Paths of analysis*

Y3A

Synthia

October 10, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: Exclude Diastereoselecitve reactions, Tunnels, FGI, FGI with protections

Max. paths returned: 50

Max. iterations: 2000

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1500 $/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 5

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

FGI Coeff: 0

Tunnels Coeff: 0

JSON Parameters: {}

2 Paths

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

2.1 Path 1

Score: `1000151.35`

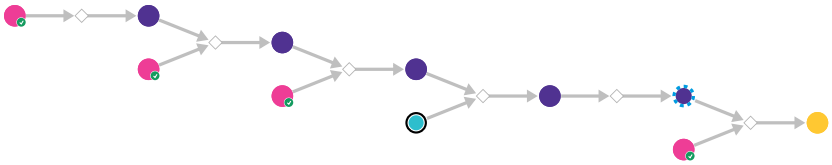
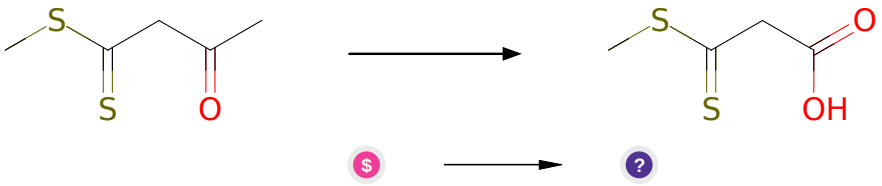


Figure 1: Outline of path 1

2.1.1 Synthesis of Carboxylic Acids via Haloform Reaction



Substrates:

1. 4-(methylsulfanyl)-4-sulfanylidenebutan-2-one - *available at Sigma-Aldrich*

Products:

1. CSC(=S)CC(=O)O

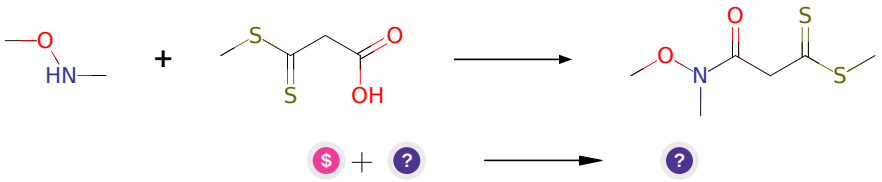
Typical conditions: I2.KI.KOH.H2O.dioxane

Protections: none

Reference: *10.1021/jacs.8b12242* SI p. S25 and *10.1021/ol5025025* SI p. S27

Retrosynthesis ID: 10366

2.1.2 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. n-methoxymethylamine - *available at Sigma-Aldrich*
2. CSC(=S)CC(=O)O

Products:

1. CON(C)C(=O)CC(=S)SC

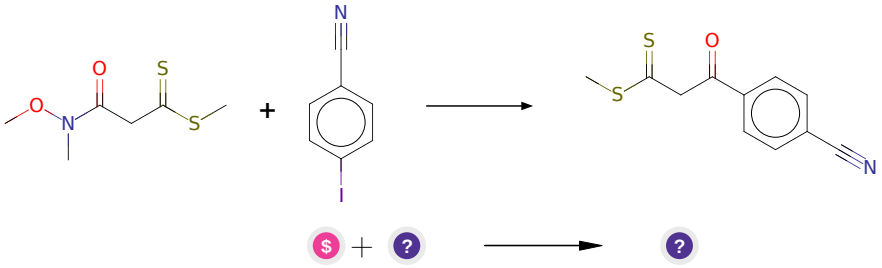
Typical conditions: DCC.DMAP or CDI.TEA.DCM

Protections: none

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

Retrosynthesis ID: 1152

2.1.3 Synthesis of ketones from Weinreb amides



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. CON(C)C(=O)CC(=S)SC

Products:

1. CSC(=S)CC(=O)c1ccc(C#N)cc1

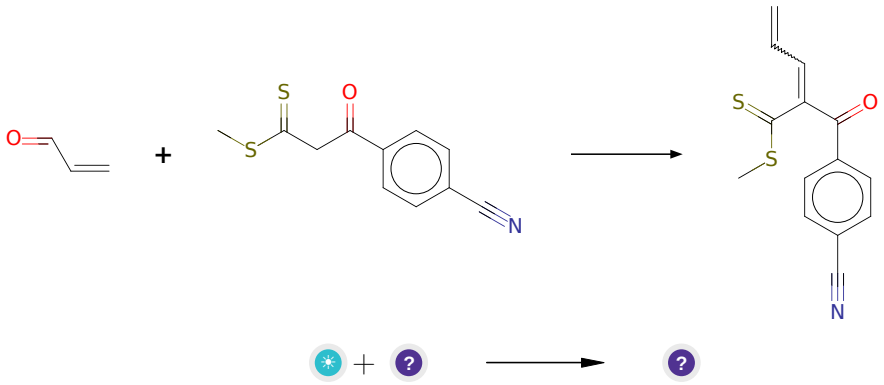
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

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

Retrosynthesis ID: 5060

2.1.4 Aldol Condensation



Substrates:

1. Acrolein
2. CSC(=S)CC(=O)c1ccc(C#N)cc1

Products:

