Chemistry

Extended Essay

Creation and evaluation of total synthesis scheme for Aripiprazole

Words: 3989

Is it possible to synthesize Aripiprazole in an amateur chemistry laboratory at a lower cost than market price?

Session: May 2021

Contents

1 Introduction

Drug synthesis is a significant application of organic chemistry. Most drugs have large and complex structures, and take a series of organic reactions to make from existing precursors.
In 2017, a chemist synthesized the anti-malarial drug pyrimethamine from household products and common laboratory reagents in a small scale, at a lower cost than market price. (Day, 2017)
This endeavour ignited my interest in total synthesis. As a secondary school student, although I cannot conduct syntheses myself, I wished to take on the challenge of proposing a synthesis route that is hopefully feasible for most chemists.
Aripiprazole, sold under the name Abilify, is a prescription antipsychotic used for mental disorders like schizophrenia (Casey & Canal, 2017). In this study, I will devise a route to synthesize it using common reagents and calculate its theoretical production cost.

This involves the research question:

Is it feasible to synthesize Aripiprazole using common reagents in a laboratory?

1.1 Aim

This is a theoretical endeavour to ponder if such a feat is feasible. This small-scale process is unrelated to industrial synthesis of the drug.

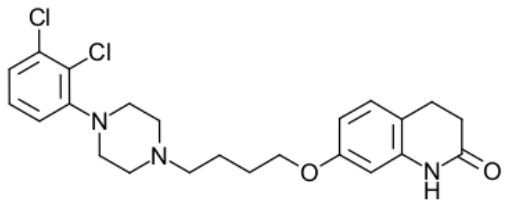


Figure 1: Structure of aripiprazole
IUPAC Name: 7-4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy-3,4-dihydro-2(1H)-quinolinone

2 Devising a synthetic route

A total synthetic route is aimed to be accessible to as many as possible. There are several criteria:

- Reagents should be available as commercial products, or commonly used in organic labs (e.g. Solvents)
- Reactions should not require specialised equipment (e.g. High pressure apparatus)
- There should not be serious hazards (e.g. Explosion) Toxic reagents are acceptable if they can be safely handled given common precautions (e.g. Fume hood)
- One-pot synthesis strategy should be considered to minimise product loss (i.e. As few purification steps as possible)

As the route may be long, the reactions involved should have few side products and high product yield. Literature proof will be found for all reactions whenever possible. Required conditions and yields from literature will be listed.

3 Synthesis from precursors

In almost all reported routes, Aripiprazole is synthesized from three precursors:

- 7-hydroxy-3,4-dihydro-2(1H)-quinolinone (7-HQ)
- 1,4-dibromobutane
- 1-(2,3-dichlorophenyl)piperazine (DCP)

The first two react under basic conditions to create 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, which then reacts with DCP (also in basic conditions) to form Aripiprazole.

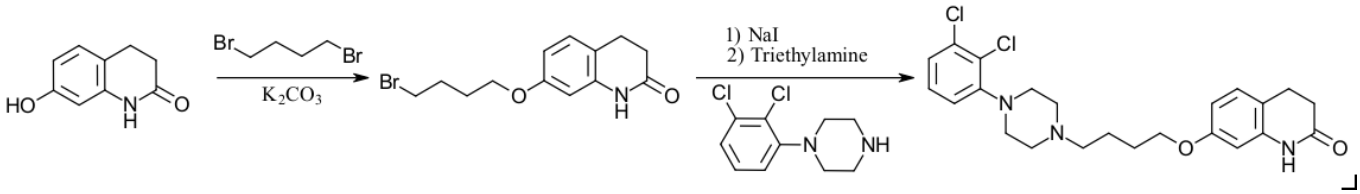


Figure 2: Common synthesis route of Aripiprazole
Adapted from "Classics in chemical neuroscience: Aripiprazole" by A.B. Casey & C. E. Canal, 2017

This synthesis took up to 12 hours using expensive, toxic solvents, with several extraction steps. (Casey & Canal, 2017) In 2018, Jaskowska et al. reported a one-step synthesis using microwave irradiation. (Jaskowska et al., 2018)

Conditions and yield
Jaskowska et al. reported these conditions:

	1,4-dibromobutane	7-HQ	DCP	K_2CO_3
Molar equivalent	1	1	1	3.5

- Solid reactants compacted with phase-transfer catalyst (PTC) to promote reaction
- Tetra-n-butylammonium bromide (TBAB) as PTC
- 10% dimethylformamide by mass
- 100W microwave irradiation for 120 seconds

They reported a 45% percentage yield after filtering and recrystallizing in isopropanol.
This is not only accessible for most chemists, but also cost-effective, safe, and only takes a short time. Hence, for small-scale syntheses, this should be the final step.

4 Flowchart for retrosynthesis process

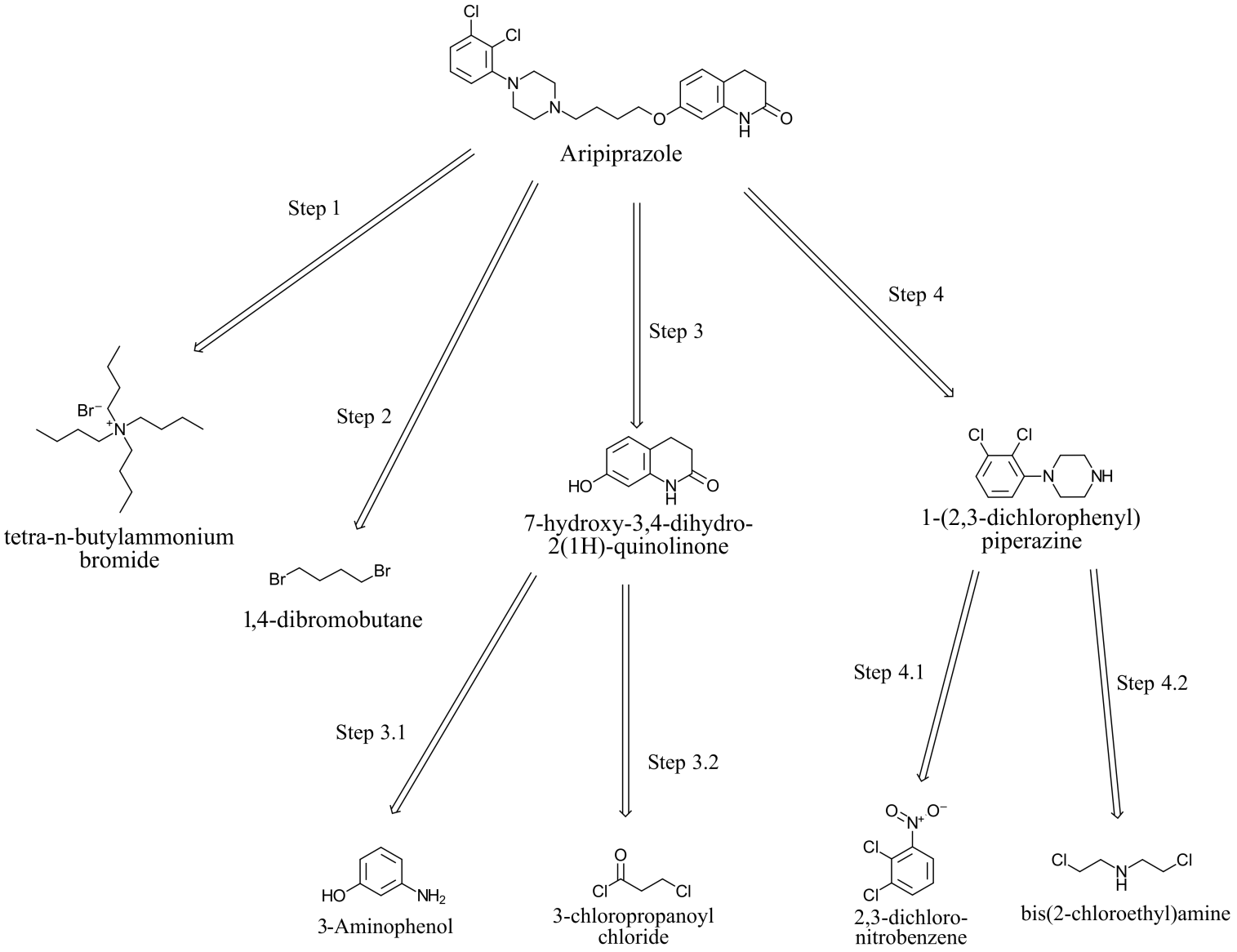


Figure 3: Flowchart for developing the synthetic route
Steps 3.1, 3.2, 4.1, and 4.2 are explained in later sections

5 Synthesis of catalyst: Tetra-n-butylammonium bromide

For retrosynthesis of this catalyst, the disconnection should be the C-N bond. The most obvious reaction is nucleophilic substitution (S_N), as nitrogen compounds act as nucleophiles. Since there are 4 identical n-butyl groups, the only required electrophile is an n-butyl halide. As bromide ions are needed, 1-bromobutane should be used.

