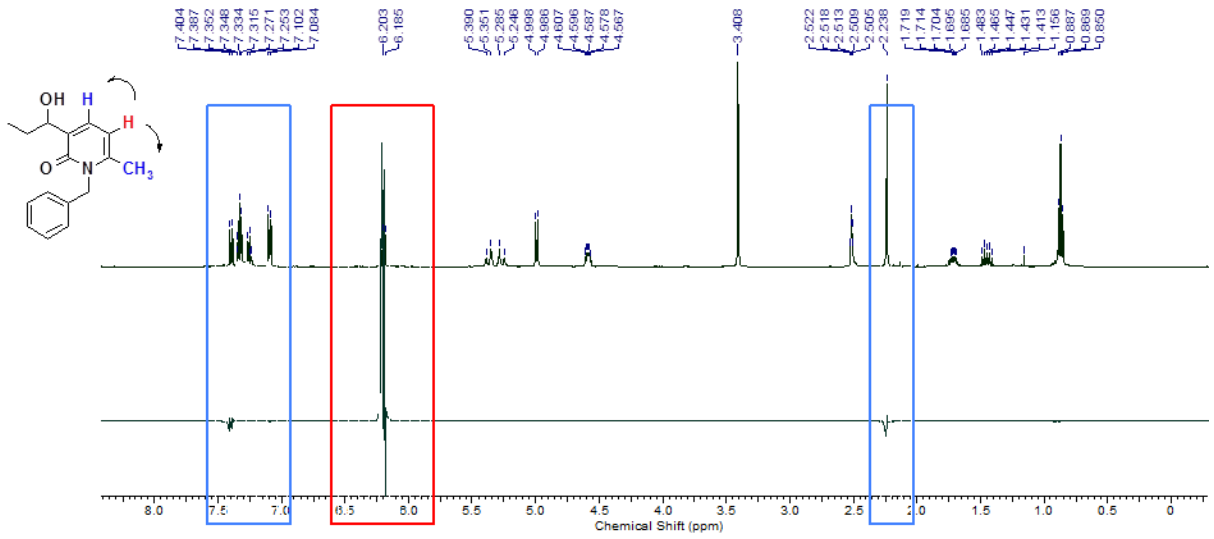


Figure 38: Irradiation at 6.23 ppm (CH) of pyridone 236.

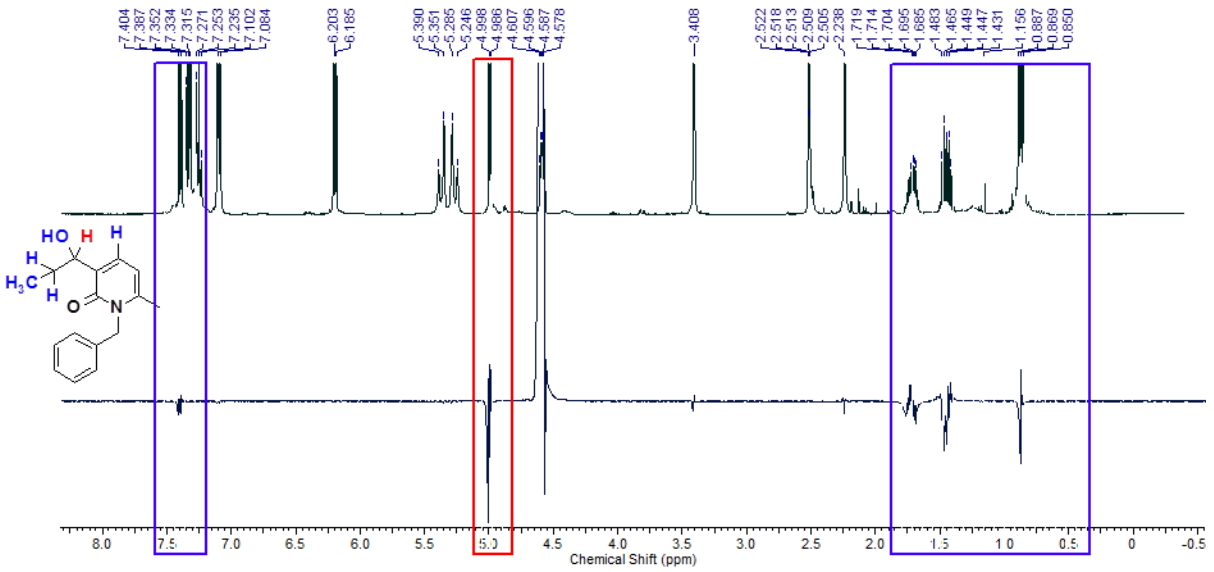


Figure 39: Irradiation at 4.99 ppm (CH) of pyridone 236.

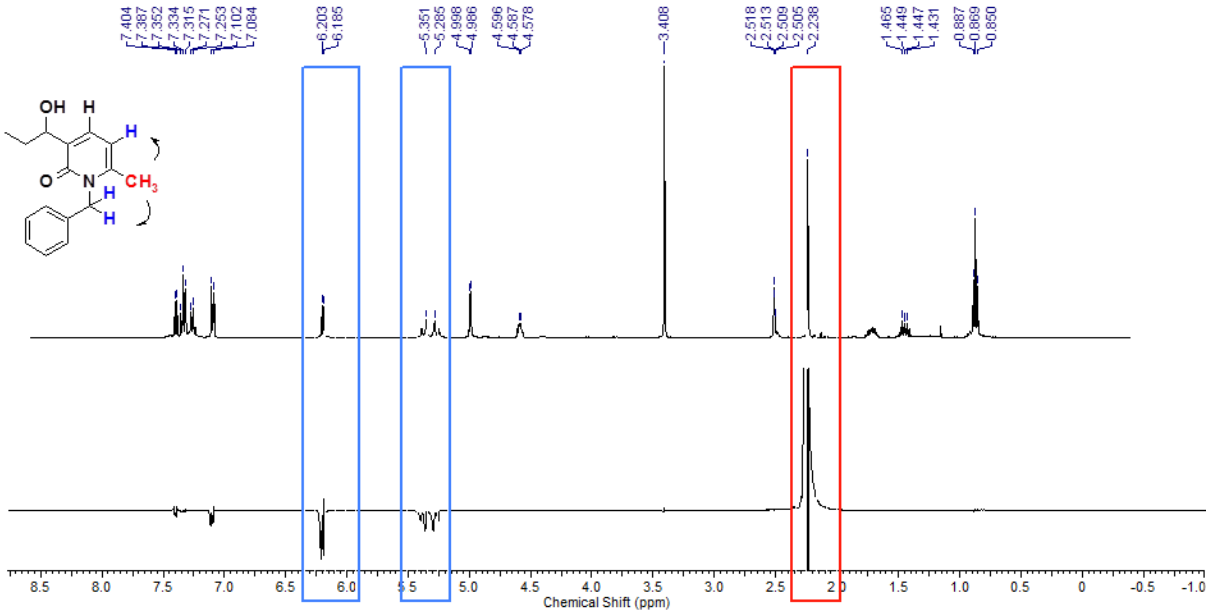


Figure 40: Irradiation at 2.38 ppm (CH_3) of pyridone 236.

Using the nOe study we could confirm that the alkylation was in position 3. The reaction was set up again, under the same conditions, to confirm the product obtained by alkylation in position 3 was the predictable product. The reaction gave as the same outcome; the alkylation occurred at position 3 instead of position 7.

In the following spectra, **Figure 41** shows the comparison between the starting material **228c** spectrum, the pyridone **236** spectrum and the reaction mixture spectrum. Also in the **Figure 42** is shown the expansion of **Figure 41** which shows that the reaction was reproducible:

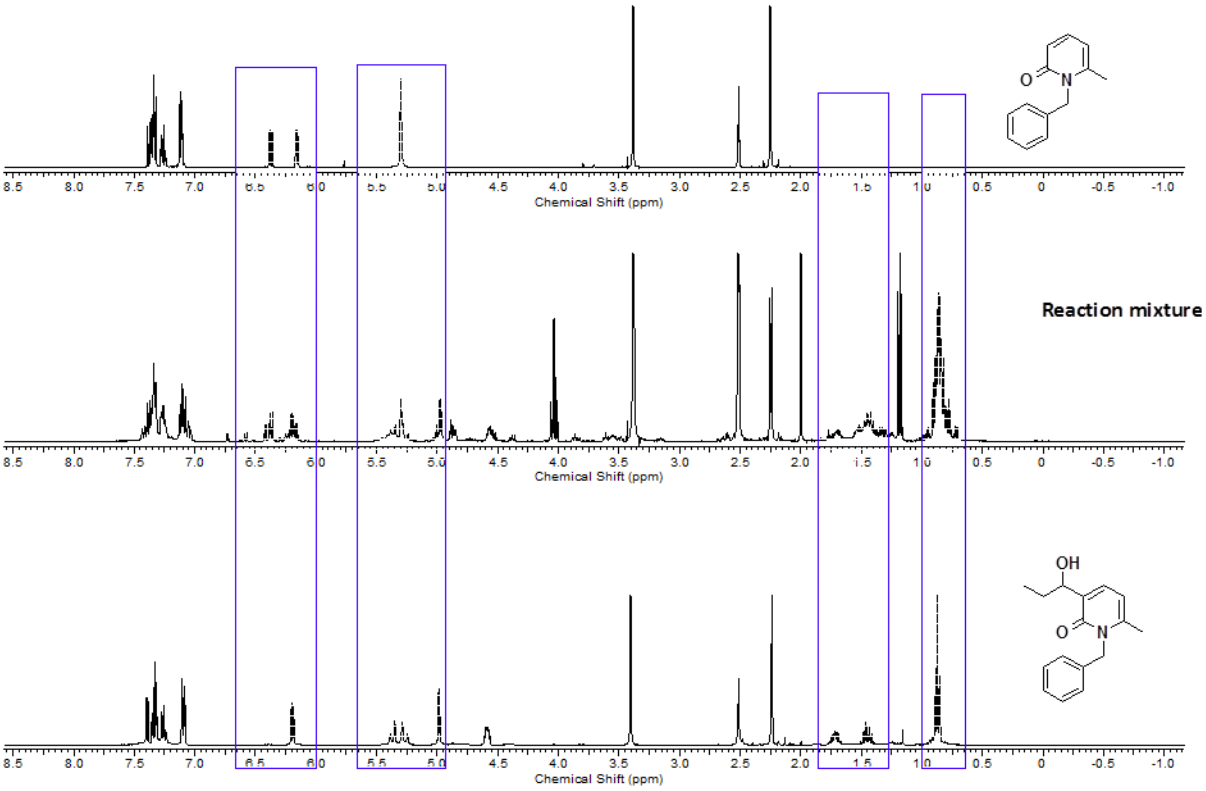


Figure 41: Confirmation of pyridone 236 and reaction mixture.

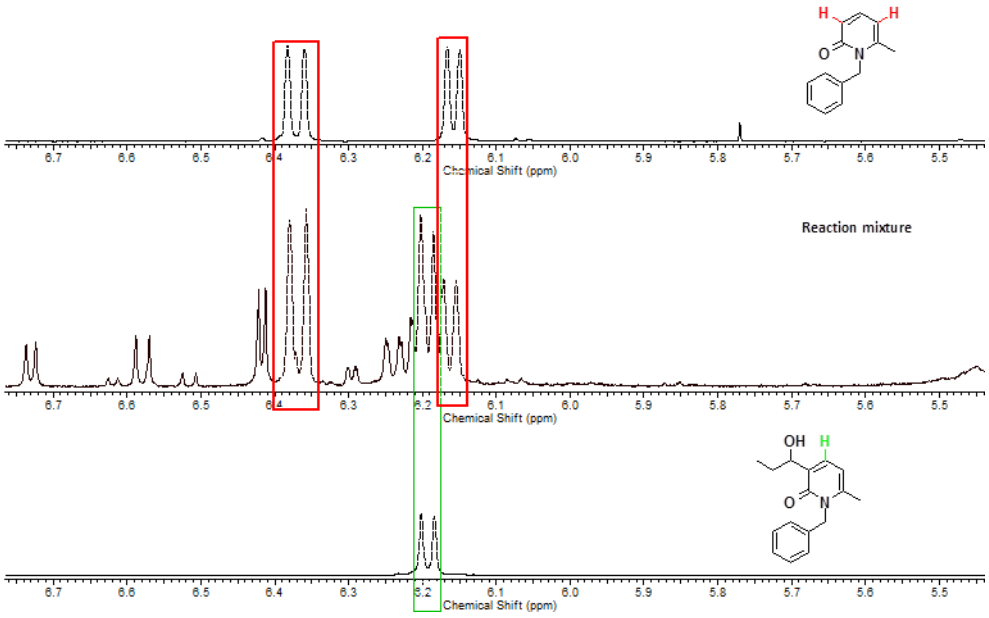


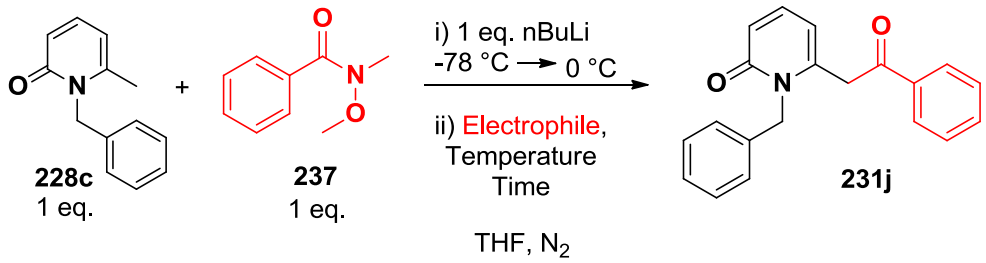
Figure 42: Expansion of Figure 41 .

In entry 4, **Table 27**, we also investigated the reaction with a conjugated carbonyl compound, (α,β unsaturated carbonyl). The standard conditions were used with cinnamaldehyde as an electrophile.

There were two possible additions, either 1,2 or 1,4 nucleophilic addition to cinnammaldehyde. The 1,2-additon product was isolated in 33% yield. Also, the reaction mixture showed new peak, that could have been the 1,4-addition product, however, only the 1,2-addition product **231i** could be isolated and fully characterised (**Table 27**, entry 4).

In order to finish the study of the carbonyl electrophile set, a Weinreb amide was chosen as an electrophile as this would be a useful route to keto substituted pyridones.

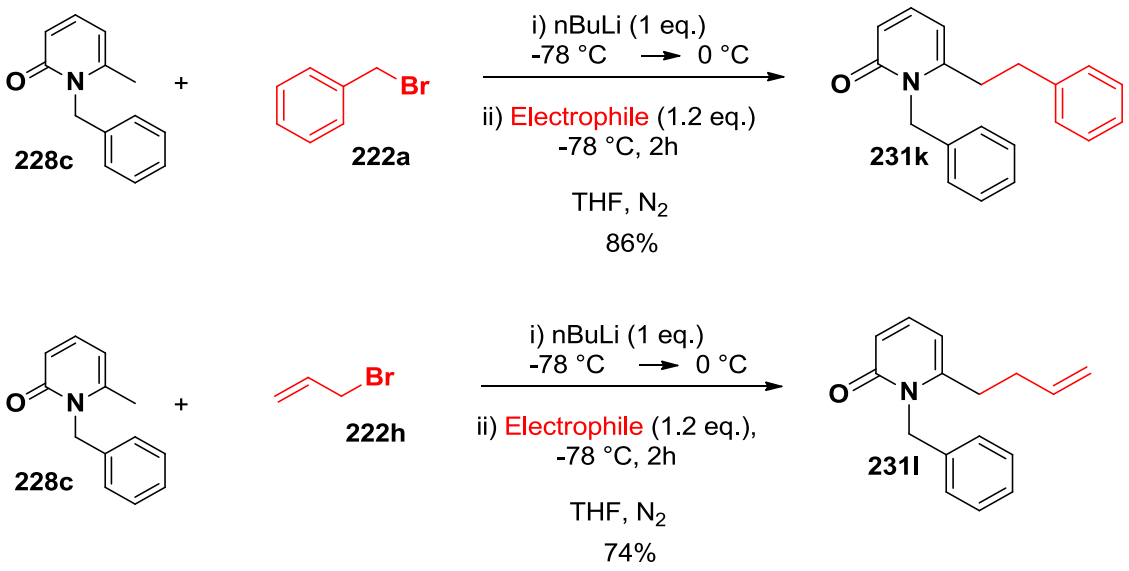
Table 28: Attempted synthesize of pyridone 231j.



Entry	Time	Temperature	Conclusion
1	2 h	-78 °C	Starting material
2	3 h 30 min	-78 °C	Starting material and new product
3	2h	0 °C	Starting material and new product

In entry 1 (**Table 28**), the reaction was performed under the previous standard conditions. After 2 hours at -78 °C, the reaction was quenched and the crude product was isolated and purified, obtaining almost all of the starting material back. After this surprising result, the reaction was set up again (entry 2). The reaction was monitored by TLC, and after 3h and 30 min, there were only signs of starting material, so the temperature was increased to 0 °C, and the reaction stirred at 0°C over 2 h and 30 min before the work-up. In entry 3 the reaction was performed at 0°C over 2 h. The same result than in entry 2 was obtained. The crude product was purified by flash chromatography, however the pyridone starting material and the new pyridone had similar polarity and it was not possible to isolate the new product.

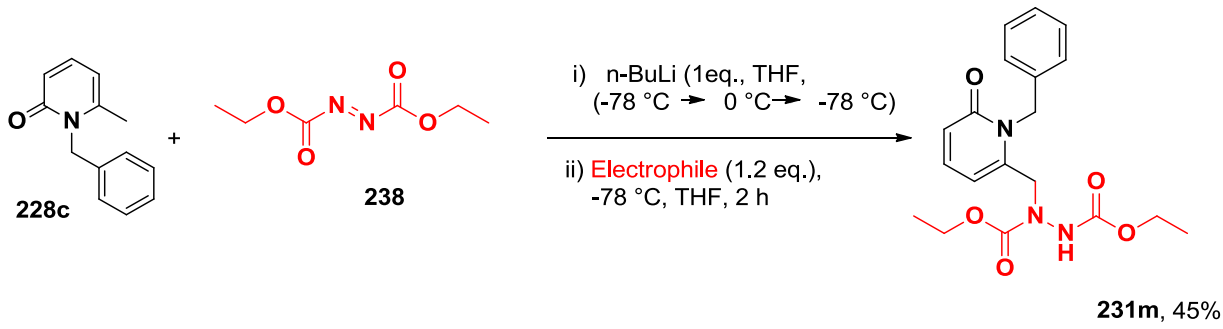
Continuing the study of methyl C6-lithiated N-benzyl-2-pyridones, two different halides were chosen as electrophiles, in order to show that our standard conditions could also be used in alkylation reactions (**Scheme 75**).



Scheme 75: Reaction with halides.

As we can see in **Scheme 75**, the reactions worked in excellent yields.

In order to expand the study, we wanted to show that we could add a heteroatom to the pyridone scaffold at the methyl position, so the following reaction with the azo compound diethyl azodicarboxylate (DEAD) was designed (**Scheme 76**). The reaction worked in 45% yield.



Scheme 76: Reaction of methyl lithiated N-benzyl-2-pyridone with DEAD reagent.

In summary, the product of C6-methyl lithiation of 1-benzyl-6-methylpyridin-2(1H)-one **296c**, reacts with a variety of carbonyl electrophiles such as: diketones, ketones and aldehydes, and the reactions worked in good to excellent yields. Furthermore, other groups of electrophiles such as the halides, benzyl bromide, allyl bromide, or an aza-electrophile such as diethyl azodicarboxylate are also compatible with this methodology.

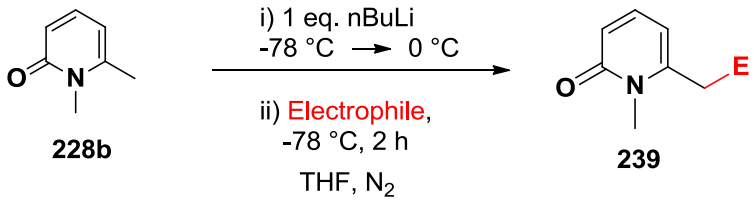
3.1.3- Study of metallation of 1,6-dimethyl-2-pyridones.

After the lithiation study of N-benzyl-2-pyridones with a wide range of electrophiles, we decided to expand the chemistry, moving onto another N-substituted-2-pyridone. The aim of this part was to try the optimised conditions for the new pyridone 1,6-dimethylpyridone **228b**. In order to prove that the reaction works with a wide range of electrophiles, we chose one representative electrophile for each group, diketone, aldehyde, halide, and an aza-electrophile, all of which worked very well in the previous study.

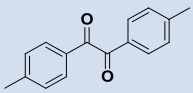
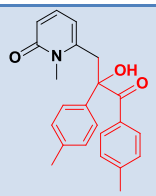
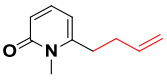
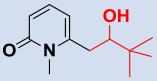
We conducted the following reactions under the newly found optimized conditions. Our first electrophile was the diketone **232a**, and the results are shown in **Table 29**. In entry 1, the reaction worked in 38% yield, but the NMR spectrum of the crude product showed several by-products, and the yield was not very good. Using allyl bromide as an electrophile (entry 2), the reaction did not work as we expected. The product **239b** was formed, but the NMR spectrum showed some by-products which were not identified. For this reason, in *entry 3* the same reaction was set up, but the reaction was stopped after one hour to try to discover when the by-products were formed. After only one hour, the reaction was quenched, but the result was the same as that in entry 2. The nucleophilic addition to the carbonyl group was achieved, however there were other by-products, and it was impossible to isolate or identify them.

The last experiment under the standard conditions employed pivaldehyde as an electrophile, since it had been an excellent reagent in the reaction with lithiated N-benzyl-6-methyl-2-pyridone **228c**. The excess of pivaldehyde was removed under vacuum, and the NMR spectrum of the crude product showed a very clean product, so no further purification was needed. The same result was expected when the reaction was performed with 1,6-dimethyl-2-pyridone. However, the reaction worked in only 37% yield, (entry 4) and 1H NMR showed that by products had formed. However the by-products were not isolated. In entry 5, the same reaction conditions as in entry 4 were used, and the reaction was stirred for only one hour, trying to avoid the formation of by-products. The same results occurred and, the NMR spectra showed some by-products.

Table 29: Selective mono-lithiation at the 6-methyl position of 1,6-dimethylpyridin-2(1H)-one.

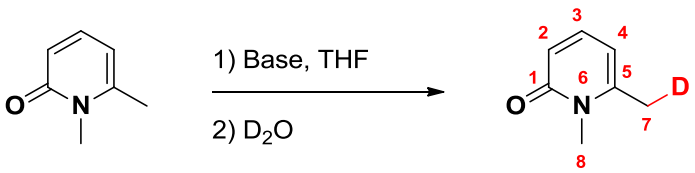


228b 239

Entry	Electrophile	Temperature/time	Compound	Yield/comments
1	 232a	78 °C → +5 °C → -78 °C 2h	 239a	38%
2	 222h	-78 °C → +5 °C →-78 °C 1h	 239b	Very complex spectrum
3	 235b	78 °C → +5 °C →-78 °C 2h	 239c	37%

Because of the low yield obtained and the formation of by-products in the lithiation of 1,6 dimethyl-2-pyridone **228b** using n-BuLi as a base, the following deuteration study using two different bases was carried out to gain an understanding of the deprotonation behaviour of **228b**.

Table 30: Deuteration study of 1,6-dimethylpyridin-2(1H)-one.



228b 239d

Entry	Base (eq)	temperature	Compound	Yield
1	n-BuLi (1 eq.)	-78 °C	Very messy spectrum	-
2	KHMDS (1 eq.)	-78 °C	**239d**	55%
3	KHMDS (2.5 eq.)	78 °C → +5 °C →-78 °C	**239d**	45%

Treatment of 1,6-dimethyl-2-pyridone **228b** with 1 eq. of n-BuLi in THF at -78 °C, (entry 1, **Table 30**) resulted in a light orange solution. The mixture was stirred over 10 min, and then quenched with D_2O at -78 °C which produced a mixture of starting material and by-products. Analysis of the NMR spectrum showed that the use of n-BuLi generated a very complex product mixture (**Figure 43**, entry 1).

For the reaction described in **Table 30**, entries 2 and 3, KHMDS was then studied as a base, due to its non-nucleophilic properties. **Figure 43**, entry 2 is shown the ^{1}H NMR spectrum of the metallation of 1,6-dimethyl pyridone **228b** using the conditions of entry 2, **Table 30**, and in entry 3 is shown the ^{1}H NMR spectrum of the metallation of 1,6-dimethyl pyridone using the conditions of entry 3, **Table 30**.

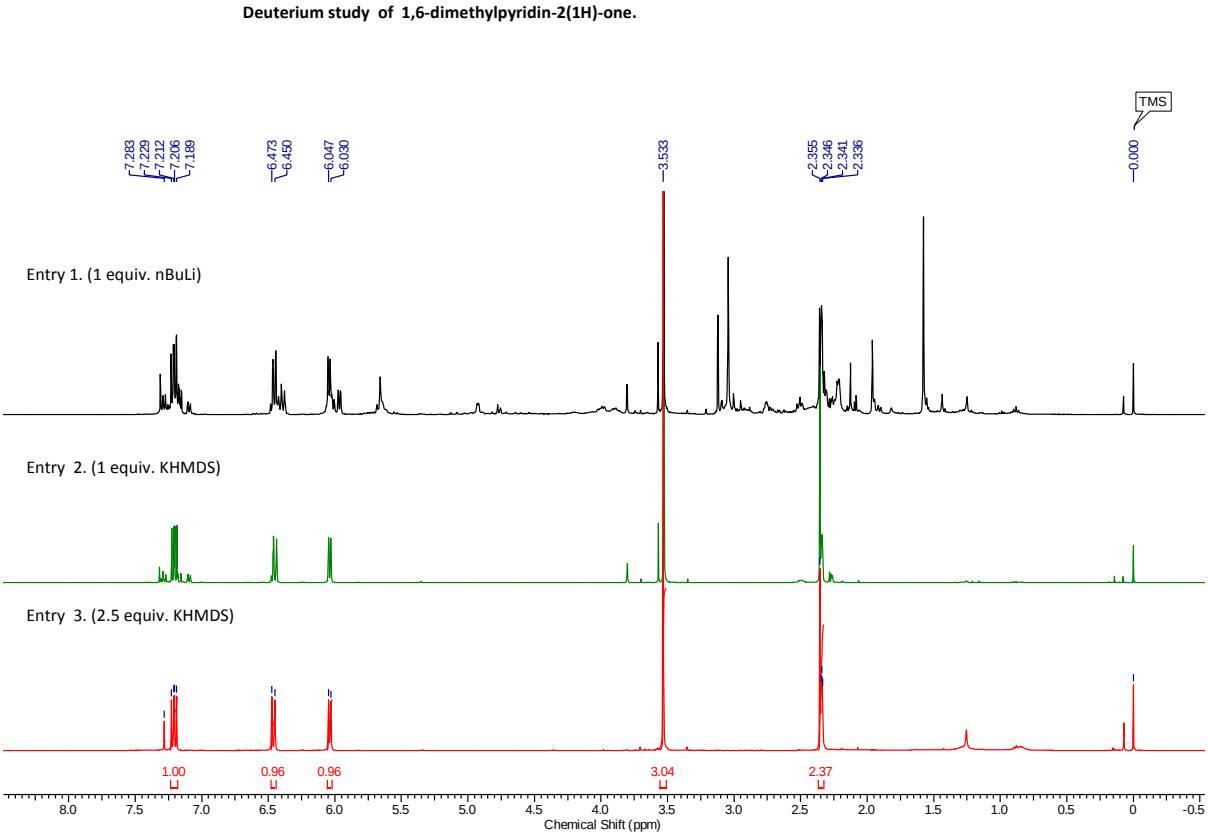


Figure 43: Spectra of entries 1 to 3.

As can be seen in **Figure 43** the nBuLi generated new unknown peaks at 6.4 ppm and 6.0 ppm, and the KHMDS did not generate any new unknown peaks, and the spectrum shows only the pyridone peaks for the two products, a mixture of deuterated pyridone **239d** and the non-deuterated pyridone.

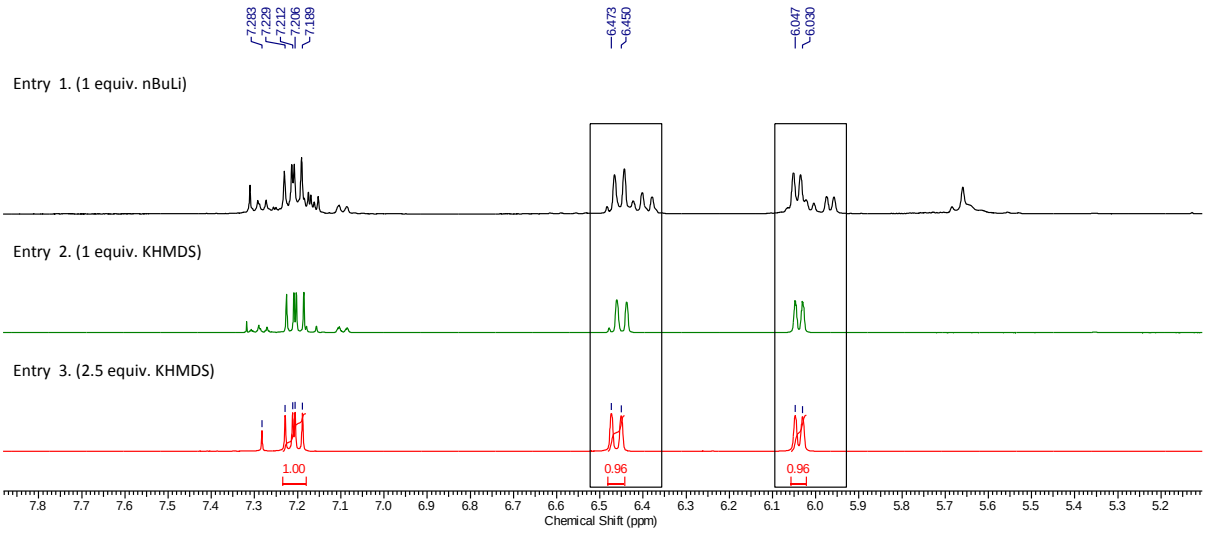


Figure 44: Expansion of spectra 6 (7.8 ppm-5.2 ppm).

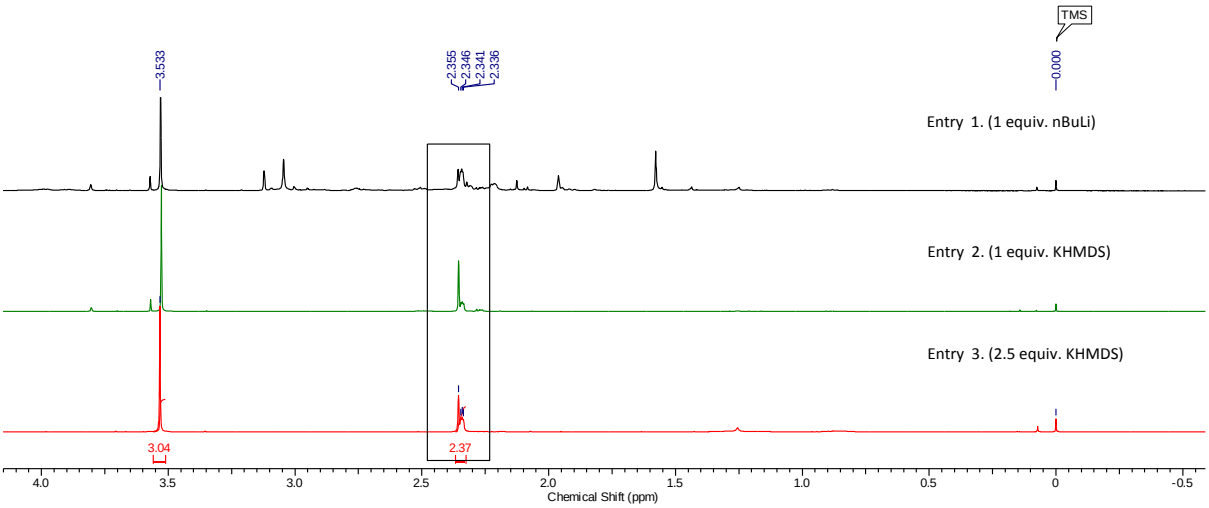


Figure 45: Zoom of spectra 6 (4.0 ppm - 0 ppm).

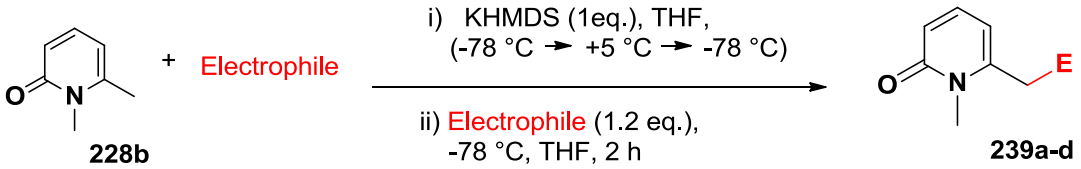
In **Figure 45** is shown that the use of nBuli in entry 1 generated unknown peaks from 4 to 2.35 ppm. And in entry 2 and 3 are shown only the peaks at 2.35 ppm for the deuterated pyridone and 2.34 ppm for the non-deuterated pyridone

In entry 3, **Table 30,** we proved that an excess of KHMDS (2.5 eq.) was not able to deprotonate more than one position and the reaction did not show any by-products. KHMDS was only strong enough to deprotonate the methyl group at position 6. This is shown in entry 3, the peak at 2.35 ppm integrates 2 H for a CH_2D, instead of 3H for a CH3 group.

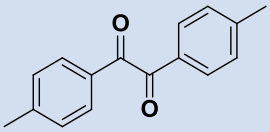
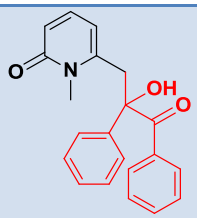
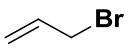
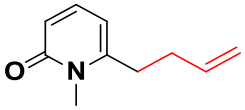
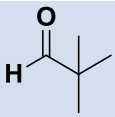
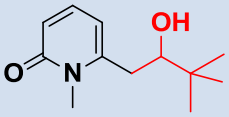
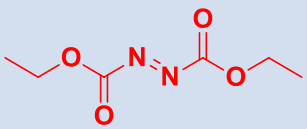
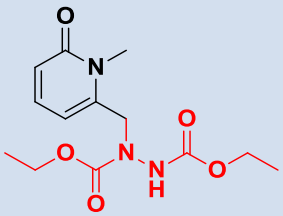
After this screening, we could conclude that the n-BuLi generated several by-products, and consequently the yield decreased. The problem was solved, using KHMDS, as the optimum base, a regioselective deprotonation at the methyl position, the monodeuterated pyridone **239d**, was obtained. The location of the label was easily established by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. In subsequent experiments, we selected to employ KHMDS as the base.

After the deuterium study, the new standard deprotonation conditions using 1,6-dimethyl-2-pyridone **228b**, and a range of electrophiles afforded products in good yield as shown in **Table 31**:

Table 31: Reactions of 1,6-dimethyl-2-pyridone and different electrophiles.



228b **239a-d**

Entry	Electrophile	Compound	Yield (%)
1	 **232a**	 **239a**	65%
2	 **222h**	 **239b**	75%
3	 **235b**	 **239c**	84%
4	 **238**	 **239e**	70%

The pyridone **239e** was fully characterised by ^{1}H and ^{13}C NMR spectroscopy and the structure was verified by X-ray crystallography (**Figure 46**).

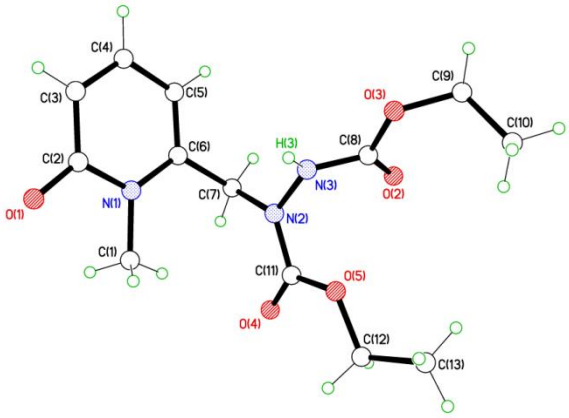


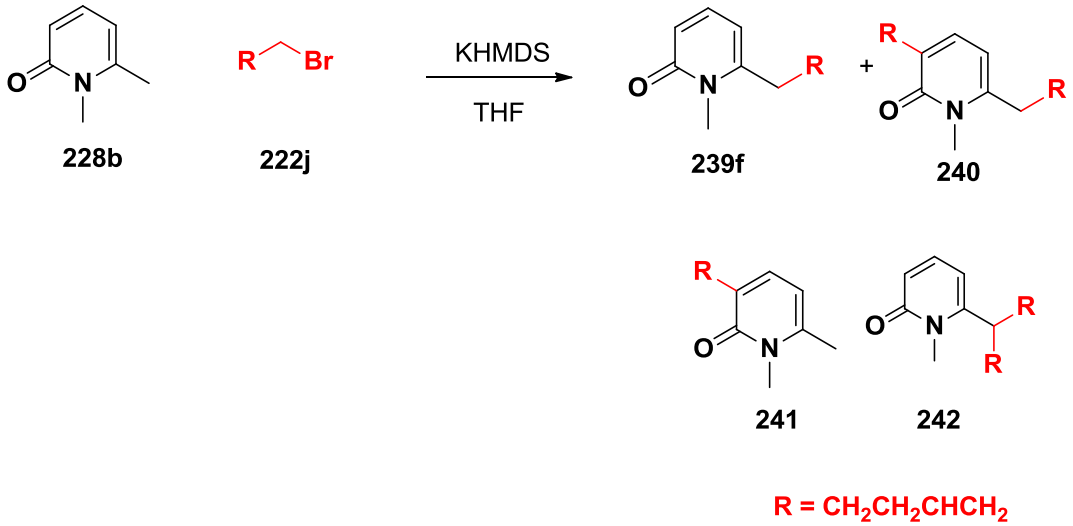
Figure 46: Crystallography structure of compound 239e.

The last experiment we carried out in order to complete the 1,6-dimethyl-2-pyridone **228b** study was the following set of reactions (**Table 32**). Sammes had reported in 1982[78] the synthesis of 6-hex-5-enyl-1-methyl-2(1H)-pyridone in 6.6% yield by lithiation of a methyl pyridone. We believe this to be the only report of this type of lithiation in the literature, and we wished to test our reaction conditions to compare yield.

We first tried to synthesize 6-hex-5-enyl-1-methyl-2(1H)-pyridone using our optimized conditions; however the conditions did not work and we recovered all the starting material (entry 1, **Table 32**).

In entry 2 double amount of base was added and the reaction was stirred for 1 hour, but the reaction again was unsuccessful. In *entry 3*, the same amount of base was used and the reaction was stirred at -78 °C for 3 h and temperature allowed to rise to -35 °C and the reaction was then stirred for 1 h. However this method also failed.

Table 32: Reactions of 1,6-dimethyl-2-pyridone and 5-bromo-1-pentene.

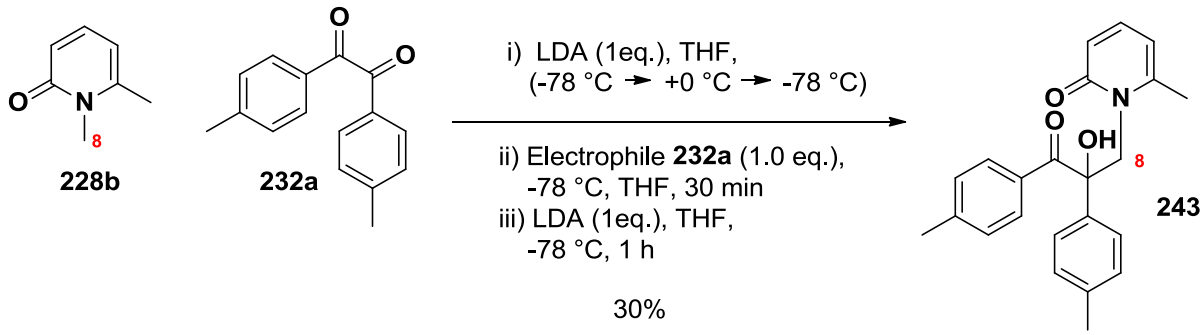


Entry	KHMDS	Temperature addition electrophile	Reaction time and Temperature	Compounds
1	1 eq.	-78 °C	2h at -78 °C	Starting material
2	2 eq.	-78 °C	1h at -78 °C	Starting material
3	2 eq.	0 °C	3h at -78 °C 1h at -35 °C	Starting material
4	2.5 eq.	0 °C	2h at 0 °C	**240** (8%) + **241** (8%) + **242** (18%)
5	1 eq.	-10 °C	1h at -10 °C	**239f** (20%)

In entry 4, 2.5 eq. of base were used and the reaction was performed at 0°C for 2 h. The reaction delivered 3 different products **240**, **241**, **242**. The excess of base at -78 °C was able to deprotonate only position 7. However, an excess of base at 0°C was able to deprotonate more than one position.

Taking this information into account, in entry 5, the reaction was performed at -10 °C and the desired pyridone **239f** was obtained in 13% higher than recorded by Sammes. The formation of the products **240**, **241** and **242** shows that very subtle effects are in operation in these metallation reactions and obtaining high selectivity is very challenging.

We wanted to expand the chemistry and to control the alkylation at the N-methyl position (8).We were able to alkylate the 1,6-dimethyl-2-pyridone **228b** at the N-methyl position (position 8) depending on the reaction conditions. Using in total 2 eq. of LDA, a regioselective deprotonation at the N-methyl position was obtained as shown in **Scheme 77**.



Scheme 77: Synthesis of compound 243.

This regioselective deprotonation at the N-methyl position is under investigation.

3.2- Study of N-substituted-2-methyl-4-pyridones

4-Pyridone compounds are very important as substructures of natural products and they are found in several bioactive compounds. For this reason, we wished to continue the metallation study at the methyl position of 1-benzyl-2-methylpyridin-4(1*H*)-one **226a** and 1,2-dimethylpyridin-4(1*H*)-one **226b**, as structural isomers of 1-benzyl-6-methylpyridin-2(1*H*)-one **228c** and 1,6-dimethylpyridin-2(1*H*)-one **228b** already studied.

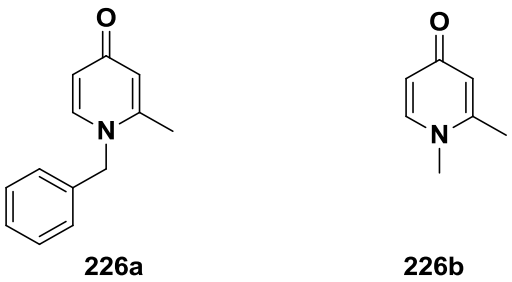
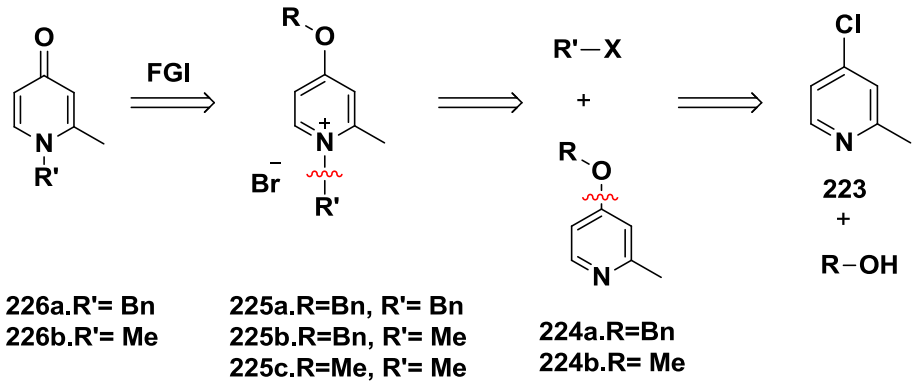


Figure 47: 1-benzyl-2-methylpyridin-4(1H)-one and 1,2-dimethylpyridin-4(1H)-one.

In this section, we present firstly the synthesis of 1-benzyl-2-methylpyridin-4(1H)-one and 1,2-dimethylpyridin-4(1H)-one. Secondly, results of metallation at the methyl position and the products of subsequent reactions with different electrophiles are described.

3.2.1- Synthesis of N-alkylated-4-pyridones.

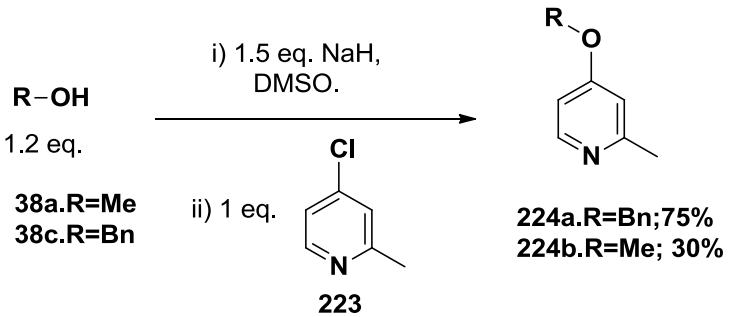
Alkoxy pyridines have been explored as a means of accessing N-alkyl pyridones.[11,80] This is a particular attractive strategy for the synthesis of N-substituted 4-pyridones over 3 steps. Firstly, alkoxy pyridines **224a**, **224b** can be accessed directly and in high yield from 4-chloro-6-methyl pyridine **223** and an appropriate alcohol via nucleophilic aromatic substitution. Secondly, the pyridinium salts **225a**, **225b** and **225c** can be accessed by direct N-alkylation of alkoxy pyridines such as **224**. The pyridinium salts **225a**, **225b** and **225c** were exposed to basic conditions over 3 h leading to the desired pyridones 1-benzyl-2-methylpyridin-4(1H)-one **226a** and 1,2-dimethyl-4-pyridone **226b.**



Scheme 78: Retrosynthesis of of N-substituted-4-pyridone 226a and 226b from 4-chloropyridines.

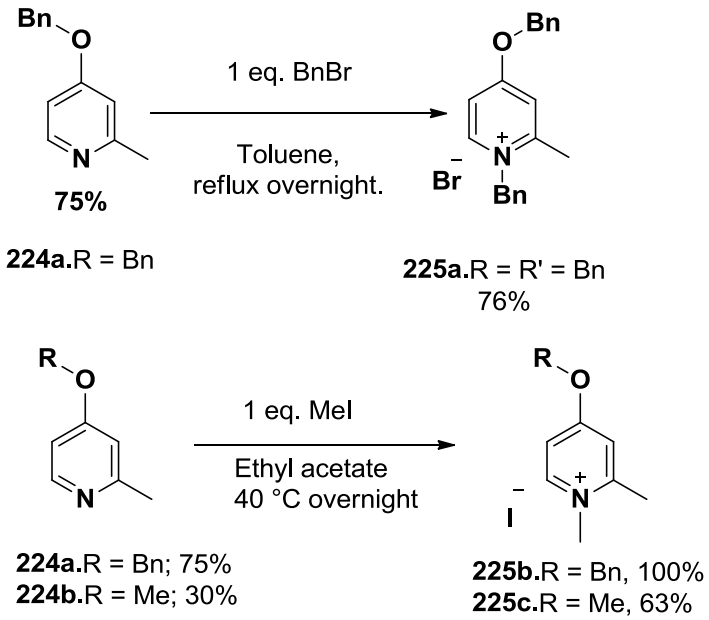
3.2.1.1- Synthesis of 1,2-dimethyl-4-pyridone and 1-benzyl-2-methylpyridin-4(1H)-one.

The syntheses of the required alkoxy pyridines **224a** and **224b** were achieved by treating 4-chloro-2-methyl pyridine **223** with benzyl alcohol or methanol in presence of NaH.



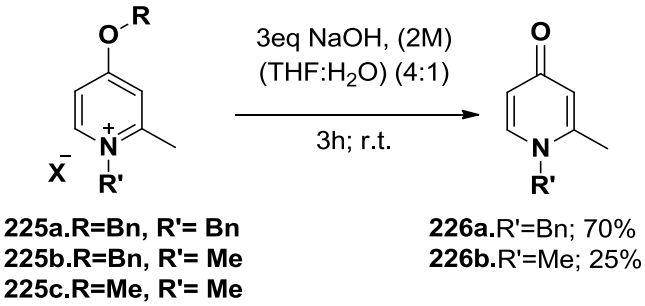
Scheme 79:Synthesis of O-alkylated pyridines.

In order to synthesize the required intermediate pyridinium salts **225a** the 4-benzyloxy-pyridine **224a** was alkylated with benzyl bromide in toluene. For the synthesis of piridinium salts **225b** and **225c**, the 4-methoxy-pyridine **224b** was alkylated with methyl iodide in EtOAc.



Scheme 80: Synthesis of the intermediate pyridinium salts 225a, 225b and 225c.

In the last step in the synthesis of 1,2-dimethyl pyridine-4(1*H*)-one and 1-benzyl-2-methylpyridin-4(1*H*)-one, the pyridinium salts **225a**, **225b**, **225c** were dissolved in THF and exposed to aq NaOH solution (2M). The debenzylation reaction was completed over 3 h to give the required 4-pyridones **226a** and **226b** in 70 and 25% yields respectively.

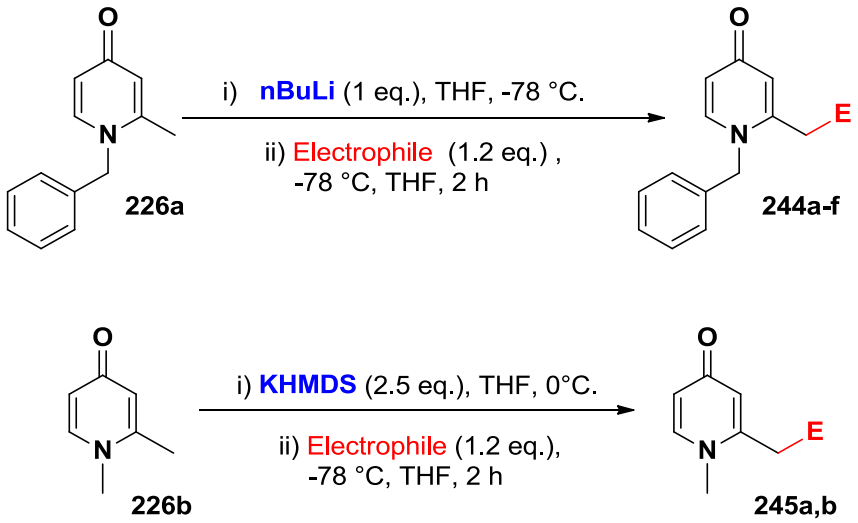


Scheme 81: Synthesis of 1-benzyl-2-methylpyridin-4(1H)-one and 1,2-dimethylpyridin-4(1H)-one.

This general methodology allowed for the preparation of a wide range of N-substituted-4-pyridones in good yields over 3 steps.

3.2.2- Study of the metallation of 2-methyl-4-pyridone derivatives

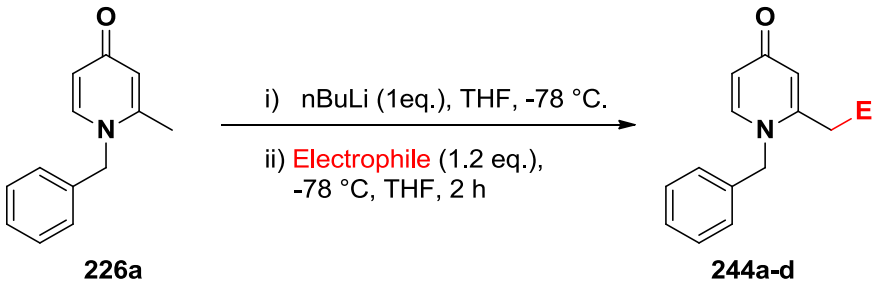
For the second part of this study, 4-pyridones **226a** and **226b** were used as starting materials for the investigation of the selective methyl metallation of 1-substituted-2-methyl-4-pyridones so that their behaviour could be compared with the reactions of the 2-pyridones described earlier.



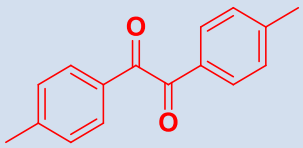
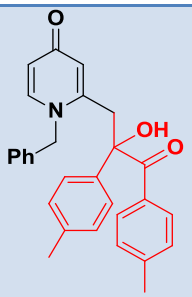
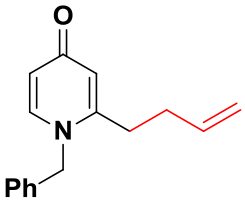
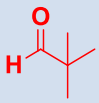
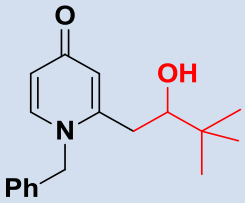
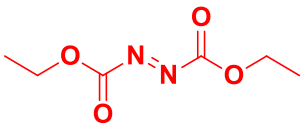
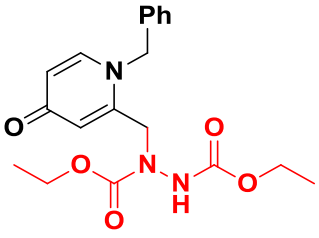
3.2.2.1- Study of methyl lithiation of 1-benzyl-2-methylpyridin-4(1H)-one.

The product of methyl lithiation of 1-benzyl-2-methylpyridin-4(1*H*)-one was reacted with a variety of electrophiles. As shown in **Table 33**, the reaction worked under the same standard conditions used successfully in the study of methyl lithiation of 1-benzyl-6-methyl-2-pyridone. The yields were generally not high as for the 2-pyridones series; mainly due difficulties in the purification step caused by the higher polarity of the 4-pyridone derivatives.

Table 33: Methyl lithiation of 1-benzyl-2-methyl-4-pyridone.



226a 244a-d

Entry	Electrophile	Time	Product	Yield[a]
1	 232a	2h	 244a	45 %
2	 222b	2h	 244b	57 %
3	 235b	2h	 244c	40 %
4	 238	2h	 244d	35 %

[a] Isolated product after purification.

3.2.2.2- Study of methyl metallation of 1,2-dimethyl-4-pyridone.

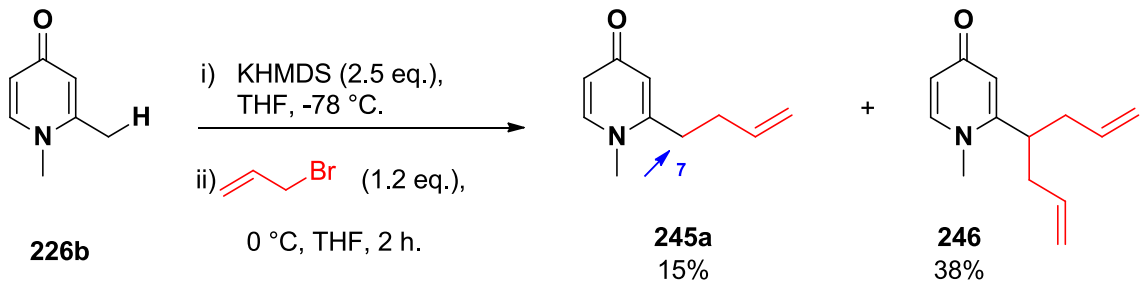
Although the studies described in the previous sections showed clearly that efficient metallation of 1-benzyl-6-methylpyridin-2(1H)-one **228c**; 1,6-dimethylpyridin-2(1H)-one **228b** and 1-benzyl-2-methylpyridin-4(1H)-one **226a** was possible, considerably less success was achived with the mono-metallation of the 1,2-dimethylpyridin-4(1H)-one analogue **226b**.

Different reaction conditions were therefore systematically investigated in order to find a set of conditions which would favour the monoalkylation.

The standard conditions were used with 1,2-dimethylpyridin-4(1H)-one **226b**, 1 mol eq. of KHMDS at -78 °C, increasing the temperature to 0 °C, and quenching with the electrophile after cooling back to -78 °C (2 h). Unfortunately no alkylated pyridone was obtained. Screening the quantity of base from 1 eq. to 2.5 eq. was studied, while the temperature of the electrophile addition (-78 °C) and 2 h as a reaction time were maintained as constant conditions. However the reaction was again unsuccessful and only starting material was recovered.

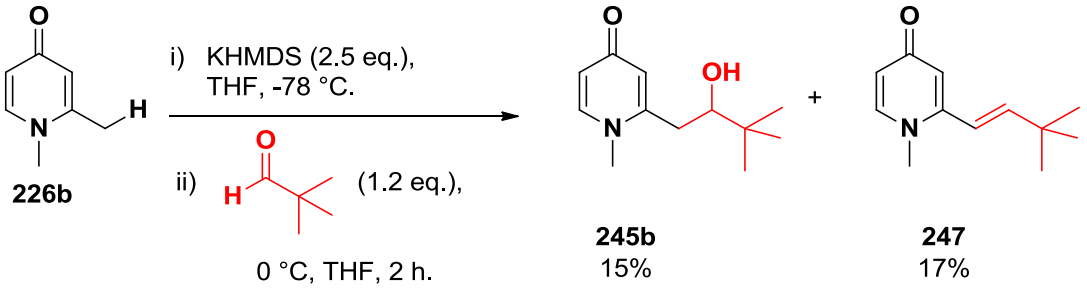
In a final attempt to circumvent the difficulties encountered in the alkylation, the reaction was performed with the addition of 2.5 eq. of base to the pyridone at -78 °C and as in the previous reactions, warming the mixture to 0°C and at this point adding the electrophile at 0°C (2 h).

These conditions were used to generate 2-(metallated-methyl)-1-methyl-4-pyridinone which was evaluated with carbon electrophiles such as alkyl halides (allyl bromide). The desired alkylated pyridone **245a** was obtained in 15%. However, the reaction was complicated by the subsequent deprotonation of the alkylated-pyridone product **245a** again in position 7 and further alkylation at this position, delivering the dialkylated compound **246a** in 38% yield (**Scheme 82**).



Scheme 82: Synthesis of 1-methyl-2-substituted-4-pyridones

We also evaluated this metallated-methyl pyridone with pivaldehyde and the reaction proceeded under the same conditions. The desired pyridone **245b** was obtained in 15% yield and once again, the reaction was complicated by the subsequence deprotonation in position C-7. At this step an E2 elimination took place and the unsaturated product **247** was delivered in 17% yield (**Scheme 83**).



Scheme 83: Conditions for the synthesis of 6-methyl-pyridone.

To conclude, the reaction of 1,2-dimethylpyridin-4(1H)-one with 2.5 eq. of KHMDS and two different electrophiles, allyl bromide and pivaldehyde, under the conditions shown in **Scheme 82** and **Scheme 83,** delivered a mixture of mono (**245a**,**b**) and double deprotonated product (**246** and **247**) in both cases. It was impossible to control the second deprotonation, and as by-product pyridones **246** and **247** were obtained in higher yields.

4- Synthesis of quinolizinones.

4*H*-Quinolizin-4-one **1** and 2H-quinolizin-2-one **2** represent neutral carbonyl-bearing derivatives of the quinolizinium ring system **248**, a bridgehead azanaphthalene. Such compounds have potential applications in drug development as alternatives to quinoline **249** and isoquinoline **250** derivatives, which are much exploited in medicinal chemistry. A number of quinolizin-4-one based drug candidates have been developed, but considerable scope remains to employ this ring as a central building block in drug discovery.

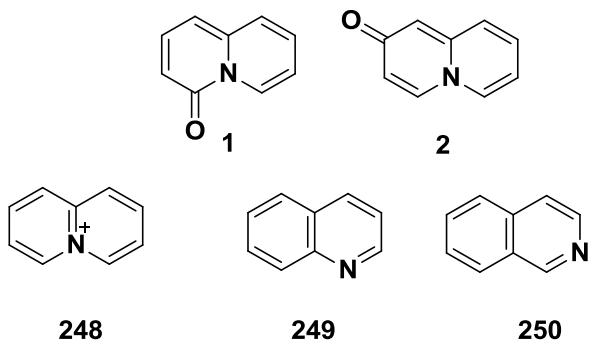


Figure 48: Azanaphthalene rings employed in medicinal chemistry.

The synthesis of 2- and 4-oxoquinolizine derivatives as new drug scaffolds is still needed, due to increasing bacterial resistance to quinolones. Consequently, new analogues need to be developed urgently.

We wanted to develop new synthetic routes for the synthesis of quinolizinone derivatives, from readily available starting materials, (such as 2-picoline, and 2-methoxy-6-methylpyridine).

In our study, formation of the quinolizinone scaffold was attempted using two different synthetic pathways.

In *route A*, 2-picoline **141** was used as the starting material and the goal was to build the pyridone ring onto the existing pyridine. On the other hand, in *route B* 2-methoxy-6-methyl-pyridone **221** was used as the starting material, which would become the pyridone ring at an early state of the synthesis, and the new pyridine ring would then be built onto the pyridone.

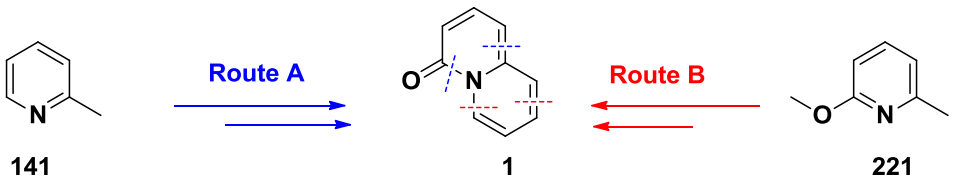
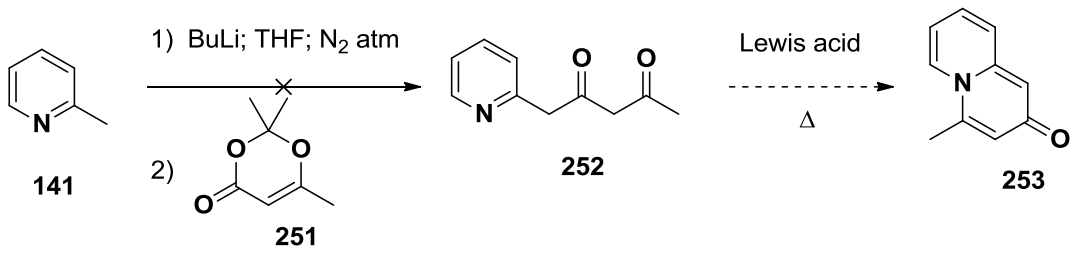


Figure 49 : Quinolizinone scaffold.

Route A and *Route B* will be explained in the following pages.

4.1- From 2-picoline as starting material.

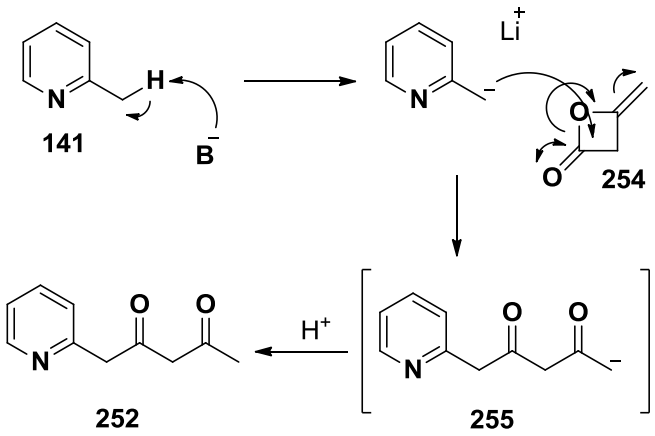
The target was to develop new routes for the synthesis of quinolizinone derivatives from readily available starting materials, such as 2-picoline **141**. In the quinolizinone synthesis the goal was to synthesize compounds based on scaffold **1**, such as compound **253**. The preparation of the required precursor 1-(pyridin-2-yl)pentane-2,4-dione compound **252** was initially planned from 2-picoline **141** and diketene or 2,2,6-trimethyl-4H-1,3-dioxin-4-one **251** a diketene equivalent (**Scheme 84**).



Scheme 84 : Attempted synthesis of quinolizinone.

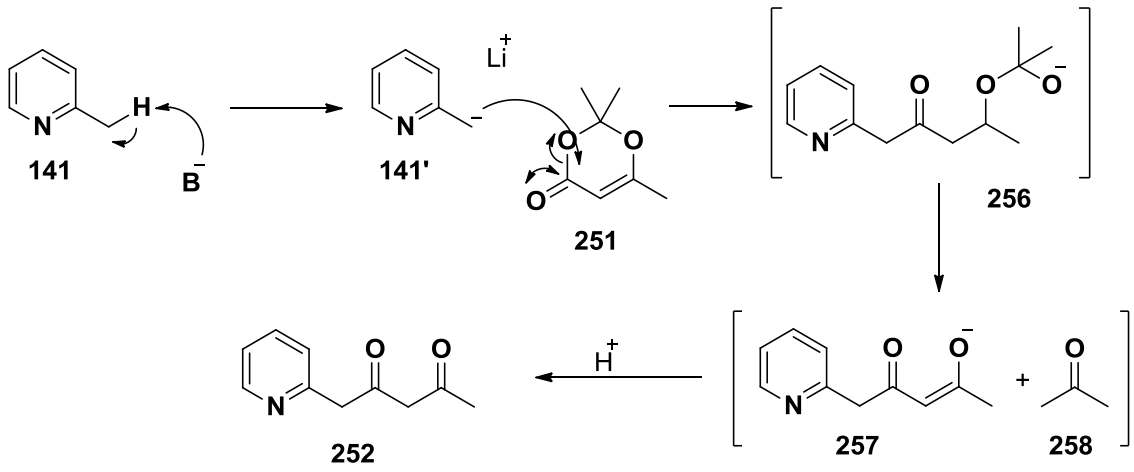
Our attempt to synthesize compound **252** was unsuccessful to date. It was, therefore, impossible to carry out the second step and attempt to synthesize compound **253**, as proposed in **Scheme 84**.

