

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

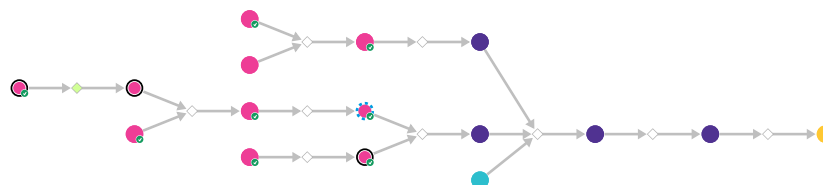
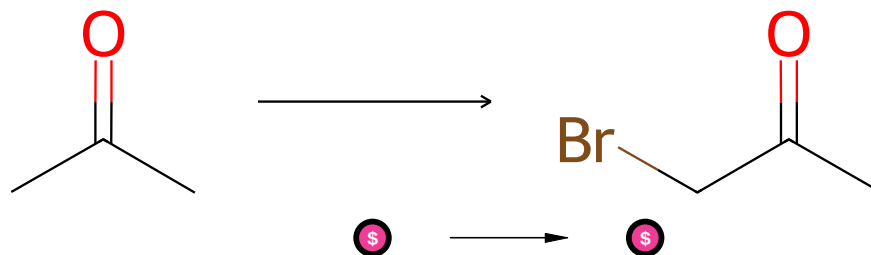


Figure 1: Outline of path 1

2.1.1 Published reaction



Substrates:

1. Acetone - *available at Sigma-Aldrich*

Products:

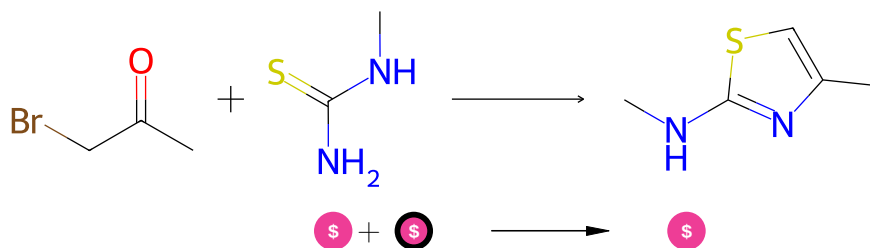
1. Bromoacetone - *AstaTech*

Protections: none

Reference: ORIPOV EH.; SHAXIDOYATOV X. M.; KADYROV CH. SH.; ABDULLAEV N. D.; KHIM. GETEROTSIKL. SOEDIN., 1979, Vol. , P. 684-691

Retrosynthesis ID: 78315

2.1.2 Synthesis of substituted 2-thiazolamine



Substrates:

1. N-methylthiourea - *available at Sigma-Aldrich*
2. Brom-aceton - *AstaTech*

Products:

1. Methyl-(4-methyl-thiazol-2-yl)-amine - *available at Sigma-Aldrich*

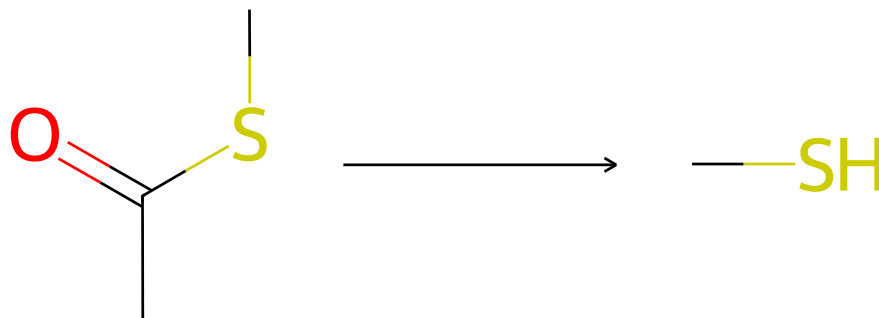
Typical conditions: ethanol.reflux

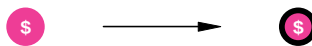
Protections: none

Reference: [10.1016/j.tetlet.2005.02.022](#) and [10.1002/jhet.5570280412](#)
and [10.1016/j.tetlet.2006.05.053](#) and [10.1016/j.ejmech.2014.07.025](#) and [10.1021/jm8016249](#)

Retrosynthesis ID: 26265

2.1.3 Hydrolysis of thioesters





Substrates:

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

Products:

1. Methanethiol - *available at Sigma-Aldrich*

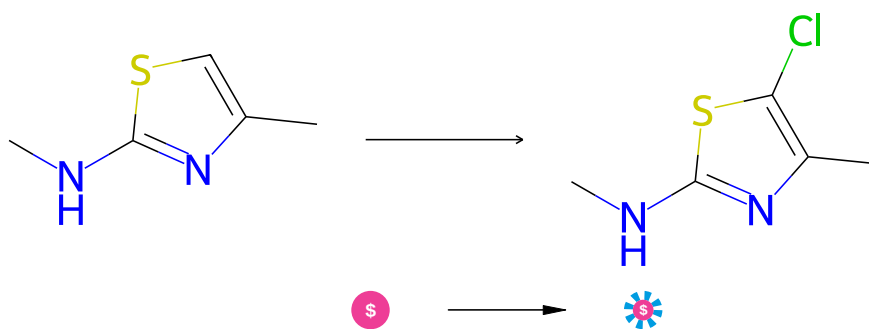
Typical conditions: K₂CO₃.MeOH.rt

Protections: none

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

Retrosynthesis ID: 22941

2.1.4 Chlorination of aromatic compounds



Substrates:

1. Methyl-(4-methyl-thiazol-2-yl)-amine - *available at Sigma-Aldrich*

Products:

1. 5-Chloro-N,4-dimethyl-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

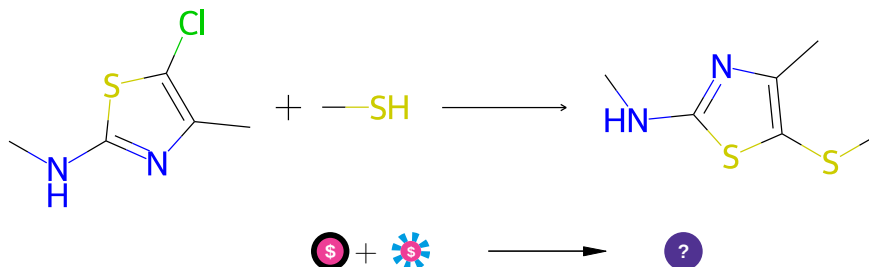
Typical conditions: Cl₂ or other chlorinating agent like NCS

Protections: none

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

Retrosynthesis ID: 11125

2.1.5 Pd-catalyzed synthesis of aryl sulfides



Substrates:

1. Methanethiol - *available at Sigma-Aldrich*
2. 5-Chloro-N,4-dimethyl-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

Products:

1. CNc1nc(C)c(SC)s1

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

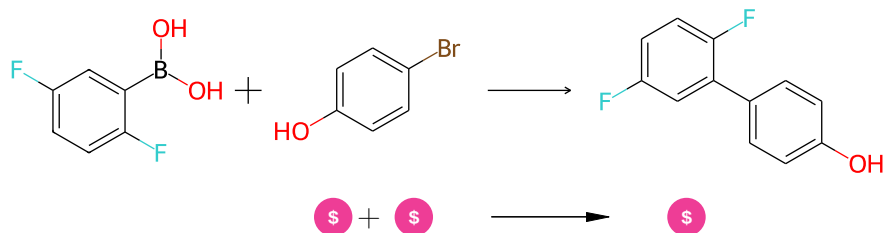
Protections:

Functional group SMARTS	Classification	Protecting groups
[CX4,c][NH][CX4,c]	amines	t-Butyl Carbamate Benzyl Carbamate 9-Fluorenylmethyl Carbamate N-Acetyl N-Benzyl N-Benzylidene

Reference: [10.1021/ja0580340](#)

Retrosynthesis ID: 1299

2.1.6 Suzuki coupling of arylboronic acids with aryl bromides



Substrates:

1. 4-Bromophenol - *available at Sigma-Aldrich*
2. 2,5-Difluorophenylboronic acid - *Combi-Blocks*

Products:

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

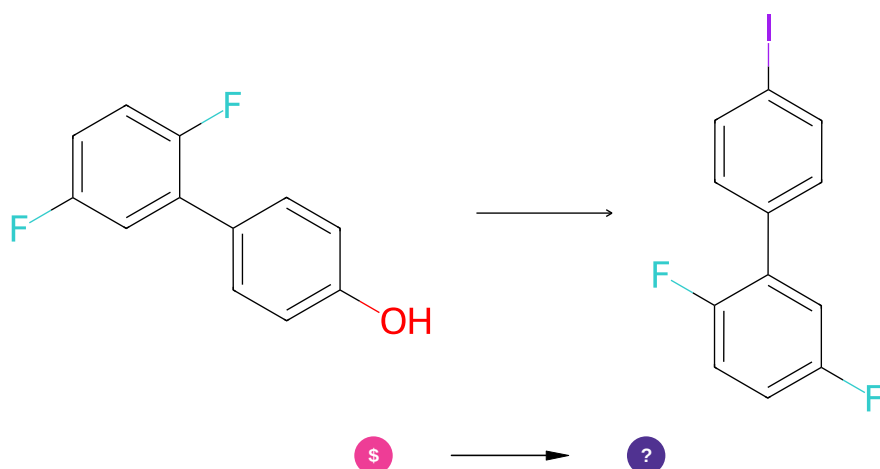
Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: [10.1021/cr00039a007](#) and [10.1007/3418_2012_32](#) and [10.1021/cr0505268](#) and [10.1016/j.jfluchem.2016.01.018](#) and [10.1039/C3CS60197H](#) and [10.1016/j.ejmech.2018.08.092](#) and [10.1038/s41929-020-00564-z](#) (metal-free coupling)