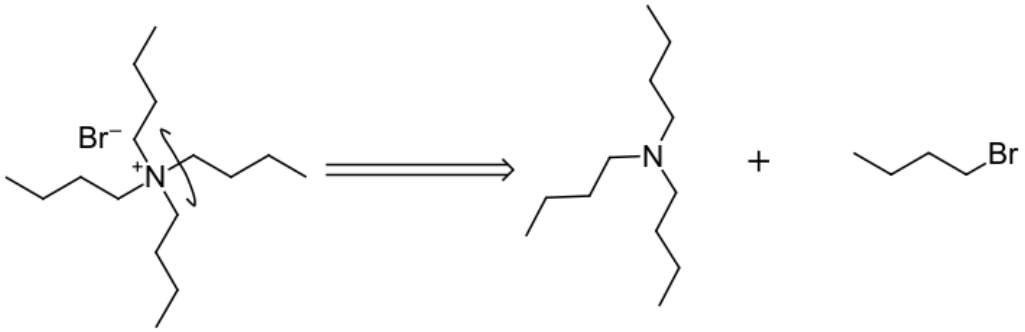


Figure 4: Retrosynthesis of tetra-n-butylammonium bromide

Here, ammonia acts as the initial nucleophile, forming n-butylamine. As alkyl groups have an inductive effect, the nitrogen atom on the amine gains electron density, strengthening its nucleophilicity, accelerating subsequent subtitutions. This effect continues until the quaternary amine is produced, giving a high yield. (Clayden et al., 2012, p.353)

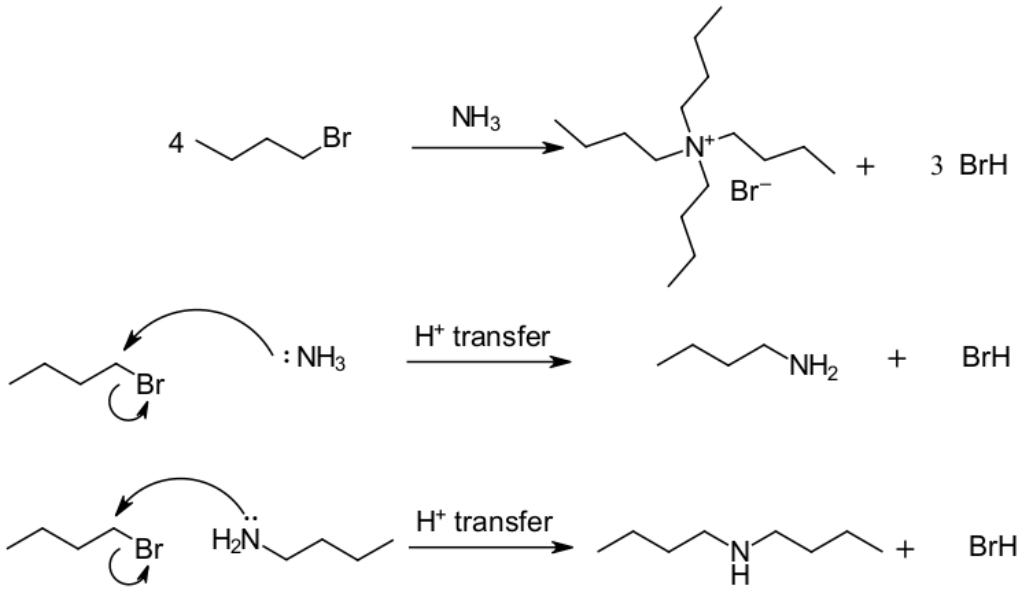


Figure 5: Equation and partial mechanism for synthesis of the catalyst from ammonia and 1-bromobutane
The next steps are similar, with the amine as the nucleophile

Since 1-bromobutane is only miscible with aprotic solvents, the ammonia used should be dissolved in ethanol. The final solution can be evaporated to dryness to obtain the ionic substance.

For 1-bromobutane, the obvious disconnection is the C-Br bond. Possible reactions for adding bromide are S_N or electrophilic addition. For the latter, Markovnikov's Rule states that halides are rarely added to a primary carbon. Therefore, S_N2 to a terminal carbon was chosen.

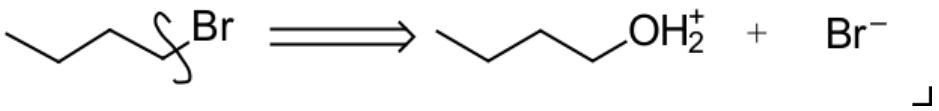


Figure 6: Retrosynthesis of 1-bromobutane

For the leaving group, it should be stable on its own to make the reaction favourable. A common choice is a protonated hydroxyl leaving as water. This is made by adding an alcohol to a concentrated acid. HBr is a good choice as it also provides bromide.

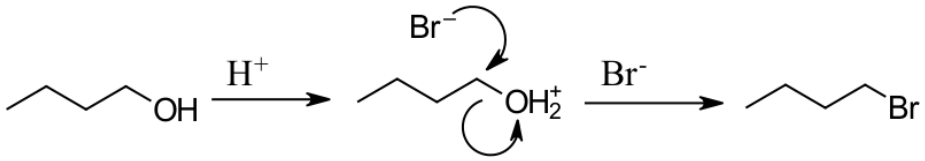


Figure 7: Mechanism of conversion from alcohol to bromide

As there are no other functional groups, there are few side reactions. After reaction, the organic product can be separated from the aqueous acid.

Conditions and yield

The halogenation requires reflux above 120^oC. (Pavia, 2013, pp.194-195) For alkanols, a three-fold molar excess leads to 91% yield. (Clayden et al., 2012, p.348)

Precautions

However, the reaction requires concentrated HBr. Essential precautions include skin and eye protection, fume hood, and leading acidic fumes to an alkaline solution. (Pavia, 2013, pp.194-195) Waste also has to be neutralised before disposal.

For the alcohol, it can be made by Grignard reactions or reduction from aldehydes and carboxylic acids. As reducing agents are more common, I chose reduction. Reduction to alcohol is often done by refluxing an acid with $LiAlH_4$. They react in a 1:2 ratio. (Clark, 2015b)

$$RCOOH + 4\,[H] \longrightarrow RCH_2OH + H_2O$$

Conditions and yield
As $LiAlH_4$ reacts with water, the reaction should be done in dry diethyl ether, which most alkanoic acids are miscible in. It is a very strong reducing agent, so incomplete reduction is unlikely and the yield will be high.

Precautions
$LiAlH_4$ reacts with water to form flammable H_2, so both the equipment and solvent have to be dry. The latter can be done using drying agents or molecular sieves. The reaction atmosphere also has to be dried using a $CaCl_2$-filled drying tube. (Vogel & Furniss, 1989, pp.530-531)
After reflux, the reaction has to be quenched by adding water slowly. Then, the ether can be removed by evaporation, and HBr can be directly added for halogenation, so purification of the alcohol is not necessary.

The reduced acid is butanoic acid, or butyric acid. Butyrate is commercially available as a supplement for gut health. (Eyvazzadeh, 2019) It is also miscible with diethyl ether, making the reduction convenient. Its solubility in water allows it to be separated from solid pill filler.
Therefore, the catalyst needed for Aripiprazole synthesis can be made in one pot from ammonia and a commercially available supplement with high yield.