In this approach, the goal was to deprotonate the methyl group of 2-picoline and to react the anion with diketene **254** (**Scheme 85**), or its synthetic equivalent **251** (**Scheme 86**). Thus, the following reaction was attempted using the 2-picoline **141** anion and 2,2,6-trimethyl-4H-1,3-dioxin-4-one **251**. The anion, was assumed to be formed because the intermediate was orange in colour, as reported in the literature.[81]



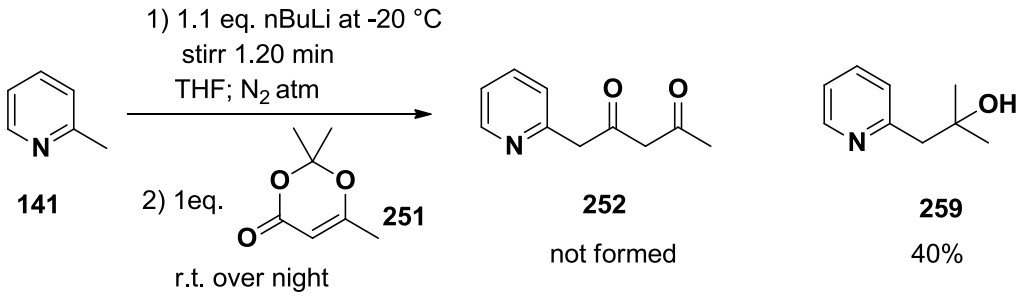
Scheme 85: Proposed mechanism of the reaction with diketene.

Due to the unavailability of diketene, dioxinone **251** was used as substitute**.** The dioxinone ring was expected to be opened by nucleophilic attack to give product **252** and a molecule of acetone.



Scheme 86: Proposed mechanism for the synthesis of 1-(pyridin-2-yl)pentane-2,4-dione 252.

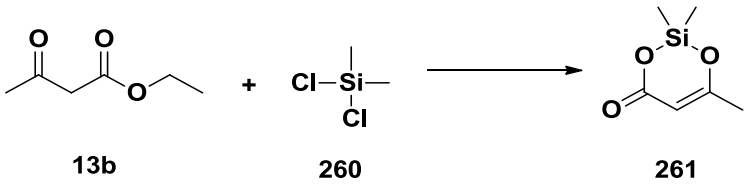
However, the reaction did not work in the expected way, and the only product isolated was tertiary alcohol **259**. The 2-picoline anion reacted with a molecule of acetone, presumably formed by breakdown of **251**, and no evidence for the formation of **252** was obtained.



Scheme 87: Attempted synthesis of 1-(pyridin-2-yl)pentane-2,4-dione.

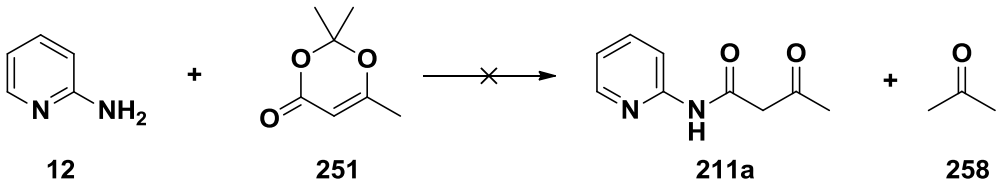
We decided therefore to synthesize an alternative starting material **261**, (**Table 34**) containing a bridging silicon atom. The formation of acetone during the reaction could be avoided which came from the decomposition of compound **251**. As a result, attempts were made to synthesise **331** by treating ethyl acetoacetate with dichlorodimethysilane **260** (**Table 34**).

Table 34: Conditions for the attempted synthesis of compound 261.



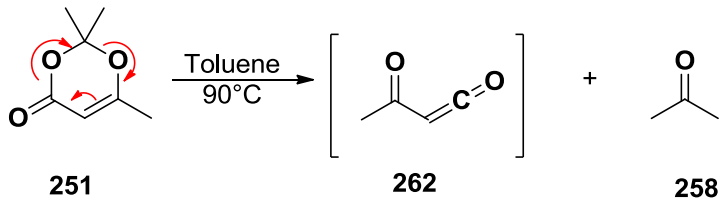
Entry	Base (eq)	Catalyst	Solvent	time (h)	T ° C	Product
1	Et_3N (2.2eq)		Acetonitrile	2	65	Complex mixture
2	Et_3N (2.2eq)		Acetonitrile	4	65	Complex mixture
3	NaH(2.2eq)		Acetonitrile	3	55	Complex mixture
4	-	$ZnCl_2$ (10%)	Acetonitrile	6	65	Complex mixture
5	NaH (2.2eq)	$ZnCl_2$ (10%)	Acetonitrile	5	55	Complex mixture

Disappointingly all of the attempts to synthesize **261** were unsuccessful. Consequently, the following reaction was investigated, in order to check the reactivity of reagent **251**. 2-Aminopyridine **12** was employed as a nucleophile reagent and used to react with compound **251** (**Scheme 88**).

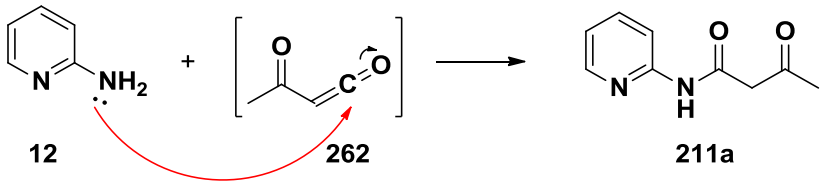


Scheme 88: Attempted synthesis of acetylacetamide.

2-Aminopyridine **12** was chosen because it could act as a bis-nucleophile, although it is less reactive than 2-picoline anion. We hope that a thermal reaction would lead to breakdown of the dioxinone **251** (**Scheme 89**), and following the mechanism proposed by Basset and co-workers[82] this would generate acetyl ketene **262**, which may possibly react with 2-aminopyridine to form the acetylacetamide **211a** as shown **Scheme 90**.



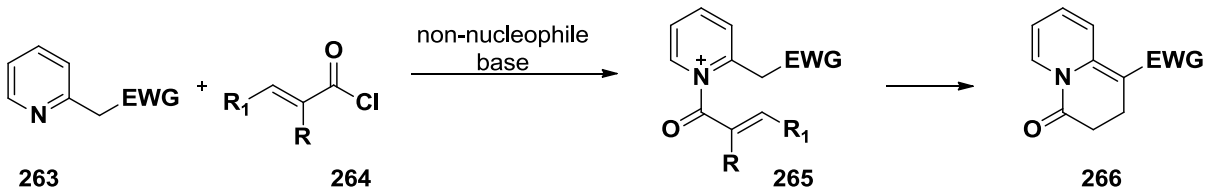
Scheme 89: Retro-cycloaddition



Scheme 90: Proposed nucleophilic attack of 2-aminopirimidine on ketene 262.

However, after heating 2-aminopyrimidine **12** and the dioxinone **262** in toluene, the NMR spectrum only showed starting material signals.

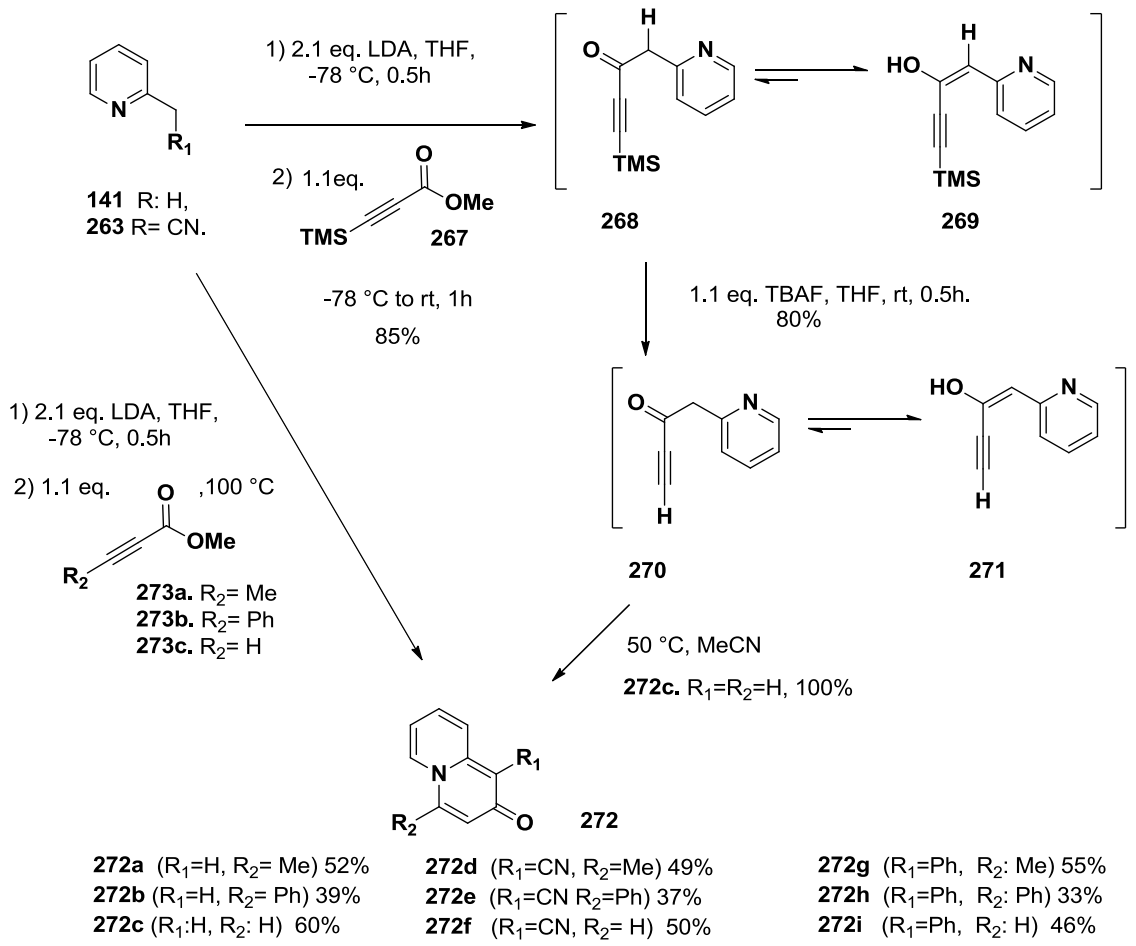
Disappointingly, all of the attempts to use 2,2,6-trimethyl-4H-1,3-dioxin-4-one **251** as an electrophilic reagent, to be opened by nucleophilic attack as shown in **Scheme 87**, failed. The investigation was then directed towards a new general synthetic approach, as shown in **Scheme 91**.



Scheme 91: New general synthetic route to synthesise quinolizinones.

2-Picoline **141** was retained as the nucleophilic reagent, but, 2,2,6-trimethyl-4H-1,3-dioxin-4-one **251** was changed for acryloyl chloride **264**, because it is more reactive.

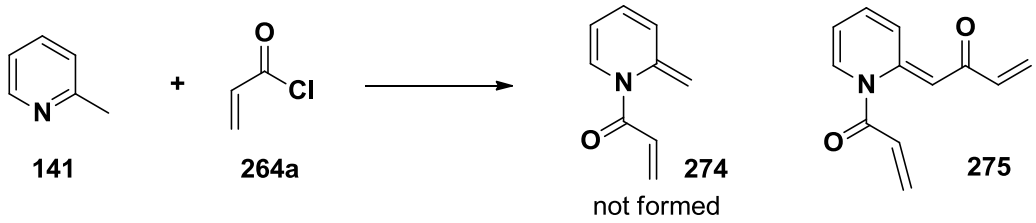
Our work was based on Natarajan and co-workers' research.[57] They reported the synthesis of the 2*H*-quinolizin-2-one scaffold **272** from initial deprotonation of 2-picoline **141** with LDA, followed by acylation with propynoate electrophiles. In their study, β-TMS-propynoate derivatives **267** and 3-alkyl or arylpropynoate **273** were used. In the case of β-TMS-propynoate derivatives used as the acylating agent, the deprotonation of the triple bond was required to allow a 6-*endo*-trig-cyclization to yield the desired 2*H*-quinolizinone derivatives **272**. However, in the reaction with 3-alkyl or aryl propionate derivatives **273a-c**, after the initial acylation, ring closure was found to occur spontaneously. In other examples the crude reaction mixture had to be heated to 100 °C to complete the ring closure reaction.



Scheme 92: Assembly of 2H-quinolizin-2-one scaffolds.[57]

In our synthetic route, we wanted to study the N-acylation of 2-picoline to synthesize the corresponding 4*H*-quinolizin-4-one scaffold. Hence, a strong base was not required as the lone pair on the nitrogen atom was nucleophilic and we hoped that this was sufficient to achieve N-acylation. A mild base was required in order to neutralize the hydrogen chloride by-product which would form in the reaction mixture. The base chosen was a non-nucleophilic base in order to avoid side reactions between the base and the acryloyl chloride. The nitrogen atom in 2-picoline ring was therefore employed as the nucleophilic reagent and used to react with carbonyl of acryloyl chloride **264a**, to afford compound **274**. No product was obtained using the reaction conditions in entry 1. In entries 2 and 3, 10 % of Lewis acid was employed, but not product was obtained in both entries. However, in entry 4, no base was used and the addition of the acryloyl chloride **264a** was at 0 °C. Under these conditions, a molecule of 2-picoline **141** reacted with two molecules of acryloyl chloride **264a** to afford compound **275** (**Table 35**).

Table 35: Attempt to monoacylation of 2-picoline.



141 264a 274 not formed 275

Entry	2-picoline (mmol)	Acyl chloride (mmol)	Solvent (mL)	Base (mmol)	Catalyst	Temp. addition (°C)	Time (h)[a]	Product (yield %)[b]
1	3	3	DCM 1 mL	DIPEA 3mmol	-	-78	48	**141** [b]
2	3	3	1 mL	DIPEA	$ZnCl_2$ (10%)	-78	24	**141** [b]
3	2	2	THF 6 mL	DIPEA	$ZnCl_2$ (10%)	-78	24	**141** [b]
4	2	2	DCM 10 mL	-	-	0	12	**275** (10%)

[a]The reaction stirred at r.t.

In conclusion the N-acylation of 2-picoline, the addition of acryloyl chloride was a 0 °C and followed by warming up at room temperature, and stirring overnight in order to promote ring closure, only a 10 % of the diacylation compound **275** was isolated (entry 4). When the addition of the acyl-reagent was at -78°C followed by warming up to room temperature and stirring overnight, a black oil was obtained. From this complex mixture only 2-picoline was recovered, and no acryloyl signals appeared in the NMR spectrum.

The reason could be that the acryloyl chloride presumably decomposed, due for the black oil obtained, and the lone pair of the nitrogen atom did not react with the acryloyl chloride.

Route A, in **Figure 50,** has been discussed so far. However the synthesis of 4*H*-quinolizin-4-one, with acryloyl chloride as N-acylating reagent was unsuccessful and the synthesis of 2*H*-quinolizin-2-one, with similar reagents, was reported by Natarajan in 2006.[57]

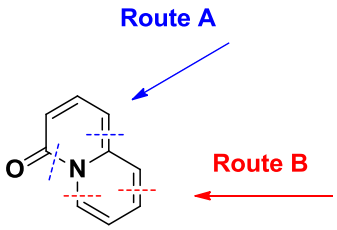
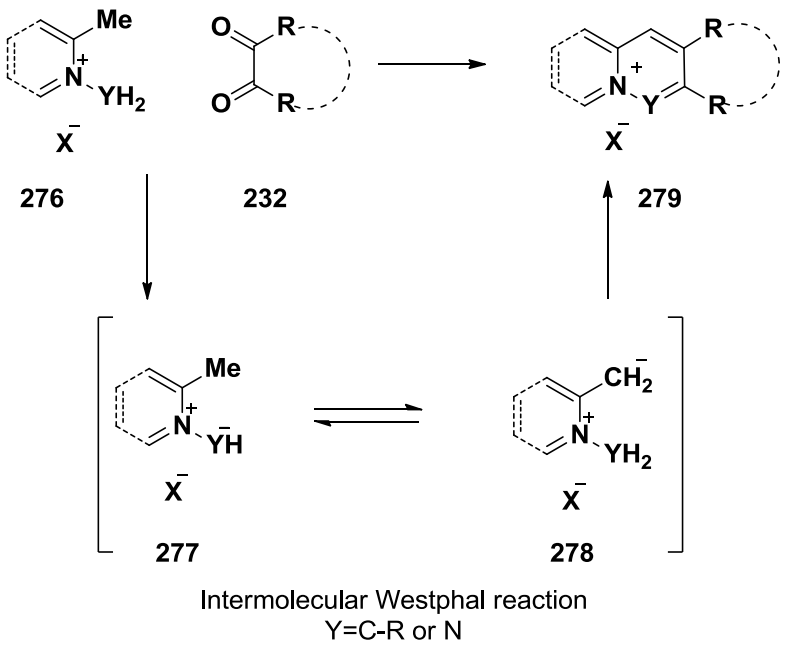


Figure 50: Pathways to synthesize 4*H*-quinolizin-4-one scaffold.

The research continued with a different approach, but still with 2-picoline as the starting material. The electrophilic reagent however was changed to an alkylating reagent, ethyl bromoacetate. We decided to alkylate the 2-picoline instead of acylating it, with the aim of making pyridium salts suitable for annelation to quinolizinium derivatives which could, in turn, be converted into quinolizinones.

We devised a new route to synthesize 2- and 4-oxoquinolizinones which involved the Westphal reaction followed by the oxidation of the resulting quinolizinium salts with nucleophilic oxidation reagents, to convert them into the corresponding quinolizinone derivatives.

Westphal *et al.*[83] reported in 1961 the condensation of a cycloimmonium salt, such as an N alkyl-substituted 2-picolinium salt **276**, acting as an 1,4-dinucleophile on 1,2-diketones **232** in the presence of an organic base, to give the corresponding substituted quinolizinium salts **279**.



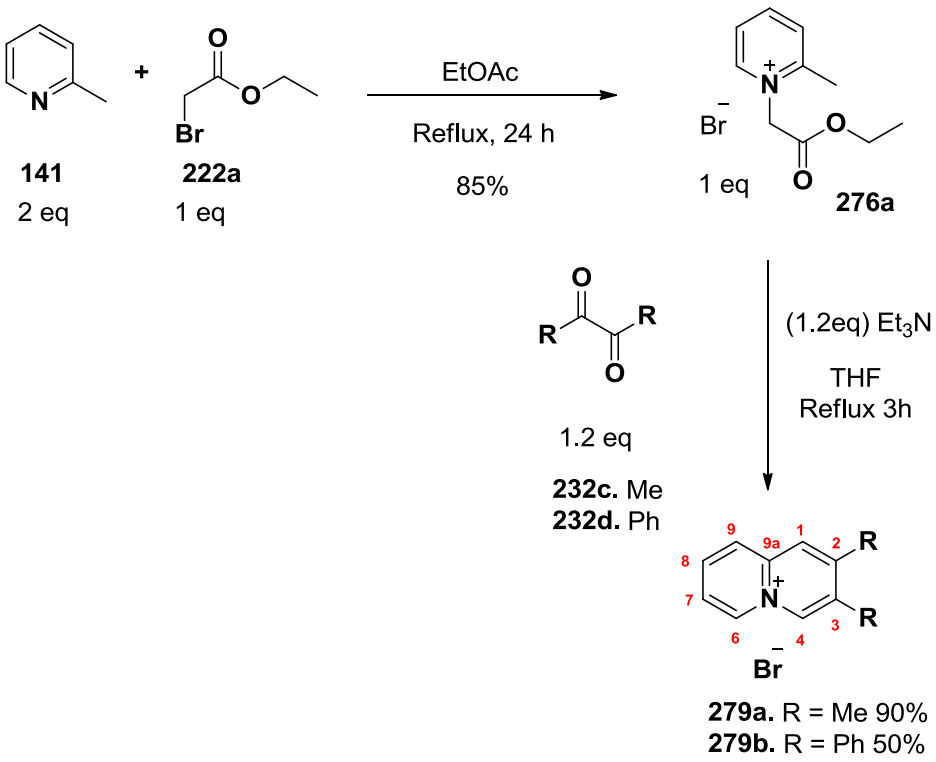
Scheme 93: Intermolecular Westphal reaction.

The Westphal reaction is an efficient and straightforward method for the synthesis of the quinolizinium ring system. It involves a condensation between α-methylcycloimmonium salt **276** and 1,2-diketones **232**. The Westphal reaction had usually been carried out with symmetrical 1,2-diketones, until Diaz and co-workers[84] reported in 1994, their study on the regioselectivity of this condensation reaction with unsymmetrical 1,2-diketones.

In 2003, a study of the Westphal reaction on a solid-support was reported by Alvarez-Builla and his co-workers.[85] They reported the preparation of a library of cycloimonium salts, which were synthesized in good to high yields.

In 2011 Chen and his co-workers reported the synthesis of quinolizinium salts **279a,b**[86] by the Westphal reaction, the procedure being modified from the previously reported solid-phase procedure.

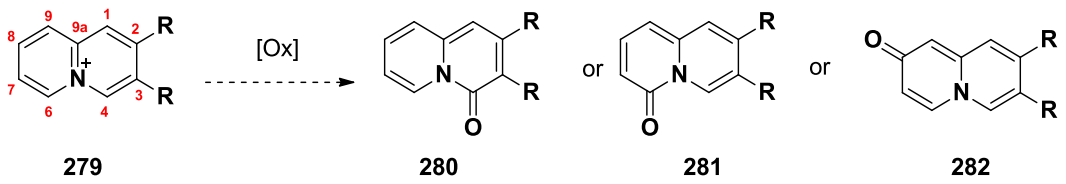
Our synthesis of quinolizinium salts was based on the work of Chen *et al*,[86] however we modified the procedure, and changed the solvent and the reaction time as shown in **Scheme 94.**



Scheme 94: Synthesis of quinolizinium salt by Westphal reaction.[86]

We prepared the pyridinium salt **276a**, via a quaternization reaction between 2-picoline **141** and ethyl 2-bromoacetate **222a**, in ethyl acetate under reflux for 24 h. The quinolizinium salts **279a** and **279b** were then synthesized through a Westphal reaction, modified from a previously reported solid-phase procedure. The best conditions were when the mixture of 1,2-diketone and 1 eq. of triethylamine was added dropwise into a THF solution of 1.2 eq. of the pyridinium salt, and the mixture heated under reflux for 3 h. This afforded compounds **279a** and **279b** as solids in good yields.

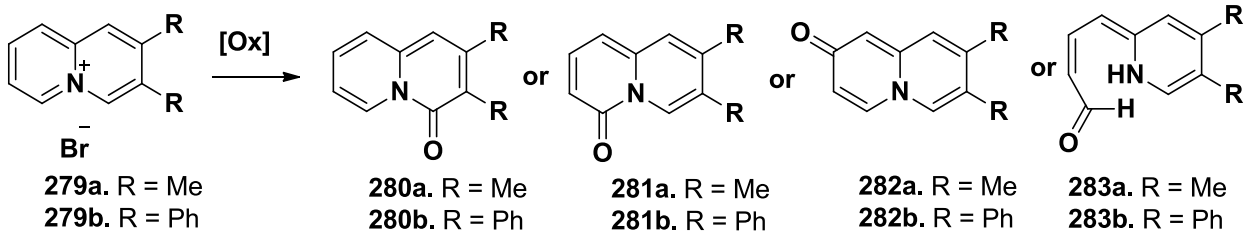
It was now hoped that the quinolizinium salts could be oxidized in positions (4, 6 or 8) (*ortho* or *para* to the pyridinium nitrogen) to afford quinolizinone derivatives, potentially isomers **280**, **281** or **282** (**Scheme 95**).



Scheme 95: Attempted of oxidation of pyridinium salt in position 4, 6 or 8.

Starting the oxidation study, the quinolizinium salts were exposed to the oxidising reagents, hydrogen peroxide and potassium ferricyanide in the presence of hydroxide and MCPBA as a shown in **Table 36**.

Table 36: Conditions of the attempt to synthesize quinolizinone derivatives.



279a. R = Me
279b. R = Ph

280a. R = Me
280b. R = Ph

281a. R = Me
281b. R = Ph

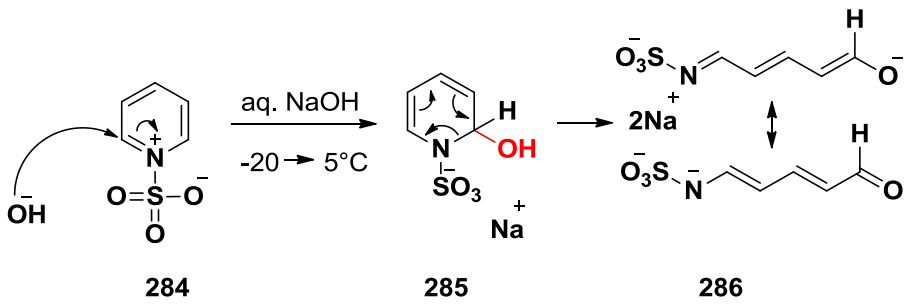
282a. R = Me
282b. R = Ph

283a. R = Me
283b. R = Ph

Entry	Quinolizinium salt	Oxidant Reagents (eq)	Solvent	Time	T (°C)	Product
1	**279a** (1eq.)	H_2O_2 29% (2 eq)	H_2O/MeOH	24 h	Rt	-
2	**279a** (1eq.)	H_2O_2 29% (2 eq)	H_2O/MeOH	48 h	Rt	-
3	**279a** (1eq.)	H_2O_2 29% (5 eq)	H_2O/MeOH	48 h	Rt	-
4	**279a** (1eq.)	H_2O_2 29% (5 eq)	H_2O/MeOH	6 h	50	-
5	**279b** (1eq.)	H_2O_2 29% (5 eq)	H_2O/MeOH	36 h	Rt	-
6	**279a** (1eq.)	$K_3Fe(CN)_6$ (2eq)/ NaOH (4eq)	H_2O	24 h	Rt	**283a***
7	**279b** (1eq.)	$K_3Fe(CN)_6$ (2eq)/ NaOH (4eq)	H_2O	24 h	Rt	-
8	**279a** (1eq.)	$K_3Fe(CN)_6$ (2eq)/NaOH (1eq)	H_2O	48 h	Rt	**283a***
9	**279a** (1eq.)	-	DMSO	96 h	110-150	-
10	**279b** (1eq.)	-	DMSO	96 h	110-150	-
11	**279a** (1eq.)	MPCBA (2eq.)	H_2O/MeOH	48 h	Rt	-
12	**279a** (1eq.)	MPCBA (2eq.)	H_2O/MeOH	48 h	Rt	-
*** NMR spectrum of compound 12a showed aldehyde signal and alkene signal.**						

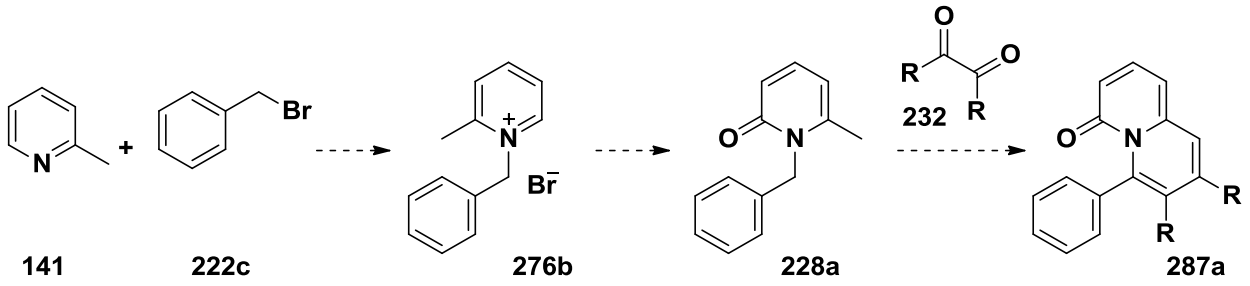
As shown in **Table 36**, using mild conditions the reaction did not work, however when stronger oxidising conditions were used, compound **283a** was obtained.

Ring opening was one of the most important considerations, since there are some examples of pyridinium salts, particularly, but not exclusively, those with powerful electron-withdrawing N-substituents, adding a nucleophile at C-2 and then undergoing a ring opening.[87] A typical example of ring-opening is the addition of sodium hydroxide to the pyridine sulphur trioxide complex, as shown in **Scheme 96**.



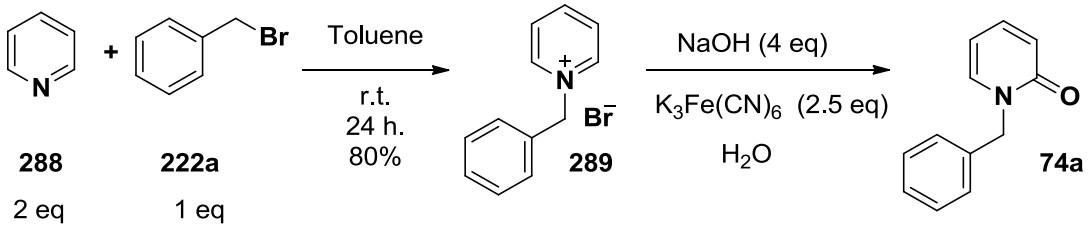
Scheme 96: Ring opening mechanism.[88]

After the difficulty encountered in oxidising the quinolizinium salts in positions 1, 4 or 6, we decided to alkylate 2-picoline **141** to afford the pyridinium salt **276** and afterwards to oxidise the pyridinium salt at position 6. Finally, the synthesis of the desired quinolizinone scaffold could be achieved via double condensation reaction with the diketone (**Scheme 97**).



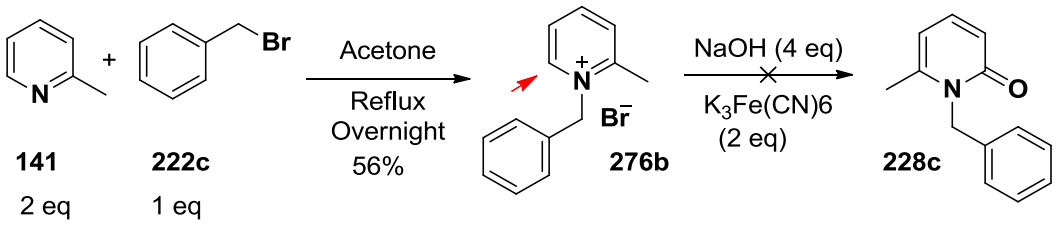
Scheme 97: Proposed synthesis pathway.

The proposed synthesis of compound **228c** was based on Pasarella's work[89], shown below.



Scheme 98 : Synthesis of pyridone compound 346 reported by Passarella *et al.*

To obtain the 2-pyridone **228c**, the picolinium salt **276b** was treated with NaOH/$KF(CN)_6$, following Passarella's procedure (**Scheme 98**). However, this reaction did not generate the desired 2-pyridone **228c** (**Scheme 99**), and only delivered a complex product mixture.

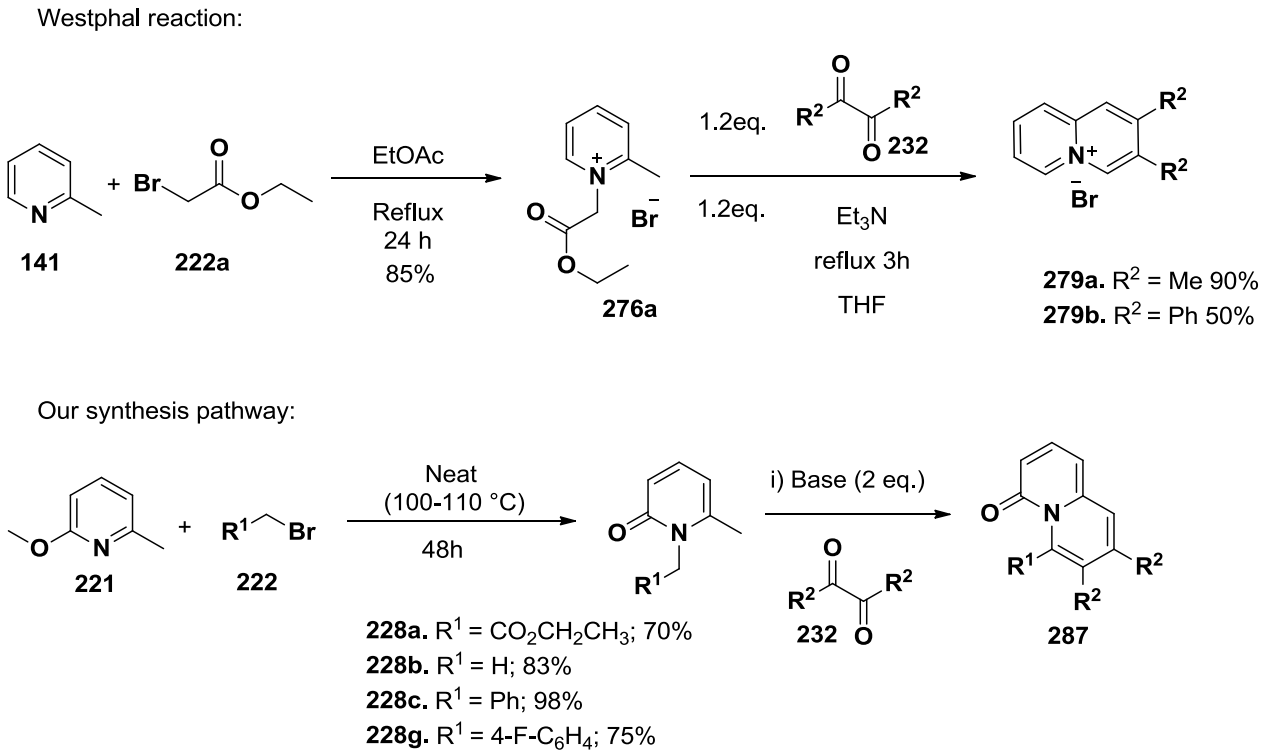


Scheme 99: Attempted oxidation of compound 276b in position 6.

Due to the lack of success with the oxidation of the pyridinium salt, we decided to change the starting material to one with a substituent at position 2 or 4 which could be converted into the carbonyl group at a later stage of the synthesis.

4.2- From 2-methoxy-6-methylpyridine.

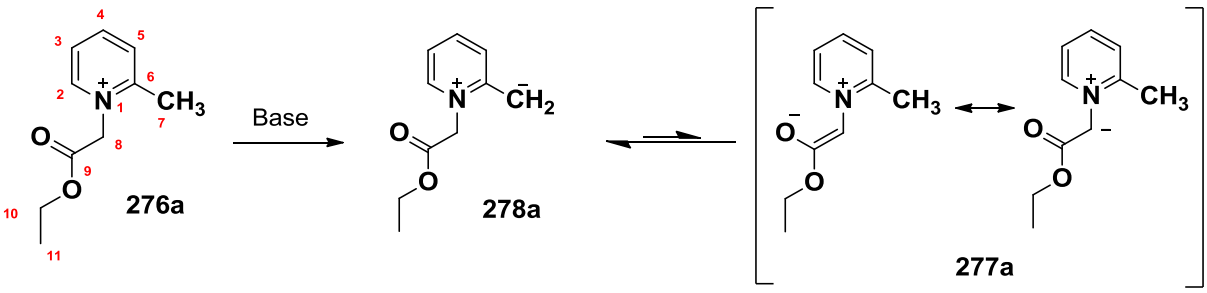
2-Methoxy-6-methylpyridine **221** was chosen as the starting material, since it bears a methoxy group in position 2 which, during the reaction could undergo de-alkylation to give the pyridone derivative, once the pyridine was activated by the alkylating agent. This synthetic approach to 2-pyridone derivatives has been discussed in **section 3.1.1**.



Scheme 100: Comparison of Westphal reaction and our synthetic pathway.

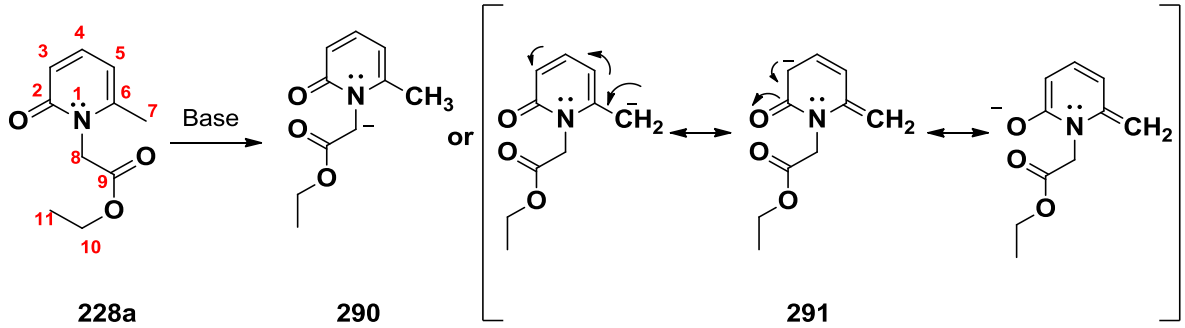
We based our synthesis of quinolizinones on the Westphal reaction, and employed a similar pathway to synthesize quinolizinone derivatives, as shown in **Scheme 100**. We were focussed on the following pyridones **228a,b,c,g**. Due to its properties, pyridone **228a** was chosen because it bears an ester group, which can stabilise anion formation at α-position to the carbonyl of the ester group, and pyridones **228c** and **228g** were chosen because the phenyl group can similarly, though to a lesser extent, stabilise an anion at the same position. On the other hand, pyridone **228b** was also selected because it is an interesting building block due to the lack of substituents.

In the synthesis of 4*H*-quinolizin-4-one derivatives, a stronger base was used in order to deprotonate CH_2 position α to the carbonyl (position 8, **Scheme 101**), in comparison with Westphal reaction, where triethylamine was strong enough to deprotonate position 8 in a α-methylcycloimmonium salt, to obtain an equilibrium amount of N-ylide intermediate. The anion was stable because it has a positive charge on the nitrogen atom close to the negative charge in position 8, and for the ester group as shown in the **Scheme 101**:



Scheme 101: Structures of N-ylide intermediate (277a and 278a).

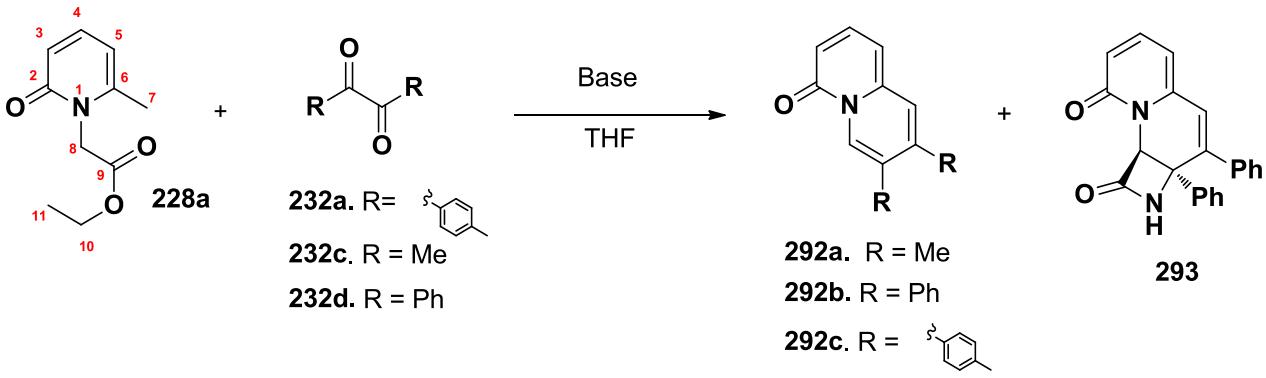
However in ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** the nitrogen atom has a lone pair, reducing the electron withdrawing effect of the carbonyl group, so the anion is less stable (**Scheme 102**), and a stronger base was required.



Scheme 102 : Equilibrium of N-ylide intermediate.

As shown in the following **Table 37**, NaH was chosen as a base in order to deprotonate compound **228a**, because NaH is considerably stronger than triethylamine. However, NaH proved not to be strong enough to deprotonate positions 8 or 7, and 2-pyridone **228a** was recovered (entry 1). Considering this result, in entry 2, potassium bis(trimethylsilyl)amide (KHMDS) was next used to deprotonate the pyridone compound. This base was chosen due to its strength (pK_a= 30), and non-nucleophilic properties.

Table 37: Conditions for the synthesis of 4H-quinolizin-4-one.



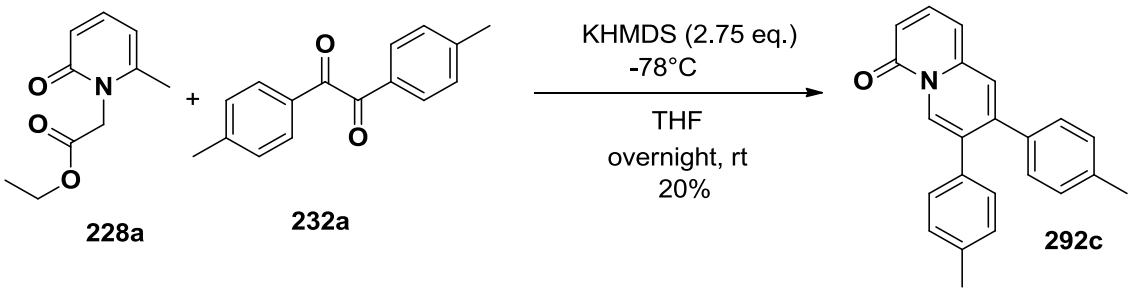
Entry	Pyridone 296a	1,2-Dicarbonyl (eq.)	Base (eq.)	Time (h)	Temp (°C)	Product Yield (%)
1	1 eq.	**a** 1.2 eq	NaH (4)	24	-78 °C *	SM
2	1 eq.	**c** 1.2 eq.	KHMDS (2.75)	24	-78 °C *	Complex mixture
3	1 eq.	**a** 1.2 eq	KHMDS (2.75)	24	-78 °C *	**292c** (20%)
4	1 eq.	**d** 1.2 eq.	KHMDS (2.75)	24	-78 °C *	**293** (12%)

*** The base was added to the mixture of compound 296 and 306 at -78 °C and then the reaction was slowly warmed up to room temperature (20 °C).**

As a general procedure in all the reactions in **Table 37**, Ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** and the diketone were dissolved in THF and then the base was added to the reaction mixture, an excess of base was needed to deprotonate both positions, the pyridone methyl group (C-7) and the CH_2 of (C-8). In order to generate the dianion in the presence of the electrophile (1,2-diketone). This way should decrease the probability of pyridone dimerization, and also could increase the rate of the reaction.

In entry 2, 1,2-butanedione **232c** was used as electrophile and the reaction led to a complex product mixture. The reason could be that both starting materials, 2-pyridone and 1,2-butanedione, were susceptible to deprotonation allowing side reactions to occur.

The same conditions to generate the dianion were used in entry 3, in order to react with 4,4'-dimethylbenzil **232a**, and pleasingly afforded the expected quinolizinone **292c**, albeit in a low 20 % yield. The structure was confirmed by ^{1}H NMR spectroscopy and HRMS, however, the sample was insufficient to obtain a ^{13}C NMR spectrum.



Scheme 103: Synthesis of 4H-quinolizin-4-one 292c.

The same conditions were used to generate the dianion, and benzil was used as an electrophile for the attempted synthesis of 4H-quinolizin-4-one **292b**, (entry 4, **Table 37**). The formation of quinazolin-4-one **293** was expected, however the reaction formed a complex mixture of products, and none of the expected quinolizinone **292b** was obtained after chromatographic separation of the crude product mixture. The only compound that could be obtained pure was the fused azetidinone **293**, in which the quinolizin-4-one ring skeleton had formed, but to which was attached a fused 4-membered lactam ring.

The presence of a 4-memebered lactam ring in the molecule was suggested by IR spectrum which showed absorption at 1776cm^{-1} indicating the presence of a small ring carbonyl group, and by ^{1}H NMR spectroscopy, which showed an broad signal at δ 10.29 ppm consistent with NH and a CH singlet at δ 5.86 ppm (H-9a). The absence of triplet and quartet signals for an ethyl ester indicated that this group had been transformed. The ^{13}C NMR spectrum showed a signal at δ 68.1 ppm consistent with a saturated CH (C-9a) and two carbonyl signals at δ 164.7 and 160.5 ppm.

The structure of the molecule was confirmed by single crystal X-ray diffraction analysis, which confirmed the presence of the 4-membered lactam. The compound was found to exist as a mono-ethanol solvate **363** (**Figure 51**).

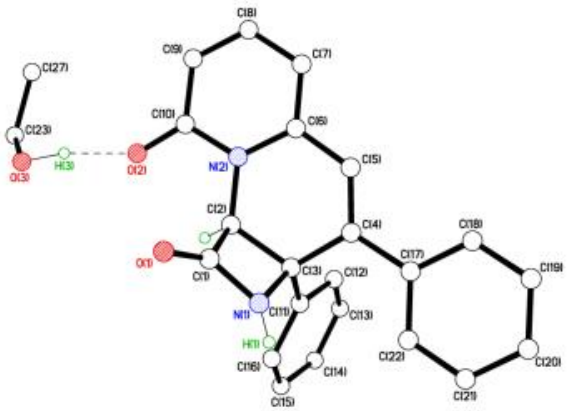


Figure 51: X-Ray crystal structure of compound 293.

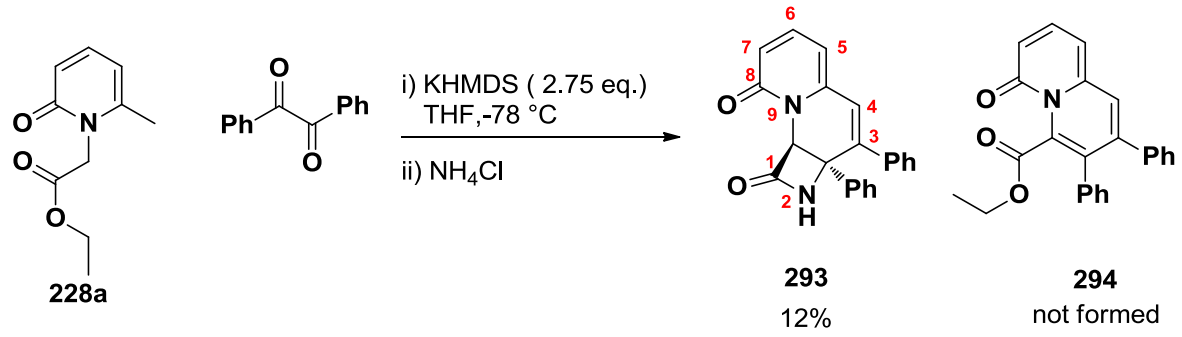
Yellow crystals with a plate morphology were formed by slow evaporation of an ethanolic solution of **293**. Due to their small size and weak diffracting power, data were collected using synchrotron radiation at the Advance Light Source in the US. The molecules were found to form head-to-tail $R^4_4(18)$ H-bonded pairs via inserted ethanol molecules. Hydrogen bond geometry is shown in **Table 38**.

Table 38: Hydrogen-bond geometry (Å,°) for 9·EtOH.

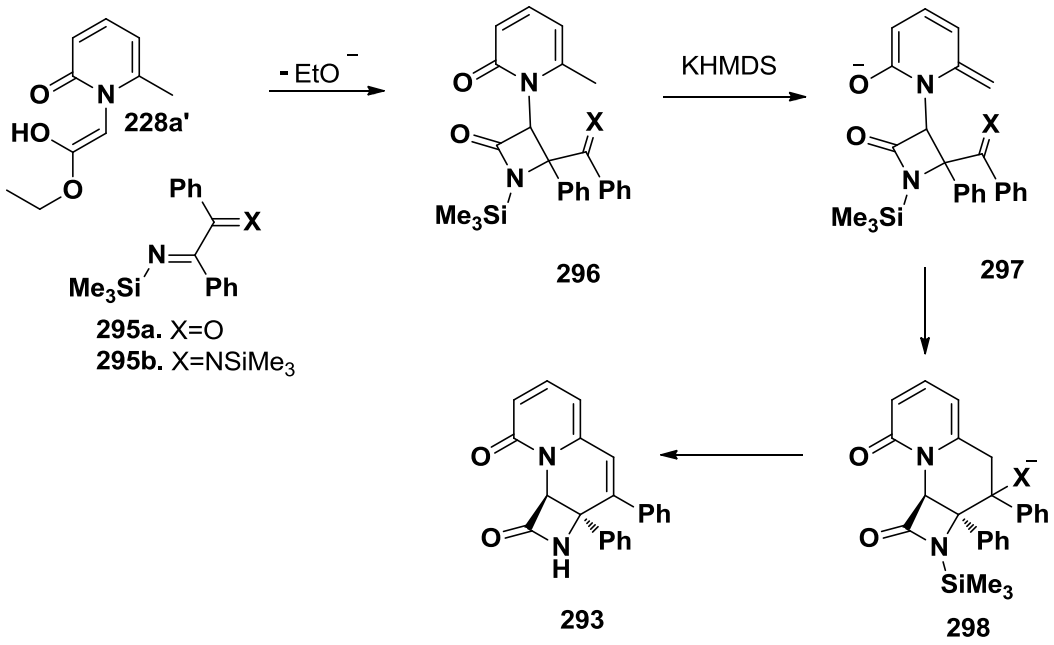
D-H•••A	D-H	H···A	D···A	D-H···A
N1-H1···O3(A)	0.92 (2)	1.92 (2)	2.8305 (17)	168 (2)
O3-H3···O2	0.98 (3)	1.71 (3)	2.6651 (16)	165 (2)
Symmetry code: (A) *–x*, *-y* + 1, *-z* + 1.				

The formation of the fused azetidinone product **293** was unexpected and a number mechanisms for generation of the 4-membered lactam ring compound can be imagined. It is not clear how the nitrogen atom of the lactam ring was introduced into the molecule, or the order of the ring forming steps. The azetidinone nitrogen is most likely to be derived from the hexamethyldisilazane (HMDS) formed as a by-product during deprotonation by the KHMDS. The most plausible mechanism proposed in **Scheme 105** involves formation of the ester enolate **294** by deprotonation of **228a** with KHMDS, and reaction of the HMDS produced *in situ*, or the excess KHMDS, with benzil **232d** to form either the mono-(**295a**) or bis-imine(**295b**). Either electrophile could then condense with the anion

228a' to form the azetidinone derivative **296**. The reaction of imines with ester enolates is a well established method to form 4-membered lactams. Subsequent deprotonation of the 6-methyl group of the pyridone ring would generate enolate **297**, the *cis* diastereoisomer of which could undergo intramolecular aldol reaction with the ketone (X=O) or silylimine (X=NSiMe$_3$) group forming **298.** Subsequent elimination would then generate the observed product **293**, which was isolated after aqueous work-up and extraction.



Scheme 104: Synthesis of 2a,3-diphenyl-2,2a-dihydro-1H-azeto[2,3-c]quinolizine-1,8(9aH)-dione (293).



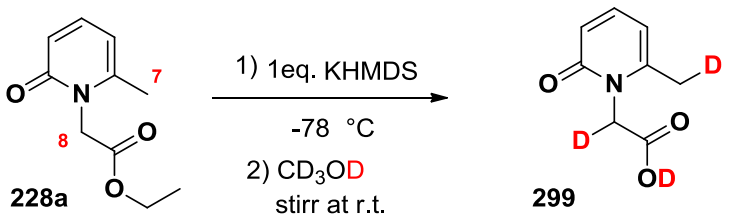
Scheme 105: Possible mechanism for formation of azeto[2,3-c]quinolizine (293).

The formation of a 4-membered β-lactam ring was unexpected, however, it demonstrated that ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** was acting as a 1,4-dinucleophile (C-C substrate) in the presence of the 1,2-diketones. The quinolizinone scaffold was therefore successfully formed, as shown in the **Scheme 104.**

When pyridone **228a** was used as the starting material, a side reaction took place resulting as decarboxylation, so the ethoxy group was lost in the reaction. The NMR spectrum of the crude product did not show any ester group signals of the pyridone signals. The pyridone compound disappeared in the reaction. However, only a small quantity of desired products **292c** and **293** were isolated. In order to synthesize 4*H*-quinolizin-4-one compounds, different conditions were studied, such as different temperatures, and numbers of equivalents of base, and the order of the reagent addition was altered to investigate changes in the reactivity. However, in all the reactions, poor yields and significant quantities of by-products were obtained. In order to understand the behaviour of the pyridone, a deuteration study was undertaken, as outlined below.

4.2.1- Study of selective deprotonation of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate.

In order to study the deprotonation reactivity of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate **228a**, we decided to employ CD_3OD as electrophile. Ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** was firstly treated with one equivalent of base at -78 °C. The reaction was stirred over 20 to 30 min and then quenched with CD_3OD, and the reaction mixture was then warmed up to room temperature and stirred at room temperature overnight. The solvent was removed under vacuum after the quenching, but before the extraction with ethyl acetate. The base was shown to deprotonate both position 7 and 8, however also the ester group was cleaved.



Scheme 106: Deuterated study of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate.

In the following figure is the comparison of starting material **228a** and the deuterated product **299**.

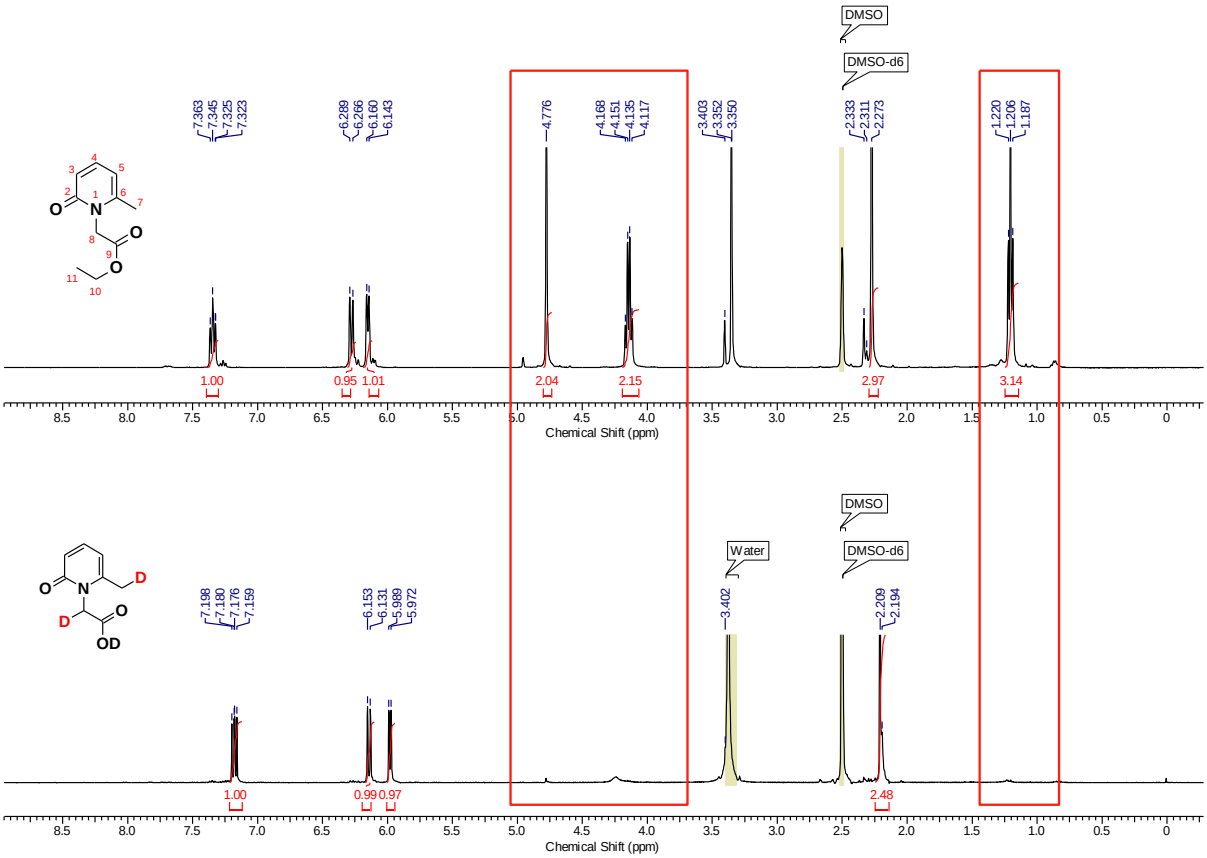


Figure 52: ^{1}H NMR spectra comparison of the starting material pyridone (228a) and the deuterated derivative (299).

Comparing the starting material **228a** with the deuterated product, ^{1}H NMR analysis showed that the ethoxy group is fully lost, the quartet signal (CH_2, C-10) at 4.15 ppm and the triplet signal (CH_3, C-11) at 1.21 ppm had disappeared.

The NMR spectrum (**Figure 52**) showed that when the pyridone was treated only with 1 eq. of base, the methyl group and the methylene group of the acetate substituent were deprotonated, but the main product had deuterium at position C-8, as the methylene signal was absent and the signal for the methyl group at 2.21 ppm still showed. Nevertheless, a new signal at 2.19 ppm appeared in the spectrum and this corresponding to a CH_2D group at C-7.

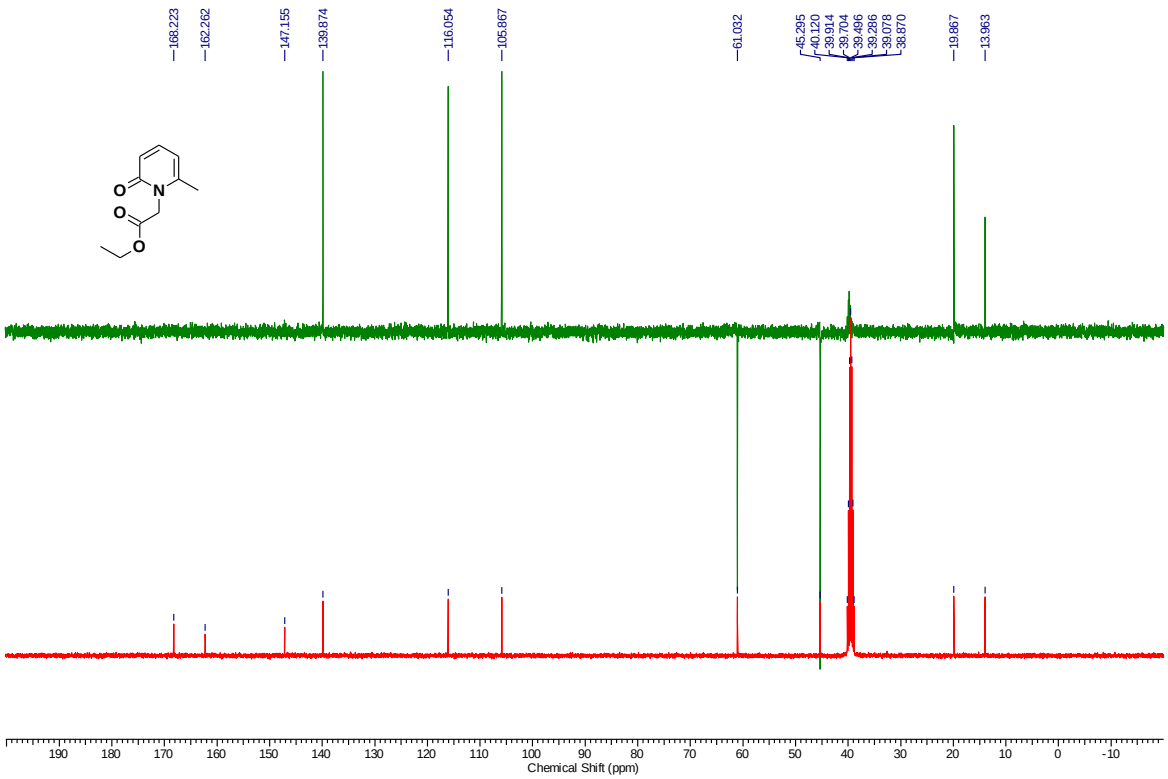


Figure 53: ^{13}C and DEPT spectra of Ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate (228a) in DMSO-d_6.

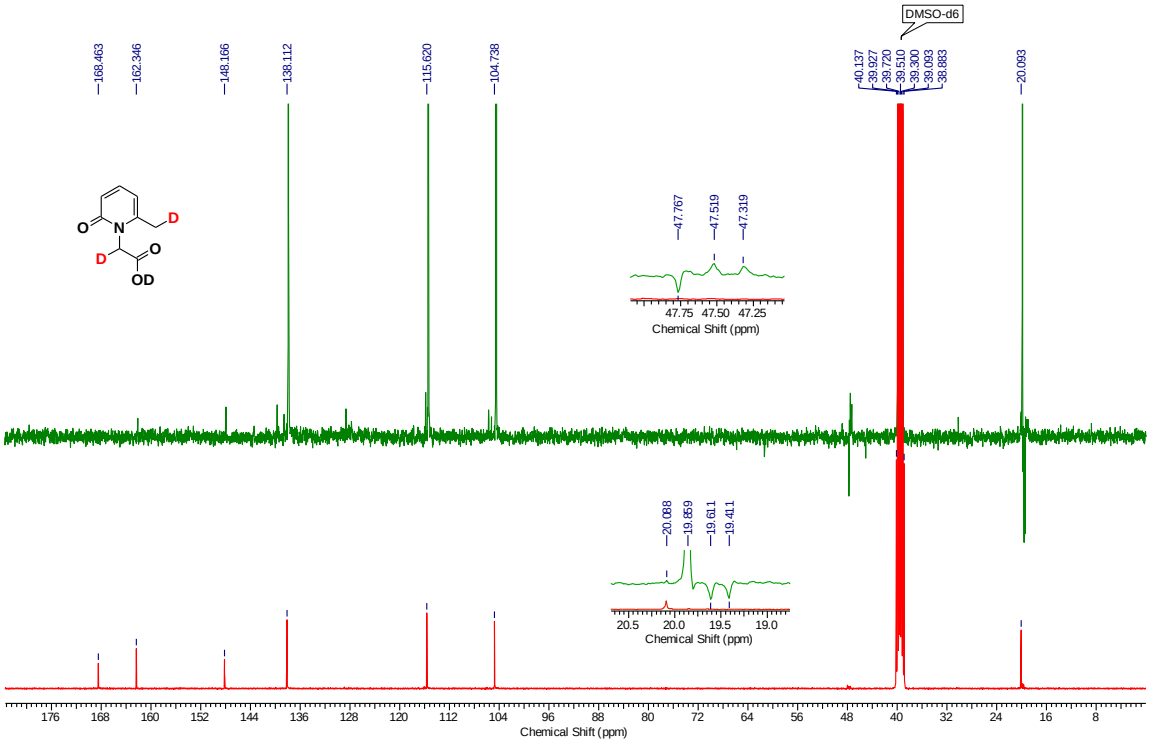


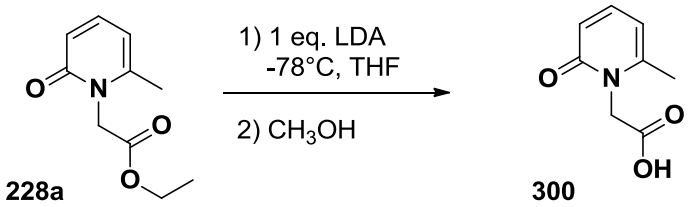
Figure 54: ^{13}C and DEPT spectra of the deuterated compound (299).

The formation of the deuterated compound was confirmed by ^{13}C NMR spectroscopy. The ^{13}C and DEPT spectra for the starting material are shown in **Figure 53**. The corresponding ^{13}C and DEPT for the deuterated material are shown in **Figure 54**. And also, the disappearance of the ester group was confirmed by ^{13}C and DEPT NMR spectra, the CH_2 signal at 61 ppm and the CH_3 at 14 ppm disappeared.

The peaks at 61 and 45 ppm correspond to C-10 and C-8 in **228a**, (**Figure 53**). In the spectra of the deuterated material, the signals at 61 ppm had disappeared, while the C-8 signal showed a positive triplet for CHD and reduced negative singlet for the remaining CH_2 **Figure 54**. The lack of signals at 61 and 13 ppm confirmed that the ester group disappeared. The information in the ^{13}C and DEPT NMR spectra confirmed that the ester had hydrolysed to the acid group, because there was a signal at 168 ppm, which corresponding to C-9.

Likewise a negative triplet at 19.6 ppm indicated CH_2D (C-7) for the partially deuterated methyl group.

Also, in order to confirm that the ester group is hydrolysed to the acid, the following study was designed (**Scheme 107**) where the quenching step was with non-deuterated methanol at -78°C:



228a 300

Scheme 107: Formation of compound 300.

