

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

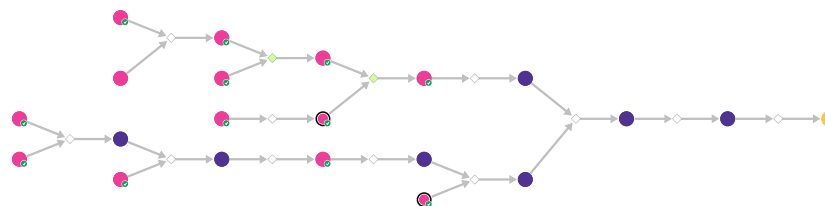
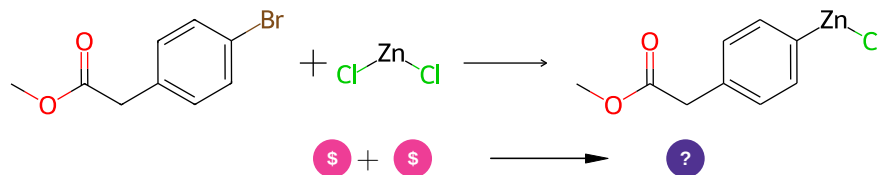


Figure 1: Outline of path 1

2.1.1 Synthesis of Arylzinc compounds



Substrates:

1. Methyl 4-bromophenylacetate - *available at Sigma-Aldrich*
2. Dichlorozinc - *available at Sigma-Aldrich*

Products:

1. COC(=O)Cc1ccc([Zn]Cl)cc1

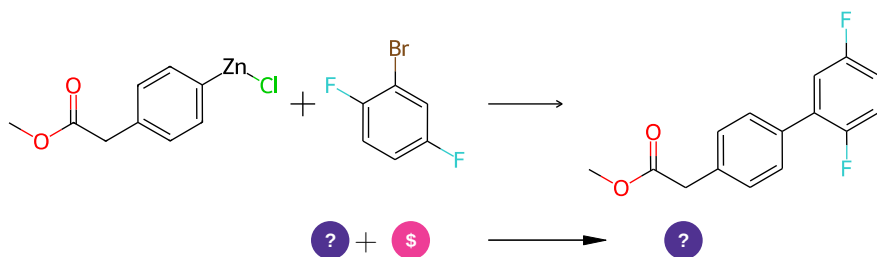
Typical conditions: IPrMgClxLiCl or nBuLi(-78C).ZnCl2.THF

Protections: none

Reference: [10.1016/j.tet.2011.01.030](https://doi.org/10.1016/j.tet.2011.01.030) [10.1021/jo801063c](https://doi.org/10.1021/jo801063c)

Retrosynthesis ID: 10149

2.1.2 Palladium mediated aryl-aryl cross coupling



Substrates:

1. COC(=O)Cc1ccc([Zn]Cl)cc1
2. 2-Bromo-1,4-difluorobenzene - [available at Sigma-Aldrich](#)

Products:

1. COC(=O)Cc1ccc(-c2cc(F)cc(F)c2)cc1

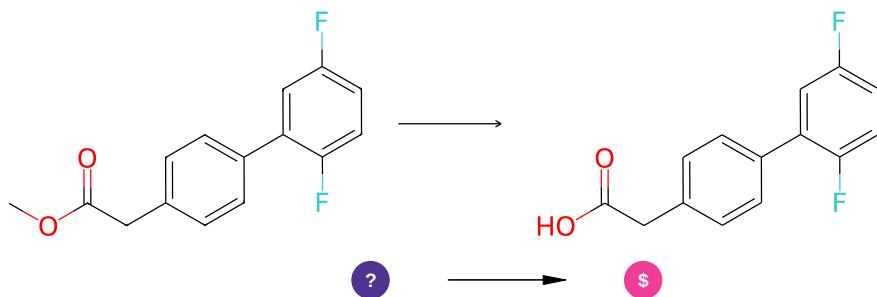
Typical conditions: [Pd].catalyst

Protections: none

Reference: [10.1016/j.tet.2011.01.030](https://doi.org/10.1016/j.tet.2011.01.030) and [10.1016/S0040-4020\(01\)00241-1](https://doi.org/10.1016/S0040-4020(01)00241-1) and [10.1021/ol1007026](https://doi.org/10.1021/ol1007026) and [10.1021/jo801063c](https://doi.org/10.1021/jo801063c) and [10.1002/anie.201207750](https://doi.org/10.1002/anie.201207750) and [10.1002/9780470638859.conrr456](https://doi.org/10.1002/9780470638859.conrr456)

