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** (Figure 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]

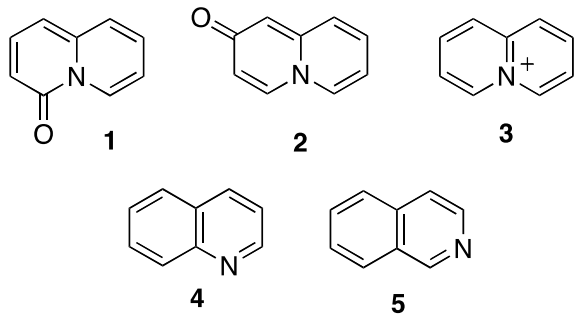
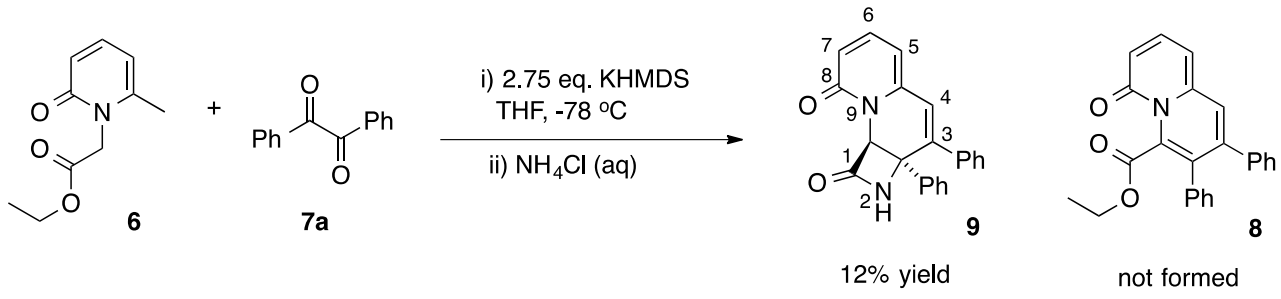


Figure 1: Azanaphthalene rings employed in medicinal chemistry

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 paper 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 equivalents 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.



Scheme 1: Reaction of activated pyridone **6** with benzil

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 ^{1}H 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 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 (Figure 2).

