

Paths of analysis*

(re)Analysis 1381 - No Filter - Rerun

Synthia

November 28, 2023

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Saved Configuration: General

Rules: Expert-Coded Rules

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

Filters: none selected

Max. paths returned: 50

Max. iterations: 2000

Commercial:

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

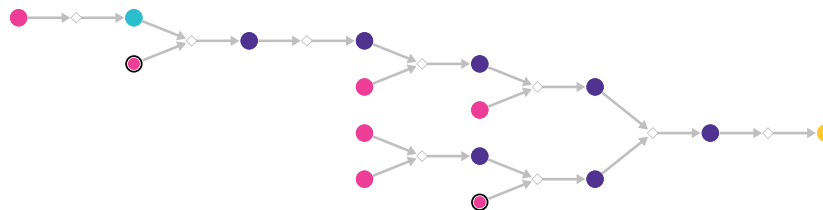
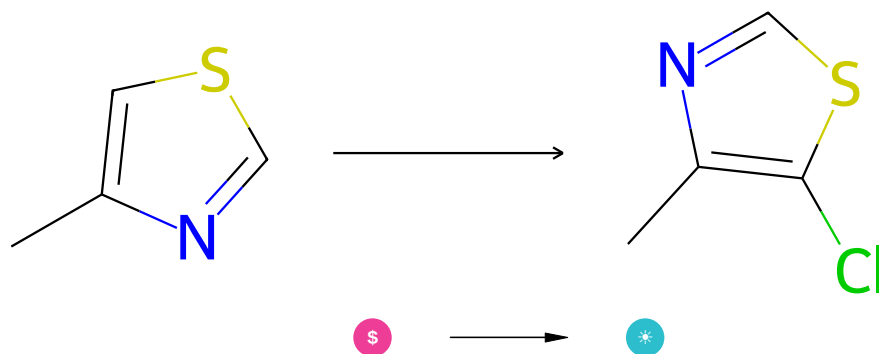


Figure 1: Outline of path 1

2.1.1 Chlorination of aromatic compounds



Substrates:

1. 4-Methylthiazole - *available at Sigma-Aldrich*

Products:

1. 4-Methyl-5-chlorothiazole

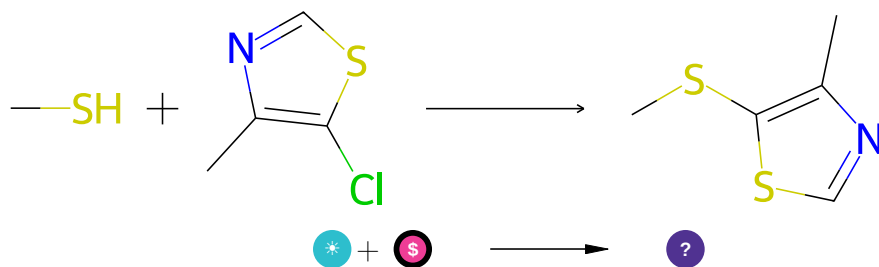
Typical conditions: Cl₂ or other chlorinating agent like NCS

Protections: none

Reference: DOI: [10.1007/s11178-005-0256-1](https://doi.org/10.1007/s11178-005-0256-1)

Retrosynthesis ID: 11125

2.1.2 Pd-catalyzed synthesis of aryl sulfides



Substrates:

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

Products:

1. CSc1scnc1C

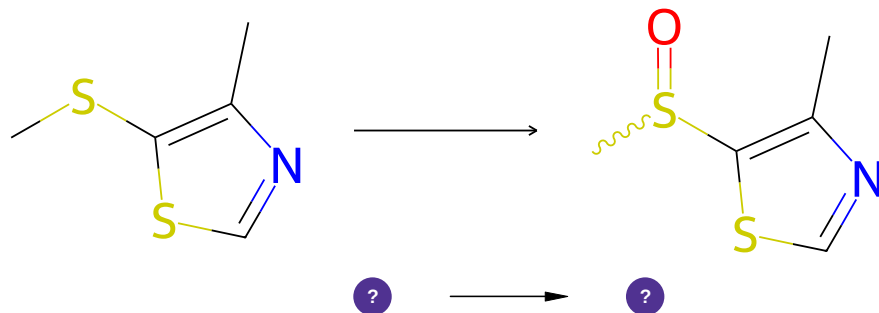
Typical conditions: Pd(OAc)₂.tBuONa.DME.110C

