

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

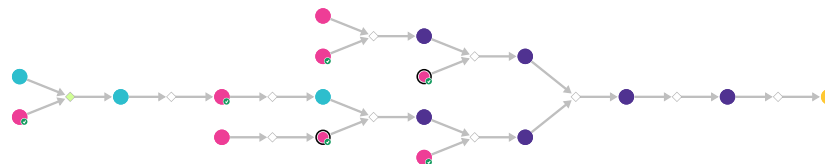
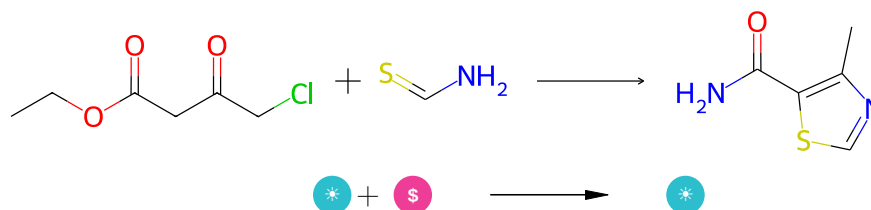


Figure 1: Outline of path 1

2.1.1 Published reaction



Substrates:

1. Thioformamide
2. Ethyl chloroacetoacetate - *available at Sigma-Aldrich*

Products:

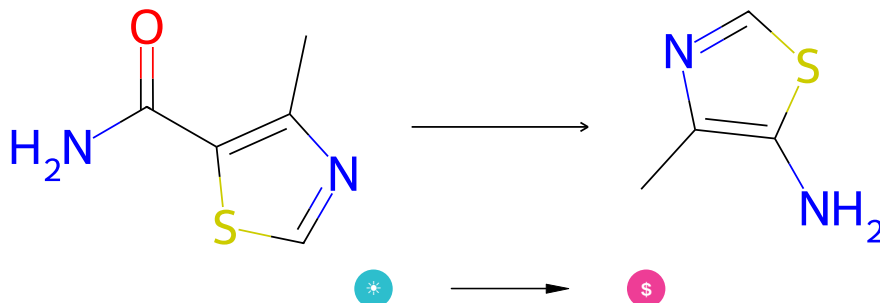
1. 4-Methyl-thiazole-5-carboxylic acid amide

Protections: none

Reference: US20100087448A1

Retrosynthesis ID: 8591586

2.1.2 Hofmann rearrangement



Substrates:

1. 4-Methyl-thiazole-5-carboxylic acid amide

Products:

1. 4-Methylthiazol-5-amine - *available at Sigma-Aldrich*

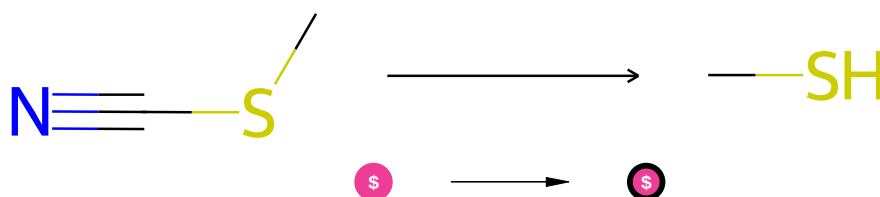
Typical conditions: Br₂.OH-

Protections: none

Reference: [10.1021/jo00912a019](#)

Retrosynthesis ID: 11480

2.1.3 Reduction of thiocyanates to thiols



Substrates:

1. Methyl thiocyanate

Products:

1. Methanethiol - *available at Sigma-Aldrich*

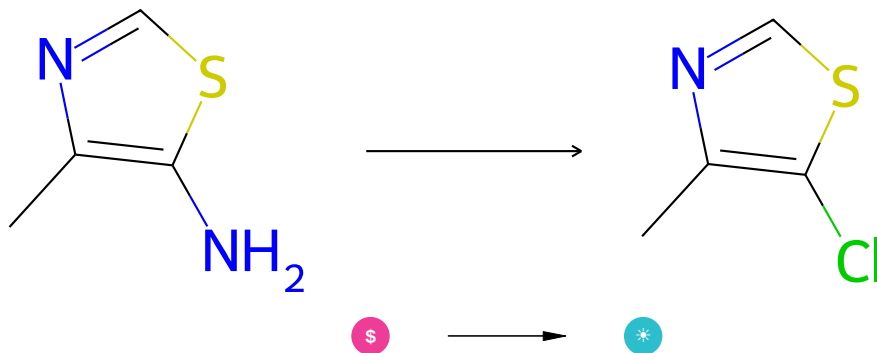
Typical conditions: NaBH₄.EtOH

Protections: none

Reference: [10.1021/jm100213c](#) p. 4864, 4873 and [10.1016/j.ejmech.2014.09.071](#) p. 308, 310

Retrosynthesis ID: 50811

2.1.4 Sandmeyer Reaction



Substrates:

1. 4-Methylthiazol-5-amine - *available at Sigma-Aldrich*

Products:

1. 4-Methyl-5-chlorothiazole

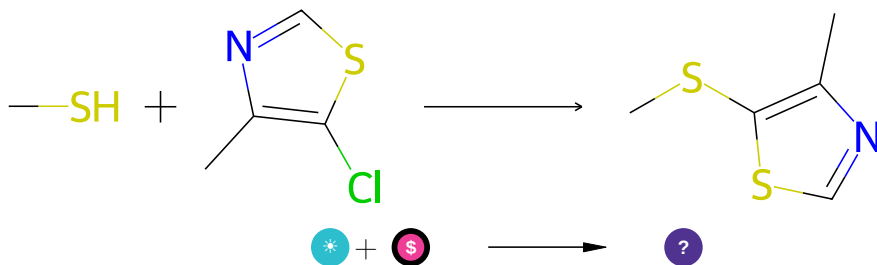
Typical conditions: $t\text{-BuONO}\cdot\text{CuCl}_2$ or $\text{TMSCl}\cdot\text{MeCN}$.reflux or $\text{NaNO}_2\cdot\text{HCl}\cdot\text{CuCl}$

Protections: none

Reference: [10.1016/j.ejmech.2013.01.046](https://doi.org/10.1016/j.ejmech.2013.01.046) and [10.1021/jm040185a](https://doi.org/10.1021/jm040185a) and [10.1021/acs.jmedchem.5b00152](https://doi.org/10.1021/acs.jmedchem.5b00152) and [10.1021/ja066472g](https://doi.org/10.1021/ja066472g) (SI, page S14) and [10.1021/jm3012273](https://doi.org/10.1021/jm3012273) and [10.1002/ejoc.201001395](https://doi.org/10.1002/ejoc.201001395) and [10.1002/ejic.201501400](https://doi.org/10.1002/ejic.201501400) and [10.1016/j.bmcl.2011.08.073](https://doi.org/10.1016/j.bmcl.2011.08.073)

Retrosynthesis ID: 29905

2.1.5 Pd-catalyzed synthesis of aryl sulfides



Substrates:

1. 4-Methyl-5-chlorothiazole
2. Methanethiol - *available at Sigma-Aldrich*

Products:

1. CSc1scnc1C

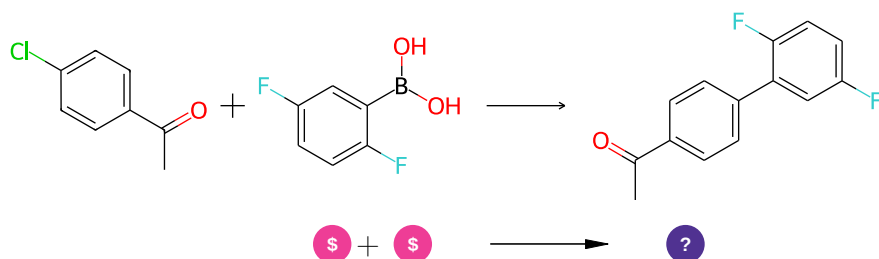
Typical conditions: Pd(OAc)₂.tBuONa.DME.110C