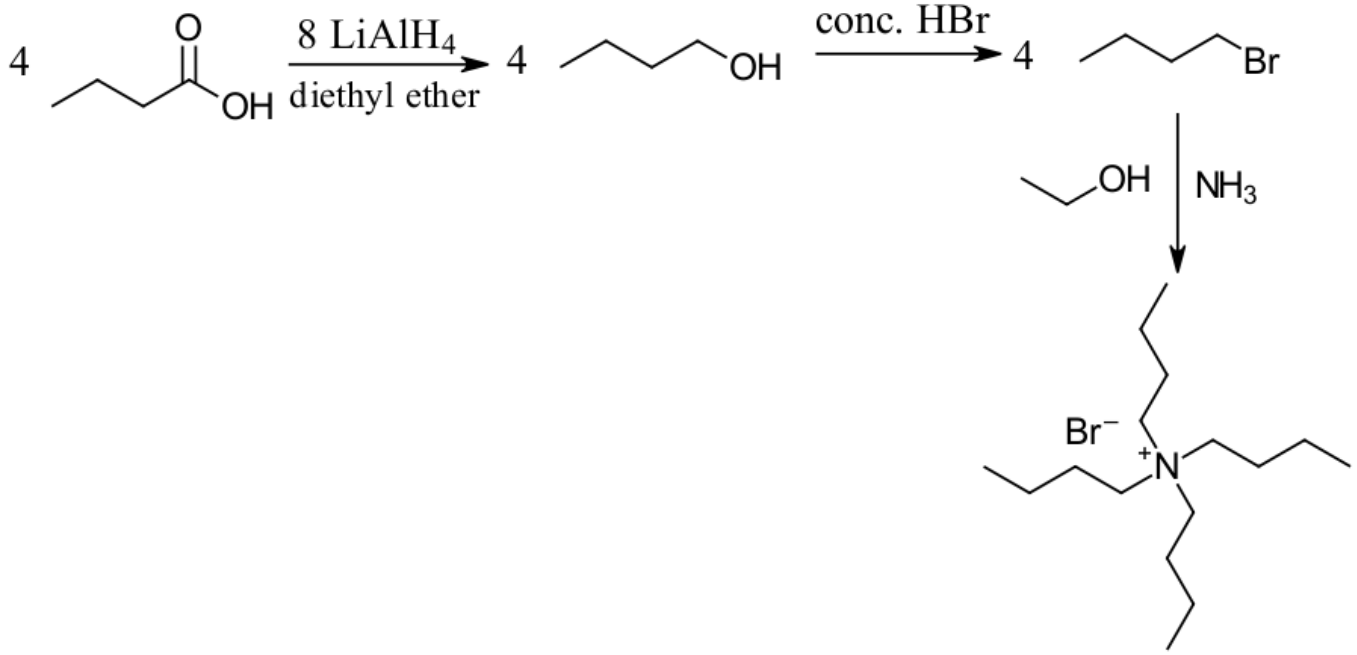


Figure 8: Synthesis of tetra-n-butylammonium bromide from butanoic acid and ammonia

6 Synthesis of 1,4-dibromobutane

Like 1-bromobutane, the bromide can be synthesized from alcohol, except a diol is used this time. 1,4-butanediol can be made from a dicarboxylic acid using $LiAlH_4$.

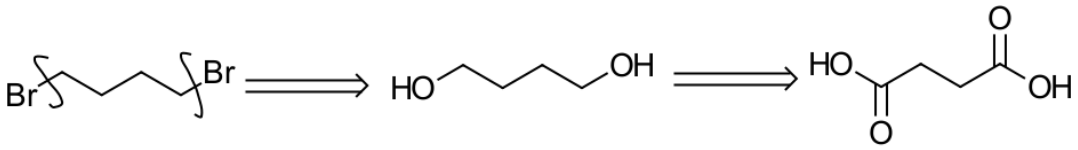


Figure 9: Retrosynthesis of 1,4-dibromobutane to succinic acid

The procedure and yield are similar, but twice the amount of HBr and $LiAlH_4$ are needed.
The reduced reagent is butanedioic acid, or succinic acid. It is sold as a supplement for joint pain, or as an acidity regulator. ("Succinate Supplement", 2019) Like butanoic acid, it is soluble in ether for reaction with $LiAlH_4$, and in water for separation.

Therefore, we can conclude that it is feasible for chemists to synthesize 1,4-dibromobutane from a commercial product with common reagents in a one-pot synthesis.

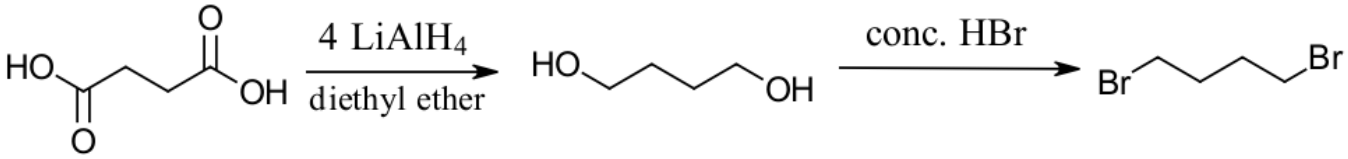


Figure 10: Synthesis of 1,4-dibromobutane from succinic acid

7 Synthesis of 7-hydroxy-3,4-dihydro-2(1H)-quinolinone

7-HQ is bicyclic. The non-aromatic ring can be formed by attaching an acyclic compound to the benzene ring. There are two disconnections: C-C and C-N bonds. For the former, alkyl groups can be attached via Friedel-Crafts alkylation (Clayden et al., 2012, p.477), using an alkyl halide and a Lewis acid. The most common option is chloride and $AlCl_3$.

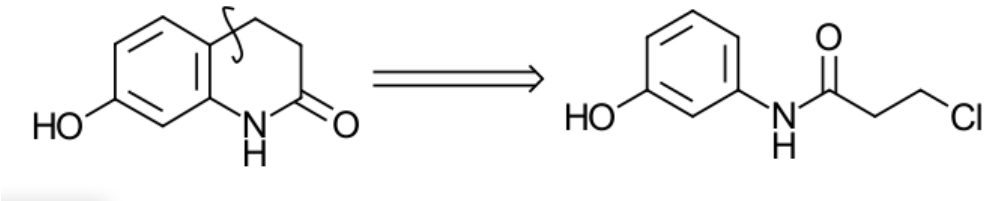


Figure 11: First step in 7-HQ retrosynthesis

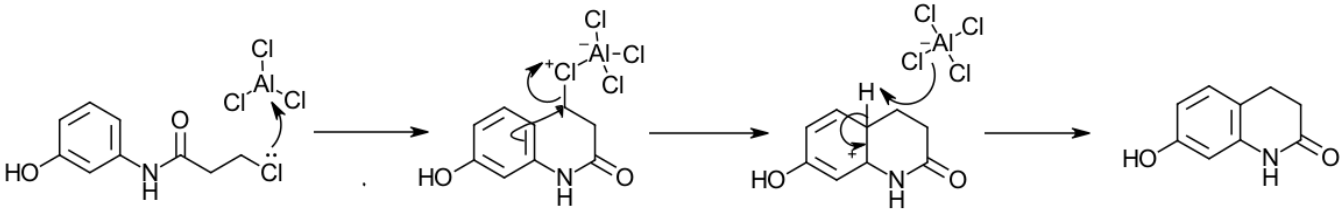


Figure 12: Mechanism of the Friedel-Crafts alkylation

This reaction is favourable, as the intermediate can be stabilised by electron-donating hydroxyl and amine groups. A six-member ring also has the lowest strain (Clayden et al., 2012, pp.367-368), so the substitution will occur in the ortho- or para- positions (relative to -OH). However, the former suffers from steric hindrance.

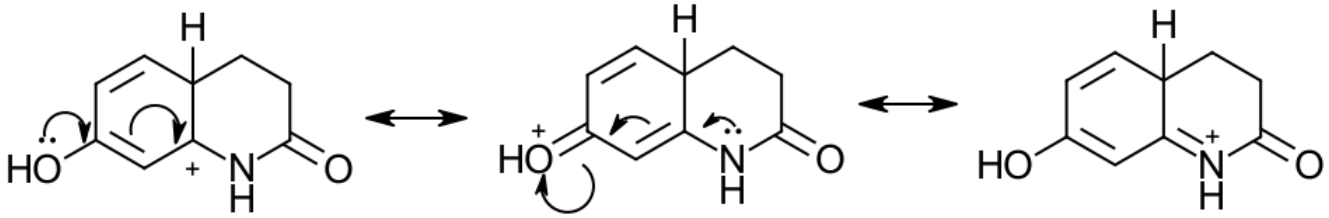


Figure 13: Stabilization of the charged intermediate

The second disconnection is the amide group. It can be synthesized from an amine and a carbonyl.

