

# 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

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\*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

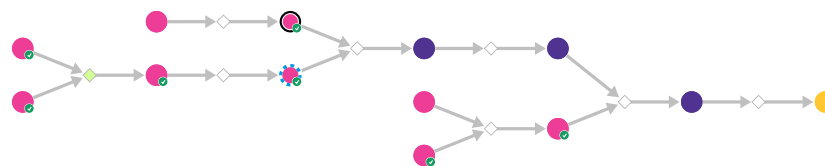
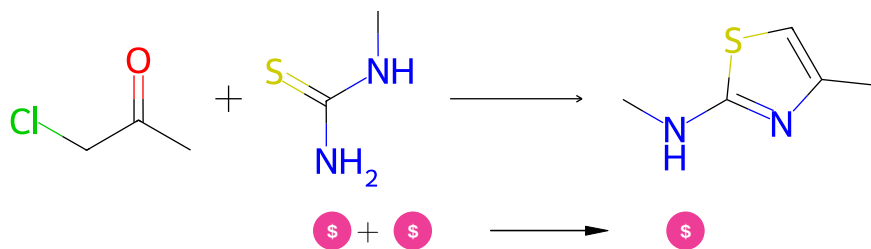


Figure 1: Outline of path 1

#### 2.1.1 Published reaction



**Substrates:**

1. Chloroacetone - *available at Sigma-Aldrich*
2. N-methylthiourea - *available at Sigma-Aldrich*

**Products:**

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

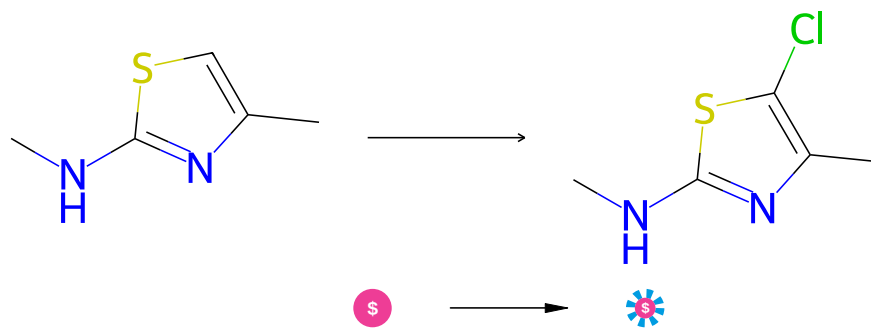
**Typical conditions:** HCl, NH<sub>3</sub>

**Protections:** none

**Reference:** BRAMLEY S. E.; DUPPLIN V.; GOBERDHAN D. G. C.; MEAKINS G. D.; J. Chem. Soc., Perkin Trans., 1987, Vol. , P. 639

**Retrosynthesis ID:** 1243026

### 2.1.2 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:** Cl<sub>2</sub> 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 Reduction of thiocyanates to thiols



**Substrates:**

1. Methyl thiocyanate

**Products:**

1. Methanethiol - *available at Sigma-Aldrich*

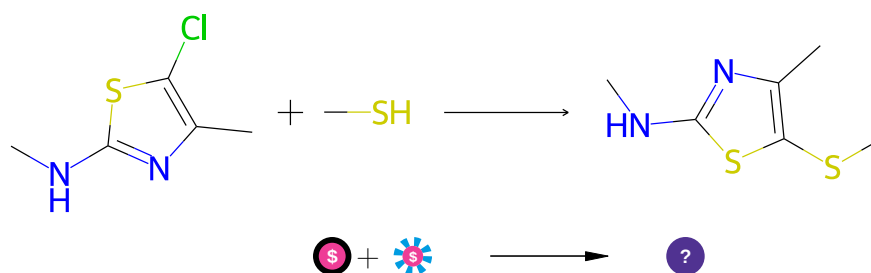
**Typical conditions:** NaBH<sub>4</sub>.EtOH

**Protections:** none

**Reference:** *10.1021/jm100213c* p. 4864, 4873 and *10.1016/j.ejmech.2014.09.071* p. 308, 310

**Retrosynthesis ID:** 50811

#### 2.1.4 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)<sub>2</sub>.tBuONa.DME.110C

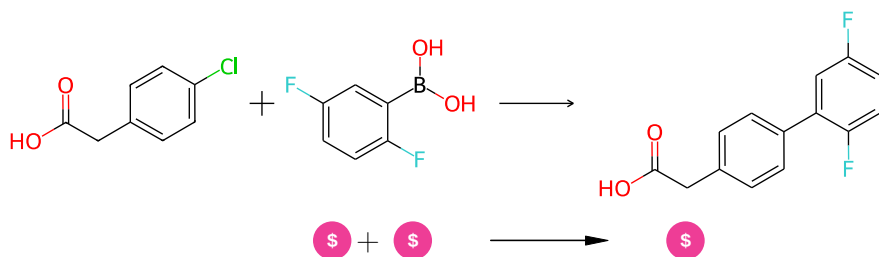
**Protections:**

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

### 2.1.5 Suzuki coupling with aryl chlorides



Substrates:

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

Products:

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

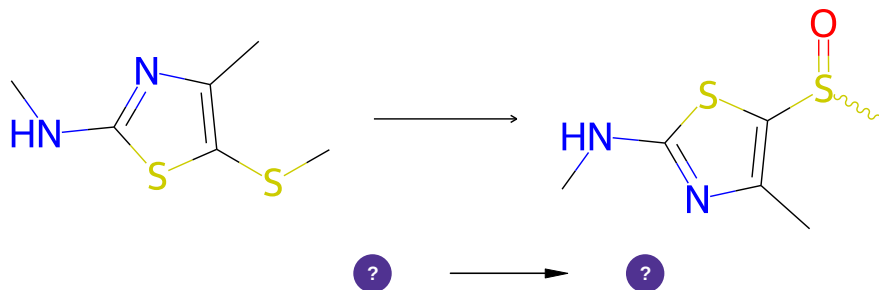
Typical conditions: [Pd].catalyst.base.

Protections: none

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

Retrosynthesis ID: 26284

### 2.1.6 Oxidation of sulfides to sulfoxides



Substrates:

1. CNc1nc(C)c(SC)s1

**Products:**

1. CNc1nc(C)c(S(C)=O)s1

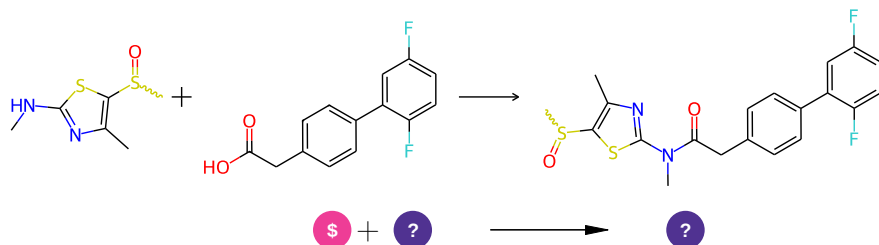
**Typical conditions:** TaC.H2O2.MeOH.45C

**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

**2.1.7 Amide coupling**



**Substrates:**

1. 2',5'-Difluoro-biphenyl-4-acetic acid - *available at Sigma-Aldrich*
2. CNc1nc(C)c(S(C)=O)s1

**Products:**

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

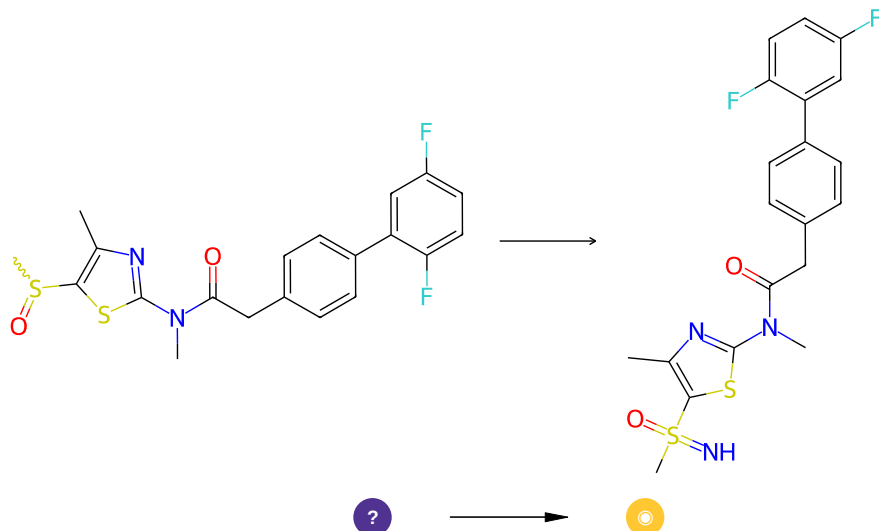
**Typical conditions:** DCC.DCM or EDC.DCM or SOCl2.DCM

**Protections:** none

**Reference:** [10.1021/ol400686f](https://doi.org/10.1021/ol400686f) and [10.1021/jo00200a057](https://doi.org/10.1021/jo00200a057) and [10.1021/cr100048w](https://doi.org/10.1021/cr100048w) and [10.1039/B701677H](https://doi.org/10.1039/B701677H) and [10.1039/C5RA24527C](https://doi.org/10.1039/C5RA24527C) and [10.3727/000000006783981206](https://doi.org/10.3727/000000006783981206) and [10.1021/np060007f](https://doi.org/10.1021/np060007f) and [10.1021/jo00012a058](https://doi.org/10.1021/jo00012a058) and [10.1016/j.bmcl.2007.08.037](https://doi.org/10.1016/j.bmcl.2007.08.037) and [10.1039/C0OB00355G](https://doi.org/10.1039/C0OB00355G) and [10.1021/jm500031w](https://doi.org/10.1021/jm500031w) (p.3056) and [10.1016/j.tet.2011.03.046](https://doi.org/10.1016/j.tet.2011.03.046)

**Retrosynthesis ID:** 9147

### 2.1.8 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:** NaN<sub>3</sub>.Eaton's reagent.50C or FeSO<sub>4</sub>.1,10-phen.NbzONH<sub>2</sub>\*TfOH.MeCN or H<sub>2</sub>NCO<sub>2</sub>NH<sub>4</sub>.PhI(OAc)<sub>2</sub>.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