1. C=CC=C(C(=O)c1ccc(C#N)cc1)C(=S)SC

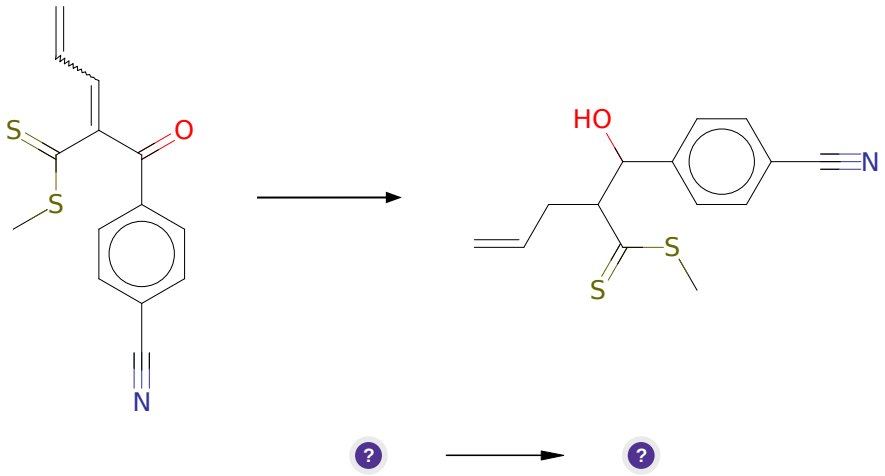
Typical conditions: NaOEt.base

Protections: none

Reference: *10.1080/00397911.2016.1206938*

Retrosynthesis ID: 10049

2.1.5 Reduction of enones to saturated alcohols



Substrates:

1. C=CC=C(C(=O)c1ccc(C#N)cc1)C(=S)SC

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1

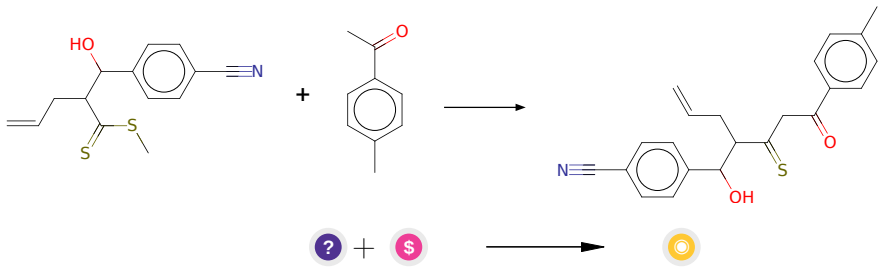
Typical conditions: NaBH4.transition.metal.salt.(eg.Pd(OAc)2.or.CeCl3)

Protections: none

Reference: *10.1080/00397910902788117* AND *10.1021/jo00235a009* AND *10.1016/0040-4020(95)00125-R* AND *10.1021/ja01327a041* AND *10.1021/jo00302a056* AND *10.1002/adsc.200900628*

Retrosynthesis ID: 15304

2.1.6 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1

2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc(C#N)cc1

Typical conditions: NaH.DMF

Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM) 2-Methoxyethoxymethyl Ether (MEM) Tetrahydropyranyl Ether (THP) Benzyl Ether (PMB) t-Butyldimethylsilyl Ether (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413

2.2 Path 2

Score: `1000151.35`

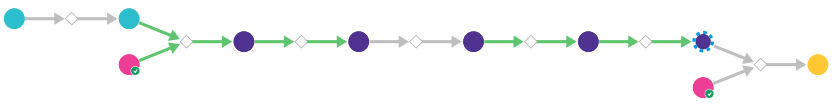
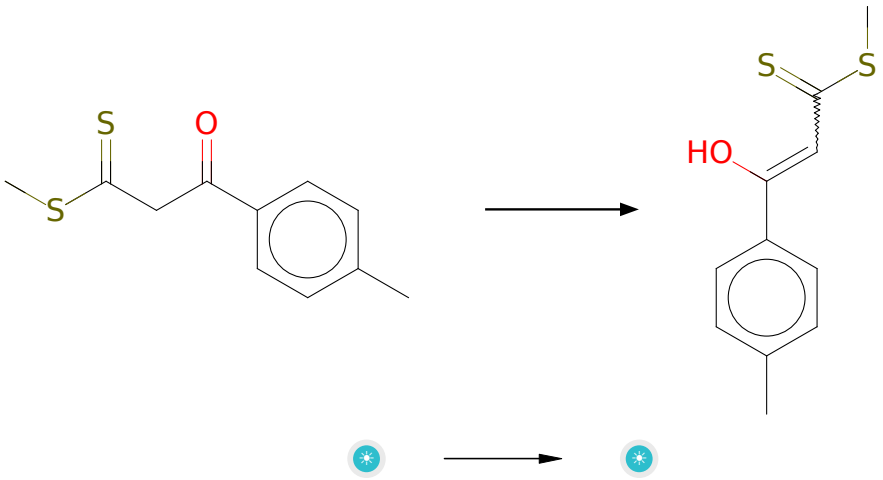


Figure 2: Outline of path 2

2.2.1 Keto-enol Tautomerism



Substrates:

1. 4-methyl-benzoyl-dithioessigsaeure-methylester (p-toluoyl-dithioessigsaeure-methylester)

Products:

1. 3-hydroxy-3-p-tolyl-dithioacrylic acid methyl ester

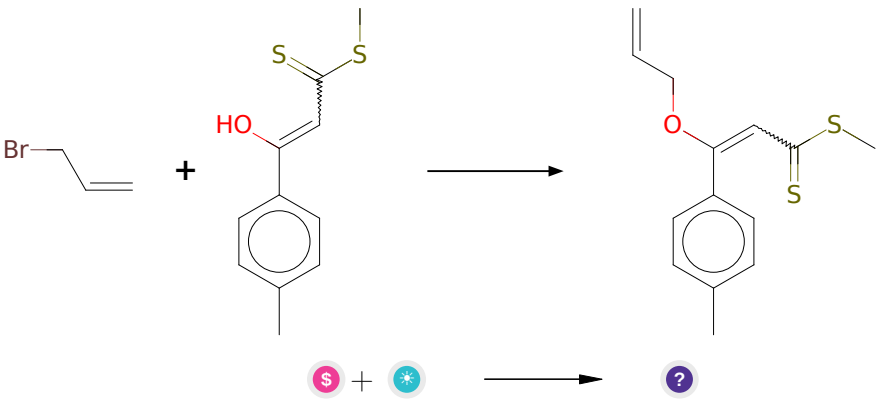
Typical conditions: solvent

Protections: none

Reference: *10.1021/ja01065a003* AND *10.1021/jo8012385*

Retrosynthesis ID: 7780

2.2.2 Enolate O-Alkylation



Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. 3-hydroxy-3-p-tolyl-dithioacrylic acid methyl ester

Products:

1. C=CCOC(=CC(=S)SC)c1ccc(C)cc1

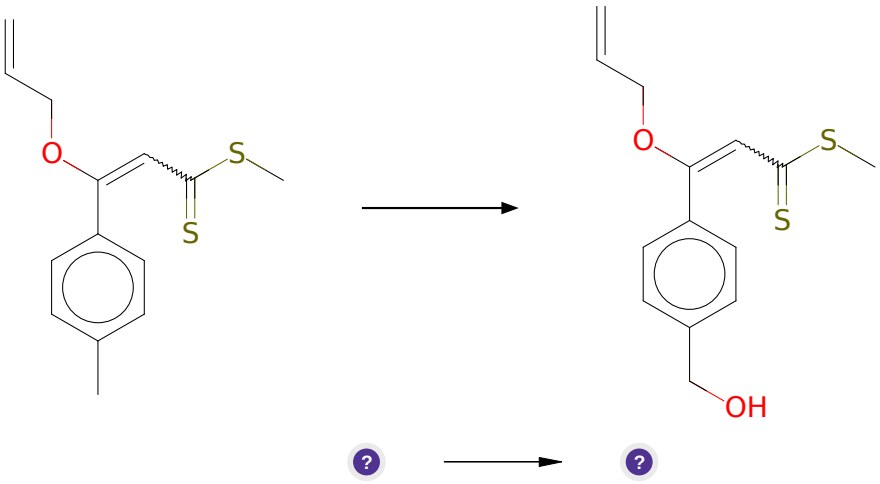
Typical conditions: Cs2CO3.DMF

Protections: none

Reference: *10.1016/j.bmcl.2012.05.070* and *10.1039/b612336h*

Retrosynthesis ID: 14841

2.2.3 Hydroxylation of benzylic position



Substrates:

1. C=CCOC(=CC(=S)SC)c1ccc(C)cc1

Products:

1. C=CCOC(=CC(=S)SC)c1ccc(CO)cc1

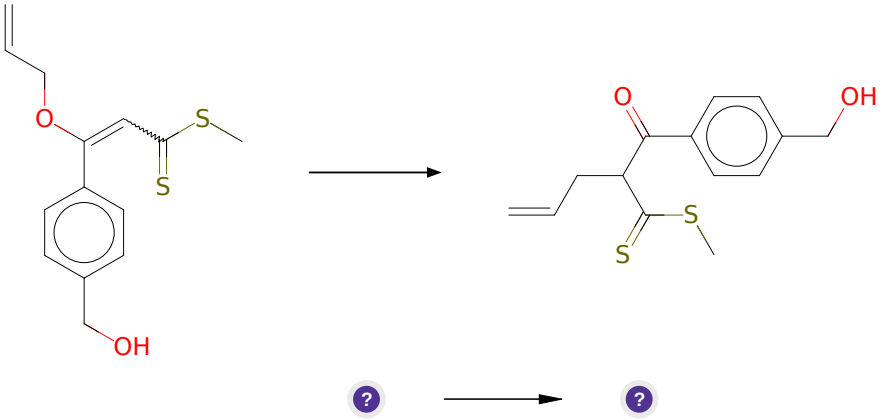
Typical conditions: 1.Ce(OTf)4.MeCN.2.NaBH4

Protections: none

Reference: *10.1039/B008843I* and WO2012137047 p.12

Retrosynthesis ID: 27139

2.2.4 Claisen Rearrangement



Substrates:

1. C=CCOC(=CC(=S)SC)c1ccc(CO)cc1

Products:

1. C=CCC(C(=O)c1ccc(CO)cc1)C(=S)SC

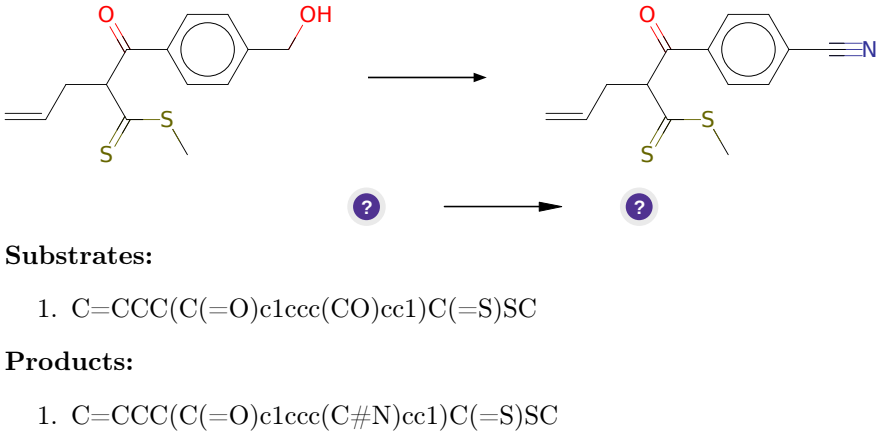
Typical conditions: heat

Protections: none

Reference: DOI: *10.1021/ja00206a017* and *10.1016/S0022-1139(98)00313-3*

Retrosynthesis ID: 1226

2.2.5 Synthesis of nitriles from alcohols



Substrates:

1. C=CCC(C(=O)c1ccc(CO)cc1)C(=S)SC

Products:

1. C=CCC(C(=O)c1ccc(C#N)cc1)C(=S)SC

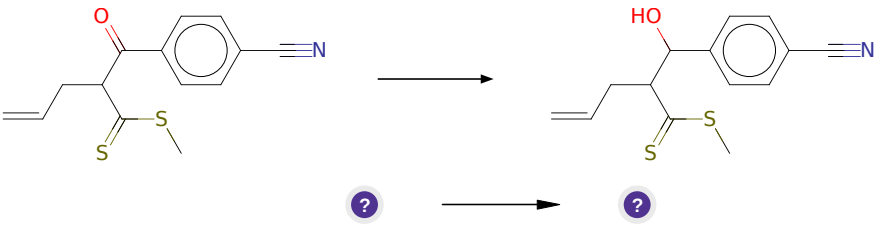
Typical conditions: 1) TEMPO.DCM.rt. 2) NH3.I2 or NH3.tBuOCl

Protections: none

Reference: *10.1055/s-0033-1338489*

Retrosynthesis ID: 50205

2.2.6 Reduction of ketones with NaBH4



Substrates:

1. C=CCC(C(=O)c1ccc(C#N)cc1)C(=S)SC

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1

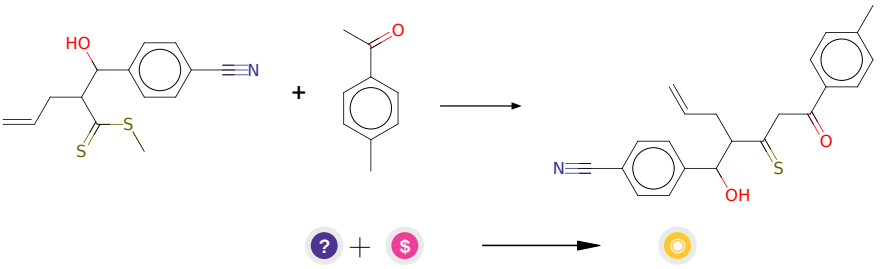
Typical conditions: NaBH4.EtOH.0-20 C

Protections: none

Reference: *10.1016/j.ejmech.2020.112360* p. 3, 8 and *10.1016/j.ejmech.2010.10.012* p. 434, 436

Retrosynthesis ID: 50432

2.2.7 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc(C#N)cc1

Typical conditions: NaH.DMF

Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM) 2-Methoxyethoxymethyl Ether (MEM) Tetrahydropyranyl Ether (THP) Benzyl Ether (PMB) t-Butyldimethylsilyl Ether (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413

2.3 Path 3

Score: `1000151.35`

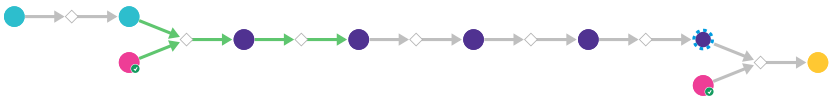
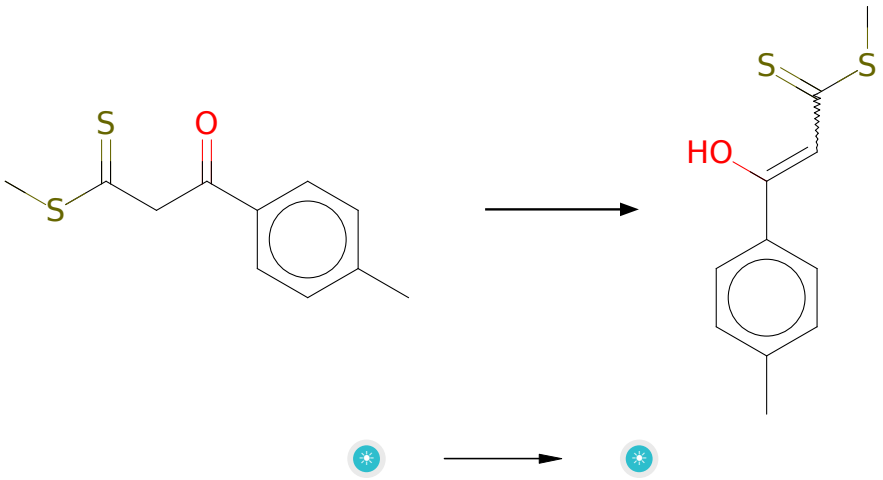


