

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: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 1000 * (\text{FILTERS} + \text{CONFLICT} + \text{NON_SELECTIVITY}) + 40 * \text{PROTECT}$

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

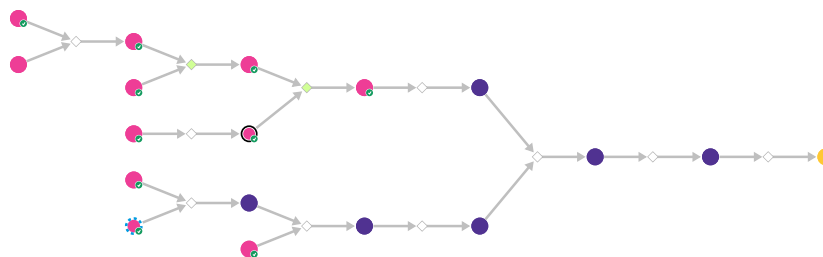
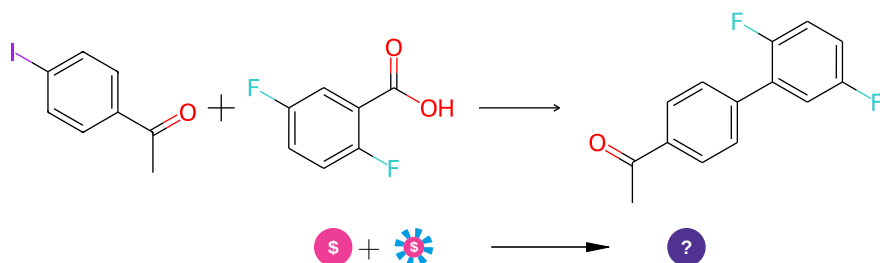


Figure 1: Outline of path 1

2.1.1 Decarboxylative cross-coupling



Substrates:

1. 2,5-Difluorobenzoic acid - *available at Sigma-Aldrich*
2. 4-Iodoacetophenone - *available at Sigma-Aldrich*

Products:

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

Typical conditions: eg. CuI.PdI2.phenanthroline.K2CO3.NMP.MS.170 deg C

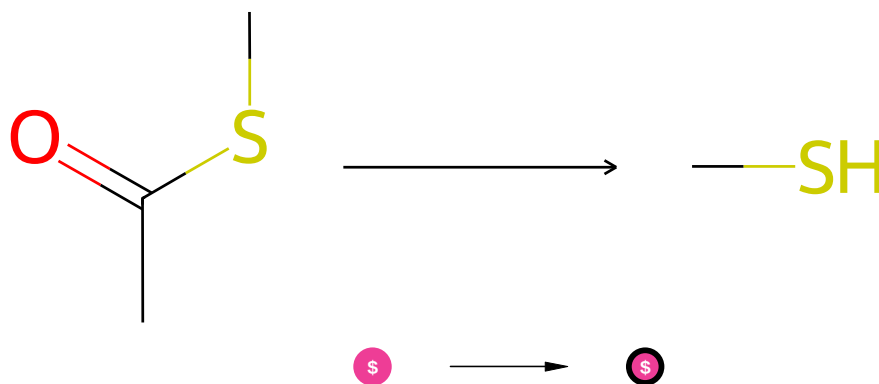
Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CX3](=[O])[CX4!H0]	carbonyls	1.3-Dioxanes 1.3-Dioxolanes Dimethyl Acetals and Ketals 5-Methylene-1.3-dioxanes 4-o-Nitrophenyl-1.3-dioxolanes O-Trimethylsilyl Cyanohydrins

Reference: [10.1039/C1CS15093F](#) and [10.1002/anie.200800728](#) and [10.1021/ja068993+](#) and [10.1016/j.tet.2009.04.047](#) and [10.1021/jacs.0c06244](#)

Retrosynthesis ID: 31019483

2.1.2 Hydrolysis of thioesters



Substrates:

1. S-Methyl thioacetate - [available at Sigma-Aldrich](#)

Products:

1. Methanethiol - [available at Sigma-Aldrich](#)

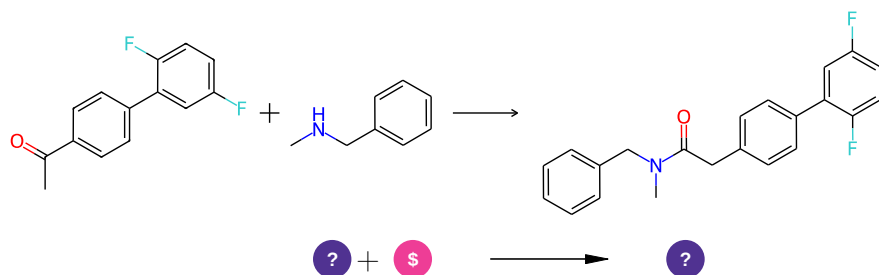
Typical conditions: K2CO3.MeOH.rt

Protections: none

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

Retrosynthesis ID: 22941

2.1.3 Willgerodt-Kindler Reaction



Substrates:

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

Products:

1. CN(Cc1ccccc1)C(=O)Cc1ccc(-c2cc(F)ccc2F)cc1

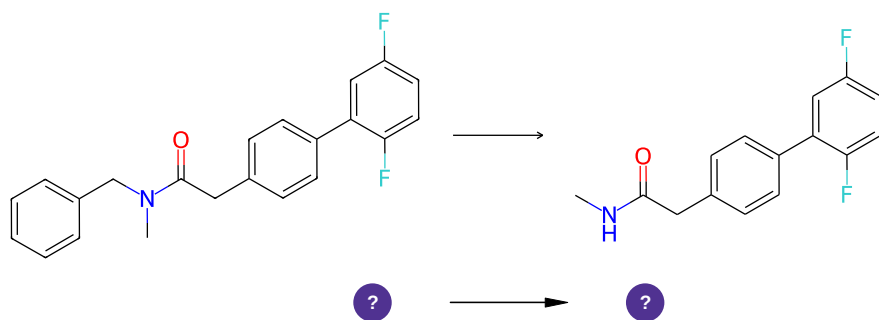
Typical conditions: (NH₄)₂S.H₂O

Protections: none

Reference: [10.1039/C3CS60154D](#)

Retrosynthesis ID: 11695

2.1.4 Debenzylation



Substrates:

1. CN(Cc1ccccc1)C(=O)Cc1ccc(-c2cc(F)ccc2F)cc1

Products:

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

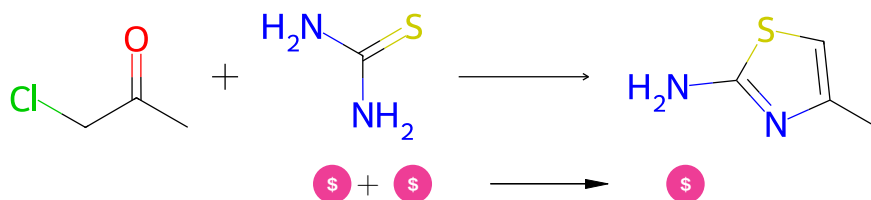
Typical conditions: H₂. Pd/C or Pd(OH)₂

Protections: none

Reference: DOI: [10.1002/1521-3773\(20020603\)41:11<1895::AID-ANIE1895>3.0.CO;2-3](https://doi.org/10.1002/1521-3773(20020603)41:11<1895::AID-ANIE1895>3.0.CO;2-3) and [10.1021/jo400589j](https://doi.org/10.1021/jo400589j) and [10.1021/jm8012932](https://doi.org/10.1021/jm8012932) (SI,page S6) and [10.1080/00397911.2016.1261164](https://doi.org/10.1080/00397911.2016.1261164)

Retrosynthesis ID: 9995661

2.1.5 Synthesis of thiazoles from thioureas



Substrates:

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

Products:

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

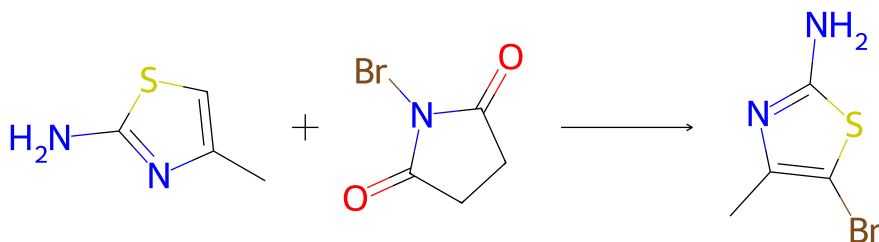
Typical conditions: ethanol.80C

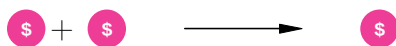
Protections: none

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

Retrosynthesis ID: 4

2.1.6 Published reaction





Substrates:

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

Products:

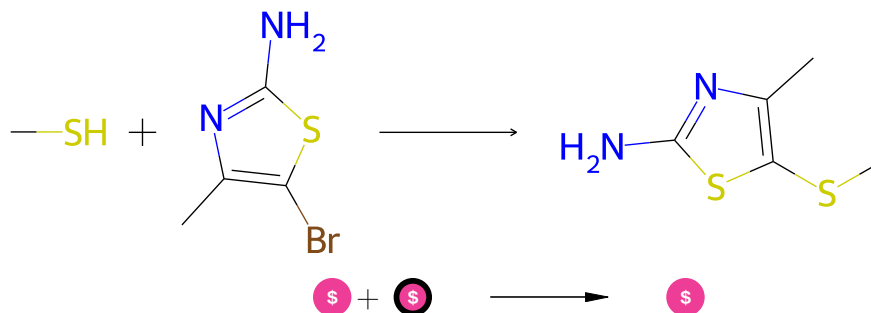
1. 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US05369107