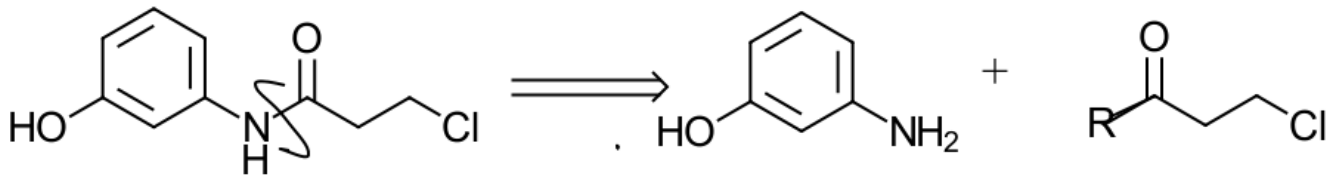


Figure 14: Second step in 7-HQ retrosynthesis

The most reactive carbonyl group is the acyl chloride, so it can give a high yield. (Keeler & Wothers, 2014, pp.375-376).

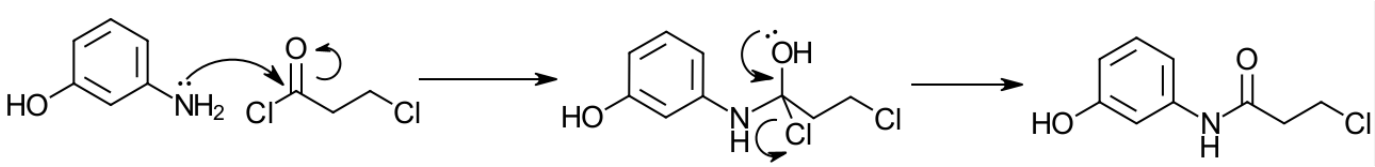


Figure 15: Mechanism of amide formation in 7-HQ

Both the amide and ring formation can also be done in the same polar solvent.

Conditions and yield

Naddaka et al. reported the optimal reaction conditions for a reaction using 3-anisidine, which only differs from 3-aminophenol with a methoxy group. They used dry dimethylformamide as the polar solvent (water can act as a nucleophile and lower yield of the amide), with 5 molar equivalents of $AlCl_3$, at 140^oC. They reported a 60% yield after recrystallization in ethanol.

Precautions

3-aminophenol is toxic when inhaled and harmful to aquatic life. (*3-Aminophenol Material Safety Data Sheet, MSDS 100242*, 2019). 3-chloropropanoyl chloride is toxic under skin and eye contact. (*3-chloropropionyl chloride Material Safety Data Sheet, MSDS C69128*, 2020) While these dangers make industrial production difficult, lab synthesis is still feasible with fume hood, goggles and gloves.

7.1 Synthesis of 3-Aminophenol

Possible disconnections for 3-aminophenol are the C-O bond and C-N bonds. Let's consider the -OH group first. Since OH is nucleophilic but aromatic compounds rarely undergo S_N reactions, a good leaving group is needed. A stable option is nitrogen from a diazonium ion. The reaction proceeds via S_N1 under heating (Clayden et al., 2012, p.520).

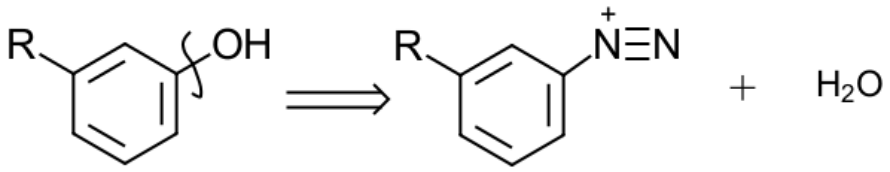


Figure 16: First step in retrosynthesis of phenol

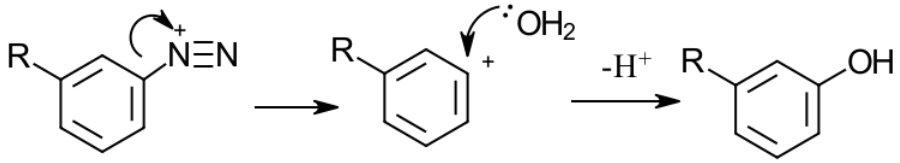


Figure 17: Formation of phenol

The diazonium group can be synthesized by amine diazotization using the electrophile NO^+ (Clayden et al., 2012, p.521). Similar to $NO_2{}^+$, it is formed from protonated $NO_2{}^+$. (Clayden et al., 2012, p.464)

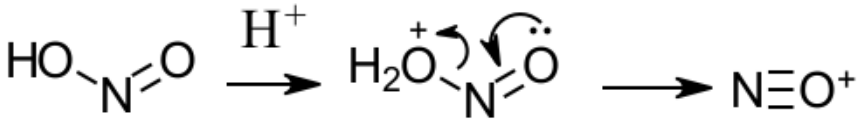


Figure 18: Formation of NO^+ from nitrous acid

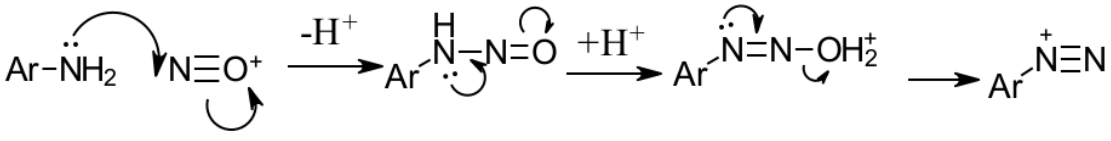


Figure 19: Diazotization of amine

Conditions and yield
To form enough NO^+ ions, this reaction has to be done at around $0 - 5^oC$. Usage of aqueous H_2SO_4 for protonation is also recommended.
As the nucleophile in phenol formation is water, it can be done directly after diazotization by diluting and heating the reaction mixture. The final yield of phenol from phenylamine can be up to 65% after recrystallization in acid. (Vogel & Furniss, 1989, pp.927-928)

However, the amine group needed for 7-HQ formation may also be converted. Therefore, it cannot be present until the end.
The amine can be converted from a nitro group via reduction. As the latter is non-nucleophilic, it cannot be converted to diazonium. The reduction is simple, and can be done using tin in HCl according to the equation below. (Vanderzee & Edgell, 1950)

$$3\,\mathrm{Sn} + 6\,\mathrm{HCl} + \mathrm{RNO_2} \longrightarrow 3\,\mathrm{SnCl_2} + 2\,\mathrm{H_2O} + \mathrm{RNH_2}$$

The next retrosynthesis is that of 3-nitroaniline. The amine can be obtained by reduction, but the

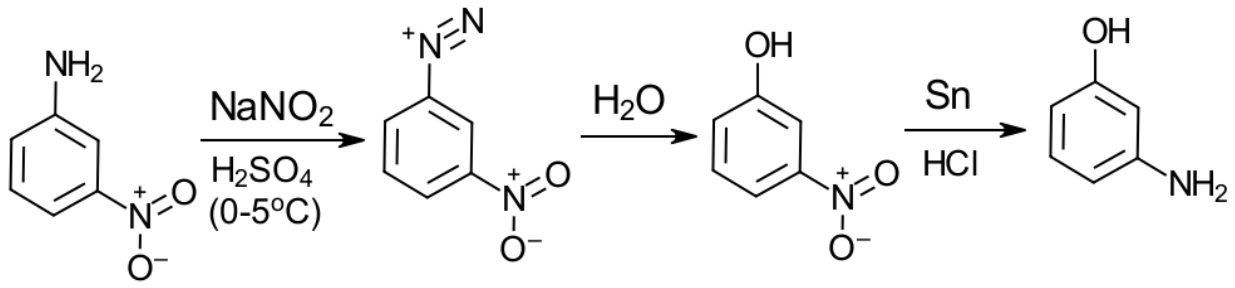


Figure 20: Partial synthesis scheme for 3-aminophenol

nitro group in the meta-position must be retained. This requires a reduction method that is selective, or weaker.
One method is Zinin reduction of aromatic nitro compounds, which uses sulfides or hydrosulfides (Porter, 2011).

$$4\,\mathrm{ArNO_2} + 6\,\mathrm{S^{2-}} + 7\,\mathrm{H_2O} \longrightarrow 4\,\mathrm{ArNH_2} + 3\,{\mathrm{S_2O_3}}^{2-} + 6\,\mathrm{OH^-}$$
$$4\,\mathrm{ArNO_2} + 6\,\mathrm{SH^-} + \mathrm{H_2O} \longrightarrow 4\,\mathrm{ArNH_2} + 3\,{\mathrm{S_2O_3}}^{2-}$$

This reaction has a lower reduction potential than other methods (Porter, 2011), so only one nitro group is reduced, even when multiple are present.

