Paths of analysis*

C125

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: TUNNEL_COEF*FGI_COEF*STEP*20+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,SMALLER^ 1.5

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

*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.

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: 127.54

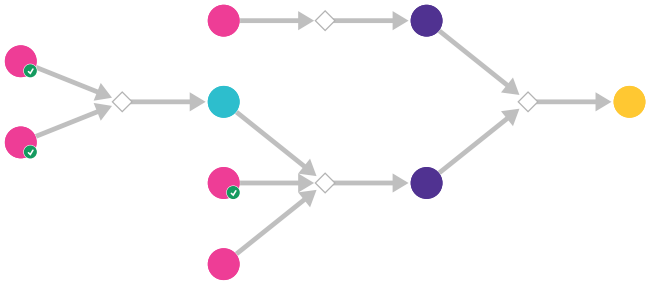
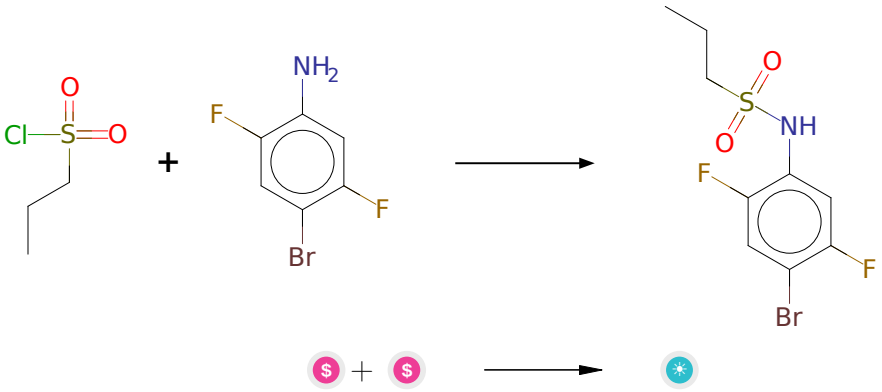


Figure 1: Outline of path 1

2.1.1 N-Sulfonylation



Substrates:

1. 4-Bromo-2,5-difluoroaniline - *available at Sigma-Aldrich*
2. 1-Propanesulfonyl chloride - *available at Sigma-Aldrich*

Products:

1. N-(4-bromo-2,5-difluorophenyl)propane-1-sulfonamide

Typical conditions: THF.rt

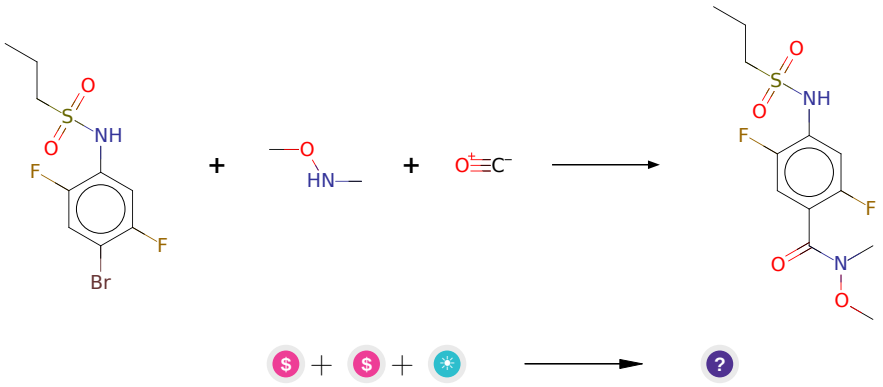
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14717

2.1.2 Pd-catalyzed conversion of aryl bromides to Weinreb amides



Substrates:

1. Carbon monoxide - *available at Sigma-Aldrich*
2. n-methoxymethylamine - *ChemImpexInternational*
3. N-(4-bromo-2,5-difluorophenyl)propane-1-sulfonamide

