

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

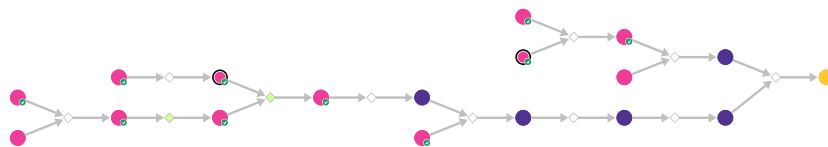
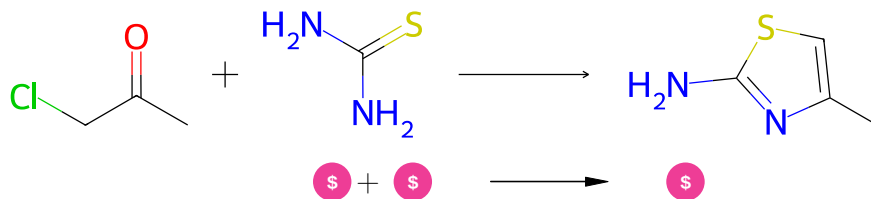


Figure 1: Outline of path 1

2.1.1 Synthesis of thiazoles from thioureas



Substrates:

1. Chloroacetone - *available at Sigma-Aldrich*
2. Thiourea

Products:

1. 2-Amino-4-methylthiazole - *available at Sigma-Aldrich*

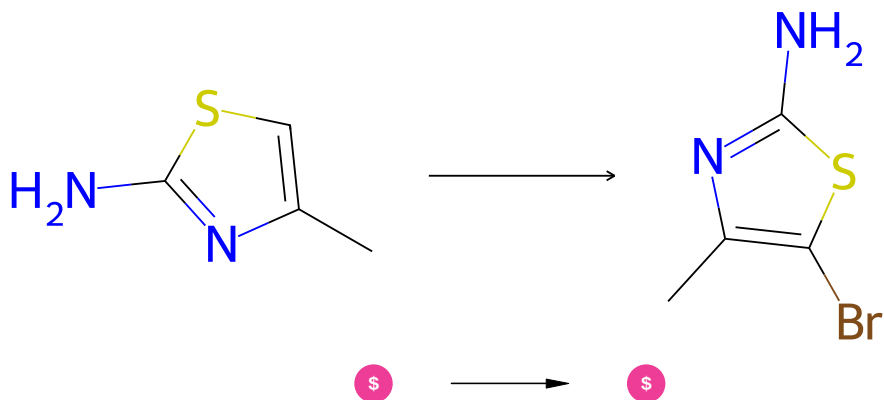
Typical conditions: ethanol.80C

Protections: none

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

Retrosynthesis ID: 4

2.1.2 Published reaction



Substrates:

1. 2-Amino-4-methylthiazole - *available at Sigma-Aldrich*

Products:

1. 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*

Typical conditions: Br₂

Protections: none

Reference: PATENT: INSTITUT DE RECHERCHES CHIMIQUES ET BIOLOGIQUES APPLIQUEES; FR2658514, 1993

Retrosynthesis ID: 2753330

2.1.3 Synthesis of thiols from disulfides



Substrates:

1. Methyl disulfide - *available at Sigma-Aldrich*

Products:

1. Methanethiol - *available at Sigma-Aldrich*

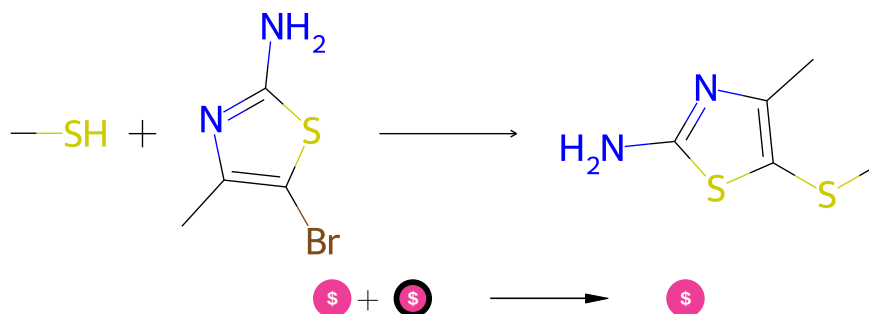
Typical conditions: NaBH₄.THF.0 C or NaBH₄.EtOH.70 C

Protections: none

Reference: [10.1021/jm0510880](#) p. 4073, 4080 and [10.1016/S0968-0896\(00\)00257-1](#) p. 504, 506

Retrosynthesis ID: 10982

2.1.4 Published reaction



Substrates:

- 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*
- Methanethiol - *available at Sigma-Aldrich*

Products:

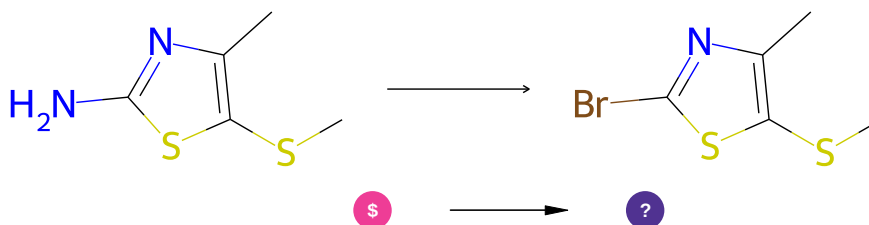
- 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US20090143448A1

Retrosynthesis ID: 8454157

2.1.5 Sandmeyer Reaction



Substrates:

1. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

Products:

1. CSc1sc(Br)nc1C

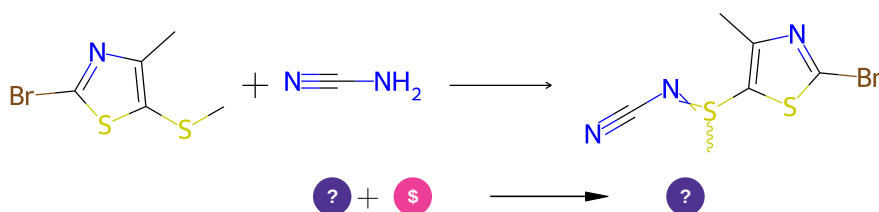
Typical conditions: IsoAmONO or t-BuONO.CuBr2.MeCN or HBr.CuBr2.NaNO2

Protections: none

Reference: [10.1002/chem.201600278](#) and [10.1016/j.bmcl.2011.12.131](#) and [10.1016/j.ejmech.2013.01.046](#) and [10.1021/jm0002782](#) and [10.1002/ejoc.201300443](#) and [10.1021/jo052589w](#) (SI, page S3) and [10.1021/jm800527x](#) and [10.1016/j.bmcl.2015.04.098](#) and [10.1021/ja034563x](#)

Retrosynthesis ID: 29904

2.1.6 Synthesis of N-cyano sulfilimines



Substrates:

1. CSc1sc(Br)nc1C
2. Cyanamide - *available at Sigma-Aldrich*

Products:

1. Cc1nc(Br)sc1S(C)=NC#N

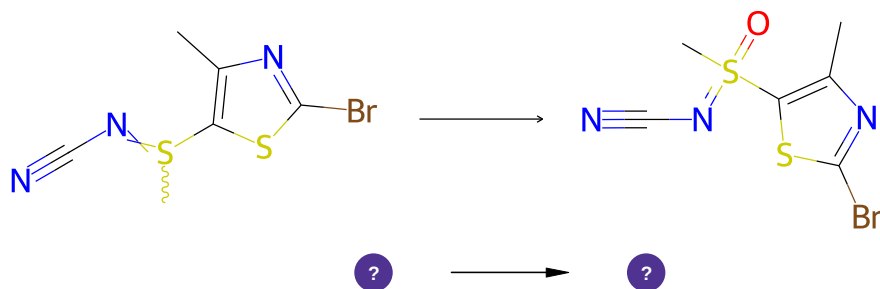
Typical conditions: PhI(OAc)2.CH₃CN.0C

Protections: none

Reference: US3505401A p.3-6 and [10.1021/ol7016577](#)

Retrosynthesis ID: 10033463

2.1.7 Synthesis of N-cyanosulfoximines by oxidation of N-cyano sulfilimines



Substrates:

1. Cc1nc(Br)sc1S(C)=NC#N

Products:

1. Cc1nc(Br)sc1S(C)(=O)=NC#N

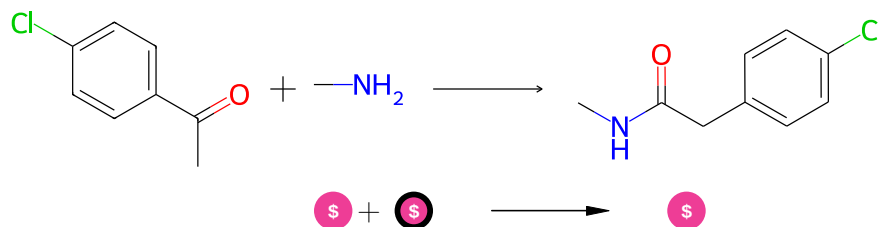
Typical conditions: mCPBA.MeOH.K₂CO₃

Protections: none

Reference: [10.1055/s-0030-1258192](#)

Retrosynthesis ID: 10037382

2.1.8 Willgerodt-Kindler Reaction



Substrates:

1. 4-Chloroacetophenone - *available at Sigma-Aldrich*
2. Methanamine - *available at Sigma-Aldrich*