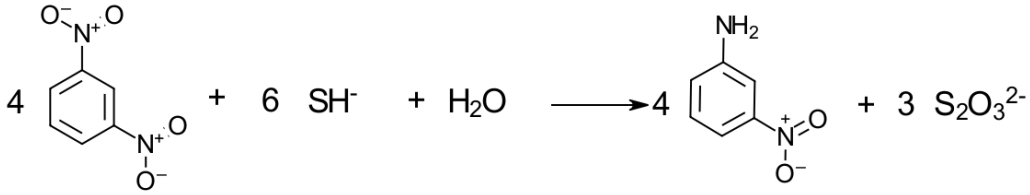


Figure 21: Zinin reduction of 3-nitroaniline

The sulfide can be provided in the form of Na_2S, which can be made by reacting sodium and sulfur in dry NH_3 (El-Shinawi et al., 2018).

$$2\,Na + S \longrightarrow Na_2S$$

Using pure elements is the most direct and accessible method. El-Shinawi et al. reported a novel synthesis without their usage, but it requires uncommon solvents such as tetraglyme.
Zinin reduction has potential side reactions, such as dehalogenation or hydroxylation (Porter, 2011). However, as there are only nitro and amino groups in 3-nitroaniline, these will be rare.
To dissolve all involved comoounds, a mix of aqueous and organic solvents is needed. Aqueous methanol is a common solvent. (Vogel & Furniss, 1989) However, as it is acutely toxic, aqueous ethanol is also used (Porter, 2011). However, the yield could be lowered.

Conditions and yield
This reduction requires continuous reflux. With reaction done in methanol for 20 minutes and 1.9 molar equivalents of Na_2S, the yield can be above 60% after recrystallization in methanol (Vogel & Furniss, 1989, p.895). Higher excess of Na_2S is advised, especially if ethanol is used.

Precautions
Handling of pure sodium and sulfur can be hazardous. Normal skin protection should be worn, the environment should be dry, and the fume hood has to be used as poisonous H_2S gas can be released. The 3-nitroaniline should also be recrystallized before proceeding. The next step requires acid, which can promote formation of H_2S if S^{2-} ions remain.

The final step is retrosynthesis of 1,3-dinitrobenzene. It can be produced by double nitration of benzene, or singular nitration of nitrobenzene. Both utilize concentrated HNO_3 and H_2SO_4.

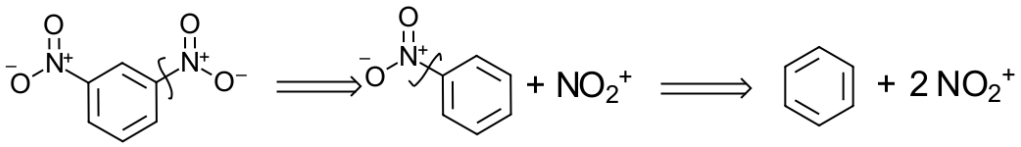


Figure 22: Retrosynthesis of 1,3-dinitrobenzene

This reaction is unlikely to have side products. Once the benzene is nitrated, the second nitration is likely to occur at the meta-position. This is because the nitro group conjugates with the benzene ring to withdraw electrons from the ortho- and para- carbons (Clayden et al., 2012, p.279), making them less nucleophilic.

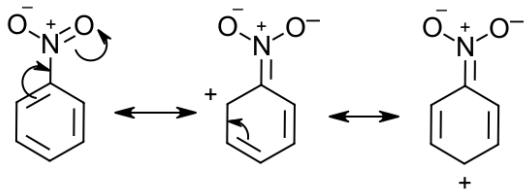


Figure 23: Electron withdrawal from aromatic carbons in nitrobenzene
This explains unreactivity of the ortho- and para- carbons

Trinitration is unlikely. Electron withdrawal from the nitro group lowers the rate of substitution overall, and having two only strengthens the effect. In fact, trinitration requires oleum and fuming nitric acid (Kyprianou et al., 2020).

Conditions and yield
The dinitration requires both concentrated HNO_3 and H_2SO_4 , as well as reflux for multiple hours, unless fuming nitric acid is used (Vogel & Furniss, 1989, p.855). The yield for single nitration is commonly over 80%, while that for dinitration is often over 70%.(Vogel & Furniss, 1989, pp.854-855) The dinitrobenzene should also be recrystallized in ethanol, as residual acid from nitration will release H_2S during reduction.

Precautions
The usage of concentrated acids requires both skin protection and a fume hood.
Benzene or nitrobenzene can also be hazardous. Benzene is carcinogenic and irritant ("CDC: Facts About Benzene", 2018). Meanwhile, nitrobenzene causes methemoglobinemia ("Toxic Substances Portal - Nitrobenzene", 2015). Therefore, skin protection is essential. The reaction mixture also cannot be distilled to dryness as explosion can result.
Through all these reactions, 3-aminophenol can be synthesized from benzene or nitrobenzene using common reagents, with purification of 1,3-dinitrobenzene and 3-nitroaniline.

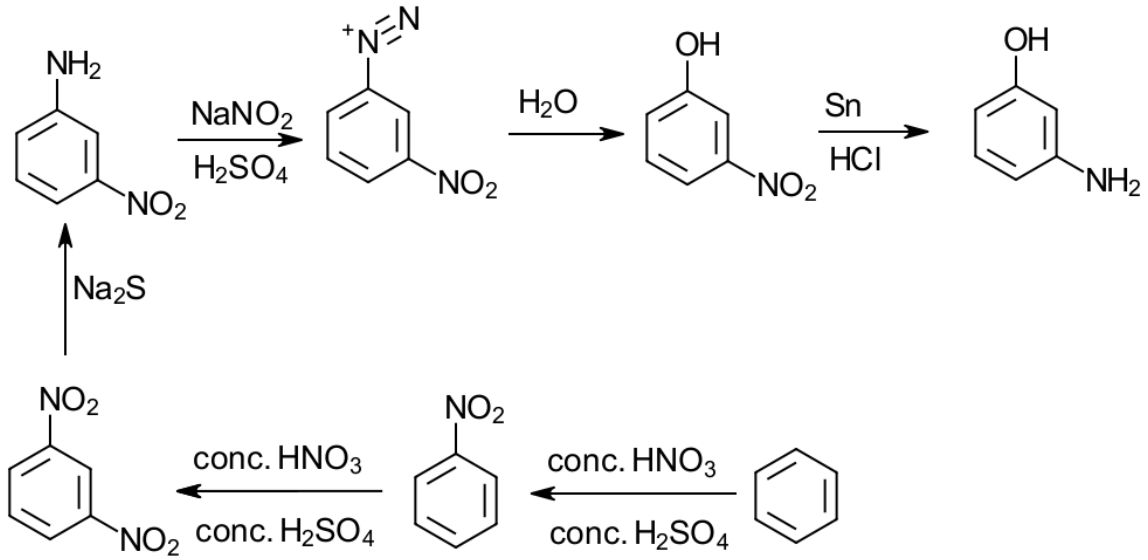


Figure 24: Synthesis of 3-aminophenol from benzene

7.2 Synthesis of 3-chloropropanoyl chloride

There are two possible first steps in this retrosynthesis: creating the acyl chloride group or adding the terminal chloride. The former can be converted from a carboxylic acid (Clayden et al., 2012, p.215), while the latter can be made by addition of HCl to a conjugated alkene. (Clayden et al., 2012, p.500)

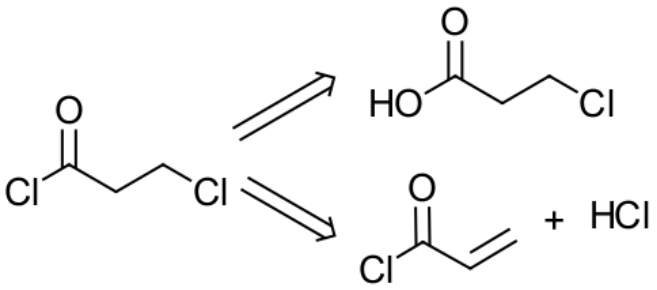


Figure 25: Potential retrosyntheses of 3-chloropropanoyl chloride

To determine the order of reactions, potential side reactions and the effect of other functional groups should be considered. For this purpose, the mechanisms of both reactions should be known.
Conversion of acyl chloride from the carboxylic acid can be done with $SOCl_2$, PCl_3, or PCl_5 (Vogel & Furniss, 1989, p.692).

