

# 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:**  $\text{TUNNEL\_COEF} * \text{FGI\_COEF} * \text{STEP} * 20 + 1000 * (\text{FILTERS} + \text{CONFLICT} + \text{NON\_SELECTIVITY}) + 40 * \text{PROTECT}$

**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

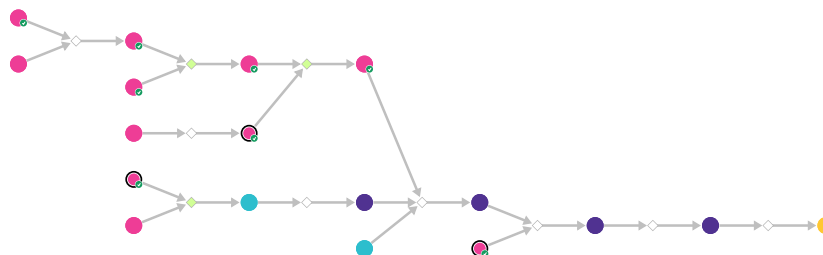
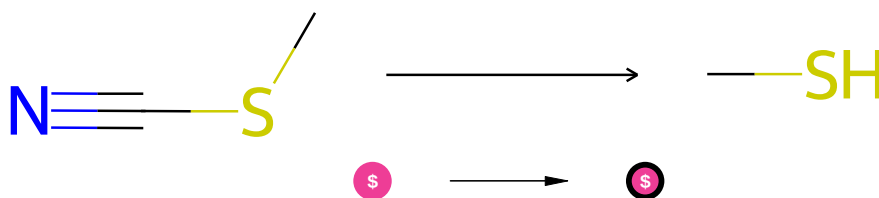


Figure 1: Outline of path 1

#### 2.1.1 Reduction of thiocyanates to thiols



**Substrates:**

1. Methyl thiocyanate

**Products:**

1. Methanethiol - *available at Sigma-Aldrich*

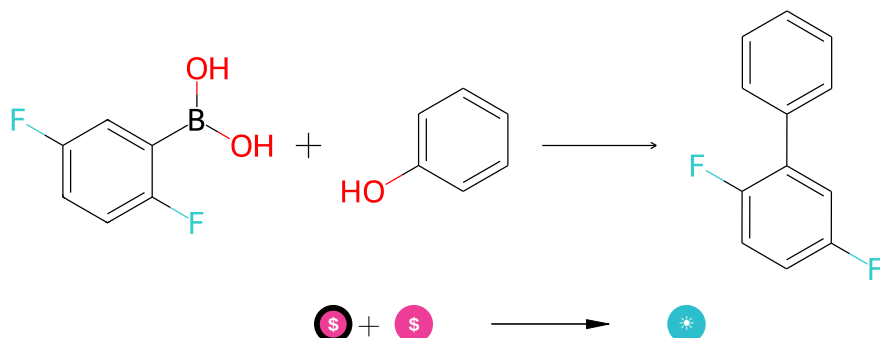
**Typical conditions:** NaBH<sub>4</sub>.EtOH

**Protections:** none

**Reference:** [10.1021/jm100213c](#) p. 4864, 4873 and [10.1016/j.ejmech.2014.09.071](#) p. 308, 310

**Retrosynthesis ID:** 50811

### 2.1.2 Published reaction



#### Substrates:

1. C<sub>6</sub>H<sub>6</sub>O - *available at Sigma-Aldrich*
2. 2,5-Difluorophenylboronic acid - *Combi-Blocks*

#### Products:

1. 2,5-Difluorobiphenyl

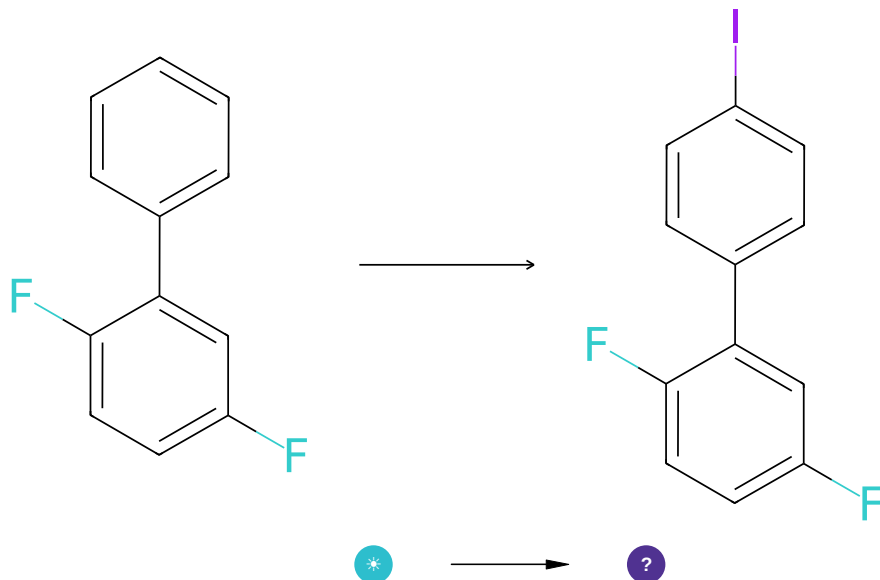
**Typical conditions:** Stage 1: 240 s, 90 degree, Tetrabutylammonium bromide, C<sub>45</sub>H<sub>59</sub>Cl<sub>11</sub>N<sub>1</sub>P<sub>1</sub>Pd<sub>1</sub>, N-Methyl-2-pyrrolidone, Toluene, Water, K<sub>3</sub>O<sub>4</sub>P Potassium phosphate, tribasic | Stage 2: null | Stage 3: null

