

Paths of analysis*

Analysis 4

Synthia

March 3, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: FGI, FGI with protections

Max. paths returned: 5

Max. iterations: 300

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1000 \$/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 10

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Reaction scoring formula: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 1000000 * (\text{CONFLICT} + \text{NON_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

Chemical scoring formula: $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

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FGI Coeff: 0

JSON Parameters: {}

2 Paths

3 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

2.1 Path 1

Score: 122.76

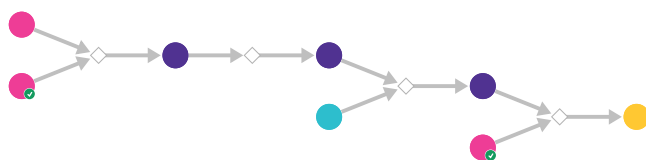
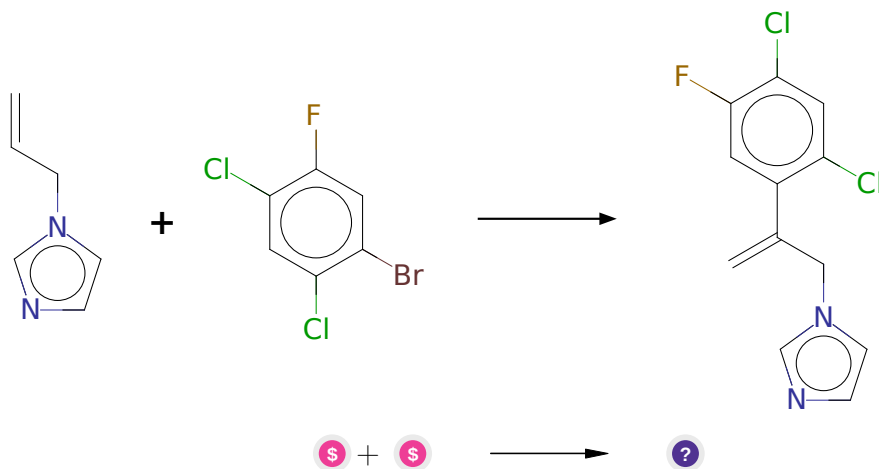


Figure 1: Outline of path 1

2.1.1 Heck Reaction



Substrates:

- 1-Bromo-2,4-dichloro-5-fluorobenzene - *Combi-Blocks*
- 1-(prop-2-en-1-yl)-1H-imidazole - *available at Sigma-Aldrich*

Products:

1. C=C(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl

Typical conditions: Pd (cat). Ligand e.g. TXPTS. Base. Temp

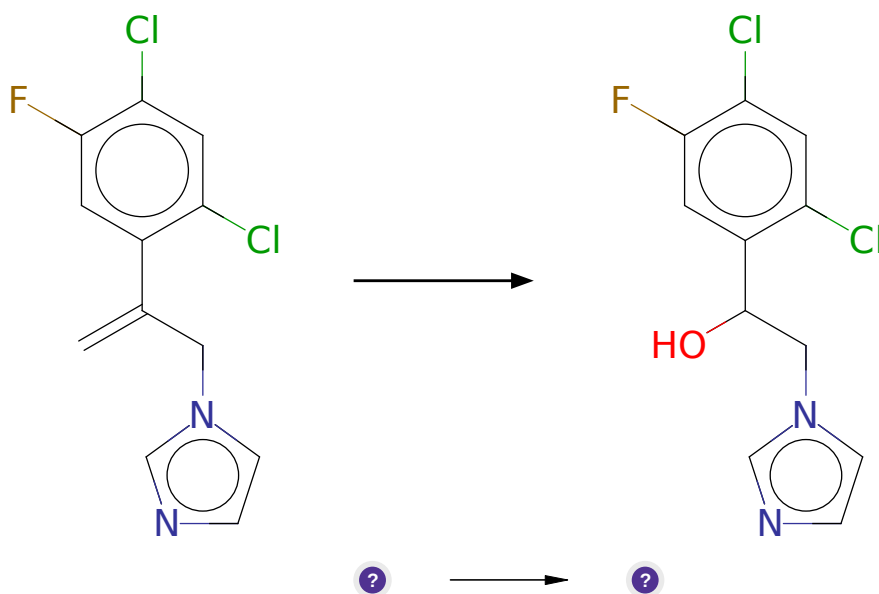
Protections: none

Yield: moderate

Reference: [10.1039/C3CC45911J](#) or [10.1021/ar00049a001](#) or [10.1002/anie.201201806](#) or [10.1002/9780470716076](#)