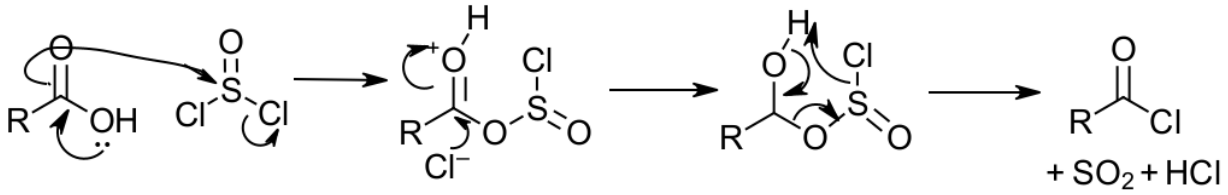
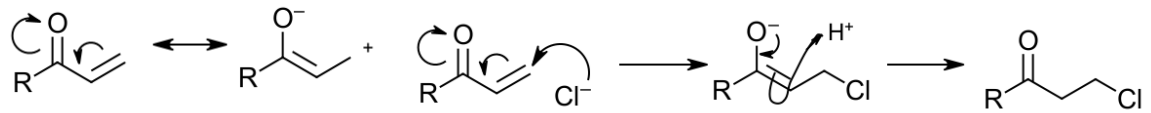


Figure 26: Mechanism of conversion to acyl chloride using $SOCl_2$, adapted from "Organic Chemistry" p.214 by Clayden et al. 2012

The first step is nucleophilic attack on sulfur by the carbonyl oxygen. This is unlikely to be affected by a chloride at the terminal carbon.
As for the addition of HCl, the conjugation of the alkene means unlike normal electrophilic addition, Markovnikov's Rule does not apply. The β-carbon becomes partially positive and electrophilic, leading to nucleophilic attack on it. This is known as Michael addition (Clayden et al., 2012, p.500).

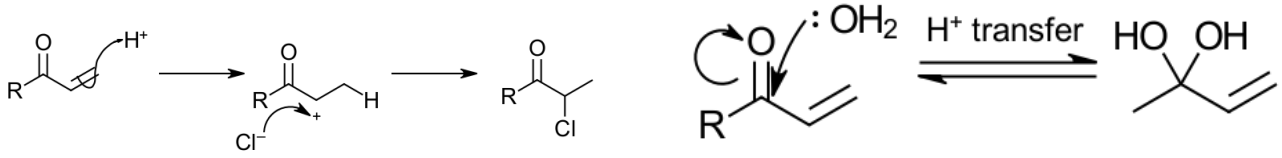


(a) Resonance in a conjugated alkene

(b) Addition of conjugated alkene

Figure 27: Reactivity of a conjugated alkene
Figure b adapted from "Organic Chemistry" p.499 by Clayden et al., 2012

This reaction has some common side reactions. The carbonyl is also electrophilic due to partial positive charge from the polar C=O bond, and the alkene is still susceptible to non-conjugated addition.



(a) Non-conjugated addition of alkene by HCl

(b) Direct addition of carbonyl by water in the acid

Figure 28: Possible side reactions of conjugated alkenes

The R-group above is unlikely to influence electrophilic addition, but it can affect addition to carbonyl. As aforementioned, acyl chlorides are likely to undergo addition while carboxylic acids are less likely. (Keeler & Wothers, 2014, p.373)
So, the conjugate addition should be done first with a carboxylic acid, before hydrochlorination. The initial reagent is prop-2-enoic acid, or acrylic acid.

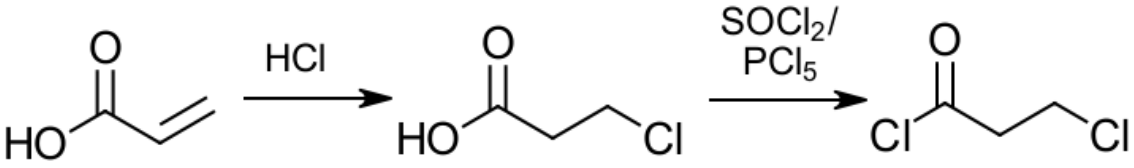


Figure 29: Acrylic acid to 3-chloropropanoyl chloride

For maximum yield of 3-chloropropanoic acid, conditions must also be chosen to avoid side reaction. Carbonyl addition has a low activation energy (E_a) but is reversible (Clayden et al., 2012, pp.208-209). Although conjugate addition has higher E_a, it is irreversible (Clayden et al., 2012, p.504). Therefore, with a higher temperature for molecules to reach E_a, and longer time to allow conjugate addition, the yield can be increased.

Conditions and yield
Zhang et al. reported a 95% yield after 2 hours of reaction at 60^oC with three-fold molar excess of 35% HCl to acrylic acid. (Zhang et al., 2005)

As for the conversion to 3-chloropropanoyl chloride, $SOCl_2$ or PCl_5 can be used. However, PCl_5 is toxic, and is mostly reserved for aromatic acids (Vogel & Furniss, 1989, p.692). $SOCl_2$ can be produced via the following reactions (Alphonse, 1947):

$$S_8 + 4\,Cl_2 \rightleftharpoons 4\,S_2Cl_2$$
$$S_2Cl_2 + 2\,SO_2 + 3\,Cl_2 \rightleftharpoons 4\,SOCl_2$$

The side products of chlorination escape as gases, making the equilibrium tend toward the product side. After the reaction, as $SOCl_2$ has a low boiling point, the excess can be distilled off. 3-chloropropanoyl chloride, lacking the hydrogen bonding in the acid, will be the next separated fraction.

Conditions and yield
After refluxing for an hour with 1.2 times molar excess of $SOCl_2$, the typical yield is above 80% (Vogel & Furniss, 1989, pp.692-693).

Precautions
Released gases should be led into water to prevent escape, as they dissolve to form acids.
The reaction mixture should be anhydrous, as $SOCl_2$ reacts with water:

$$SOCl_2 + H_2O \longrightarrow SO_2 + 2\,HCl$$

The final step is retrosynthesis of acrylic acid. The double bond can be created by an elimination reaction:

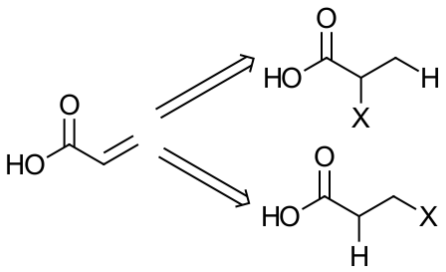


Figure 30: Possible retrosyntheses of acrylic acid

X is the leaving group. When X is OH and is on the 2nd carbon , the compound is 2-hydroxypropanoic acid, or lactic acid, and the elimination reaction is a dehydration, producing water.
Alcohol dehydration is often done under high heat, with a catalyst, such as Al_2O_3. However, literature states that in this case, the most suitable catalyst is an alkali or alkaline earth metal phosphate (Sawicki, 1988).

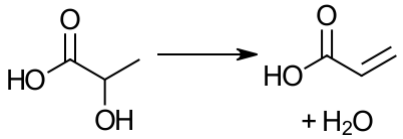


Figure 31: Dehydration of lactic acid to acrylic acid

One possible side reaction promoted by high heating is decomposition of lactic acid into acetaldehyde, CO_2, and H_2 (Komesu et al., 2017).