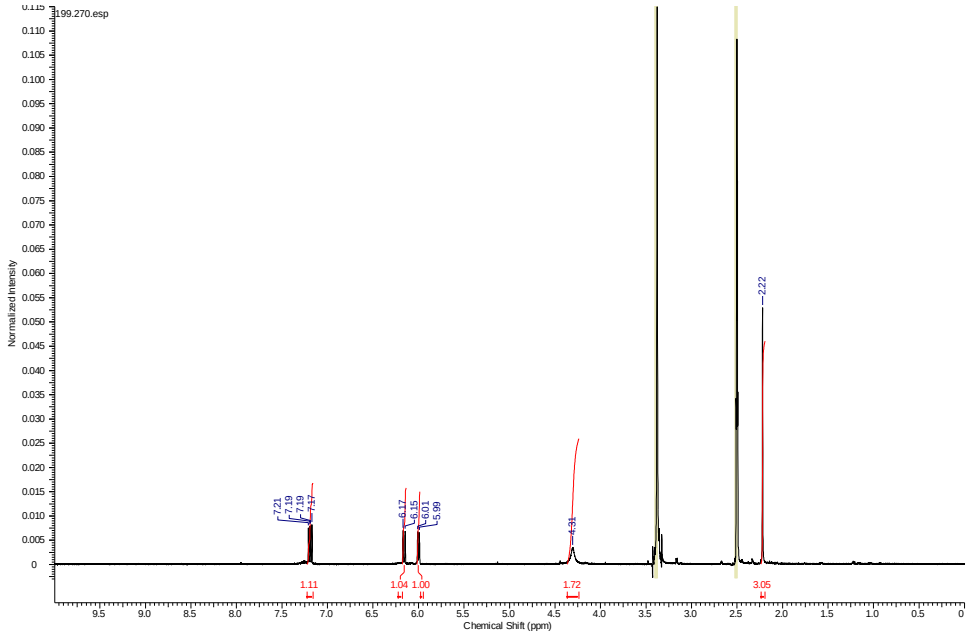


Figure 55: 1H spectrum of the non-deuterated compound (300).

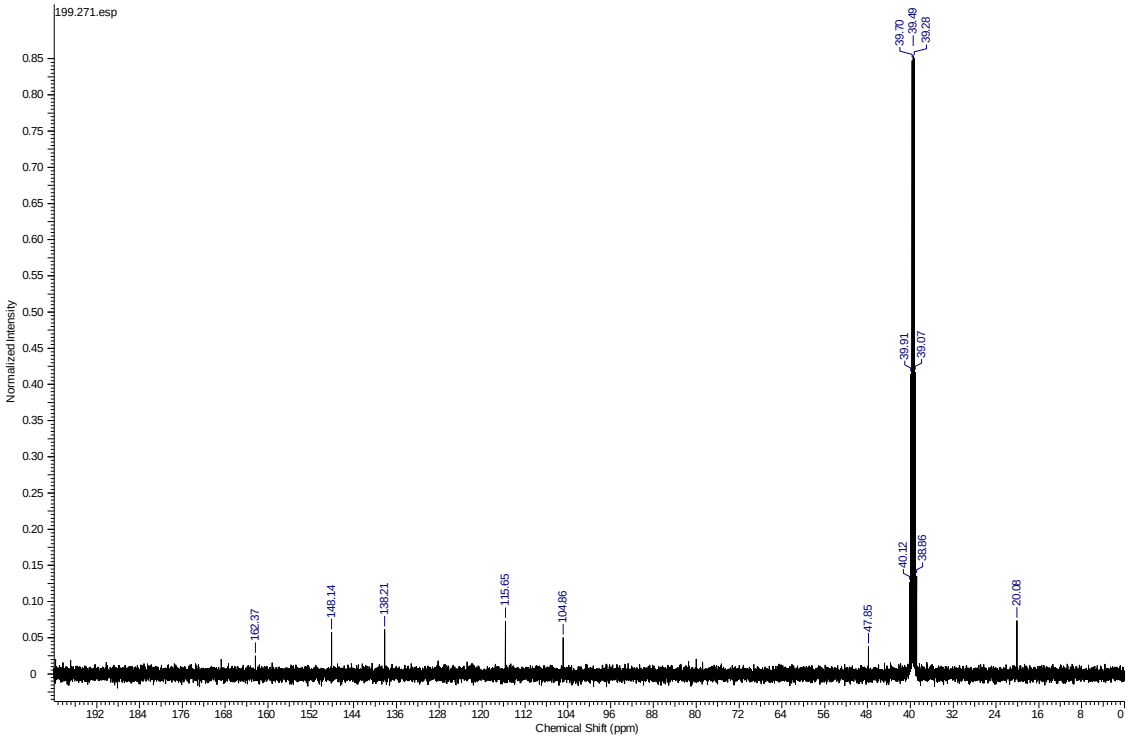


Figure 56: 13C spectrum of the non-deuterated compound (300).

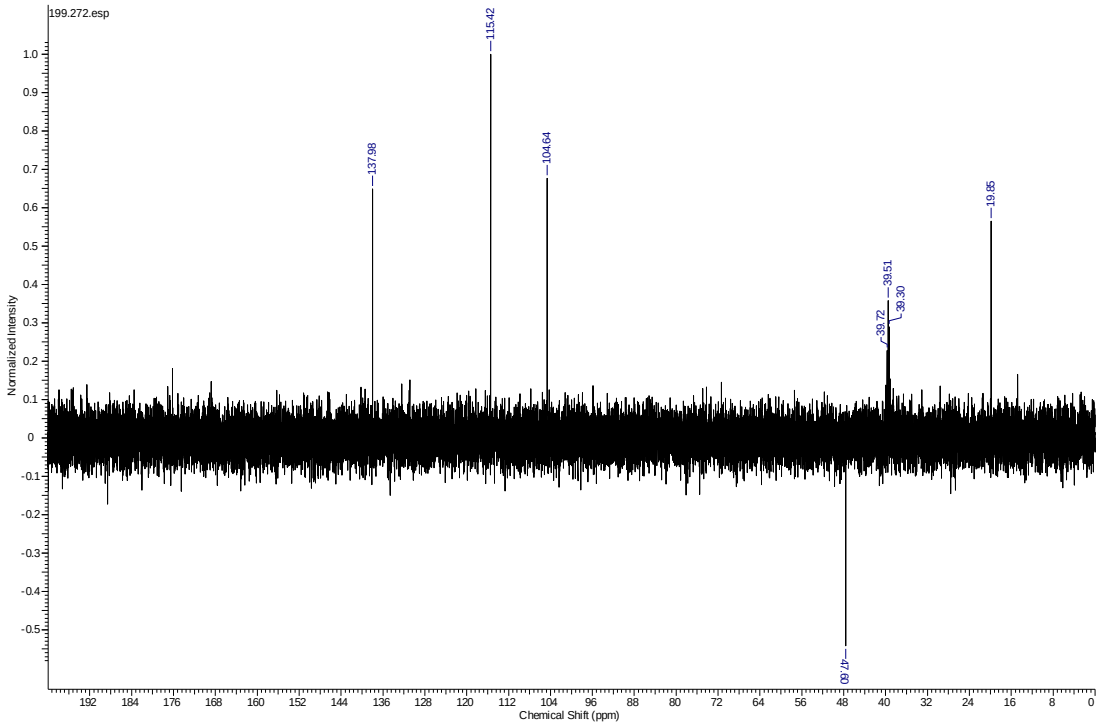
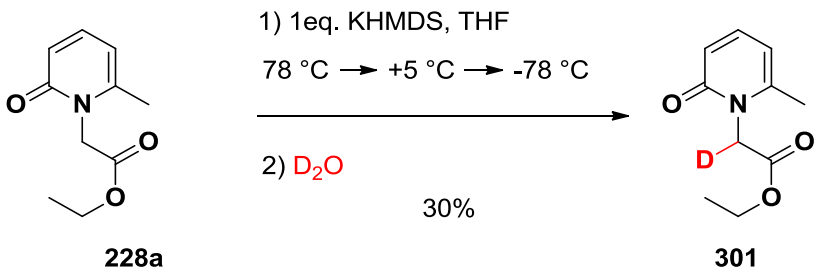


Figure 57: DEPT spectrum of the non-deuterated compound (300).

The conclusion of this reaction was that the ester group was cleaved, as the ^{1}H NMR spectrum shows the C-10 (quartet at 4.15) and C-11 (triplet at 1.21) signals of the ester group had disappeared. However, the signal at 4.31 ppm of CH_2 (C-8) was still present in the ^{1}H NMR spectrum.

The last experiment we did to conclude the study was to control the temperature. The pyridone **228a** was dissolved in THF and the solution was cooled at -78 °C. The base, KHMDS, was added at -78 °C and then the reaction was warmed up to 0 °C, and then cooled down to -78 °C. Then D_2O was added at -78 °C and the reaction was allowed to proceed for 10 min at -78 °C. NH_4Cl(aq) was added and the product extracted with ethyl acetate. The solvent was removed under vacuum and the mono-deuterated product at C-8 was obtained in 30% yield.

The mains differences were that the reaction did not reach room temperature, and the THF was not removed under vacuum before the extraction, so the work-up was performed directly on the reaction mixture.



Scheme 108: Deuterated study of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate at -78 °C.

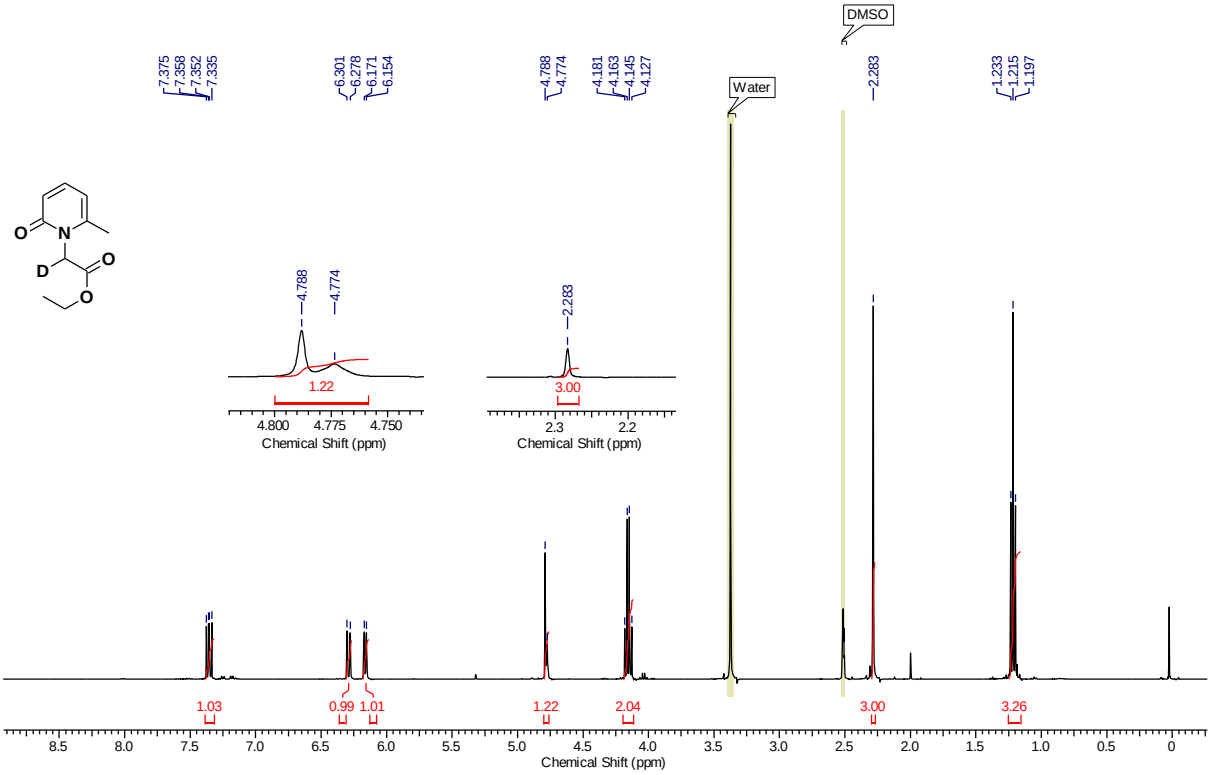


Figure 58: ^{1}H NMR Spectrum of mono-deuterated ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate.

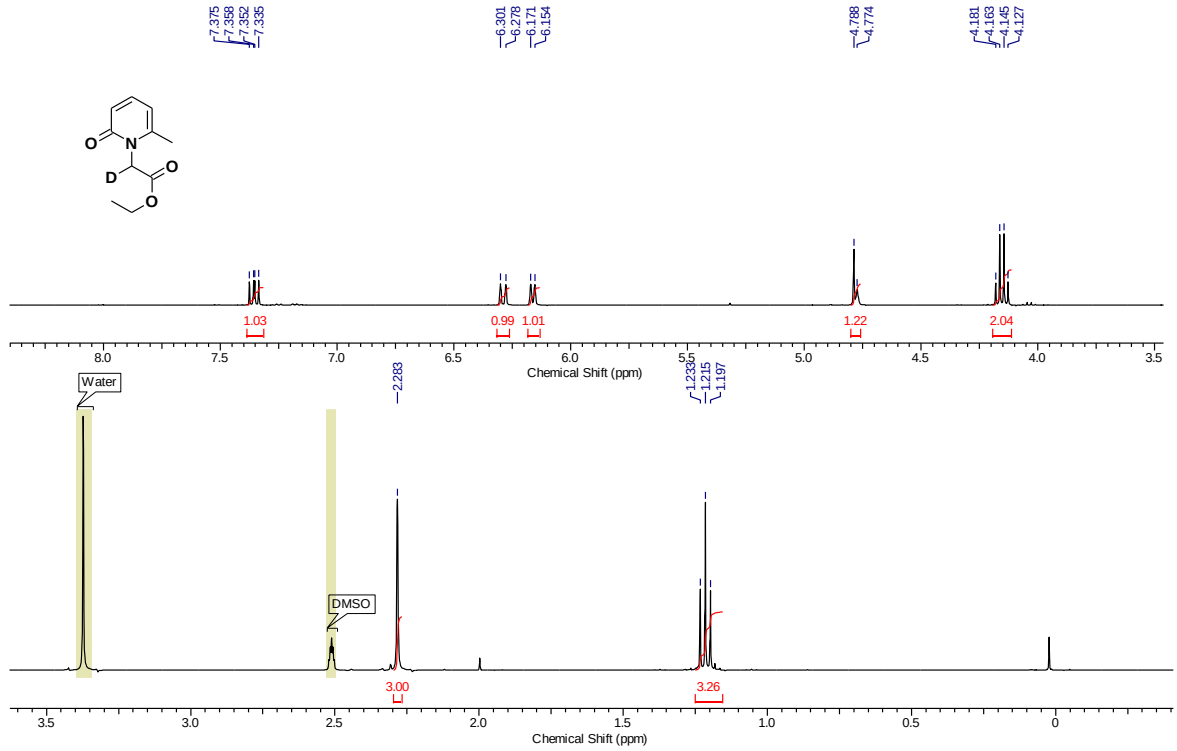


Figure 59: Expansion of mono-deuterated ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate.

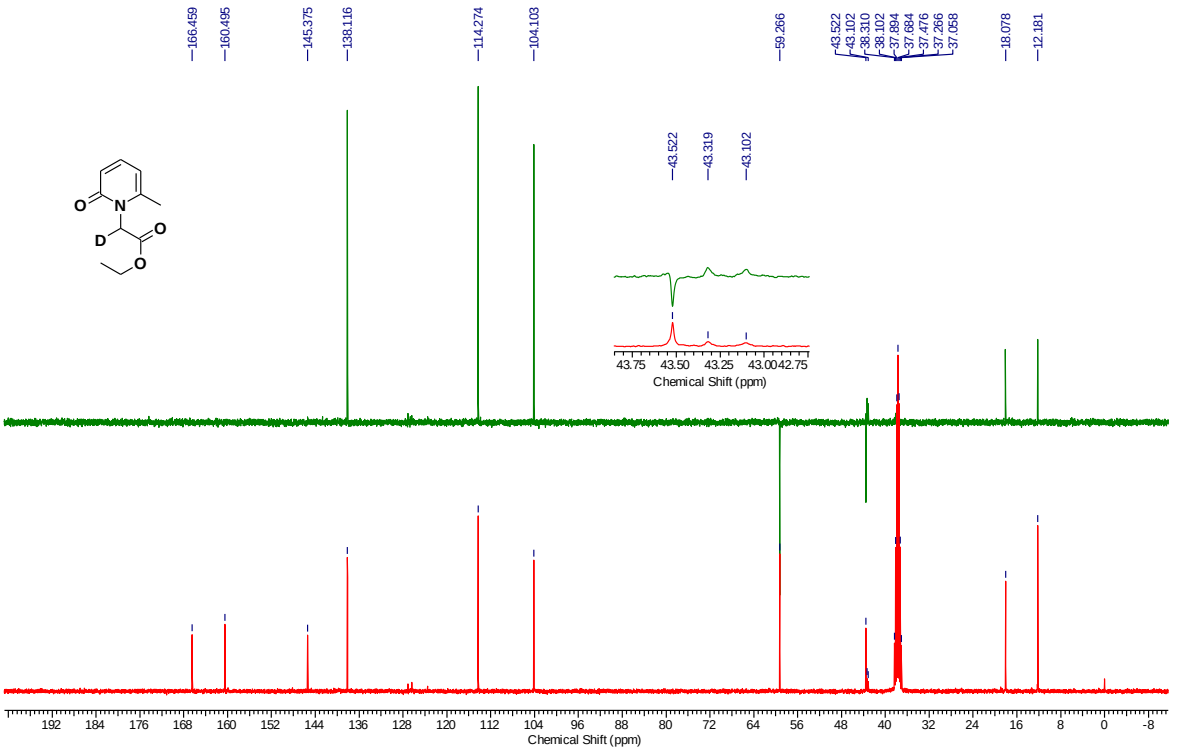


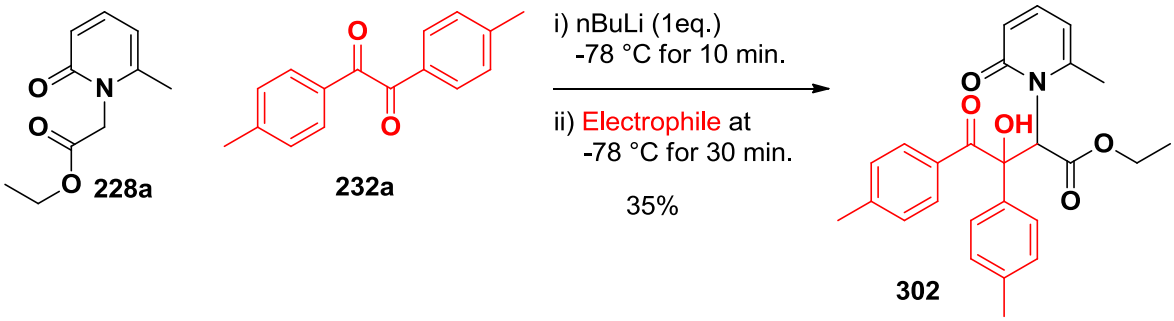
Figure 60: ^{13}C and DEPT NMR spectra of mono-deuterated ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl) acetate.

Only position C-8 was deprotonated, and the ester group was not cleaved.

These experiments showed that the ester group was cleaved during the work-up step. Because the solvent was removed before the extraction, the residue would become basic due to the deuteriomethoxide formed, and the ester group could be hydrolysed on contact with water.

The studies highlighted the importance of neutralising the reaction mixture before evaporation.

To continue the study, the following experiment showed that it was possible to alkylate the ester pyridone at the C-8 position under the following conditions (**Scheme 109**). When the work-up was carried out at -78 °C, the alkylated product at C-8 position was isolated in 35% yield.

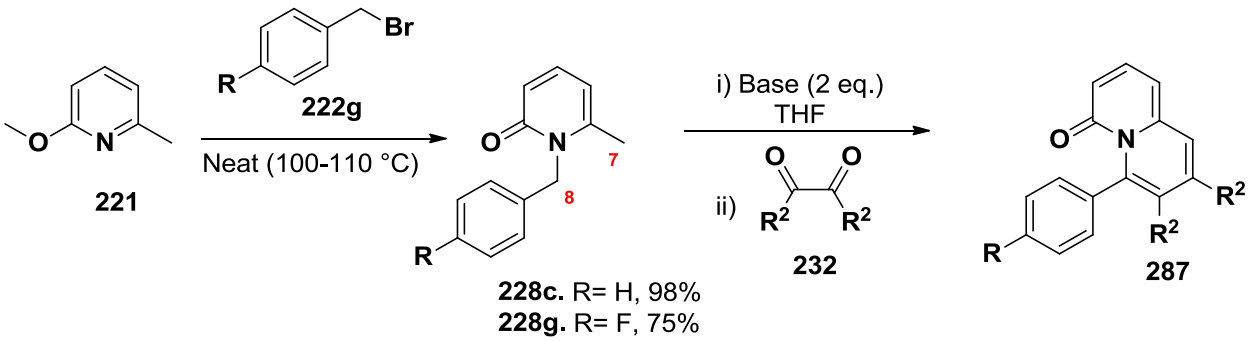


Scheme 109: Synthesis of ethyl 3-hydroxy-2-(6-methyl-2-oxopyridin-1(2H)-yl)-4-oxo-3,4-di-p-tolylbutanoate.

In conclusion, the temperature was a very important variable, as was the work-up step, as demonstrated by the last deuteration experiment and the last synthetic reaction (**Scheme 109**). Also, pyridone **228a** and product **302** are highly soluble in water and THF, and during the work-up step it was not possible to extract all the product from the aqueous layer and the yield was low. However, removing the solvent before the extraction, the ester group would cleave, and side reactions could also occur.

Another possible reason for the by-product formation could be the use of strong base such as LDA or KHMDS, allowing a reactive intermediate forming in the reaction mixture could facilitate side reactions. This could also account for the low yields obtained so far.

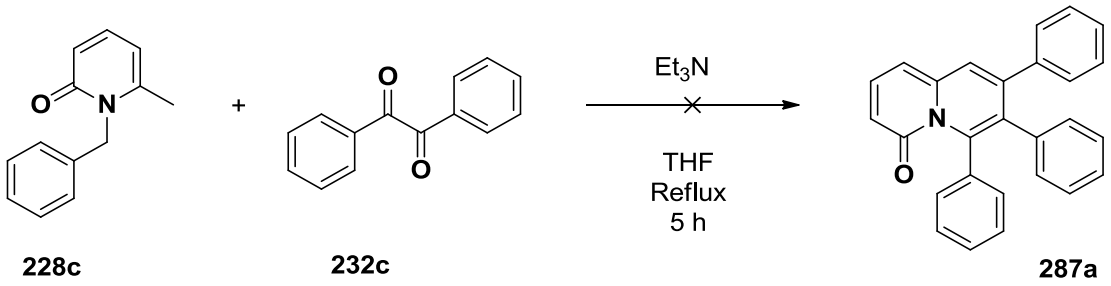
Continuing the quinolizinone study, another pyridone was investigated. In order to avoid the problem of the ester group, **228c** pyridone was chosen as the object of the study.



Scheme 110: General synthesis of 4*H*-quinolizinone derivatives

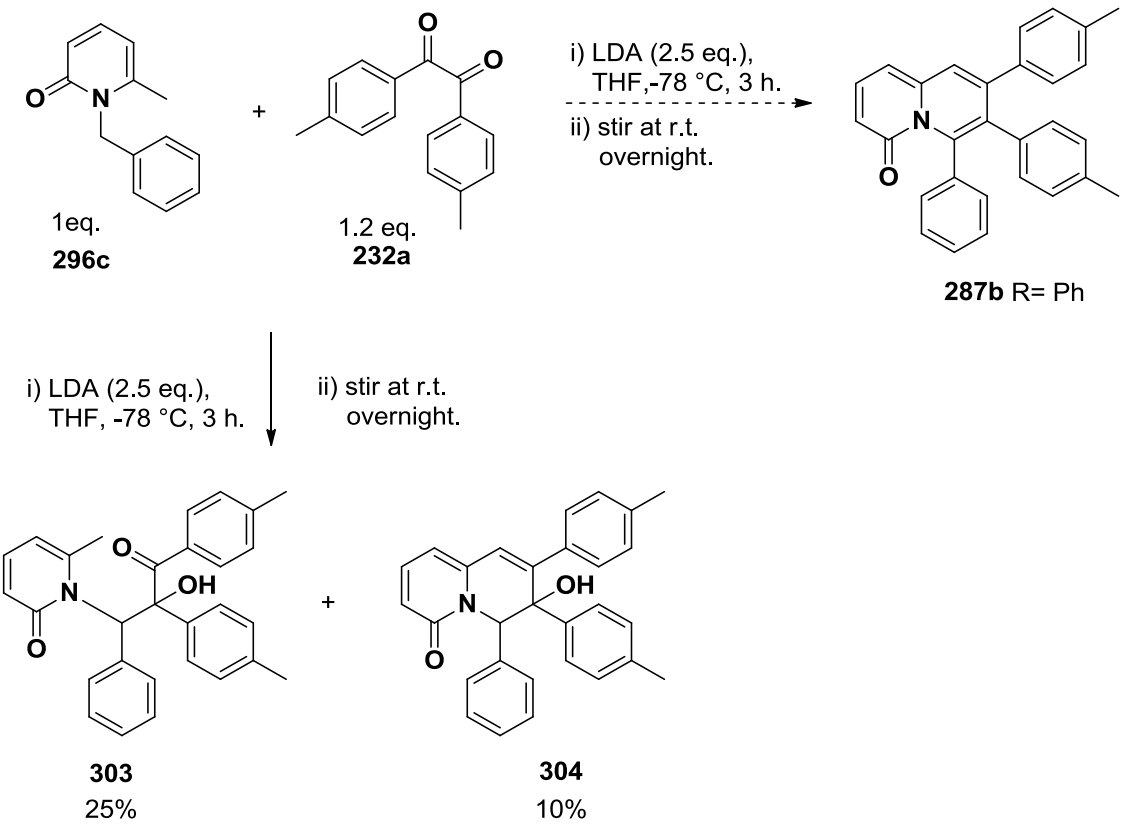
The new pyridone starting material had to have some essential characteristics such as an electron withdrawing group on carbon 8, in order to make this H-atom more acid, therefore ensuring easy deprotonation. Also, the new pyridones would be less soluble in water which would hopefully allow easier isolation.

Using N-benzyl-6-methyl-2-pyridone **228c** we tried to effect the condensation reaction under Westphal conditions (**Scheme 111**), however the reaction did not work. After 5 h under reflux, the reaction mixture became black, so the reaction was stopped, and after the work-up, the NMR spectrum showed only starting material signals. It was concluded that a stronger base was needed and a lower temperature, in order to avoid side reactions.



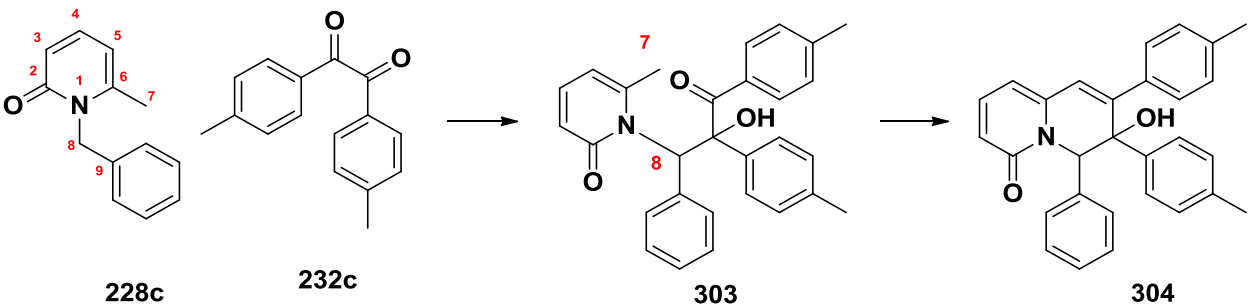
Scheme 111: Atempt to synthesize 287a using westphal reaction condictions.

In the following reaction LDA was used as a base due to its strong and non-nucleophilic properties. The base used was a commercially available solution and the colour was brown. For this reason it was impossible to titrate the base; so, an excess of base was employed. The pyridone and the diketone were dissolved in THF and the reaction mixture cooled to -78 °C. The base was then added and the reaction stirred at -78°C for 3 h. Later, the reaction was warmed up to r.t. and it was stirred overnight. **Scheme 112** shows the synthetic pathway used here to attempt to synthesize compound **287a** however the reaction yielded only the intermediate compounds **303** and **304**.



Scheme 112: Attempt to synthesize quinolizinone 287b.

This experiment confirmed that it was possible to achieve the double alkylation. The compounds **303** and **304** represent intermediates in the synthesis of compound **287b**. Compound **303** was generated via mono addition of pyridone anion at C-8 to diketone **303** in 25 % yield after the purification step.



Scheme 113: Synthesis of compound 303 and 304.

From this intermediate compound **303**, another equivalent of base must have reacted to promote a further nucleophilic addition to the second carbonyl group, affording compound **304** in 10% yield.

Intermediates **303** and **304** were isolated in a combined 35 % yield, and characterised by their ^{1}H and ^{13}C NMR spectra, IR spectra and mass spectra. The ^{1}H NMR spectrum for **303** showed signals for the presence of three methyl groups indicating the pyridone methyl was still present, while the ^{1}H NMR spectrum of **304** showed a signal for the new alkene proton.

Taking into consideration this information led us to make a study of different bases, temperatures, and reaction times.

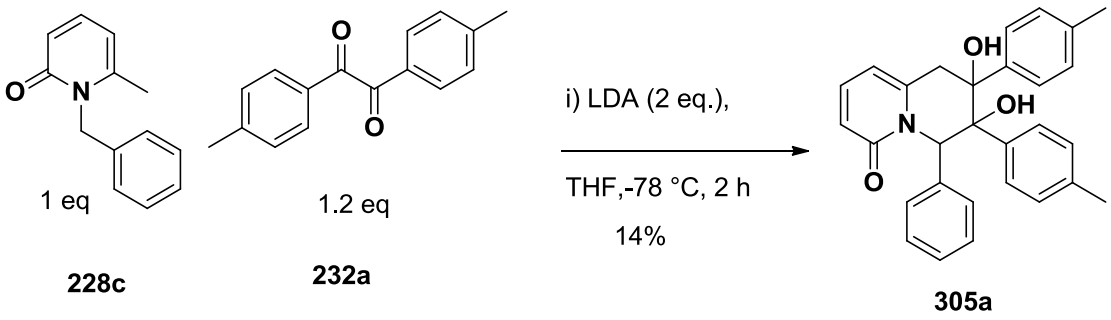
The double alkylation was possible under the previous conditions. Now, we wanted to control the reaction more carefully, in order to better understand the mechanism, and ascertain why the second condensation step had not taken place. One of the reasons could be that the temperature was not high enough.

Following Westphal reaction conditions as a basis to synthesize pyridinium salts, we tried to use a similar pathway to synthesize quinolizinone derivatives. In the Westphal reaction a high temperature was needed to synthesize the pyridinium salt, in order to effect the dehydration step; however in the case of pyridones, when we tried to carry out the reaction at high temperature very messy product mixtures resulted.

The previous reaction (**Scheme 112**) showed that the C-C bond in the methyl and benzylic position could be formed, and at r.t we could obtain one dehydration step.

We decided to carry out the reaction at lower temperature to avoid the uncharacterized by-product formation, and the reaction was attempted under the following conditions. The LDA was prepared *in-situ*, and only 2 eq. of base were used. The reaction was performed at -78 °C, over 2 h and also the work-up was conducted at -78 °C.

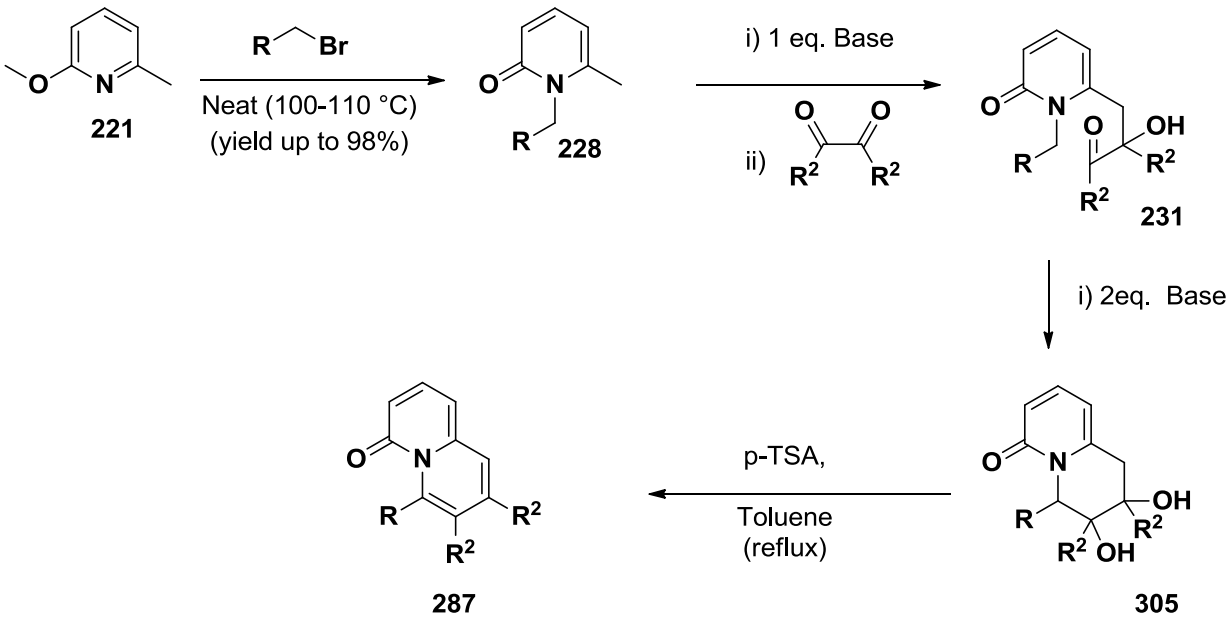
Under these conditions, double alkylation was achieved, and no condensation step occurred, as we predicted due to the low temperature. The final product achieved was the double alkylation product, diol **305**.



Scheme 114: Synthesis of 2,3-dihydroxy-4-phenyl-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one.

The yield obtained was only 14%, and a large number of uncharacterised by-products appeared in the reaction mixture.

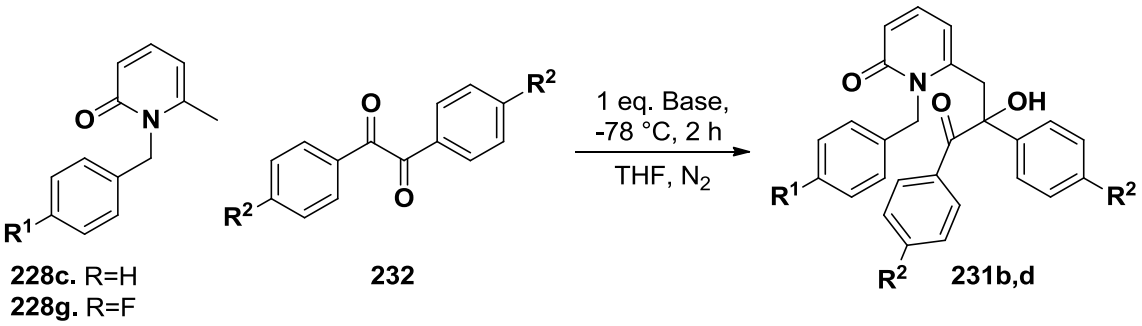
Considering this information, the reaction was carried out in a step-wise manner. Because the yield was low, and a large number of by-products were formed, we needed to know which step was the problematic one. The reaction was broken down in further steps. The carbonyl addition was done in two further steps and also a dehydration step was added to the total synthesis. **Scheme 115** shows the new synthesis pathway.



Scheme 115: Total synthesis pathway of quinolizinone derivatives.

In the new synthesis pathway, 2-pyridone was treated with 1 eq. of base at 78 °C over 2 h and the work-up was also at -78 °C. The results are shown in **Table 39**.

Table 39: Second step in the synthesis of quinolizinone derivatives (mono addition of the diketone to the pyridone scaffold).



228c. R=H
228g. R=F

232

231b,d

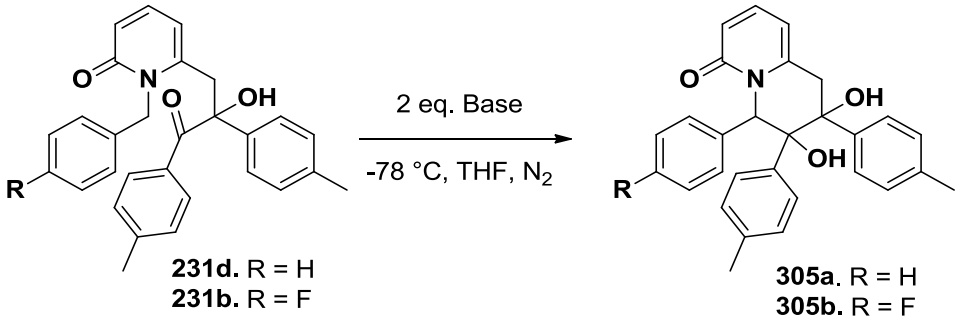
Entry	R^1	R^2	Base	Yield
1	H	CH_3	LDA	80 %
2	H	CH_3	n-BuLi	89 %
3	F	CH_3	LDA	94 %
4	F	Br	LDA	19 %

The addition of different diketones to the mono-metallated 1-benzyl-6-methyl-2-pyridinone, was performed successfully, and in very good yield, except for the case of 4,4'-dibromobenzil which is not very soluble in THF and therefore, gave a reduced yield of 19%.

The mono-alkylation at -78°C went smoothly to the methyl position C-7 in all cases, and no signals corresponding to alkylation in position C-8 appeared. Under these reaction conditions, we obtained a selective alkylation.

Knowing the excellent yield for the mono-alkylation, the second alkylation step was then studied with compounds **231b** and **231d**.

Table 40: Third step in the synthesis of quinolizinone derivatives (second alkylation).



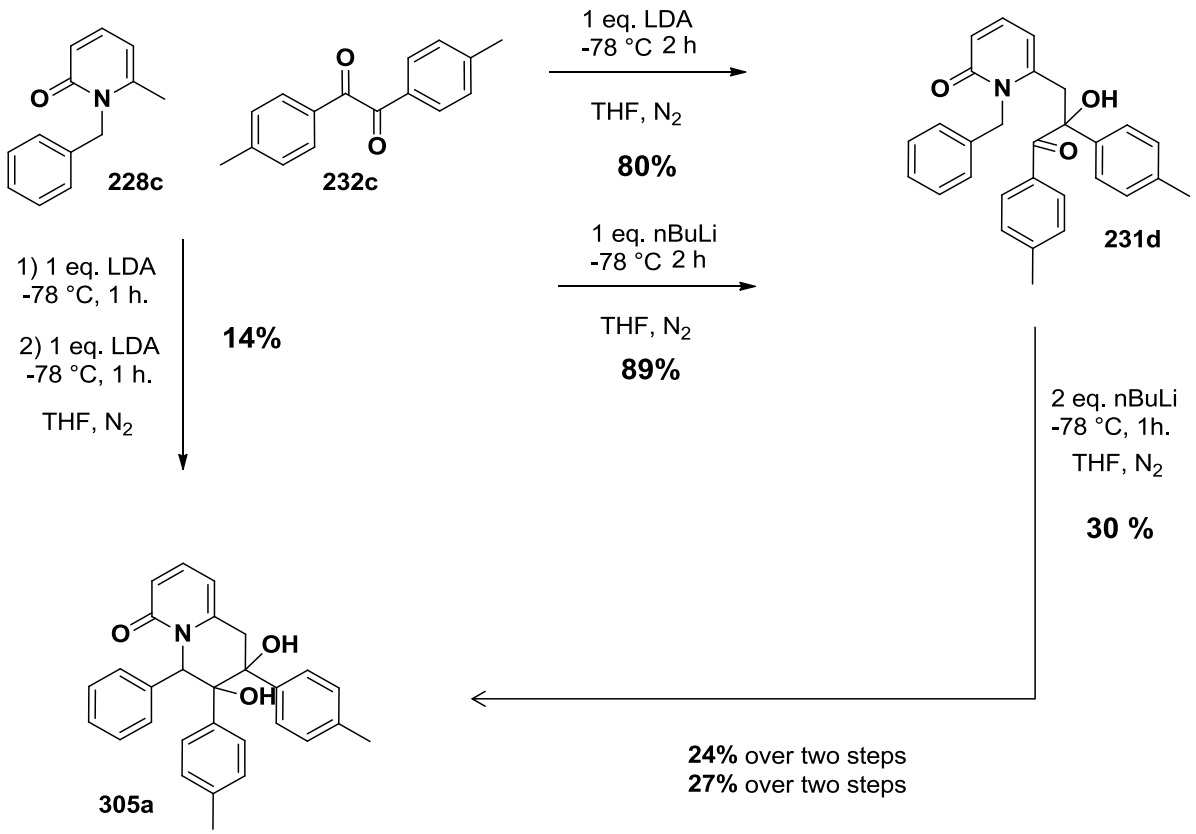
231d. R = H
231b. R = F

305a. R = H
305b. R = F

Entry	R	Base	Time	Yield
1	H	n-BuLi	3 h	13%
2	F	n-BuLi	3 h	10 %
3	H	n-BuLi	**1 h**	30 %

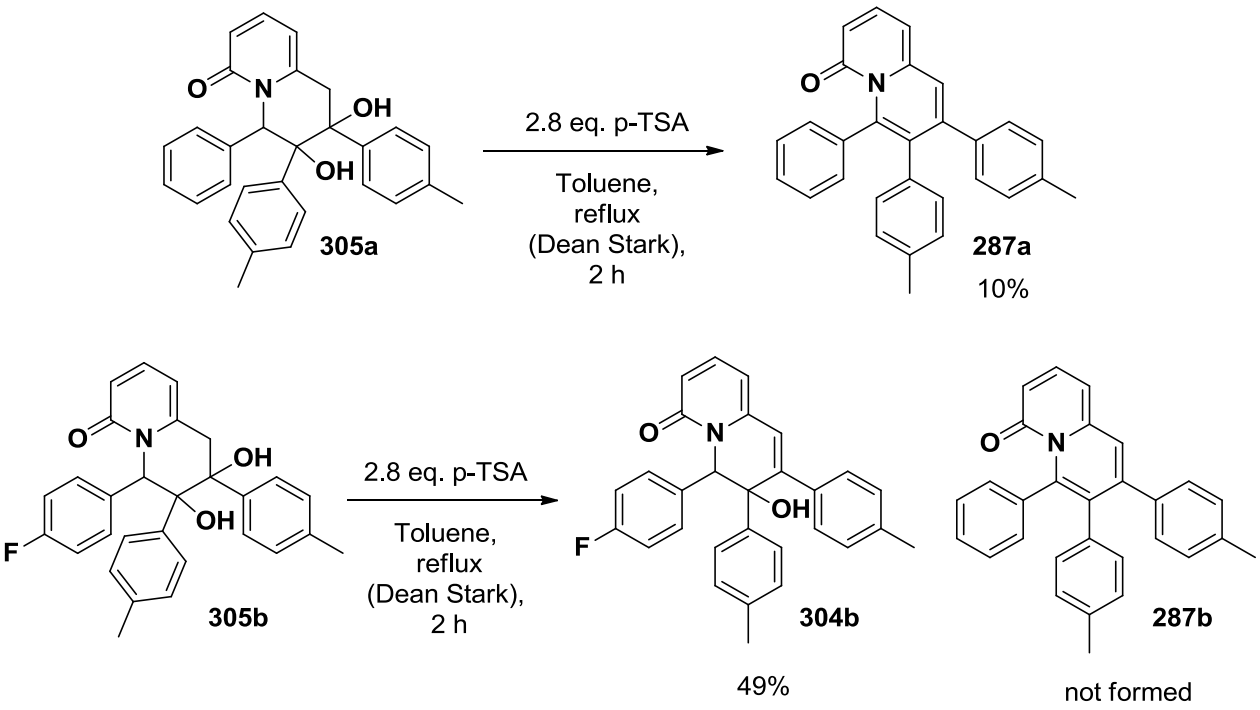
In this reaction, 2 eq. of base were needed, the first equivalent to deprotonate the alcohol and the second one was needed to deprotonate C-8. The diol was achieved, however a large number of by-products appeared during the reaction. The reaction time was an important factor. In entries 1 and 2, the reaction was stirred for 3 h, and the reaction delivered many by-products. In entry 3, the reaction was stirred for only 1 hour at -78°C and yielded the product **305b** in 30%.

In the following scheme, there is the comparison between the one-pot reaction and the stepwise of compound **305a**.



Scheme 116: Comparison between one pot reaction and stepwise reaction.

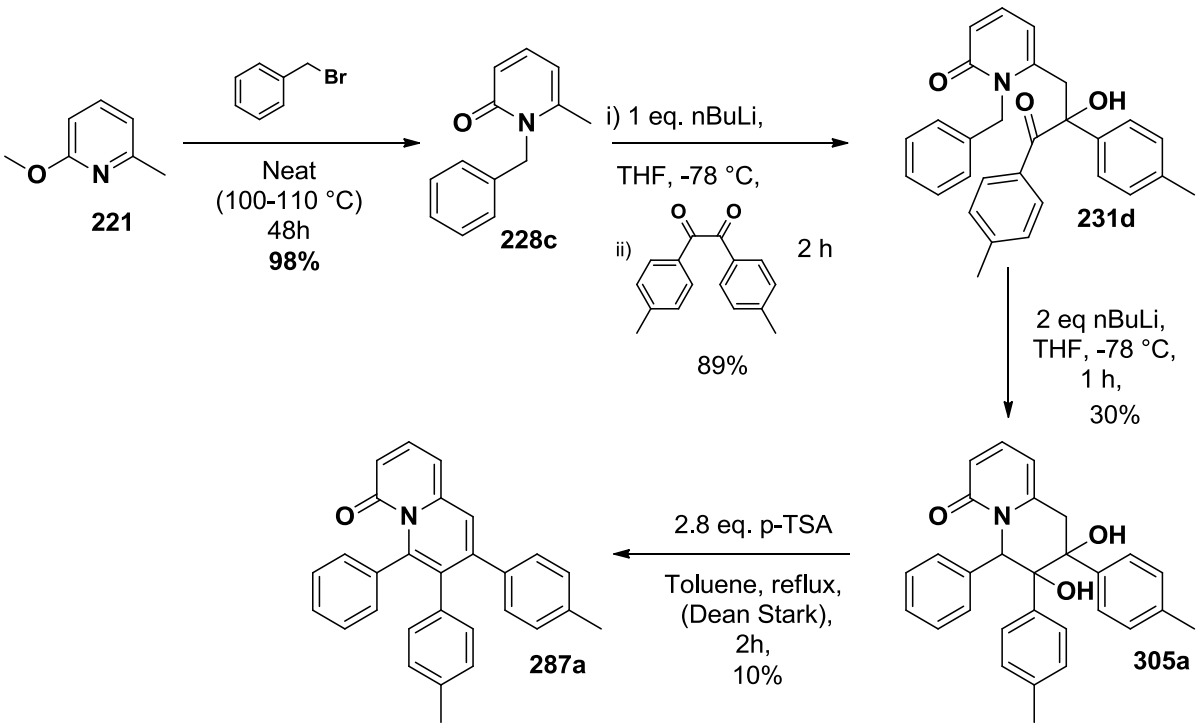
The yield was higher when the reaction was performed stepwise. Having the diol **305a** in hand, the final step (dehydration step) was then performed **Scheme 117**.



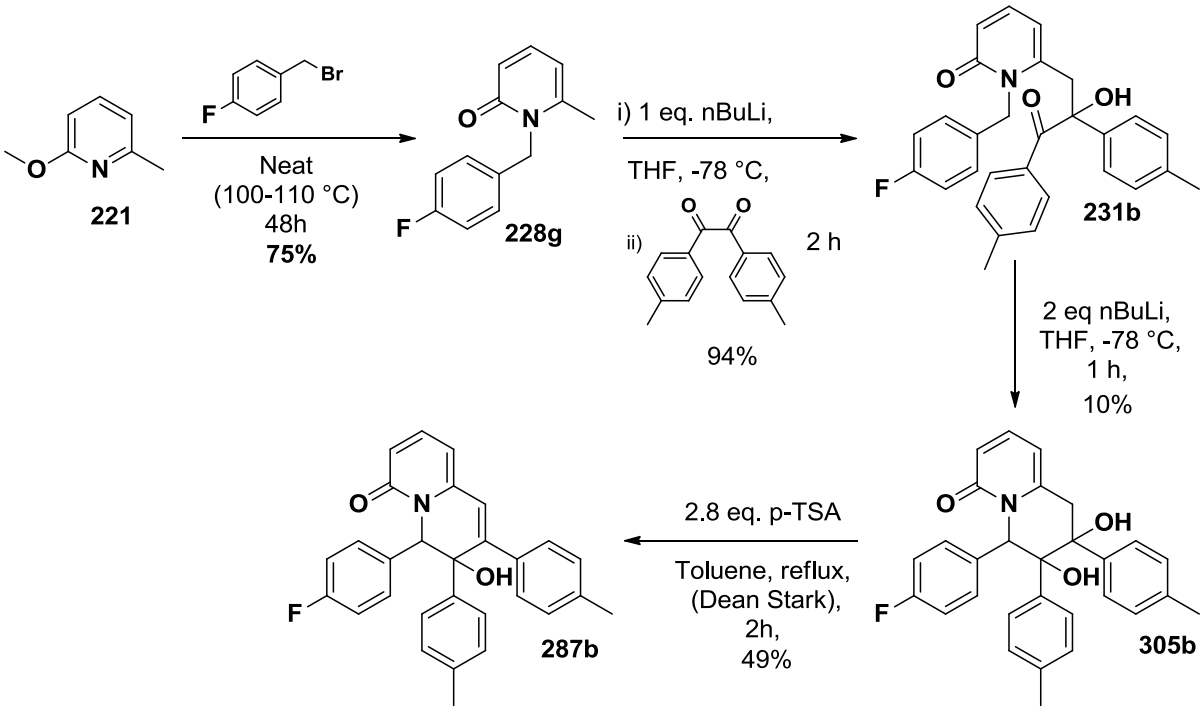
Scheme 117: Fourth step in the synthesis of quinolizinone derivatives (dehydration step).

The total synthesis of compound **287a** was achieved in 10% yield, but for the compound **305b**, only partial dehydration occurred, and one further dehydration step would be needed to form the fully unsaturated quinolizinone **287b**.

In summary, the total synthesis of 4*H*-quinolizinone **287a** and the synthesis of 4-(4-fluorophenyl)-3-hydroxy-2,3-di-p-tolyl-3H-quinolizin-6(4H)-one **304b** are shown in **Scheme 118** and **Scheme 119** respectively.



Scheme 118: Synthesis of 6-phenyl-7,8-di-p-tolyl-4H-quinolizin-4-one.

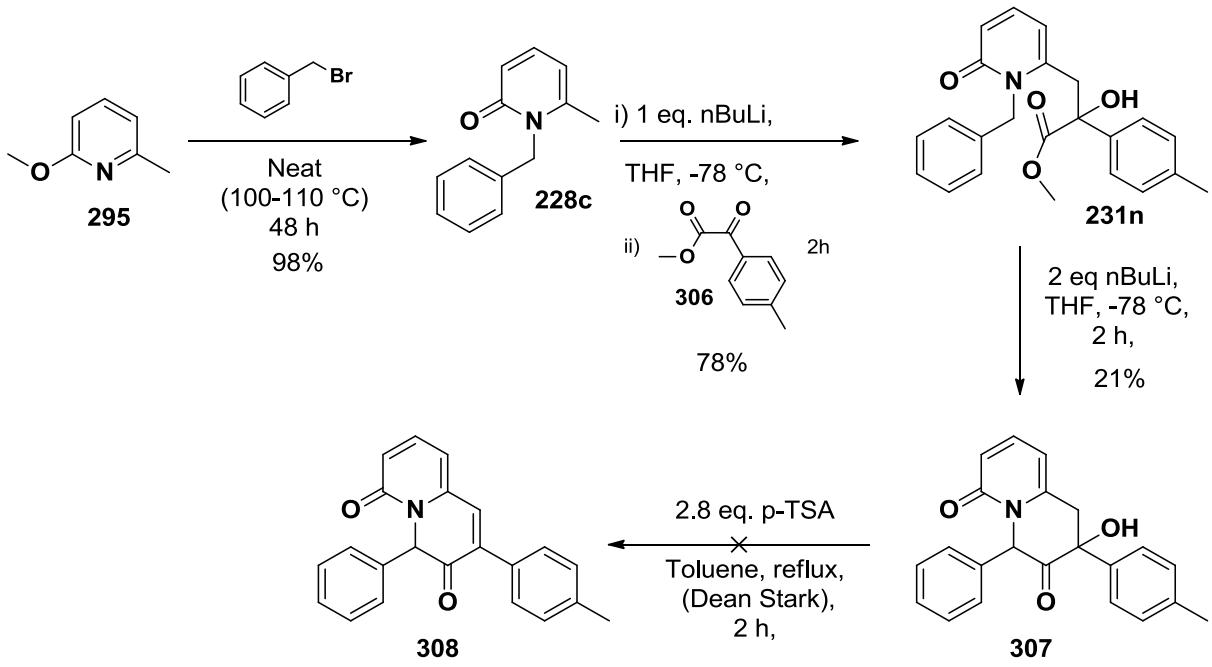


Scheme 119: Synthesis of 4-(4-fluorophenyl)-3-hydroxy-2,3-di-p-tolyl-3H-quinolizin-6(4H)-one.

Continuing the study, the keto-ester electrophile **306** was investigated as another way to synthesize quinolizinone scaffolds.

We chose this new electrophile, due to it being an unsymmetrical dicarbonyl compound, and it was less hindered than the previous diaryl diketones. Also this interesting new scaffold **308** possess a new carbonyl position, which could be a key position for further transformations in drug development.

The two-step alkylation-acylation (compound **307**) was achieved in 21%. The dehydration step has not been achieved so far, and the starting material was recovered after heating in the presence of acid. However, this scaffold **307** bears a ketone group which could be very useful for further reactions.



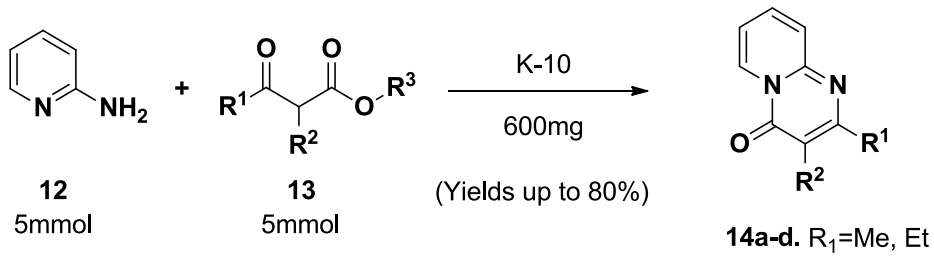
Scheme 120: Synthesis of 4-phenyl-2-(p-tolyl)-3H-quinolizine-3,6(4H)-dione.

These synthesis pathways represent an interesting method to deliver quinolizinone derivatives with different substituents in positions 8, 9 and 10.

In conclusion we developed a straightforward synthesis of the desirable 4H-quinolizin-4-one scaffold, albeit in low yield. Further investigation is required to improve the yield in the second ring-closing step at position 8.

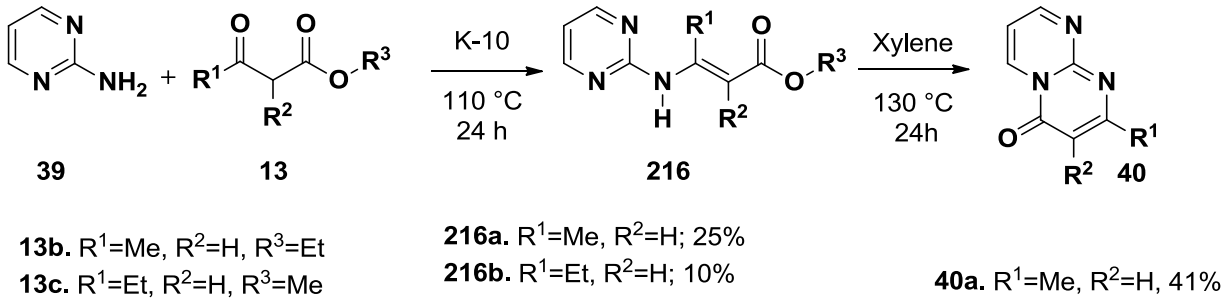
Conclusions

We have developed an efficient, new methodology for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives from commercially available 2-aminopyridines and β-oxoesters. We designed a more environmentally friendly pathway, replacing the corrosive acids conventionally used with milder reagents. In this investigation, the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives were carried out by direct condensation/cyclization of 2-aminopyridine **12** with substituted β-keto esters **13**, catalysed by the clay mineral montmorillonite (K-10) under solvent-free conditions. It was found that the method was an effective, clean process with easy work-up, and also good yields were obtained (**Scheme 121**).



Scheme 121: Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives.

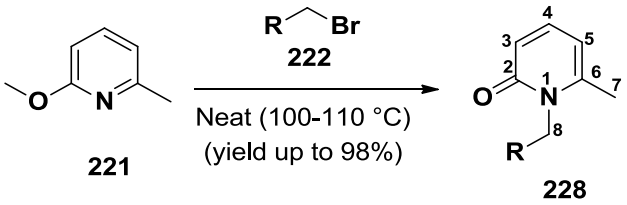
This methodology was expanded for the synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivatives from 2-aminopyrimidine with different β-keto esters, however only mono-addition products, the enamines **216a** and **216b**, were obtained. The synthesis of the 2-methyl-4H-pyrimido[1,2-a]pyrimidin-4-one **40a** required an extra condensation reaction, to cyclise the enamine which occurred only in low yield (**Scheme 122**).



Scheme 122: Synthesis of a 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivative.

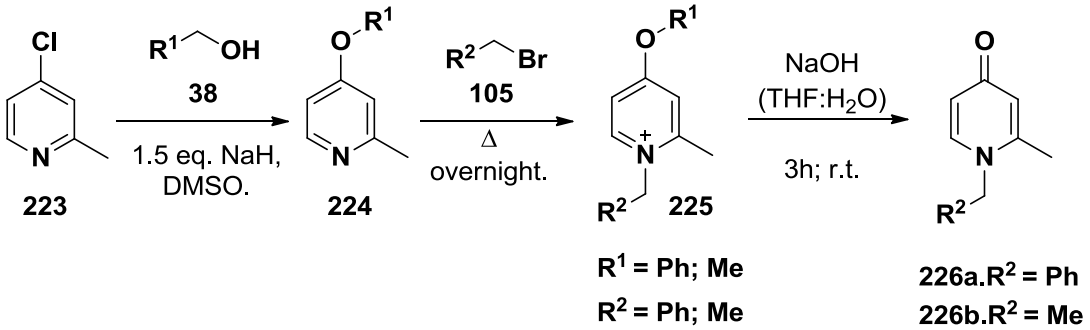
We developed new methodology for the synthesis of N-alkylated 6-methyl 2-pyridones **228** and N-alkylated 2-methyl 4-pyridones **226**, from commercially available starting materials. Selective mono-metallation of the methyl substituent of N-alkylated 6-methyl 2-pyridones and N-alkylated 2-methyl 4-pyridones with n-BuLi/KHMDS at -78 °C proceded smoothly, and the resulting lithiated intermediates were shown to react with a wide range of electrophiles (diketones, aldehydes, alkylating reagents and azo-compounds) to give novel sidechain functionalised pyridones.

In the synthesis of N-alkylated 6-methyl 2-pyridones **228**, 2-methoxy-6-methyl pyridine **221** and a number of different alkylating reagents were used (**Scheme 123**) to successfully generate a series of pyridone building blocks.



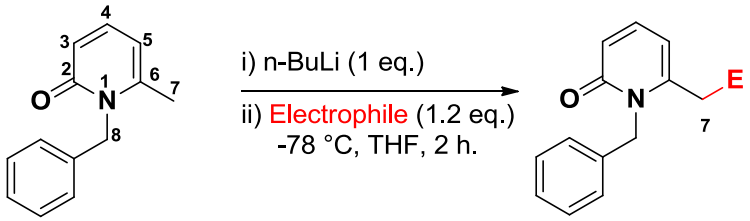
Scheme 123: Synthesis of N-alkylated-6-methyl 2-pyridones.

For the synthesis of N-alkylated 2-methyl 4-pyridones **226**, 4-chloro-2-methyl pyridine **223** was used as the starting material, and the desired pyridone was obtained in 3 steps by S_NAr substitution, N-alkylation and concomitant O-dealkylation (**Scheme 124**).



Scheme 124: Synthesis route of N-alkyl 2-pyridone and N-alkyl 4-pyridone.

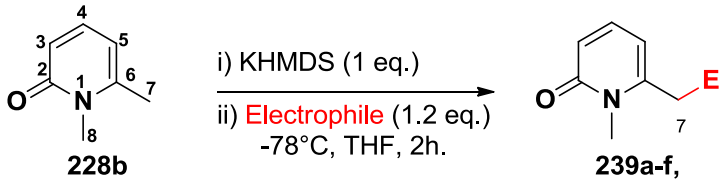
The product of methyl lithiation of 1-benzyl-6-methylpyridin-2(1H)-one **228c**, was found to react with a variety of carbonyl electrophiles such as diketones, ketones and aldehydes, and the reactions worked in good to excellent yields. Furthermore, other groups of electrophiles including the halides, benzyl bromide, and allyl bromide, and an aza-electrophile, diethyl azodicarboxylate, reacted successfully (**Scheme 125**).



228c **231a-n**

Scheme 125: Synthesis of 1-benzyl-6-alkylated-2-pyridones 231a-n by regioselective metallation at the methyl substituent.

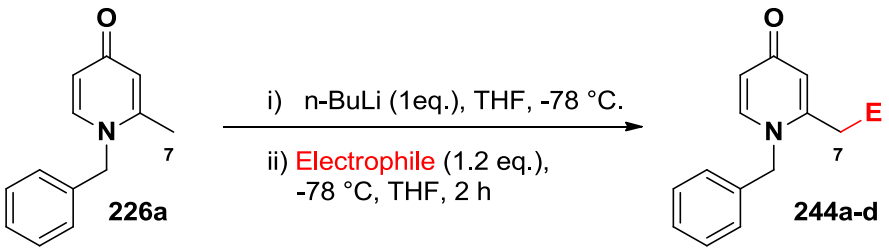
In the study of the highly selective methyl lithiation of 1,6-dimethylpyridin-2(1H)-one **228b**, metallation was shown to take place very efficiently when KHMDS was used as the base. In this study ketones, aldehydes, and alkyl halides were used successfully as electrophiles to trap the 6-(metallated-methyl)-1-methyl-2-pyridinone intermediate. All the reactions took place in good yield, except when 5-bromo-1-pentene was used as the electrophile. In this case an increase in the temperature of the electrophile addition from -78 °C to 0 °C was needed in order to obtain the desired product **239f** in a moderate 20% yield (**Scheme 126**).



228b **239a-f,**

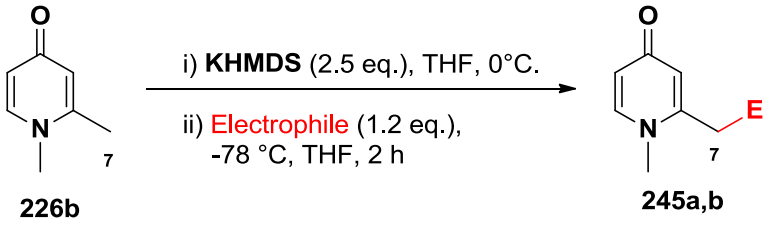
Scheme 126: Synthesis of 1-methyl-6-alkylated-2-pyridones 239a-f by regioselective metallation at methyl position.

The product of methyl lithiation of 1-benzyl-2-methylpyridin-4(1H)-one **226a** reacted successfully with a variety of electrophiles. The reactions worked under the same standard conditions used successfully in the study of methyl lithiation of 1-benzyl-6-methyl-2-pyridone **228c**. The yields were generally not high as for the 2-pyridones series, and this is believed to be due to the difficulty in the purification due to the higher polarity of the 4-pyridone derivatives.



