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

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

2.1 Path 1

Score: `1000100.08`

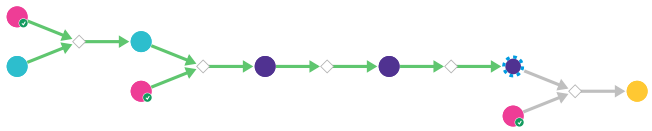
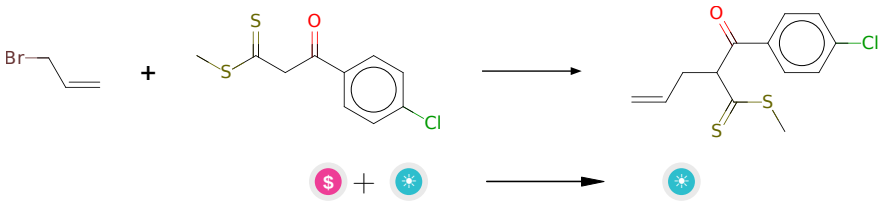


Figure 1: Outline of path 1

2.1.1 Alkylation of ketones



Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. p-chlor-benzoyl-dithioessigsaeure-methylester

Products:

1. a-allyl-a-(p-chlorobenzoyl)dithioacetate

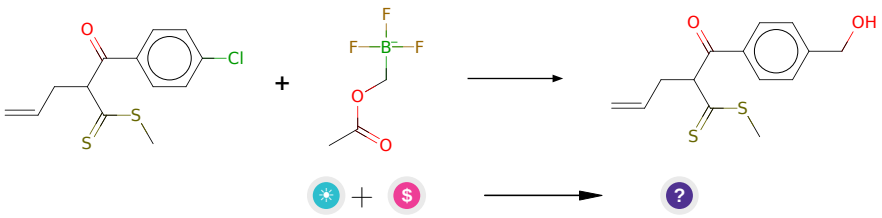
Typical conditions: LDA or other base.THF.-78C

Protections: none

Reference: DOI: *10.1021/jo1019738* OR DOI: *10.1021/jm00114a016*

Retrosynthesis ID: 1866

2.1.2 Hydroxymethylation of aryl chlorides with acetoxymethyltrifluoroborate



Substrates:

1. a-allyl-a-(p-chlorobenzoyl)dithioacetate
2. potassium (acetoxymethyl)trifluoroborate - *available at Sigma-Aldrich*

Products:

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

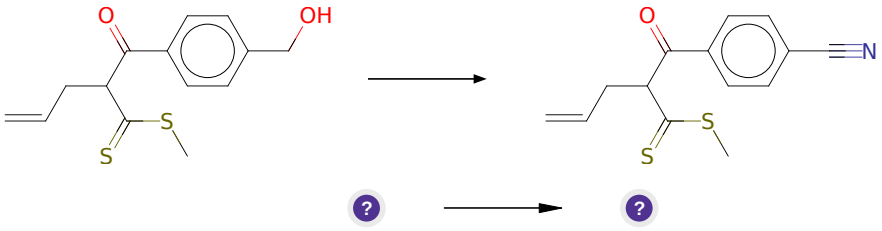
Typical conditions: Pd(dba)2.RuPhos.Na2CO3.dioxane/H2O.reflux

Protections: none

Reference: *10.1021/ol300149b*

Retrosynthesis ID: 10033559

2.1.3 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

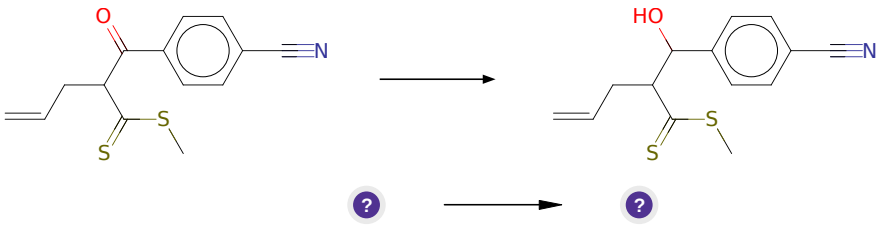
Typical conditions: 1) TEMPO.DCM.rt. 2) NH3.I2 or NH3.tBuOCl

