

Paths of analysis*

(re)(re)(re)Analysis 1381 - Heterocycle

Synthia

November 28, 2023

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: Expert-Coded Rules

Published Reactions: SPRESI by DeepMatter, USPTO, Enzyme-Catalyzed Reactions

Filters: Cut All Heterocycles

Max. paths returned: 50

Max. iterations: 2000

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 10 \$/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 15

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Shorter paths: no

Pathway linearity: COMBO

Protecting groups: BALANCED

*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

Reaction scoring formula: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 100000 * (\text{FILTERS} + \text{CONFLICT} + \text{NON_SELECTIVITY}) + 40 * \text{PROTECT}$

Chemical scoring formula: $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

Min. search width: 400

Max. reactions per product: 60

2 Paths

1 path found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

2.1 Path 1

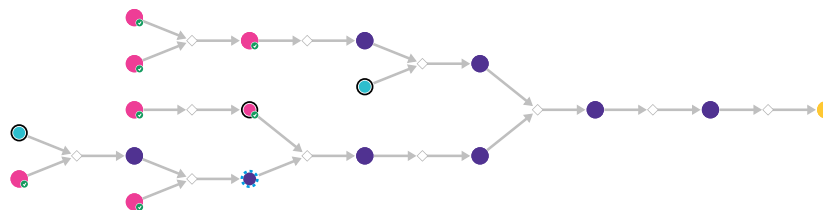
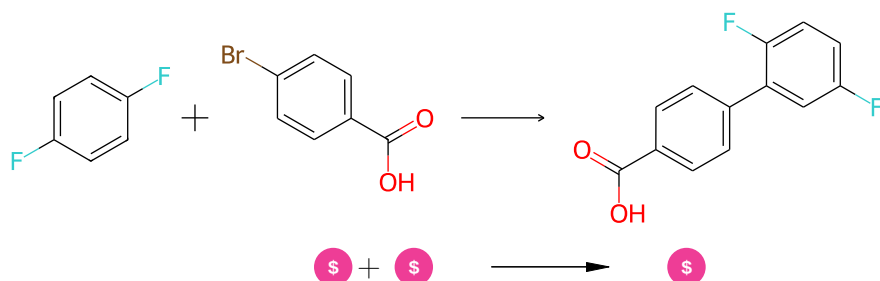


Figure 1: Outline of path 1

2.1.1 Directed Ortho Metalation followed by Reaction with Electrophile



Substrates:

1. 4-Bromobenzoic acid - *available at Sigma-Aldrich*
2. 1,4-Difluorobenzene - *available at Sigma-Aldrich*

Products:

1. 4-(2,5-Difluorophenyl)benzoic acid - *available at Sigma-Aldrich*

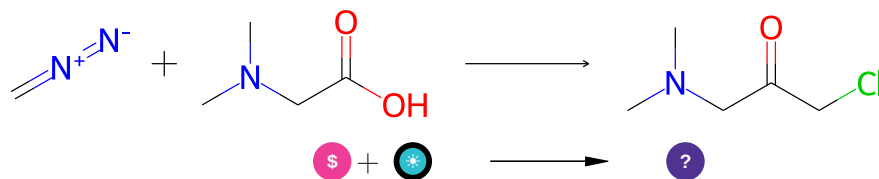
Typical conditions: RLi.or.LiNR2.-78C.THF.then.ArBr.PdCl2dppf.or.Pd-PEPPSI

Protections: none

Reference: [10.1016/S0040-4039\(00\)60805-5](#) and [10.1002/anie.201306427](#)

Retrosynthesis ID: 4383

2.1.2 Synthesis of alfa-haloketone



Substrates:

1. N,N-Dimethylglycine - *available at Sigma-Aldrich*
2. Diazomethane

Products:

1. CN(C)CC(=O)CCl

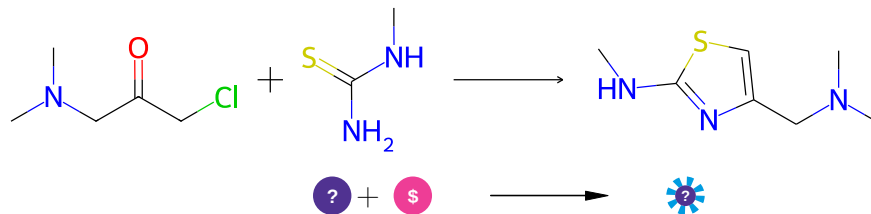
Typical conditions: 1.ClCOOEt.2.CH2N2.HX