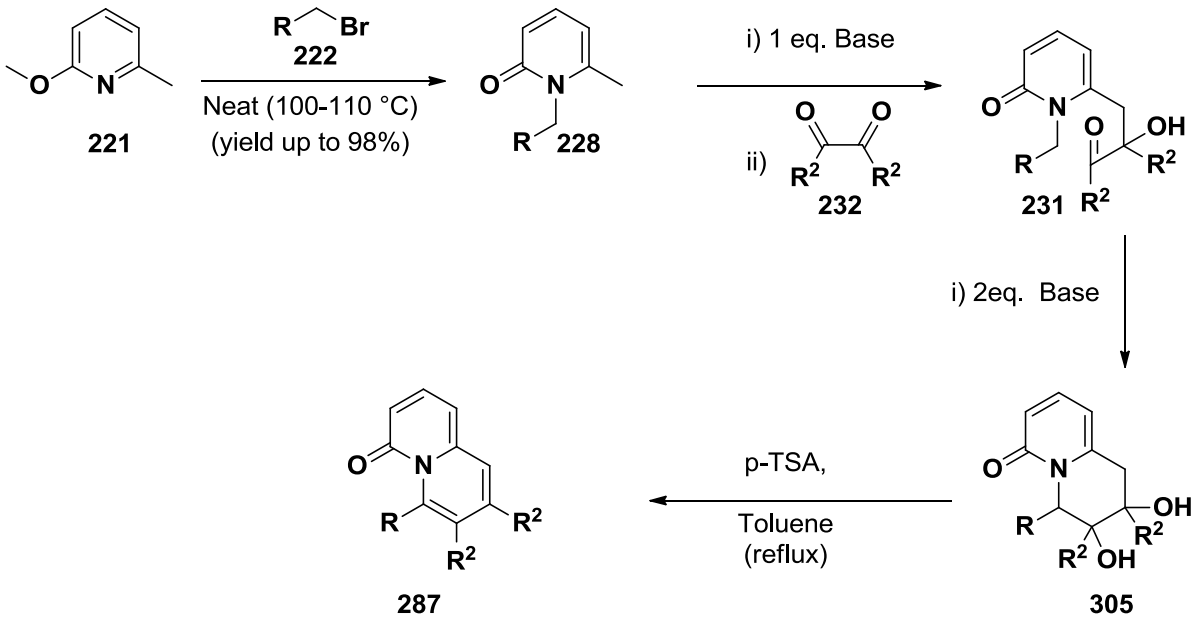
Scheme 127: Synthesis of 1-benzyl-2-alkylated-4-pyridone (244a-d).

The reaction of 1,2-dimethylpyridin-4(1H)-one **226b** was evaluated with two different electrophiles (allyl bromide and pivaldehyde) under the conditions shown in **Scheme 128.** However, the reaction was complicated by the subsequent deprotonation of the alkylated-pyridone product **245a,b** again in position 7. The desired alkylated pyridones **245a,b** were both obtained in only 10% yield.



Scheme 128 : Synthesis of 1-methyl-2-alkylated-4-pyridones (245a,b)

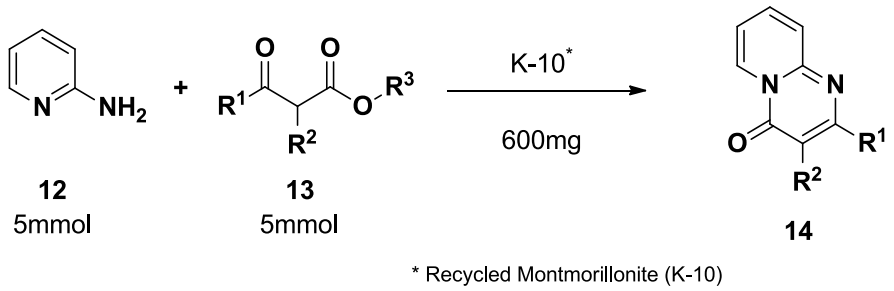
A straightforward synthesis of the desired 4*H*-quinolizin-4-one **287** scaffold by condensation of the N-benzyl 6-methyl 2-pyridones **228** with dicarbonyl compounds, and the formation of the desired quinolizinone after the condensation step was also developed. A number of novel quinolizinone derivatives, representing potential new scaffolds for medicinal chemistry, were successfully synthesized and characterized.



Scheme 129: Synthesis of the desired 4*H*-quinolizin-4-one.

Future work

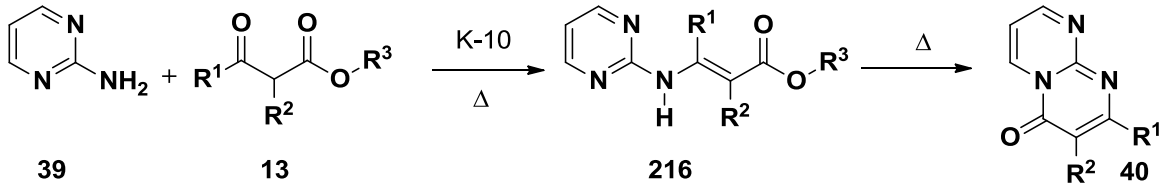
♦To continue the study into the investigation of the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives direct condensation/cyclization of 2-aminopyridine **12** with substituted β-keto esters **13**, catalysed by the clay mineral montmorillonite (K-10) under solvent-free conditions should be attempted (**Scheme 130**).



Scheme 130: Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives using K-10.

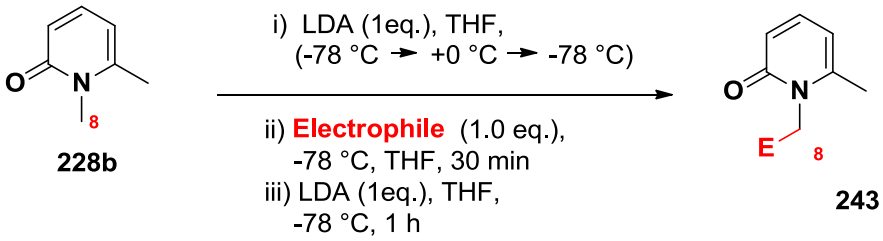
It will be very interesting to show that the clay mineral montmorillonite (K-10), could be filtered off after the reaction and used again in another reaction. It will prove that montmorillonite (K-10) can be recycled and this characteristic will add value as a green catalyst.

♦The synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivatives from 2-aminopyrimidine with different β-keto esters could be studied as a two-step synthesis. Development of the conditions for the new steps, and optimisation of the yield in each step, and synthesis of a new library of 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivative in good yields will be an excellent extension of the work (**Scheme 131**).



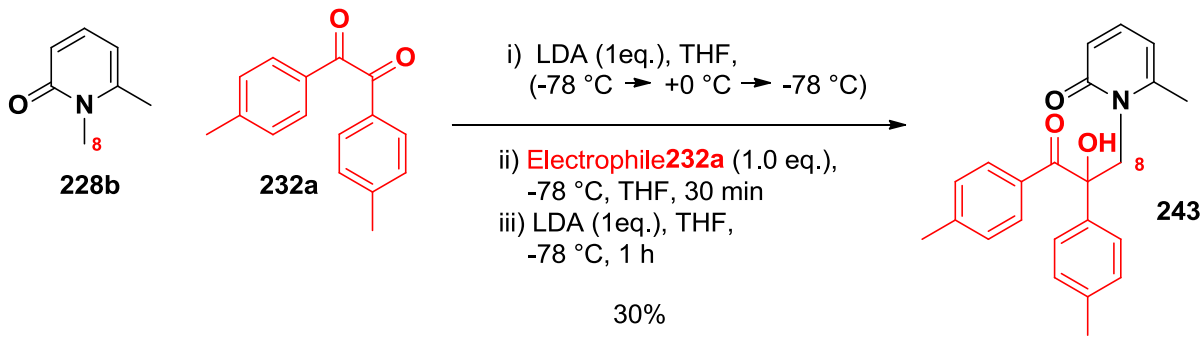
Scheme 131: New conditions for the synthesis of a 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one derivative.

♦After the excellent work developed in the regioselective methyllithiation and subsequent electrophilic quenching of N-alkyl-6 methyl-2-pyridones, it will be desirable to study the selective alkylation at the N-methyl position (8).



Scheme 132: Regioselective methyllithiation and subsequent electrophilic quenching of N-aklkyl-6 methyl-2-pyridones.

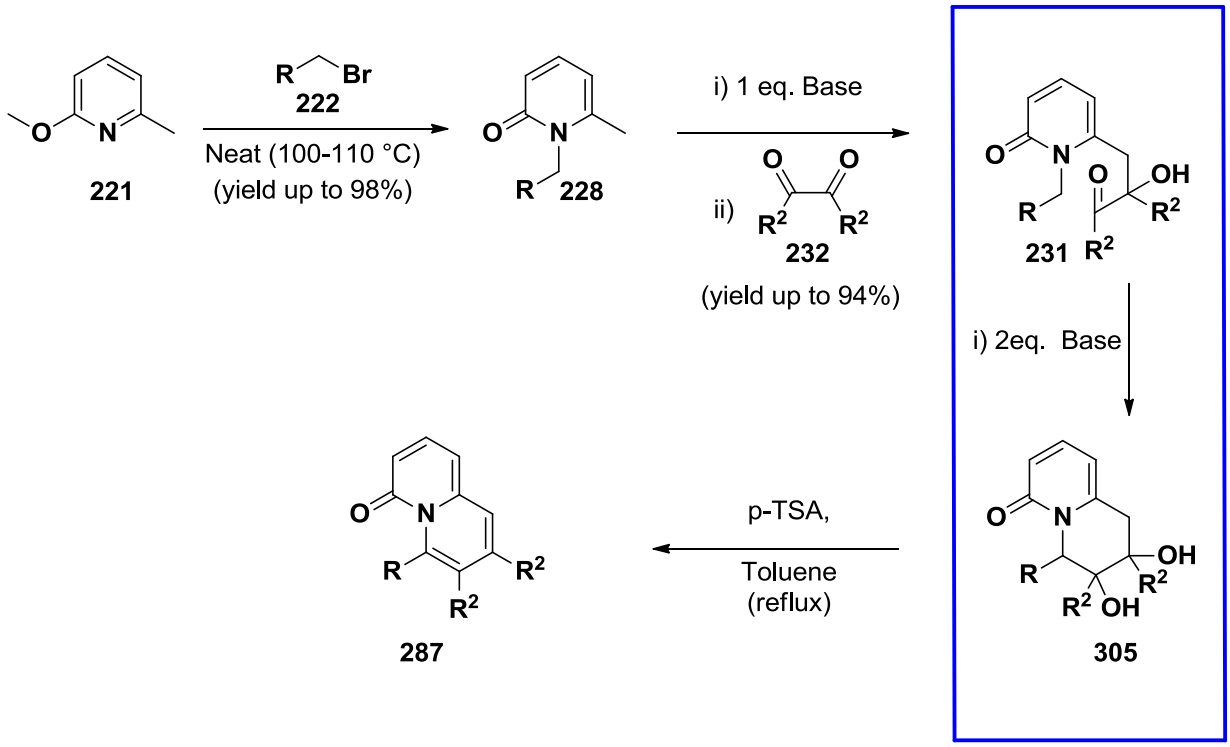
Scheme 133 shows that we were able to alkylate the 1,6-dimethyl-2-pyridone **228b** at the N-methyl position (position 8) by appropriate choice of reaction conditions. Using in total 2 eq. of LDA, a regioselective deprotonation at the N-methyl position was obtained.



Scheme 133: First example of N-methyl alkylation of 1,6-dimethyl-2-pyridone.

It would be important to continue the study of the regioselective deprotonation at the N-methyl position of 2-pyridones and to obtain alkylation of several 2-pyridones at the N-methyl position (8). This scaffold will represent an interesting synthetic intermediate for the synthesis of more complex molecules.

♦To continue the research on the synthesis of 4-*H*-quinolizinones would be an exciting development to find the optimum third step of the total synthesis conditions in order to avoid the side reactions and therefore to improve the yield and synthesize of other examples of this important and emerging scaffold.



Scheme 134: Third step of the total synthesis of 4*H*-quinolizin-4-one.

Experimental

General information

Commercially available solvents were used and not subjected to further purification, except Tetrahydrofuran (THF) which was distilled from sodium using benzophenone as an indicator. DMSO was purchased dry from commercial suppliers. Light petroleum ether refers to the fraction with a boiling point between 40-60°C. All chemicals were acquired from Alfa-Aesar or Sigma-Aldrich and used as recived. Sodium hydride was a 60% w/w dispersion in mineral oil.

Anhydrous reactions were carried out in oven-dried glassware (or flame-dried under nitrogen) and under an atmosphere of nitrogen and dry solvents were used.

All the reactions and columns were monitored by thin layer chromatography (TLC) using silica gel (Merk TLC Silica gel 60 F_{214}) as the absorbent on aluminium-backed plates and were visualized by UV light at 254nm using a UVP chromato-vue cabinet model CC-60 or via staining with a solution of phosphomolybdic acid (PMA).

The reactions were purified by flash column chromatography on silica gel (Merck Kieselgel 60H silica) as the absorbent or by recrystallization.

Melting points were recorded using a Stuart Scientific SMP3 melting points apparatus.

A Pelkin-Elmer spectrum 65 FT-IR spectrophotometer was used to obtain infrared spectra. Liquid samples were acquired using a thin film on a sodium chloride disc. Solid samples were prepared and measured in a KBr disc.

^{1}H and ^{13}C NMR spectra were obtained either from a Bruker 400MHz or a JEOL 400 MHz (^{1}H: 400 MHz, ^{13}C: 101 MHz), NMR spectrometer; 500 MHz (^{1}H: 500 MHz, ^{13}C: 126MHz) or 700 MHz (^{1}H: 700 MHz, ^{13}C: 176MHz) spectrometer. ^{1}H and ^{13}C shifts are given in parts per million (ppm), and are measured relative to residual protonated (or deuterated as appropriate) solvent. Chemical shifts were quoted in ppm, relative to tetramethylsilane (TMS) and referenced to the proper solvent peak. Multiplicity is denoted as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), multiplet (m), or broad (b). Coupling constant (*J*) values are giving in hertz (Hz).

Diffraction data for compound **388•**EtOH were collected at the Advanced Light Source Station 11.3.1 using silicon 111 monochromated, synchrotron X-radiation on a Bruker Apex 2 CCD diffractometer.

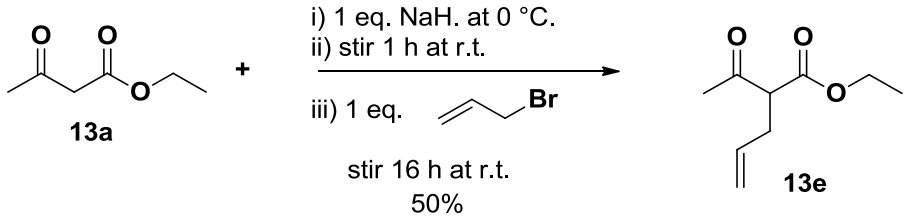
The crystal structures were resolved using Bruker APEX 2 CCD diffractometer with Oxford Cryosystems low temperature device. High-resolution mass spectrometry was obtained on a Thermo Exactive Benchtop Orbitrap MS coupled to Advion TriVersa NanoMate injection system. The GC-MS was carried out in the Fisons GC 8000 series (AS 800).

Accurate mass and MSMS fragmentation data were obtained using a Thermo Scientific hybrid LTQ-FT Mass Spectrometer with an Agilent 1100 Quaternary pump with PDA and Autosampler. 5μL of sample dissolved in 50:50 Acetonitrile:water 0.1% formic acid was injected onto a Thermo Scientific Hypersil Gold 50 x 2.1mm 5μm particle LC Column. The gradient was 5 to 100% B over 17 min with 3 min re-equilibration time at 5% B. The flow rate is 0.5 mL/min with A being 0.1% formic acid in water and B 0.1% formic acid in acetonitrile. The MS and MSMS spectra were obtained in ESI +ve mode in both the ion trap and Ion Cyclotron Resonance (ICR) cell using helium as the collision gas at a normalised collision energy of 35eV. The ICR cell was run at resolution settings of 25000 in MS mode and 12500 in MSMS mode.

A Thermofisher Exactive (orbi) mass spectrometer was used to obtain high resolution mass spectra, with ESI as the ionisation mode. The solvent used for all samples was methanol/acetic acid.

1- Pyridopyrimidine.

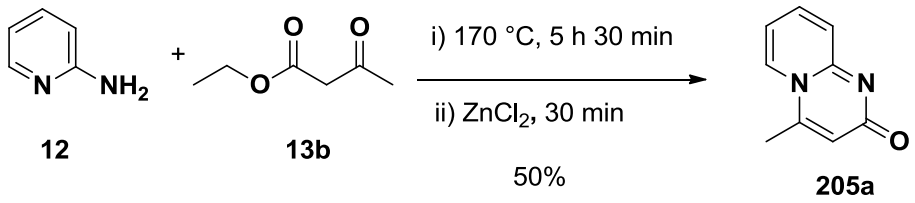
Preparation of ethyl 2-acetylpent-4-enoate (13e).



To a suspension of NaH (60% dispersion in mineral oil) (0.40 g, 10 mmol) in THF (25 mL) in THF under an N_2 atmosphere, was added drop-wise ethyl acetoacetate **13a** (1.4 mL, 11 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Allyl bromide (0.87 mL, 10 mmol) was added to the resulting solution. The reaction was allowed to proceed for 16 h at room temperature, before quenching with H_2O (5 mL). EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether (40-60°) to afford ethyl 2-acetylpent-4-enoate **13e** as colourless oil, (0.88 g, 50%). **IR (Neat)** 2983, 1742 (C=O), 1717 (C=O), 1643 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 5.73 (ddt, *J*=17.1, 10.2, 6.8 Hz, 1H), 5.00 - 5.12 (m, 2H), 4.18 (qd, *J*=7.2, 0.8 Hz, 2H), 3.50 (t, *J*=7.2 Hz, 1H), 2.58 (t, *J*=7.2 Hz, 2H), 2.22 (s, 3H), 1.25 (t, *J*=7.2 Hz, 3H). **GC-MS :** *(m/z)* 170 (M^+).

Synthesis of 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one using different reagents (205a).

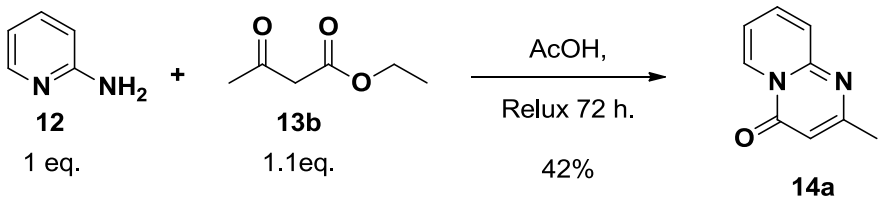
Using $ZnCl_2$.



12 **13b** **205a**

A mixture of 2-aminopyridine **12** (0.94 g, 10 mmol) and ethyl acetoacetate **13b** (1.30 mL, 10 mmol) was stirred at 170 °C for 5.30 h, and then $ZnCl_2$ (1.40 g, 10 mmol) was added to the reaction mixture which was then stirred for 30 min. The reaction mixture was diluted H_2O (10 mL), and extracted with EtOAc (3 x 25 mL). The combined extracted were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was the crude product was recrystallized from diethyl ether to afford 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **205a** as white solid (0.34 g, 50%). **m.p.** 80-82 °C. **IR (Neat)** 1710 (C=O), 1632.73 (C=N) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.06 (d, *J*=6.8 Hz, 1H), 7.76 (ddd, *J*=8.8, 6.8, 1.6 Hz, 1H), 7.65 (d, *J*=8.8 Hz, 1H), 7.15 (td, *J*=6.8, 1.4 Hz, 1H), 6.37 (s, 1H), 2.50 (s, 3H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 165.1 (C=O), 157.8 (C), 150.7 (C), 136.4 (CH), 127.3 (CH), 125.7 (CH), 115.1 (CH), 103.4 (CH), 24.6 (CH_3). **GC-MS :** *(m/z)* 160 (M^+).

Using acetic acid.

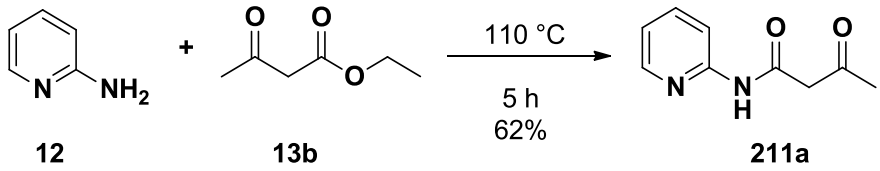


12 1 eq. **13b** 1.1eq. **14a**

A mixture of 2-aminopyridine **12** (0.58 g, 6.2 mmol) and ethyl acetoactetate **13b** (0.73 mL, 5.0 mmol) in acetic acid (3.0 mL) was stirred under reflux for 5 h. After cooling the reaction, the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude product was recrystallized from diethyl ether to afford 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **14a** as colourless crystals, (0.33 g, 42%). **m.p.** 75-77 °C. **IR (Neat)** 1711 (C=O), 1632 (C=N) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.04 (d, *J*=6.8 Hz, 1H), 7.73 (ddd, *J*=8.8, 6.8, 1.6 Hz, 1H), 7.60 (d, *J*=8.8 Hz, 1H), 7.12 (td, *J*=6.8, 1.2 Hz, 1H), 6.36 (s, 1H), 2.48 (s, 3H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 165.3 (C=O), 157.9 (C), 150.7 (C), 136.3 (CH), 127.3 (CH), 125.8 (CH), 115.0 (CH), 103.4 (CH), 24.7 (CH_3). **GC-MS :** *(m/z)* 160 (M^+).

Synthesis of 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one stepwise.

Synthesis of 3-oxo-N-(pyridin-2-yl)butanamide (211a).[73]

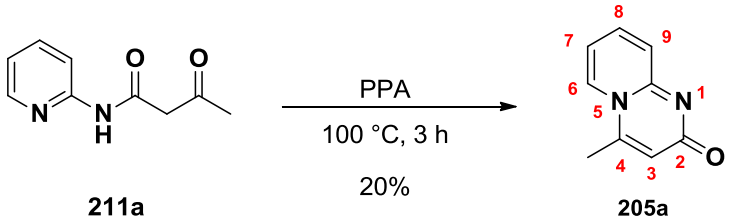


12 **13b** **211a**

A solution of 2-aminopyridine (0.28 g, 3.0 mmol) and ethyl acetoacetate (1.1 mL, 9.0 mmol) was stirred at 110 °C for 5 h. The resulting brown oil was recrystallized from dichloromethane/petrol to afford 3-oxo-*N*-(pyridin-2-yl)butanamide as a white solid, (0.33 g, 62%). **m.p.**111-113 °C. **IR (Neat)** 1720 (C=O), 1686 (CONH) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.29 (br. s., 1H), 8.32 (dd, *J*=4.9, 1.0 Hz, 1H), 8.16 (d, *J*=8.0 Hz, 1H), 7.67 - 7.74 (m, 1H), 7.06 (ddd, *J*=7.4, 4.9, 1.0 Hz, 1H), 3.61 (s, 2H), 2.34 (s, 3H).

Literature data: **m.p.**109-110 °C. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.68 (br. s., 1H), 8.32 (dt, *J*=8.32, *J*=2.36 Hz, 1H), 8.21 (bd, *J*=8.32 Hz, 1H), 7.71 (dt, *J*=8.32, *J*=2.36 Hz, 1H), 7.07 (dt, *J*=8.32, 2.36 Hz, 1H), 3.61 (s, 2H), 2.31 (s, 3H).[73]

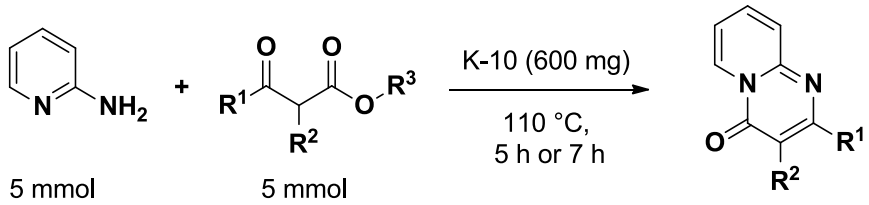
Synthesis of 4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one(205a).



211a **205a**

A solution of N-acetoacetylated **211a** (0.1 g, 0.56 mmol) and polyphosphoric acid (PPA) in the ratio 1:10 w:w (0.1 g: 1.0 g) was placed in a round bottomed flask fitted with a reflux condenser and a drying tube. The reaction mixture was heated at 100 °C with frequent shaking. The progress of the reaction was monitored on TLC and after 3 h the reaction was completed. The reaction mixture was diluted with distilled H_2O (10 mL), basified with ammonia solution (10 mL) and then extracted with EtOAc (3 x 25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by filtration through a small silica gel column using petrol: EtOAc (1:1) to afford 4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one as a yellow solid, (17 mg, 20%). **m.p**. 85-87 °C. **IR (Neat)** 1709 (C=O), 1632 (C=N) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.07 (d, *J*=6.8 Hz, 1H), 7.77 (ddd, *J*=8.8, 6.8, 1.5 Hz, 1H), 7.68 (d, *J*=8.8 Hz, 1H), 7.12 - 7.19 (t, *J*= 6.8 Hz, 1H), 6.37 (s, 1H), 2.51 (s, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm)** 165.28 (C=O), 157.7 (C), 150.6 (C), 136.5 (CH, C-8), 127.3 (CH, C-6), 125.6 (CH, C-9), 115.2 (CH, C-7), 103.3 (CH, C-3), 24.5 (CH_3, C-11). **GS-MS :** *(m/z)* 160 (M^+).

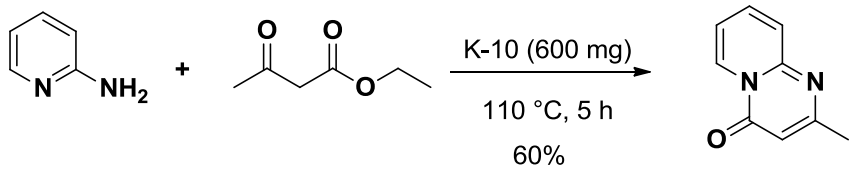
General procedure (B): Synthesis of Substituted Pyrido[1,2]pyrimidin-4-one.



12 **13** **14**

A mixture of 2-aminopyridine (5.0 mmol, 1 eq.) and β-keto ester (5.0 mmol, 1 eq.) and montmorillonite (600 mg) was stirred at 110 °C for 5 or 7 h. After cooling, the catalyst was removed by filtration through a pad of celite and the catalyst was washed with ethyl acetate. The solvent was evaporated under reduced pressure. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether (40-60°).

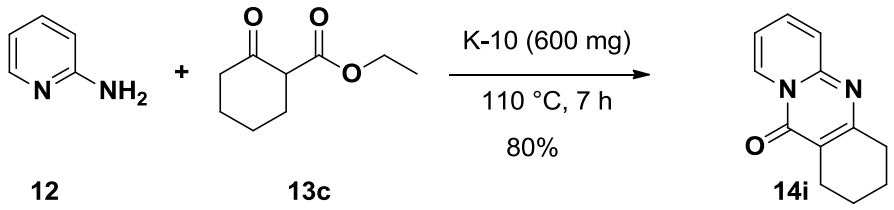
Synthesis of 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (14a).



12 **13b** **14a**

Following general procedure (B) 2-aminopyridine was added to ethyl acetoacetate and the reaction mixture was stirred at 110 °C for 5 h. The crude was recrystallized from diethyl ether to afford 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one as a pale yellow solid, (0.45g, 60%). **m.p.** 98-100 °C. **IR (Neat)** 1708 (C=O), 1630 (C=N) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.04 (d, *J*=7.1 Hz, 1H), 7.68 - 7.76 (m, 1H), 7.59 (d, *J*=9.0 Hz, 1H), 7.05 - 7.15 (m, 1H), 6.35 (s, 1H), 2.46 (s, 3H).

Synthesis of 3,4-dihydro-1H-pyrido[2,1-b]quinazolin-11(2H)-one (14i).[13]

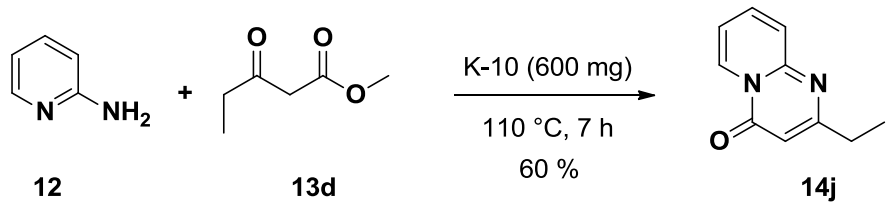


12 **13c** **14i**

Following general procedure (B): 2-aminopiridine (5.8 mmol, 0.54 g) was added to ethyl 2-oxocyclohexanecarboxylate (5.8 mmol, 0.92 mL) and the reaction mixture was stirred at 110 °C for 7 h. The crude was recrystallized from diethyl ether, to give pale yellow solid (0.80 g, 80%) **m.p.** 115-117 °C. **IR (Neat)** 2934 ($CHsp^3$), 1676 (C=O), 1634 (C=N) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 8.97 (d, *J*=7.2 Hz, 1H), 7.57 - 7.64 (m, 1H), 7.51 (d, *J*=8.8 Hz, 1H), 6.97 - 7.06 (m, 1H), 2.82 (t, *J*=6.0 Hz, 2H), 2.73 (t, *J*=6.0 Hz, 2H), 1.79 - 1.95 (m, 4H). **GC-MS:** *(m/z)* 200 (M^+).

Literature data: **^{1}H NMR ($CDCl_3$, 300MHz): δ (ppm)** 8.90 (d, *J*=7.2 Hz, 1H), 7.60 (t, *J*=7.7 Hz, 1H), 7.52 (d, *J*=8.7 Hz, 1H), 7.02 (t, *J*=6.8 Hz, 1H), 2.79 (t, *J*=5.7 Hz, 2H), 2.70 (t, *J*=5.7 Hz, 2H) 1.90-1.77 (m, 4H).

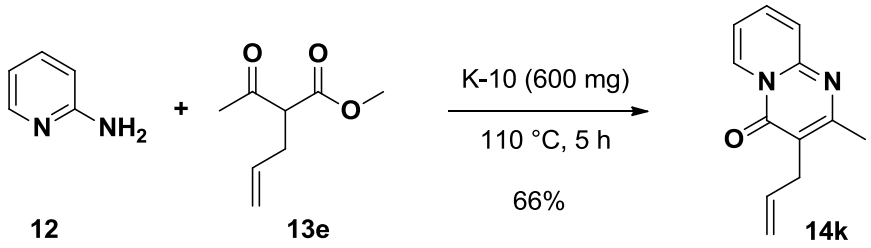
Synthesis of 2-ethyl-4H-pyrido[1,2-a]pyrimidin-4-one (14j).



12 **13d** **14j**

Following general procedure (B): 2-aminopyridine was added to methyl propionyl acetate and the reaction mixture was stirred at 110 °C for 7 h. This afforded 2-ethyl-4H-pyrido[1,2-a]pyrimidin-4-one as a red oil, (0.54g, 60 %). **^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm)** 9.02 (d, *J*=7.2 Hz, 1H), 7.71 (dd, *J*=7.6, 6.8 Hz, 1H), 7.62 (d, *J*=9.2 Hz, 1H), 7.10 (t, *J*=6.8 Hz, 1H), 6.35 (s, 1H), 2.72 (q, *J*=7.6 Hz, 2H), 1.31 (t, *J*=7.6, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm)** 170.1 (C=O), 158.3 (C), 150.8 (C), 136.3 (CH), 127.3 (CH), 125.9 (CH), 115.1 (CH), 102.1 (CH), 31.4 (CH_2), 12.9 (CH_3).

Synthesis of 3-allyl-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (14k).

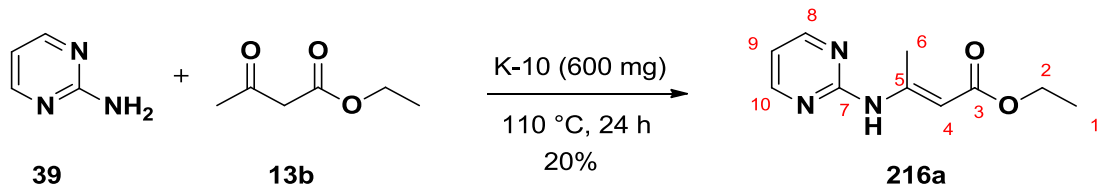


12 13e 14k

Following general procedure (B): 2-aminopyridine was added to ethyl 2-acetylpent-4-enoate and the reaction mixture was stirred at 110 °C for 5 h. This afforded 3-allyl-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one as a brown oil, (0.67 g, 66%). **IR (Neat)** 1670 (C=O), 1636 (C=N), 1569 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 8.99 (d, *J*=7.2 Hz, 1H), 7.60 - 7.67 (m, 1H), 7.55 (d, *J*=8.7 Hz, 1H), 7.07 (t, *J*=7.2 Hz, 1H), 5.94 (dd, *J*=17.1, 10.1 Hz, 1H), 4.99 - 5.15 (m, 2H), 3.49 (d, *J*=6.1 Hz, 2H), 2.49 (s, 3H). **GC-MS :** *(m/z)* 200 (M^+).

2- Pyrimidopyrimidine.

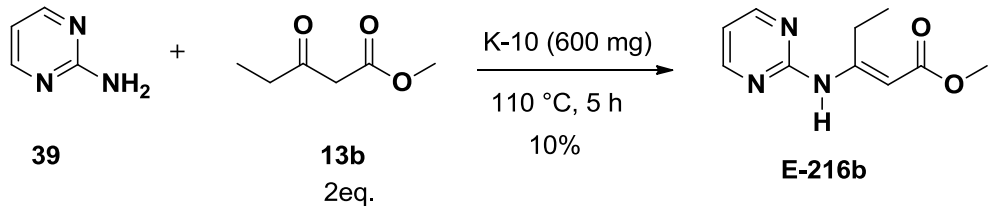
Synthesis of ethyl 3-(pyrimidin-2-ylamino)but-2-enoate (216a).



39 **13b** **216a**

A mixture of 2-aminopyrimidine (0.47 g, 5 mmol) and ethyl acetoacetate (0.63 mL, 5 mmol) and montmorillonite (600 mg) was stirred at 110 °C for 24 h. After cooling, the catalyst was removed by filtration and washed with diethyl ether. The solvent was evaporated under reduced pressure and the crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford ethyl 3-(pyrimidin-2-ylamino)but-2-enoate **216a**, as pale yellow crystals (0.2 g, 20%). **m.p.** 81-83°C. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 11.27 (br. s., 1H), 8.42 (d, *J*=4.8 Hz, 2H), 6.80 (t, *J*=4.8 Hz, 1H), 4.85 (s, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 2.50 (s, 3H), 1.23 - 1.33 (m, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz)** 169.2 (C-3), 159.3 (C-5), 157.9 (CH, C-8), 157.8 (CH, C-10), 156.0 (C-7), 114.3 (C-9), 93.0 (C-4), 59.3 (C-2), 22.9 (C-6), 14.4 (C-1). **GC-MS:** *(m/z)* 207 (M^+).

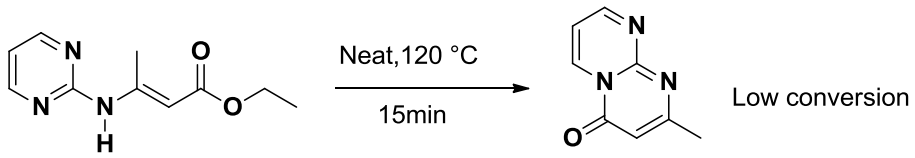
Synthesis of (E)-methyl 3-(pyrimidin-2-ylamino)pent-2-enoate (E-216b).



39 **13b** 2eq. **E-216b**

A mixture of 2-aminopyrimidine (0.24 g, 2.5 mmol,) and ethyl acetoacetate (0.97 g, 5 mmol) and montmorillonite (600 mg) in xylene was stirred at 110 °C for 5 h. After cooling, the catalyst was removed by filtration and washed with EtOAc. The solvent was evaporated under reduced pressure and the crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford methyl 3-(pyrimidin-2-ylamino)pent-2-enoate **216b** as a yellow oil, (60 mg, 10%). **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** Z isomer 11.21 (s, 1 H), 8.44 (d, *J*=4.8 Hz, 2H), 6.80 (t, *J*= 4.8 Hz, 1H), 4.92 (d, *J*= 0.9 Hz, 1H), 3.72 (s, 3H), 2.99 (qd, *J*=7.4, 0.9 Hz, 2H), 1.17 (t, *J*=7.4 Hz, 3H).

Synthesis of 2-methyl-4H-pyrimido[1,2-a]pyrimidin-4-one (40a).

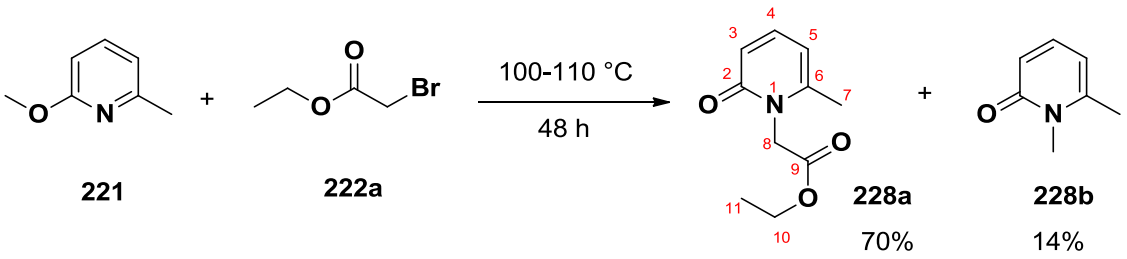


216a **40a**

Ethyl 3-(pyrimidin-2-ylamino)but-2-enoate (25 mg, 0.12 mmol) was heated at 120 °C for 15 min. The reaction mixture was purified by prepTLC (petrol : EtOAc; 1 : 1), to afford 2-methyl-4H-pyrimido[1,2-a]pyrimidin-4-one as white solid, (8 mg, 41%). **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 9.32 – 9.24 (m, 1H), 9.08 – 9.01 (m, 1H), 7.17 – 7.11 (m, 1H), 6.40 (s, 1H), 2.54 (s, 3H). **GC-MS :** *(m/z)* 161 (M^+).

3- Synthesis of 2- and 4-pyridone derivatives.

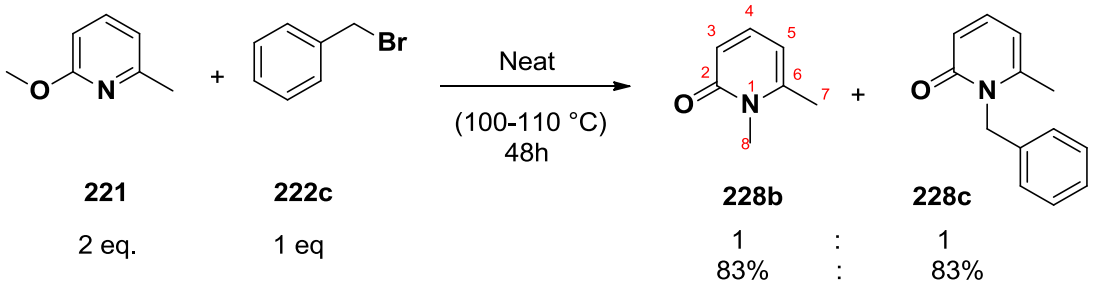
Ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate (296a) and 1,6-dimethylpyridin-2(1H)-one (228b).



A mixture of 2-methoxy-6-methylpyridine (1.2 mL, 10 mmol) and ethyl 2-bromoacetate (1.1 mL, 10 mmol) was stirred at 100-110 °C for 48 h, to afford a brown oil. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford ethyl 2-(6-methyl-2-oxopyridin-1(2*H*)-yl)acetate **228a** as white crystals (1.3 g, 70%), and 1,6-dimethylpyridin-2(1H)-one **228b** a pale brown oil (0.17 g, 14%).

Ethyl 2-(6-methyl-2-oxopyridin-1(2*H*)-yl)acetate **228a: m.p.** 80-82 °C. **IR (KBr)** 3068 ($CHsp^2$), 2987 ($CHsp^3$), 1742 (C=O), 1661 (C=O), 1575 (C=C), 1552 (C=C), 1219 (C-O) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.58 (dd, *J*=9.2, 6.8 Hz, 1H, H-4), 6.51 (d, *J*=9.2 Hz, 1H, H-3), 6.38 (d, *J*=6.8 Hz, 1H, H-5), 5.01 (s, 2H, H-8), 4.38 (q, *J*=7.2 Hz, 2H, H-10), 2.51 (s, 3H, H-7), 1.44 (t, *J*=7.2 Hz, 3H, H-11). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 168.2 (C=O, C-2), 162.3 (C=O, C-9), 147.2 (C, C-6), 139.9 (CH, C-4), 116.1 (CH, C-3), 105.9 (CH, C-5), 61.0 (CH_2, C-10), 45.3 (CH_2, C-8), 19.9 (CH_3), 14.0 (CH_3). **HRMS [ES]: calcd. for** $C_{10}H_{14}NO_3^+$ **(M-H)$^+$**: 196.0974, found: 196.0964. **UPLC, MS,** r.t: 0.55 min, *m/z*: ES^+ $[M+H]^+$ 196.

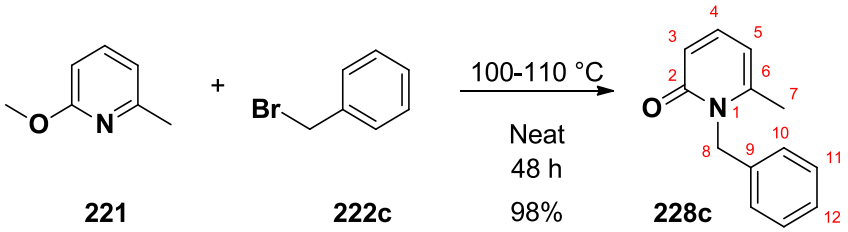
1,6-dimethylpyridin-2(1H)-one (228b) and N*-benzyl-6-methyl-2-pyridone (228c).*[90,45]



A mixture of 2-methoxy-6-methylpyridine (2.4 mL, 20 mmol,) and benzyl bromide (1.2 mL, 10 mmol) was heated at 100-110 °C for 48 h to afford a brown oil. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford 1,6-dimethylpyridin-2(1H)-one **228b** as white crystals in 83% yield (1.0 g, 8.3 mmol) and *N*-benzyl-6-methyl-2-pyridone **228c** in 83% yield (1.6 g, 8.3 mmol).

1,6-Dimethylpyridin-2(1H)-one **228b**: **IR (neat)** 2994 ($CHsp^3$), 2959 ($CHsp^3$), 1652 (C=O) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.28 (dd, *J*=8.8, 6.8 Hz, 1H, H-4), 6.25 (d, *J*=8.8 Hz, 1H, H-3), 6.12 (d, *J*= 6.8 Hz, 1H, H-5), 3.41 (s, 3H, H-8), 2.34 (s, 3H, H-7). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 162.5 (C=O, C-2), 147.7 (C, C-6), 138.8 (CH, C-4), 115.7 (CH, C-3), 105.5 (CH, C-5), 30.4 (CH_3, C-8), 20.3 (CH3, C-7). **HRMS [ES] $(M+H)^+$** required $C_7H_{10}NO^+$: 124.0762; found: 124.0763.

N-Benzyl-6-methyl-2-pyridone (228c).[90,45,47]

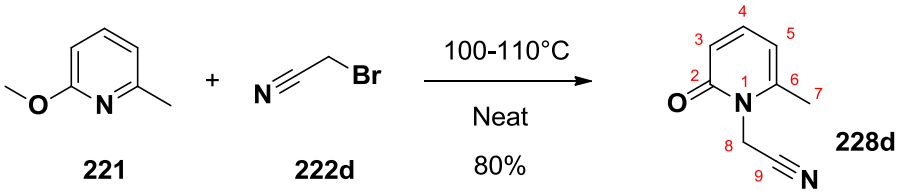


221 **222c** **228c**

A mixture of 2-methoxy-6-methylpyridine (0.49 mL, 4.0 mmol) and benzyl bromide (0.48 mL, 4.0 mmol) was heated at 100 °C for 48 h to afford a brown oil. The product precipitated out with the addition of petrol, and the solid was filtered off to afford *N*-benzyl-6-methyl-2-pyridone **228c** (0.78 g, 98%) as white crystals. **m.p.** 110-112 °C. **IR** (KBr) 3086 ($CHsp^2$), 2991 ($CHsp^3$), 1656 (C=O), 1572(C=C), 1651 (C=C), 790-732 (C_{Ar}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.30 - 7.42 (m, 3H), 7.21 - 7.30 (m, 1H), 7.11 (d, *J*=7.2 Hz, 2H), 6.37 (d, *J*=9.2 Hz, 1H), 6.16 (d, *J*=6.8 Hz, 1H), 5.29 (s, 2H), 2.25 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 162.7 (C=O, C-2), 147.4 (C, C-6), 139.6 (CH, C-4), 137.0 (C, C-9), 128.6 (CHx2, C-11), 127.0 (CH, C-12), 126.1 (CHx2, C-10), 116.5 (CH, C-3), 106.2 (CH, C-5), 46.1 (CH_2, C-8), 19.9 (CH_3, C-7).[90] **HRMS [ES] (M+Na^+)**, $C_{13}H_{13}NONa^+$ required 222.0895, found 222.0889.

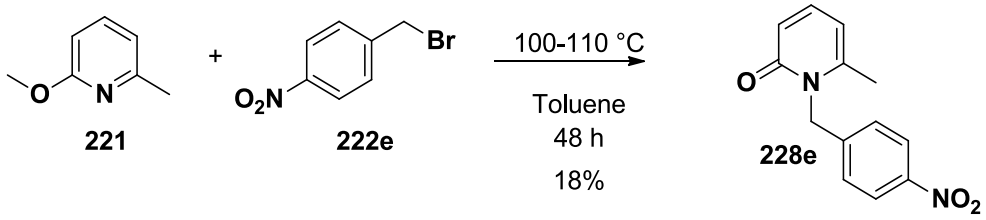
Literature data: **m.p.** 103−105 °C; **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.18− 7.31 (m, 4H), 7.12 (d, J = 7.1 Hz, 2H), 6.52 (d, J = 9.0 Hz, 1H), 6.00 (d, J = 6.9 Hz, 1H), 5.33 (s, 2H), 2.24 (s, 3H); HRMS (ESI-TOF) m/z 222.0888 [222.0895 calcd for C13H13NONa (M + Na)+].[47]

2-(6-methyl-2-oxopyridin-1(2H)-yl)acetonitrile (228d).



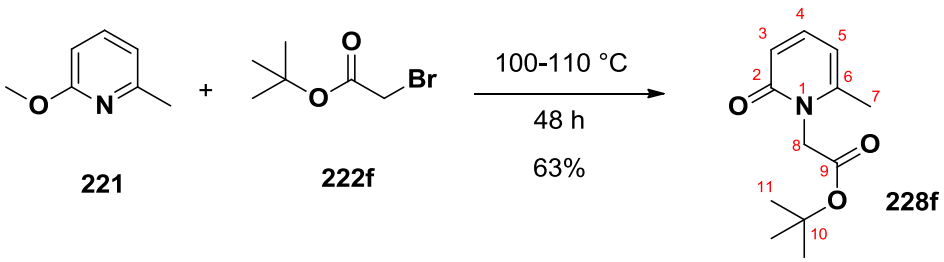
A mixture of 2-methoxy-6-methylpyridine (0.60 mL, 4.9 mmol) and bromoacetonitrile (0.34 mL, 4.9 mmol) was stirred at 100-110°C for 2h, and then for 48 h at room temperature to afford a brown oil. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetonitrile **228d** as a white solid, (0.57 g, 80 %). **m.p.** 105 °C. **IR (Neat)** 2249 (-CN), 1661 (C=O), 1572 (C=C), 1553(C=C) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.41 (dd, *J*=9.2, 6.8 Hz, 1H, H-4), 6.38 (d, *J*=9.2 Hz, 1H, H-3), 6.24 (d, *J*=6.8 Hz, 1H, H-5), 5.11 (s, 2H, C-8), 2.44 (s, 3H, C-7). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 162.5 (C=O, C-2), 147.3 (C, C-6), 141.4 (CH, C-4), 117.1 (C-H, C-3), 116.8 (C, C-9), 107.5 (CH, C-5), 32.5 (CH_2, C-8), 20.5 (CH_3, C-7). **HRMS [ES] (M+H$^+$)**, $C_8H_9N_2O^+$ required 149.0708 found 149.0709.

6-methyl-1-(4-nitrobenzyl)pyridin-2(1H)-one (228e).[91]



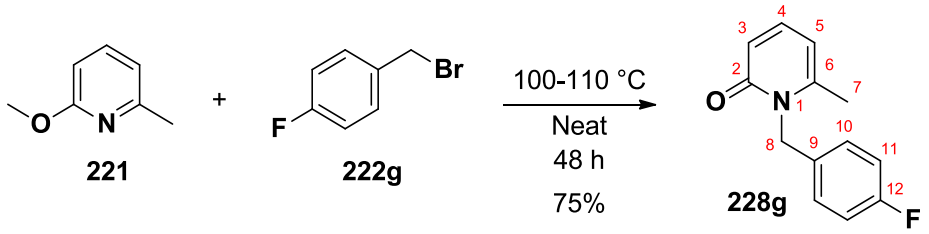
1-(Bromomethyl)-4-nitrobenzene (1.1 g, 5.0 mmol) was added to a solution of 2-methoxy-6-methylpyridine (0.61 mL, 5.0 mmol) in toluene (2.0 mL), and the reaction mixture was heated at 110 °C over a period of 40 h to afford a brown oil. The crude product was purified by flash silica chromatography, with elution gradient 0 to 100% EtOAc in heptane to afford 6-methyl-1-(4-nitrobenzyl)pyridin-2(1H)-one **228e** (0.21 g, 18%) as a colourless solid. **m.p.** 163 °C. **IR (KBr)** 3075 ($CHsp^2$), 3066 ($CHsp^2$), 1659 (C=O), 1578 (C=C), 1550 (C-NO), 1510 (C=C), 1340 (C-NO), 803 (CH_{Ar}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 8.20 (d, *J*=8.8, 2H), 7.33 - 7.42 (m, 3H), 6.37 (d, *J*=8.4 1H), 6.19 (d, *J*=6.6 Hz, 1H), 5.40 (s, 2H), 2.24 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 162.5 (C=O), 147.1 (C), 146.6 (C), 145.0 (C), 139.9 (CH), 127.4 (CHx2), 123.8 (CHx2), 116.6 (CH), 106.4 (CH), 46.0 (CH_2), 19.9 (CH_3). **UPLC, MS,** r.t: 0.76 min, *m/z*: ES$^+$ $[M+H]^+$ 245. **HRMS (ES):** calcd. for $C_{13}H_{12}N_2O_3$ **(M)$^+$**: 244.0848, found 244.0864.

Tert-butyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate (228f).



2-methoxy-6-methylpyridine (0.79 mL, 6.5 mmol) was added in one portion to tert-butyl 2-bromoacetate (0.96 mL, 6.5 mmol). The resulting solution was stirred at 110 °C for 22 h. The crude product was purified by flash silica chromatography, with elution gradient 5 to 100% EtOAc in heptane to afford tert-butyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228f** (0.91 mg, 63%) as a white solid. **m.p.** 110-111 °C. **IR (KBr)** 3046 ($CHsp^2$), 2965 ($CHsp^3$), 1737 (C=O), 1662 (C=O), 1581 (C=C), 1552 (C=C), 1457 ($CHsp^3$), 1381 ($CHsp^3$), 1367 ($CHsp^3$) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.32 (dd, *J*=9.0, 6.8 Hz, 1H, H-4), 6.26 (d, *J*=9.0 Hz, 1H, H-3), 6.12 (d, *J*=6.8 Hz, 1H, H-5), 4.69 (s, 2H, H-8), 2.25 (s, 3H, H-7), 1.41 (s, 9H, H-11). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 167.3 (C=O, C-2), 162.2 (C=O, C-9), 147.1 (C, C-6), 139.7 (CH, C-4), 116.0 (CH, C-3), 105.7 (CH, C-5), 81.6 (C, C-10), 45.7 (CH_2, C-8), 27.6 (CH_3, C-7), 19.8 (CH_3, C-11). **UPLC, MS,** r.t: 0.73 min, *m/z*: ES^+ $[M+H]^+$ 224. **HRMS (ESI):** calcd. for $C_{12}H_{18}NO_3$ **$(M+H)^+$**: 224.1281, found 224.1281.

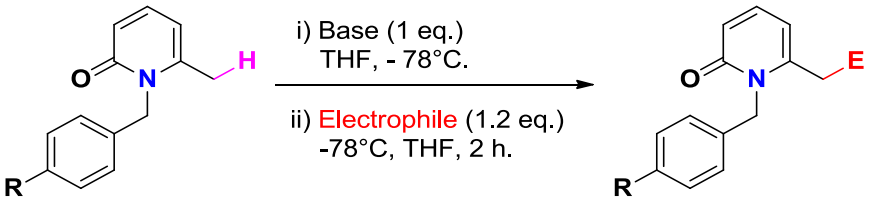
1-(4-fluorobenzyl)-6-methylpyridin-2(1H)-one (228g).



1-(Bromomethyl)-4-fluorobenzene (1.2 ml, 10 mmol) was added in one portion to 2-methoxy-6-methylpyridine (1.2 ml, 10 mmol). The reaction mixture was stirred at 100-110 °C for 48 h. The crude product was purified by flash silica chromatography, with elution gradient 0 to 100% EtOAc in heptane to afford 1-(4-fluorobenzyl)-6-methylpyridin-2(1H)-one (1.6 g, 75 %) as a white solid. **m.p.** 102 °C. **IR** (KBr) 3072 ($CHsp^2$), 2995 ($CHsp^3$), 1655 (C=O), 1569 (C=C), 1655 (C=C), 811-794 (C_{Ar}) cm^{-1}. **^{1}H NMR (DMSO-d$_6$, 700MHz): δ (ppm)** 7.33 (dd, *J*=9.1, 6.8 Hz, 1H, H-4), 7.12 - 7.19 (m, 4H), 6.34 (d, *J*=9.1 Hz, 1H, H-3), 6.12 (d, *J*=6.8 Hz, 1H, H-5), 5.25 (s, 2H), 2.24 (s, 3H). **^{13}C NMR (DMSO-d6, 176MHz): δ (ppm)** 162.6 (C=O, C-2), 161.0(C, d, J_F = 243 Hz, C-12), 147.2 (C, C-6), 139.5 (CH, C-4), 133.2 (C, C-9), 128.4 (CHx2, C-10), 116.5 (CH, C-3), 115.4 (CHx2, C-11), 106.2 (CH, C-5), 45.5 (CH_2), 19.8 (CH_3). **UPLC, MS,** r.t. 0.77min, *m/z*: ES+ $[M+H]^+$ 218. **HRMS [ES]: c**alcd for $C_{13}H_{12}FNO$ **(M+):** 217.0903; found: 217.0898.

Methyl alkylation of N-benzyl-2-pyridones.

General experimental procedure for the deprotonation of 1-benzyl-6-methylpyridin-2(1H)-one and nucleophilic addition to several electrophiles.



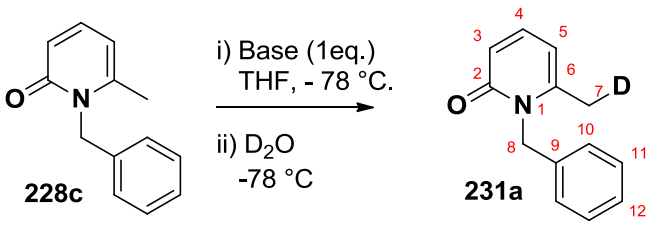
228c; R=H
228g; R=F

231a-g

General procedure I:

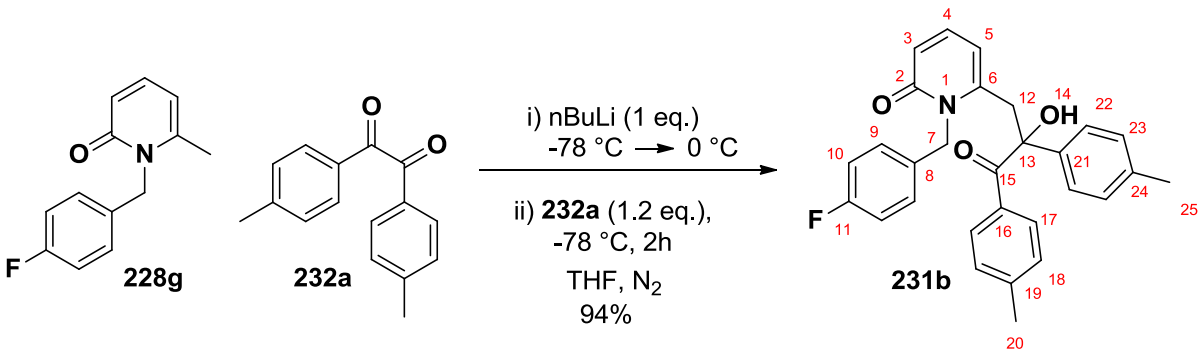
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 2-pyridone **228c** or **228g** (1 eq.) and dissolved in dry THF. The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. Base (n-butyllithium / LDA) (1 eq.) was added to the pale transparent yellow solution dropwise over 5 min and the reaction become an intense blue colour. The reaction mixture was warmed up to 0 °C and changed to an intense dark red colour, and then the reaction was cooled to -78 °C. Concurrently, an additional oven-dried flask was purged with N_2 and then was charged with the electrophile (1.2 eq.) which was then dissolved in dry THF. The electrophile solution was added dropwise to the pyridone solution at -78 °C via syringe over 5 min. The reaction was allowed to proceed for 2 h at -78 °C, before quenching with saturated $NH_4Cl_{(aq)}$. EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine. The combined organic phases were then dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude product was purified by flash silica chromatography.

Methyl deuterated N-benzyl-6-methyl-2-pyridone (231a).



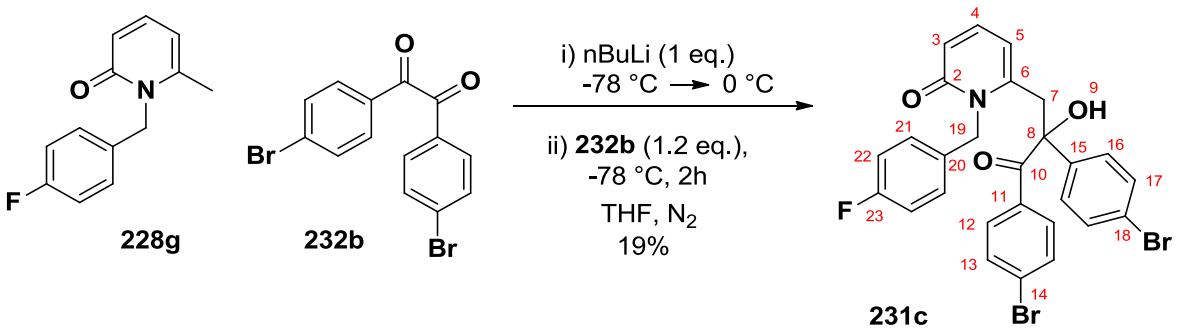
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.16 g, 0.82 mmol), in THF (6.0 mL), n-butyllithium (0.61 mL, 0.82 mmol) and then D_2O (20 µL, 1.6 mmol) was carried out. The reaction mixture was stirred for 30 min to afford compound **231a** as a pale yellow solid (0.14 g, 87%). **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 7.30 - 7.40 (m, 3H), 7.23 - 7.30 (m, 1H), 7.11 (d, *J*=7.0 Hz, 2H), 6.37 (d, *J*=9.2 Hz, 1H), 6.16 (d, *J*=6.8 Hz, 1H), 5.30 (s, 2H), 2.23 (s, CH_2D). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 162.7 (C=O), 147.3 (C), 139.6 (CH), 137.0 (C), 128.6 (CHx2), 127.0 (CH), 126.1 (CHx2), 116.5 (CH), 106.2 (CH), 46.1 (CH_2), 19.6 (t, $J_{C\text{-}D}$=20,CH_2D).

1-(4-fluorobenzyl)-6-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)pyridin-2(1H)-one (231b).



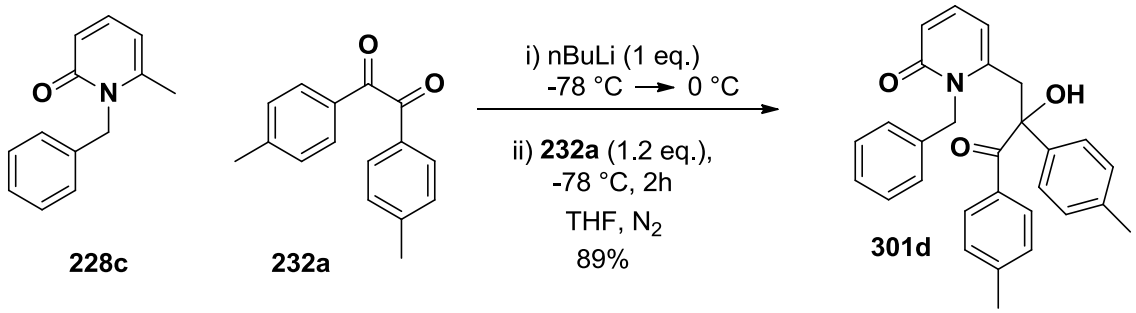
Following general procedure **I**, the reaction between 1-(4-fluorobenzyl)-6-methylpyridin-2(1H)-one **228g** (0.53 g, 2.5 mmol) in THF (8.8 mL), LDA (3.1 mL, 2.5 mmol) and 1,2-di-p-tolylethane-1,2-dione **232a** (0.70 g, 2.9 mmol) in THF (5 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in heptane to afford compound **231b** as a white solid (1.0 g, 94%). **m.p.** 203-204 °C. **IR (KBr)** 3269 (OH), 3038 ($CHsp^2_{Ar}$), 2920 ($CHsp^3$), 1664(C=O), 1649 (C=O), 1560 (C=C), 1546 (C=C), 1509(C=C), 1158 (CO), 1140 (C-F), 809-720 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 700MHz): δ (ppm)** 7.79 (d, *J*=8.1 Hz, 2H), 7.21 (d, *J*=8.1 Hz, 2H), 7.18 (dd, *J*=9.1, 7.0 Hz, 1H), 7.09 - 7.14 (m, 6H), 7.03 - 7.07 (m, 2H), 6.71 (br. s., 1H), 6.26 (d, *J*=9.1 Hz, 1H), 5.92 (d, *J*=7.0 Hz, 1H), 5.28 (d, *J*=15.8 Hz, 1H), 5.03 (d, *J*=15.8 Hz, 1H), 3.40 (d, *J*=15.4 Hz, 1H), 3.31 (d, *J*=15.4 Hz, 1H), 2.27 (s, 3H), 2.25 (s, 3H). **^{13}C NMR (DMSO-d_6, 176MHz): δ (ppm)** 196.5 (C=O), 160.2 (C=O), 158.8 (C, d, J_F = 242.8 Hz), 143.9 (C), 140.4 (C), 136.1 (CH), 135.9 (C), 134.4 (C), 131.2 (C), 129.8 (C), 128.0 (2 x CH), 127.6 (CH), 127.1 (CH), 126.6 (CHx2), 125.8 (2xCH), 122.5 (CHx2), 114.6 (CH), 113.0 (CHx2), 106.3 (CH), 80.1 (C), 42.8 (CH_2), 39.9 (CH_2), 18.6 (CH_3), 18.1 (CH_3). **UPLC, MS,** r.t: 1.19 min, *m/z*: ES^+ $[M+H]^+$ 456. **HRMS (ESI):** calcd. for $C_{29}H_{27}NO_3F$ **$(M+H)^+$**: 456.1969, found 456.1970.

6-(2,3-bis(4-bromophenyl)-2-hydroxy-3-oxopropyl)-1-(4-fluorobenzyl)pyridin-2(1H)-one (231c).



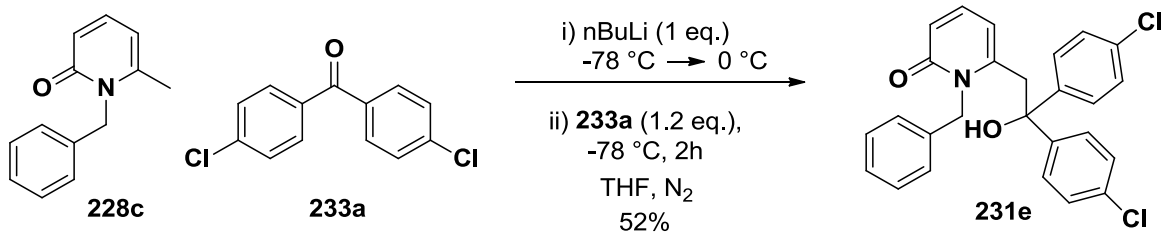
Following general procedure **I**, the reaction between 1-(4-fluorobenzyl)-6-methylpyridin-2(1H)-one **228g** (0.53 g, 2.5 mmol), in THF (14 mL), LDA (3.1 mL, 2.5 mmol) and 1,2-bis(4-bromophenyl)ethane-1,2-dione **232b** (1.1 g, 2.9 mmol) in THF (3 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in heptane to afford compound **231c** as a white solid (0.27 g, 19%). **m.p.** 215-216 °C. **IR (KBr)** 3187 (OH), 2965 ($CHsp^2_{Ar}$), 2843 ($CHsp^3$), 1677 (C=O), 1648 (C=O), 1581 (C=C), 1544 (C=C), 1507 (C=C), 1228 (C-F), 1146 (CO), 1073 (C-Br), 819-809 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 700MHz): δ (ppm)** 7.77 (d, *J*=9.1 Hz, 2H, H-12), 7.57 (d, *J*=9.1 Hz, 2H, H-13), 7.51 (d, *J*=8.4 Hz, 2H, H-16), 7.27 (d, *J*=9.1 Hz, 2H, H-17), 7.19 (dd, *J*=9.1, 6.8 Hz, 1H, H-4), 7.09 - 7.15 (m, 2H, H-22), 7.02 - 7.09 (m, 3H, H-21, H-9), 6.27 (dd, *J*=9.1, 1H, H-3), 5.87 (d, *J*=6.8 Hz, 1H, H-5), 5.28 (d, *J*=16.1 Hz, 1H, H-19), 5.13 (d, *J*=16.1 Hz, 1H, H-19'), 3.41 (d, *J*=15.4 Hz, 1H, H-7), 3.34 (d, *J*=15.4 Hz, 1H, H-7'). **^{13}C NMR (DMSO-d_6, 176MHz): δ (ppm)** 197.8 (C=O, C-10), 162.2 (C=O, C-2), 161 (C, *d*, J_F = 246 Hz, C-23), 145.1 (C, C-6), 139.7 (C, C-15), 138.1 (CH, C-4), 133.2 (C, C-11), 133.1 (C, C-20), 131.7 (CHx2, C-12), 131.1 (CHx2, C-16), 130.8 (CHx2, C-13), 127.9 (CHx2, C-21), 126.9 (CHx2, C-17), 126.4 (C, C-14), 120.8 (C, C-18), 117.0 (CH, C-3), 115.0 (CHx2, C-22), 108.3 (CH, C-5), 82.1 (C, C-8), 44.9 (CH_2, C-19), 41.5 (CH_2, C-7). **UPLC, MS,** r.t: 1.26 min, *m/z*: ES^+ $[M+H]^+$ 584. **HRMS (ESI):** calcd. for $C_{27}H_{21}{}^{79}Br_2FNO_3$ **$(M+H)^+$**: 583.9867, found 583.9868.