Retrosynthesis ID: 9266

2.1.2 Ozonolysis followed by reduction



Substrates:

1. C=C(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl

Products:

1. OC(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl

Typical conditions: O₃.MeOH.CH₂Cl₂.NaBH₄.low temperature

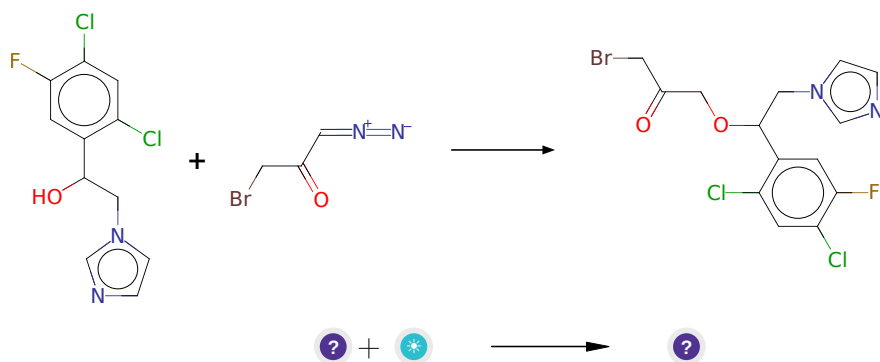
Protections: none

Yield: good

Reference: [10.1021/ja043506g](#)(SI,page S2) and [10.1016/j.jfluchem.2011.05.031](#) and [10.1021/ja304872j](#) and [10.1021/jo026004z](#)

Retrosynthesis ID: 28553

2.1.3 Alcoholysis of alpha-diazo compounds



Substrates:

1. OC(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl
2. 1-bromo-3-diazo-propan-2-one

Products:

1. O=C(CBr)COC(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl

Typical conditions: Rh2(OAc)4

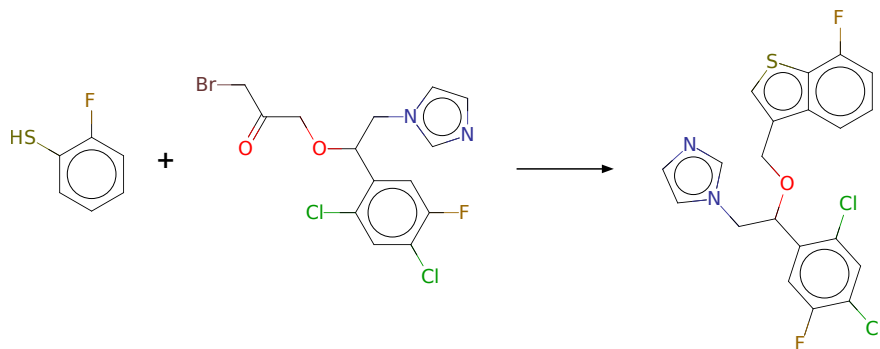
Protections: none

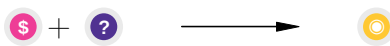
Yield: moderate

Reference: [10.1016/j.tetlet.2014.06.024](https://doi.org/10.1016/j.tetlet.2014.06.024) AND [10.1021/ja074729k](https://doi.org/10.1021/ja074729k) AND [10.1021/ja0607739](https://doi.org/10.1021/ja0607739) AND [10.1039/c4cc06395c](https://doi.org/10.1039/c4cc06395c)

Retrosynthesis ID: 15014

2.1.4 Synthesis of benzothiophenes from thiophenols





Substrates:

1. 2-Fluorothiophenol - *available at Sigma-Aldrich*
2. O=C(CBr)COC(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl

Products:

1. Fc1cc(C(Cn2ccnc2)OCc2csc3c(F)cccc23)c(Cl)cc1Cl

Typical conditions: Na2CO3.SiO2.PPA.PhCl.135C

Protections: none

Yield: moderate

Reference: DOI: [10.1055/s-2005-918928](https://doi.org/10.1055/s-2005-918928)