Retrosynthesis ID: 25150

2.1.7 Synthesis of haloarenes via triflates



Substrates:

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

Products:

1. Fc1ccc(F)c(-c2ccc(I)cc2)c1

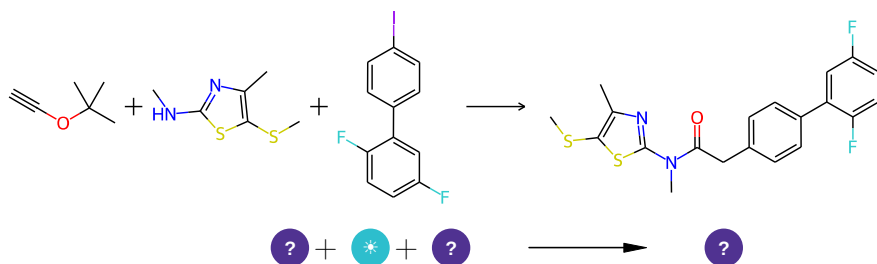
Typical conditions: 1. Tf₂O.pyridine. 2. CsF.[(AlPhosPd)₂xCOD].cyclohexane.120degC or KBr or KCl.KF.Pd₂(dba)₃.t-BuBrettPhos.1,4-dioxan.140degC or NaI.[CpxRu(MeCN)₃]OTf.DMI

Protections: none

Reference: [10.1021/ol202098h](#) (Chlorination and Bromination) and [10.1021/ja307771d](#) (Chlorination, Bromination, Iodination) and [10.1126/science.1178239](#) (Fluorination) and [10.1021/ol402859k](#) (Fluorination) and [10.1021/jacs.5b09308](#) (Fluorination)

Retrosynthesis ID: 23940

2.1.8 Synthesis of amides from aryl iodides through ynol ethers



Substrates:

1. CNc1nc(C)c(SC)s1
2. Tert-butoxy-ethyne
3. Fc1ccc(F)c(-c2ccc(I)cc2)c1

Products:

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

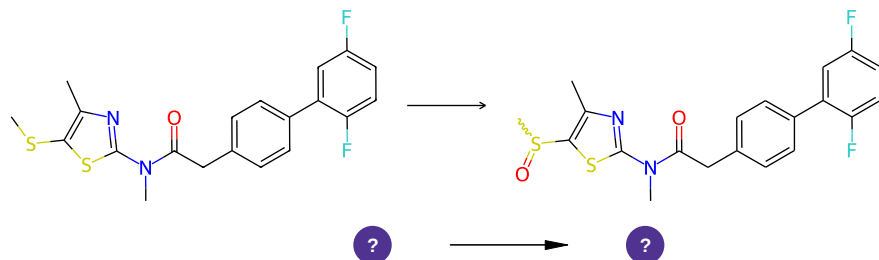
Typical conditions: [Pd₂(dba)₃].PPh₃.CuI.DIPEA.4A MS 2. amine.75C.toluene

Protections: none

Reference: DOI: [10.1002/anie.201405036](#)

Retrosynthesis ID: 1678

2.1.9 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

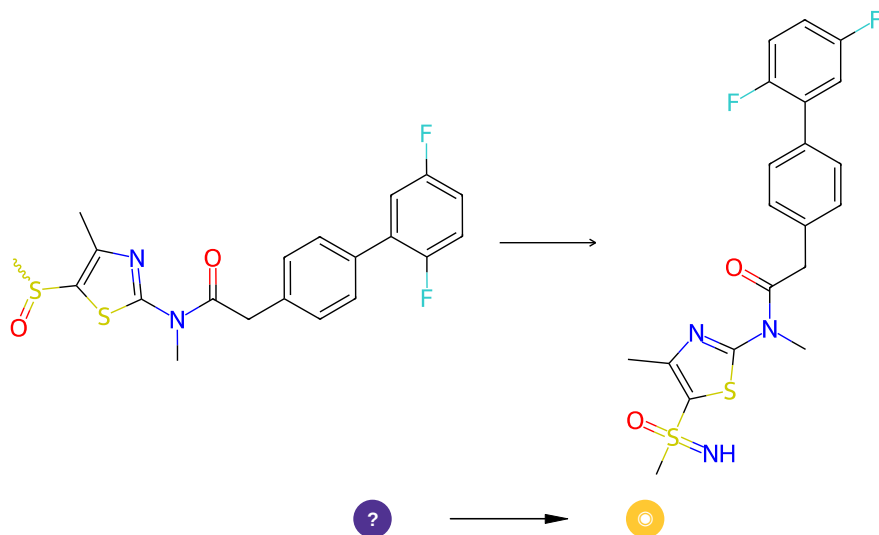
Typical conditions: TaC.H₂O₂.MeOH.45C

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

2.1.10 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