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(C(=O)N(C)OC)cc1F

Typical conditions: Pd(OAc)2.Xantphos.CO(1 atm).Na2CO3.toluene.80C

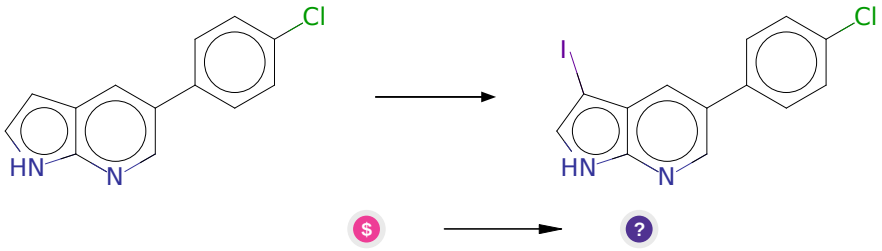
Protections: none

Yield: moderate

Reference: DOI: *10.1021/ol061902t*

Retrosynthesis ID: 1688

2.1.3 Iodination of aromatic compounds



Substrates:

1. 5-(4-Chlorophenyl)-1H-pyrrolo[2,3-b]pyridine - *Combi-Blocks*

Products:

1. Clc1ccc(-c2cnc3[nH]cc(I)c3c2)cc1

Typical conditions: I2 or other iodinating agent e.g. NIS

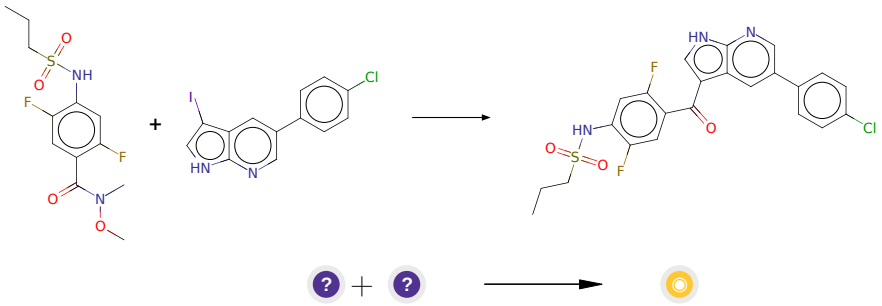
Protections: none

Yield: good

Reference: DOI: *10.1039/C5SC00964B* and *10.1016/j.tetlet.2005.05.117* and *10.1007/s11178-005-0256-1*

Retrosynthesis ID: 10697

2.1.4 Synthesis of ketones from Weinreb amides



Substrates:

1. Clc1ccc(-c2cnc3[nH]cc(I)c3c2)cc1
2. CCCS(=O)(=O)Nc1cc(F)c(C(=O)N(C)OC)cc1F

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(C(=O)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)cc1F

Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Yield: good

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.2 Path 2

Score: `155.08`

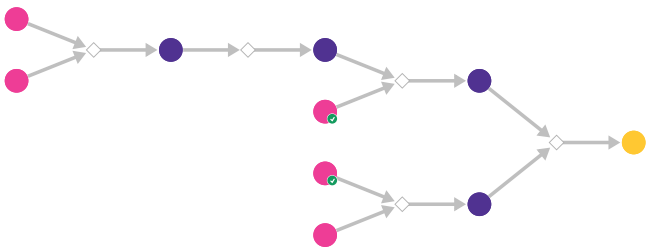
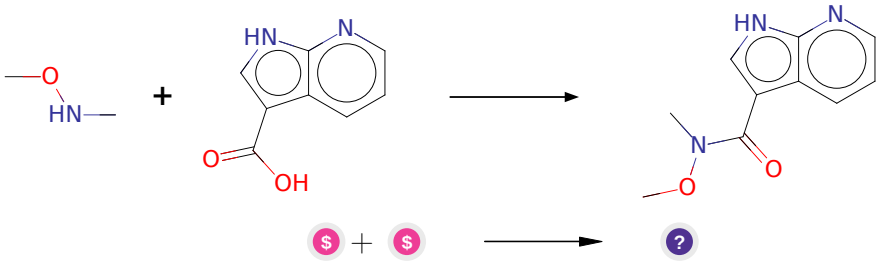


Figure 2: Outline of path 2

2.2.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. n-methoxymethylamine - *ChemImpexInternational*
2. 7-Azaindole-3-carboxylic acid - *Combi-Blocks*

Products:

1. CON(C)C(=O)c1c[nH]c2ncccc12

Typical conditions: DCC.DMAP or CDI.TEA.DCM

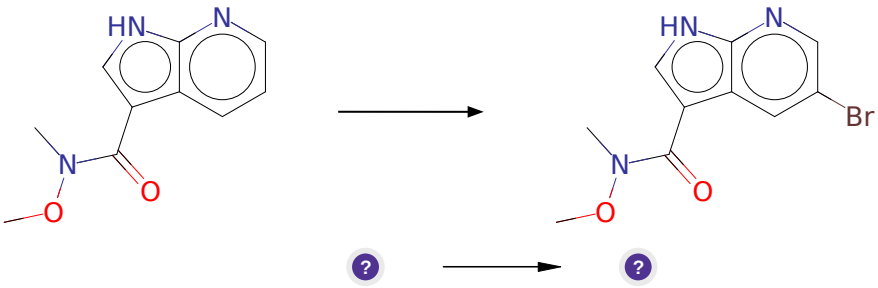
Protections: none

Yield: good

Reference: Patent: WO2007/67333A2, 2007 & *10.1016/j.bmcl.2008.09.100*

Retrosynthesis ID: 1152

2.2.2 Bromination of aromatic compounds



Substrates:

1. CON(C)C(=O)c1c[nH]c2ncccc12

Products:

1. CON(C)C(=O)c1c[nH]c2ncc(Br)cc12

Typical conditions: Br2.Fe

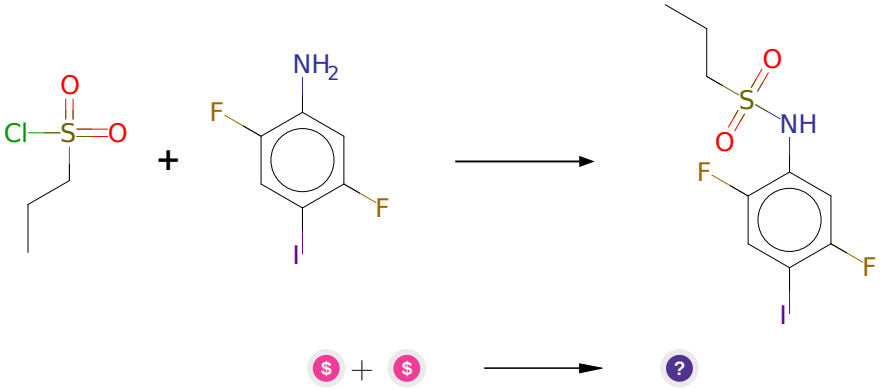
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.2.3 N-Sulfonylation



Substrates:

1. 1-Propanesulfonyl chloride - *available at Sigma-Aldrich*
2. 2,5-Difluoro-4-iodoaniline - *SynthonixCorporation*

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(I)cc1F

Typical conditions: THF.rt

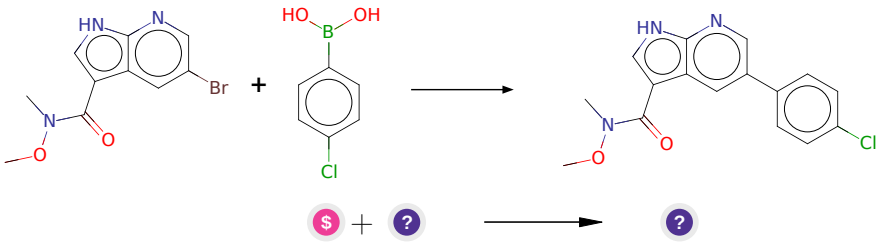
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14717

2.2.4 Suzuki coupling of arylboronic acids with aryl bromides



Substrates:

1. 4-Chlorophenylboronic acid - *available at Sigma-Aldrich*

2. CON(C)C(=O)c1c[nH]c2ncc(Br)cc12

Products:

1. CON(C)C(=O)c1c[nH]c2ncc(-c3ccc(Cl)cc3)cc12

Typical conditions: Pd catalyst.base.solvent

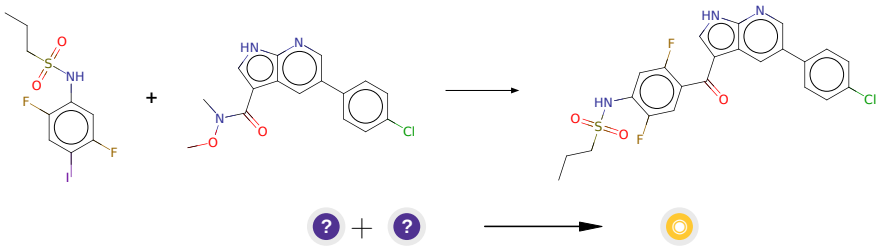
Protections: none

Yield: good

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

2.2.5 Synthesis of ketones from Weinreb amides



Substrates:

1. CCCS(=O)(=O)Nc1cc(F)c(I)cc1F
2. CON(C)C(=O)c1c[nH]c2ncc(-c3ccc(Cl)cc3)cc12

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(C(=O)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)cc1F

Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Yield: good

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.3 Path 3

Score: 184.88

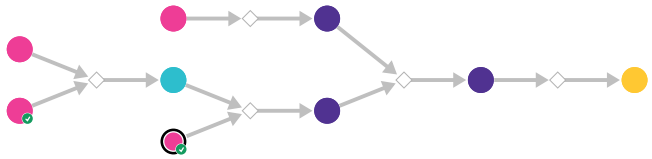
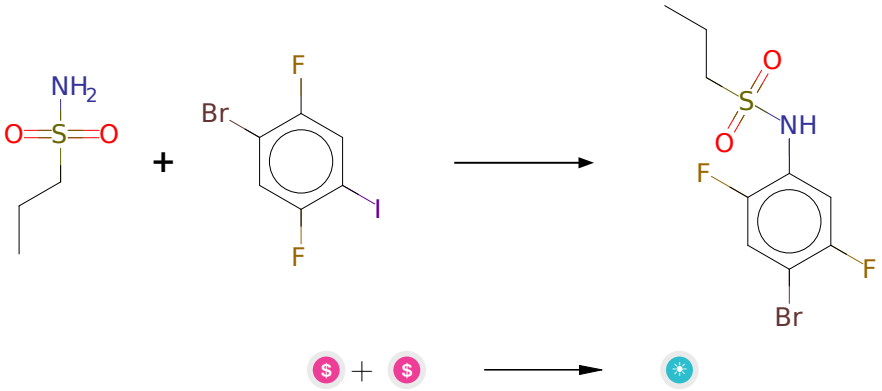


Figure 3: Outline of path 3

2.3.1 Arylation of sulfonamides with aryl iodides



Substrates:

1. Propane-1-sulfonamide - *Combi-Blocks*
2. 4-Bromo-2,5-difluoroiodobenzene - *available at Sigma-Aldrich*

Products:

1. N-(4-bromo-2,5-difluorophenyl)propane-1-sulfonamide

Typical conditions: Cu.salt.diamine.base.DMF.heat

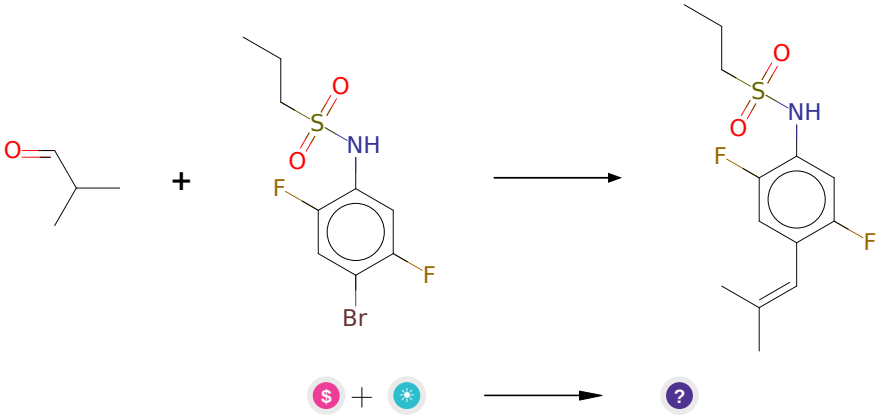
Protections: none

Yield: good

Reference: *10.1016/j.tetlet.2006.04.041* and *10.1016/j.tetlet.2011.10.113* and *10.1016/j.tetlet.2005.08.149* and *10.1021/ol035942y* and *10.1021/acs.jmedchem.6b00685*

Retrosynthesis ID: 10012567

2.3.2 Arylation of hydrazones with bromoarene



Substrates:

1. Isobutanal - *available at Sigma-Aldrich*
2. N-(4-bromo-2,5-difluorophenyl)propane-1-sulfonamide

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(C=C(C)C)cc1F

Typical conditions: 1.TsNH2NH2.2.PdCl2(MeCN)2/Xphos.tBuOLi.ArX.dioxane.heating

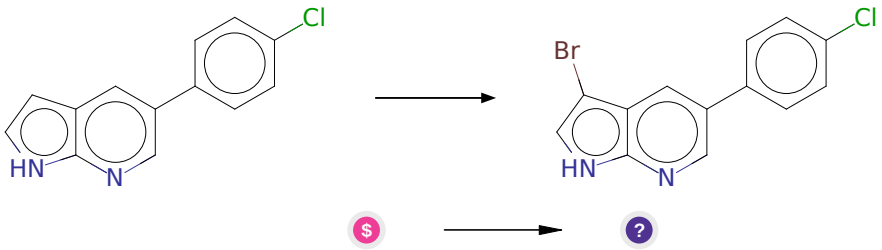
Protections: none

Yield: good

Reference: *10.1002/anie.200701815*

Retrosynthesis ID: 9990497

2.3.3 Bromination of aromatic compounds



Substrates:

1. 5-(4-Chlorophenyl)-1H-pyrrolo[2,3-b]pyridine - *Combi-Blocks*

Products:

1. Clc1ccc(-c2cnc3[nH]cc(Br)c3c2)cc1

Typical conditions: Br2.Fe

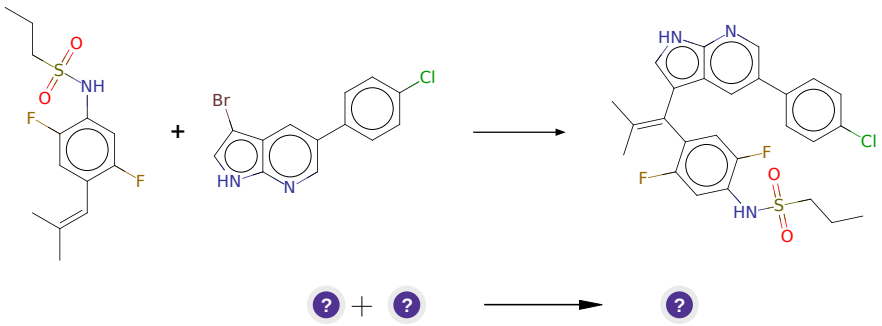
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.3.4 Heck Reaction



Substrates:

1. Clc1ccc(-c2cnc3[nH]cc(Br)c3c2)cc1
2. CCCS(=O)(=O)Nc1cc(F)c(C=C(C)C)cc1F

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(C(=C(C)C)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)cc1F

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

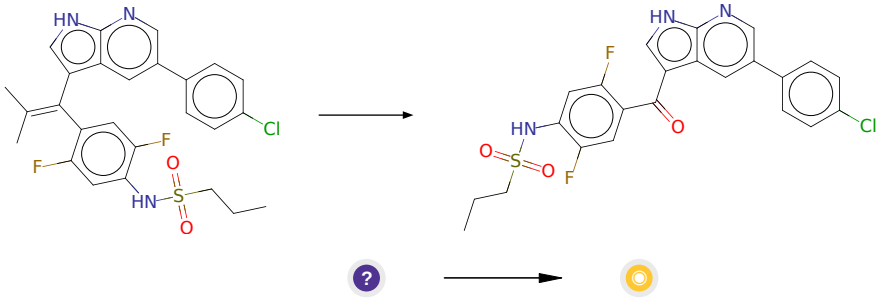
Protections: none

Yield: good

Reference: *10.1016/j.tetlet.2013.01.077* or *10.1021/ja508165a* *10.3390/molecules16108353* or *10.1039/C3GC40493E* *10.1021/ol0360288* or *10.1021/ol702755g* or *10.1055/s-0033-1340319* or *10.1016/j.tet.2004.10.049*

Retrosynthesis ID: 9174

2.3.5 Ozonolysis



Substrates:

1. CCCS(=O)(=O)Nc1cc(F)c(C(=C(C)C)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)cc1F

Products:

1. CCCS(=O)(=O)Nc1cc(F)c(C(=O)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)cc1F

Typical conditions: O3.MeOH.CH2Cl2.PPh3 or Me2S.low temperature

Protections: none

Yield: good

Reference: *10.1016/j.tet.2017.03.039*

Retrosynthesis ID: 5079