Retrosynthesis ID: 295032

2.2 Path 2

Score: 158.93

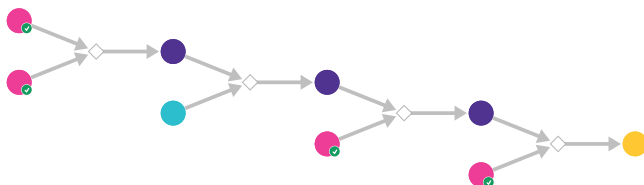
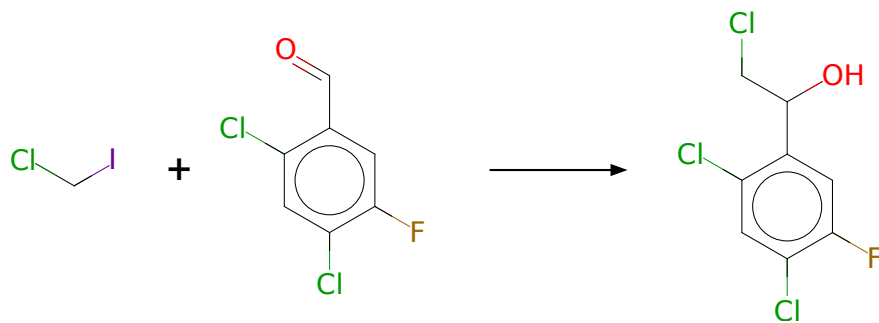
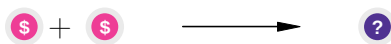


Figure 2: Outline of path 2

2.2.1 Addition of dihalomethane to aldehyde





Substrates:

1. Chloriodomethane - *available at Sigma-Aldrich*
2. 2,4-Dichloro-5-fluorobenzaldehyde - *available at Sigma-Aldrich*

Products:

1. OC(CCl)c1cc(F)c(Cl)cc1Cl

Typical conditions: SmI2.THF

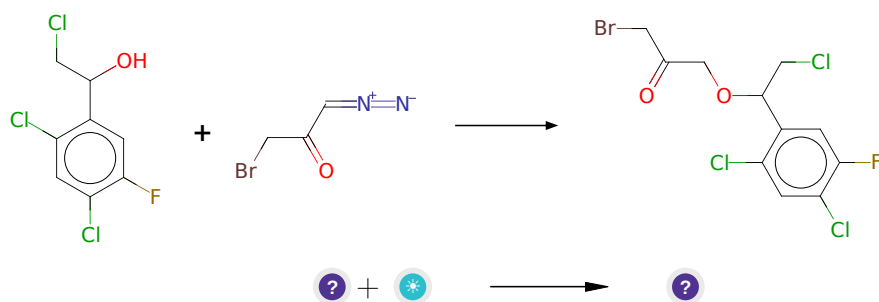
Protections: none

Yield: good

Reference: [10.1016/j.tet.2012.02.033](#) and [10.1016/j.tetlet.2005.02.093](#) and [10.1021/jo970318i](#)

Retrosynthesis ID: 25218

2.2.2 Alcoholysis of alpha-diazo compounds



Substrates:

1. OC(CCl)c1cc(F)c(Cl)cc1Cl
2. 1-bromo-3-diazo-propan-2-one

Products:

1. O=C(CBr)COC(CCl)c1cc(F)c(Cl)cc1Cl

Typical conditions: Rh2(OAc)4

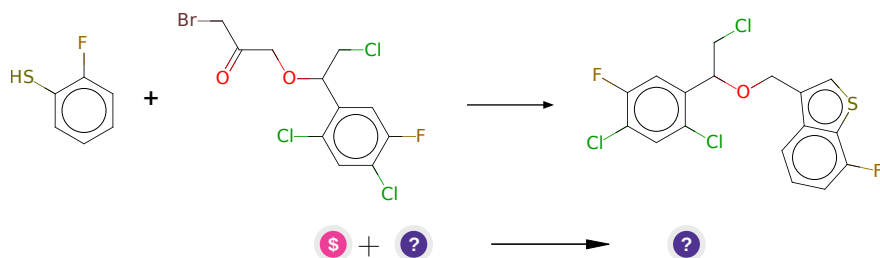
Protections: none

Yield: moderate

Reference: [10.1016/j.tetlet.2014.06.024](https://doi.org/10.1016/j.tetlet.2014.06.024) AND [10.1021/ja074729k](https://doi.org/10.1021/ja074729k) AND [10.1021/ja0607739](https://doi.org/10.1021/ja0607739) AND [10.1039/c4cc06395c](https://doi.org/10.1039/c4cc06395c)

Retrosynthesis ID: 15014

2.2.3 Synthesis of benzothiophenes from thiophenols



Substrates:

1. 2-Fluorothiophenol - *available at Sigma-Aldrich*
2. O=C(CBr)COC(CCl)c1cc(F)c(Cl)cc1Cl

Products:

1. Fc1cc(C(CCl)OCc2csc3c(F)cccc23)c(Cl)cc1Cl

Typical conditions: Na2CO3.SiO2.PPA.PhCl.135C

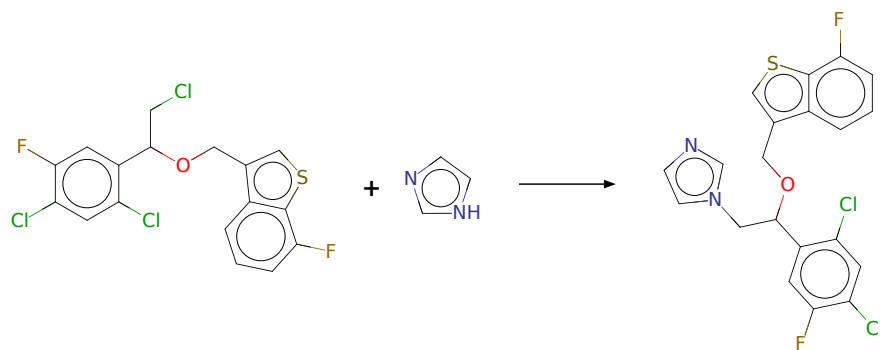
Protections: none

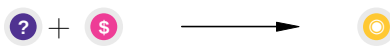
Yield: moderate

Reference: DOI: [10.1055/s-2005-918928](https://doi.org/10.1055/s-2005-918928)

Retrosynthesis ID: 295032

2.2.4 N-alkylation of Heterocycles





Substrates:

1. Fc1cc(C(CCl)OCc2csc3c(F)cccc23)c(Cl)cc1Cl
2. Imidazole - *available at Sigma-Aldrich*

Products:

1. Fc1cc(C(Cn2ccnc2)OCc2csc3c(F)cccc23)c(Cl)cc1Cl

Typical conditions: NaH.DMF

Protections: none

Yield: good

Reference: [10.1021/ol503625z](#) and [10.1081/SCC-120022467](#) (experimental) and [10.1021/ol2018328](#) (SI, p.5) and [10.1021/jo8026565](#) (SI, p.2)

Retrosynthesis ID: 28538

2.3 Path 3

Score: 161.93

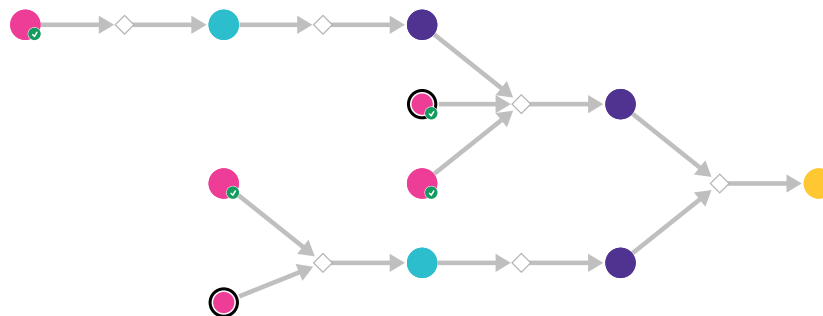
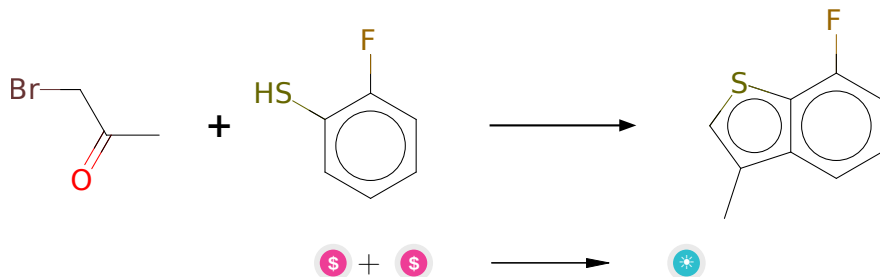


Figure 3: Outline of path 3

2.3.1 Synthesis of benzothiophenes from thiophenols



Substrates:

1. 2-Fluorothiophenol - *available at Sigma-Aldrich*
2. brom-aceton - *AstaTech*

Products:

1. 7-fluoro-3-methyl-benzo[b]thiophene

Typical conditions: Na₂CO₃.SiO₂.PPA.PhCl.135C

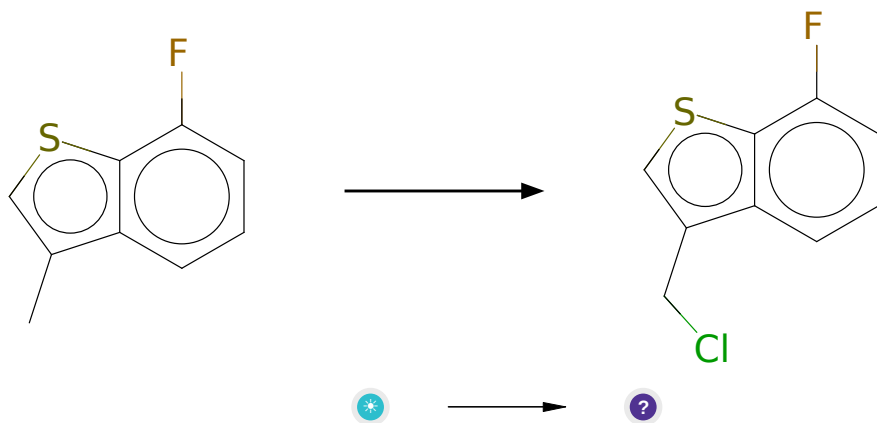
Protections: none

Yield: good

Reference: DOI: *10.1055/s-2005-918928*

Retrosynthesis ID: 295032

2.3.2 Chlorination of benzylic position



Substrates:

1. 7-fluoro-3-methyl-benzo[b]thiophene

Products:

1. Fc1cccc2c(CCl)csc12

Typical conditions: SOCl₂.AIBN or NCS/SiCl₄ or [BnNMe₃]ICl₄.AIBN

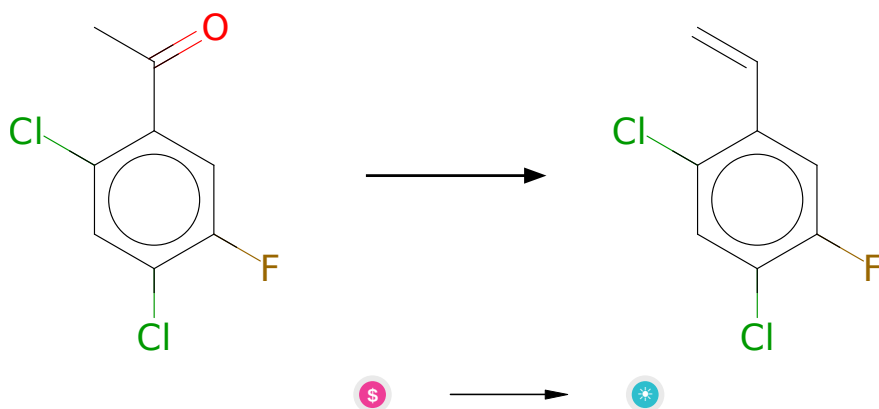
Protections: none

Yield: good

Reference: [10.1039/B803741H](#) and [10.1016/S0040-4039\(00\)82191-7](#) and [10.1016/j.tetlet.2011.05.135](#)

Retrosynthesis ID: 10001786

2.3.3 Shapiro reaction



Substrates:

1. 2',4'-Dichloro-5'-fluoroacetophenone - *available at Sigma-Aldrich*

Products:

1. 2,4-dichlor-5-fluor-styrol

Typical conditions: 1.TsNH₂NH₂2.2.nBuLi.THF

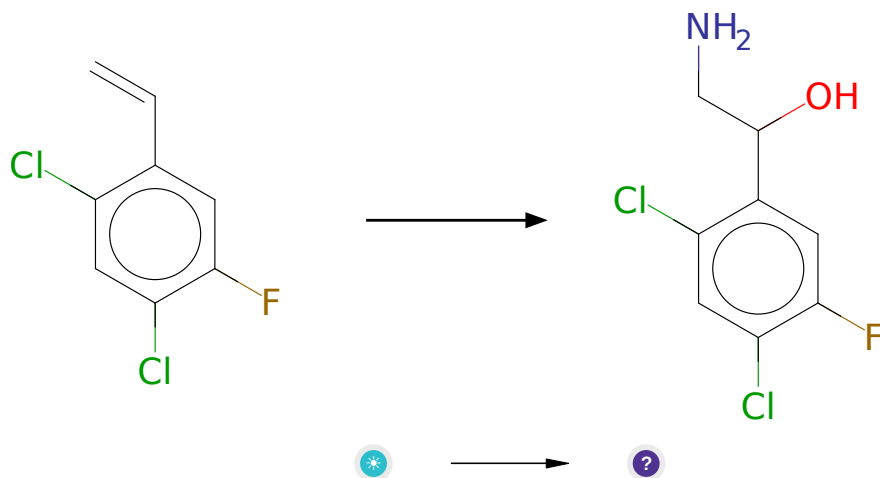
Protections: none

Yield: moderate

Reference: [10.1021/ol300652k](#) and [10.1055/s-0030-1261184](#)