Protections: none

Reference: [10.1021/ja0580340](https://doi.org/10.1021/ja0580340)

Retrosynthesis ID: 1299

2.1.3 Oxidation of sulfides to sulfoxides



Substrates:

1. CSc1scnc1C

Products:

1. Cc1ncsc1S(C)=O

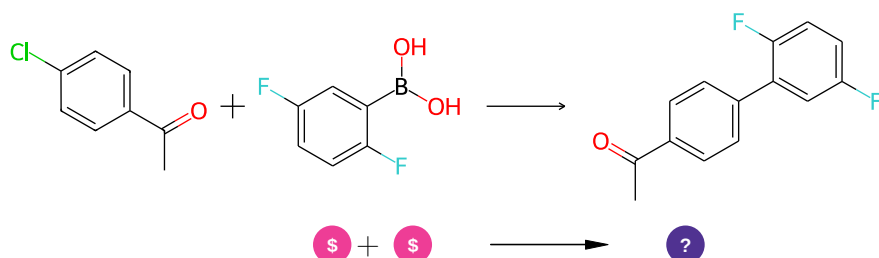
Typical conditions: TaC.H2O2.MeOH.45C

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

2.1.4 Suzuki coupling with aryl chlorides



Substrates:

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

Products:

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

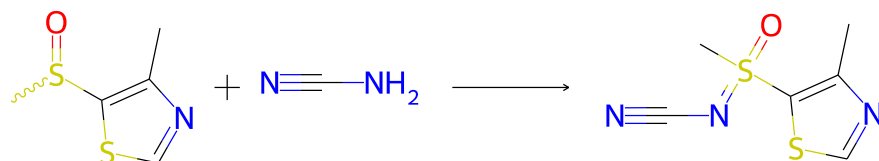
Typical conditions: [Pd].catalyst.base.

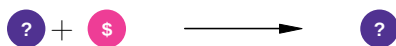
Protections: none

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

Retrosynthesis ID: 26284

2.1.5 Synthesis of N-cyano sulfilimines





Substrates:

1. Cc1ncsc1S(C)=O
2. Cyanamide - *available at Sigma-Aldrich*

Products:

1. Cc1ncsc1S(C)(=O)=NC#N

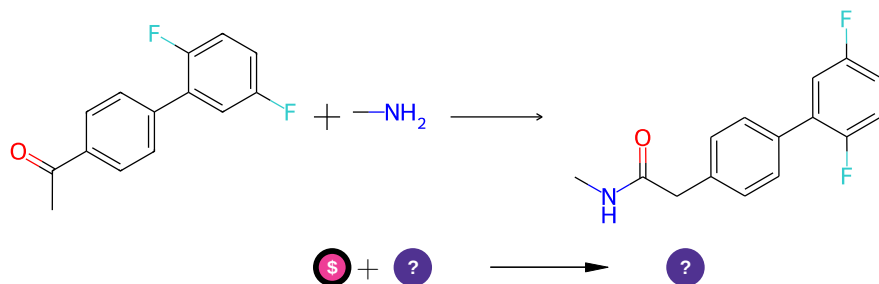
Typical conditions: PhI(OAc)2.CH3CN.0C

Protections: none

Reference: DOI: [10.1021/ol071302+](https://doi.org/10.1021/ol071302+)

Retrosynthesis ID: 50208

2.1.6 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

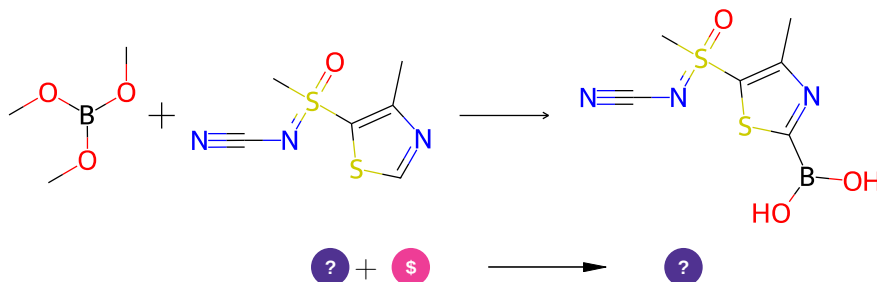
Typical conditions: (NH4)2S.H₂O

Protections: none

Reference: [10.1039/C3CS60154D](https://doi.org/10.1039/C3CS60154D)