1-Benzyl-6-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)pyridin-2(1H)-one (231d).



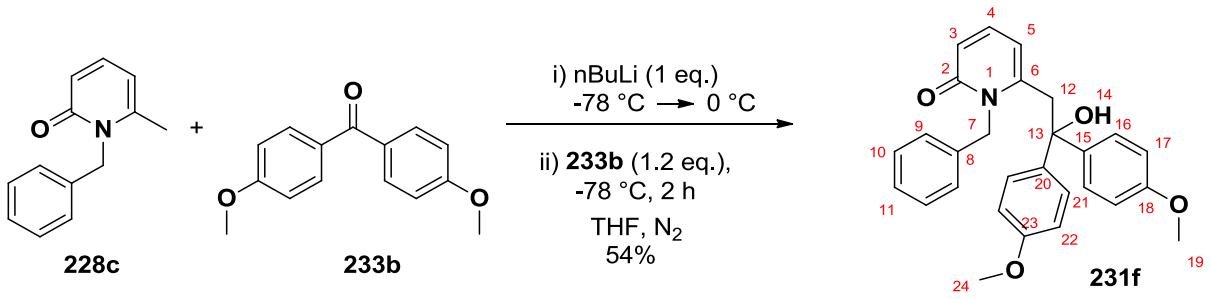
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.56 mg, 2.8 mmol) in THF (15 mL), n-BuLi (1.8 mL, 2.8 mmol) and 1,2-di-p-tolylethane-1,2-dione **232a** (0.74 g, 3.1 mmol) in THF (5.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in heptane to afford compound **231d** as a pale yellow solid (1.1 g, 89%). **m.p.** 197-198 °C. **IR (KBr)** 3267 (OH), 3057 ($CHsp^2_{Ar}$), 3027 ($CHsp^2$), 2963 ($CHsp^3$), 1667 (C=O), 1646 (C=O), 1562 (C=C), 1545 (C=C), 1142 (CO), 812-720 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 500 MHz): δ(ppm)** 7.74 - 7.78 (m, 2H), 7.27 - 7.32 (m, 2H), 7.20 - 7.25 (m, 3H), 7.17 (dd, *J*=9.1, 7.1 Hz, 1H), 7.11 (d, *J*=7.9 Hz, 4H), 7.02 (d, *J*=7.3 Hz, 2H), 6.48 (s, OH), 6.26 (dd, *J*=9.1, 1.3 Hz, 1H), 5.97 (dd, *J*=7.1, 1.3 Hz, 1H), 5.32 (d, *J*=16.1 Hz, 1H), 5.07 (d, *J*=16.1 Hz, 1H), 3.44 (d, *J*=15.3 Hz, 1H), 3.33 (d, *J*=15.3 Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ(ppm)** 198.6 (C=O), 162.5 (C=O), 146.1 (C), 142.9 (C), 138.5 (CH), 138.1 (C), 137.3 (C), 136.7 (C), 131.7 (C), 130.5 (CHx2), 129.0 (CHx2), 128.5 (CHx2), 128.4 (CHx2), 126.8 (CHx2), 125.9 (CHx2), 124.7 (CH), 116.8 (CH), 108.7 (CH), 82.2 (C), 45.4 (CH_2), 42.2 (CH_2), 21.0 (CH_3), 20.5 (CH_3). **UPLC, MS,** r.t: 1.17 min, *m/z*: ES^+ $[M+H]^+$ 438. **HRMS (ESI):** calcd. for $C_{29}H_{28}NO_3$ **$(M+H)^+$**: 438.2064, found 438.2063.

1-benzyl-6-(2,2-bis(4-chlorophenyl)-2-hydroxyethyl)pyridin-2(1H)-one (231e).



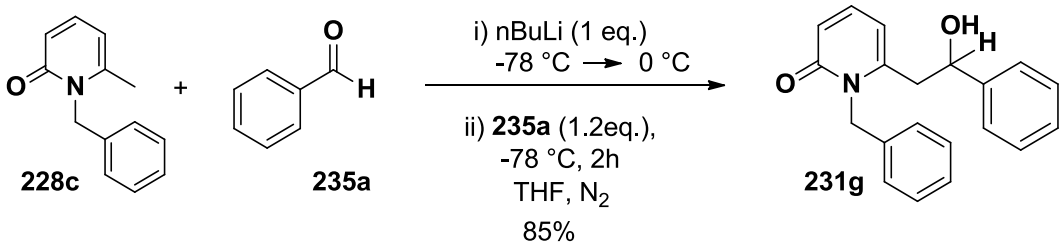
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.29 g, 1.5 mmol), in THF (17 mL), n-BuLi (1.0 mL, 1.5 mmol) and 4,4'-dichlorobenzophenone **233a** (0.45 g, 1.8 mmol) in THF (3 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231e** as a white solid (0.35 g, 52%). **m.p.** 212 °C. **IR (KBr)** 3323 (OH), 3057 ($CHsp^2_{Ar}$), 3030 ($CHsp^2$), 2965 ($CHsp^3$), 1651 (C=O), 1567 (C=C), 1552 (C=C), 1364 (C-OH), 1142 (C-OH), 1086 (CO), 815-794 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ(ppm)** 7.30 - 7.38 (m, 10H), 7.24 - 7.30 (m, 1H), 7.18 (dd, *J*=9.2, 7.2 Hz, 1H), 7.04 (d, *J*=7.2 Hz, 2H), 6.46 (s, 1H), 6.3 (d, *J*=9.2 1H), 5.78 (d, *J*=7.2 Hz, 1H), 5.43 (br. s., 2H), 3.55 (s, 2H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 162.7 (C=O), 146.2 (Cx2), 145.8 (Cx2), 138.6 (CH), 137.8 (C), 137.5 (C), 131.5 (CHx2), 128.8 (CH), 128.7 (CHx2), 127.9 (CHx4), 127.1 (CHx2), 126.1 (CHx2), 116.9 (CH), 108.7 (CH), 76.8 (C), 45.8 (CH_2), 42.5 (CH2). **HRMS (ESI):** calcd. for $C_{26}H_{21}NO_2{}^{35}Cl_2$ **$(M+H)^+$**: 450.1022 found 450.1012.

1-benzyl-6-(2-hydroxy-2,2-bis(4-methoxyphenyl)ethyl)pyridin-2(1H)-one (231f).



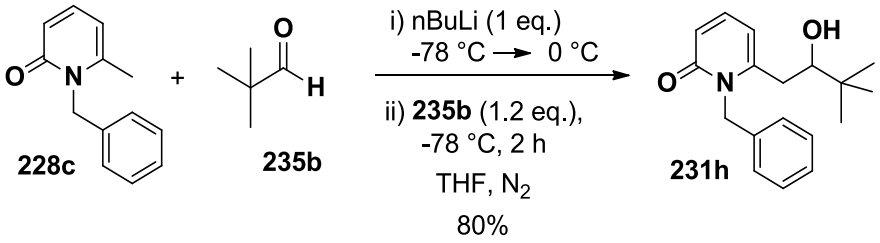
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.33 g, 1.7 mmol), in THF (15 mL), n-BuLi (1.2 mL, 1.7 mmol) and 4,4'-dimethoxybenzophenone **233b** (0.48 mg, 2.1 mmol) in THF (5 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231f** as a white solid (0.39 g, 54%). **m.p.** 180-181 °C. **IR (KBr)** 3392 (OH), 3034 ($CHsp^2$), 3002 ($CHsp^2_{Ar}$), 2943 ($CHsp^3$), 1649 (C=O), 1565 (C=C), 1507 (C=C), 1302 (C-OH), 1081 (CO), 833-797 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm)** 7.30 (t, J=7.2 Hz, 2H, H-10,H-10'), 7.21 (t, J=7.2 Hz, 1H, H-11), 7.15 - 7.11 (m, 1H, H-4), 7.14 (d, J=8.8 Hz, 4H), 6.97 (d, J=7.2 Hz, 2H, H-9,H-9'), 6.77 (d, J=8.6 Hz, 4H), 6.23 (dd, J=8.8, 1.0 Hz, 1H, H-3), 5.99 (s, 1H, OH), 5.76 (dd, J=7.0, 1.0 Hz, 1H, H-5), 5.31 (br. s., 2H, H-7, H-7´), 3.66 (s, 6H), 3.41 (s, 2H, H-12, H-12´). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 162.7 (C=O, C-2), 157.8 (C), 146.9 (C), 139.5 (C), 138.6 (CH, C-4), 137.5 (C), 128.7 (CHx2), 127.2 (CHx2), 127.0 (CH, C-11), 126.0 (CH), 116.6 (CH, C-3), 113.1 (CHx4, C-16, C-21), 108.9 (CH, C-5), 76.8 (C, C-13), 55.0 (2 x CH_3, C-19, C-24), 45.7 (CH_2, C-7), 43.4 (CH_2, C-12). **HRMS (ESI):** calcd. for $C_{28}H_{28}NO_4$ **$(M+H)^+$**: 442.2013 found 442.1997.

1-benzyl-6-(2-hydroxy-2-phenylethyl)pyridin-2(1H)-one (301g).



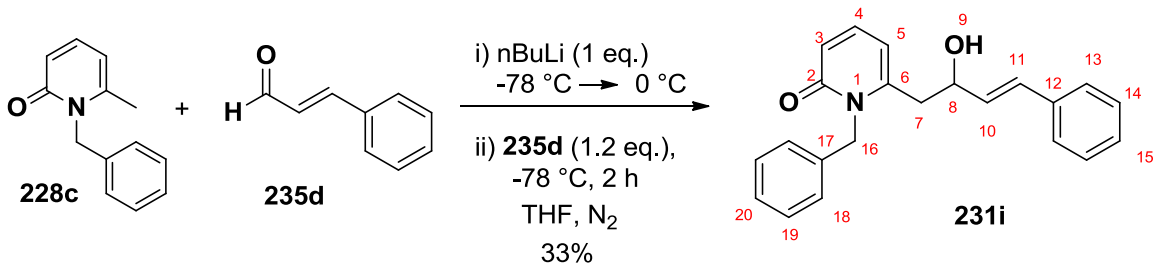
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.11 g, 0.55 mmol), in THF (9.0 mL), n-BuLi (0.40 mL, 0.55 mmol) and benzaldehyde **235a** (60 µL, 0.66 mmol) in THF (3.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231g** as a colourless solid (0.14 g, 85%). **m.p.** 130-131 °C. **IR (Neat)** 3320 (OH), 3062 ($CHsp^2$), 3030 ($CHsp^2_{Ar}$), 2960 ($CHsp^3$), 1651 (C=O), 1567 (C=C), 1550 $(C=C)_{Ar}$, 1402 (C-OH), 1145 (CO), 715-699 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm)** 7.40 (dd, *J*=9.0, 6.8 Hz, 1H), 7.28 - 7.36 (m, 6H), 7.22 - 7.27 (m, 2H), 7.02 - 7.09 (m, *J*=7.2 Hz, 2H), 6.38 (dd, *J*=9.0, 1.0 Hz, 1H), 6.20 (dd, *J*=6.8, 1.0 Hz, 1H), 5.67 (d, *J*=4.4 Hz, 1H), 5.41 (br. s., 2H), 4.75 - 4.85 (m, 1H), 2.81 (d, *J*=6.6 Hz, 2H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 163.2 (C=O), 148.6 (C), 145.3 (C), 139.8 (CH), 137.8 (C), 129.2 (CHx2), 128.6 (CHx2), 127.7 (CH), 127.5 (CH), 126.5 (CHx2), 126.2 (CHx2), 117.4 (CH), 107.9 (CH), 72.5 (CH), 46.4 (CH_2), 42.8 (CH_2). **HRMS (ESI):** calcd. for $C_{20}H_{20}NO_2$ **$(M+H)^+$**: 306.1489 found 306.1488.

1-benzyl-6-(2-hydroxy-3,3-dimethylbutyl)pyridin-2(1H)-one (231h).



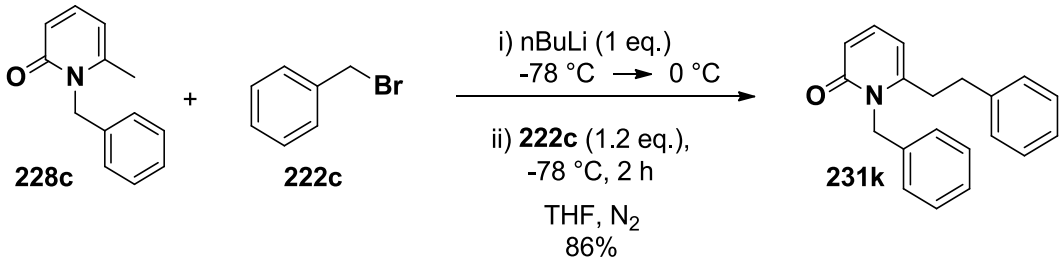
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.16 g, 0.79 mmol), in THF (8.0 mL), n-BuLi (0.58 mL, 0.79 mmol) and trimethylacetaldehyde **235b** (0.10 mL, 0.95 mmol) in THF (2.0 mL) gave compound **231h** as a pale yellow solid (0.18 g, 80%). **m.p.** 130 °C. **IR (KBr)** 3265 (OH), 3062 ($CHsp^2$), 3026 ($CHsp^2_{Ar}$), 2956 ($CHsp^3$), 1652 (C=O), 1567 (C=C), 1552 $(C=C)_{Ar}$, 1289 (C-OH), 1081 (CO), 732-697 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm)** 7.42 (dd, *J*=9.0, 6.8 Hz, 1H), 7.31 - 7.37 (m, 2H), 7.23 - 7.28 (m, 1H), 7.05 (d, *J*=7.0 Hz, 2H), 6.37 (dd, *J*=9.0, 1.2 Hz, 1H), 6.23 (dd, *J*=6.8, 1.2 Hz, 1H), 5.43 (br. s., 2H), 4.94 (d, *J*=6.2 Hz, 1H), 3.33 (ddd, *J*=10.4, 6.2, 2.0 Hz, 1H), 2.57 - 2.63 (m, 1H), 2.40 (dd, *J*=14.6, 10.4 Hz, 1H), 0.82 (s, 9H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 162.8 (C=O), 150.2 (C), 139.4 (CH), 137.3 (C), 128.6 (2 x CH), 126.9 (CH), 125.9 (2 x CH), 116.3 (CH), 107.0 (CH), 77.4 (CH), 45.8 (CH_2), 35.2 (CH_2), 34.8 (C), 25.5 (3 x CH_3). **HRMS (ESI):** calcd. for $C_{18}H_{24}O_2N$ **$(M+H)^+$**: 286.1802 found 286.1798.

(E)-1-benzyl-6-(2-hydroxy-4-phenylbut-3-en-1-yl)pyridin-2(1H)-one (231i).



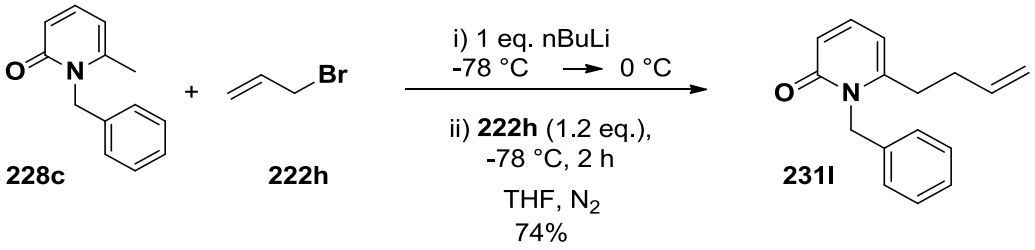
Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.16 g, 0.82 mmol), in THF (8.0 mL), n-BuLi (0.60 mL, 0.82 mmol) and cinnamaldehyde **235d** (0.12 mL, 0.98 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231i** as a pale yellow solid (89 mg, 33%). **m.p.** 78-79 °C. **IR (KBr)** 3339 (OH), 3029 ($CHsp^2$), 1650 (C=O), 1566 (C=C), 1550 $(C=C)_{Ar}$, 1145 (CO), 732-694 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.38 - 7.44 (m, 3H), 7.30 - 7.36 (m, 4H), 7.21 - 7.28 (m, 2H), 7.09 (d, *J*=7.0 Hz, 2H), 6.47 - 6.54 (m, 1H), 6.38 (dd, *J*=9.0, 1.2 Hz, 1H), 6.24 - 6.35 (m, 2H), 5.37 - 5.50 (m, 2H), 5.41 (d, *J*=4.8, 1H), 4.33 - 4.42 (m, 1H), 2.67 - 2.86 (m, 2H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 162.7 (C=O, C-2), 148.1 (C, C-6), 139.4 (CH, C-4), 137.4 (C), 136.5 (C), 132.8 (CH), 128.9 (CH), 128.7 (CHx4), 127.5 (CH), 127.0 (CH), 126.3 (CHx2), 126.1 (CHx2), 116.9 (CH, C-3), 107.4 (CH, C-5), 70.5 (CH, C-8), 46.0 (CH_2, C-16), 40.4 (CH_2, C-7). **HRMS (ESI):** calcd. for $C_{22}H_{22}NO_2$ **$(M+H)^+$**: 332.1645 found 332.1639. **HRMS (ESI):** calcd. for $C_{22}H_{21}NO_2Na$ **$(M+Na)^+$**: 354.1465 found 354.1459.

1-benzyl-6-phenethylpyridin-2(1H)-one (231k).



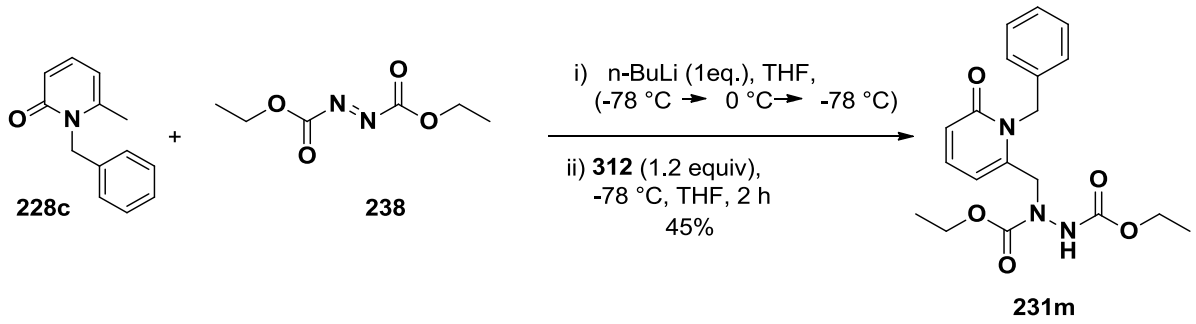
Following general procedure I, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.14 g, 0.73 mmol) in THF (7.0 mL), n-BuLi (0.54 mL, 0.73 mmol) and benzyl bromide **222c** (0.10 mL, 0.87 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231k** as a white solid (0.18 g, 86%). **m.p.** 83 °C. **IR (KBr)** 3057 ($CHsp^2$), 2930 ($CHsp^3$), 1654 (C=O), 1573 (C=C), 1547 $(C=C)_{Ar}$, 789-702 (CH_{Arom}). **^{1}H NMR (DMSO-d$_6$, 400 MHz): δ (ppm)** 7.42 (dd, *J*=9.0, 6.0 Hz, 1H), 7.30 - 7.37 (m, 2H), 7.22 - 7.29 (m, 3H), 7.16 - 7.21 (m, 1H), 7.11 - 7.16 (m, 2H), 7.08 (d, *J*=7.2 Hz, 2H), 6.40 (d, *J*=9.0 Hz, 1H), 6.20 (d, *J*=6.0 Hz, 1H), 5.36 (br. s., 2H), 2.73 - 2.88 (m, 4H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 162.6 (C=O), 149.9 (C), 140.1 (C), 139.4 (CH), 137.1 (C), 128.6 (CHx2), 128.2 (CHx2), 128.1 (CHx2), 126.9 (CH), 126.1 (CH), 125.9 (CHx2), 116.7 (CH), 105.4 (CH), 45.4 (CH_2), 33.7 (CH_2), 33.6 (CH_2). **HRMS (ESI):** calcd. for $C_{20}H_{20}NO$ **$(M+H)^+$**: 290.1539 found 290.1536.

1-benzyl-6-(but-3-en-1-yl)pyridin-2(1H)-one (231l).



Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.16 g, 0.81 mmol) in THF (8.0 mL), n-BuLi (0.60 mL, 0.81 mmol) and allyl bromide **222h** (84 µL, 0.98 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231l** as pale brown oil (0.14 g, 74%). **IR** (Neat) 3064 ($CHsp^2$), 3031 ($CHsp^2$), 3003 ($CHsp^2_{Arm}$), 1659 (C=O), 1580 (C=C), 1550 $(C=C)_{Ar}$, 731-696 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm)** 7.42 (dd, *J*=9.2, 6.8 Hz, 1H), 7.31 - 7.36 (m, 2H), 7.23 - 7.28 (m, 1H), 7.07 - 7.11 (m, 2H), 6.39 (d, *J*=9.2 Hz, 1H), 6.16 (d, *J*=6.8 Hz, 1H), 5.76 (ddt, *J*=17.0, 10.4, 6.5 Hz, 1H), 5.33 (br. s., 2H), 4.94 - 5.02 (m, 2H), 2.60 - 2.67 (m, 2H), 2.18 - 2.28 (m, 2H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 162.7 (C=O), 150.0 (C), 139.5 (CH), 137.3 (C), 136.8 (CH), 128.7 (CHx2), 127.0 (CH), 126.1 (CHx2), 116.8 (CH), 115.9 (CH_2), 105.3 (CH), 45.6 (CH_2), 31.5 (CH_2), 31.2 (CH_2). **HRMS (ESI):** calcd. for $C_{16}H_{18}NO$ **$(M+H)^+$**: 240.1383 found 240.1382. **HRMS (ESI):** calcd. for $C_{16}H_{17}NONa$ **$(M+Na)^+$**: 262.1202 found 262.1202.

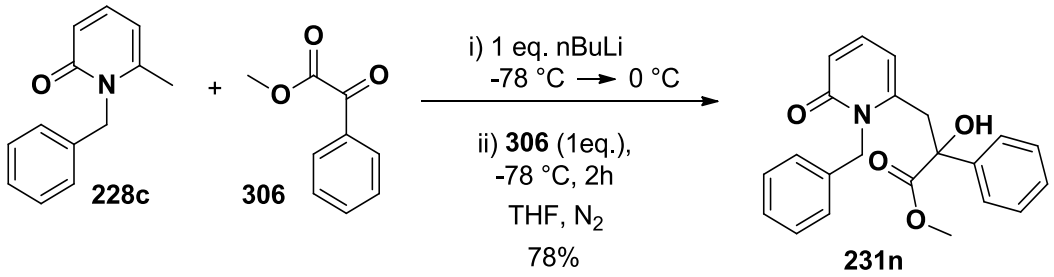
Diethyl 1-((1-benzyl-6-oxo-1,6-dihydropyridin-2-yl)methyl)hydrazine-1,2-dicarboxylate (231m).



228c + **238** → **231m**

Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.10 g, 0.5 mmol) in THF (5.0 mL), n-BuLi (0.4 mL, 0.5 mmol) and diethyl azodicarboxylate **238** (94 µL, 0.60 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **231m** as yellow oil (83 mg, 45%). **IR (Neat)** 3430 (NH), 3063 ($CHsp^2$), 2983 ($CHsp^3$), 1723 (C=O), 1657 (C=O), 1577 (C=C), 1267 (C-O), 1223 (CO), 770-735 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 9.12 (br. s., 1H), 7.36 (dd, *J*=9.0, 7.2 Hz, 1H), 7.28 (t, *J*=7.5 Hz, 2H), 7.21 (t, *J*=7.2 Hz, 1H), 7.08 (d, *J*=7.2 Hz, 2H), 6.41 (d, *J*=9.0 Hz, 1H), 6.20 (d, *J*=7.2 Hz, 1H), 5.26 (s, 2H), 4.45 (s, 2H), 3.92 - 4.09 (m, 4H), 1.06 - 1.16 (m, 6H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 163.0 (C=Ox2), 139.8 (CH), 129.1 (CHx3), 127.6 (CH), 126.5 (CH), 119.8 (CH), 107.9 (CH), 62.78 (CH_2), 61.5 (CH_2x2), 45.8 (CH_2), 14.9 (CH_3x2). **HRMS (ESI):** calcd. for $C_{19}H_{24}N_3O_5$ **$(M+H)^+$**: 374.1710 found 374.1705.

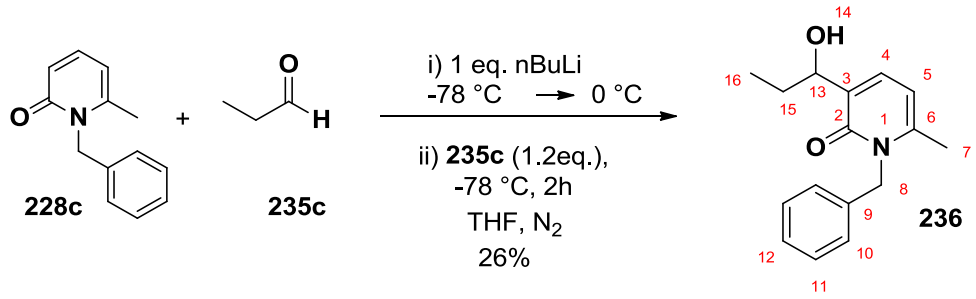
Methyl 3-(1-benzyl-6-oxo-1,6-dihydropyridin-2-yl)-2-hydroxy-2-phenylpropanoate (231n).



Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.50 g, 2.5 mmol) in THF (15 mL), n-BuLi (1.6 mL, 2.5 mmol) and methyl 2-oxo-2-phenylacetate **306** (0.43 mL, 3.0 mmol) was performed. The resulting solution was stirred at -78 °C for 45 min. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in heptane to afford compound **231n** as a white solid (0.71 g, 78%). **m.p.** 158-159 °C. **IR (KBr)** 3144 (OH), 3061 ($CHsp^2$), 3026 ($CHsp^2_{Ar}$), 2969 ($CHsp^3$), 1727(C=O), 1648 (C=O), 1565 (C=C), 1384 (OH), 1070 (C-O), 726-648 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.38 - 7.43 (m, 2H), 7.26 - 7.37 (m, 6H), 7.20 - 7.26 (m, 1H), 6.99 (d, *J*=7.1 Hz, 2H), 6.61 (s, 1H), 6.35 (dd, *J*=9.0, 1.1 Hz, 1H), 6.02 (d, *J*=6.8 Hz, 1H), 5.52 (d, *J*=16.2 Hz, 1H), 5.30 (d, *J*=16.2 Hz, 1H), 3.65 (s, 3H), 3.45 (d, *J*=15.2 Hz, 1H), 3.13 (d, *J*=15.2 Hz, 1H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 173.2 (C=O), 162.5 (C=O), 145.9 (C), 141.7 (C), 138.9 (CH), 137.2 (C), 128.6 (2xCH), 128.2 (2xCH), 127.8 (CH), 126.9 (CH), 125.9 (2xCH), 125.1 (2xCH), 117.4 (CH), 107.3 (CH), 78.7 (C), 52.5 (CH_3), 45.9 (CH_2), 40.1 (CH_2). **UPLC, MS,** r.t: 0.93 min, *m/z*: ES^+ $[M+H]^+$ 364. **HRMS (ESI):** calcd. for $C_{22}H_{22}NO_4$ **$(M+H)^+$**: 364.1543, found 364.1545.

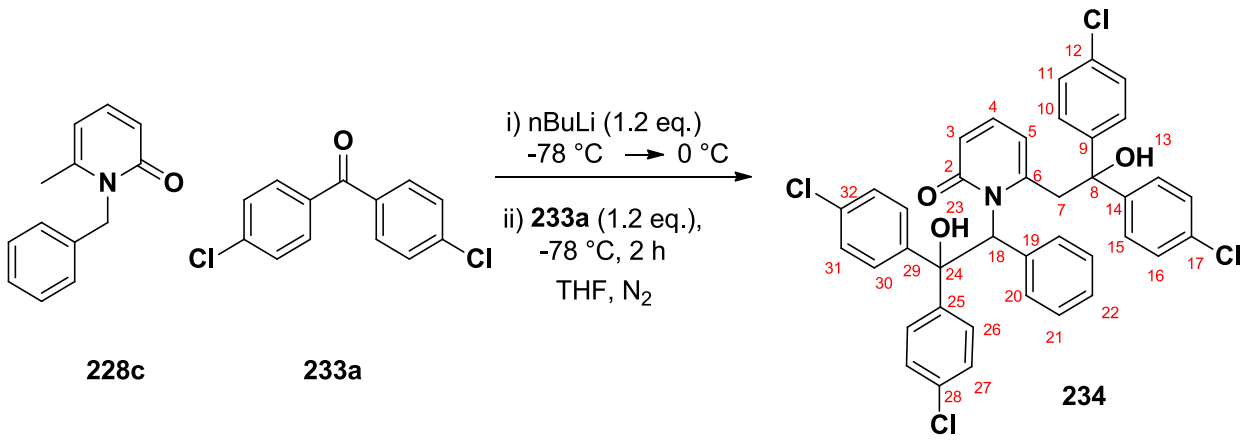
Alkylation of N-benzyl-2-pyridone.

Synthesis of 1-benzyl-3-(1-hydroxypropyl)-6-methylpyridin-2(1H)-one(236).



Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.15 g, 0.73 mmol) in THF (5.0 mL), n-BuLi (0.54 mL, 0.73 mmol) and propionaldehyde **235c** (62 µL, 0.87 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **236** as a colourless oil (49 mg, 26%). **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 7.40 (d, *J*=7.0 Hz, 1H. H-4), 7.30 - 7.37 (m, 2H, H-11), 7.23 - 7.28 (m, 1H, H-12), 7.09 (d, *J*=7.1 Hz, 2H, H-10), 6.19 (d, *J*=7.0 Hz, 1H, H-5), 5.37 (d, *J*=15.7 Hz, 1H, H-8), 5.27 (d, *J*=15.7 Hz, 1H, H-8'), 4.99 (d, *J*=5.0 Hz, 1H, H-14), 4.55 - 4.62 (m, 1H, H-13), 2.24 (s, 3H, H-7), 1.72 (ddd, *J*=13.4, 7.4, 3.9 Hz, 1H, H-15), 1.45 (dt, *J*=13.4, 7.4 Hz, 1H, H-15'), 0.87 (t, *J*=7.4 Hz, 3H, H-16). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 161.5 (C=O), 144.5 (C), 137.3 (C), 133.9 (C), 132.4 (CH), 128.7 (CHx2), 127.0 (CH), 126.2 (CHx2), 105.8 (CH), 68.6 (CH), 46.2 (CH_2), 29.1 (CH_2), 19.9 (CH_3), 10.0 (CH_3). **HRMS (ESI):** calcd. for $C_{16}H_{20}NO_2$ **(M+H)$^+$**: 258.1489 found 258.1487.

Synthesis of 1-(2,2-bis(4-chlorophenyl)-2-hydroxy-1-phenylethyl)-6-(2,2-bis(4-chlorophenyl)-2-hydroxyethyl)pyridin-2(1H)-one (234).

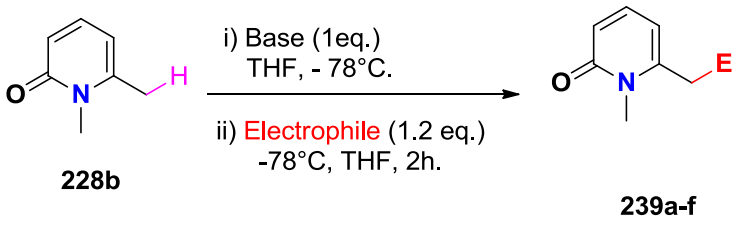


Following general procedure **I**, the reaction between 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.22 g, 1.12 mmol) in THF (13 mL), n-BuLi (0.84 mL, 1.34 mmol), 4,4'-Dichlorobenzophenone **233a** (0.34 g, 1.34 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **234** as a white solid (0.11 g, 15%). **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 8.93 (s, 1H), 7.63 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 7.20 - 7.26 (m, 5H), 7.13 - 7.20 (m, 3H), 7.02 - 7.08 (m, 1H), 7.00 (s, 1H), 6.79 - 6.86 (d, *J*=7.6 Hz, 2H), 6.08 (d, *J*=8.8 Hz, 1H), 5.62 (d, *J*=7.2 Hz, 1H), 3.58 (d, *J*=15.3 Hz, 1H), 3.43 (d, *J*=15.3 Hz, 1H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 166.3 (C, C-2), 147.6 (C), 146.4 (C), 146.3 (C), 144.9 (C), 144.8 (C), 139.9 (CH), 137.3 (C), 132.5 (C), 132.3 (C), 132.1 (C), 131.8 (C), 129.4 (CH), 129.0 (CH), 128.7 (CH), 128.54 (CH), 128.50 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.01 (CH), 127.96 (CH), 119.7 (CH), 113.3 (CH), 79.2 (C), 78.8 (C), 73.1 (CH), 43.4 (CH_2).

Methyl alkylation of 1,6-dimethyl-2-pyridone

Experimental section

General experimental procedure for the deprotonation of 1,6-dimethylpyridin-2(1H)-one and nucleophilic addition to several electrophiles.

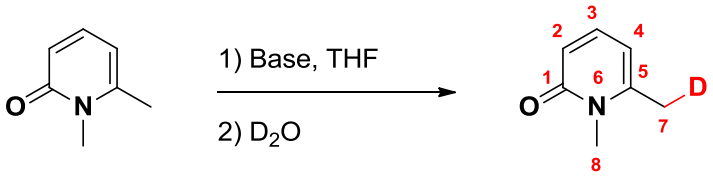


228b **239a-f**

General procedure II:

An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1,6-dimethylpyridin-2(1H)-one **228b** (1 eq.) and dissolved in dry THF. The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. KHMDS (1 eq.) was added to the pale transparent yellow solution dropwise over 5 min and the reaction became orange in colour. The reaction mixture was warmed up to 0 °C and changed to a dark brown/green colour, and was then cooled to -78 °C. Concurrently, an additional oven-dried flask was purged with N_2 and then was charged with the electrophile (1.2 eq.) which was then dissolved in dry THF. The electrophile solution was added dropwise to the pyridone solution at -78 °C via syringe over 5 min. The reaction was allowed to proceed for 2 h at -78 °C, before quenching with saturated $NH_4Cl_{(aq)}$. EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude product was purified by flash silica chromatography.

Synthesis of 1-methyl-2-methyl-deuterated-pyridin-4(1H)-one (239d).

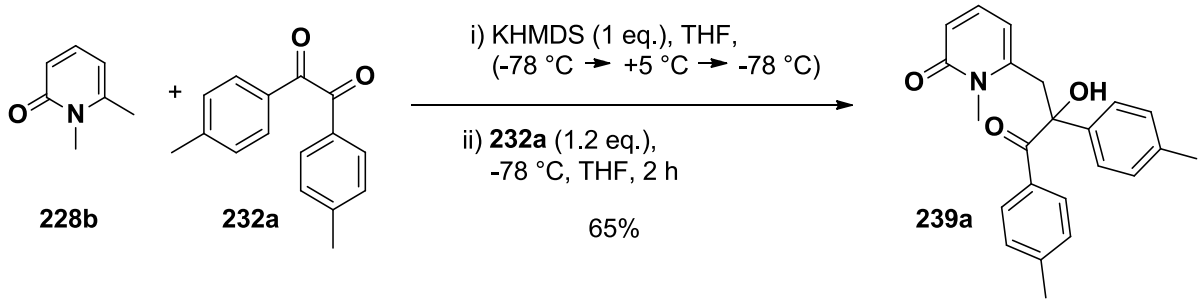


228b **239d**

Following general set up of procedure **II**, 1,6-dimethylpyridin-2(1H)-one **228b** (90 mg, 0.73 mmol) was dissolved in THF (6.0 mL). KHMDS (1.5 mL, 0.73 mmol) was added at -78 °C, and the reaction was stirred for 10 min at -78°C. D_2O was added to the solution at -78°C, the reaction was stirred for 5 min and quenched at -78°C to give compound **239d** as a white solid (49 mg, 55%).

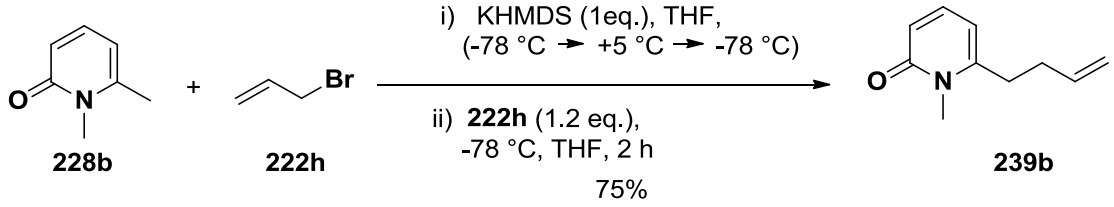
Following general procedure **II**, reaction between 1,6-dimethylpyridin-2(1H)-one **228b** (43 mg, 0.35 mmol) in THF (12 mL), KHMDS (1.7 mL, 0.87 mmol) and quenching with D_2O gave compound **239d** as a white solid (22 mg, 51%). **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.21 (dd, *J*=9.2, 6.8 Hz, 1H), 6.47 (d, *J*=9.2 Hz, 1H), 6.04 (d, *J*=6.8 Hz, 1H), 3.54 (s, 3H), 2.33 - 2.37 (m, 2H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 164.0 (C=O), 146.4 (C), 138.7 (CH), 117.3 (CH), 106.5 (CH), 31.2 (CH_3), 20.75 (t, $J_{C\text{-}D}$=19.6,CH_2D).

6-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)-1-methylpyridin-2(1H)-one (239a).



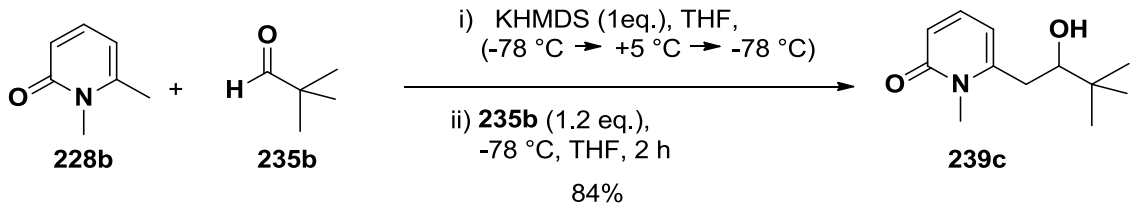
Following general procedure **II**, the reaction between 1,6-dimethylpyridin-2(1H)-one **228b** (61 mg, 0.50 mmol) in THF (6.0 mL), KHMDS (1.0 mL, 0.50 mmol) and 1,2-di-p-tolylethane-1,2-dione **232a** (0.145 g, 0.60 mmol) in THF (8.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **239a** as a white solid (0.11 g, 65%). **m.p.** 174-175 °C. **IR (KBr)** 3071 (OH), 3030 ($CHsp^2$), 2918 ($CHsp^3$), 1672 (C=O), 1644 (C=O), 1605 (C=C), 1559 (C=C), 1509 (C=C), 1379(C-OH), 1096 (CO), 826, 804 (CH_{Arom}) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm)** 7.67 - 7.71 (m, 2H), 7.31 - 7.36 (m, 2H), 7.19 (d, *J*=8.0 Hz, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 7.02 (dd, *J*=9.0, 6.8 Hz, 1H), 6.32 (dd, *J*=9.0, 1.2 Hz, 1H), 5.70 (dd, *J*=6.8, 1.2 Hz, 1H), 5.08 (s, 1H), 3.64 - 3.77 (m, 2H), 3.44 (s, 3H), 2.35 (s, 3H), 2.35 (s, 3H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 199.3 (C=O), 164.1 (C=O), 145.2 (C), 144.1 (C), 138.4 (C), 138.3 (C), 137.9 (CH), 131.2 (C), 130.5 (CHx2), 129.8 (CHx2), 129.2 (CHx2), 125.2 (CHx2), 118.1 (CH), 108.9 (CH), 82.2 (C), 41.6 (CH_2), 32.4 (CH_3), 21.6 (CH_3), 21.1 (CH_3). **HRMS (ESI):** calcd. for $C_{23}H_{24}NO_3$ **$(M+H)^+$**: 362.1751 found 362.1751. **HRMS (ESI):** calcd. for $C_{23}H_{23}NO_3Na$ **$(M+Na)^+$**: 384.1570 found 384.1565.

6-(But-3-en-1-yl)-1-methylpyridin-2(1H)-on (239b).



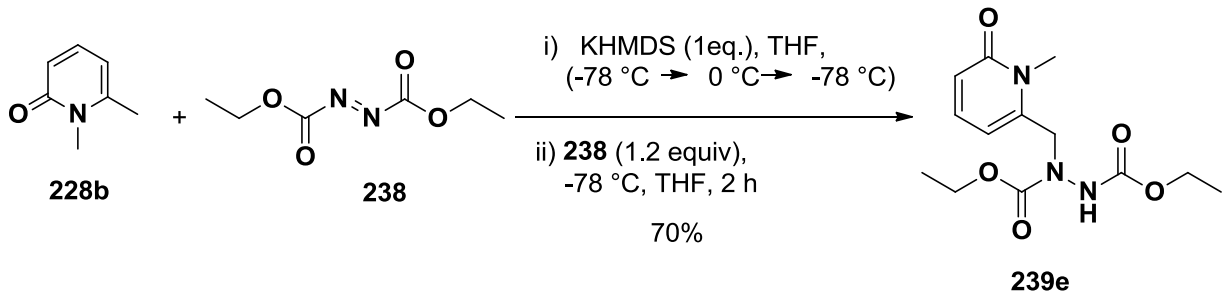
Following general procedure **II**, the reaction between 1,6-dimethylpyridin-2(1H)-one **228b** (0.11 g, 0.85 mmol) in THF (8.0 mL), KHMDS (1.7 mL, 0.85 mmol) and allylbromide **222h** (80 µL, 1.0 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **239b** as light brown oil (0.10 g, 75%). **IR (Neat)** 3077 ($CHsp^2$), 2976 ($CHsp^3$), 2923 ($CHsp^3$), 1656 (C=O), 1571 (C=C), 1554 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.25 (dd, *J*=9.2, 6.8 Hz, 1H), 6.48 (d, *J*=9.2 Hz, 1H), 6.04 (d, *J*=6.8 Hz, 1H), 5.86 (ddt, *J*=17.0, 10.2, 6.5 Hz, 1H), 5.07 - 5.16 (m, 2H), 3.57 (s, 3H), 2.69 - 2.75 (m, 2H), 2.34 - 2.46 (m, 2H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 164.1 (C=O), 149.2 (C), 138.5 (CH), 136.0 (CH), 117.5 (CH), 116.4 (CH_2), 105.7 (CH), 32.9 (CH_2), 31.9 (CH_2), 30.9 (CH_3). **HRMS (ESI):** calcd. for $C_{10}H_{14}NO$ **$(M+H)^+$**: 164.1070 found 164.1065.

6-(2-hydroxy-3,3-dimethylbutyl)-1-methylpyridin-2(1H)-one (239c).



Following general procedure **II**, the reaction between 1,6-dimethylpyridin-2(1H)-one **228b** (99 mg, 0.80 mmol) in THF (8.0 mL), KHMDS (1.6 mL, 0.80 mmol) and trimethylacetaldehyde **235b** (0.10 mL, 0.96 mmol) in THF (2.0 mL) gave compound **239c** as a pale yellow solid (0.14 g, 84%). **m.p.** 93-94 °C. **IR (KBr)** 3391 (OH), 2958 ($CHsp^3$), 2867 ($CHsp^3$), 1647 (C=O), 1570 (C=C), 1384 (OH), 1148 (CO) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm)** 7.23 (dd, *J*=9.0, 6.8 Hz, 1H, H-4), 6.42 (dd, *J*=9.0, 1.2 Hz, 1H, H-3), 6.14 (dd, *J*=6.8, 1.2 Hz, 1H, H-5), 3.55 (s, 3H, CH_3, H-7), 3.53 (m, 1H, H-9), 2.89 (dd, *J*=14.6, 1.8 Hz, 1H, H-8), 2.61 (dd, *J*=14.6, 10.4 Hz, 1H, H-8´), 1.03 (s, 9H, 3xCH_3, H-11). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 164.2 (C=O, C2), 148.7 (C, C-6), 138.6 (CH, C-4), 117.4 (CH, C-3), 107.8 (CH, C-5), 77.7 (CH, C-9), 36.2 (CH_2, C-8), 35.4 (C, C-10), 31.5 (CH_3, C-7), 25.6 (CH_3, C-11). **HRMS (ESI):** calcd. for $C_{12}H_{20}NO_2$ **$(M+H)^+$**: 210.1489 found 210.1484. **HRMS (ESI):** calcd. for $C_{12}H_{19}NO_2Na$ **$(M+Na)^+$**: 232.1308 found 232.1305.

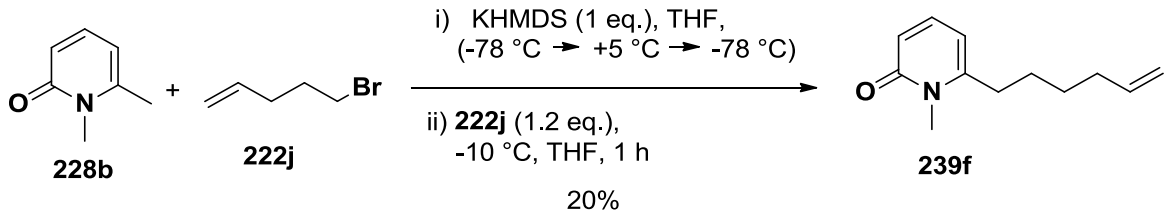
Diethyl 1-((1-methyl-6-oxo-1,6-dihydropyridin-2-yl)methyl)hydrazine-1,2-dicarboxylate (239e).



228b **238** **239e**

Following general procedure **II**, the reaction between 1,6-dimethylpyridin-2(1H)-one **228b** (59 mg, 0.48 mmol) in THF (6.0 mL), KHMDS (0.96 mL, 0.48 mmol) and diethyl azodicarboxylate **238** (90 µL, 0.57 mmol) in THF (2.0 mL) was performed. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **239e** as white oil (0.10 g, 70%). **IR (Neat)** 3210 (N-H), 2983 ($CHsp^3$), 2933 ($CHsp^3$), 1730 (C=O), 1655 (C=O), 1266-1238 (RCO-O-C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm)** 7.60 (br. s., 1H), 7.16 (dd, *J*=9.0, 6.6 Hz, 1H), 6.44 (d, *J*=9.0 Hz, 1H), 6.07 (d, *J*=6.6 Hz, 1H), 4.64 (br. s., 2H), 4.22 (q, *J*=7.0 Hz, 2H), 4.14 (q, *J*=7.0 Hz, 2H), 3.47 (s, 3H), 1.15 - 1.29 (m, 6H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 163.8 (CO), 156.1 (CO), 155.9 (CO), 143.5 (C), 138.2 (CH), 138.1 (CH), 119.6 (CH), 108.6 (CH), 63.2 (CH_2), 62.1 (CH_2), 51.5 (CH_2), 31.0 (N-CH_3), 14.44 (CH_3), 14.42 (CH_3). **HRMS (ESI):** calcd. for $C_{13}H_{20}N_3O_5$ **$(M+H)^+$**: 298.1397 found 298.1407. **HRMS (ESI):** calcd. for $C_{13}H_{19}N_3O_5Na$ **$(M+Na)^+$**: 320.1217 found 320.1226.

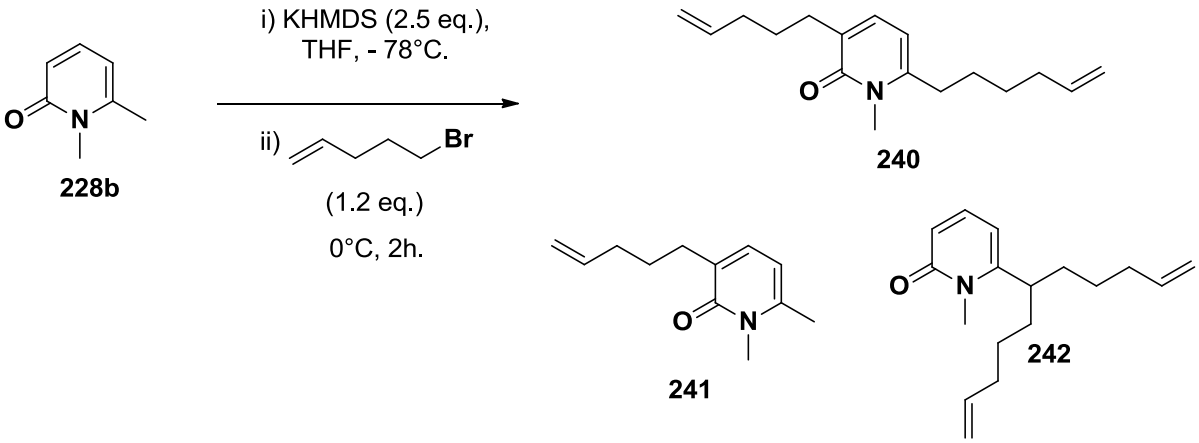
6-(hex-5-en-1-yl)-1-methylpyridin-2(1H)-one (239f).[78]



1,6-Didimethylpyridin-2(1*H*)-one **228b** (0.11 g, 0.88 mmol) was dissolved in THF (6.0 mL) and the resulting solution was cooled to -78 °C. KHMDS (1.7 mL, 0.88 mmol) was added to the pyridone solution at -78 °C, the reaction mixture was warmed up to 0 °C. The reaction was cooled again to -78 °C and 5-bromopent-1-ene **222j** (0.12 mL, 1.1 mmol) in THF (2.0 mL) was added to the solution over 5 min. The reaction was allowed to proceed for 1 h. at -10 °C, before quenching with saturated $NH_4Cl_{(aq)}$. EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude product was purified by flash silica chromatography, with elution gradient 0 to 100 % EtOAc in petroleum ether 40-60° to afford compound **239f** as a light colorless oil (34 mg, 20%). **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.23 (dd, *J*=8.8, 7.0 Hz, 1H), 6.46 (d, *J*=8.8 Hz, 1H), 6.02 (d, *J*=7.0 Hz, 1H), 5.80 (ddt, *J*=17.0, 10.2, 6.5 Hz, 1H), 4.96 - 5.07 (m, 2H), 3.54 (s, 3H), 2.58 - 2.65 (m, 2H), 2.12 (q, *J*=7.0 Hz, 2H), 1.59 - 1.70 (m, 2H), 1.51 (dt, *J*=15.0, 7.4 Hz, 2H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 164.2 (C=O), 150.1 (C), 138.7 (CH), 138.2 (CH), 117.4 (CH), 115.2 (CH_2), 105.7 (CH), 33.6 (CH_2), 33.4 (CH_2), 31.0 (CH_3), 28.4 (CH_2), 27.4 (CH_2). **HRMS (ESI):** calcd. for $C_{12}H_{17}NO$ **$(M+H)^+$**: 192.1383 found 192.1381. **HRMS (ESI):** calcd. for $C_{12}H_{17}NONa$ **$(M+Na)^+$**: 214.1202 found 214.1202.

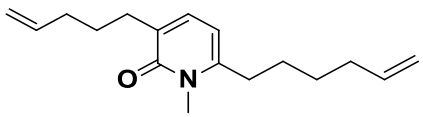
Literature reference: **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.26 (dd, *J*=7.9 Hz, 1H), 6.47 (d, *J*=10 Hz, 1H), 6.07 (d, *J*=7.0 Hz, 1H), 5.63-6.08 (m, 1H), 4.83 - 5.18 (m, 2H), 3.56 (s, 3H), 2.64 (t, *J*= 7 Hz, 2H), 1.91-2.33 (m, 2H), 1.41 - 1.84 (m, 4H).[78]

Alkylation of 1,6-dimethyl-2-pyridone.



An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1,6-dimethylpyridin-2(1H)-one **228b** (69 mg, 0.56 mmol) in dry THF (6.0 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. KHMDS (2.8 mL, 1.4 mmol) was added to the flask dropwise over 5 min. The reaction mixture was warmed up to 0 °C. Concurrently, an additional oven-dried flask was purged with N_2 and then was charged with 5-bromo-1-pentane **222j** (79 µL, 0.67 mmol) which was then dissolved in dry THF (2.0 mL). The electrophile solution was added dropwise to the pyridone solution at 0 °C via syringe over 5 min. The reaction was allowed to proceed for 2 h at 0 °C by immersion in an ice bath, before quenching with saturated $NH_4Cl_{(aq)}$. EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude product was purified by flash silica chromatography, with elution gradient 0 to 100 % EtOAc in petroleum ether 40-60°. To afford compound **240** colourless oil, (12 mg, 8%); compound **241** colourless oil, (8 mg, 8%) and **242** as a colourless oil, (26 mg, 18%).

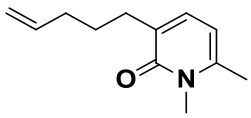
6-(hex-5-en-1-yl)-1-methyl-3-(pent-4-en-1-yl)pyridin-2(1H)-one (240).



240

IR (Neat) 3075 ($CHsp^2$), 2978 ($CHsp^3$), 2928 ($CHsp^3$), 1648 (C=O), 1597 (C=C), 1569 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.05 (d, *J*=7.0 Hz, 1H), 5.94 (d, *J*=7.2 Hz, 1H), 5.69 - 5.89 (m, 2H), 4.87 - 5.06 (m, 4H), 3.51 (s, 3H), 2.52 - 2.60 (m, 2H), 2.44 - 2.52 (m, 2H), 2.08 (q, *J*=6.9 Hz, 4H), 1.53 - 1.71 (m, 4H), 1.43 - 1.53 (m, 2H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 164.0 (C), 147.1 (C), 138.8 (CH), 138.2 (CH), 135.5 (CH), 129.7 (C), 115.1 (CH_2), 114.6 (CH_2), 105.1 (CH), 33.6 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 31.1 (CH_3), 30.5 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 27.5 (CH_2). **HRMS (ESI):** calcd. for $C_{17}H_{25}NONa$ **$(M+Na)^+$**: 282.1828 found 282.1830.

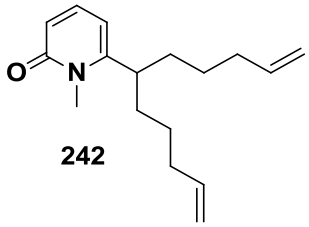
1,6-dimethyl-3-(pent-4-en-1-yl)pyridin-2(1H)-one (241).



241

IR (Neat) 3075 ($CHsp^2$), 2924 ($CHsp^3$), 2923 ($CHsp^3$), 1648 (C=O), 1594 (C=C), 1570 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.04 (d, *J*=6.8 Hz, 1H), 5.96 (d, *J*=6.8 Hz, 1H), 5.74 - 5.90 (m, 1H), 4.87 - 5.06 (m, 2H), 3.52 (s, 3H), 2.50 (t, *J*=7.6 Hz, 2H), 2.30 (s, 3H), 2.09 (q, *J*=7.0 Hz, 2H), 1.65 (m, 2H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 163.8 (C), 143.4 (C), 138.8 (CH), 135.5 (CH), 129.8 (C), 114.6 (CH_2), 105.9 (CH), 33.6 (CH_2), 31.4 (CH_3), 30.5 (CH_2), 27.6 (CH_2), 20.9 (CH_3). **HRMS (ESI):** calcd. for $C_{12}H_{18}NO$ **$(M+H)^+$**: 192.1383 found 192.1382.

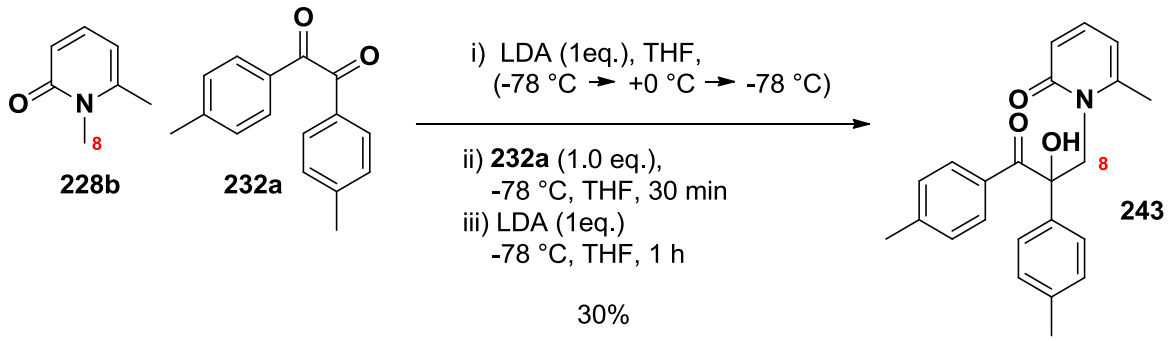
1-methyl-6-(undeca-1,10-dien-6-yl)pyridin-2(1H)-one (242).



242

IR (Neat) 3075 ($CHsp^2$), 2975 ($CHsp^3$), 2931 ($CHsp^3$), 1661 (C=O), 1583 (C=C), 1549 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.19 - 7.31 (m, 1H), 6.37 - 6.47 (m, 1H), 6.01 (d, *J*=6.9 Hz, 1H), 5.70 (ddt, *J*=17.0, 10.2, 6.5 Hz, 2H), 4.88 - 5.01 (m, 4H), 3.56 (s, 3H), 2.76 - 2.90 (m, 1H), 1.93 - 2.04 (m, 4H), 1.46 - 1.70 (m, 4H), 1.23 - 1.39 (m, 4H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 164.3 (C), 154.5 (C), 138.7 (CH), 138.1 (CHx2), 117.0 (CH), 115.1 (CH_2x2), 103.6 (CH), 40.9 (CH), 34.7 (CH_2x2), 33.7 (CH_2x2), 30.8 (CH_3), 26.4 (CH_2x2). **HRMS (ESI):** calcd. for $C_{17}H_{26}NO$ **$(M+H)^+$**: 260.2009 found 260.2010. **HRMS (ESI):** calcd. for $C_{17}H_{25}NONa$ **$(M+Na)^+$**: 282.1828 found 282.1829.

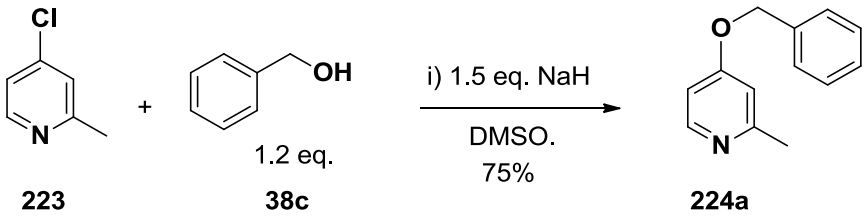
Synthesis of 1-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)-6-methylpyridin-2(1H)-one (243).



An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1,6-dimethylpyridin-2(1H)-one **228b** (0.31 g, 2.5 mmol) which was then dissolved in dry THF (15 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. LDA (3.1 ml, 2.5 mmol, 0.8 M) was added to the solution dropwise. After 10 min, the resulting solution was warmed up and stirred at 0 °C over 2 min and then was then cooled to -78 °C. A solution of 1,2-di-p-tolylethane-1,2-dione **232a** (0.60 g, 2.50 mmol) in THF (5 mL) was added to a stirred solution. The resulting solution was stirred at -78°C, for 30 min under N_2. A solution of LDA (3.1 mL, 2.50 mmol, 0.8 M) was added to reaction mixture. The resulting solution was stirred at -78 °C for 1 h. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL), extracted with EtOAc (3 x 15 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 1-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)-6-methylpyridin-2(1H)-one **243** (0.27 g, 30%) as a colourless crystalline solid. **m.p.** 148 °C **IR (KBr)** 3137 (OH), 3032($CHsp^2$), 2950, 2920, 2855 ($CHsp^3$), 1664 (C=O), 1650 (C=O), 1606 (C=C), 1560 (C=C), 1509 (C=C), 1403(C-OH), 1109(C-OH), 800 (CH_{Arom}) cm^{-1}. m.p. 148 °C. **^{1}H NMR (DMSO-d_6, 700MHz): δ (ppm)** 8.23 (s, 1H), 7.71 (d, *J*=8.4 Hz, 2H), 7.36 (dd, *J*=9.1, 8.4 Hz, 1H), 7.18 (d, *J*=8.4 Hz, 2H), 7.09 - 7.14 (m, 4H), 6.40 (d, *J*=9.1 Hz, 1H), 6.11 (d, *J*=6.3 Hz, 1H), 4.80 (d, *J*=14.7 Hz, 1H), 4.62 (d, *J*=14.7 Hz, 1H), 2.26 (s, 3H), 2.23 (s, 3H), 1.87 (s, 3H). **^{13}C NMR (DMSO-d_6, 176MHz): δ (ppm)** 198.3 (C=O, C-11), 166.0 (C=O, C-2), 148.5 (C, C-6), 143.0 (C, C-15), 140.7 (CH, C-4), 137.5 (C, C-17), 137.2 (C, C-20), 131.4 (C, C-12), 130.5 (CHx2, C-13), 129.1 (CHx2, C-19), 128.4 (CHx2, C-14), 124.8 (CHx2, C-18), 116.1 (CH, C-3), 108.4 (CH, C-5), 82.8 (C, C-9), 54.4 (CH_2, C-8), 21.0 (CH_3, C-16), 20.5 (CH_3, C-21), 20.1 (CH_3, C-7). **LCMS *r.t.*** *1.15 min.* ***m/z*:** ES+ [M+H]+ 362.

Synthesis of 4-pyridone derivatives.

4-(benzyloxy)-2-methylpyridine (224a).[92]

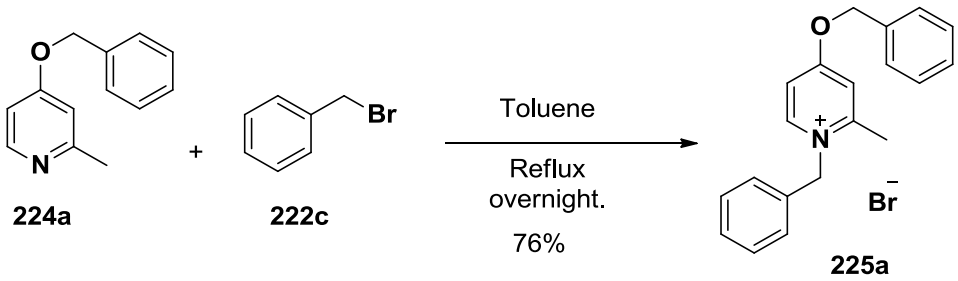


223 **38c** **224a**

Sodium hydride (60% dispersion in mineral oil) (0.24 g, 6.0 mmol) was added to dry DMSO (6.9 mL) under N_2 atmosphere and benzyl alcohol **38c** (0.50 mL, 4.8 mmol) was added dropwise to the reaction mixture. The reaction mixture stirred at room temperature over 10 min. 4-Chloro-2-methylpyridine **223** (0.44 mL, 4.0 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at r.t for 3 h and saturated $NH_4Cl_{(aq)}$ was added slowly. CH_2Cl_2 (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow solid. The crude product was purified by flash silica chromatography, with elution gradient 0 to 100 % EtOAc in petroleum ether 40-60°, to give 4-(benzyloxy)-2-methylpyridine **224a** as a white solid (0.60 g, 75%). **m.p.** 99 °C. **IR (KBr)** 3034 ($CHsp^2$), 3027 ($CHsp^2$), 2945 ($CHsp^3$), 1599 (C=C), 1566 (C=C), 743-700 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm)** 8.25 (d, *J*=5.8 Hz, 1H), 7.32 - 7.49 (m, 5H), 6.92 (d, *J*=2.4 Hz, 1H), 6.85 (dd, *J*=5.8, 2.4 Hz, 1H), 5.17 (s, 2H), 2.41 (s, 3H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 165.0 (C), 160.0 (C), 150.6 (CH), 136.7 (C), 129.0 (CHx2), 128.6 (CH), 128.3 (CHx2), 110.0 (CH), 108.5 (CH), 69.5 (CH_2), 24.6 (CH_3). **HRMS (ESI):** calcd. for $C_{13}H_{13}NO$ **$(M+H)^+$**: 200.1070 found 200.1065. **HRMS (ESI):** calcd. for $C_{13}H_{13}NONa$ **$(M+Na)^+$**: 222.0889 found 222.0885.

