

Paths of analysis*

(re)(re)Analysis 1381 - \$10/g

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: none selected

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

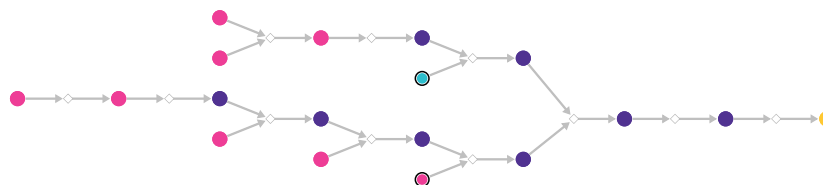
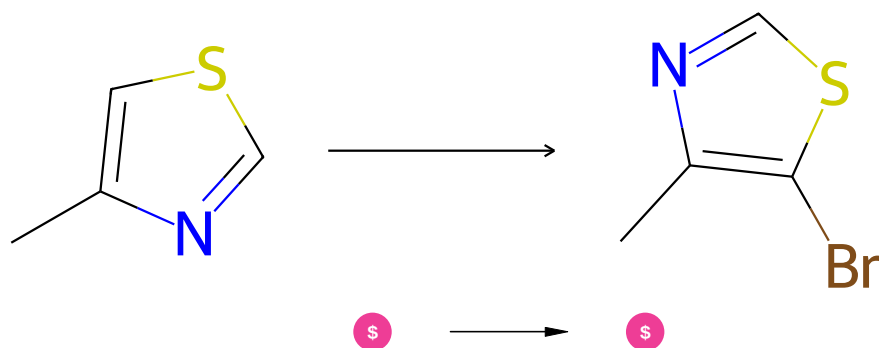


Figure 1: Outline of path 1

2.1.1 Bromination of aromatic compounds



Substrates:

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

Products:

1. 5-Bromo-4-methylthiazole - *available at Sigma-Aldrich*

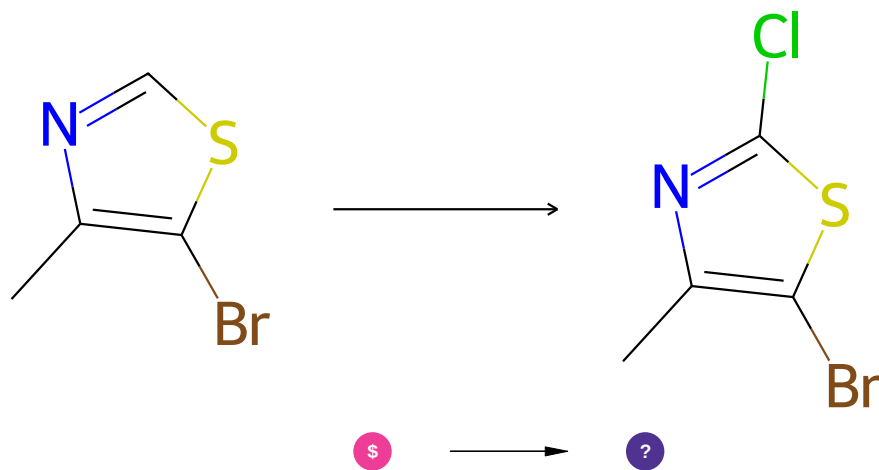
Typical conditions: Br₂.Fe

Protections: none

Reference: [10.1021/acs.accounts.6b00120](https://doi.org/10.1021/acs.accounts.6b00120)

Retrosynthesis ID: 7777000

2.1.2 Chlorination of aromatic compounds



Substrates:

1. 5-Bromo-4-methylthiazole - [available at Sigma-Aldrich](#)

Products:

1. Cc1nc(Cl)sc1Br

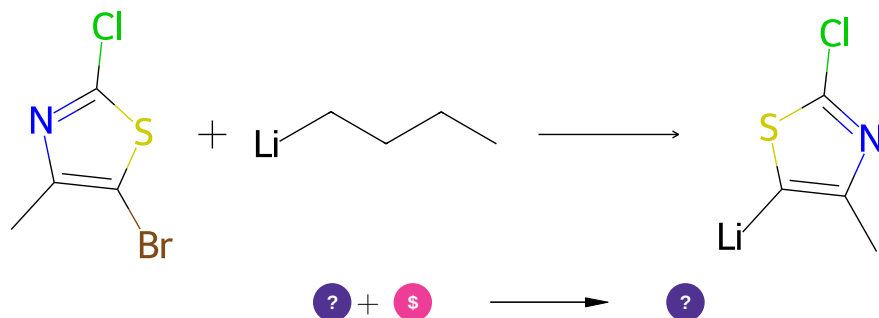
Typical conditions: Cl₂ or other chlorinating agent like NCS

Protections: none

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

Retrosynthesis ID: 11125

2.1.3 Br/Li exchange



Substrates:

1. Cc1nc(Cl)sc1Br
2. n-BuLi - *available at Sigma-Aldrich*

Products:

1. [Li]c1sc(Cl)nc1C

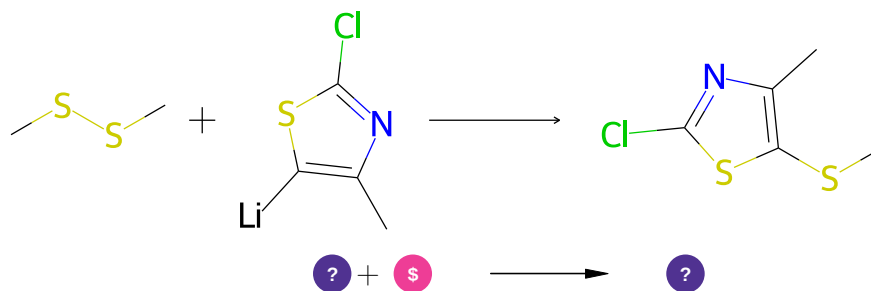
Typical conditions: nBuLi.or.tBuLi.THF.-78C

Protections: none

Reference: [10.1002/ejoc.201101490](https://doi.org/10.1002/ejoc.201101490) and [10.1016/j.tet.2012.03.058](https://doi.org/10.1016/j.tet.2012.03.058)
and [10.1016/j.tetlet.2015.01.032](https://doi.org/10.1016/j.tetlet.2015.01.032) and [10.1021/ja0541175](https://doi.org/10.1021/ja0541175) and [10.1016/j.tetlet.2016.06.123](https://doi.org/10.1016/j.tetlet.2016.06.123)

Retrosynthesis ID: 30672

2.1.4 Addition of electrophiles to lithiated arenes/heteroarenes



Substrates:

1. [Li]c1sc(Cl)nc1C
2. Methyl disulfide - *available at Sigma-Aldrich*

Products:

1. CSc1sc(Cl)nc1C

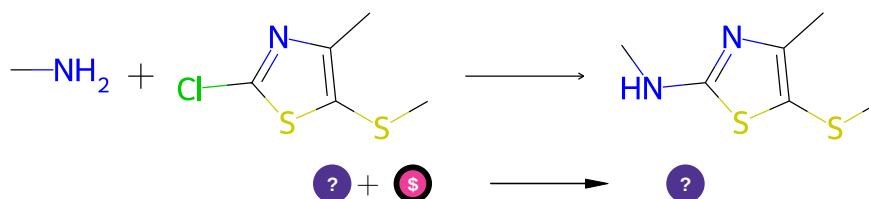
Typical conditions: THF

Protections: none

Reference: [10.1016/j.tet.2011.06.082](#) and [10.3987/COM-15-S\(T\)21](#) and [10.1021/ja2065522](#) (SI) and [10.1021/jm800824d](#) and [10.1021/ol2010837](#)

Retrosynthesis ID: 10019534

2.1.5 Amination of aryl chlorides



Substrates:

1. CSc1sc(Cl)nc1C
2. Methanamine - *available at Sigma-Aldrich*

Products:

1. CNc1nc(C)c(SC)s1

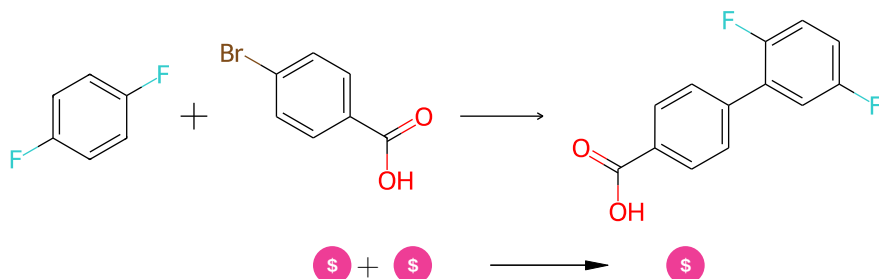
Typical conditions: [Pd].Ligand.base

Protections: none

Reference: [10.1021/ja903049z](#) and [10.1021/jo060945k](#) and [10.1021/jo060190h](#) and [10.1021/ja8055358](#) and [10.1021/ja068926f](#) and [10.1002/anie.200601612](#) and [10.1021/acscatal.0c04280](#)

Retrosynthesis ID: 28545

2.1.6 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*

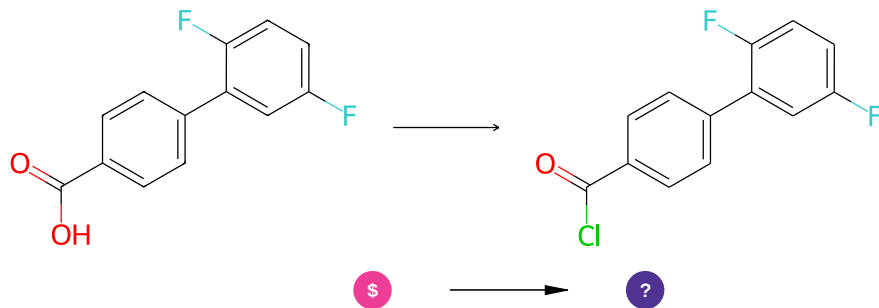
Typical conditions: RLi.or.LiNR₂.-78C.THF.then.ArBr.PdCl₂dppf.or.Pd-PEPPSI