Retrosynthesis ID: 6299162

2.1.7 Published reaction



Substrates:

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

Products:

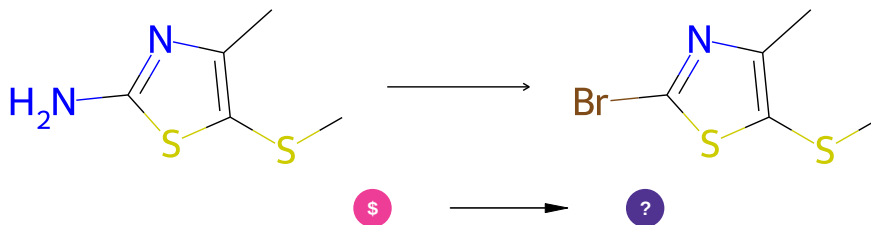
1. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US20090143448A1

Retrosynthesis ID: 8454157

2.1.8 Sandmeyer Reaction



Substrates:

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

Products:

1. CSc1sc(Br)nc1C

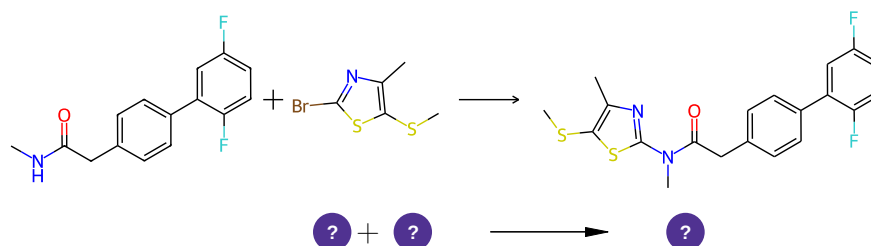
Typical conditions: IsoAmONO or t-BuONO.CuBr2.MeCN or HBr.CuBr2.NaNO2

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

2.1.9 N-arylation of amides



Substrates:

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

Products:

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

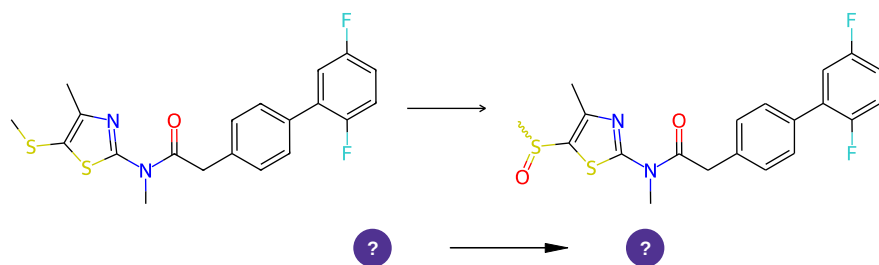
Typical conditions: Cs₂CO₃.CuX₂/CuX.toluene.130C

Protections: none

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

Retrosynthesis ID: 10207

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

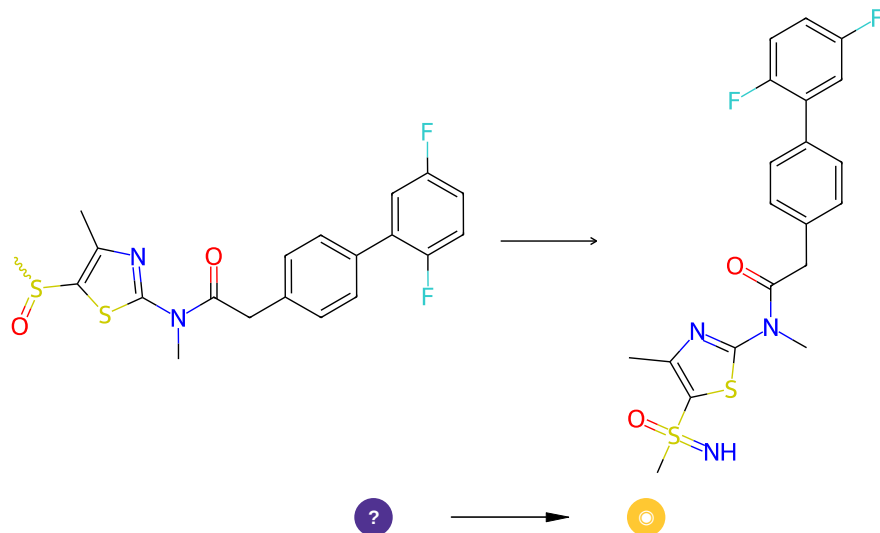
Typical conditions: TaC.H₂O₂.MeOH.45C

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