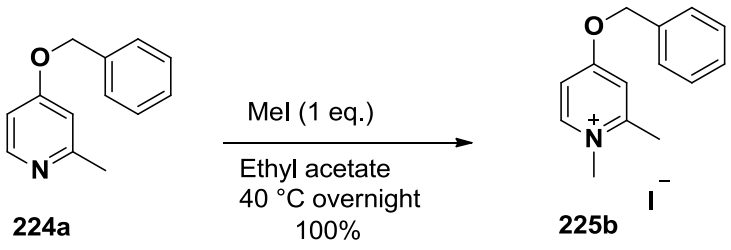
Literature reference: **^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm)** 8.31 (d, *J*= 5.7 Hz, 1H) 7.40-7.32 (m, 5H) 6.75-6.74 (m, 1H) 6.71-6.69 (m, 1H) 5.08 (s, 2H) 2.50 (s, 3H).[92]

Synthesis of 1-benzyl-4-(benzyloxy)-2-methylpyridin-1-ium bromide (225a).



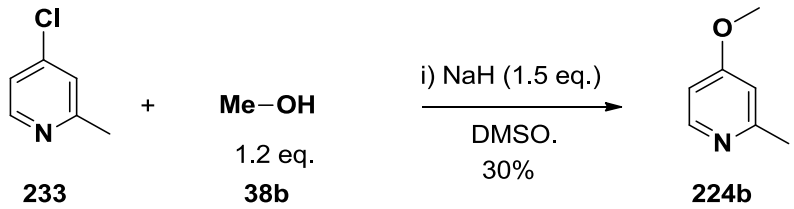
4-(Benzyloxy)-2-methylpyridine **224a** (0.42 mg, 2.0 mmol) was suspended in toluene (2.0 mL). Benzyl bromide **222c** (0.25 mL, 2.0 mmol) was added, the reaction was stirred under reflux overnight. The white precipitate formed was filtered off, and was washed with cold diethyl ether to afford 1-benzyl-4-(benzyloxy)-2-methylpyridin-1-ium bromide **225a** as a white solid (0.56 mg, 76%). **m.p.** 168°C. **IR (KBr)** 3267 (OH), 3057 ($CHsp^2_{Ar}$), 3027 ($CHsp^2$), 2963 ($CHsp^3$), 1667 (C=O), 1646 (C=O), 1562 (C=C), 1545 (C=C), 1142 (CO), 812-720 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 8.97 (d, *J*=7.2 Hz, 1H), 7.77 (d, *J*=3.0 Hz, 1H), 7.68 (dd, *J*=7.2, 3.0 Hz, 1H), 7.51 - 7.56 (m, 2H), 7.37 - 7.50 (m, 6H), 7.21 - 7.26 (m, 2H), 5.76 (s, 2H), 5.47 (s, 2H), 2.65 (s, 3H). **^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm)** 169.6 (C), 156.4 (C), 147.5 (CH), 134.4 (C), 133.9 (C), 129.2 (CHx2), 128.9 (CH), 128.7 (CHx2), 128.6 (CH), 128.5 (CHx2), 127.1 (CHx2), 115.2 (CH), 112.5 (CH), 72.0 (CH_2), 58.4 (CH_2), 19.8 (CH_3). **HRMS (ESI):** calcd. for $C_{20}H_{20}NO^+$ **(M-Br)$^+$**: 290.1539 found 290.1536. **HRMS (ESI):** calcd. for $C_{40}H_{40}{}^{79}BrN_2O_2$ **(2M+Br)$^+$**: 659.2268 found 659.2253.

Synthesis of 4-(benzyloxy)-1,2-dimethylpyridin-1-ium iodide (225b).



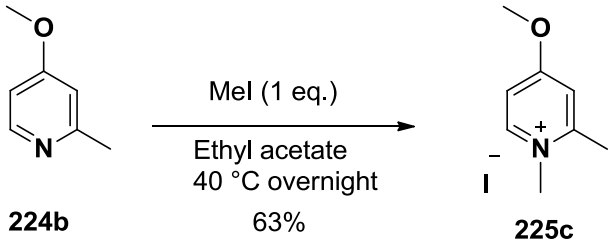
4-(Benzyloxy)-2-methylpyridine **224a** (0.44 g, 2.2 mmol) was dissolved in EtOAc (6.0 mL). Iodomethane (0.14 mL, 2.2 mmol) was added to the reaction mixture which was then stirred at 40 °C overnight. The white precipitate product was filtered off and was washed with cold EtOAc to afford 4-(benzyloxy)-1,2-dimethylpyridin-1-ium iodide **225b** as a white solid (0.75 g, 100%). **m.p.** 160 °C. **IR (KBr)** 3031 ($CHsp^2$), 2946 ($CHsp^3$), 1643 (C=C), 1572 (C=C), 1516 (C=C), 1145 (CO), 773-706 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 8.72 (d, *J*=7.2 Hz, 1H), 7.65 (br. s., 1H), 7.44 - 7.53 (m, 3H), 7.32 - 7.44 (m, 3H), 5.40 (s, 2H), 4.01 (s, 3H), 2.64 (s, 3H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 169.6 (C), 157.4 (C), 147.9 (CH), 135.0 (C), 129.3 (CH), 129.2 (CHx2), 128.9 (CHx2), 114.6 (CH), 112.3 (CH), 72.2 (CH_2), 44.2 (CH_3), 20.5 (CH_3). **HRMS (ESI):** calcd. for $C_{14}H_{16}NO$ **(M-I)$^+$**: 214.1226 found 214.1221. **HRMS (ESI):** calcd. for $C_{28}H_{32}IN_2O_2$ **(2M+I)$^+$**: 555.1503 found 555.1484.

Synthesis of 4-methoxy-2-methylpyridine (224b).



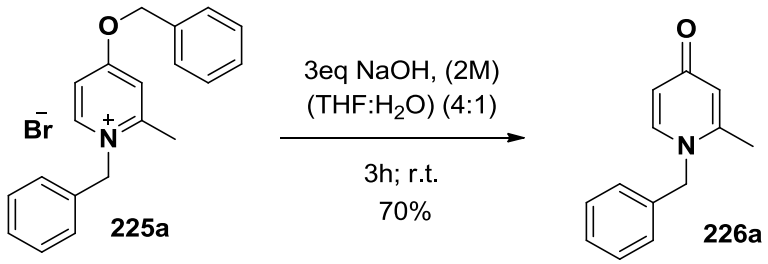
Sodium hydride 60% dispersion (0.48 g, 12 mmol) was added to dry DMSO (12 mL) under N_2 atmosphere; dry methanol **38b** (0.38 mL, 9.6 mmol) was added dropwise to the reaction mixture. The reaction mixture stirred at r.t. for 10 min, and 4-chloro-2-methylpyridine **233** (0.89 mL, 8.0 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at r.t. for 3 h and saturated $NH_4Cl_{(aq)}$ was added slowly. CH_2Cl_2 (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography, with elution gradient 0 to 100% EtOAc in petroleum ether 40-60°, to give 4-methoxy-2-methylpyridine **224b** as colourless oil (0.32 g, 30%). **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 8.23 (d, *J*=5.6 Hz, 1H), 6.61 (d, *J*=1.6 Hz, 1H), 6.58 (d, *J*=5.6 Hz, 1H), 3.77 (s, 3H), 2.44 (s, 3H). **^{13}C ($CDCl_3$):** 166.0 (C), 159.9 (C), 150.2 (CH), 109.0 (CH), 107.3 (CH), 55.0 (CH_3), 24.5 (CH_3).

Synthesis of 4-methoxy-1,2-dimethylpyridin-1-ium iodide (225c).



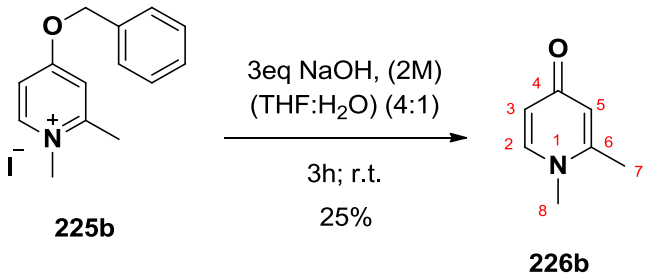
4-methoxy-2-methylpyridine **224b** (0.32 g, 2.6 mmol) was dissolved in EtOAc (6.0 mL). Iodomethane (0.16 mL, 2.6 mmol) was added to the reaction mixture which was then stirred at r.t. for 48 h. The white precipitate product was filtered off and was washed with cold EtOAc to afford 4-methoxy-1,2-dimethylpyridin-1-ium iodide **225c** as a white solid (0.44 g, 63%). **m.p.** 165 °C. **IR (KBr)** 3013 ($CHsp^2$), 2990 ($CHsp^3$), 1637 (C=C), 1434 ($CHsp^3$), 1197 (C-O-C), cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 8.75 (d, *J*=7.2 Hz, 1H), 7.60 (d, *J*=3.0 Hz, 1H), 7.47 (dd, *J*=7.2, 3.0 Hz, 1H), 4.05 (s, 6H), 2.68 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 170.5 (C), 157.4 (C), 147.8 (CH), 114.0 (CH), 111.9 (CH), 58.3 (CH_3), 44.1 (CH_3), 20.4 (CH_3). **HRMS (ESI):** calcd. for $C_8H_{12}NO$ **(M-I)$^+$**: 138.0913 found 138.0908. **HRMS (ESI):** calcd. for $C_{16}H_{24}IN_2O_2$ **(2M+I)$^+$**: 403.0877 found 403.0864.

Synthesis of 1-benzyl-2-methylpyridin-4(1H)-one (226a).



1-Benzyl-4-(benzyloxy)-2-methylpyridin-1-ium bromide **225a** (0.72 g, 2.0 mmol) was dissolved in THF:H_2O (23 mL : 5.7 mL) and 2M aqueous NaOH (2.9 mL, 5.8 mmol) was added. The mixture was stirred at r.t. and monitored by TLC, (CH_2Cl_2 : MeOH 9:1), the reaction was complete in 3 h. The mixture was diluted with CH_2Cl_2 (20 mL), and the phases were separated, and then the aqueous layer was re-extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with aqueous NaOH 2M. The organic phase was dried over $MgSO_4$ to afford crude product as orange oil. The crude product was purified by flash silica chromatography (CH_2Cl_2 : MeOH 9:1) to give 1-benzyl-2-methylpyridin-4(1H)-one **226a** as a colourless crystals (0.28 g, 70%). **m.p.** 99 °C. **IR** (KBr) 3063 ($CHsp^2$), 2927 ($CHsp^3$), 1637 (C=O), 1543(C=C), 1496 (C=C), 736 (C_{Ar}) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz):** δ (ppm) 7.27 - 7.40 (m, 4H), 7.03 (d, *J*=6.8 Hz, 2H), 6.34 (dd, *J*=7.4, 2.2 Hz, 1H), 6.28 (d, *J*=2.2 Hz, 1H), 5.03 (s, 2H), 2.19 (s, 3H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 178.5 (CO), 147.4 (C), 140.8 (CH), 134.3 (C), 128.3 (2 x CH_{Ar}), 127.4 (CH_{Ar}), 124.9 (2 x CH_{Ar}), 118.5 (CH, C3), 116.7 (CH, C5), 55.3 (CH_2), 18.7 (CH_3). **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.79 (d, *J*=7.6 Hz, 1H), 7.40 (dd, J= 7.2, 7.6 Hz, 2H), 7.324 (t, *J*=7.2 Hz, 1H), 7.11 (d, *J*=7.2 Hz, 2H), 6.06 - 6.12 (m, 2H), 5.19 (s, 2H), 2.15 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 177.8 (C=O), 148.8 (C), 142.9 (CH), 137.0 (C), 129.0 (CHx2), 127.8 (CH), 126.2 (CHx2), 118.4 (CH), 116.4 (CH), 55.0 (CH_2), 18.9 (CH_3). **HRMS (ESI):** calcd. for $C_{13}H_{14}NO$ **$(M+H)^+$**: 200.1070 found 200.1065.

Synthesis of 1,2-dimethylpyridin-4(1H)-one (226b).

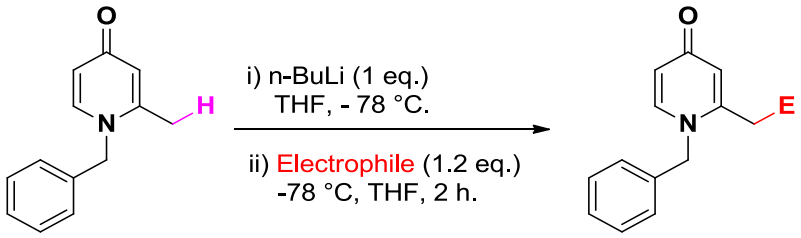


225b **226b**

4-(Benzyloxy)-1,2-dimethylpyridin-1-ium iodide **225b** (1.2 g, 3.6 mmol) was dissolved in THF : H_2O (5.3 mL : 2.6 mL) and 2M aqueous NaOH (5.3 mL, 11 mmol) was added. The mixture was stirred at r.t. and monitored by TLC, (CH_2Cl_2 : MeOH 9 : 1), the reaction was complete in 4 h. The mixture was diluted with CH_2Cl_2 (20 mL), and the phases were separated, and then the aqueous layer was re-extracted with CH_2Cl_2 (4 x 20 mL). The organic phase was dried over Na_2SO_4 to afford crude product as an orange oil. The crude product was purified by flash silica chromatography (CH_2Cl_2 : MeOH 9 : 1) which gave 1,2-dimethylpyridin-4(1H)-one **226b** as a colourless crystals (0.44 g, 25%). **m.p.** 46 °C. **IR(Neat)** 3072 ($CHsp^2$), 2959 ($CHsp^3$), 1639 (C=O), 1543(C=C) cm^{-1}. **^{1}H NMR (DMSO-d6, 400 MHz): δ (ppm)** 7.56 (d, J=7.2 Hz, 1H), 5.99 (d, J=2.6 Hz, 1H), 5.93 (dd, J=7.2, 2.6 Hz, 1H), 3.50 (s, 3H), 2.19 (s, 3H). **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.27 - 7.29 (m, 1H), 6.29 - 6.30 (m, 2H), 3.59 (s, 3H), 2.30 (s, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm)** 178.4 (C=O, C-4), 149.5 (C, C-6), 142.8 (CH, C-2), 118.4 (CH, C-5), 116.9 (CH, C-3), 41.3 (CH_3, C-8), 20.1 (CH_3, C-7).

Methyl alkylation of N-benzyl-4-pyridones.

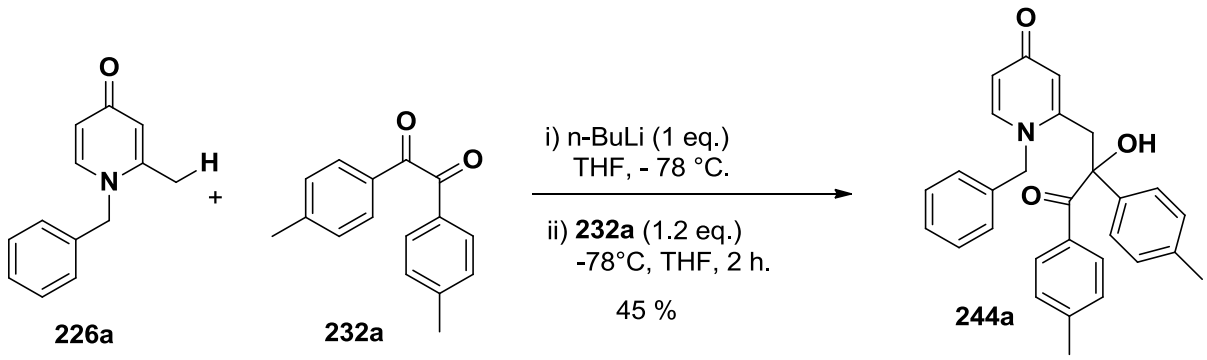
General procedure III:



226a **244a-d**

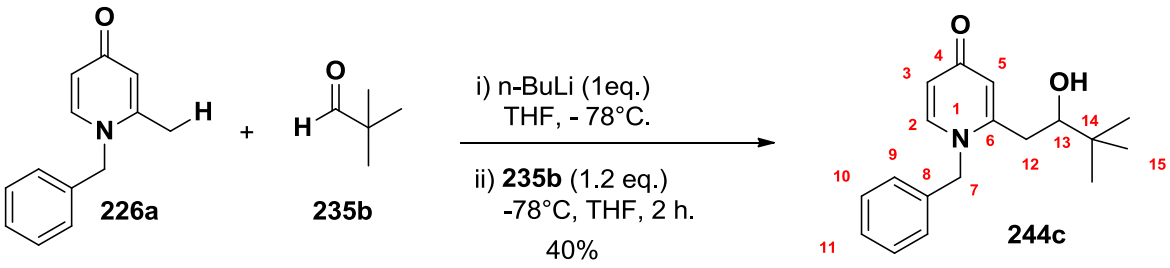
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1-benzyl-2-methylpyridin-4(1H)-one **226a** (1eq.) and dissolved in dry THF. The flask was cooled to -78 °C by submerging in a bath of dry ice/acetone. n-Butyllithium (1eq.) was added to the pale transparent yellow solution dropwise over 5 min and the reaction became an intense purple colour. The reaction mixture was warmed up to 0°C and showed a red colour, and then the reaction was cooled to -78 °C. Concurrently, an additional oven-dried flask was purged with N_2 and then was charged with the electrophile (1.2 eq.) dissolved/ diluted in dry THF. The electrophile solution was added dropwise to the pyridone solution at -78 °C via syringe over 5 min. The reaction was allowed to proceed for 2 h at -78 °C, before quenching with saturated $NH_4Cl_{(aq)}$ EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, filtered and concentrated under reduced pressure and the crude product was purified by flash silica chromatography (95 : 5 CH_2Cl_2 : MeOH).

1-benzyl-2-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)pyridin-4(1H)-one (244a).



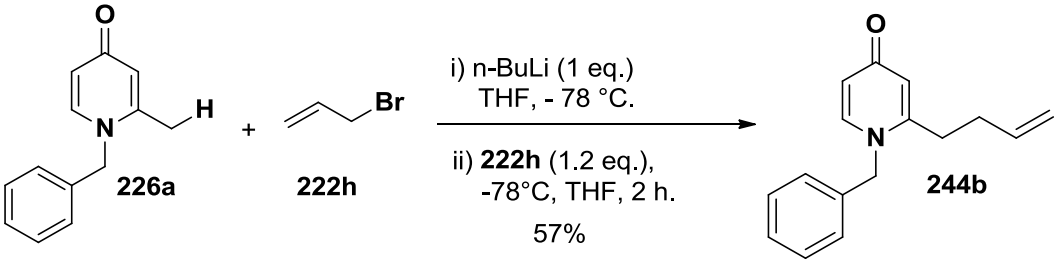
Following general procedure **III**, the reaction between 1-benzyl-2-methylpyridin-4(1H)-one **226a** (80 mg, 0.40 mmol) in THF (8.0 mL), n-butyllithium (0.40 ml, 0.40 mmol) and 1,2-di-p-tolylethane-1,2-dione **232a** (0.11 g, 0.48 mmol) in THF (3.0 mL) was carried out. The crude product was purified by silica chromatography (95 : 5 CH_2Cl_2 : MeOH) to afford compound **244a** as a yellow solid (81 mg, 45 %). **m.p.** 188 °C. **IR** (KBr) 3428 (C-OH), 3063 ($CHsp^2$), 2923 ($CHsp^3$), 1673 (C=O), 1631 (C=O), 1539 (C=C), 732 (C_{Ar}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.77 (d, *J*=7.9 Hz, 2H), 7.58 (d, *J*=7.5 Hz, 1H), 7.32 - 7.37 (m, 2H), 7.27 (d, *J*=7.5 Hz, 1H), 7.08 - 7.16 (m, 6H), 6.93 (d, *J*=7.5 Hz, 2H), 6.91 (s, 1H), 5.94 (dd, *J*=7.5, 2.8 Hz, 1H), 5.74 (d, *J*=2.4 Hz, 1H), 5.08 (d, *J*=16.7 Hz, 1H), 4.75 (d, *J*=16.7 Hz, 1H), 3.04 - 3.17 (m, 2H), 2.22 (d, *J*=5.6 Hz, 6H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 199.0 (C=O), 177.5 (C=O), 147.8 (C), 143.7 (CH), 143.6 (C), 138.4 (C), 137.7 (C), 137.3 (C), 132.1 (C), 131.1 (CHx2), 129.7 (CHx2), 129.5 (CHx2), 129.1 (CHx2), 128.2 (CH), 126.4 (CHx2), 125.3 (CHx2), 122.0 (CH), 116.9 (CH), 82.5 (C), 55.6 (CH_2), 41.7 (CH_2), 21.6 (CH_3), 21.2 (CH_3). **HRMS (ESI):** calcd. for $C_{29}H_{28}NO_3$ **$(M+H)^+$**: 438.2064 found 438.2054. **HRMS (ESI):** calcd. for $C_{29}H_{27}NO_3Na$ **$(M+Na)^+$**: 460.1883 found 460.1871.

Synthesis of 1-benzyl-2-(2-hydroxy-3,3-dimethylbutyl)pyridin-4(1H)-one (244c).



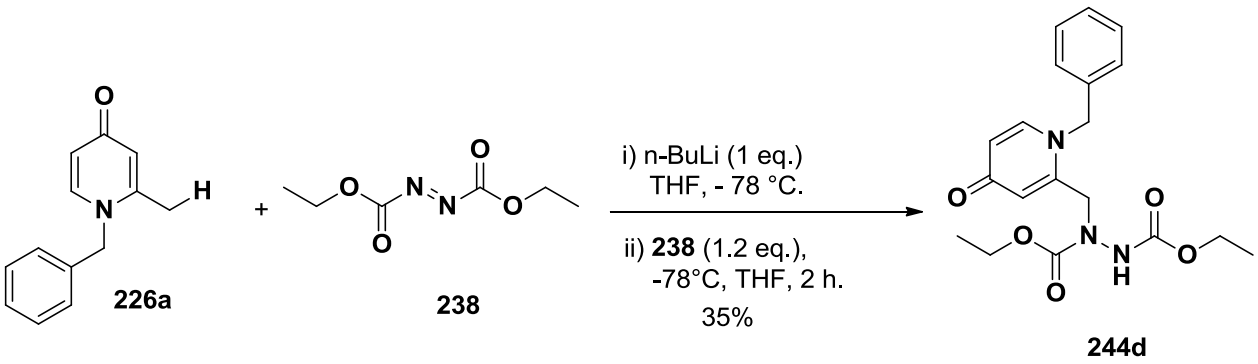
Following general procedure **III**, the reaction between 1-benzyl-2-methylpyridin-4(1H)-one **226a** (83 mg, 0.42 mmol) in THF (6.0 mL), n-butyllithium (0.40 ml, 0.42 mmol) and trimethylacetaldehyde (52 µL, 0.50 mmol) in THF (2.0 mL) was carried out. The crude product was purified by silica chromatography (95 : 5 CH_2Cl_2 : MeOH) to afford compound **244c** as a pale orange solid (46 mg, 40%). **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 7.78 (d, *J*=7.6 Hz, 1H), 7.36 - 7.42 (m, 2H), 7.29 - 7.35 (m, 1H), 7.07 (d, *J*=7.2 Hz, 2H), 6.16 (d, *J*=2.8 Hz, 1H), 6.10 (dd, *J*=7.6, 2.8 Hz, 1H), 5.44 (d, *J*=16.8 Hz, 1H), 5.13 (d, *J*=16.8 Hz, 1H), 4.99 (d, *J*=6.4 Hz, 1H), 3.26 - 3.34 (m, 1H), 2.45 - 2.49 (m, 1H), 2.28 (dd, *J*=14.6, 10.6 Hz, 1H), 0.81 (s, 9H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 177.8 (C=O), 151.7 (C, C-6), 143.3 (CH, C-2), 137.3 (C, C-8), 129.1 (CH_{Ar}x2), 127.7 (CH_{Ar}x2), 125.9 (CH, C-11), 119.2 (CH, C-5), 116.3 (CH, C-3), 77.6 (CH, C-13), 55.4 (CH_2, C-7), 35.3 (C, C-14), 33.8 (CH_2, C-12), 25.6 (CH_3x3, C-15). **HRMS (ESI):** calcd. for $C_{18}H_{24}NO_2$ **(M+H)$^+$**: 286.1802 found 286.1800. **HRMS (ESI):** calcd. for $C_{18}H_{23}NO_2Na$ **(M+Na)$^+$**: 308.1621 found 308.1620.

1-Benzyl-2-(but-3-en-1-yl)pyridin-4(1H)-one (244b).



Following general procedure **III**, the reaction between 1-benzyl-2-methylpyridin-4(1H)-one **226a** (74 mg, 0.37 mmol) in THF (6.0 mL), n-butyllithium (0.37 ml, 0.37 mmol) and allylbromide **222h** (38 µL, 0.44 mmol) in THF (2.0 mL) was carried out. The crude product was purified by silica chromatography (95 : 5 CH_2Cl_2 : MeOH) to afford compound **244b** as pale brown oil (50 mg, 57%). **IR** (KBr) 3079 ($CHsp^2$), 2920 ($CHsp^3$), 2850 ($CHsp^3$), 1634 (C=O), 1543 (C=C), 1496 ($C=C_{Arm}$), 733-696 (C_{Ar}) cm^{-1}. **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 7.79 (d, *J*=7.2 Hz, 1H), 7.40 (dd, *J*=7.2, 7.6 Hz, 2H), 7.32 (dd, *J*=7.2, 7.6 Hz, 1H), 7.10 (d, *J*=7.2 Hz, 2H), 6.07 - 6.12 (m, 2H), 5.75 (ddt, *J*=16.8, 10.4, 6.4 Hz, 1H), 5.23 (s, 2H), 4.91 - 5.04 (m, 2H), 2.55 (m, , 2H), 2.15 - 2.24 (m, 2H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 177.8 (C=O), 151.5 (C, C-6), 143.4 (CH, C-3), 137.2 (C, C-12), 136.8 (CH), 129.0 (CHx2, C-14), 127.8 (CH, C-15), 126.1 (CHx2, C-13), 117.6 (CH, C-5), 116.3 (CH, C-4), 116.0 (CH_2), 54.9 (CH_2, C-11), 31.4 (CH_2), 30.1 (CH_2). **HRMS (ESI):** calcd. for $C_{16}H_{18}NO$ **$(M+H)^+$**: 240.1383 found 240.1381. **HRMS (ESI):** calcd. for $C_{16}H_{17}NONa$ **$(M+Na)^+$**: 262.1202 found 262.1200.

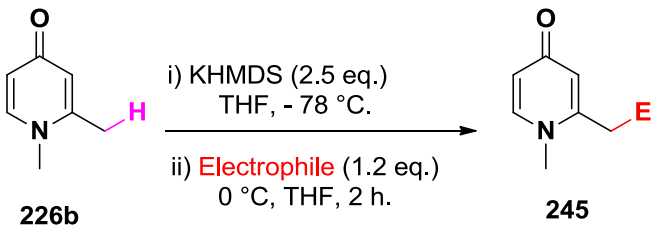
Synthesis of diethyl 1-((1-benzyl-4-oxo-1,4-dihydropyridin-2-yl)methyl)hydrazine-1,2-dicarboxylate (244d).



Following general procedure **III**, the reaction between 1-benzyl-2-methylpyridin-4(1H)-one **226a** (85 mg, 0.43 mmol) in THF (8.0 mL), n-butyllithium (0.41 ml, 0.43 mmol) and diethyl azodicarboxylate **238** (80 µL, 0.51 mmol) in THF (2.0 mL) was carried out. The crude product was purified by silica chromatography (95 : 5 CH_2Cl_2 : MeOH) to afford compound **244d** as white solid (56 mg, 35%). **IR** (Neat) 3284 (NH), 2982 ($CHsp^3$), 2937 ($CHsp^3$), 1714 (C=O), 1637 (C=O), 1556 (C=C), 1217 (RCO-O-C), 734 (C_{Ar}) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.34 - 7.38 (m, 4H), 7.07 - 7.11 (m, 2H), 6.43 (m, 1H), 6.33 (br. s., 1H), 5.18 (s, 2H), 4.54 (br. s., 2H), 4.12 - 4. 91 (m, 4H), 1.98 (br. s., 1H), 1.20 - 1.25 (m, 6H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 179.4 (C), 156.3 (C), 155.9 (C), 146.1 (C), 142.9 (CHx2), 135.5 (C), 129.4 (CHx2), 128.5 (CHx2), 126.3 (CH), 118.1 (CH), 63.3 (CH_2), 62.1 (CH_2), 56.2 (CH_2x2), 14.6 (CH_3), 14.5 (CH_3). **HRMS (ESI):** calcd. for $C_{19}H_{24}O_5N_3$ **$(M+H)^+$**: 374.1710 found 374.1705. **HRMS (ESI):** calcd. for $C_{19}H_{23}O_5N_3Na$ **$(M+Na)^+$**: 396.1530 found 396.1522.

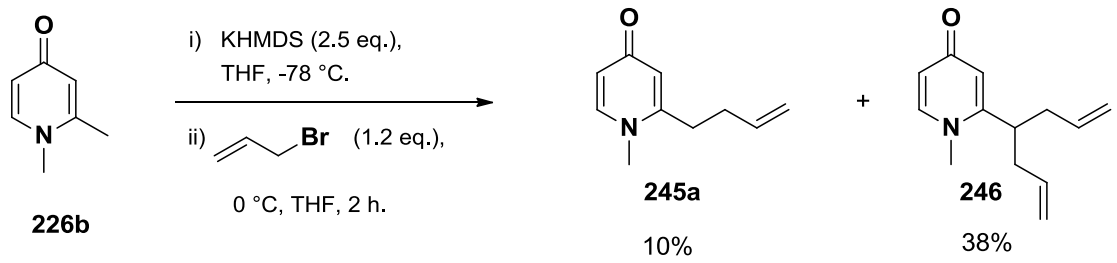
Methyl alkylation of 1,6-dimethyl-4-pyridone

General procedure IV: General experimental procedure for the deprotonation of 1,2-dimethylpyridin-4(1H)-one and nucleophilic addition to several electrophiles.



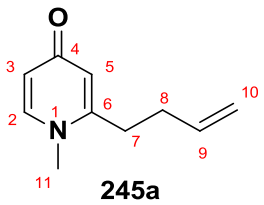
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1,2-dimethylpyridin-4(1H)-one **226b** (1eq.) and was dissolved in dry THF. The flask was cooled to -78 °C by submerging in a bath of dry ice/acetone. KHMDS (2.5 eq.) was added to the transparent pale yellow solution dropwise over 5 min. The reaction mixture was warmed up at 0 °C and the reaction changed colour from yellow to bright pink. Concurrently, an additional oven-dried flask was purged with N_2 and then was charged with the electrophile (1.2 eq.) which was then dissolved/ diluted in dry THF. The electrophile solution was added to the pyridone solution at 0 °C by dropwise addition via syringe over 5 min. The reaction was allowed to proceed for 2 h at 0 °C by submerging in an ice bath, before quenching with saturated $NH_4Cl_{(aq)}$. EtOAc (3 mL) was added and the phases were separated. The aqueous layer was re-extracted with dichloromethane (5 x 10 mL). The combined organic layers were washed with brine. The combined organic phases were dried Na_2SO_4, filtered and concentrated under reduced pressure and the crude product was purified by flash silica chromatography. The crude product was purified by flash column chromatography (95 : 5 CH_2Cl_2 : MeOH).

Synthesis of 2-(but-3-en-1-yl)-1-methylpyridin-4(1H)-one (245a) and 2-(hepta-1,6-dien-4-yl)-1-methylpyridin-4(1H)-one (246).



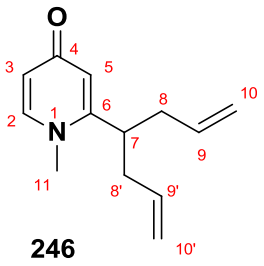
Following general procedure **IV**, the reaction of 1,2-dimethylpyridin-4(1H)-one **226b** (76 mg, 0.62 mmol) in THF (5.0 mL), KHMDS (3.1 mL, 1.5 mmol) and allylbromide (60 µL, 0.74 mmol) in THF (1.0 mL) was carried out. The crude product was purified by silica chromatography (95 : 0.5 CH_2Cl_2 : MeOH) to afford compound **245a** as a white oil (10 mg, 10%) and compound **246** as a yellow oil (49 mg, 38%).

2-(but-3-en-1-yl)-1-methylpyridin-4(1H)-one (245a).



IR (Neat) 2923 ($CHsp^3$), 1636 (C=O), 1541 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.29 (s, 1H, H-2), 6.30 - 6.36 (m, 2H, H-3, H-5), 5.80 - 5.91 (m, 1H, H-9), 5.07 - 5.17 (m, 2H, H-10), 3.62 (s, 3H, CH_3), 2.62 - 2.68 (m, 2H, H8), 2.37 - 2.45 (m, 2H, H-7). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 179.6 (C=O), 151.3 (C), 142.2 (CH), 135.7 (CH), 118.2 (CH), 117.5 (CH), 116.8 (CH_2), 40.5 (CH_3), 31.8 (CH_2), 31.7 (CH_2). **HRMS (ESI):** calcd. for $C_{10}H_{14}NO$ **$(M+H)^+$**: 164.1070 found 164.1064. **HRMS (ESI):** calcd. for $C_{10}H_{13}NONa$ **$(M+Na)^+$**: 186.0889 found 186.0884.

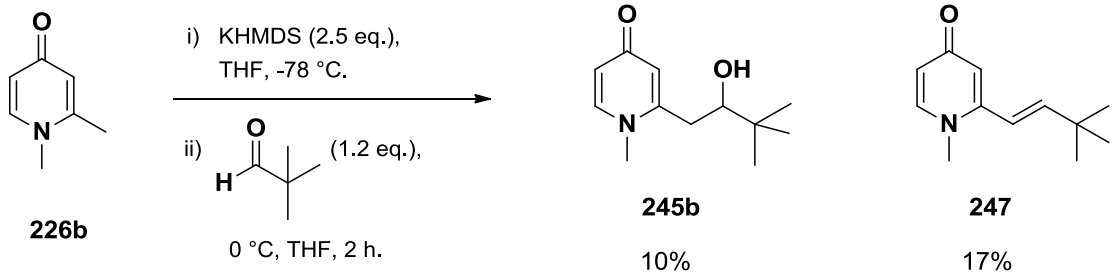
2-(hepta-1,6-dien-4-yl)-1-methylpyridin-4(1H)-one (246).



246

IR (Neat) 3077 ($CHsp^2$), 2927 ($CHsp^3$), 1634 (C=O), 1542 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.22 (d, *J*=7.2 Hz, 1H, H-2), 6.29 (d, *J*=2.8 Hz, 1H, H-5), 6.22 (dd, *J*=7.8, 2.8 Hz, 1H, H-3), 5.50 - 5.66 (m, 2H, H-9, H-9'), 4.97 (m, 4H, H-10, H-10'), 3.54 (s, 3H, H-11), 2.67 - 2.81 (m, 1H, H-7), 2.21 - 2.40 (m, 4H, H-8, H-8'). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 179.3 (C, C-4), 154.9 (C, C-6), 142.5 (CH, C-2), 134.4 (CHx2, C-9, C-9'), 118.3 (CH_2x2, C-10, C-10'), 117.3 (CH, C-3), 116.9 (CH, C-5), 41.4 (CH_3, C-11), 40.3 (CH, C-7), 39.1 (CH_2x2, C-8, C-8'). **HRMS (ESI):** calcd. for $C_{13}H_{18}NO$ **$(M+H)^+$**: 204.1383 found 204.1378. **HRMS (ESI):** calcd. for $C_{13}H_{17}NONa$ **$(M+Na)^+$**: 226.1202 found 226.1199.

Synthesis of 2-(2-hydroxy-3,3-dimethylbutyl)-1-methylpyridin-4(1H)-one (245b) and (E)-2-(3,3-dimethylbut-1-en-1-yl)-1-methylpyridin-4(1H)-one (247).

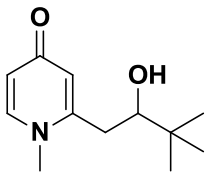


226b **245b** **247**

10% 17%

Following general procedure **IV**, the reaction of 1,2-dimethylpyridin-4(1H)-one **226b** (62 mg, 0.50 mmol) in THF (5.0 mL), KHMDS (2.5 ml, 1.3 mmol) and trimethylacetaldehyde (60 µL, 0.60 mmol) in THF (1.0 mL) was carried out. The crude product was purified by silica chromatography (95 : 5 CH_2Cl_2 : MeOH) to afford compound **245b** as a white oil (10 mg, 10%) and compound **247b** as a yellow oil (16 mg, 17%).

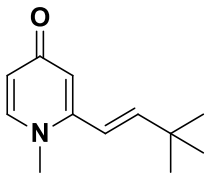
2-(2-hydroxy-3,3-dimethylbutyl)-1-methylpyridin-4(1H)-one (245b)



245b

IR (Neat) 3412 (OH), 2959 (CHsp^3), 2921 (CHsp^3), 2872 (CHsp^3), 2850 (CHsp^3), 1636 (C=O), 1528 (C=C), 1201 (C-O) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.21 - 7.26 (m, 2H), 6.29 (d, *J*=3.2 Hz, 1H), 6.19 (d, *J*=7.8 Hz, 1H), 3.67 (d, *J*=2.7 Hz, 3H), 3.48 - 3.58 (m, 1H), 2.64 - 2.72 (m, 1H), 2.51 - 2.61 (m, 1H), 0.99 (d, *J*=2.7 Hz, 9H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 179.1 (C=O), 152.1 (C), 142.5 (CH), 119.4 (CH), 117.2 (CH), 79.1 (CH), 41.6 (CH_3), 35.5 (C), 34.8 (CH_2), 25.8 (CH_3). **HRMS (ESI):** calcd. for $C_{12}H_{20}NO_2$ **(M+H)$^+$**: 210.1489 found 210.1483. **HRMS (ESI):** calcd. for $C_{12}H_{19}NO_2Na$ **(M+Na)$^+$**: 232.1308 found 232.1304.

(E)-2-(3,3-dimethylbut-1-en-1-yl)-1-methylpyridin-4(1H)-one (247).

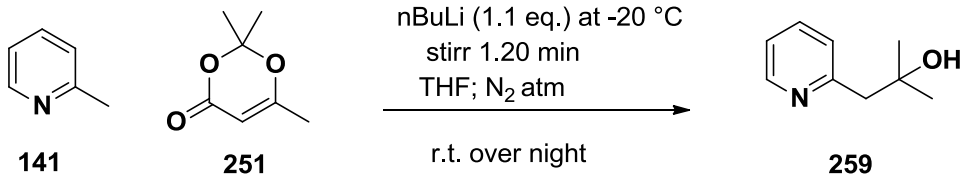


247

IR (Neat) 3000 (CHsp^2), 2958 (CHsp^3), 1632 (C=O), 1539 (C=C) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 7.20 (dd, *J*=7.6, 4.4 Hz, 1H), 6.40 - 6.45 (m, 1H), 6.22 - 6.31 (m, 2H), 6.08 (dd, *J*=15.6, 4.1 Hz, 1H), 3.54 (d, *J*=4.1 Hz, 3H), 1.07 (d, *J*=4.1 Hz, 9H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 179.5 (C=O), 151.9 (CH), 149.9 (C), 141.5 (CH), 117.8 (CH), 117.0 (CH), 116.4 (CH), 41.1 (CH_3), 34.1 (C), 29.0 (CH_3). **HRMS (ESI):** calcd. for $C_{12}H_{18}NO$ **(M+H)$^+$**: 192.1383 found 192.1378.

4-Quinolizinones.

Attempted synthesis of 1-(pyridin-2-yl)pentane-2,4-dione (259).

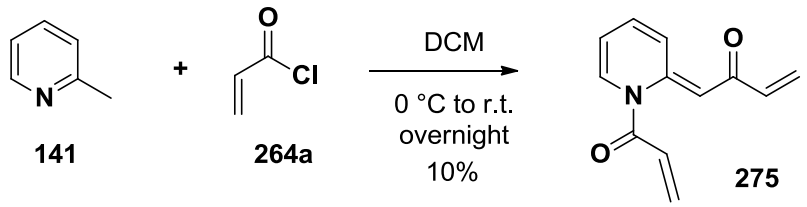


141 **251** **259**

40%

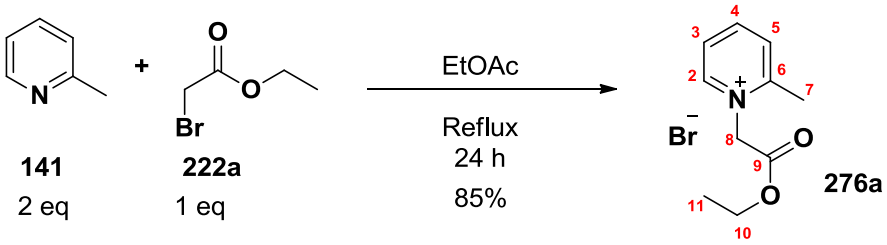
A solution of 2-picoline **141** (0.46 g, 5.0 mmol) in THF (15 mL) at -20°C was stirred for 20 min, *n*-butyllithium (3.8 mL, 5.5 mmol) was added dropwise to the reaction mixture which was then stirred for 1 h. 2,2,6-Trimethyl-4H-1,3-dioxin-4-one **251** was previously dissolved in THF (3 mL) and the solution was added dropwise to mixture and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with few drops of MeOH and 20 mL of H_2O. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the organic layer was washed with brine and dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the product was purified by flash chromatography column to afford a brown solid (0.29 g, 40%). **m.p.** decomposes above 190 °C. **IR** (Neat) 3368, 2970 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 8.51 (d, *J*=4.0 Hz, 1H), 7.636 (dt, *J*= 7.6, 1.6 Hz, 1H), 7.17 (m, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 5.81 (br. s., 1H), 2.92 (s, 2H), 1.22 (s, 6H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 160.0 (C), 148.4 (CH), 136.8 (CH), 124.4 (CH), 121.5 (CH), 70.7 (C), 48.6 (CH_2), 29.5 (CH_3x2). **HRMS [ES]** calcd. for $C_9H_{14}NO$ **$(M+H)^+$**: 152.1025 found 152.1069.

Preparation of 1-(1-acryloylpyridin-2(1H)-ylidene)but-3-en-2-one (275):



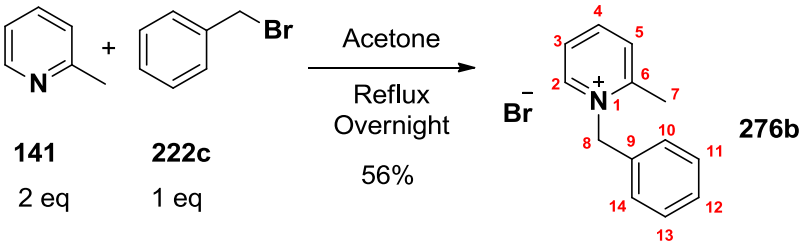
A solution of 2-picoline **141** (0.19 g, 2.0 mmol) in dry DCM (10 mL) under a N_2 atmosphere was stirred for 10 min. The reaction was cooled to 0 °C and acryloyl chloride **264a** (0.18 g, 2.0 mmol) previously dissolved in DCM (5 mL) was added and the reaction mixture stirred overnight while warming to room temperature. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford an orange oil, (9 mg, 10%). **IR (Neat)** 1742 (C=O), 1607, 1146 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm)** 8.54 (d, *J*=8 Hz, 1H), 7.60 (dd, *J*= 8.0, 8.0 Hz, 1H), 7.40 (d, *J*= 8.0 Hz, 1H), 7.10 (dd, *J*= 8.0, 8.0 Hz, 1H), 6.62 (s, 1H), 6.52 – 6.34 (m, 3H), 6.05 (dd, *J*= 10.4, 1.3 Hz, 1H), 5.45 (1 H, d, *J* =17.1 Hz, 1H), 5.31 (d, *J*=10.4 Hz, 1H). **^{13}C NMR ($CDCl_3$, 101MHz): δ (ppm)** 163.3, 153.1, 149.6, 147.7, 136.2, 132.7, 132.2, 127.7, 123.8, 122.0, 120.2, 116.6.

Synthesis of 1-(2-ethoxy-2-oxoethyl)-2-methylpyridin-1-ium (276a)[86].



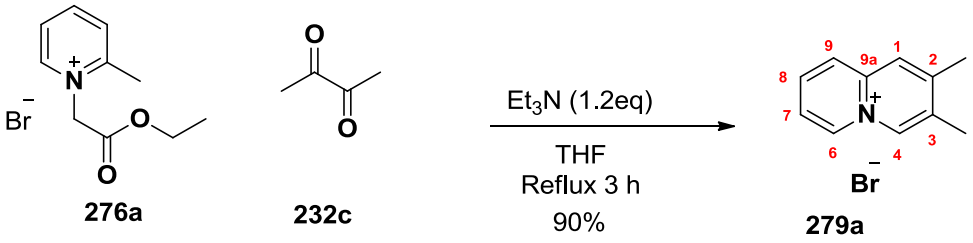
A mixture of 2-picoline **141** (3.9 mL, 40 mmol) and ethyl bromoacetate **222a** (2.2 mL, 20 mmol) in EtOAc (100 mL) was vigorously stirred under reflux for 24 h. The product that precipitated out was filtered and washed with cold EtOAc to afford a pale yellow solid (4.4 g, 85% yield). **m.p.** 115 °C. **IR** (neat) 3077, 2963, 1747 (C=O), 773 cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 9.07 (d, *J*=6.0 Hz, 1H), 8.63 (t, *J*=8.0 Hz, 1H), 8.18 (d, *J*=8.0 Hz, 1H), 8.10 (t, *J*=6.9 Hz, 1H), 5.77 (s, 2H), 4.26 (q, *J*=7.1 Hz, 2H), 2.78 (s, 3H), 1.26 (t, *J*=7.1 Hz, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 165.9 (C=O), 156.3 (C), 146.8(CH), 146.7(CH), 129.7(CH), 125.6(CH), 62.5(CH_2), 57.7 (CH_2), 19.61(CH_3), 13.87(CH_3). **HRMS (ES):** calcd. for $C_{10}H_{14}NO_2^+$ **(M-Br)$^+$**: 180.1025 found 180.1014.

Synthesis of 1-benzyl-2-methylpyridin-1-ium bromide (276b)[89].



To a solution of 2-picoline **141** (2.0 mL, 20 mmol) in acetone (15 mL), was added benzyl bromide **222c** (1.2 mL, 10 mmol) in one portion and the resulting mixture was heated under reflux overnight. The product precipitated out, and was filtered off to afford a white solid (3.0 g, 56%). **m.p.** 62-64 °C. **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 9.22 (d, *J*= 6.4 Hz, 1H), 8.59 (dd, *J*= 8.0, 7.6 Hz, 1H), 8.14 (d, *J*= 8.0 Hz, 1H), 8.09 (dd, *J*= 7.6, 6.4 Hz, 1H), 7.47-7.41 (m, 3H), 7.38-7.28 (m, 2H), 5.97 (s, 2H), 2.77 (s, 3H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 155.5 (C), 146.0 (CH), 145.8 (CH), 133.0 (C), 130.33 (CH), 129.2 (CH), 129.2 (CH), 128.8 (CH), 127.6 (CH), 127.6 (CH), 125.9 (CH), 60.1(CH_2), 19.99 (CH_3). **HRMS (ES):** calcd. for $C_{13}H_{14}N^+$ **(M-Br)$^+$**: 184.1126 found 184.1128.

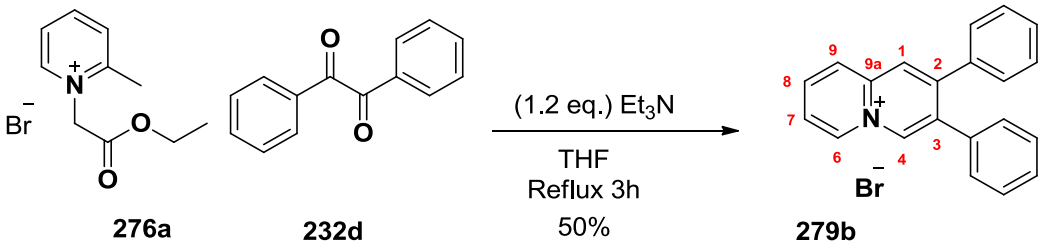
Synthesis of 2,3-dimethylquinolizin-5-ium bromide (279a).[86]



A mixture of 2,3-butanedione **232c** (3.12 mL, 38.3 mmol) and triethylamine (5.38 mL, 38.3 mmol) was added dropwise to a solution of pyridinium salt **276a** (8.3 g, 31.9 mmol) in THF (6.0 mL) under reflux, and then the mixture was heated under reflux for 3 h. When the reaction was complete, the resulting solid was immediately collected by filtration and washed with boiling acetone. The solid was purified by recrystallization from methanol by addition of diethyl ether to afford a white solid (6.6 g, 90%). **m.p.** 115-116 °C. **IR (KBr)** 3062 ($CHsp^2$), 3029 ($CHsp^2$),, 3007 ($CHsp^2$), 2952 ($CHsp^3$), 1646 (C=C), 1635 (C=C), 1495 ($C\text{-}C_{Arom}$), 1405 ($C\text{-}C_{Arom}$), 1158 (C-N) cm^{-1}. **^{1}H NMR ($CDCl_3$, 400MHz):** δ (ppm) 9.15 (s, 1H), 9.06 (d, *J*=6.6 Hz, 1H), 8.24 - 8.32 (m, 2H), 8.16 (t, *J*=7.8 Hz, 1H), 7.89 (t, *J*=6.7 Hz, 1H), 2.41 (br. s., 6H)**. ^{1}H (δ ppm, 400 MHz, DMSO-d_6)** [86] 9.28 (s, 1H), 9.17 (d, J= 6.8 Hz, 1H), 8.39 (s, 2H), 8.26 (t, J= 7.8 Hz, 1H), 7.99 (t, J = 6.8 Hz, 1H), 2.59 (s, 3H), 2.5 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 149.9, 140.8, 135.7, 135.3, 134.7, 134.0, 125.8, 125.1, 122.7, 19.5, 16.5. **HRMS (ES):** calcd. for $C_{11}H_{12}N^+$ **(M-Br)$^+$:** 158.0964 found 158.0960.

Literature reference: **^{1}H (δ ppm, 400 MHz, DMSO-d_6)** 9.350 (s, 1H), 9.232 (d, 1H), 8.411 (d, 2H), 8.269 (t, 1H), 7.999 (t, 1H), 2.597 (s, 3H), 2.480 (s, 3H); **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 149.9, 140.8, 135.7, 135.2, 134.7, 134.0, 125.8, 125.1, 122.7, 19.5, 16.5.

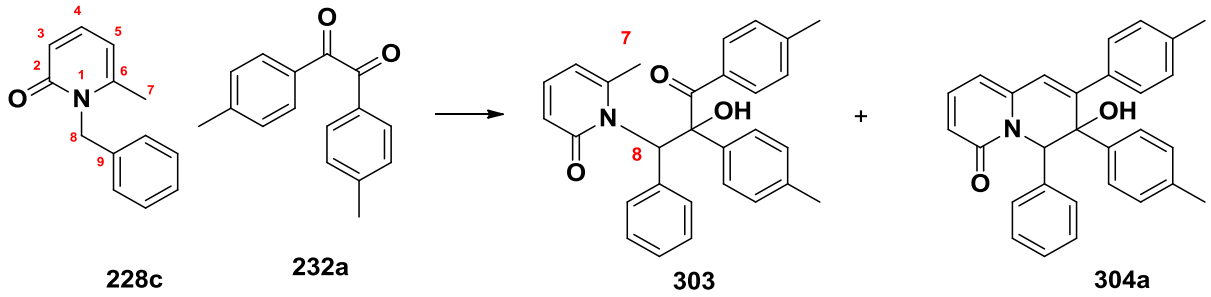
Synthesis of 2,3-diphenylquinolizin-5-ium bromide (279b).



276a 232d 279b

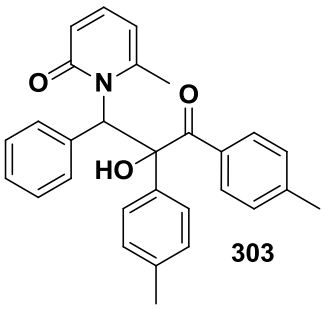
A mixture of benzil (1.1 g, 5.2 mmol) and triethylamine (0.73 mL, 5.2 mmol) was added dropwise to a solution of pyridinium salt **276a** (1.1 g, 4.3 mmol) in THF (20 mL) under reflux, and then the mixture was heated under reflux for 4 h. When the reaction was complete, the resulting solid was immediately collected by filtration and washed with acetone. The solid was purified by recrystallization from methanol by addition of diethyl ether to afford a pale orange solid (0.76 g, 50%). **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 9.58 (s, 1H), 9.38 (d, *J*=6.8 Hz, 1H), 8.75 (s, 1H), 8.62 (d, *J*=8.4 Hz, 1H), 8.42 (t, *J*=7.6 Hz, 1H), 8.11 - 8.20 (m, 1H), 7.38 - 7.50 (m, 6H), 7.29 - 7.38 (m, 4H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 148.2, 141.4, 136.8, 136.6, 136.1, 135.7, 135.6, 134.2, 129.7, 129.7, 129.4, 129.3, 129.3, 128.8, 128.8, 128.7, 126.7, 126.7, 123.8. **HRMS (ES):** calcd. for $C_{21}H_{16}N^{+}$ **(M-Br)$^{+}$**: 282.1283; found: 282.1271.

Synthesis of 1-(2-hydroxy-3-oxo-1-phenyl-2,3-di-p-tolylpropyl)-6-methylpyridin-2(1H)-one (303) and 3-hydroxy-4-phenyl-2,3-di-p-tolyl-3H-quinolizin-6(4H)-one (304).



An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with N-benzyl-6-methyl-2-pyridone **228c** (0.22 g, 1.2 mmol) and 4,4'-dimethylbenzil **232a** (0.33 g, 1.4 mmol) and the reagents were dissolved in dry THF and the reaction mixture was stirred for 20 min at room temperature. The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone and LDA (1.5 mL, 2.9 mmol, 1.9 M) was added to the flask dropwise over 5 min. The reaction mixture was stirred at -78 °C for 3 h, and was then warmed up at room temperature and stirred for 12 h. The reaction was worked-up with H_2O (5 mL) and the solvent was removed under vacuum. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford compound **303** as a yellow oil, (0.12 g, 25% yield) and compound **304a**, also a yellow oil (40 mg, 10% yield).

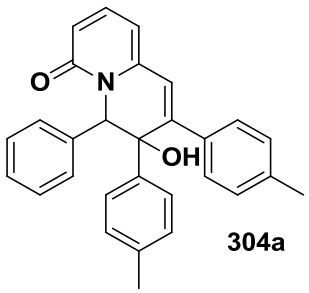
♦*1-(2-hydroxy-3-oxo-1-phenyl-2,3-di-p-tolylpropyl)-6-methylpyridin-2(1H)-one(303).*



303

IR (Neat) 3413 (OH), 3025 ($CHsp^2$), 2989 ($CHsp^3$), 1679 (C=O), 1650 (C=O), 1064 (CO), 771-720 (CH_{Arom}) cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 9.03 (s, 1H), 7.86 (d, *J*=8.4 Hz, 2H), 7.39 (d, *J*=8.0 Hz, 2H), 7.17 - 7.36 (m, 7H), 7.10 (d, *J*=8.0 Hz, 4H), 6.88 (s, 1H), 6.28 (d, *J*=8.8 Hz, 1H), 6.22 (d, *J*=6.8 Hz, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 198.2(C=O),164.7(C=O), 147.1 (C), 142.9 (C), 140.6 (CH), 136.6 (C), 136.5 (C), 135.1 (C), 131.2 (C), 130.3 (CH), 130.3 (CH), 128.5 (CHx2), 128.1 (CHx2), 127.7 (CHx2), 127.0 (CHx2), 126.5 (CH), 124.1 (CHx2), 117.7 (CH), 108.6 (CH), 85.2 (C), 67.1 (CH), 20.6 (CH_3), 20.5 (CH_3), 20.0 (CH_3). **HRMS (ES):** calcd. for $C_{29}H_{27}NO_3$ **$(M+H)^+$**: 438.2075 found: 438.2063.

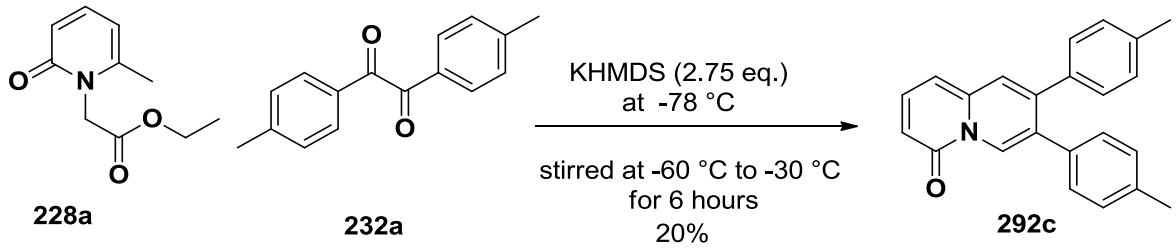
♦ *3-hydroxy-4-phenyl-2,3-di-p-tolyl-3H-quinolizin-6(4H)-one (304a).*



304a

IR (Neat) 3302 (OH), 3030 ($CHsp^2$), 2962 ($CHsp^3$), 1656 (C=O), 1539 cm^{-1}. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.44 (d, *J*=8.4 Hz, 2H), 7.34 - 7.41 (m, 3H), 7.19 - 7.29 (m, 6H), 7.15 (d, *J*=8.4 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 6.99 (s, 1H), 6.45 (d, *J*=6.8 Hz, 1H), 6.13 (dd, *J*=9.0, 1.2 Hz, 1H), 6.03 (s, 1H), 5.69 (s, 1H), 2.28 (s, 3H), 2.25 (s, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 159.5 (C=O), 144.0 (C), 141.6 (C), 140.7 (CH), 139.0 (C), 137.0 (C), 136.5 (C), 136.4 (C), 133.0 (C), 129.0 (CHx2), 128.4 (CHx2), 127.7 (CHx2), 127.6(CHx2), 126.9 (CHx2), 126.7 (CH), 125.0 (CHx2), 120.4 (CH), 118.3 (CH), 105.7 (CH), 75.2 (C), 62.4 (CH), 20.2 (CH_3), 20.0 (CH_3). **HRMS (ES):** calcd. for $C_{29}H_{25}NO_2$ **$(M+H)^+$**: 420.1958 found: 420.1967.

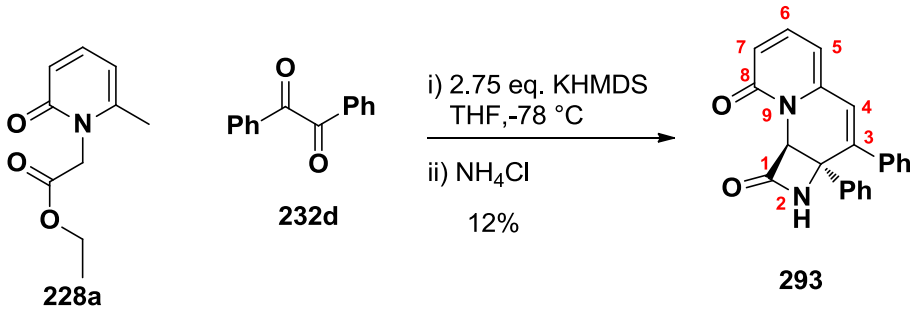
Synthesis of 7,8-di-p-tolyl-4H-quinolizin-4-one (292c).



228a **232a** **292c**

An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was charged with ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** (0.19 g, 0.95 mmol) and 4,4'-dimethylbenzil **232a** (0.30 g, 1.2 mmol) and the mixture was dissolved in THF (10 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. KHMDS (5.2 mL, 2.6 mmol, 0.5 M) was added at -78 °C and the reaction mixture was stirred at -60 °C to -30 °C for 6 hours and then the reaction was slowly warmed up to room temperature (20 °C) and stirred overnight. The reaction was worked-up with saturated $NH_4Cl_{(aq)}$ (6 mL). The solvent was removed under vacuum and the product was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine to afford a dark yellow oil. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford a yellow solid. The product fraction was recrystallized from ethanol to afford a yellow solid, (30 mg, 20%). **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.28 - 7.34 (m, 3H), 7.22 (d, *J*=8.2 Hz, 2H), 7.07 (d, *J*=7.6 Hz, 4H), 6.83 (s, 1H), 6.30 (d, *J*=6.4 Hz, 1H), 6.10 (d, *J*=9.0 Hz, 1H), 5.14 (br. s., 1H), 2.26 (s, 3H), 2.24 (s, 3H). **HRMS (ESI):** calcd. for $C_{23}H_{20}NO$ **$(M+H)^+$**: 326.1539 found 326.1538. (The sample was very weak to run ^{13}C).

Synthesis of (2aR,9aS)-2a,3-diphenyl-2,2a-dihydro-1H-azeto[2,3-c]quinolizine-1,8(9aH)-dione (293).

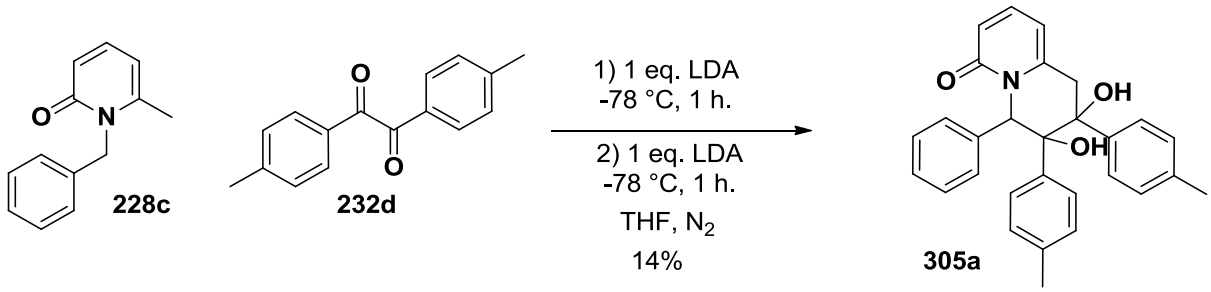


228a 232d 293

An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228** (0.36 g, 1.8 mmol) and benzil (0.37 g, 1.7 mmol) and the mixture was dissolved in THF (10 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone and stirred for 10 min. KHMDS (10 mL, 5.1 mmol, 0.5 M) was added at -78 °C and then the reaction mixture and warmed up to room temperature and stirred overnight. The reaction was worked-up with saturated $NH_4Cl_{(aq)}$ (6mL). The solvent was removed under vacuum and the product was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine to afford a dark yellow oil. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60 ° to afford 78 mg of yellow solid. The fraction was recrystallized in ethanol to afford yellow solid, (80 mg, 12% yield). (the compound crystallized with one molecule of ethanol, this is the reason why the weigh increased from 78 mg to 80 mg) **m.p.** 249-250 °C. **IR (KBr)** 1776 (C=O), 1654 (C=O), 1535 (NH), 1613 (C=C), 795-731 ($CH_{Arom.}$) cm^{-1}. **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 10.25 (s, 1H), 7.50 (dd, *J*=9.2, 6.8 Hz, 1H), 7.36 - 7.42 (m, 2H), 7.26 - 7.35 (m, 5H), 7.19 - 7.25 (m, 4H), 6.57 (d, *J*=6.8 Hz, 1H), 6.41 (d, *J*=9.2 Hz, 1H), 5.52 (s, 1H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 164.7 (CO), 160.5 (CO), 141.7 (C), 140.7 (CH), 140.5 (C), 140.3 (C), 135.4 (C), 129.6 (CHx2), 129.3 (CH), 129.0 (CHx2), 128.4 (CH), 128.0 (CHx2), 125.3 (CHx2), 120.6 (CH), 120.2 (CH), 108.9 (CH), 68.1 (CH) 60.5 (C). **HRMS (ES):** calcd. for $C_{22}H_{17}N_2O_2$ **$(M+H)^+$** 341.1285 found 341.1286.