Protections: none

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

Retrosynthesis ID: 4383

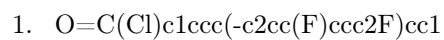
2.1.7 Synthesis of acid chlorides from carboxylic acids



Substrates:

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

Products:



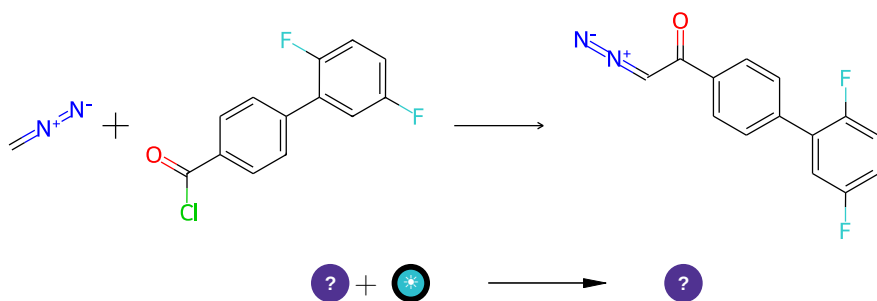
Typical conditions: oxalyl.chloride.or.SOCl₂

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

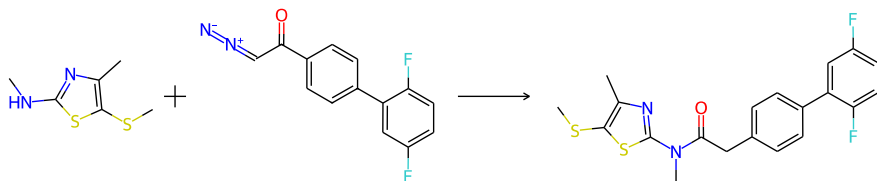
Typical conditions: EtOH.DCM.RT

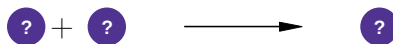
Protections: none

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

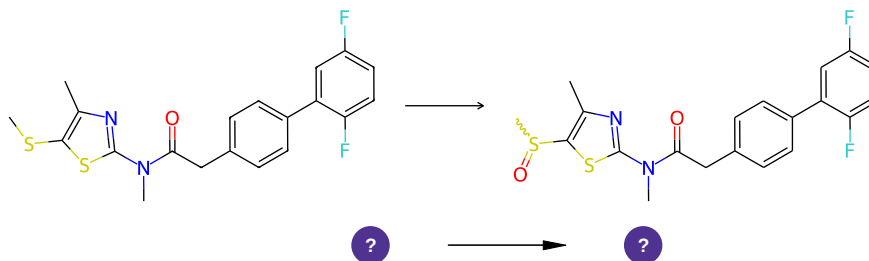
Typical conditions: 1. Ag(I)(cat).hv 2. Amine

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

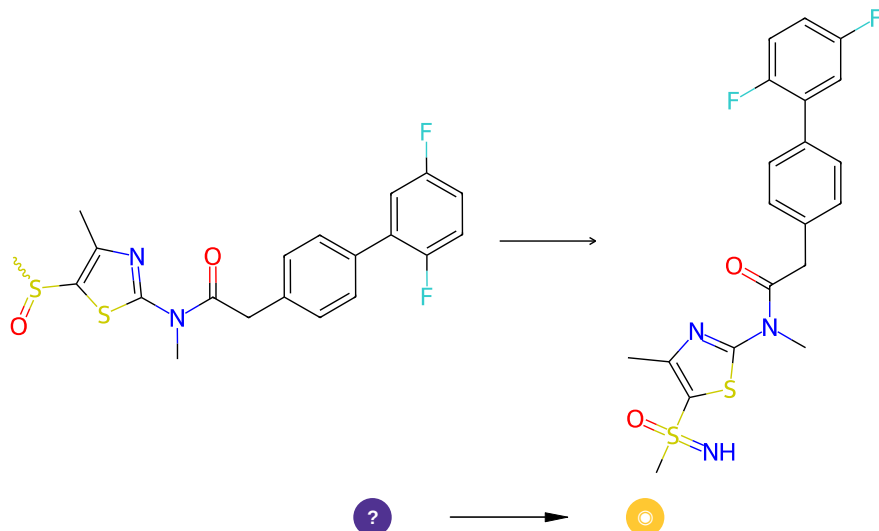
Typical conditions: TaC.H₂O₂.MeOH.45C

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