Figure 3: Outline of path 3

2.3.1 Keto-enol Tautomerism



Substrates:

1. 4-methyl-benzoyl-dithioessigsaeure-methylester (p-toluoyl-dithioessigsaeure-methylester)

Products:

1. 3-hydroxy-3-p-tolyl-dithioacrylic acid methyl ester

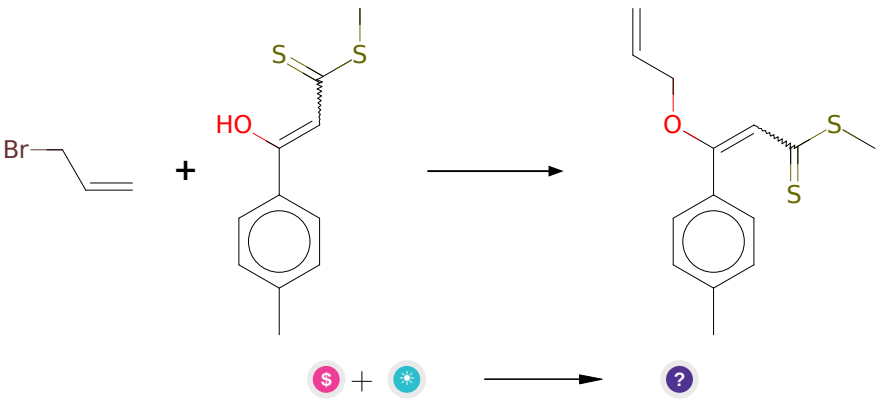
Typical conditions: solvent

Protections: none

Reference: *10.1021/ja01065a003* AND *10.1021/jo8012385*

Retrosynthesis ID: 7780

2.3.2 Enolate O-Alkylation



Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. 3-hydroxy-3-p-tolyl-dithioacrylic acid methyl ester

Products:

1. C=CCOC(=CC(=S)SC)c1ccc(C)cc1

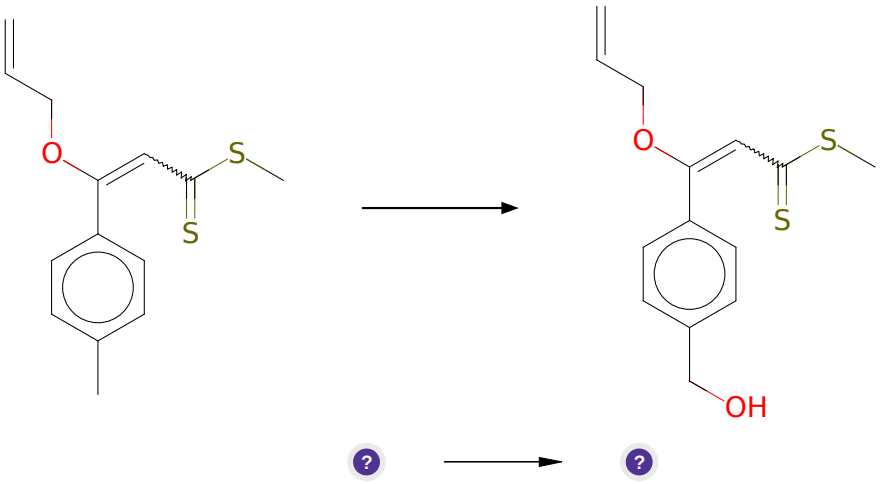
Typical conditions: Cs2CO3.DMF

Protections: none

Reference: *10.1016/j.bmcl.2012.05.070* and *10.1039/b612336h*

Retrosynthesis ID: 14841

2.3.3 Hydroxylation of benzylic position



Substrates:

1. C=CCOC(=CC(=S)SC)c1ccc(C)cc1

Products:

1. C=CCOC(=CC(=S)SC)c1ccc(CO)cc1

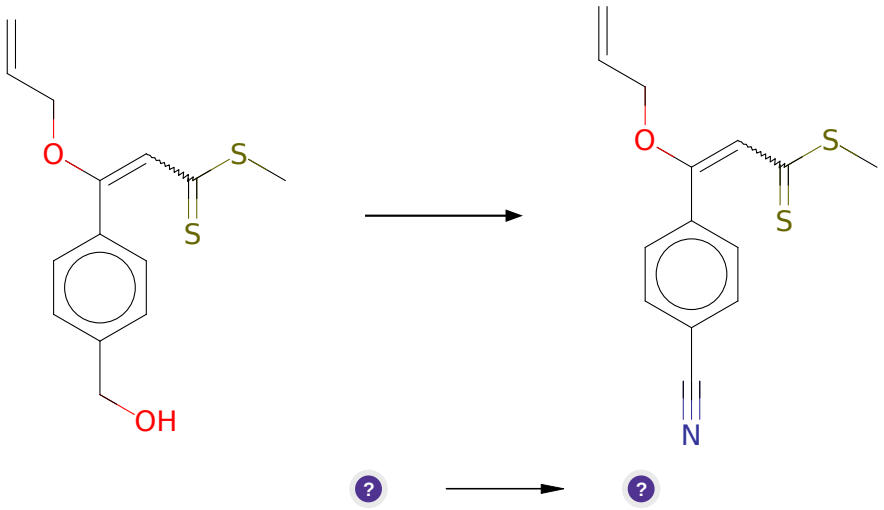
Typical conditions: 1.Ce(OTf)4.MeCN.2.NaBH4