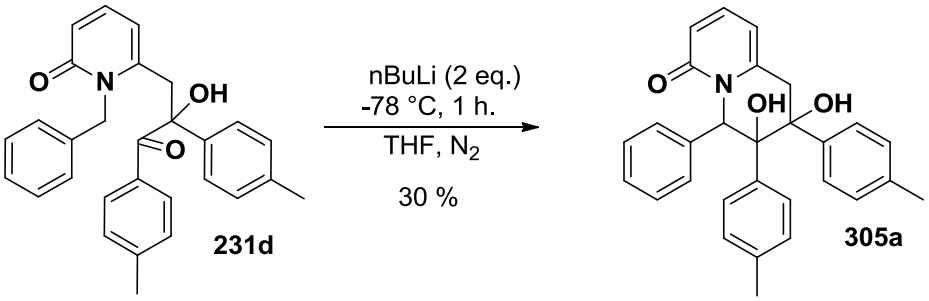
Synthesis of 2,3-dihydroxy-4-phenyl-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one (305a).

Procedure 1.



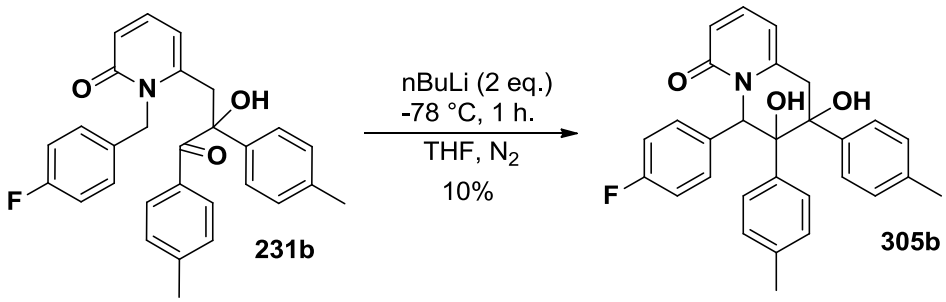
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1-benzyl-6-methylpyridin-2(1H)-one **228c** (0.70 g, 3.5 mmol) and dissolved in dry THF (15 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. LDA (4.4 mL, 3.5 mmol, 0.8 M) was added to the solution dropwise over 5 min. The reaction mixture was warmed up to 0 °C, and then the reaction was cooled to -78 °C. Concurrently, an additional oven-dried flask was purged with N_2 and then was charged with a solution of 1,2-di-p-tolylethane-1,2-dione **232a** (1.0 g, 4.2 mmol) in dry THF (6.0 mL). The electrophile solution was added dropwise to the pyridone solution at -78 °C via syringe over 5 min. The reaction was allowed to proceed for 1 h at -78 °C. LDA (4.4 mL, 3.5 mmol, 0.8 M) was added to the mixture at -78 °C and the reaction mixture was stirred at -78 °C for 1 h before quenching with saturated $NH_4Cl_{(aq)}$ (10 mL). EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in petroleum ether 40-60° to afford 2,3-dihydroxy-4-phenyl-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one **305a** (0.21 g, 14%) as a pale yellow solid. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 7.44 (dd, *J*=9.0, 6.8 Hz, 1H), 6.98 (d, *J*=7.2 Hz, 2H), 6.90 (t, *J*=7.6 Hz, 2H), 6.77 - 6.87 (m, 5H), 6.54 - 6.66 (m, 4H), 6.26 (d, *J*=6.8 Hz, 1H), 6.22 (d, *J*=9.0 Hz, 1H), 5.91 - 5.98 (m, 2H), 5.86 (s, 1H), 3.96 - 4.09 (m, 1H), 3.04 (d, *J*=18.0 Hz, 1H), 2.18 (s, 3H), 2.02 (s, 3H). **^{13}C NMR (DMSO-d_6 ,101MHz): δ (ppm)** 162.6 (C), 147.2 (C), 139.4 (C), 138.7 (CH), 138.7 (C), 136.5 (C), 135.4 (C), 134.6 (C), 128.5 (CHx2), 127.2 (CHx2), 127.0 (CHx2), 126.9 (CHx2), 126.4 (CHx2), 126.2 (CHx2), 125.1 (CH), 116.5 (CH), 105.9 (CH), 80.6 (C), 74.4 (C), 68.2 (CH), 39.3 (CH_2), 20.5 (CH_3), 20.4 (CH_3).

Procedure 2:



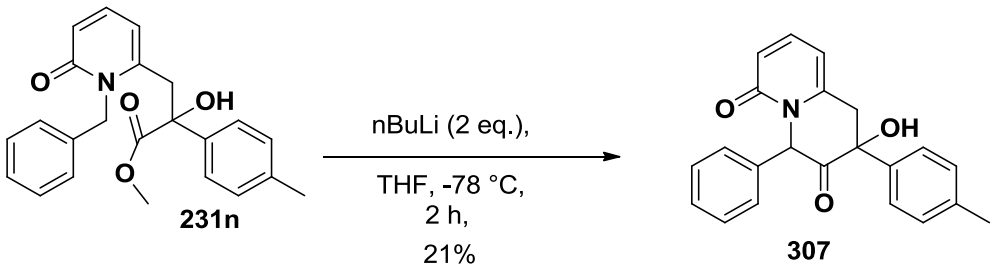
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1-benzyl-6-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)pyridin-2(1H)-one **231d** (0.30 g, 0.69 mmol) and dissolved in dry THF (14 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. nBuLi (0.87 mL, 1.4 mmol, 1.6 M) was added to the solution dropwise over 5 min. The reaction mixture was warmed up to 0 °C, and then was cooled to -78 °C. The reaction mixture was then stirred at -78 °C for 1 h before quenching with saturated $NH_4Cl_{(aq)}$ (15 mL). EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica chromatography with elution gradient 0 to 100% EtOAc in heptane to afford 2,3-dihydroxy-4-phenyl-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one **305a** (90 mg, 30%) as a pale yellow solid. **^{1}H NMR (DMSO-d$_6$, 700MHz): δ (ppm)** 7.44 (dd, *J*=9.0, 6.8 Hz, 1H), 6.98 (d, *J*=7.7 Hz, 2H), 6.90 (t, *J*=7.9 Hz, 2H), 6.79 - 6.86 (m, 5H), 6.61 - 6.65 (m, *J*=8.4 Hz, 2H), 6.57 - 6.61 (m, *J*=8.1 Hz, 2H), 6.25 (d, *J*=6.8 Hz, 1H), 6.21 (d, *J*=9.0 Hz, 1H), 5.96 (s, 1H), 5.93 (s, 1H), 5.83 (s, 1H), 4.01 - 4.06 (m, 1H), 3.04 (d, *J*=17.8 Hz, 1H), 2.18 (s, 3H), 2.02 (s, 3H). **^{13}C NMR (DMSO-d$_6$, 176MHz): δ (ppm)** 162.5 (C), 147.1 (C), 139.4 (C), 138.7 (CH), 138.6 (C), 136.5 (C), 135.3 (C), 134.6 (C), 128.4 (CHx2), 127.2 (CHx2), 126.94 (CHx2), 126.85 (CHx2), 126.33 (CHx2), 126.2 (CHx2), 125.1 (CH), 116.4 (CH), 105.8 (CH), 80.6 (C), 74.4 (C), 68.2 (CH), 39.3 (CH_2), 20.4 (CH_3), 20.3 (CH_3).

Synthesis of 4-(4-fluorophenyl)-2,3-dihydroxy-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one (305b).



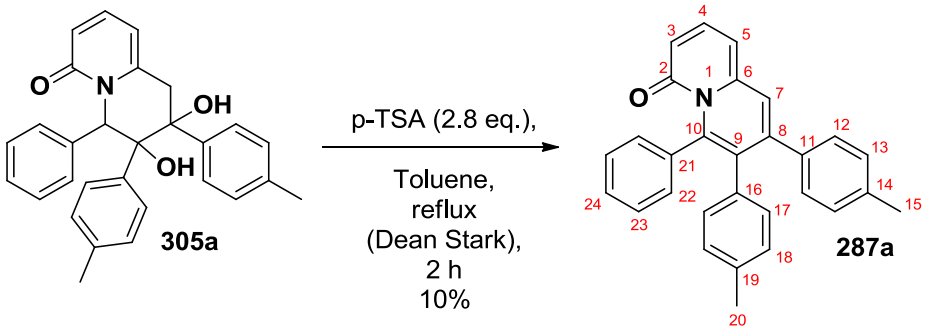
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with 1-(4-fluorobenzyl)-6-(2-hydroxy-3-oxo-2,3-di-p-tolylpropyl)pyridin-2(1H)-one **231b** (0.33 g, 0.73 mmol) and dissolved in dry THF (15 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. nBuLi (0.91 mL, 1.5 mmol, 1.6 M) was added to the solution dropwise over 2 min. The reaction mixture was warmed up to 0 °C, and then was cooled to -78 °C. The reaction mixture was then stirred at -78 °C for 3 h before quenching with saturated $NH_4Cl_{(aq)}$ (5 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow solid. The crude product was recrystallized in CH_2Cl_2 to obtain 4-(4-fluorophenyl)-2,3-dihydroxy-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one **305b** (30 mg, 10%) as a white solid. **^{1}H NMR (DMSO-d$_6$, 400MHz): δ (ppm)** 7.48 (dd, *J*=9.2, 6.8 Hz, 1H), 6.87 - 6.98 (m, 8H), 6.79 (d, *J*=8.4 Hz, 2H), 6.69 (d, *J*=8.4 Hz, 2H), 6.31 (d, *J*=6.8 Hz, 1H), 6.22 (d, *J*=9.2 Hz, 1H), 5.81 (s, 1H), 5.74 (s, 1H), 5.58 (s, 1H), 4.67 (s, 1H), 3.45 (d, *J*=17.5 Hz, 1H), 3.34 (d, *J*=17.5 Hz, 1H), 2.22 (s, 3H), 2.21 (s, 3H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 161.8 (C), 160.6 (C, d, J_F = 239 Hz), 146.8 (C), 139.9 (C), 139.5 (CH), 139.1 (C), 136.2 (C), 136.0 (C), 135.9 (C), 131.2 (CH), 131.2 (CH), 127.5 (CHx2), 127.4 (CHx2), 127.1 (CHx2), 126.9 (CHx2), 116.8 (CH), 113.0 (CH), 112.8 (CH), 105.3 (CH), 77.0 (C), 74.8 (C), 66.2 (CH), 39.9 (CH_2), 20.5 (CH_3x2). **UPLC, MS,** r.t: 1.09 min, *m/z*: ES$^+$ $[M+H]^+$ 456. **HRMS (ESI):** calcd. for $C_{29}H_{26}FNO_3$ **$(M+H)^+$**: 456.1969 found 456.1969.

Synthesis of 2-hydroxy-2,4-diphenyl-1H-quinolizine-3,6(2H,4H)-dione (307).



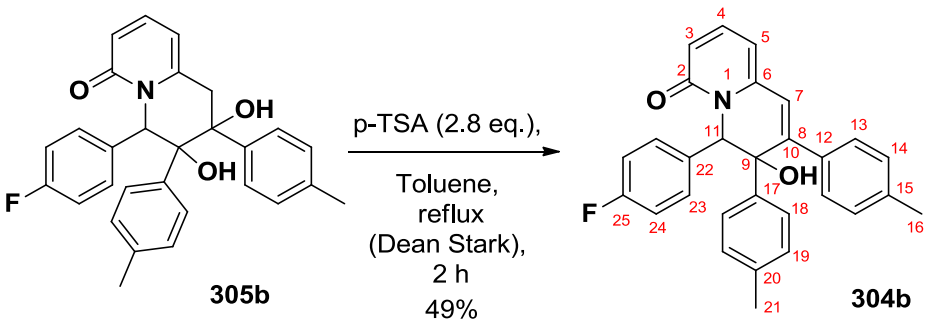
An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with methyl 3-(1-benzyl-6-oxo-1,6-dihydropyridin-2-yl)-2-hydroxy-2-phenylpropanoate **231n** (0.44 g, 1.2 mmol) and was dissolved in dry THF (20 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. nBuLi (1.5 mL, 2.4 mmol, 1.6 M) was added to the solution dropwise. The reaction mixture was warmed up to 0 °C, and then the reaction was cooled to -78 °C. The reaction mixture was then stirred at -78 °C for 2 h before quenching with saturated $NH_4Cl_{(aq)}$ (5 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were dried over $MgSO_4$, filtered and evaporated to afford a green oil. The crude product was purified by flash silica chromatography, elution gradient 5 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 2-hydroxy-2,4-diphenyl-1*H*-quinolizine-3,6(2*H*,4*H*)-dione a pale yellow solid (82 mg, 21%). **^{1}H NMR (DMSO-d_6, 700MHz): δ (ppm)** 7.53 (dd, *J*=9.2, 6.8 Hz, 1H), 7.39 - 7.44 (m, 2H), 7.35 - 7.38 (m, 1H), 7.25 - 7.30 (m, 3H), 7.15 (dd, *J*=8.1, 1.1 Hz, 2H), 7.04 - 7.10 (m, 2H), 6.90 (s, 1H), 6.48 (s, 1H), 6.42 (d, *J*=9.2 Hz, 1H), 6.37 (d, *J*=6.8 Hz, 1H), 3.46 (d, *J*=16.8 Hz, 1H), 3.19 (d, *J*=16.8 Hz, 1H). **^{13}C NMR (DMSO-d_6, 176MHz): δ (ppm)** 200.8 (C=O), 161.0 (C=O), 144.2 (C), 140.7 (C), 140.1 (CH), 134.0 (C), 129.0 (CHx2), 128.1 (CH), 127.8 (CHx2), 127.6 (CH), 125.7 (CHx2), 125.5 (CHx2), 117.0 (CH), 106.3 (CH), 74.4 (C), 62.9 (CH), 41.4 (CH_2). **UPLC, MS,** r.t: 0.85 min, *m/z*: ES^- $[M-H]^-$ 330.

Synthesis of 6-phenyl-7,8-di-p-tolyl-4H-quinolizin-4-one (287a).



p-Toluenesulfonic acid monohydrate (0.16 g, 0.82 mmol) was added to a solution of 2,3-dihydroxy-4-phenyl-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one **305a** (0.13 g, 0.29 mmol) in toluene (7.0 mL). The resulting solution was stirred at 120 °C for 2 h with a Dean-Stark apparatus. The reaction mixture was washed sequentially with saturated aqueous Na_2CO_3 (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product. The crude product was purified by preparative HPLC (Waters SunFire column, 5µ silica, 19 mm internal diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-phenyl-7,8-di-p-tolyl-4H-quinolizin-4-one **287a** as a dark yellow solid (12 mg, 10%). The amount of product that had been submitted for purification was 60 mg, and it yielded 12 mg of pure compound. Therefore, the real yield of the reaction should be 19%. **^{1}H NMR (DMSO-d$_6$, 700MHz): δ (ppm)** 7.62 (dd, *J*=8.4, 7.0 Hz, 1H, H-4), 7.59 (s, 1H, H-7), 6.97 - 7.03 (m, 7H), 6.92 - 6.97 (m, 2H), 6.75 - 6.79 (m, 2H), 6.8 (d, *J*=7.0 Hz, 1H, H-5), 6.71 - 6.75 (m, 2H), 6.14 (dd, *J*=8.4, 1.3 Hz, 1H, H-3), 2.20 (s, 3H), 2.08 (s, 3H). **^{13}C NMR (DMSO-d$_6$, 176MHz): δ (ppm)** 159.8 (C=O), 143.4 (C, C-6), 142.3 (C, C-10), 139.7 (C), 137.8 (CH, C-4), 137.3 (C), 136.7 (C), 135.3 (C), 135.2 (C), 132.9 (C), 131.0 (CHx2), 130.7 (C), 128.7 (CHx2), 128.3 (CHx4), 127.5 (CHx2), 126.0 (CHx2), 125.9 (CH), 125.0 (CH, C-7), 111.2 (CH, C-3), 102.8 (CH, C-5), 20.5 (CH_3 x2). **UPLC, MS,** r.t: 1.31 min, *m/z*: ES$^+$ $[M+H]^+$ 401.9. **HRMS (ESI):** calcd. for $C_{29}H_{25}NO$ **$(M+H)^+$**: 402.1852 found 402.1852.

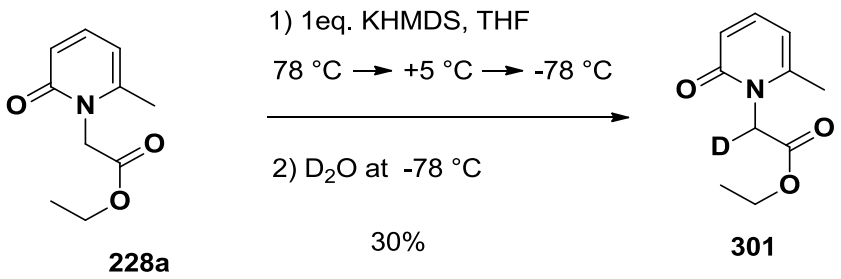
Synthesis of 4-(4-fluorophenyl)-3-hydroxy-2,3-di-p-tolyl-3H-quinolizin-6(4H)-one (304b).



p-toluenesulfonic acid monohydrate (15 mg, 0.080 mmol) was added to a solution of 4-(4-fluorophenyl)-2,3-dihydroxy-2,3-di-p-tolyl-3,4-dihydro-1H-quinolizin-6(2H)-one **305b** (15 mg, 0.030 mmol) in toluene (0.78 ml). The resulting solution was stirred at 120 °C for 2 h with a Dean-Stark apparatus. The reaction mixture was washed sequentially with saturated aqueous Na_2CO_3 (3 x 2 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 4-(4-fluorophenyl)-3-hydroxy-2,3-di-p-tolyl-3H-quinolizin-6(4H)-one (7.0 mg, 49%) as a yellow gum. **^{1}H NMR (DMSO-d$_6$, 700MHz): δ (ppm)** 7.42 (d, *J*=8.1 Hz, 2H), 7.35 - 7.39 (m, 3H), 7.19 - 7.21 (m, *J*=8.1 Hz, 2H), 7.12 - 7.15 (m, *J*=8.1 Hz, 2H), 7.04 - 7.08 (m, 4H), 6.96 (s, 1H), 6.43 (dd, *J*=7.0, 1.2 Hz, 1H), 6.12 (dd, *J*=9.1, 1.2 Hz, 1H), 6.00 (s, 1H), 5.61 (s, 1H), 2.26 (s, 3H), 2.24 (s, 3H). **^{13}C NMR (DMSO-d$_6$, 176MHz): δ (ppm)** 160.7 (C), 159.9 (C), 144.5 (C), 141.9 (C), 141.0 (C), 139.5 (CH), 137.6 (C), 137.0 (C), 133.4 (C), 133.1 (C),131.3 (CHx2), 128.9 (CHx2), 128.3 (CHx2), 128.1 (CHx2), 125.5 (CHx2), 120.9 (CH, C-7), 118.8 (CH), 114.3 (CH), 114.2 (CH), 106.2 (CH), 75.6 (C), 62.3 (CH, C-11), 20.7 (CH_3), 20.4 (CH_3). **UPLC, MS,** r.t: 1.15 min, *m/z*: ES$^+$ $[M+H]^+$ 438. **HRMS (ESI):** calcd. for $C_{29}H_{24}FNO_2$ **$(M+H)^+$**: 438.1864 found 438.1864.

Alkylation at benzylic position and N-methyl position.

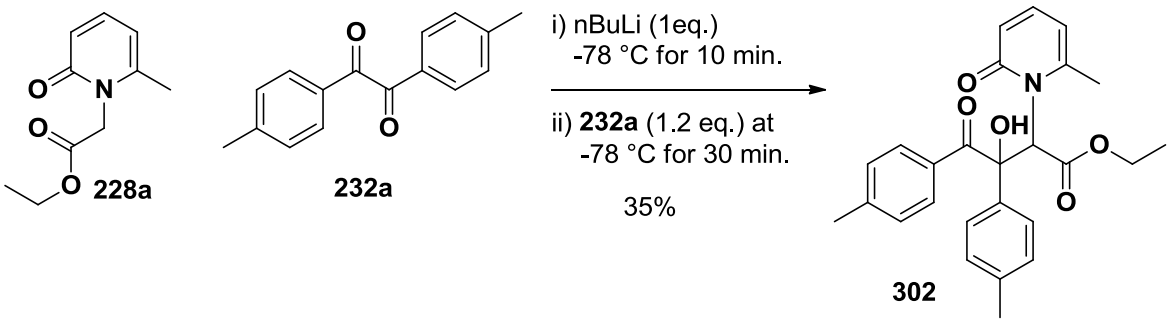
Deuteration at benzylic position of ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate (301).



228a **301**

An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum was purged with N_2. The flask was then charged with ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** (0.078 g, 0.4 mmol) and dissolved in dry THF (6.0 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. KHMDS (0.8 mL, 0.4 mmol, 5 M) was added to the flask dropwise over 5 min. The reaction mixture was warmed up to 0 °C and then was cooled to -78 °C. D_2O solution was then added to the deprotonated pyridone solution at -78 °C via syringe. The reaction was allowed to proceed for 10 min at -78 °C, and then saturated $NH_4Cl_{(aq)}$ was added (1 mL). EtOAc (10 mL) was added and the phases were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil, (0.0236 g, 30%). **^{1}H NMR (DMSO-d$_6$,400MHz): δ (ppm)** 7.36 (dd, *J*=9.2, 6.8 Hz, 1H), 6.29 (d, *J*=9.2 Hz, 1H), 6.16 (d, *J*=6.8 Hz, 1H), 4.76 - 4.80 (m, 1H), 4.15 (q, *J*=7.1 Hz, 2H), 2.28 (s, 3H), 1.22 (t, *J*=7.1 Hz, 3H). **^{13}C NMR (DMSO-d$_6$, 101MHz): δ (ppm)** 166.5 (CO), 160.5 (CO), 145.4 (C), 138.1 (CH), 114.3 (CH), 104.1 (CH), 59.3 (CH_2), 43.5 (CH), 43.3 (t, J_{C-D}=21.7, CH_2D), 18.1 (CH_3), 12.2 (CH_3).

Synthesis of afford ethyl 3-hydroxy-2-(6-methyl-2-oxopyridin-1(2H)-yl)-4-oxo-3,4-di-p-tolylbutanoate (302).



An oven-dried flask equipped with a stirrer bar, thermometer and fitted with a septum and purged with N_2. The flask was then charged with ethyl 2-(6-methyl-2-oxopyridin-1(2H)-yl)acetate **228a** (0.41 g, 2.1 mmol) and dissolved in dry THF (10 mL). The flask was cooled to -78 °C by immersion in a bath of dry ice/acetone. nBuLi (1.3 ml, 2.1 mmol, 1.6 M) was added to the solution dropwise. The resulting solution was stirred at -78 °C for 10 min. Concurrently, an additional oven-dried flask was purged with N_2 and was charged with a solution of 1,2-di-p-tolylethane-1,2-dione **232a** (0.60 g, 2.5 mmol) in THF (4 mL). The electrophile solution was added dropwise to the pyridone solution via syringe over 2 min. The resulting mixture was stirred at -78 °C for 30 min. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (2 mL) and neutralised with 2M HCl. It was then extracted with EtOAc (3 x 15 mL), and the organic layer was dried over $MgSO_4$, filtered and evaporated to afford ethyl 3-hydroxy-2-(6-methyl-2-oxopyridin-1(2H)-yl)-4-oxo-3,4-di-p-tolylbutanoate **302** (0.32 g, 35%) as a crystalline solid. **^{1}H NMR (DMSO-d_6, 400MHz): δ (ppm)** 9.14 (s, 1H), 7.69 (dd, *J*=8.2, 4.2 Hz, 4H), 7.47 (dd, *J*=8.8, 8.8 Hz, 1H), 7.23 (d, *J*=8.2 Hz, 2H), 7.11 (d, *J*=8.2 Hz, 2H), 6.47 (d, *J*=6.6 Hz, 1H), 6.36 (d, *J*=8.4 Hz, 1H), 5.74 (s, 1H), 3.98 - 4.04 (m, 1H), 3.87 (dd, *J*=10.9, 7.1 Hz, 1H), 2.60 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 0.96 (t, *J*=7.1 Hz, 3H). **^{13}C NMR (DMSO-d_6, 101MHz): δ (ppm)** 199.3 (CO), 165.2 (C), 164.7 (C), 148.1 (C), 142.8 (C), 141.1 (CH), 137.0 (C), 136.8 (C), 132.0 (C), 129.8 (CH), 128.9 (CH), 128.4 (CH), 126.0 (CH), 117.8 (CH), 109.5 (CH), 83.7 (C), 71.3 (CH), 61.1 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.5 (CH_3), 13.6 (CH_3). m/z: ES+ [M+H]+ 434.

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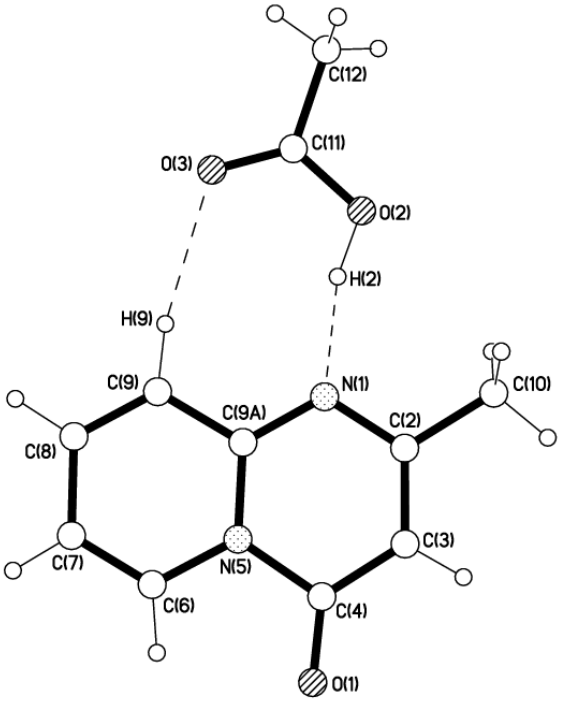
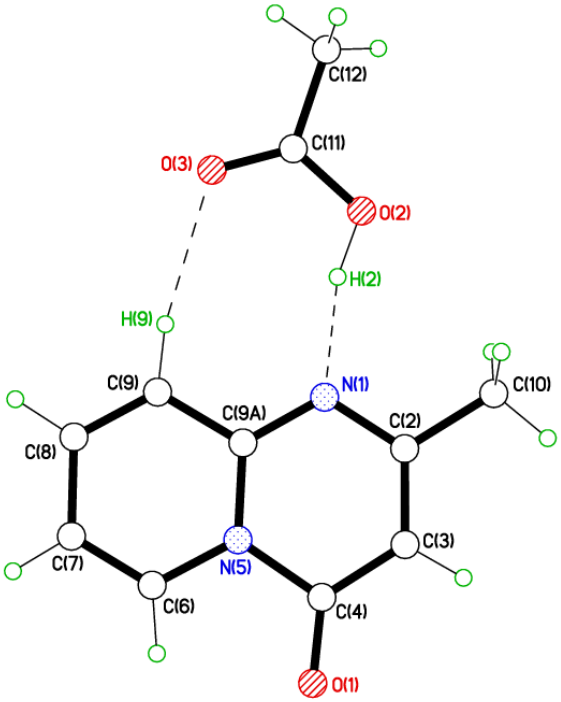
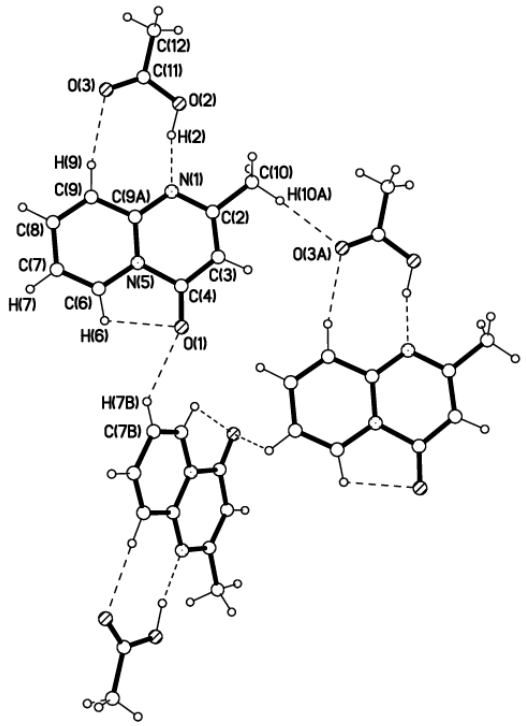
Appendix I: *X-Ray Crystallography Data*

2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (14a)



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H(6)
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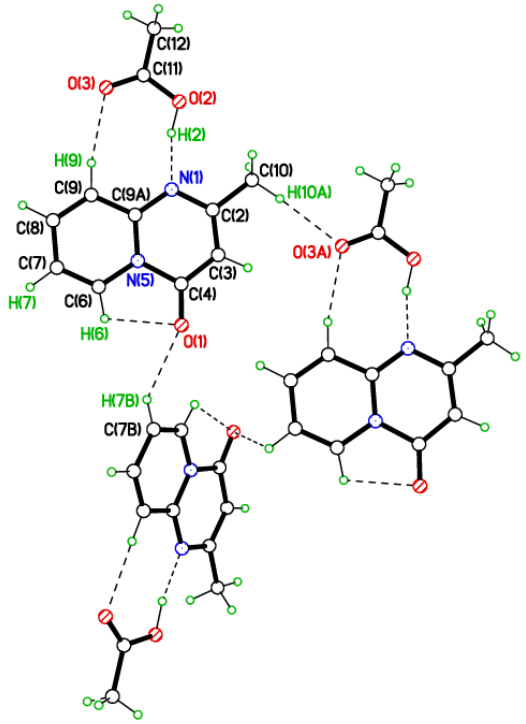
C(7B)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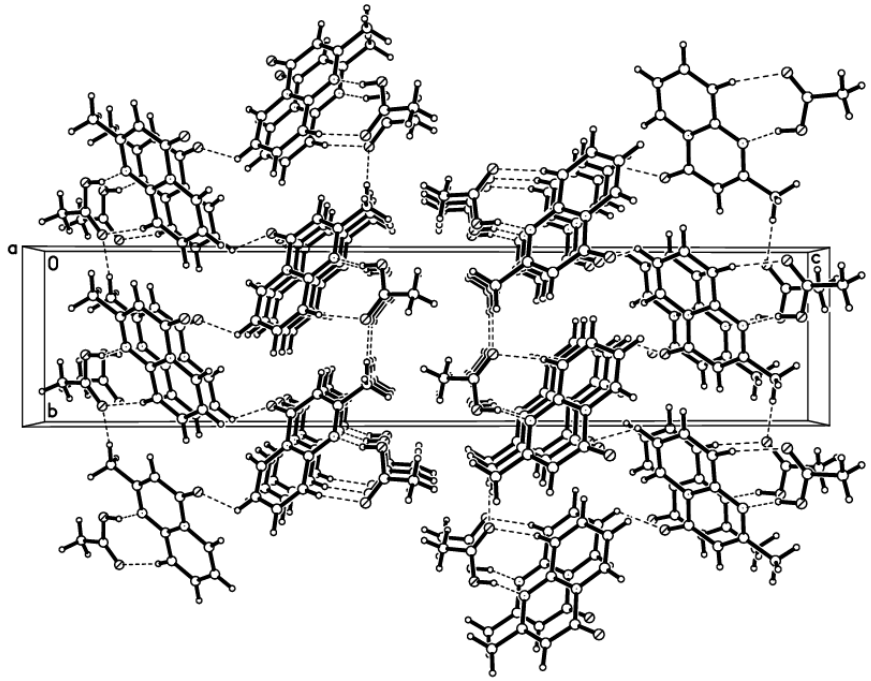
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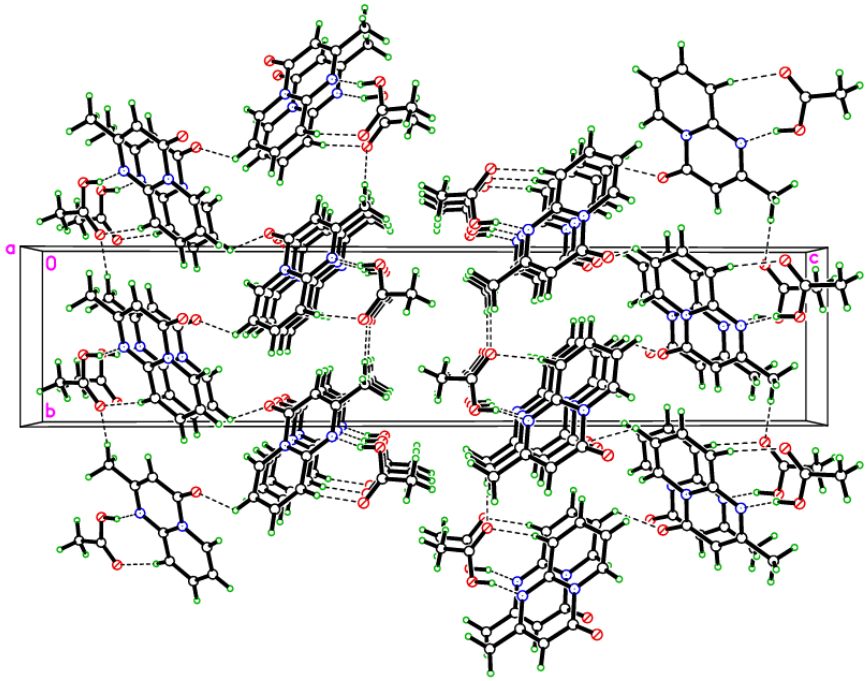
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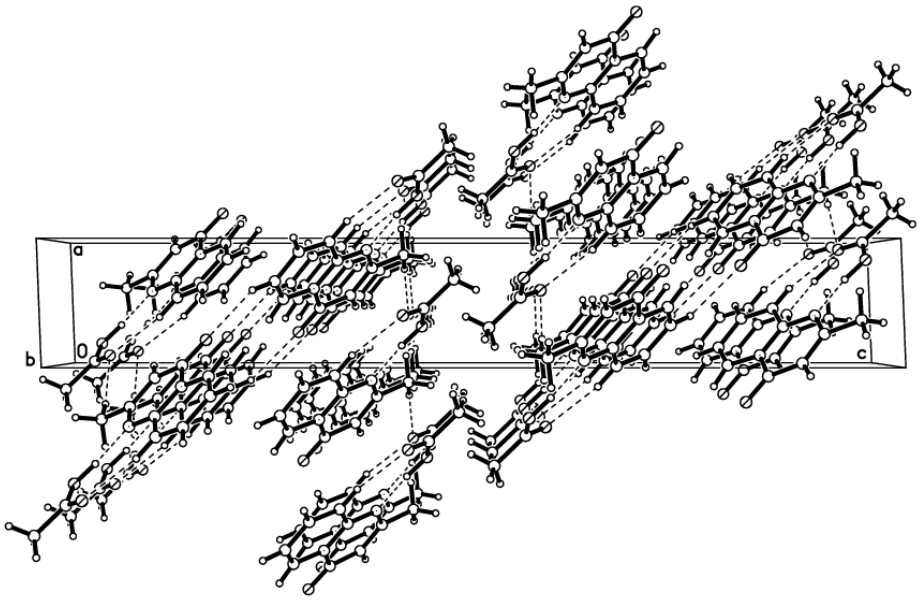
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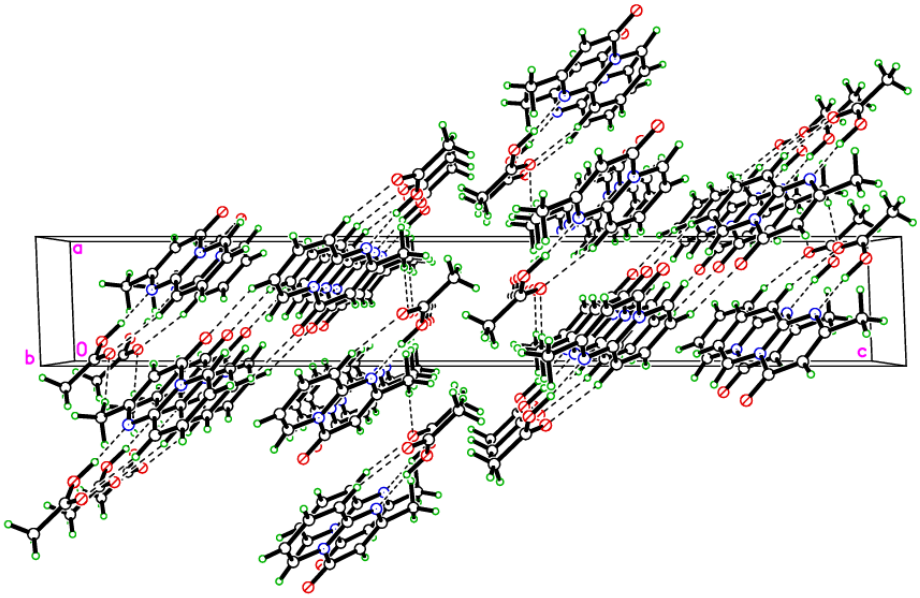
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Table 1. Crystal data and structure refinement for compound **14a**.

Identification code	**14a**	
Chemical formula	$C_{11}H_{12}N_2O_3$	
Formula weight	220.23	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 4.7298(7) Å	α = 90°
	b = 7.0031(11) Å	β = 92.212(2)°
	c = 31.563(5) Å	γ = 90°
Cell volume	1044.7(3) $Å^3$	
Z	4	
Calculated density	1.400 g/cm^3	
Absorption coefficient μ	0.104 mm^{-1}	
F(000)	464	
Crystal colour and size	colourless, 0.68 × 0.26 × 0.09 mm^3	
Reflections for cell refinement	2300 (θ range 2.58 to 28.05°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.58 to 28.32°	
Index ranges	h –6 to 6, k –9 to 9, l –41 to 42	
Completeness to θ = 28.32°	99.6 %	
Intensity decay	0%	
Reflections collected	10138	
Independent reflections	2604 (R_{int} = 0.0393)	
Reflections with $F^2>2\sigma$	1835	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.933 and 0.991	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0430, 0.3057	
Data / restraints / parameters	2604 / 0 / 193	
Final R indices [$F^2>2\sigma$]	R1 = 0.0453, wR2 = 0.1003	
R indices (all data)	R1 = 0.0720, wR2 = 0.1095	
Goodness-of-fit on F^2	1.048	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.207 and –0.182 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **14a**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.5940(3)	0.55917(18)	0.11805(4)	0.0258(3)
C(2)	0.7257(3)	0.3880(2)	0.11402(5)	0.0267(3)
C(3)	0.9388(3)	0.3280(2)	0.14124(5)	0.0289(4)
C(4)	1.0373(3)	0.4394(2)	0.17585(5)	0.0282(4)
O(1)	1.2257(2)	0.40186(18)	0.20244(4)	0.0385(3)
N(5)	0.8898(3)	0.62027(18)	0.17918(4)	0.0246(3)
C(6)	0.9698(3)	0.7399(2)	0.21255(5)	0.0288(4)
C(7)	0.8393(3)	0.9089(2)	0.21806(5)	0.0303(4)
C(8)	0.6196(3)	0.9665(2)	0.18915(5)	0.0297(4)
C(9)	0.5423(3)	0.8507(2)	0.15615(5)	0.0272(3)
C(9A)	0.6762(3)	0.6718(2)	0.15038(4)	0.0243(3)
C(10)	0.6235(4)	0.2680(3)	0.07738(6)	0.0340(4)
C(11)	0.0422(3)	0.7708(2)	0.05373(5)	0.0289(4)
C(12)	–0.1781(4)	0.7720(3)	0.01835(6)	0.0364(4)
O(2)	0.1781(2)	0.60650(17)	0.05728(4)	0.0344(3)
O(3)	0.0927(3)	0.90522(19)	0.07658(5)	0.0525(4)

Table 3. Bond lengths [Å] and angles [°] for **14a**.

N(1)–C(9A)	1.3359(19)	N(1)–C(2)	1.359(2)
C(2)–C(3)	1.365(2)	C(2)–C(10)	1.495(2)
C(3)–C(4)	1.407(2)	C(4)–O(1)	1.2290(19)
C(4)–N(5)	1.452(2)	N(5)–C(9A)	1.3808(18)
N(5)–C(6)	1.387(2)	C(6)–C(7)	1.349(2)
C(7)–C(8)	1.415(2)	C(8)–C(9)	1.359(2)
C(9)–C(9A)	1.419(2)	C(11)–O(3)	1.204(2)
C(11)–O(2)	1.3204(19)	C(11)–C(12)	1.498(2)
C(9A)–N(1)–C(2)	118.13(13)	N(1)–C(2)–C(3)	122.86(15)
N(1)–C(2)–C(10)	115.64(14)	C(3)–C(2)–C(10)	121.50(15)
C(2)–C(3)–C(4)	122.16(15)	O(1)–C(4)–C(3)	128.42(15)
O(1)–C(4)–N(5)	118.36(14)	C(3)–C(4)–N(5)	113.22(13)
C(9A)–N(5)–C(6)	120.87(13)	C(9A)–N(5)–C(4)	121.46(13)
C(6)–N(5)–C(4)	117.66(13)	C(7)–C(6)–N(5)	121.01(15)
C(6)–C(7)–C(8)	119.67(16)	C(9)–C(8)–C(7)	119.58(16)
C(8)–C(9)–C(9A)	121.13(15)	N(1)–C(9A)–N(5)	122.17(14)
N(1)–C(9A)–C(9)	120.10(13)	N(5)–C(9A)–C(9)	117.73(13)
O(3)–C(11)–O(2)	123.07(15)	O(3)–C(11)–C(12)	123.93(16)
O(2)–C(11)–C(12)	112.99(15)		

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for **14a**.

	x	y	z	U
H(3)	1.025(4)	0.206(3)	0.1371(5)	0.037(5)
H(6)	1.126(4)	0.691(3)	0.2302(5)	0.034(5)
H(7)	0.904(3)	0.989(3)	0.2417(5)	0.032(5)
H(8)	0.521(4)	1.091(3)	0.1922(5)	0.037(5)
H(9)	0.390(4)	0.878(3)	0.1354(6)	0.037(5)
H(10A)	0.731(5)	0.144(3)	0.0779(6)	0.059(6)
H(10B)	0.417(5)	0.237(3)	0.0792(7)	0.056(6)
H(10C)	0.643(5)	0.340(3)	0.0510(7)	0.060(6)
H(12A)	–0.099(6)	0.823(4)	–0.0061(10)	0.104(10)
H(12B)	–0.318(6)	0.869(4)	0.0241(8)	0.099(10)
H(12C)	–0.259(6)	0.650(5)	0.0134(9)	0.103(10)
H(2)	0.324(5)	0.609(4)	0.0813(8)	0.081(8)

Table 5. Torsion angles [°] for **14a**.

C(9A)–N(1)–C(2)–C(3)	–0.7(2)	C(9A)–N(1)–C(2)–C(10)	179.69(14)
N(1)–C(2)–C(3)–C(4)	0.4(2)	C(10)–C(2)–C(3)–C(4)	179.99(16)
C(2)–C(3)–C(4)–O(1)	179.95(16)	C(2)–C(3)–C(4)–N(5)	0.1(2)
O(1)–C(4)–N(5)–C(9A)	179.90(14)	C(3)–C(4)–N(5)–C(9A)	–0.21(19)
O(1)–C(4)–N(5)–C(6)	–0.5(2)	C(3)–C(4)–N(5)–C(6)	179.44(14)
C(9A)–N(5)–C(6)–C(7)	0.7(2)	C(4)–N(5)–C(6)–C(7)	–178.97(14)
N(5)–C(6)–C(7)–C(8)	–0.7(2)	C(6)–C(7)–C(8)–C(9)	0.0(2)
C(7)–C(8)–C(9)–C(9A)	0.7(2)	C(2)–N(1)–C(9A)–N(5)	0.5(2)
C(2)–N(1)–C(9A)–C(9)	–179.20(13)	C(6)–N(5)–C(9A)–N(1)	–179.72(14)
C(4)–N(5)–C(9A)–N(1)	–0.1(2)	C(6)–N(5)–C(9A)–C(9)	0.0(2)
C(4)–N(5)–C(9A)–C(9)	179.64(13)	C(8)–C(9)–C(9A)–N(1)	179.06(15)
C(8)–C(9)–C(9A)–N(5)	–0.7(2)		

Table 6. Hydrogen bonds for **14a** [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...N(1)	1.01(3)	1.73(3)	2.7141(17)	166(2)
C(9)–H(9)...O(3)	0.975(18)	2.292(18)	3.250(2)	167.2(15)
C(6)–H(6)...O(1)	0.971(18)	2.264(18)	2.683(2)	104.9(12)
C(10)–H(10A)...O(3')	1.00(2)	2.40(2)	3.374(2)	164.7(18)
C(7)–H(7)...O(1'')	0.973(17)	2.509(16)	3.183(2)	126.2(13)

Symmetry operations for equivalent atoms
' x+1,y–1,z '' –x+5/2,y+1/2,–z+1/2

Diethyl 1-((1-methyl-6-oxo-1,6-dihydropyridin-2-yl)methyl)hydrazine-1,2-dicarboxylate (293)

Figures & Description.

Formula.

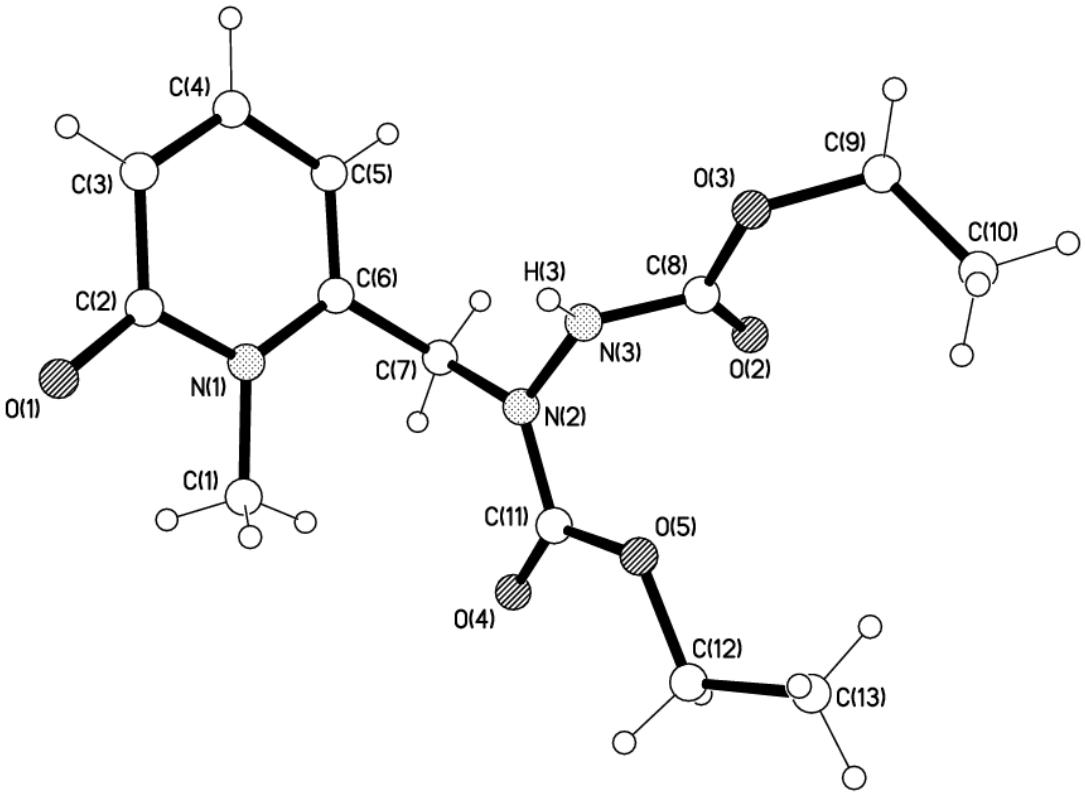
$C_{13}H_{19}N_3O_5$. One molecule in the asymmetric unit.

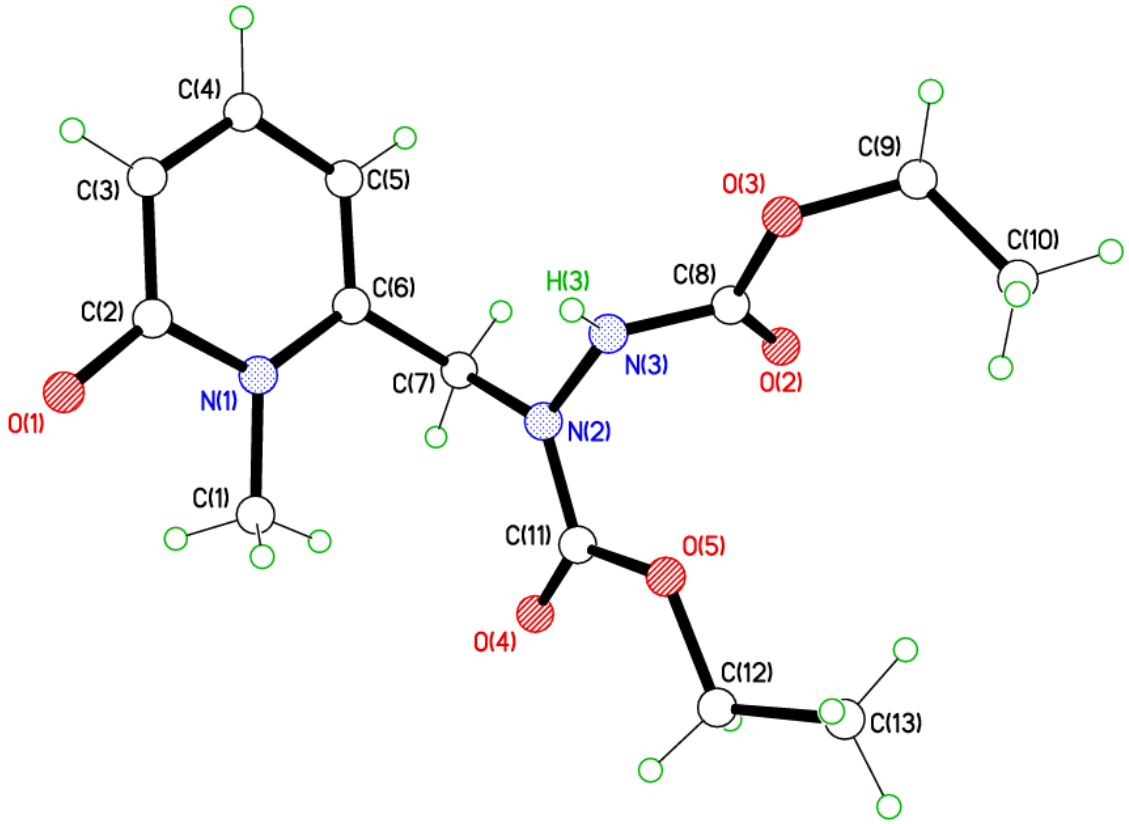
Disorder & Solvent of Crystallisation.

No disorder or solvent of crystallisation

Packing.

Molecules pair up into centro-symmetric dimers via pairs of N–H···O H-bonds. There are weaker supporting C–H···O H-bonds, but these are much less significant. Atoms C(2) and C(2') are the closest contacts at 3.454Å in a very slipped π···π stack from one side of the dimer to the other.

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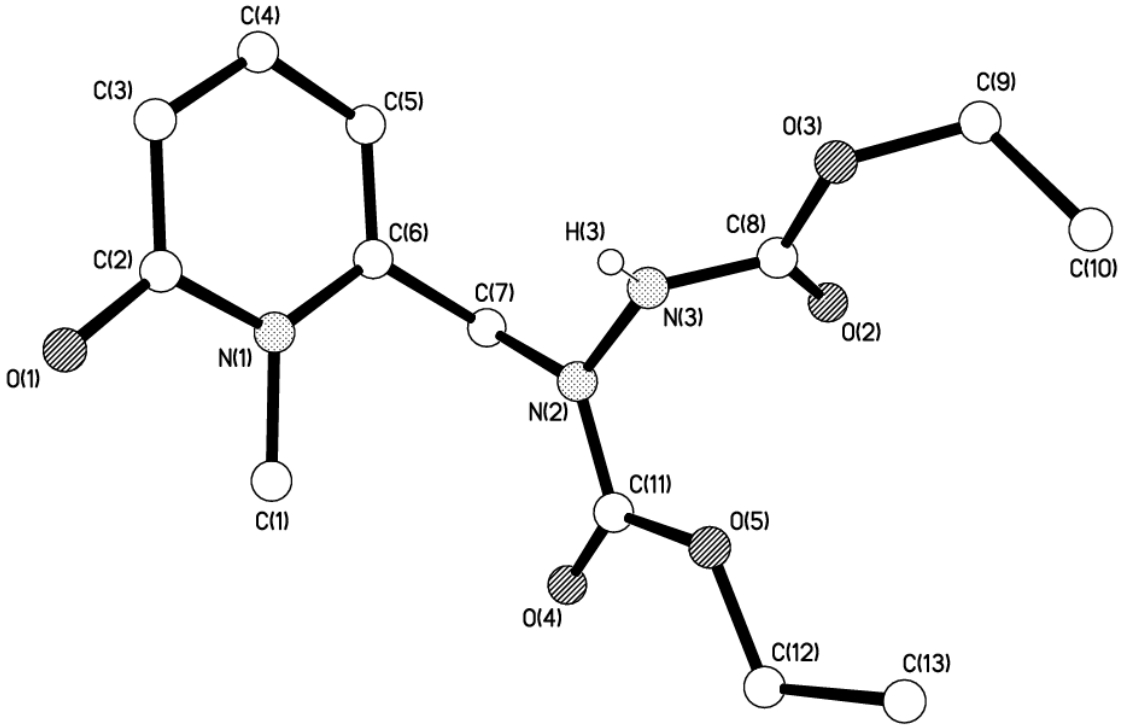
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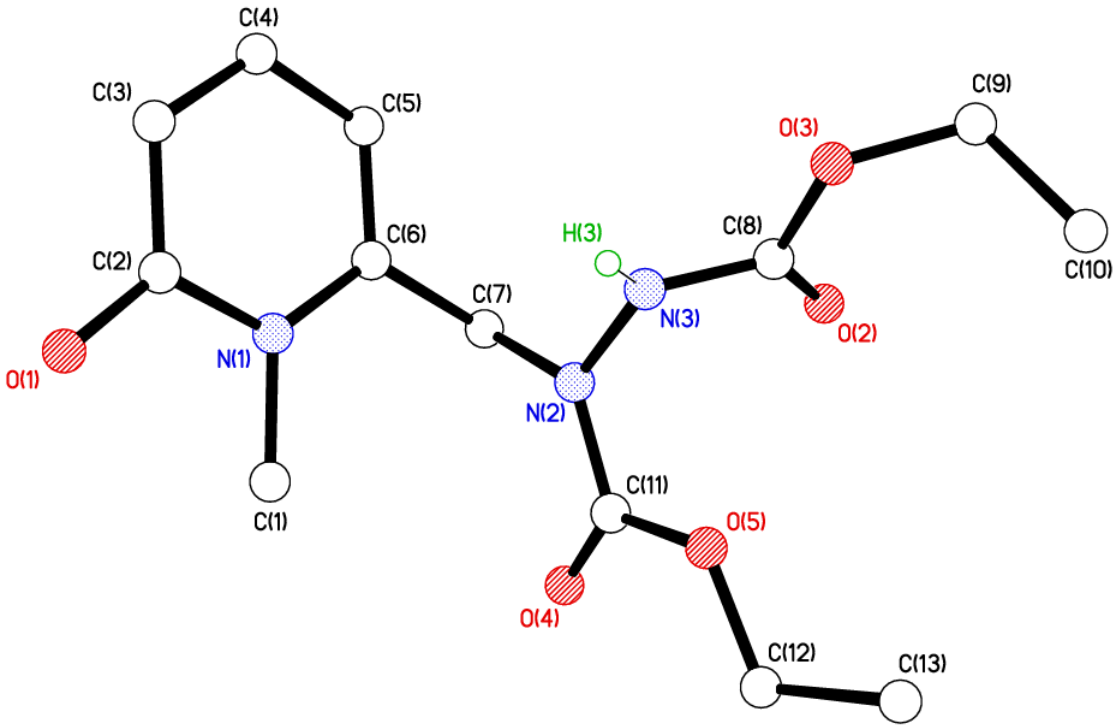
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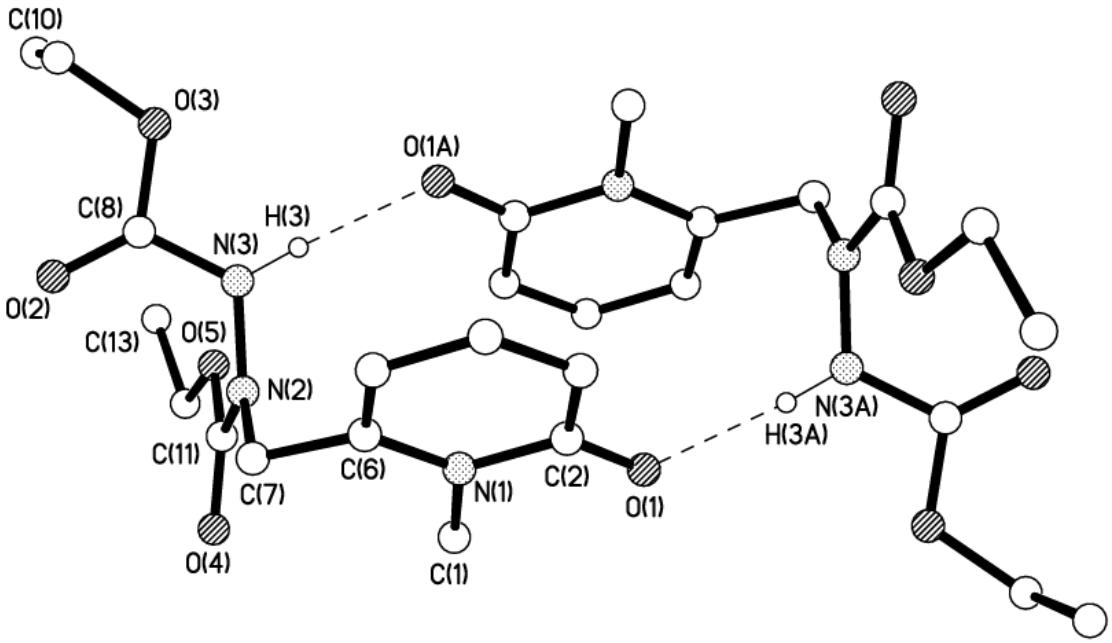
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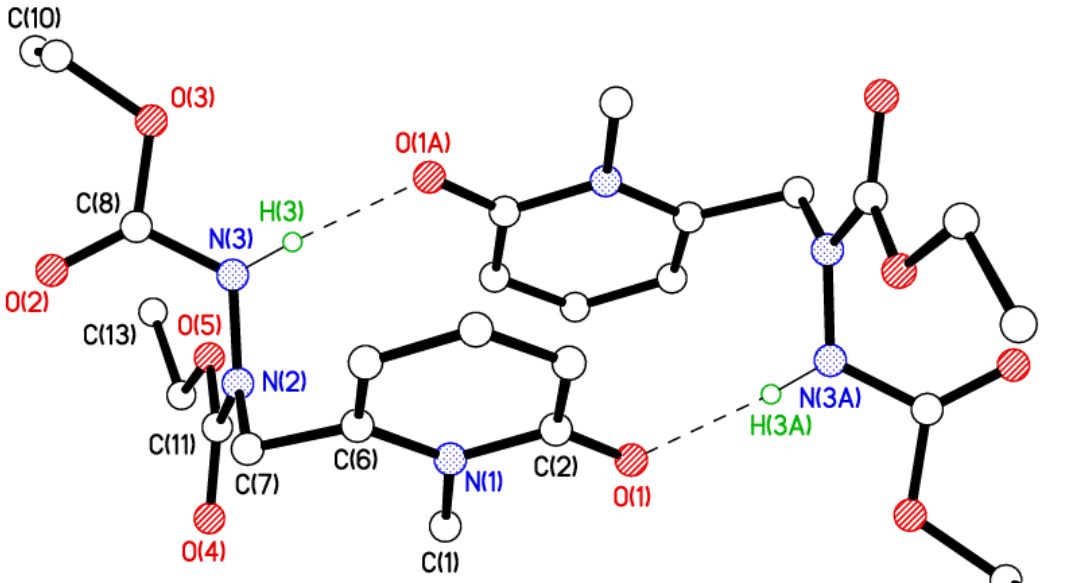
x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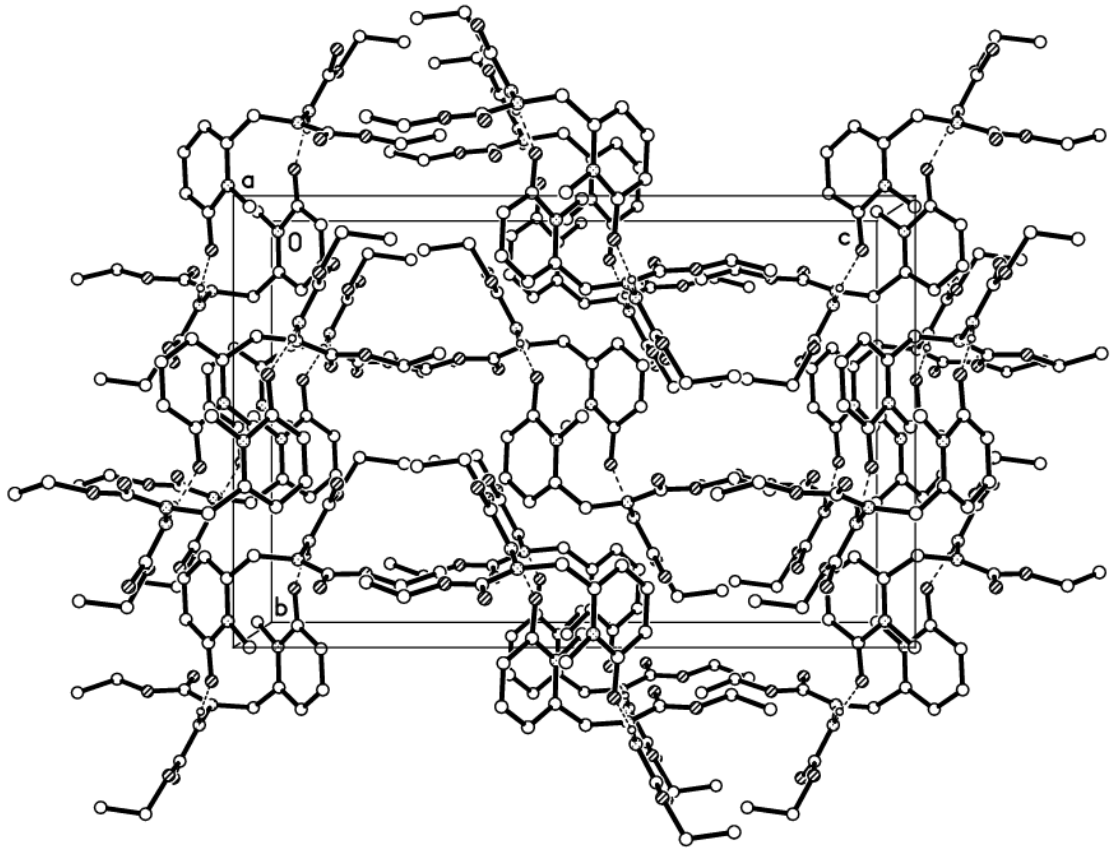
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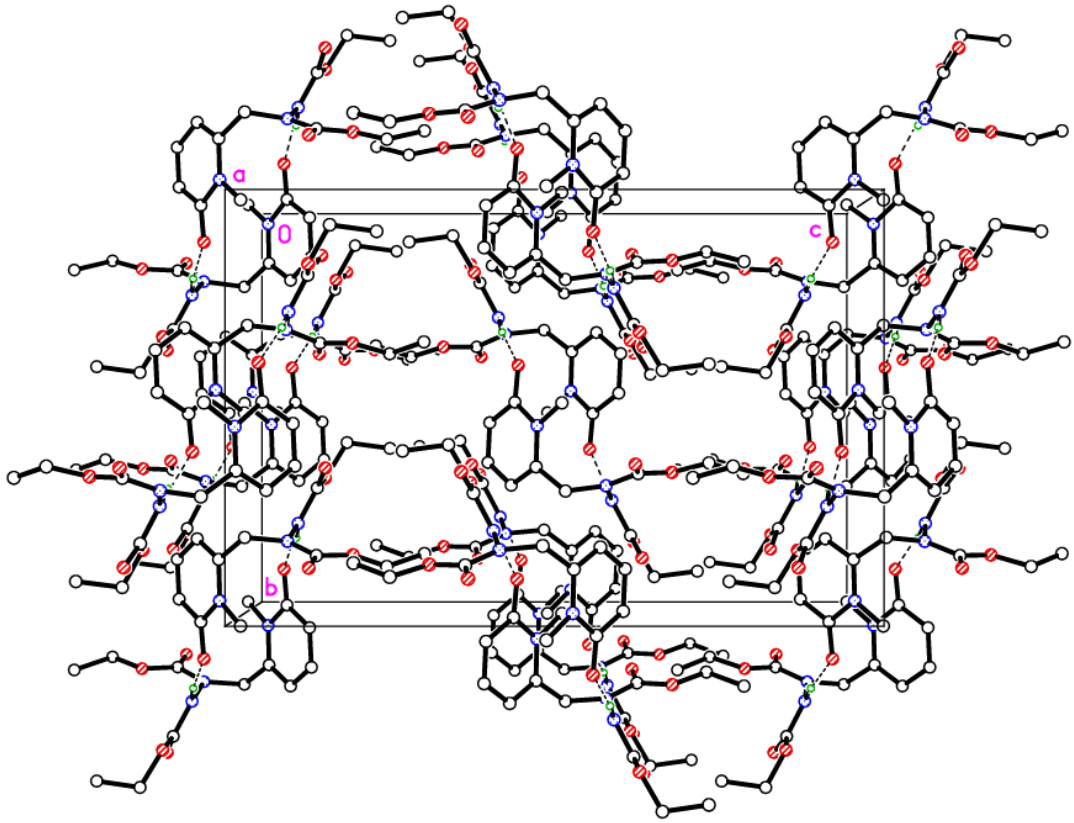
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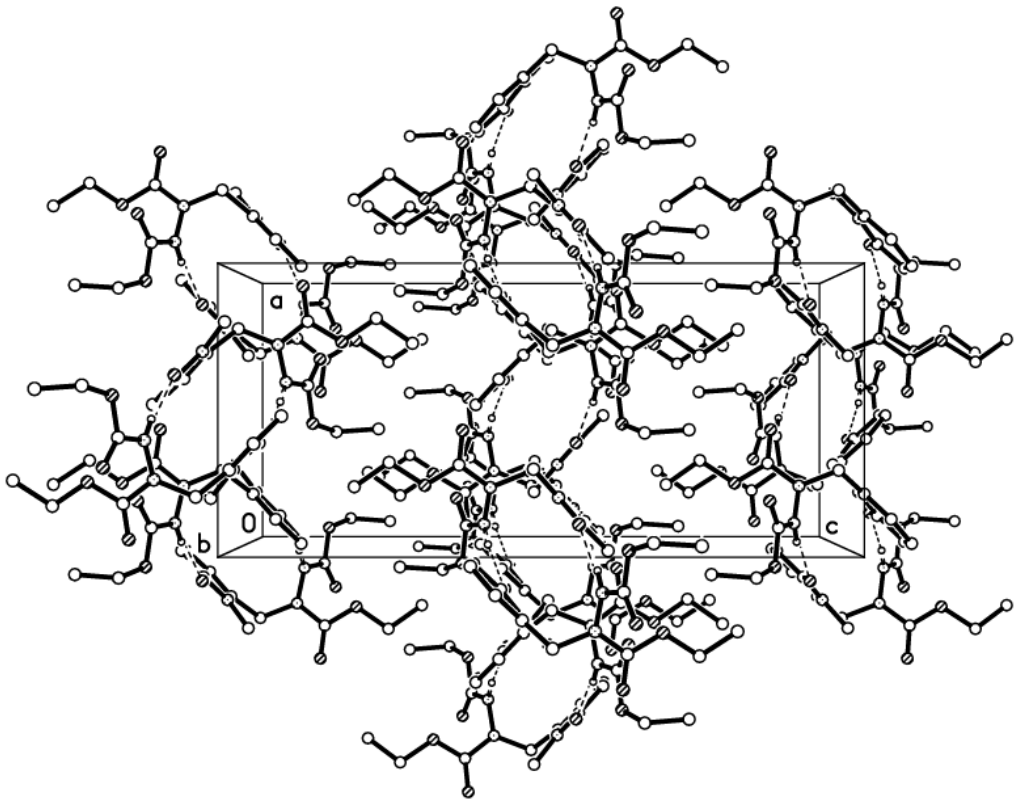
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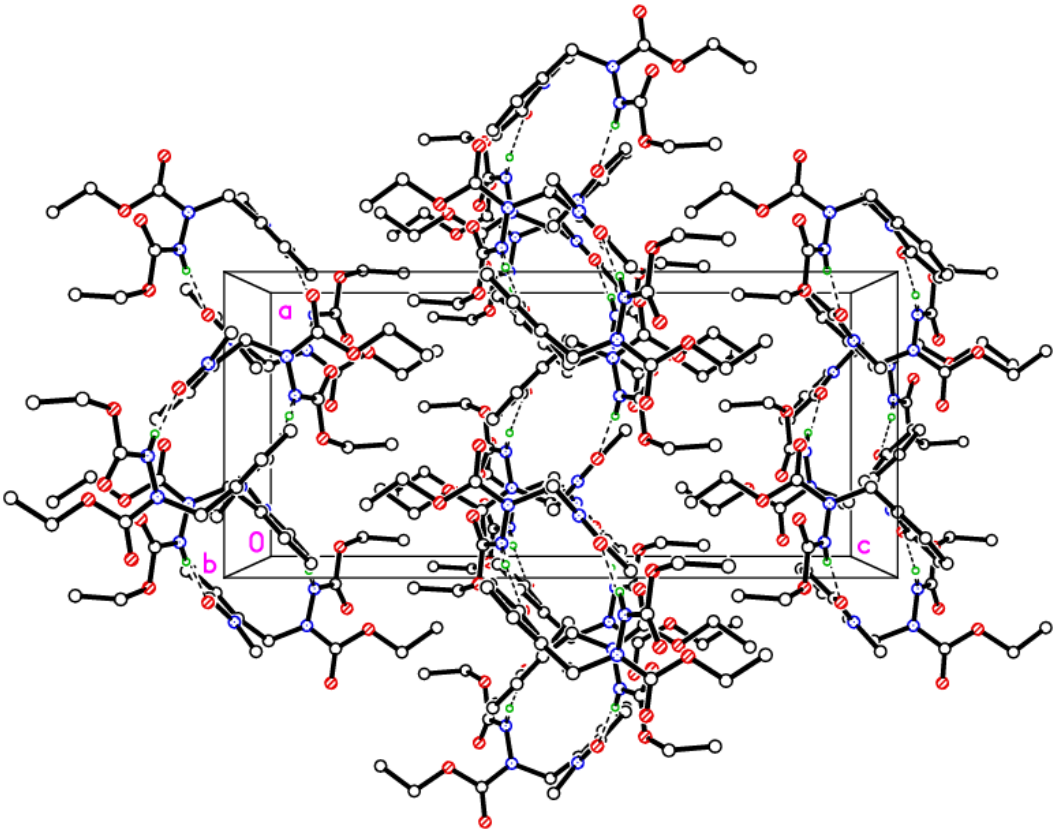