Protections: none

Reference: *10.1055/s-0033-1338489*

Retrosynthesis ID: 50205

2.1.4 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

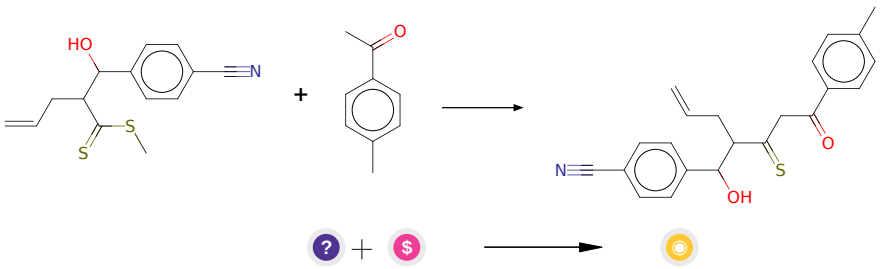
Typical conditions: NaBH4.EtOH.0-20 C

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

2.1.5 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: `1000115.31`

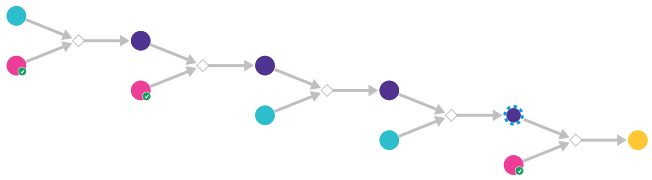
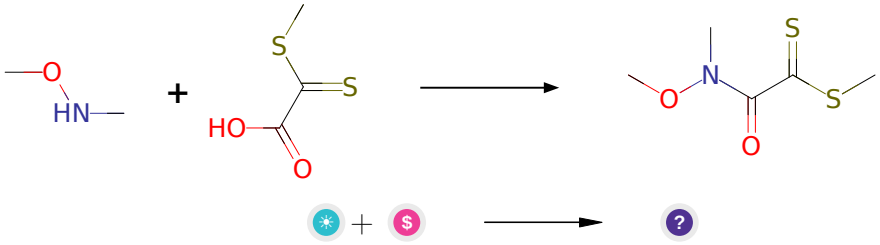


Figure 2: Outline of path 2

2.2.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. 1-methyl-1,1-dithiooxalsaeure
2. n-methoxymethylamine - *available at Sigma-Aldrich*

Products:

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

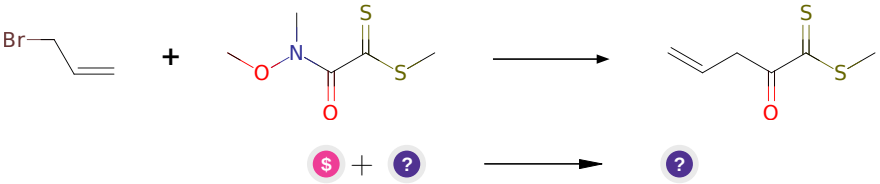
Typical conditions: DCC.DMAP or CDI.TEA.DCM

Protections: none

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

Retrosynthesis ID: 1152

2.2.2 Synthesis of ketones from Weinreb amides



Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. CON(C)C(=O)C(=S)SC

Products:

1. C=CCC(=O)C(=S)SC

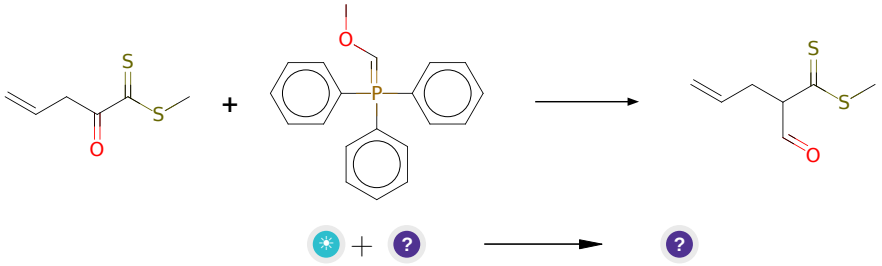
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

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

Retrosynthesis ID: 6837

2.2.3 Olefination of ketones followed by hydrolysis



Substrates:

1. triphenylphosphonium methoxymethylide
2. C=CCC(=O)C(=S)SC

Products:

1. C=CCC(C=O)C(=S)SC

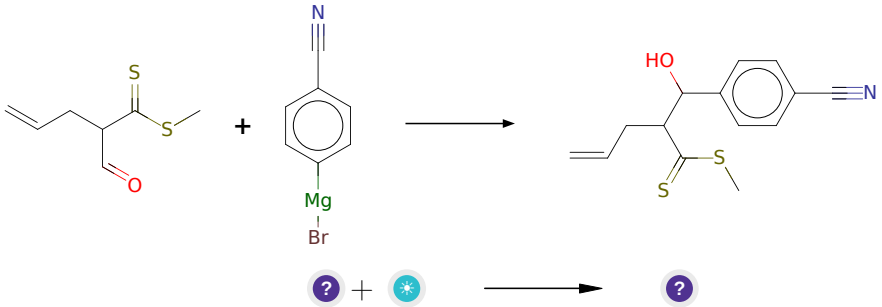
Typical conditions: KHMDS.THF hydrolysis: pTsOH.water.acetone

Protections: none

Reference: *10.1002/anie.201811403* and *10.1002/anie.201809130* and *10.1002/anie.201705809* and *10.1002/anie.201409038* and *10.1021/ol3028994* (SI)

Retrosynthesis ID: 31014861

2.2.4 Grignard-Type Reaction



Substrates:

1. C=CCC(C=O)C(=S)SC
2. C7H4BrMgN

Products:

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

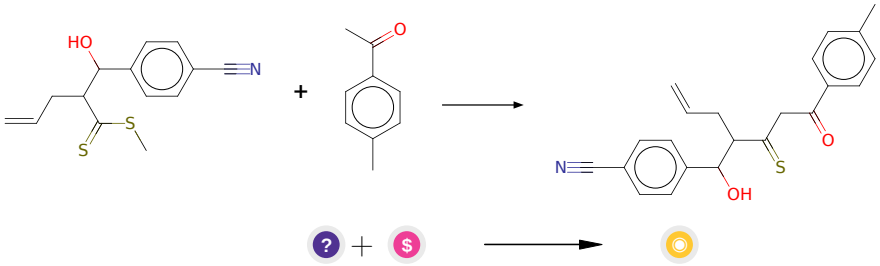
Typical conditions: Mg or Li.ether

Protections: none

Reference: *10.1055/s-0030-1260809* or *10.1021/jm061429p* or *10.1021/jo0621423* or *10.1021/ja00373a036* or *10.1016/S0040-4020(01)00457-4*

Retrosynthesis ID: 25123

2.2.5 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: 1000139.14

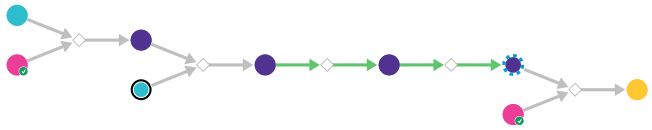
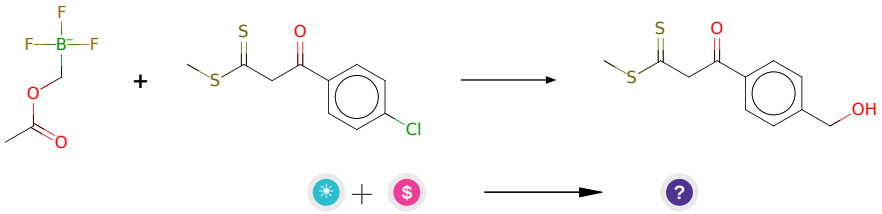


Figure 3: Outline of path 3

2.3.1 Hydroxymethylation of aryl chlorides with acetoxymethyltrifluoroborate



Substrates:

1. p-chlor-benzoyl-dithioessigsaeure-methylester
2. potassium (acetoxymethyl)trifluoroborate - *available at Sigma-Aldrich*

Products:

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

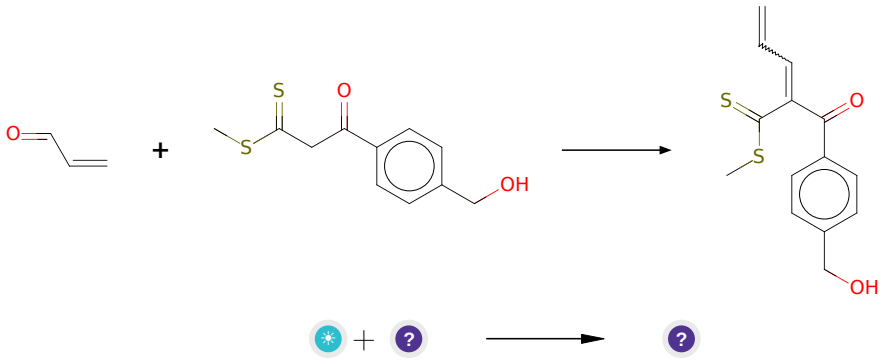
Typical conditions: Pd(dba)2.RuPhos.Na2CO3.dioxane/H2O.reflux

Protections: none

Reference: *10.1021/ol300149b*

Retrosynthesis ID: 10033559

2.3.2 Aldol Condensation



Substrates:

1. Acrolein
2. CSC(=S)CC(=O)c1ccc(CO)cc1

Products:

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

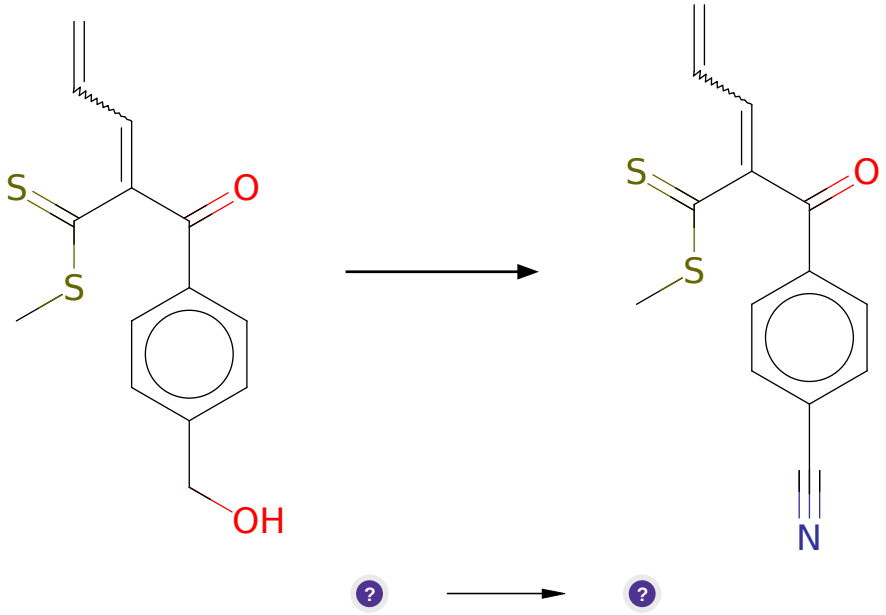
Typical conditions: NaOEt.base

Protections: none

Reference: *10.1080/00397911.2016.1206938*

Retrosynthesis ID: 10049

2.3.3 Synthesis of nitriles from alcohols



Substrates:

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

Products:

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

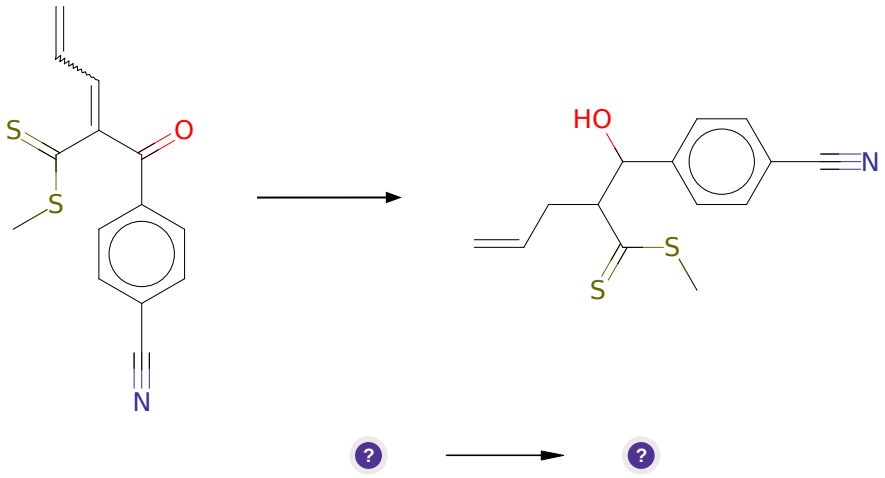
Typical conditions: 1) TEMPO.DCM.rt. 2) NH3.I2 or NH3.tBuOCl