Protections: none

Reference: *10.1039/B008843I* and WO2012137047 p.12

Retrosynthesis ID: 27139

2.3.4 Conversion of Alcohols into Nitriles



Substrates:

1. C=CCOC(=CC(=S)SC)c1ccc(CO)cc1

Products:

1. C=CCOC(=CC(=S)SC)c1ccc(C#N)cc1

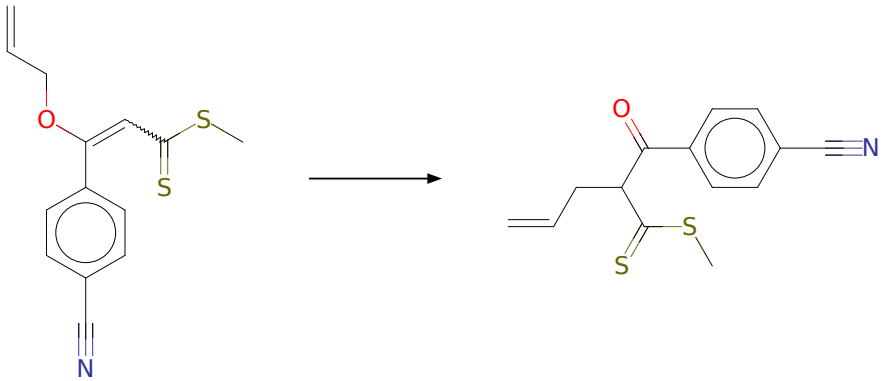
Typical conditions: I2.RT

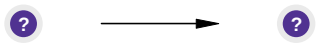
Protections: none

Reference: DOI:*10.1021/jo0625352*

Retrosynthesis ID: 10973

2.3.5 Claisen Rearrangement





Substrates:

1. C=CCOC(=CC(=S)SC)c1ccc(C#N)cc1

Products:

1. C=CCC(C(=O)c1ccc(C#N)cc1)C(=S)SC

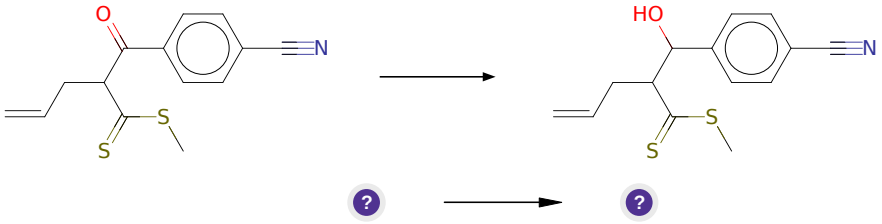
Typical conditions: heat

Protections: none

Reference: DOI: *10.1021/ja00206a017* and *10.1016/S0022-1139(98)00313-3*

Retrosynthesis ID: 1226

2.3.6 Reduction of ketones with NaBH4



Substrates:

1. C=CCC(C(=O)c1ccc(C#N)cc1)C(=S)SC

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1

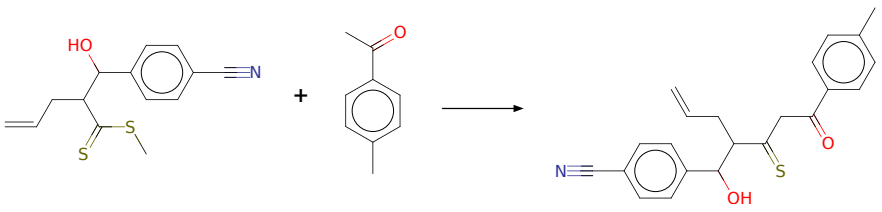
Typical conditions: NaBH4.EtOH.0-20 C

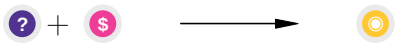
Protections: none

Reference: *10.1016/j.ejmech.2020.112360* p. 3, 8 and *10.1016/j.ejmech.2010.10.012* p. 434, 436

Retrosynthesis ID: 50432

2.3.7 Condensation of ketones with dithioesters





Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc(C#N)cc1

Typical conditions: NaH.DMF

Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM) 2-Methoxyethoxymethyl Ether (MEM) Tetrahydropyranyl Ether (THP) Benzyl Ether (PMB) t-Butyldimethylsilyl Ether (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413