**Protections:** none

**Reference:** [10.1002/ANIE.201101480](#)

**Retrosynthesis ID:** 4345800

### 2.1.3 Iodination of aromatic compounds



**Substrates:**

1. 2,5-Difluorobiphenyl

**Products:**

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

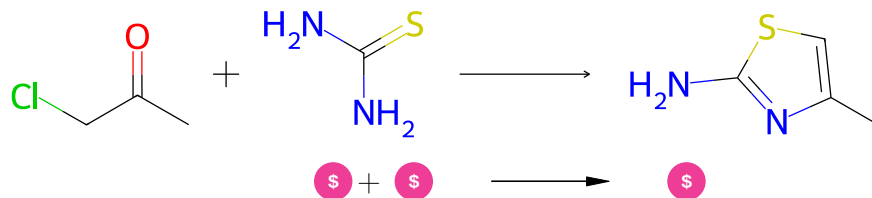
**Typical conditions:** I<sub>2</sub> or other iodinating agent e.g. NIS

**Protections:** none

**Reference:** DOI: [10.1039/C5SC00964B](https://doi.org/10.1039/C5SC00964B) and [10.1016/j.tetlet.2005.05.117](https://doi.org/10.1016/j.tetlet.2005.05.117) and [10.1007/s11178-005-0256-1](https://doi.org/10.1007/s11178-005-0256-1)

**Retrosynthesis ID:** 10697

### 2.1.4 Synthesis of thiazoles from thioureas



**Substrates:**

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

**Products:**

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

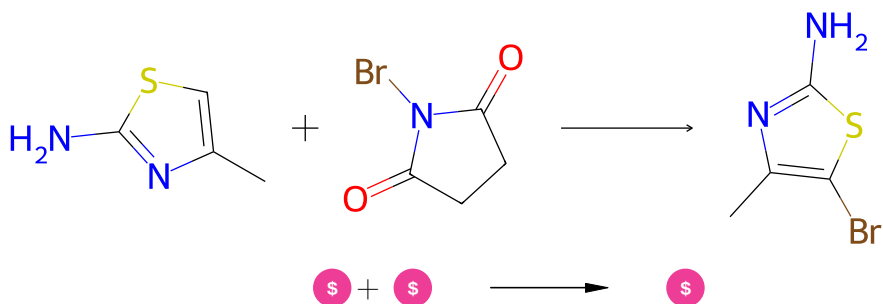
**Typical conditions:** ethanol.80C

**Protections:** none

**Reference:** DOI: *10.1021/jo00103a021*

**Retrosynthesis ID:** 4

**2.1.5 Published reaction**



**Substrates:**

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

**Products:**

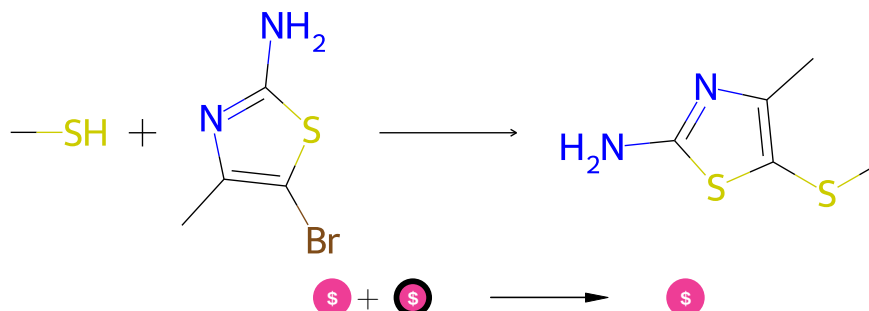
1. 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*

**Protections:** none

**Reference:** US05369107

**Retrosynthesis ID:** 6299162

### 2.1.6 Published reaction



#### Substrates:

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

#### Products:

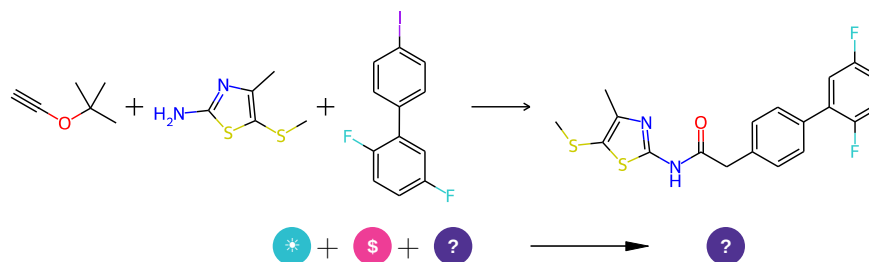
1. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