Protections: none

Reference: [10.1021/jm00047a007](#) and [10.1016/j.bmcl.2015.06.066](#) and [10.1021/ja982893p](#) and [10.1016/S0040-4020\(02\)00629-4](#)

Retrosynthesis ID: 10001754

2.1.3 Synthesis of thiazoles from thioureas



Substrates:

1. CN(C)CC(=O)CCl
2. N-methylthiourea - *available at Sigma-Aldrich*

Products:

1. CNc1nc(CN(C)C)cs1

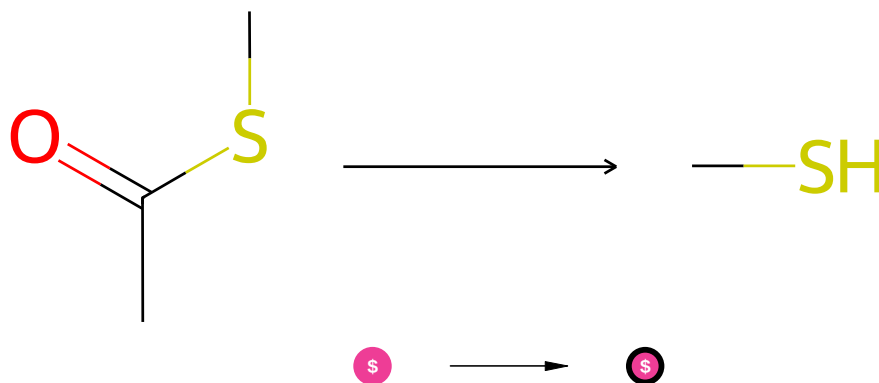
Typical conditions: ethanol.80C

Protections: none

Reference: DOI:[10.1021/jo00103a021](https://doi.org/10.1021/jo00103a021)

Retrosynthesis ID: 4

2.1.4 Hydrolysis of thioesters



Substrates:

1. S-Methyl thioacetate - *available at Sigma-Aldrich*

Products:

1. Methanethiol - *available at Sigma-Aldrich*

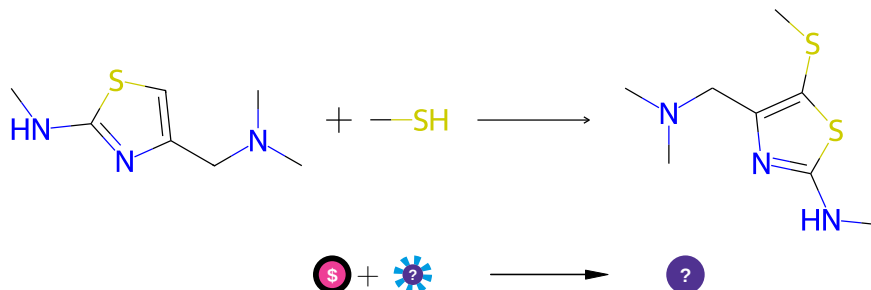
Typical conditions: K₂CO₃.MeOH.rt

Protections: none

Reference: [10.1021/ja2082334](https://doi.org/10.1021/ja2082334) (supporting info p14) and [10.1002/anie.200902843](https://doi.org/10.1002/anie.200902843) (supporting info p5)

Retrosynthesis ID: 22941

2.1.5 Directed Ortho Metalation followed by Reaction with Electrophile



Substrates:

1. Methanethiol - *available at Sigma-Aldrich*
2. CNc1nc(CN(C)C)cs1

Products:

1. CNc1nc(CN(C)C)c(SC)s1

Typical conditions: 1. Disulfide formation from RSH in oxidizing conditions
 2. nBuLi.-78C.then.RSSR.to.rt.then H^+