Retrosynthesis ID: 11694

2.1.7 Directed metalation followed by reaction with electrophile



Substrates:

1. Cc1ncsc1S(C)(=O)=NC#N
2. Methyl borate - *available at Sigma-Aldrich*

Products:

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

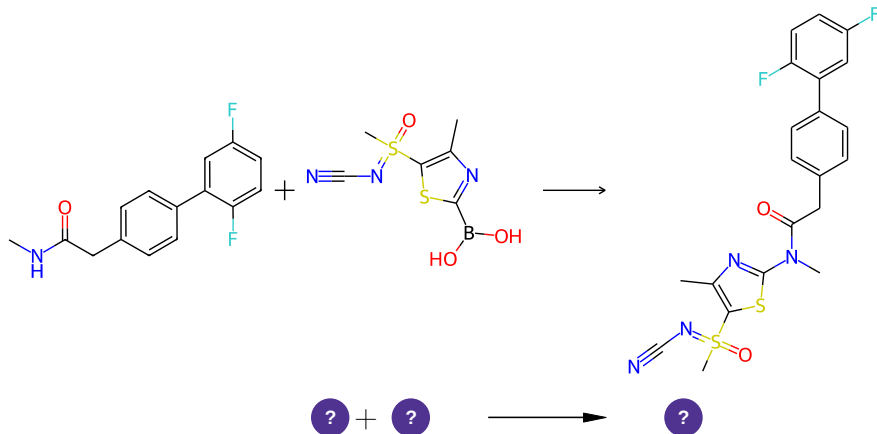
Typical conditions: RLi.or.LiNR₂.-78C.THF.then.B(OR)₃

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 Chan-Lam Coupling



Substrates:

1. CNC(=O)Cc1ccc(-c2cc(F)ccc2F)cc1
2. Cc1nc(B(O)O)sc1S(C)(=O)=NC#N

Products:

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

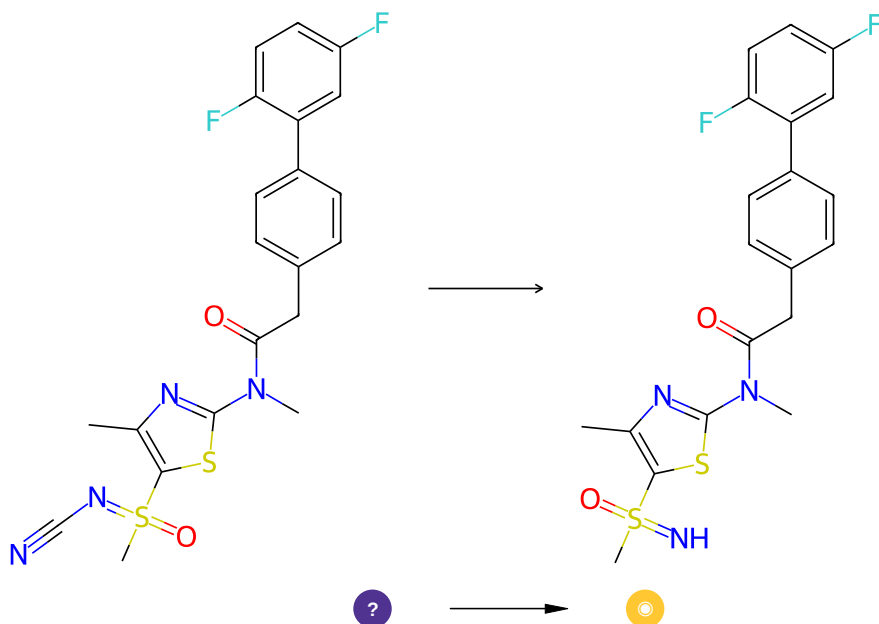
Typical conditions: Cu(Oac)₂.Et₃N.DCM

Protections: none

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

Retrosynthesis ID: 31015962

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



Substrates:

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

Products:

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