Retrosynthesis ID: 9990397

2.3.4 Aminooxylation of styrenes



Substrates:

1. 2,4-dichloro-5-fluor-styrol

Products:

1. NCC(O)c1cc(F)c(Cl)cc1Cl

Typical conditions: FePc.PivONH₃OTf.ACN

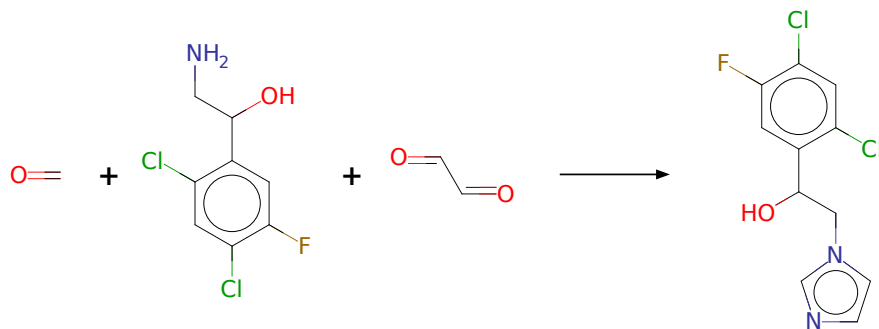
Protections: none

Yield: good

Reference: [10.1002/anie.201507630](#)

Retrosynthesis ID: 10014883

2.3.5 Debus-Radziszewski one-pot imidazole synthesis





Substrates:

1. Formalin - *available at Sigma-Aldrich*
2. Ethanedial - *available at Sigma-Aldrich*
3. NCC(O)c1cc(F)c(Cl)cc1Cl

Products:

1. OC(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl

Typical conditions: heat.ammonia or heat.ammonium salt

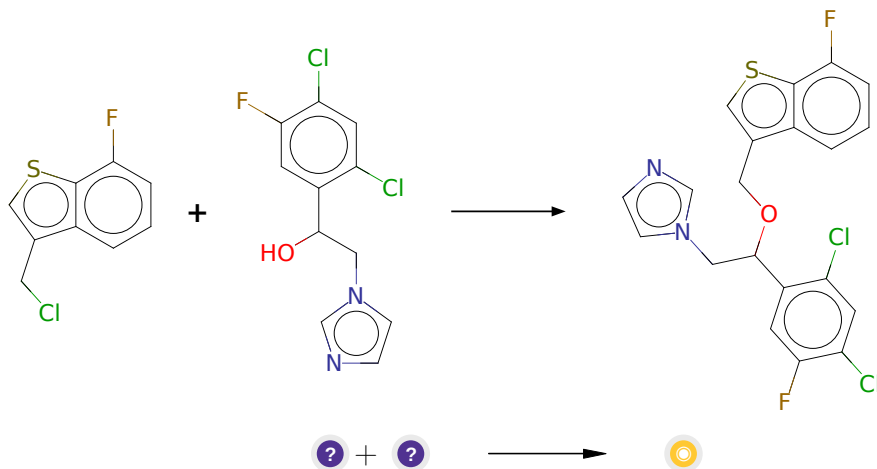
Protections: none

Yield: moderate

Reference: DOI: [10.3998/ark.5550190.p008.270](https://doi.org/10.3998/ark.5550190.p008.270) and [10.1002/14356007.a13_661](https://doi.org/10.1002/14356007.a13_661) and [10.1016/j.jpba.2011.09.011](https://doi.org/10.1016/j.jpba.2011.09.011)

Retrosynthesis ID: 7757

2.3.6 Alkylation of secondary alcohols



Substrates:

1. OC(Cn1ccnc1)c1cc(F)c(Cl)cc1Cl
2. Fc1cccc2c(CCl)csc12

Products:

1. Fc1cc(C(Cn2ccnc2)OCC2csc3c(F)cccc23)c(Cl)cc1Cl

Typical conditions: K₂CO₃.acetone.heat

Protections: none

Yield: moderate

Reference: [10.1016/S0022-1139\(00\)85021-6](#) and

Retrosynthesis ID: 31011106