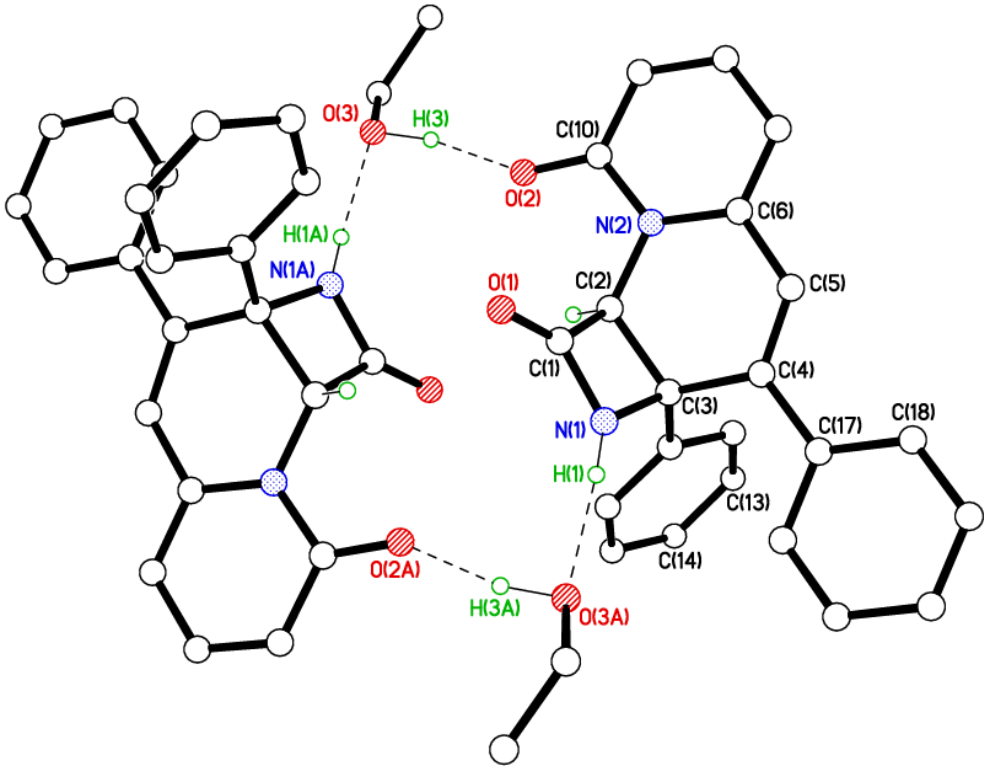


Figure 2: X-ray crystal structure of azeto[2,3-*c*]quinolizinedione, **9**·EtOH, showing the ethanol-inserted hydrogen-bonds between pairs of molecules of **9**.

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.

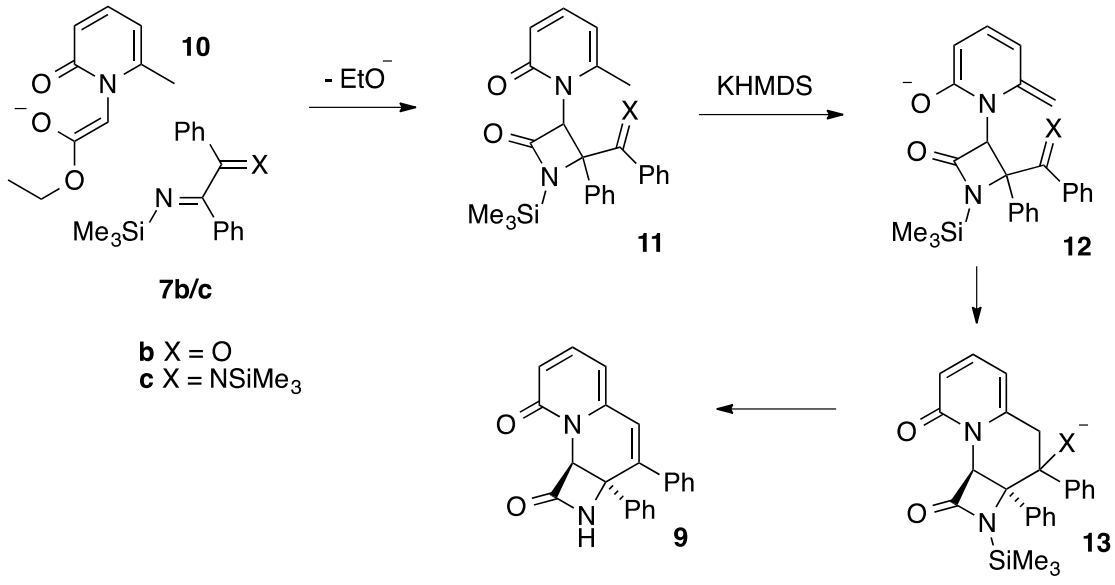
Table 1. Hydrogen-bond geometry (Å, º) for **9**·EtOH

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 **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.



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.

Acknowledgements

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Supplementary Data

Supplementary data showing the ^{1}H and ^{13}C NMR spectra of compound **9** is available.

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8. Experimental procedure for compound **9**

*2a,3-Diphenyl-2,2a-dihydro-1*H*-azeto[2,3-*c*]quinolizine-1,8(9a*H*)-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 eq.) 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 eq.) 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, m.p. 249-250 °C, IR (KBr) ν_{max} 3350-2700 (NH), 1776 (C=O), 1654 (C=O), 1613 (C=C), 1535 (NH), 795-731 (CH Arom.) cm^{-1}, ^1H (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, and solved by direct methods.[20] Structures were 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) ^{o}, 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>2σ(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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