Protections: none

Reference: *10.1055/s-0033-1338489*

Retrosynthesis ID: 50205

2.3.4 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

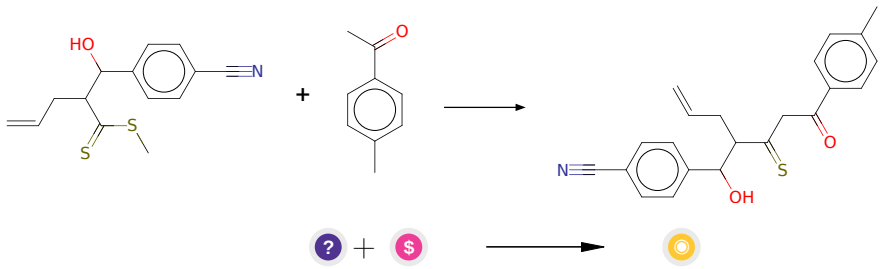
Typical conditions: NaBH4.transition.metal.salt.(eg.Pd(OAc)2.or.CeCl3)

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

2.3.5 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: `1000139.14`

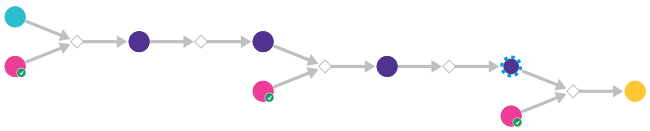
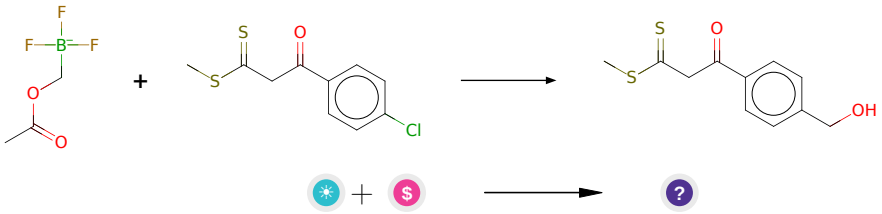


Figure 4: Outline of path 4

2.4.1 Hydroxymethylation of aryl chlorides with acetoxymethyltrifluoroborate



Substrates:

1. p-chlor-benzoyl-dithioessigsaeure-methylester
2. potassium (acetoxymethyl)trifluoroborate - *available at Sigma-Aldrich*

Products:

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

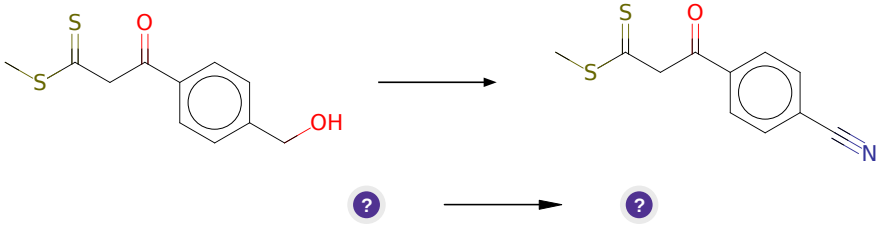
Typical conditions: Pd(dba)2.RuPhos.Na2CO3.dioxane/H2O.reflux

Protections: none

Reference: *10.1021/ol300149b*

Retrosynthesis ID: 10033559

2.4.2 Conversion of Alcohols into Nitriles



Substrates:

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

Products:

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

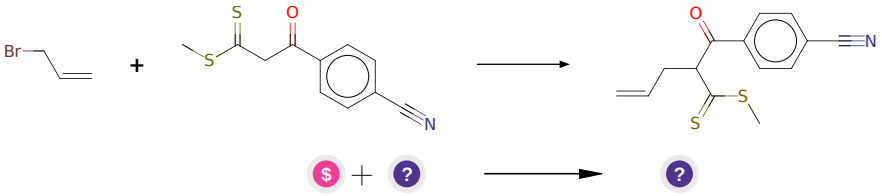
Typical conditions: I2.RT

Protections: none

Reference: DOI:*10.1021/jo0625352*

Retrosynthesis ID: 10973

2.4.3 Alkylation of ketones



Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. CSC(=S)CC(=O)c1ccc(C#N)cc1