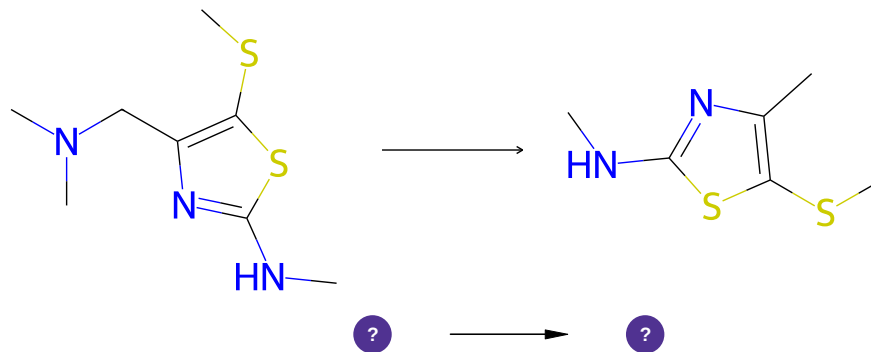
Protections:

| Functional group SMARTS | Classification | Protecting groups |
|---------------------------------|----------------|---|
| <chem>[CX4,c][NH][CX4,c]</chem> | amines | N-Benzyl N-Triphenylmethyl N-Benzyloxymethyl N-Di(p-methoxyphenyl)methyl N-Allyl N-Methoxymethyl |

Reference: [10.1021/ja010489b](#) and [10.1039/b502195b](#)

Retrosynthesis ID: 4087

2.1.6 Deamination of benzylic amines



Substrates:

1. CNc1nc(CN(C)C)c(SC)s1

Products:

1. CNc1nc(C)c(SC)s1

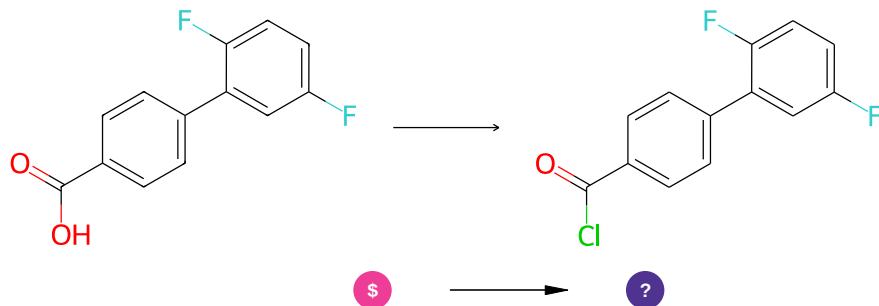
Typical conditions: H₂.Pd/C

Protections: none

Reference: [10.1021/ja070588a](#)

Retrosynthesis ID: 21173

2.1.7 Synthesis of acid chlorides from carboxylic acids



Substrates:

1. 4-(2,5-Difluorophenyl)benzoic acid - *available at Sigma-Aldrich*

Products:

1. O=C(Cl)c1ccc(-c2cc(F)ccc2F)cc1

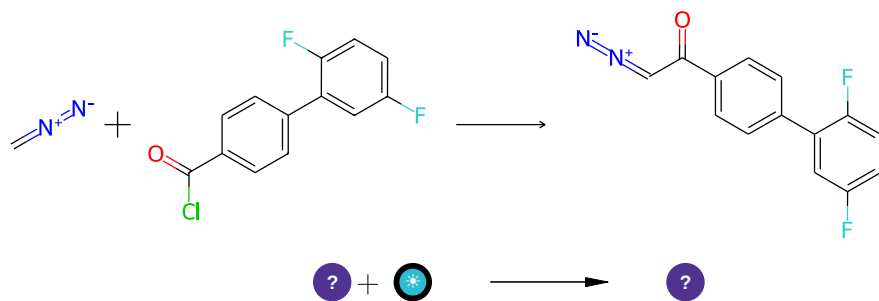
Typical conditions: oxalyl.chloride.or.SOCl2

Protections: none

Reference: [10.1002/adsc.200303011](#) and [10.3390/50500714](#)

Retrosynthesis ID: 24405

2.1.8 Synthesis of alpha-diazoketones



Substrates:

1. O=C(Cl)c1ccc(-c2cc(F)ccc2F)cc1
2. Diazomethane

Products:

1. [N-]=[N+]=CC(=O)c1ccc(-c2cc(F)ccc2F)cc1

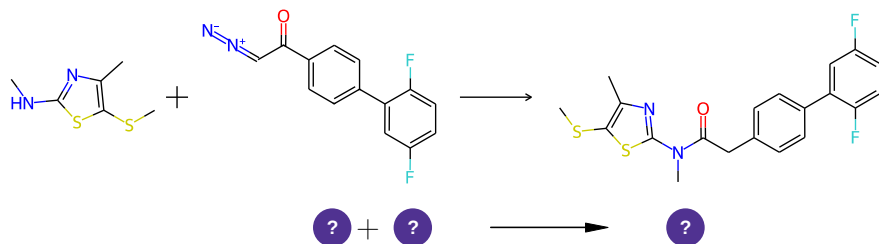
Typical conditions: EtOH.DCM.RT

Protections: none

Reference: DOI: [10.1021/ja00202a042](#)