Retrosynthesis ID: 1968

2.1.3 Synthesis of Carboxylic Acids via Ester Hydrolysis



Substrates:

1. COC(=O)Cc1ccc(-c2cc(F)cc(F)c2)cc1

Products:

1. 2',5'-Difluoro-biphenyl-4-acetic acid - *available at Sigma-Aldrich*

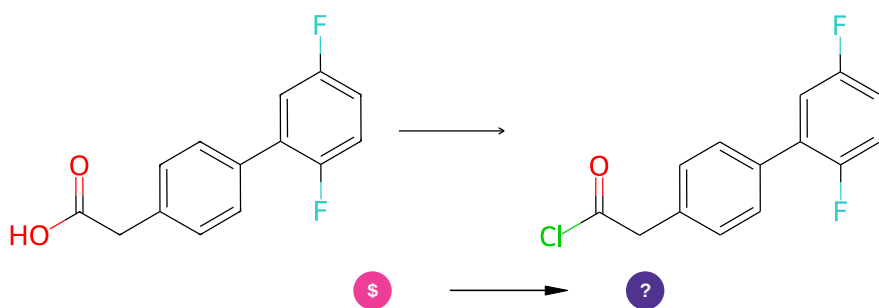
Typical conditions: water.base

Protections: none

Reference: DOI: [10.1016/j.phytochem.2012.08.001](https://doi.org/10.1016/j.phytochem.2012.08.001) and [10.1021/jm900803q](https://doi.org/10.1021/jm900803q) and [10.1002/anie.201303108](https://doi.org/10.1002/anie.201303108) (SI page S14) and [10.1016/j.ejmech.2010.09.003](https://doi.org/10.1016/j.ejmech.2010.09.003)

Retrosynthesis ID: 9224

2.1.4 Synthesis of acid chlorides from carboxylic acids



Substrates:

1. 2',5'-Difluoro-biphenyl-4-acetic acid - *available at Sigma-Aldrich*

Products:

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

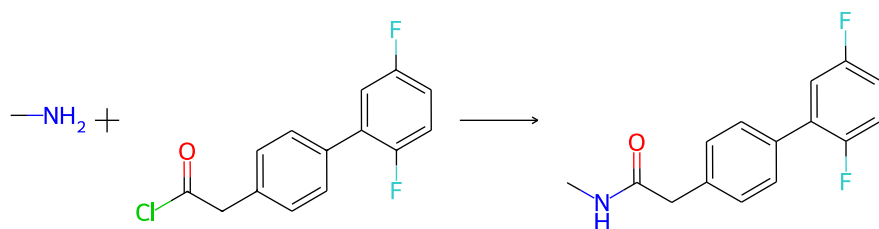
Typical conditions: oxalyl.chloride.or.SOCl₂

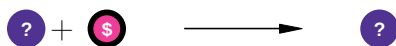
Protections: none

Reference: [10.1002/adsc.200303011](https://doi.org/10.1002/adsc.200303011) and [10.3390/50500714](https://doi.org/10.3390/50500714)

Retrosynthesis ID: 24405

2.1.5 Reaction of acyl chlorides with amines





Substrates:

1. O=C(Cl)Cc1ccc(-c2cc(F)ccc2F)cc1
2. Methanamine - *available at Sigma-Aldrich*

Products:

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

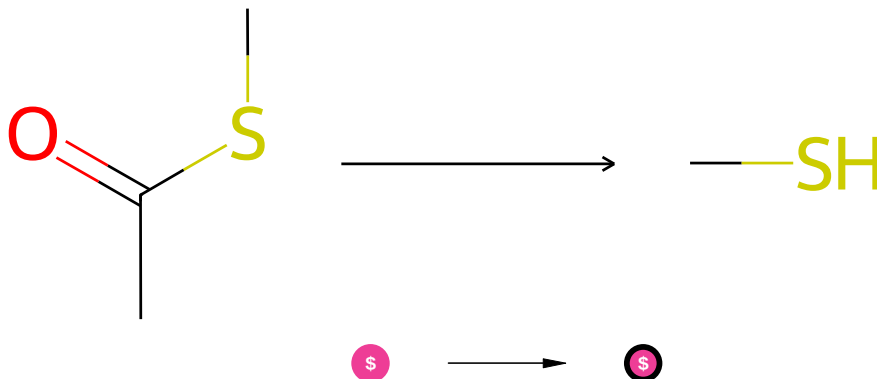
Typical conditions: Net3 or pyridine.DCM