Products:

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

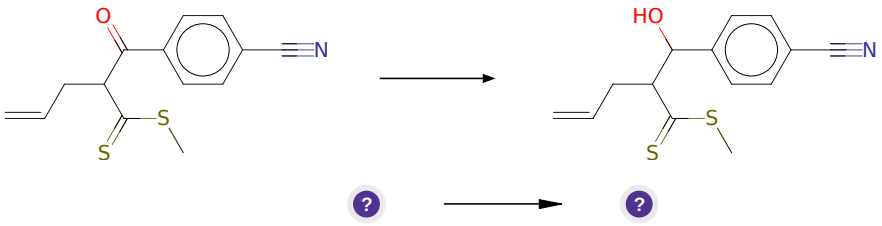
Typical conditions: LDA or other base.THF.-78C

Protections: none

Reference: DOI: *10.1021/jo1019738* OR DOI: *10.1021/jm00114a016*

Retrosynthesis ID: 1866

2.4.4 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

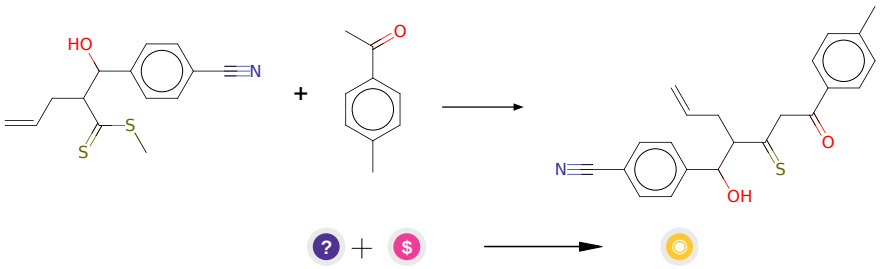
Typical conditions: NaBH4.EtOH.0-20 C

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

2.4.5 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

2.5 Path 5

Score: 1000151.35

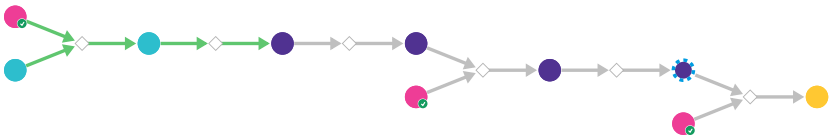
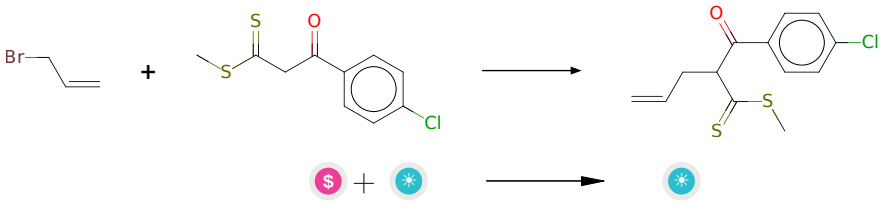


Figure 5: Outline of path 5

2.5.1 Alkylation of ketones



Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. p-chlor-benzoyl-dithioessigsaeure-methylester

Products:

1. a-allyl-a-(p-chlorobenzoyl)dithioacetate

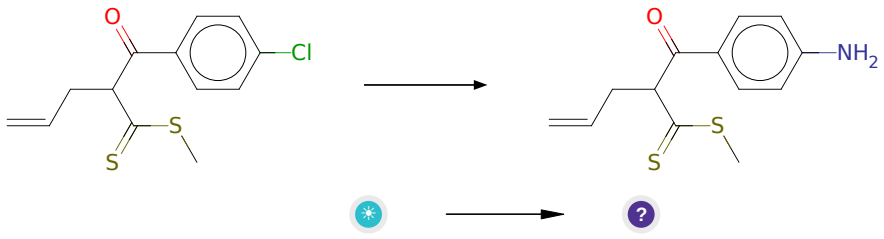
Typical conditions: LDA or other base.THF.-78C