Retrosynthesis ID: 238

2.1.9 Formation of ketenes via Wolff rearrangement followed by amidation



Substrates:

1. CNc1nc(C)c(SC)s1
2. [N-]=[N+]=CC(=O)c1ccc(-c2cc(F)ccc2F)cc1

Products:

1. CSc1sc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

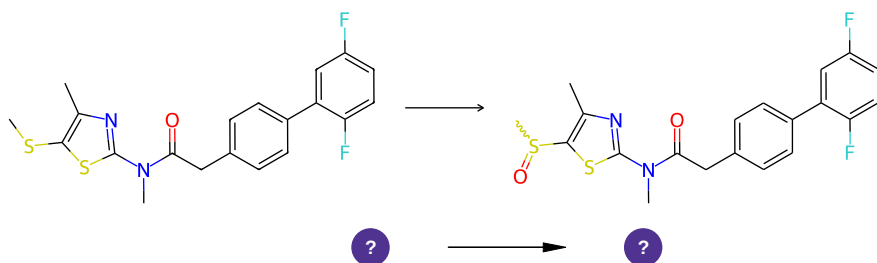
Typical conditions: 1. Ag(I)(cat).hv 2. Amine

Protections: none

Reference: [10.1002/9781118939901.ch3](#) and [10.1002/1099-0690\(200207\)2002:14<2193::AID-EJOC2193>3.0.CO;2-D](#)

Retrosynthesis ID: 31010020

2.1.10 Oxidation of sulfides to sulfoxides



Substrates:

1. CSc1sc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

Products:

1. Cc1nc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)sc1S(C)=O

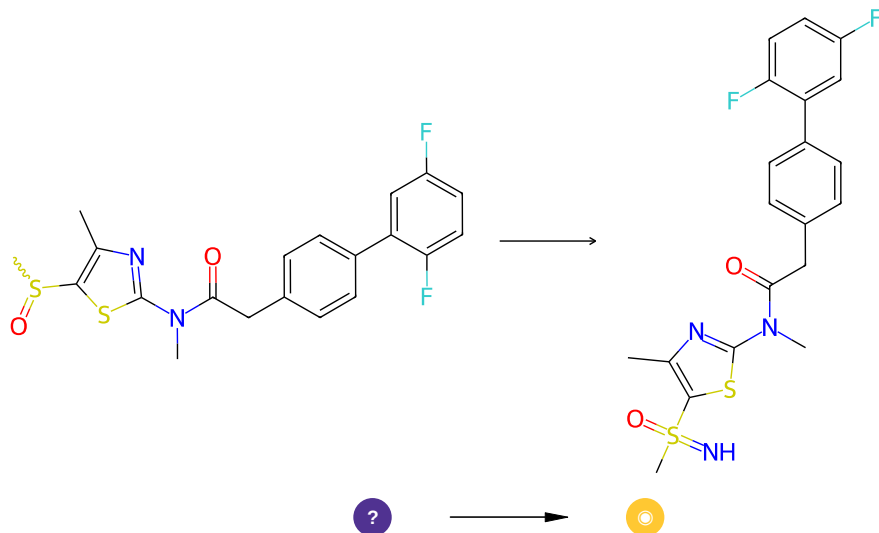
Typical conditions: TaC.H₂O₂.MeOH.45C

Protections: none

Reference: DOI: [10.1055/s-0029-1219947](#) or DOI: [10.1055/s-2008-1067019](#)

Retrosynthesis ID: 10584

2.1.11 Synthesis of NH-sulfoximines



Substrates:

1. Cc1nc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)sc1S(C)=O

Products:

1. Cc1nc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)sc1S(C)(=N)=O

Typical conditions: NaN₃.Eaton's reagent.50C or FeSO₄.1,10-phen.NbzONH₂*TfOH.MeCN or H₂NCO₂NH₄.PhI(OAc)₂.MeOH

Protections: none

Reference: [10.1016/j.tetlet.2016.12.031](#) and [10.1002/anie.201710498](#) and [10.1002/anie.201602320](#) and [10.1055/s-0036-1590874](#) and [10.1039/C7CC03386A](#)

Retrosynthesis ID: 31016630