2.4 Path 4

Score: `1000161.11`

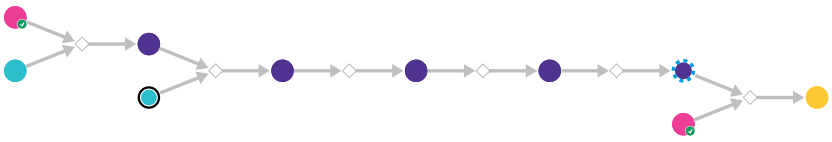
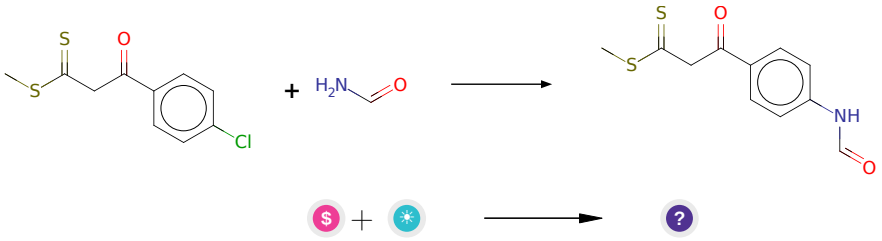


Figure 4: Outline of path 4

2.4.1 Arylation of amides with aryl chlorides



Substrates:

1. Amide C1 - *available at Sigma-Aldrich*
2. p-chlor-benzoyl-dithioessigsaeure-methylester

Products:

1. CSC(=S)CC(=O)c1ccc(NC=O)cc1

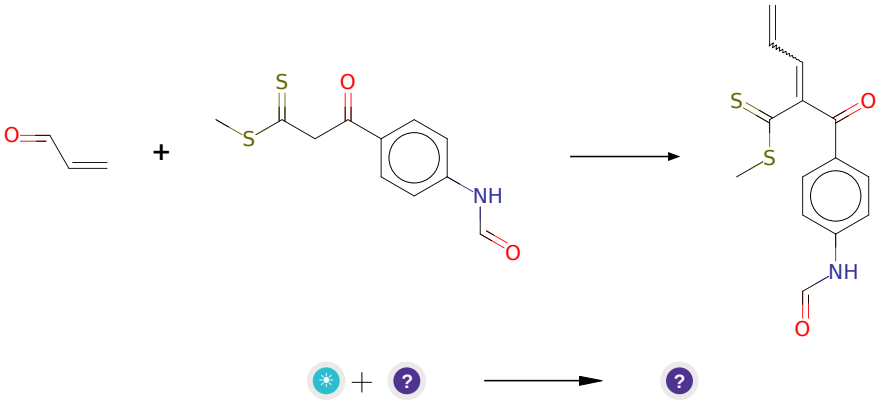
Typical conditions: Base.[Pd].catalyst.dioxane.heat or CuI.diamine.base.DMF.heat

Protections: none

Reference: *10.1021/ja0717414* and *10.1016/j.tet.2009.04.096* and *10.1002/chem.201302453* and *10.1080/00397911.2016.1195844*

Retrosynthesis ID: 10012552

2.4.2 Aldol Condensation



Substrates:

1. Acrolein

2. CSC(=S)CC(=O)c1ccc(NC=O)cc1

Products:

1. C=CC=C(C(=O)c1ccc(NC=O)cc1)C(=S)SC

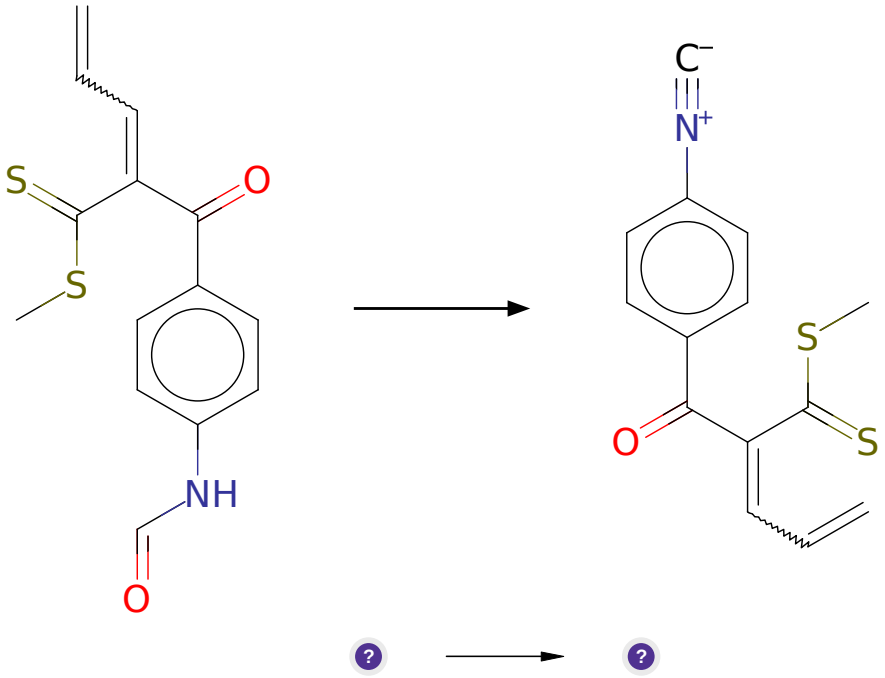
Typical conditions: NaOEt.base

Protections: none

Reference: *10.1080/00397911.2016.1206938*

Retrosynthesis ID: 10049

2.4.3 Synthesis of isocyanides from formamides



Substrates:

1. C=CC=C(C(=O)c1ccc(NC=O)cc1)C(=S)SC

Products:

1. [C-]#[N+]c1ccc(C(=O)C(=CC=C)C(=S)SC)cc1

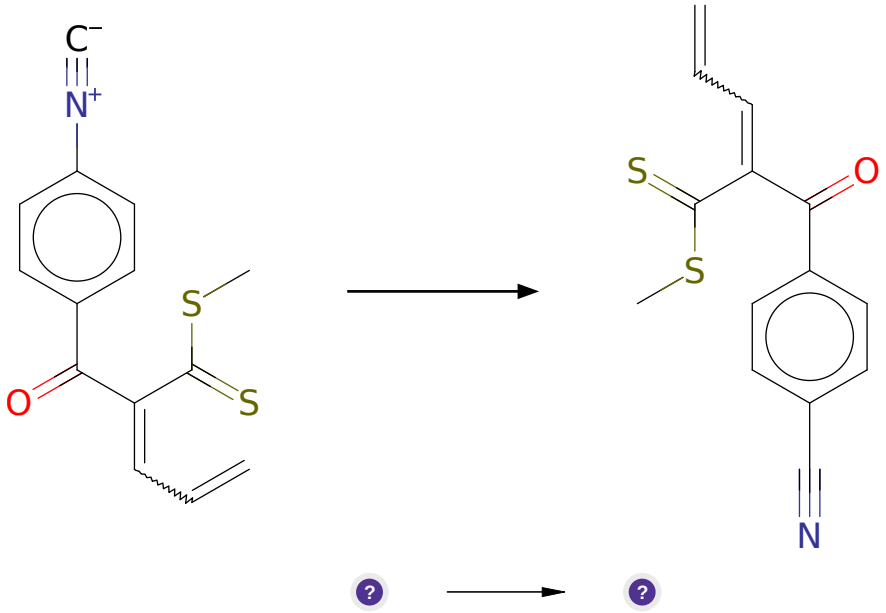
Typical conditions: TCT.DCM.TEA.MW.50-100C

Protections: none

Reference: DOI: *10.1021/jo047924f*

Retrosynthesis ID: 245867

2.4.4 Isonitrile-Nitrile Rearrangement



Substrates:

1. [C-]#[N+]c1ccc(C(=O)C(=CC=C)C(=S)SC)cc1

Products:

1. C=CC=C(C(=O)c1ccc(C#N)cc1)C(=S)SC

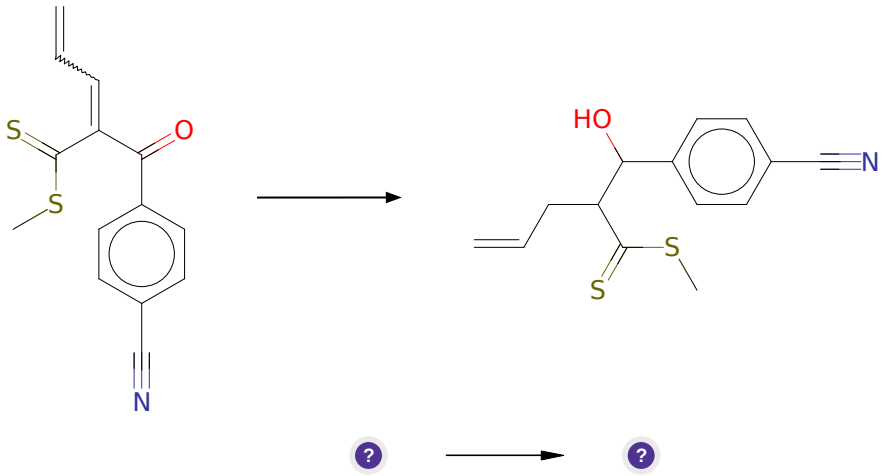
Typical conditions: (1-phenylethenyl)benzene.50C

Protections: none

Reference: DOI:*10.1021/jo00380a028*

Retrosynthesis ID: 10398

2.4.5 Reduction of enones to saturated alcohols



Substrates:

1. C=CC=C(C(=O)c1ccc(C#N)cc1)C(=S)SC

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1

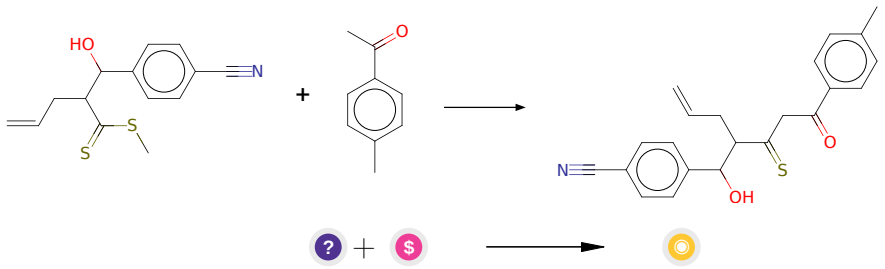
Typical conditions: NaBH4.transition.metal.salt.(eg.Pd(OAc)2.or.CeCl3)

Protections: none

Reference: *10.1080/00397910902788117* AND *10.1021/jo00235a009* AND *10.1016/0040-4020(95)00125-R* AND *10.1021/ja01327a041* AND *10.1021/jo00302a056* AND *10.1002/adsc.200900628*

Retrosynthesis ID: 15304

2.4.6 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc(C#N)cc1

2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc(C#N)cc1

Typical conditions: NaH.DMF

Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM) 2-Methoxyethoxymethyl Ether (MEM) Tetrahydropyranyl Ether (THP) Benzyl Ether (PMB) t-Butyldimethylsilyl Ether (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413