Protections: none

Reference: DOI: *10.1021/jo1019738* OR DOI: *10.1021/jm00114a016*

Retrosynthesis ID: 1866

2.5.2 Nucleophilic aromatic substitution



Substrates:

1. a-allyl-a-(p-chlorobenzoyl)dithioacetate

Products:

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

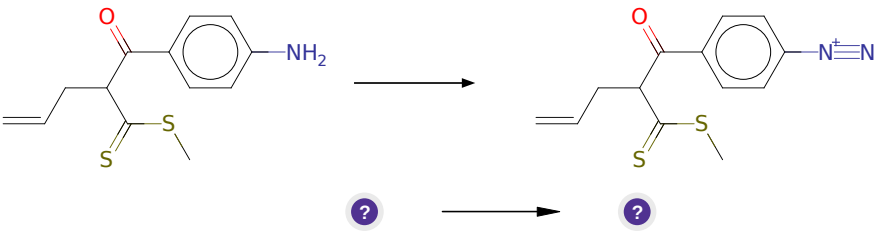
Typical conditions: solvent. Heating or pressure

Protections: none

Reference: *10.1021/jm00040a009* or *10.1111/bph.12233* or *10.1246/cl.1987.1187*

Retrosynthesis ID: 5003

2.5.3 Preparation of diazonium salts



Substrates:

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

Products:

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

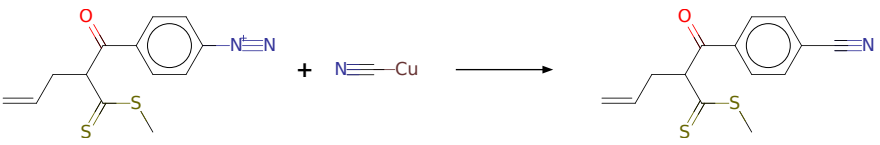
Typical conditions: HCl.NaNO2.OC

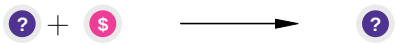
Protections: none

Reference: WO2006134111A1 p.32 and *10.1016/j.jfluchem.2012.11.007* and *10.3987/COM-97-7918*

Retrosynthesis ID: 11170

2.5.4 Sandmeyer Reaction





Substrates:

1. C=CCC(C(=O)c1ccc([N+]#N)cc1)C(=S)SC
2. Cupricin - *available at Sigma-Aldrich*

Products:

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

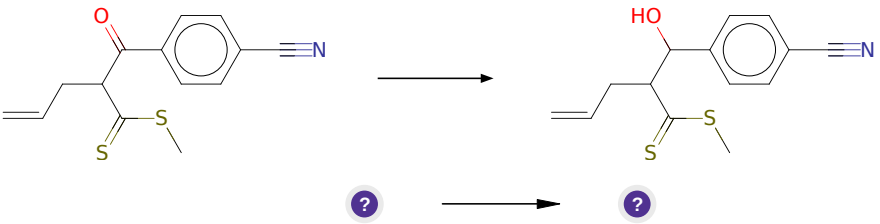
Typical conditions: Cu salt.heat

Protections: none

Reference: *10.1021/cr60126a003* and *10.1021/acs.accounts.7b00566*

Retrosynthesis ID: 11500

2.5.5 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

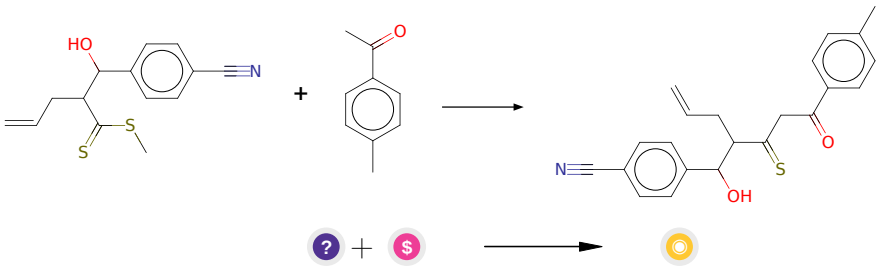
Typical conditions: NaBH4.EtOH.0-20 C

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

2.5.6 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