Protections: none

Reference: [10.1016/j.ejmech.2016.03.047](#) AND [10.1016/j.bmcl.2008.08.004](#)
AND [10.1016/j.bmc.2011.03.002](#) AND [10.1021/ja077463q](#) (SI) AND
[10.1016/j.tetlet.2014.10.006](#) (SI) AND [10.1016/j.bmcl.2008.04.018](#) AND
[10.1021/jm980712o](#) AND [10.1021/jo9906173](#) AND [10.1021/jf9607371](#) AND

Retrosynthesis ID: 28547

2.1.6 Hydrolysis of thioesters



Substrates:

1. S-Methyl thioacetate - *available at Sigma-Aldrich*

Products:

1. Methanethiol - *available at Sigma-Aldrich*

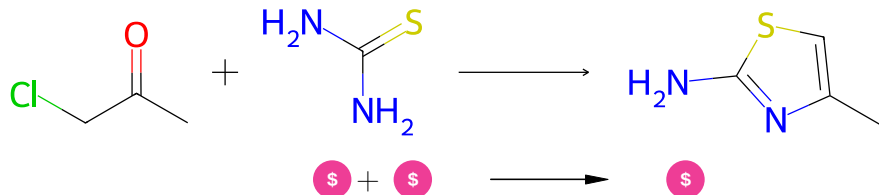
Typical conditions: K₂CO₃.MeOH.rt

Protections: none

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

Retrosynthesis ID: 22941

2.1.7 Synthesis of thiazoles from thioureas



Substrates:

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

Products:

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

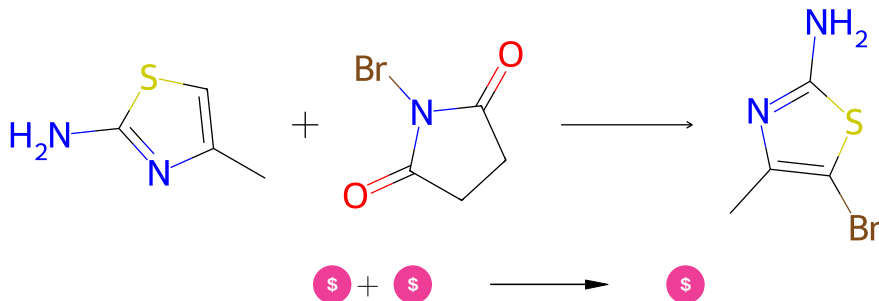
Typical conditions: ethanol.80C

Protections: none

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

Retrosynthesis ID: 4

2.1.8 Published reaction



Substrates:

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

Products:

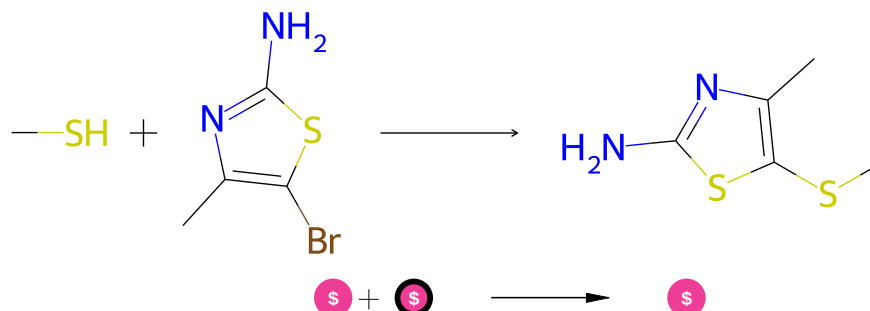
1. 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US05369107

Retrosynthesis ID: 6299162

2.1.9 Published reaction



Substrates:

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

Products:

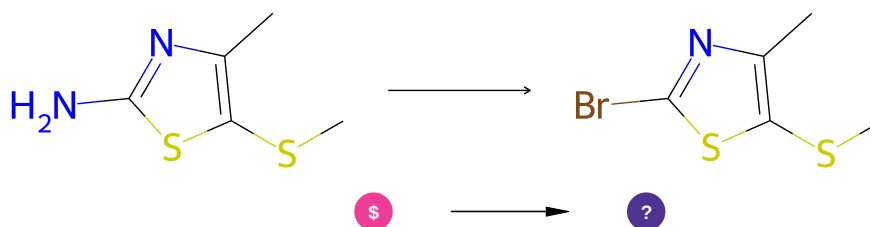
1. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US20090143448A1

Retrosynthesis ID: 8454157

2.1.10 Sandmeyer Reaction



Substrates:

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

Products:

1. CSc1sc(Br)nc1C

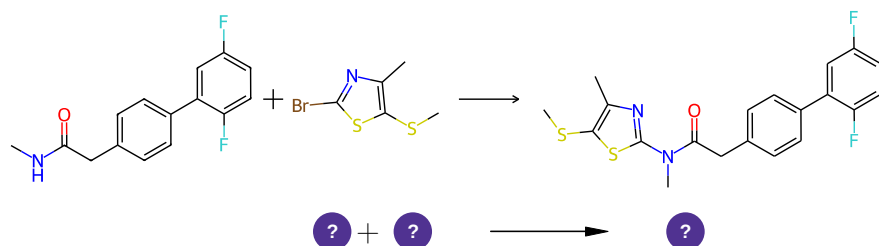
Typical conditions: IsoAmONO or t-BuONO.CuBr2.MeCN or HBr.CuBr2.NaNO2

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

2.1.11 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

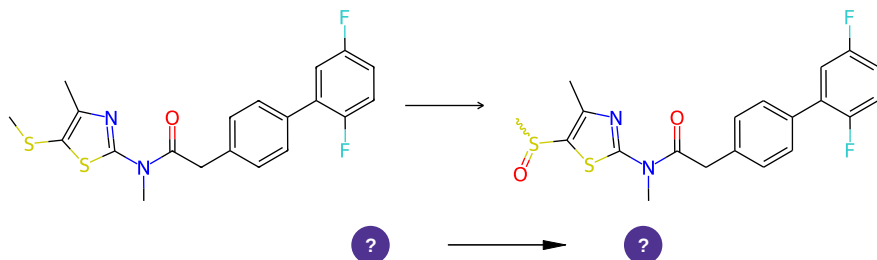
Typical conditions: Cs2CO3.CuX2/CuX.toluene.130C

Protections: none

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

Retrosynthesis ID: 10207

2.1.12 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

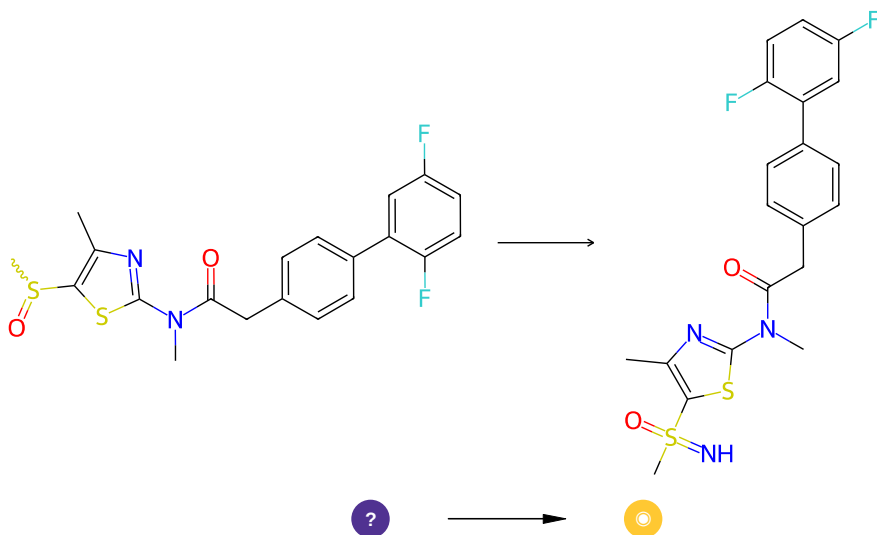
Typical conditions: TaC.H₂O₂.MeOH.45C

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

2.1.13 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