**Protections:** none

**Reference:** US20090143448A1

**Retrosynthesis ID:** 8454157

### 2.1.7 Synthesis of amides from aryl iodides through ynol ethers



#### Substrates:

1. Tert-butoxy-ethyne
2. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*
3. Fc1ccc(F)c(-c2ccc(I)cc2)c1

#### Products:

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

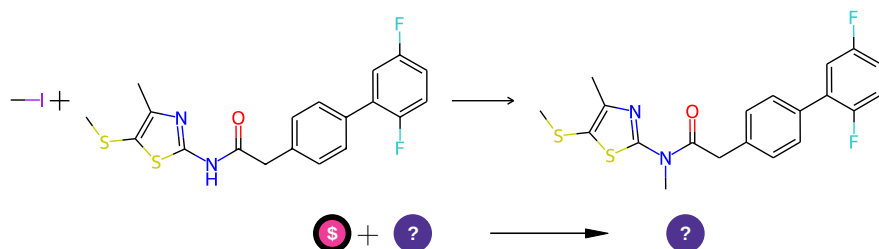
**Typical conditions:** [Pd2(dba)3].PPh3.CuI.DIPEA.4A MS 2.  
amine.75°C.toluene

**Protections:** none

**Reference:** DOI: [10.1002/anie.201405036](https://doi.org/10.1002/anie.201405036)

**Retrosynthesis ID:** 1679

### 2.1.8 N-alkylation of amides



**Substrates:**

1. Iodomethane - [available at Sigma-Aldrich](#)
2. CSc1sc(NC(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

**Products:**

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

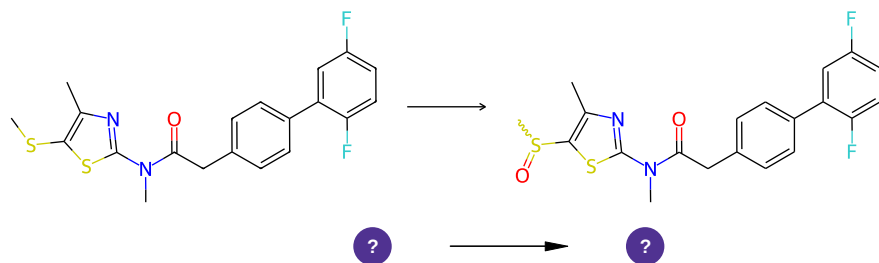
**Typical conditions:** NaH.DMF

**Protections:** none

**Reference:** DOI: [10.1016/j.bmc.2014.03.007](https://doi.org/10.1016/j.bmc.2014.03.007) and [10.1016/j.tetlet.2008.10.057](https://doi.org/10.1016/j.tetlet.2008.10.057)

**Retrosynthesis ID:** 8841

### 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

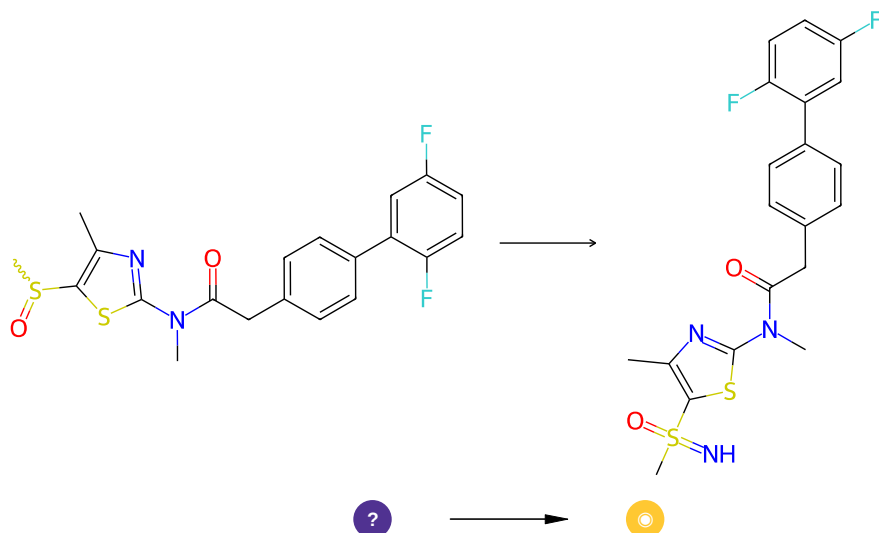
**Typical conditions:** TaC.H2O2.MeOH.45C

**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](https://doi.org/10.1016/j.tetlet.2016.12.031) and [10.1002/anie.201710498](https://doi.org/10.1002/anie.201710498) and [10.1002/anie.201602320](https://doi.org/10.1002/anie.201602320) and [10.1055/s-0036-1590874](https://doi.org/10.1055/s-0036-1590874) and [10.1039/C7CC03386A](https://doi.org/10.1039/C7CC03386A)



**Retrosynthesis ID:** 31016630