Protections: none

Reference: [10.1021/ja0580340](#)

Retrosynthesis ID: 1299

2.1.6 Suzuki coupling with aryl chlorides



Substrates:

1. 2,5-Difluorophenylboronic acid - *Combi-Blocks*
2. 4-Chloroacetophenone - *available at Sigma-Aldrich*

Products:

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

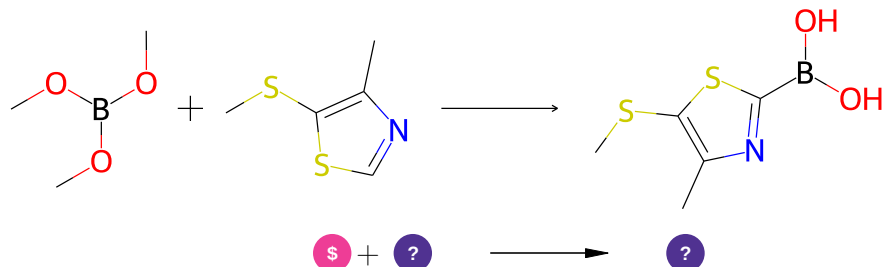
Typical conditions: [Pd].catalyst.base.

Protections: none

Reference: [10.1002/anie.201108608](#) and [10.1002/anie.200801465](#) and [10.1055/s-0033-1338293](#) and [10.1039/c1cc10708a](#) and [10.1055/s-0030-1260169](#) and [10.1016/j.tet.2005.05.071](#) and [10.1038/s41929-020-00564-z](#) (metal-free coupling)

Retrosynthesis ID: 26284

2.1.7 Directed metalation followed by reaction with electrophile



Substrates:

1. Methyl borate - *available at Sigma-Aldrich*
2. CSc1scnc1C

Products:

1. CSc1sc(B(O)O)nc1C

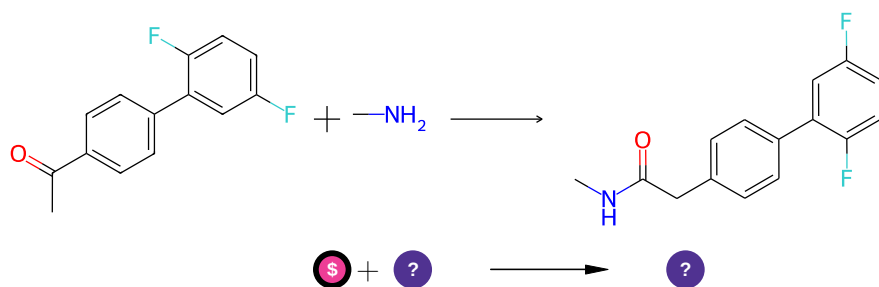
Typical conditions: RLi.or.LiNR₂.-78C.THF.then.B(OR)₃

Protections: none

Reference: [10.1016/S0040-4039\(01\)02342-5](#) (Fig. 1) and [10.1016/j.tet.2009.06.023](#) (Scheme 2) and [10.1016/j.ejmech.2013.04.054](#) (Scheme 1) and [10.1016/j.tet.2011.01.030](#) (Scheme 4) and [10.1021/ol3019665](#) (SI p.7)

Retrosynthesis ID: 31022435

2.1.8 Willgerodt-Kindler Reaction



Substrates:

1. Methanamine - *available at Sigma-Aldrich*
2. CC(=O)c1ccc(-c2cc(F)ccc2F)cc1

Products:

1. CNC(=O)Cc1ccc(-c2cc(F)ccc2F)cc1

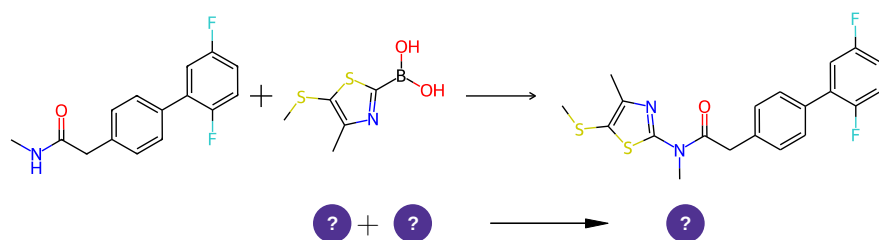
Typical conditions: (NH₄)₂S.H₂O

Protections: none

Reference: [10.1039/C3CS60154D](#)