Crystal data

$C_{13}H_{19}N_3O_5$	D_x = 1.367 Mg m^{-3}
M_r = 297.31	Mo $K\alpha$ radiation, λ = 0.71073 Å
Orthorhombic, *Pbca*	Cell parameters from 10817 reflections
a = 9.6539 (4) Å	θ = 2.7–30.5°
b = 14.0840 (6) Å	μ = 0.11 mm^{-1}
c = 21.2528 (9) Å	T = 150 K
V = 2889.6 (2) Å^3	Tablet, colourless
Z = 8	0.51 × 0.47 × 0.14 mm^3
F(000) = 1264	

Data collection

Bruker APEX 2 CCD area detector diffractometer	4416 independent reflections

Radiation source: fine-focus sealed tube	3768 reflections with $I > 2\sigma(I)$
Graphite monochromator	$R_{int} = 0.026$
ω rotation with narrow frames scans	$\theta_{max} = 30.6°$, $\theta_{min} = 1.9°$
Absorption correction: multi-scan *SADABS* v2012/1, Sheldrick, G.M., (2012)	$h = -13 \rightarrow 13$
$T_{min} = 0.948$, $T_{max} = 0.985$	$k = -19 \rightarrow 20$
32659 measured reflections	$l = -30 \rightarrow 29$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.036$	All H-atom parameters refined
$wR(F^2) = 0.102$	$w = 1/[\sigma^2(F_o^2) + (0.0566P)^2 + 0.6405P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.03$	$(\Delta/\sigma)_{max} = 0.001$
4416 reflections	$\Delta\rangle_{max} = 0.39$ e Å^{-3}
266 parameters	$\Delta\rangle_{min} = -0.23$ e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.79965 (10)	0.48822 (7)	0.51167 (5)	0.02382 (19)
H1A	0.8641 (15)	0.5296 (11)	0.5306 (7)	0.037 (4)*
H1B	0.8478 (14)	0.4452 (10)	0.4852 (7)	0.036 (4)*
H1C	0.7505 (16)	0.4502 (12)	0.5430 (7)	0.044 (4)*
N1	0.70134 (7)	0.54202 (5)	0.47287 (3)	0.01741 (15)
C2	0.61159 (9)	0.48628 (7)	0.43714 (4)	0.01952 (17)
O1	0.61785 (7)	0.39786 (5)	0.44243 (3)	0.02520 (15)
C3	0.51936 (10)	0.53588 (7)	0.39595 (5)	0.02442 (19)
H3A	0.4558 (14)	0.4994 (10)	0.3716 (7)	0.033 (3)*
C4	0.51971 (10)	0.63243 (7)	0.39298 (5)	0.02532 (19)
H4	0.4543 (15)	0.6668 (10)	0.3660 (7)	0.034 (4)*
C5	0.61047 (10)	0.68563 (7)	0.43124 (4)	0.02188 (18)
H5	0.6118 (13)	0.7526 (10)	0.4301 (6)	0.026 (3)*

C6	0.69843 (9)	0.64008 (6)	0.47120 (4)	0.01800 (16)
C7	0.78544 (9)	0.69553 (6)	0.51721 (4)	0.02027 (17)
H7A	0.8811 (14)	0.6743 (9)	0.5194 (6)	0.025 (3)*
H7B	0.7812 (12)	0.7619 (9)	0.5048 (5)	0.021 (3)*
N2	0.72925 (8)	0.68437 (6)	0.58100 (4)	0.02131 (16)
N3	0.59883 (8)	0.72226 (6)	0.59146 (4)	0.02182 (16)
H3	0.5296 (15)	0.6847 (10)	0.5847 (7)	0.032 (3)*
C8	0.58813 (9)	0.80735 (6)	0.62146 (4)	0.01908 (17)
O2	0.68372 (7)	0.85676 (5)	0.63828 (3)	0.02468 (15)
O3	0.45251 (7)	0.82767 (5)	0.62847 (3)	0.02427 (15)
C9	0.42164 (11)	0.91478 (7)	0.66237 (5)	0.02460 (19)
H9A	0.4839 (14)	0.9638 (10)	0.6486 (6)	0.029 (3)*
H9B	0.3253 (15)	0.9288 (10)	0.6499 (6)	0.031 (3)*
C10	0.43224 (14)	0.90060 (9)	0.73242 (5)	0.0329 (2)
H10A	0.4093 (16)	0.9609 (12)	0.7550 (8)	0.047 (4)*
H10B	0.5258 (19)	0.8810 (13)	0.7460 (8)	0.050 (4)*
H10C	0.372 (2)	0.8523 (13)	0.7466 (9)	0.058 (5)*
C11	0.80952 (9)	0.65383 (6)	0.63010 (4)	0.01976 (17)
O4	0.93011 (7)	0.63036 (5)	0.62402 (3)	0.02372 (15)
O5	0.73852 (7)	0.65242 (5)	0.68422 (3)	0.02476 (15)
C12	0.81889 (11)	0.62878 (8)	0.73990 (5)	0.0290 (2)
H12A	0.9093 (16)	0.6641 (11)	0.7379 (7)	0.041 (4)*
H12B	0.8383 (15)	0.5605 (11)	0.7383 (7)	0.035 (4)*
C13	0.73334 (12)	0.65536 (9)	0.79608 (5)	0.0329 (2)
H13A	0.6503 (17)	0.6182 (12)	0.7980 (7)	0.044 (4)*
H13B	0.7853 (16)	0.6453 (11)	0.8355 (8)	0.042 (4)*
H13C	0.7088 (16)	0.7229 (12)	0.7946 (7)	0.044 (4)*

Geometric parameters (Å, º) for (gw122)

C1—N1	1.4680 (11)	N3—C8	1.3615 (12)
C1—H1A	0.943 (15)	N3—H3	0.865 (15)
C1—H1B	0.948 (15)	C8—O2	1.2098 (11)
C1—H1C	0.976 (16)	C8—O3	1.3484 (11)
N1—C6	1.3819 (11)	O3—C9	1.4537 (11)
N1—C2	1.3942 (11)	C9—C10	1.5056 (15)
C2—O1	1.2518 (11)	C9—H9A	0.961 (14)
C2—C3	1.4308 (13)	C9—H9B	0.987 (14)
C3—C4	1.3613 (15)	C10—H10A	1.000 (17)
C3—H3A	0.954 (14)	C10—H10B	0.988 (18)
C4—C5	1.4108 (14)	C10—H10C	0.945 (19)

C4—H4	0.981 (14)	C11—O4	1.2171 (11)
C5—C6	1.3615 (12)	C11—O5	1.3389 (11)
C5—H5	0.943 (13)	O5—C12	1.4537 (12)
C6—C7	1.5072 (12)	C12—C13	1.4993 (15)
C7—N2	1.4686 (12)	C12—H12A	1.005 (16)
C7—H7A	0.972 (13)	C12—H12B	0.980 (15)
C7—H7B	0.972 (13)	C13—H13A	0.958 (17)
N2—C11	1.3692 (11)	C13—H13B	0.986 (16)
N2—N3	1.3854 (10)	C13—H13C	0.981 (17)
N1—C1—H1A	110.3 (9)	C8—N3—H3	124.0 (9)
N1—C1—H1B	108.3 (9)	N2—N3—H3	116.1 (9)
H1A—C1—H1B	108.9 (12)	O2—C8—O3	125.87 (8)
N1—C1—H1C	110.5 (9)	O2—C8—N3	125.93 (9)
H1A—C1—H1C	111.6 (13)	O3—C8—N3	108.19 (7)
H1B—C1—H1C	107.0 (13)	C8—O3—C9	115.65 (7)
C6—N1—C2	122.43 (7)	O3—C9—C10	111.36 (8)
C6—N1—C1	122.92 (7)	O3—C9—H9A	109.1 (8)
C2—N1—C1	114.65 (7)	C10—C9—H9A	110.7 (8)
O1—C2—N1	118.76 (8)	O3—C9—H9B	103.2 (8)
O1—C2—C3	124.81 (8)	C10—C9—H9B	110.8 (8)
N1—C2—C3	116.42 (8)	H9A—C9—H9B	111.4 (11)
C4—C3—C2	120.97 (9)	C9—C10—H10A	110.3 (10)
C4—C3—H3A	121.0 (8)	C9—C10—H10B	112.9 (10)
C2—C3—H3A	118.0 (8)	H10A—C10—H10B	107.4 (14)
C3—C4—C5	120.35 (9)	C9—C10—H10C	111.6 (11)
C3—C4—H4	121.2 (8)	H10A—C10—H10C	108.8 (15)
C5—C4—H4	118.4 (8)	H10B—C10—H10C	105.6 (15)
C6—C5—C4	119.78 (9)	O4—C11—O5	125.23 (8)
C6—C5—H5	118.6 (8)	O4—C11—N2	123.07 (8)
C4—C5—H5	121.7 (8)	O5—C11—N2	111.69 (8)
C5—C6—N1	119.97 (8)	C11—O5—C12	115.43 (7)
C5—C6—C7	120.54 (8)	O5—C12—C13	107.28 (8)
N1—C6—C7	119.33 (7)	O5—C12—H12A	108.4 (9)
N2—C7—C6	109.73 (7)	C13—C12—H12A	112.8 (9)
N2—C7—H7A	105.9 (8)	O5—C12—H12B	107.4 (8)
C6—C7—H7A	113.7 (8)	C13—C12—H12B	112.2 (8)
N2—C7—H7B	109.8 (7)	H12A—C12—H12B	108.6 (12)
C6—C7—H7B	107.4 (7)	C12—C13—H13A	111.0 (10)
H7A—C7—H7B	110.4 (10)	C12—C13—H13B	111.1 (9)

C11—N2—N3	120.87 (8)	H13A—C13—H13B	108.1 (13)
C11—N2—C7	121.88 (7)	C12—C13—H13C	110.4 (9)
N3—N2—C7	116.27 (7)	H13A—C13—H13C	109.2 (13)
C8—N3—N2	118.89 (8)	H13B—C13—H13C	106.8 (13)
C6—N1—C2—O1	-178.07 (8)	C6—C7—N2—C11	125.92 (9)
C1—N1—C2—O1	2.57 (12)	C6—C7—N2—N3	-65.34 (10)
C6—N1—C2—C3	2.80 (12)	C11—N2—N3—C8	67.68 (12)
C1—N1—C2—C3	-176.57 (8)	C7—N2—N3—C8	-101.18 (10)
O1—C2—C3—C4	-179.78 (9)	N2—N3—C8—O2	3.22 (14)
N1—C2—C3—C4	-0.70 (13)	N2—N3—C8—O3	-177.56 (8)
C2—C3—C4—C5	-0.75 (15)	O2—C8—O3—C9	-3.42 (13)
C3—C4—C5—C6	0.20 (14)	N3—C8—O3—C9	177.36 (8)
C4—C5—C6—N1	1.83 (13)	C8—O3—C9—C10	-80.22 (11)
C4—C5—C6—C7	-173.61 (8)	N3—N2—C11—O4	-171.28 (8)
C2—N1—C6—C5	-3.42 (12)	C7—N2—C11—O4	-3.05 (14)
C1—N1—C6—C5	175.89 (8)	N3—N2—C11—O5	9.36 (12)
C2—N1—C6—C7	172.07 (8)	C7—N2—C11—O5	177.59 (8)
C1—N1—C6—C7	-8.62 (12)	O4—C11—O5—C12	5.78 (13)
C5—C6—C7—N2	106.06 (9)	N2—C11—O5—C12	-174.88 (8)
N1—C6—C7—N2	-69.41 (10)	C11—O5—C12—C13	165.46 (9)

Hydrogen-bond geometry (Å, º) for (gw122)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H1*A*···O4	0.943 (15)	2.521 (15)	3.3607 (12)	148.3 (12)
C1—H1*C*···O2^{i}	0.976 (16)	2.498 (16)	3.2703 (12)	135.8 (12)
C7—H7*B*···O1^{ii}	0.972 (13)	2.525 (12)	3.3937 (11)	148.9 (9)
N3—H3···O1^{iii}	0.865 (15)	1.926 (15)	2.7850 (11)	172.1 (13)
C9—H9*A*···O4^{ii}	0.961 (14)	2.542 (14)	3.4541 (12)	158.4 (11)
C13—H13*B*···O1^{iv}	0.986 (16)	2.532 (16)	3.5073 (13)	169.9 (12)

Symmetry codes: (i) -*x*+3/2, *y*-1/2, *z*; (ii) -*x*+3/2, *y*+1/2, *z*; (iii) -*x*+1, -*y*+1, -*z*+1; (iv) -*x*+3/2, -*y*+1, *z*+1/2.

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Computing details

Data collection: Bruker *APEX* 2; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014*/7 (Sheldrick, 2014); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table 1

Experimental details

Crystal data	
Chemical formula	$C_{13}H_{19}N_3O_5$
M_r	297.31
Crystal system, space group	Orthorhombic, *Pbca*
Temperature (K)	150
a, *b*, *c* (Å)	9.6539 (4), 14.0840 (6), 21.2528 (9)
V (Å^3)	2889.6 (2)
Z	8
Radiation type	Mo *K*α
μ (mm^{-1})	0.11
Crystal size (mm^3)	0.51 × 0.47 × 0.14
Data collection	
Diffractometer	Bruker *APEX* 2 CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS* v2012/1, Sheldrick, G.M., (2012)
T_{min}, T_{max}	0.948, 0.985
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	32659, 4416, 3768
R_{int}	0.026
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.715
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.036, 0.102, 1.03
No. of reflections	4416
No. of parameters	266

H-atom treatment	All H-atom parameters refined
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.39, -0.23

Computer programs: Bruker *APEX* 2, Bruker *SAINT*, *SHELXS97* (Sheldrick, 2008), *SHELXL2014*/7 (Sheldrick, 2014), Bruker *SHELXTL*.

Table 2

Hydrogen-bond geometry (Å, º) for (gw122)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H1*A*···O4	0.943 (15)	2.521 (15)	3.3607 (12)	148.3 (12)
C1—H1*C*···O2^{i}	0.976 (16)	2.498 (16)	3.2703 (12)	135.8 (12)
C7—H7*B*···O1^{ii}	0.972 (13)	2.525 (12)	3.3937 (11)	148.9 (9)
N3—H3···O1^{iii}	0.865 (15)	1.926 (15)	2.7850 (11)	172.1 (13)
C9—H9*A*···O4^{ii}	0.961 (14)	2.542 (14)	3.4541 (12)	158.4 (11)
C13—H13*B*···O1^{iv}	0.986 (16)	2.532 (16)	3.5073 (13)	169.9 (12)

Symmetry codes: (i) -*x*+3/2, *y*-1/2, *z*; (ii) -*x*+3/2, *y*+1/2, *z*; (iii) -*x*+1, -*y*+1, -*z*+1; (iv) -*x*+3/2, -*y*+1, *z*+1/2.

2a,3-diphenyl-2,2a-dihydro-1H-azeto[2,3-c]quinolizine-1,8(9aH)-dione (239e).

Formula.

$C_{22}H_{16}N_2O_2 \cdot C_2H_6O$

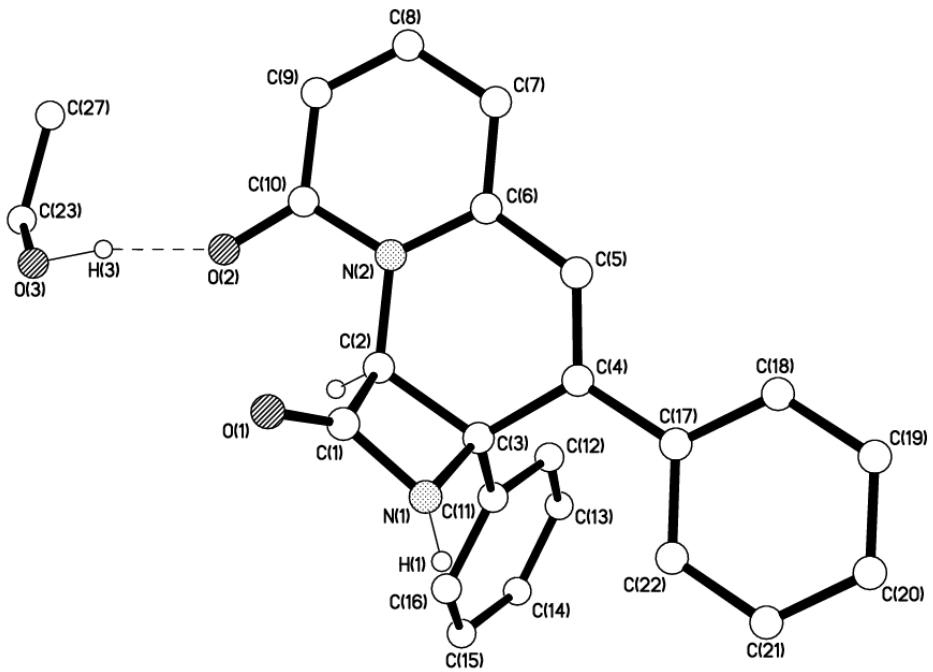
Disorder & Solvent of Crystallisation.

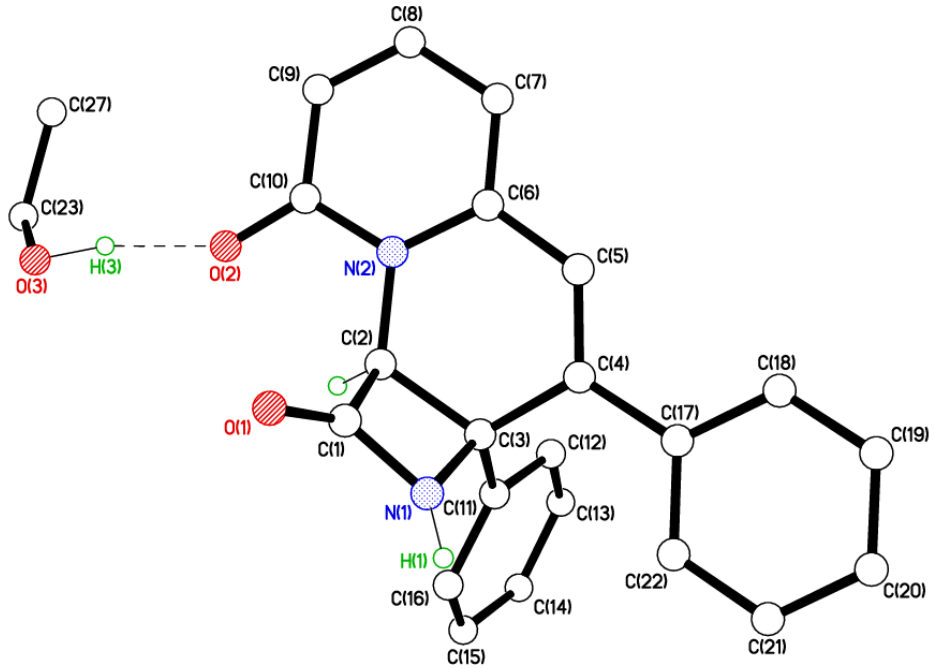
No disorder. One molecule of ethanol per formula unit, hydrogen bonded.

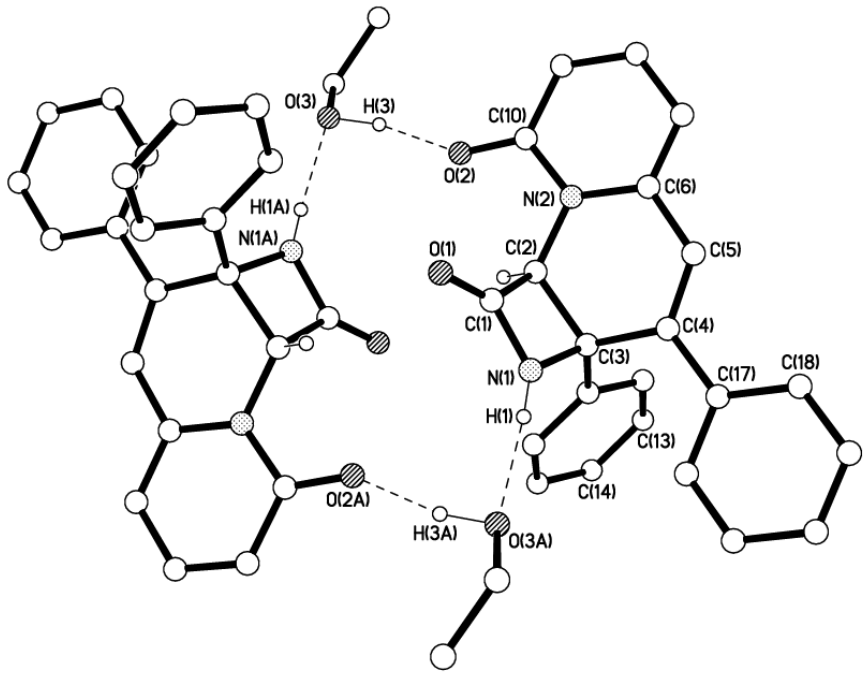
Packing.

Pairs of molecules form head-to-tail H-bonded pairs via inserted ethanol molecules. There are very weak, possibly simply coincidental, contacts between O(1) and H(2'), but these are probably not so significant.

Planar atoms C(2) > C(10), N(2), C(17) > C(22) align with the equivalent group by symmetry with closest atom···atom contacts of *ca*. 3.37 – 3.68Å. These planes are *ca*. 3.30 – 3.45Å apart.




C(8)
C(9)
C(7)
C(27)
C(10)
C(6)
C(23)
C(5)
H(3)
O(3)
O(2)
N(2)
C(2)
C(4)
C(18)
O(1)
C(17)
C(1)
C(3)
C(12)
C(19)
N(1)
C(11)
C(13)
H(1)
C(22)
C(20)
C(16)
C(14)
C(21)
C(15)


O(3)
H(3)
C(10)
O(2)
N(2)
C(6)
H(1A)
N(1A)
O(1)
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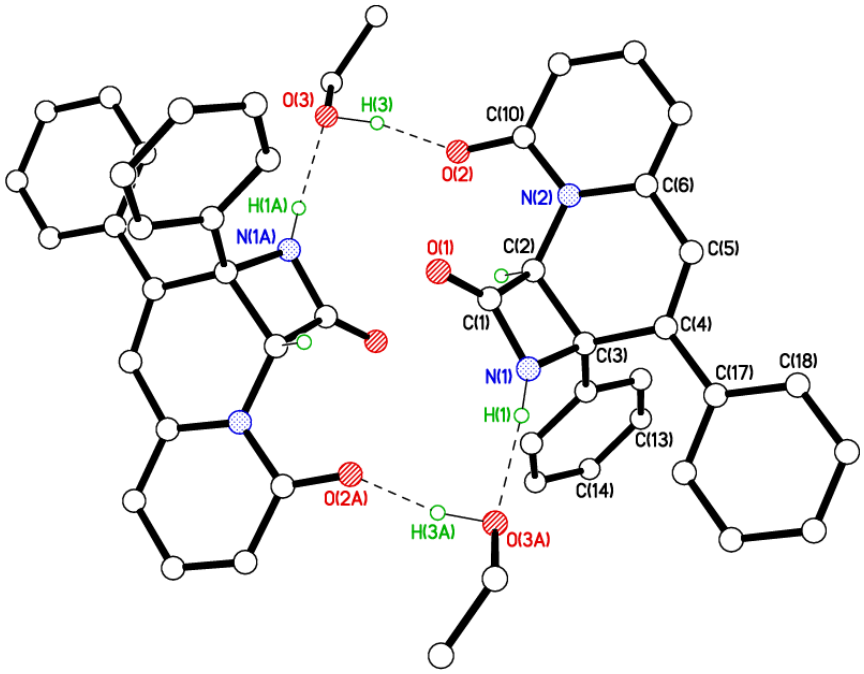
C(5)
C(1)
C(4)
C(3)
N(1)
C(17)
C(18)
H(1)
C(13)
C(14)
O(2A)
H(3A)
O(3A)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H(3)
C(10)
O(2)
N(2)
C(6)
H(1A)
N(1A)
O(1)
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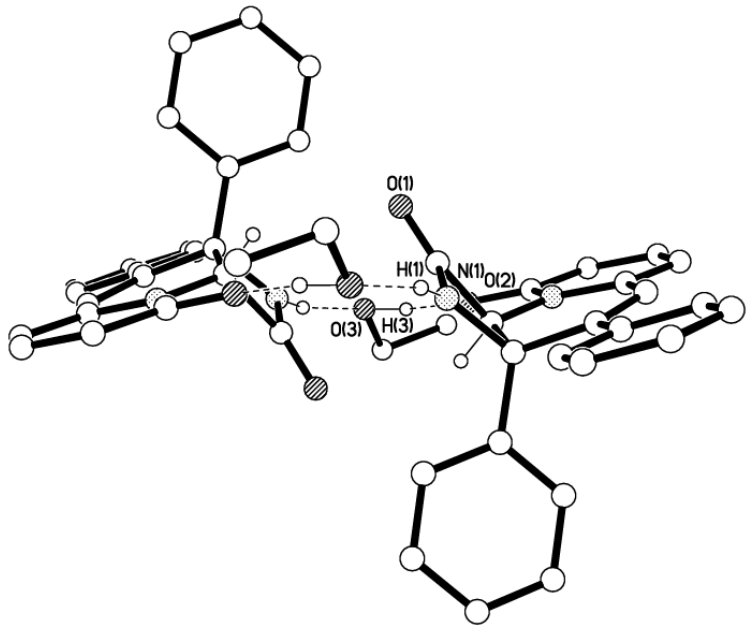
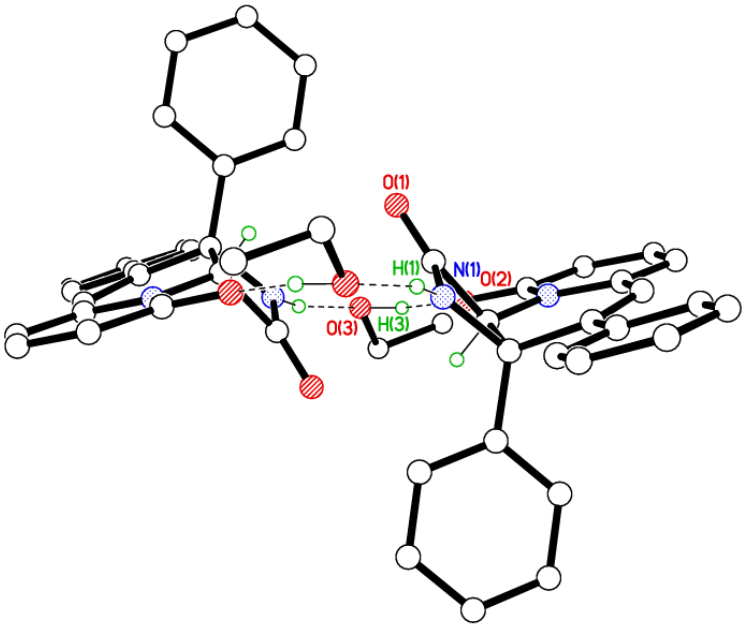
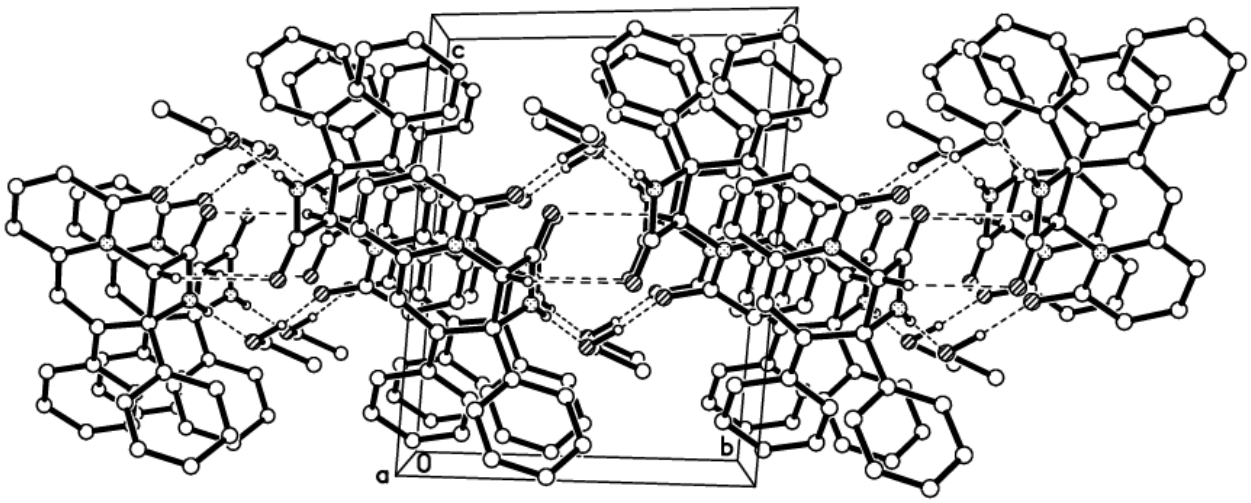
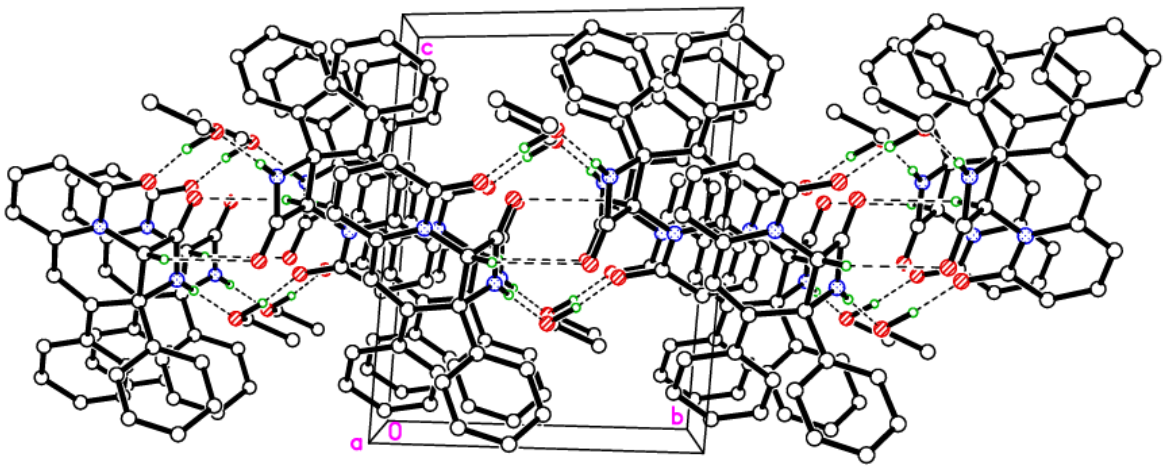
C(5)
C(1)
C(4)
C(3)
N(1)
C(17)
C(18)
H(1)
C(13)
C(14)
O(2A)
H(3A)
O(3A)


O(1)
H(1)
N(1)
O(2)
O(3)
H(3)


O(1)
H(1)
N(1)
O(2)
O(3)
H(3)


c
a
0
b


c
a
0
b

Crystal data

$C_{22}H_{16}N_2O_2 \cdot C_2H_6O$	$Z = 2$
$M_r = 386.43$	$F(000) = 408$
Triclinic, $P\bar{1}$	$D_x = 1.355$ Mg m^{-3}
$a = 9.106$ (3) Å	Synchrotron radiation, $\lambda = 0.7749$ Å
$b = 9.418$ (3) Å	Cell parameters from 3347 reflections
$c = 11.674$ (4) Å	$\theta = 3.0–33.6°$
$\alpha = 84.373$ (5)°	$\mu = 0.11$ mm^{-1}
$\beta = 85.471$ (5)°	$T = 100$ K
$\gamma = 72.114$ (5)°	Plate, yellow
$V = 946.9$ (5) Å^3	0.12 × 0.12 × 0.02 mm

Data collection

Bruker APEX 2 CCD diffractometer	5677 independent reflections
Radiation source: ALS Station 11.3.1	4237 reflections with $I > 2\sigma(I)$
silicon 111	$R_{int} = 0.050$
ω rotation with narrow frames scans	$\theta_{max} = 33.6°$, $\theta_{min} = 3.0°$
Absorption correction: multi-scan *SADABS* v2012/1, Sheldrick, G.M., (2012)	$h = -12 \rightarrow 12$
$T_{min} = 0.987$, $T_{max} = 0.998$	$k = -13 \rightarrow 13$
12999 measured reflections	$l = -16 \rightarrow 16$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.055$	Hydrogen site location: difference Fourier map
$wR(F^2) = 0.157$	All H-atom parameters refined
$S = 1.05$	$w = 1/[\sigma^2(F_o^2) + (0.0773P)^2 + 0.1504P]$ where $P = (F_o^2 + 2F_c^2)/3$
5677 reflections	$(\Delta/\sigma)_{max} < 0.001$
350 parameters	$\Delta\rangle_{max} = 0.45$ e Å^{-3}
0 restraints	$\Delta\rangle_{min} = -0.35$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	-0.08285 (14)	0.34249 (13)	0.37677 (10)	0.0177 (2)
H1	-0.180 (3)	0.387 (2)	0.3492 (18)	0.037 (6)*
C1	-0.03210 (16)	0.33761 (14)	0.48322 (11)	0.0180 (3)
O1	-0.09742 (13)	0.37781 (11)	0.57416 (8)	0.0221 (2)
C2	0.13537 (16)	0.26170 (14)	0.44119 (11)	0.0169 (3)
H2	0.1917 (19)	0.3346 (19)	0.4284 (14)	0.013 (4)*
C3	0.06436 (16)	0.24559 (14)	0.32727 (11)	0.0165 (2)
O2	0.30291 (14)	0.28322 (12)	0.60835 (10)	0.0282 (3)
C4	0.05698 (16)	0.08932 (14)	0.31621 (11)	0.0167 (2)
C5	0.13844 (16)	-0.02428 (15)	0.38725 (11)	0.0178 (3)
H5	0.136 (2)	-0.126 (2)	0.3817 (16)	0.025 (5)*
C6	0.23273 (16)	-0.01142 (15)	0.47751 (11)	0.0177 (3)
C7	0.32567 (17)	-0.13534 (16)	0.53644 (12)	0.0202 (3)
H7	0.326 (2)	-0.234 (2)	0.5165 (17)	0.033 (5)*
C8	0.41548 (17)	-0.11745 (17)	0.62393 (12)	0.0222 (3)
H8	0.481 (2)	-0.209 (2)	0.6690 (18)	0.035 (5)*
C9	0.41047 (17)	0.02109 (17)	0.65009 (12)	0.0225 (3)
H9	0.476 (2)	0.033 (2)	0.7130 (16)	0.027 (5)*
C10	0.31475 (17)	0.15297 (16)	0.58994 (12)	0.0201 (3)
N2	0.22871 (13)	0.12879 (13)	0.50449 (9)	0.0172 (2)
C11	0.13197 (16)	0.31154 (14)	0.22015 (11)	0.0172 (3)
C12	0.25559 (17)	0.22031 (16)	0.15790 (12)	0.0207 (3)
H12	0.298 (2)	0.112 (2)	0.1830 (18)	0.034 (5)*
C13	0.32048 (18)	0.27899 (17)	0.05988 (13)	0.0234 (3)
H13	0.406 (3)	0.214 (2)	0.0180 (18)	0.035 (5)*
C14	0.26180 (18)	0.42911 (17)	0.02284 (13)	0.0236 (3)
H14	0.305 (2)	0.470 (2)	-0.0481 (18)	0.031 (5)*
C15	0.13981 (19)	0.52069 (17)	0.08537 (13)	0.0248 (3)
H15	0.091 (2)	0.628 (2)	0.0582 (17)	0.033 (5)*
C16	0.07534 (18)	0.46287 (16)	0.18417 (13)	0.0224 (3)
H16	-0.010 (2)	0.528 (2)	0.2267 (18)	0.033 (5)*
C17	-0.04192 (16)	0.06715 (15)	0.22894 (11)	0.0175 (3)
C18	-0.04797 (17)	-0.07602 (16)	0.21046 (13)	0.0216 (3)
H18	0.016 (2)	-0.172 (2)	0.2584 (17)	0.029 (5)*
C19	-0.14239 (18)	-0.09504 (17)	0.12970 (13)	0.0240 (3)
H19	-0.146 (2)	-0.196 (2)	0.1180 (17)	0.033 (5)*
C20	-0.23452 (19)	0.02724 (17)	0.06614 (13)	0.0245 (3)
H20	-0.304 (2)	0.014 (2)	0.0088 (18)	0.033 (5)*
C21	-0.23251 (18)	0.16948 (17)	0.08448 (12)	0.0234 (3)

H21	-0.298 (2)	0.261 (2)	0.0412 (17)	0.029 (5)*
C22	-0.13637 (17)	0.18916 (16)	0.16416 (12)	0.0202 (3)
H22	-0.134 (2)	0.292 (2)	0.1715 (15)	0.022 (4)*
O3	0.36428 (14)	0.48908 (13)	0.72157 (11)	0.0325 (3)
H3	0.359 (3)	0.404 (3)	0.682 (2)	0.053 (7)*
C23	0.5249 (2)	0.47112 (19)	0.72648 (15)	0.0309 (3)
H23A	0.531 (3)	0.554 (3)	0.7744 (19)	0.043 (6)*
H23B	0.577 (3)	0.487 (2)	0.6437 (19)	0.043 (6)*
C27	0.6097 (2)	0.3188 (2)	0.77999 (16)	0.0314 (4)
H27A	0.603 (3)	0.238 (3)	0.734 (2)	0.044 (6)*
H27B	0.723 (3)	0.306 (3)	0.786 (2)	0.048 (6)*
H24C	0.569 (3)	0.295 (3)	0.860 (2)	0.048 (6)*

Geometric parameters (Å, º)

N1—C1	1.3514 (17)	C12—H12	0.99 (2)
N1—C3	1.4810 (18)	C13—C14	1.387 (2)
N1—H1	0.92 (2)	C13—H13	0.96 (2)
C1—O1	1.2104 (17)	C14—C15	1.385 (2)
C1—C2	1.536 (2)	C14—H14	0.98 (2)
C2—N2	1.4490 (17)	C15—C16	1.392 (2)
C2—C3	1.5638 (18)	C15—H15	1.00 (2)
C2—H2	0.970 (17)	C16—H16	0.97 (2)
C3—C4	1.5122 (18)	C17—C22	1.3990 (19)
C3—C11	1.5131 (19)	C17—C18	1.4043 (19)
O2—C10	1.2367 (18)	C18—C19	1.3842 (19)
C4—C5	1.3484 (18)	C18—H18	1.05 (2)
C4—C17	1.4815 (18)	C19—C20	1.385 (2)
C5—C6	1.4471 (18)	C19—H19	0.98 (2)
C5—H5	0.98 (2)	C20—C21	1.383 (2)
C6—C7	1.3710 (18)	C20—H20	1.00 (2)
C6—N2	1.3763 (17)	C21—C22	1.3886 (19)
C7—C8	1.411 (2)	C21—H21	0.997 (19)
C7—H7	0.98 (2)	C22—H22	0.989 (19)
C8—C9	1.355 (2)	O3—C23	1.425 (2)
C8—H8	1.01 (2)	O3—H3	0.98 (3)
C9—C10	1.434 (2)	C23—C27	1.505 (2)
C9—H9	1.016 (19)	C23—H23A	1.02 (2)
C10—N2	1.3922 (16)	C23—H23B	1.06 (2)
C11—C12	1.390 (2)	C27—H27A	0.99 (2)

C11—C16	1.3924 (19)	C27—H27B	1.01 (2)
C12—C13	1.391 (2)	C27—H24C	1.01 (2)
C1—N1—C3	95.83 (10)	C11—C12—H12	120.0 (12)
C1—N1—H1	130.0 (13)	C13—C12—H12	119.6 (12)
C3—N1—H1	134.1 (13)	C14—C13—C12	120.27 (14)
O1—C1—N1	132.78 (14)	C14—C13—H13	120.5 (13)
O1—C1—C2	135.79 (12)	C12—C13—H13	119.2 (13)
N1—C1—C2	91.43 (11)	C15—C14—C13	119.48 (14)
N2—C2—C1	120.22 (11)	C15—C14—H14	120.0 (12)
N2—C2—C3	119.28 (11)	C13—C14—H14	120.5 (12)
C1—C2—C3	85.49 (10)	C14—C15—C16	120.50 (14)
N2—C2—H2	109.3 (10)	C14—C15—H15	121.2 (12)
C1—C2—H2	110.2 (10)	C16—C15—H15	118.2 (12)
C3—C2—H2	110.5 (9)	C15—C16—C11	120.11 (14)
N1—C3—C4	111.61 (11)	C15—C16—H16	119.4 (12)
N1—C3—C11	115.95 (11)	C11—C16—H16	120.4 (12)
C4—C3—C11	113.50 (11)	C22—C17—C18	117.55 (12)
N1—C3—C2	85.66 (10)	C22—C17—C4	120.95 (12)
C4—C3—C2	113.46 (10)	C18—C17—C4	121.48 (12)
C11—C3—C2	113.82 (11)	C19—C18—C17	120.91 (13)
C5—C4—C17	122.38 (12)	C19—C18—H18	117.5 (11)
C5—C4—C3	118.93 (11)	C17—C18—H18	121.6 (11)
C17—C4—C3	118.68 (11)	C18—C19—C20	120.61 (13)
C4—C5—C6	125.89 (12)	C18—C19—H19	119.9 (12)
C4—C5—H5	120.4 (11)	C20—C19—H19	119.5 (12)
C6—C5—H5	113.7 (11)	C21—C20—C19	119.43 (13)
C7—C6—N2	119.42 (12)	C21—C20—H20	120.0 (12)
C7—C6—C5	121.57 (12)	C19—C20—H20	120.6 (12)
N2—C6—C5	119.01 (12)	C20—C21—C22	120.23 (13)
C6—C7—C8	119.62 (13)	C20—C21—H21	122.0 (11)
C6—C7—H7	118.3 (12)	C22—C21—H21	117.7 (11)
C8—C7—H7	122.1 (12)	C21—C22—C17	121.25 (13)
C9—C8—C7	120.53 (13)	C21—C22—H22	117.5 (10)
C9—C8—H8	120.1 (12)	C17—C22—H22	121.2 (10)
C7—C8—H8	119.3 (12)	C23—O3—H3	105.2 (15)
C8—C9—C10	121.24 (13)	O3—C23—C27	111.36 (14)
C8—C9—H9	120.1 (11)	O3—C23—H23A	105.5 (13)
C10—C9—H9	118.7 (11)	C27—C23—H23A	111.4 (12)
O2—C10—N2	118.68 (12)	O3—C23—H23B	111.9 (12)

O2—C10—C9	125.51 (13)	C27—C23—H23B	108.7 (12)
N2—C10—C9	115.81 (12)	H23A—C23—H23B	108.0 (18)
C6—N2—C10	123.38 (11)	C23—C27—H27A	111.5 (13)
C6—N2—C2	120.64 (11)	C23—C27—H27B	111.8 (14)
C10—N2—C2	115.96 (11)	H27A—C27—H27B	106.9 (19)
C12—C11—C16	119.21 (13)	C23—C27—H24C	114.3 (14)
C12—C11—C3	119.47 (12)	H27A—C27—H24C	104.9 (19)
C16—C11—C3	121.29 (13)	H27B—C27—H24C	106.9 (18)
C11—C12—C13	120.41 (13)		
C3—N1—C1—O1	-169.50 (15)	O2—C10—N2—C6	-179.66 (13)
C3—N1—C1—C2	10.07 (10)	C9—C10—N2—C6	0.0 (2)
O1—C1—C2—N2	48.6 (2)	O2—C10—N2—C2	2.08 (19)
N1—C1—C2—N2	-130.96 (12)	C9—C10—N2—C2	-178.23 (12)
O1—C1—C2—C3	170.04 (16)	C1—C2—N2—C6	91.16 (15)
N1—C1—C2—C3	-9.51 (10)	C3—C2—N2—C6	-11.68 (18)
C1—N1—C3—C4	103.63 (12)	C1—C2—N2—C10	-90.52 (15)
C1—N1—C3—C11	-124.33 (11)	C3—C2—N2—C10	166.63 (12)
C1—N1—C3—C2	-9.91 (10)	N1—C3—C11—C12	-169.74 (12)
N2—C2—C3—N1	131.01 (12)	C4—C3—C11—C12	-38.58 (16)
C1—C2—C3—N1	8.69 (9)	C2—C3—C11—C12	93.21 (14)
N2—C2—C3—C4	19.32 (17)	N1—C3—C11—C16	11.90 (18)
C1—C2—C3—C4	-103.00 (12)	C4—C3—C11—C16	143.06 (13)
N2—C2—C3—C11	-112.49 (13)	C2—C3—C11—C16	-85.15 (16)
C1—C2—C3—C11	125.18 (12)	C16—C11—C12—C13	-0.9 (2)
N1—C3—C4—C5	-108.95 (14)	C3—C11—C12—C13	-179.34 (12)
C11—C3—C4—C5	117.78 (14)	C11—C12—C13—C14	-0.4 (2)
C2—C3—C4—C5	-14.19 (18)	C12—C13—C14—C15	1.1 (2)
N1—C3—C4—C17	69.97 (15)	C13—C14—C15—C16	-0.5 (2)
C11—C3—C4—C17	-63.30 (16)	C14—C15—C16—C11	-0.8 (2)
C2—C3—C4—C17	164.74 (11)	C12—C11—C16—C15	1.5 (2)
C17—C4—C5—C6	-177.45 (13)	C3—C11—C16—C15	179.91 (13)
C3—C4—C5—C6	1.4 (2)	C5—C4—C17—C22	173.82 (14)
C4—C5—C6—C7	-172.23 (14)	C3—C4—C17—C22	-5.06 (19)
C4—C5—C6—N2	7.7 (2)	C5—C4—C17—C18	-4.3 (2)
N2—C6—C7—C8	0.1 (2)	C3—C4—C17—C18	176.83 (13)
C5—C6—C7—C8	-179.91 (13)	C22—C17—C18—C19	1.0 (2)
C6—C7—C8—C9	0.0 (2)	C4—C17—C18—C19	179.15 (13)
C7—C8—C9—C10	-0.2 (2)	C17—C18—C19—C20	-0.7 (2)
C8—C9—C10—O2	179.80 (15)	C18—C19—C20—C21	-0.5 (2)

C8—C9—C10—N2	0.1 (2)	C19—C20—C21—C22	1.4 (2)
C7—C6—N2—C10	-0.2 (2)	C20—C21—C22—C17	-1.2 (2)
C5—C6—N2—C10	179.88 (12)	C18—C17—C22—C21	0.0 (2)
C7—C6—N2—C2	178.02 (13)	C4—C17—C22—C21	-178.21 (13)
C5—C6—N2—C2	-1.94 (19)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.92 (2)	1.92 (2)	2.8305 (17)	168 (2)
O3—H3···O2	0.98 (3)	1.71 (3)	2.6651 (16)	165 (2)

Symmetry code: (i) -*x*, -*y*+1, -*z*+1.

Computing details

Data collection: Bruker *APEX* 2; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2013* (Sheldrick, 2013); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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Isolation and structure determination of the first example of the azeto[2,3-*c*]quinolizinedione ring system

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ABSTRACT

An unexpected azeto[2,3-*c*]quinolizinedione has been isolated during synthetic studies on the base catalyzed condensation of ethyl 6-methylpyridin-2(1*H*)-on-1-ylacetate with benzil. Closure of a fused four-membered azetidinone ring occurred when potassium hexamethyldisilazide was employed as the base. The structure of the product was confirmed by synchrotron X-ray crystallography. A possible mechanism for the formation of the product is considered.

Introduction

4*H*-Quinolizin-4-one[1] **1** and 2*H*-quinolizin-2-one[2] **2** (Fig. 1) represent neutral carbonyl-bearing derivatives of the quinolizinium ring[3] system **3**, a bridgehead azanaphthalene. Such compounds have potential application in drug development as alternatives to quinoline **4** and isoquinoline **5** derivatives, which are much exploited in medicinal chemistry.[4]

A number of quinolizin-4-one based drug candidates have been developed,[5,6] but considerable scope remains to employ this ring as a central building block in drug discovery. As part of a project to develop synthetic routes to quinolizin-4-ones **1** as new drug scaffolds we investigated the deprotonation of 1(*N*)-alkyl-6-methylpyridin-2-ones and the possibility of condensation with 1,2-dicarbonyl compounds to form the second fused pyridine ring. In this Letter we report the unexpected formation of an azeto[2,3-*c*]quinolizinedione that was isolated from the reaction of **6** with benzil **7a** (Scheme 1).

Results and discussion

During a study on the deprotonation of pyridone **6** (Scheme 1) with potassium hexamethyldisilazide (KHMDS), we investigated the reaction with benzil **7a** as a 1,2-bis electrophile, using 2.75 equiv of the base, with the expectation of performing a Westphal-type condensation[7] to form quinazolin-4-one **8**. However the reaction formed a complex mixture of products, and none of the expected quinolizinone ester **8** was obtained after chromatographic separation of the crude reaction mixture.[8] Surprisingly, the only compound that could be obtained pure was the fused azetidinone **9**, in which the quinolizin-4-one ring skeleton had formed, but which bore a fused 4-membered lactam ring.

The presence of a 4-membered lactam ring in the molecule was strongly suggested by a combination of IR and NMR spectroscopy. In particular, the IR spectrum showed a signal at 1776 cm^{-1} indicating the presence of a small ring carbonyl group. The ^1H NMR spectrum showed an exchangeable signal at δ 10.29 ppm consistent with an NH and a methine singlet at δ 5.86 ppm (H-9a). The absence of signals for an ethyl ester indicated that this group had

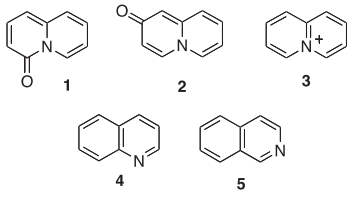

Figure 1. Azanaphthalene rings employed in medicinal chemistry.

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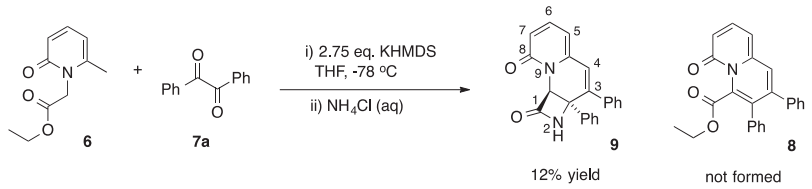


Scheme 1. Reaction of activated pyridone **6** with benzil.

been transformed. The ^{13}C NMR spectrum exhibited a signal at δ 68.1 ppm consistent with a saturated CH (C-9a) and two carbonyl signals at δ 164.7 and 160.5 ppm. The structure of the molecule was verified by single crystal X-ray diffraction analysis, confirming the presence of the 4-membered lactam, which was shown to exist as a mono-ethanol solvate **9**·EtOH (Fig. 2).

Yellow crystals with a plate morphology were formed after slow evaporation of an ethanolic solution of **9**. Due to their small size and weak diffracting power, data were collected using synchrotron radiation.[9] The molecules were found to form head-to-tail $R_4^4(18)$ H-bonded pairs via inserted ethanol molecules.[10–12] The hydrogen bond geometry is given in Table 1.

The formation of the fused azetidinone product **9** was unexpected and several mechanisms for generation of the 4-membered lactam ring compound can be considered. It is not clear how the nitrogen atom of the 4-membered lactam ring was introduced into the molecule, or the order of the ring forming steps. The azetidinone nitrogen is most likely derived from the hexamethyldisilazane (HMDS) formed as a by-product during deprotonation. The most plausible mechanism we propose here (Scheme 2) involves formation of the ester enolate **10** by deprotonation of **6** with KHMDS, and reaction of the resulting HMDS, or the excess KHMDS, with benzil **7a** to form either the mono- (**7b**) or bis-imine (**7c**). Either electrophile could then condense with anion **10** to form the azetidinone derivative **11**. The reaction of imines with ester enolates is a well established method to form medicinally important 4-membered lactams.[13] Subsequent deprotonation of the 6-methyl group of the pyridone ring would generate enolate **12**, the *cis* diastereoisomer of which could undergo intramolecular aldol reaction with the ketone (X = O) or silylimine (X = $NSiMe_3$) group forming **13**. Subsequent elimination would then generate the observed product **9**, which was isolated after aqueous work-up.

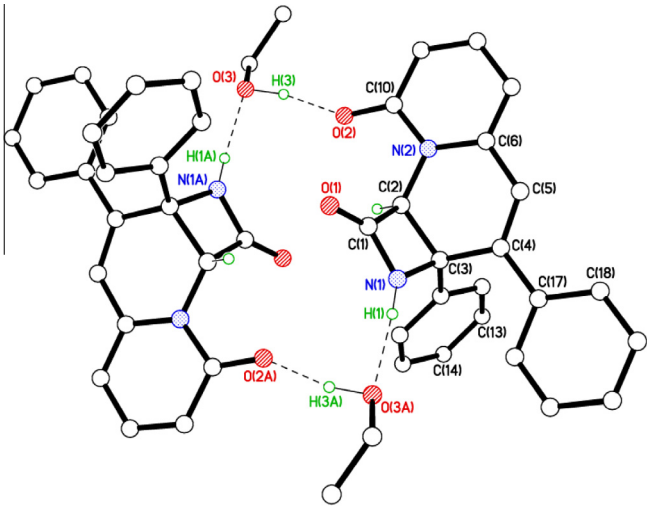
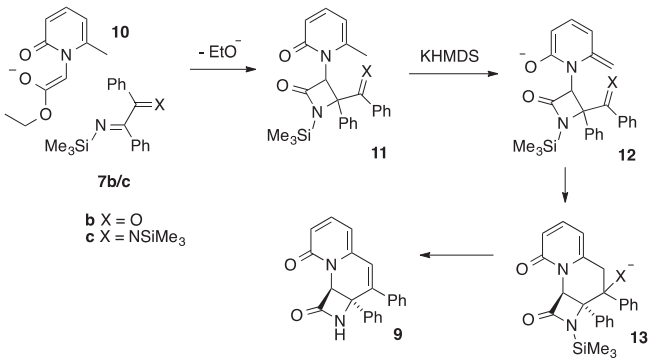


Figure 2. X-ray crystal structure of azeto[2,3-*c*]quinolizinedione, **9**·EtOH, showing the ethanol-inserted hydrogen-bonds between pairs of molecules of **9**.

Table 1
Hydrogen-bond geometry (Å, °) for **9**·EtOH

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3(A)	0.92 (2)	1.92 (2)	2.8305 (17)	168 (2)
O3—H3···O2	0.98 (3)	1.71 (3)	2.6651 (16)	165 (2)

Symmetry code: (A) $-x, -y+1, -z+1$.



Scheme 2. Possible mechanism for formation of azeto[2,3-*c*]quinolizine **9**.

An initial aldol reaction occurring next to the ester group was supported by the observation that deprotonation of **6** with one equivalent of KHMDS and quenching with D_2O at −78 °C led to deuterium incorporation predominantly at the methylene group of the acetate [δ_H $(CD_3)_2SO$ 4.79 (s, CH_2), 4.77 (bs, CHD) and δ_C 43.5 (CH_2), 43.3 (t, J_{CD} = 22 Hz, CHD)] rather than at the pyridone methyl substituent. Other pathways to give **9** can be conceived, and the mechanism of the reaction is under further investigation. Very few examples of compounds in which a β-lactam ring is fused to an otherwise unsaturated naphthalene type ring are known,[14–17] and, to the best of our knowledge, none to an unsaturated heterocyclic framework. Compounds of type **9** are likely to exhibit useful biological activity, and further work to improve the yield and scope of this reaction is in progress.

Conclusion

The first example of a derivative of the tricyclic azeto[2,3-*c*]quinolizine-1,8-dione ring system has been isolated and its structure confirmed by NMR spectroscopy, mass spectrometry, and single crystal synchrotron X-ray diffraction analysis.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compound **9**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.029.

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8. Experimental procedure for compound **9**.
   2a,3-Diphenyl-2,2a-dihydro-1H-azeto[2,3-c]quinolizine-1,8(9aH)-dione[18]
   Ethyl 2-(6-methyl-2-oxopyridin-1(2*H*)-yl)acetate (0.362 g, 1.85 mmol) and benzil (0.369 g, 1.75 mmol, 0.95 equiv) were dissolved in anhydrous THF (10 mL) and the mixture was cooled to −78 °C and stirred for 10 min. KHMDS (0.5 M solution in toluene, 10.2 mL, 5.08 mmol, 2.75 equiv) was added at −78 °C and the mixture was stirred and allowed to warm-up to room temperature overnight. The reaction mixture was treated with saturated aqueous ammonium chloride (6 mL). The THF was removed under vacuum, and the remaining mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford a dark yellow oil, which was subjected to gradient column chromatography (light petroleum/ethyl acetate) (100:0 to 0:100) to afford 78 mg of a yellow solid. The solid fraction was recrystallized from ethanol to afford the mono-ethanol solvate of the title compound, 80 mg, 12% yield, as yellow plate crystals, mp 249–250 °C, IR (KBr) ν_{max} 3350–2700 (NH), 1776 (C=O), 1654 (C=O), 1613 (CC=OC), 1535 (NH), 795–731 (CH Arom.) cm^{-1}, ^{1}H (δ ppm, 400 MHz, DMSO-d_6) 10.29 (1H, s, exchanges with D_2O), 7.56 (1H, dd, J = 9.2 Hz, J = 6.8 Hz), 7.43–7.40 (2H, m), 7.36–7.33 (4H, m), 7.27–7.24 (5H, m), 6.60 (1H, d, J = 6.8 Hz), 6.45 (1H, d, J = 9.2 Hz), 5.56 (1H, s), ^{13}C (δ ppm, 100 MHz, DMSO-d_6) 164.7 (C=O), 160.5 (C=O), 141.7 (C), 140.7 (CH), 140.5 (C), 140.4 (C), 140.3 (C), 135.4 (C), 129.6 (2CH), 129.3 (CH), 128.9 (2CH), 128.4 (CH), 128.0 (2CH), 125.3 (2CH), 120.5 (CH), 120.1 (CH), 108.8 (CH), 68.1 (CH), HRMS [ES] m/z found 341.1286 $(M+H)^+$ $C_{22}H_{17}N_2O_2$ requires 341.1285.
9. Diffraction data for **9**·EtOH were collected at the Advanced Light Source Station 11.3.1 using silicon 111 monochromated, synchrotron X-radiation on a Bruker Apex 2 CCD diffractometer.[19] Data were corrected for Lp effects and for absorption, based on repeated and symmetry equivalent reflections.[20] The structure was solved by direct methods and refined by full matrix least squares on F^2.[20] All non-H atoms were refined anisotropically. H atom positions and U_{iso} values were freely refined. The structure refinement was routine. $C_{22}H_{16}N_2O_2{\cdot}C_2H_6O$, M = 386.43, triclinic, a = 9.106(3), b = 9.418(3), c = 11.674(4) Å, α = 84.373(5), β = 85.471(5), γ = 72.114(5)°, U = 946.9(5) Å^3, T = 100(2) K, space group $P\bar{1}$, Z = 2, λ = 0.7749 Å, μ = 0.11 mm^{-1}, 12999 reflections measured, 5677 unique (R_{int} = 0.050), $R1$ for 4237 data with $I > 2\sigma(I)$ = 0.055, $wR2$ for all data = 0.157.
   CCDC 1400522 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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