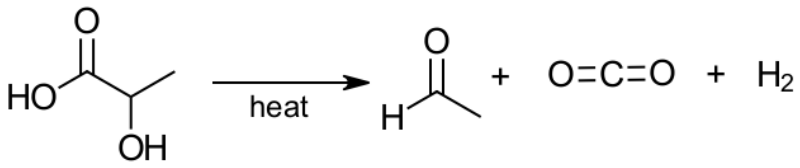


Figure 32: Decomposition of lactic acid

Conditions and yield

Dongare et al. proposed a process of heating $Ca_3(PO_4)_2$ catalyst to 375^oC over inert gas (e.g. N_2), then passing hot lactic acid solution or vapour through it. The product is obtained by condensing in water. Although this process does not avoid decomposition, it still yields up to 70% acrylic acid. (Dongare et al., 2015)

Lactic acid can be synthesized by hydrolysis of a cyanohydrin, which in turn can be made from attack on acetaldehyde by cyanide.

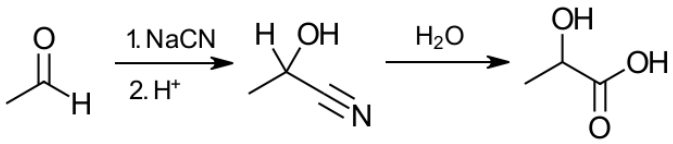


Figure 33: Synthesis of lactic acid from acetaldehyde

However, acetaldehyde and cyanide are both acutely toxic, and lactic acid is already commercially available as a beauty product and food additive. Therefore, it is better to simply use lactic acid as the first precursor.

After the dehydration of lactic acid, the series of reactions to make 3-chloropropanoyl chloride can proceed without purification. However, drying is necessary before chlorination.

7.3 Synthesis scheme of 7-hydroxy-3,4-dihydro-2(1H)-quinolinone

With all the above reactions, the synthesis of 7-hydroxy-3,4-dihydro-2(1H)-quinolinone should be possible using common reagents, with lactic acid and benzene as precursors.

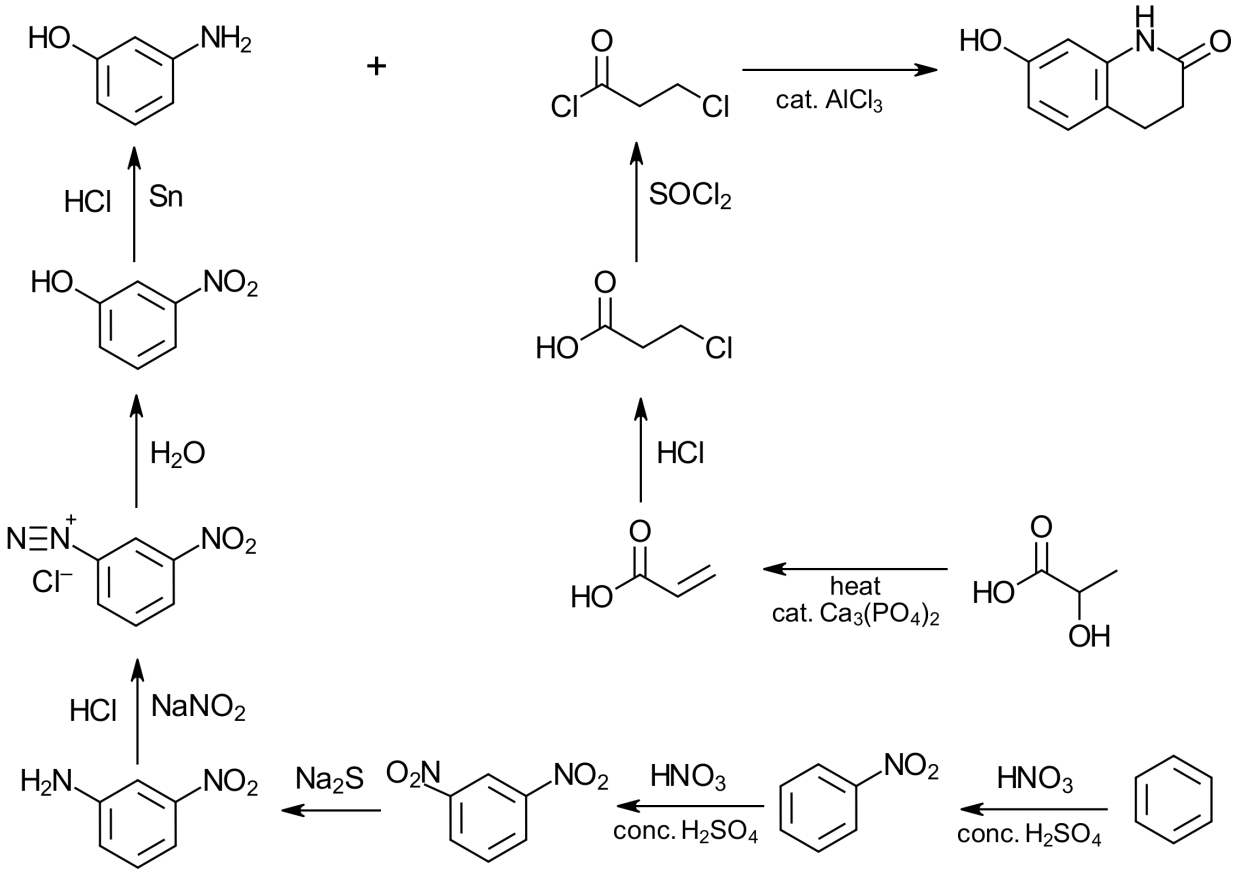


Figure 34: Total synthesis of 7-hydroxy-3,4-dihydro-2(1H)-quinolinone

8 Synthesis of 1-(2,3-dichlorophenyl)piperazine

The first step in retrosynthesis of 1-(2,3-dichlorophenyl)piperazine should be breaking the piperazine ring. The nitrogen atoms in primary and secondary amines are nucleophilic due to high electron density. As the involved carbons are secondary, it can react via both S_N1 and S_N2.

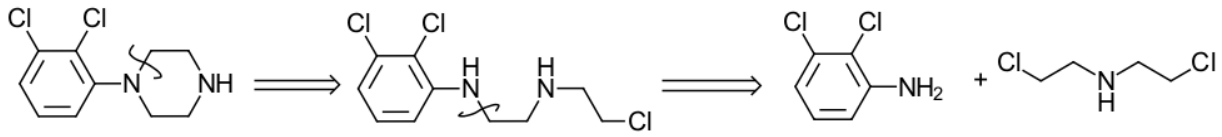


Figure 35: Retrosynthesis of the piperazine ring

For a high yield, X has to be a good leaving group, such as the stable anion Cl^-. The reaction should also be done in a polar solvent to assist deprotonation.

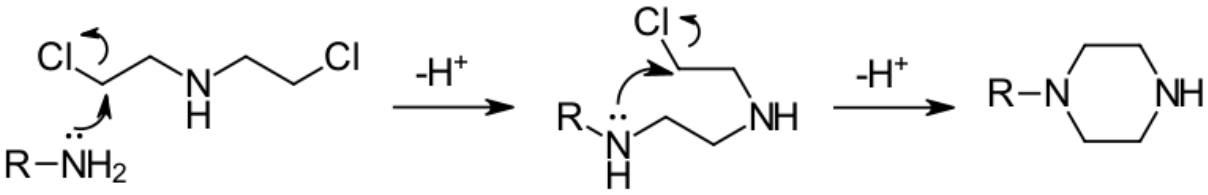


Figure 36: S_N2 mechanism in piperazine formation

Conditions and yield

Li et al. reported that the reaction can be done in high-boiling point protic solvent such as n-butanol under reflux without catalyst. After crystallization in the same solvent, the yield is approximately 60% at 99% purity. (Li et al., 2014)

There is also another high-yield way of synthesizing phenylpiperazines found by Mishani et al. which uses porous Al_2O_3 as catalyst. The reaction is done with the reactants as solvent, at around 150^oC. This gives a yield above 70% after extraction by methanol.