Retrosynthesis ID: 11694

2.1.9 Chan-Lam Coupling



Substrates:

1. CSc1sc(B(O)O)nc1C
2. CNC(=O)Cc1ccc(-c2cc(F)ccc2F)cc1

Products:

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

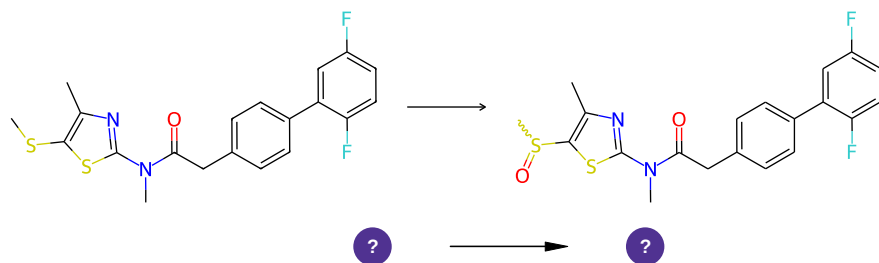
Typical conditions: Cu(OAc)₂.Et₃N.DCM

Protections: none

Reference: [10.1016/S0040-4039\(98\)00503-6](#)

Retrosynthesis ID: 31015962

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

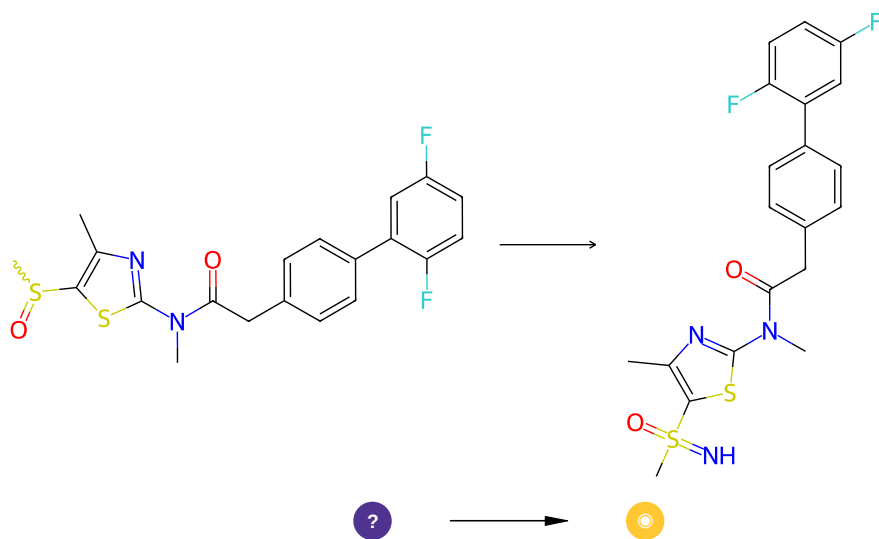
Typical conditions: TaC.H₂O₂.MeOH.45C

Protections: none

Reference: DOI: [10.1055/s-0029-1219947](https://doi.org/10.1055/s-0029-1219947) or DOI: [10.1055/s-2008-1067019](https://doi.org/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](https://doi.org/10.1016/j.tetlet.2016.12.031) and [10.1002/anie.201710498](https://doi.org/10.1002/anie.201710498) and [10.1002/anie.201602320](https://doi.org/10.1002/anie.201602320) and [10.1055/s-0036-1590874](https://doi.org/10.1055/s-0036-1590874) and [10.1039/C7CC03386A](https://doi.org/10.1039/C7CC03386A)

Retrosynthesis ID: 31016630