Products:

1. 2-(4-Chlorophenyl)-N-methylacetamide - *available at Sigma-Aldrich*

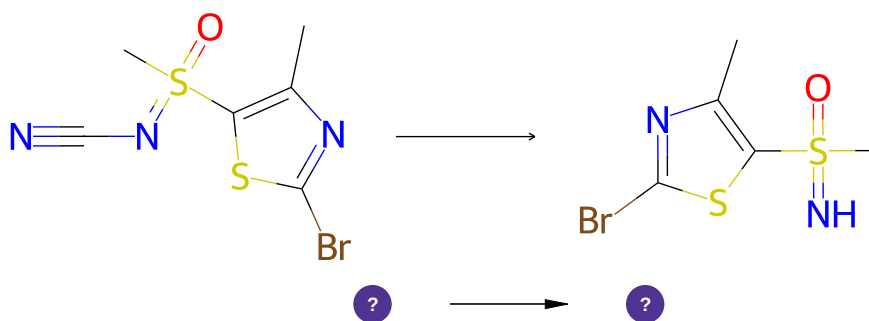
Typical conditions: (NH₄)₂S.H₂O

Protections: none

Reference: [10.1039/C3CS60154D](#)

Retrosynthesis ID: 11694

2.1.9 Synthesis of NH-sulfoximines by hydrolysis of N-cyano sulfoximines



Substrates:

1. Cc1nc(Br)sc1S(C)(=O)=NC#N

Products:

1. Cc1nc(Br)sc1S(C)(=N)=O

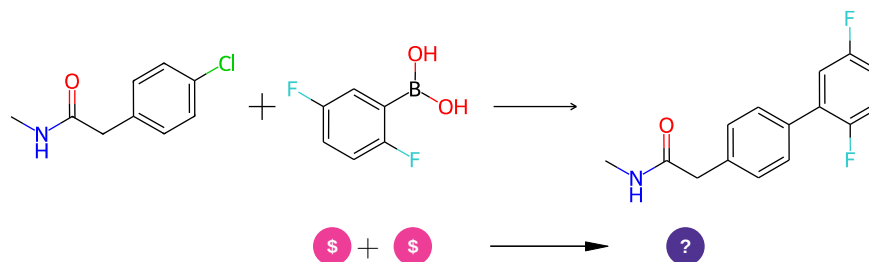
Typical conditions: H₂SO₄.H₂O or HCl.dioxane.H₂O

Protections: none

Reference: [10.1055/s-0034-1378936](#) and US2009029863 p.11

Retrosynthesis ID: 10037380

2.1.10 Suzuki coupling with aryl chlorides



Substrates:

1. 2-(4-Chlorophenyl)-N-methylacetamide - *available at Sigma-Aldrich*

2. 2,5-Difluorophenylboronic acid - *Combi-Blocks*

Products:

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

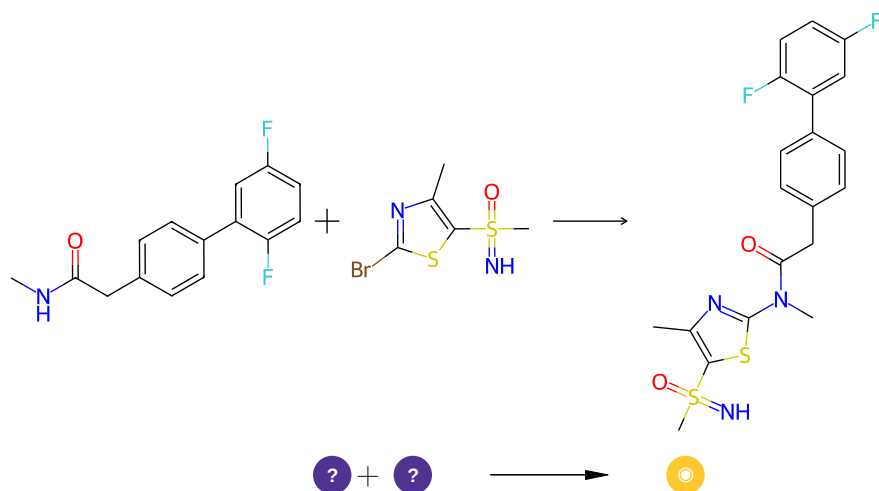
Typical conditions: [Pd].catalyst.base.

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

2.1.11 N-arylation of amides



Substrates:

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

2. Cc1nc(Br)sc1S(C)(=N)=O

Products:

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

Typical conditions: Cs₂CO₃.CuX₂/CuX.toluene.130C

Protections: none

Reference: [10.1021/ja012610k](#) and [10.1002/adsc.200700133](#) and [10.1021/jo701573w](#)

Retrosynthesis ID: 10207