Precautions

The reactants are 2,3-dichloroaniline and bis(2-chloroethyl)amine. The former is toxic when inhaled or touched. ("PubChem Compound Database: 2,3-dichloroaniline", n.d.) As it has high boiling point, inhalation of fumes is unlikely. However, the latter reagent is much more dangerous as it is a DNA alkylating agent. ("PubChem Compound Database: bis-(2-chloroethyl)amine", n.d.)

The best solution is for it to be produced *in situ*, immediately before addition of 2,3-dichloroaniline.

8.1 Synthesis of 2,3-dichloroaniline

2,3-dichloroaniline has three substitutions on the benzene ring. Chlorine can be substituted by E_{Ar} using Cl_2 and $FeCl_3$, and the amine is best converted from a nitro group (using tin and HCl).
To know the order of substitution, one must look at the effects each one has on subsequent reactions. Both chlorine and nitro substituents lower reaction rate by electron withdrawal, with the latter being stronger. Chlorine directs substitution to ortho- and para- positions while the nitro groups is meta-directing (Clayden et al., 2012, p.491).
The yields of each individual substitution must also be found.

Compound	Reaction	Position	Yield	Reference
Chlorobenzene	Most substitutions	Ortho	35%	Clayden et al., 2012, pp.488-489
Nitrobenzene		Meta	70%	
1,2-dichlorobenzene	Nitration	Ortho	15%	Neumann et al., 1995

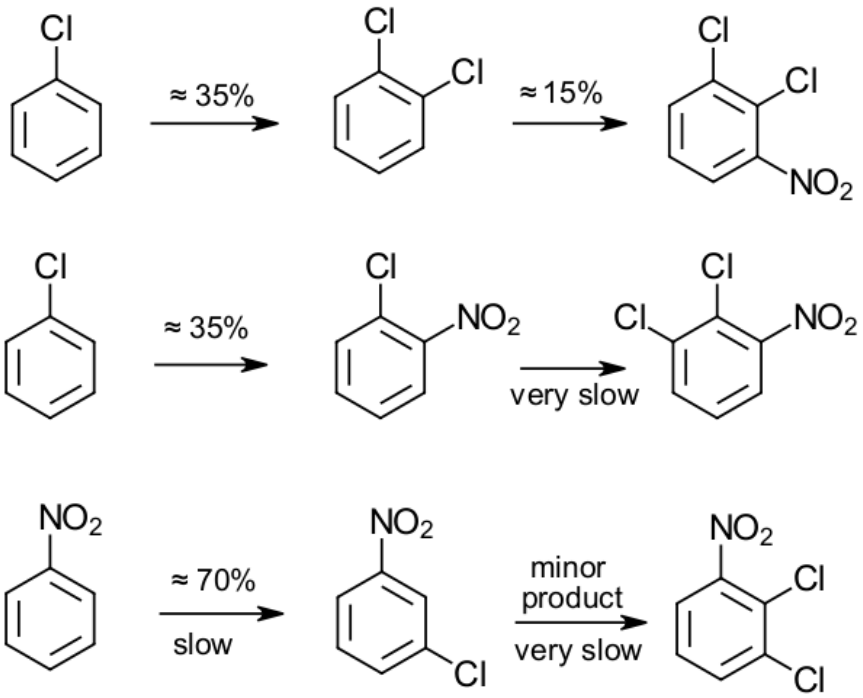


Figure 37: Possible routes to 2,3-dichloronitrobenzene

In the bottom route, as the nitro group is always present, both reactions will be very slow. Its meta-directing nature also means that 1,2-dichlorobenzene will be a minor product. As for the middle route, it would require separation of 2-chloro-nitrobenzene, and nitration would be slow. The top route is the fastest, and can be done without purification.
The chlorination uses gaseous chlorine, which can be prepared in the laboratory by multiple ways using concentrated HCl, shown below:

$$2\,KMnO_4 + 16\,HCl \longrightarrow 2\,MnCl_2 + 2\,KCl + 8\,H_2O + 5\,Cl_2$$

$$MnO_2 + 4\,HCl \longrightarrow Cl_2 + MnCl_2 + 2\,H_2O$$

Conditions and yield
The gas is passed into benzene containing iron powder or $FeCl_3$.
As water dissolves the Cl_2 gas, both the benzene and Cl_2 should be dried (The former by $CaCl_2$, and the latter by passing through concentrated H_2SO_4). A higher temperature also makes dichlorination faster and more favourable. Maintaining it at 50^oC via water bath gives the highest yield (Fierz-David et al., 1949, pp.62-64) at 35% (Clayden et al., 2012, p.488)

Precautions
The reaction produces HCl gas, which should be neutralised by passing it into alkaline solution. The reaction is also best done in fume cupboard in case toxic chlorine is leaked.
After chlorination, the solid catalyst can be separated before nitration.
After nitration, there are three significant isomeric products:

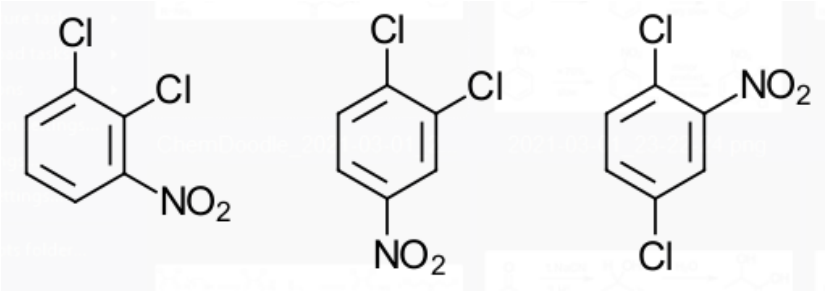


Figure 38: From left to right:
2,3-dichloronitrobenzene (desired), 3,4-dichloronitrobenzene (major), 2,5-dichloronitrobenzene

Conditions and yield
Due to the deactivating nature of the chlorine substituent, the mixture should be heated to increase rate, and be as acidic as possible. According to literature, a mixture of concentrated HNO_3, H_2SO_4, and H_3PO_4 refluxed for 2 hours gives the best yield, up to 15% after separation. (Neumann et al., 1995)
Normal precautions for handling acid must be applied.
The products can be separated by fractional crystallization. The melting points of the compounds above are 61^oC, 43^oC, and 56^oC respectively. ("PubChem Compound Database", n.d.) The desired product will be the fraction with the highest melting point, so unwanted compounds can be easily separated.
After getting 2,3-dichloronitrobenzene, it can be easily reduced with tin in HCl. Separation of 1,2-dichlorobenzene will be necessary before nitration.

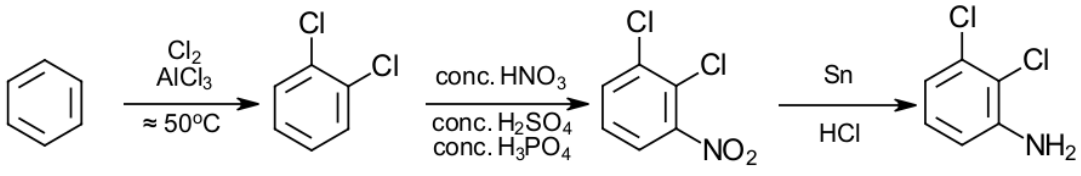


Figure 39: Synthesis scheme of 2,3-dichloroaniline from benzene

8.2 Synthesis of bis(2-chloroethyl)amine

As mentioned before, amines can be synthesized from an S_N reaction. Again, ammonia acts as the nucleophile, with a halogen being a suitable leaving group. However, the terminal carbon in the 2-chloroethyl chain is also electrophilic, which can lead to side reaction.

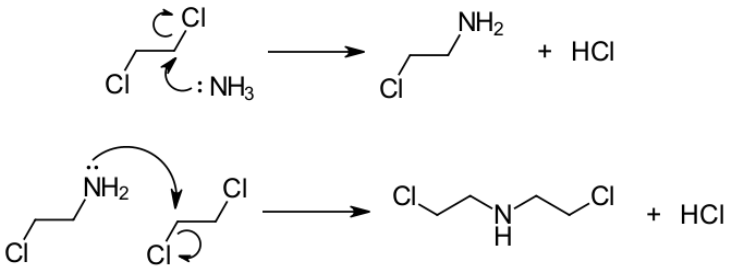


Figure 40: The desired reaction - formation of bis(2-chloroethyl)amine

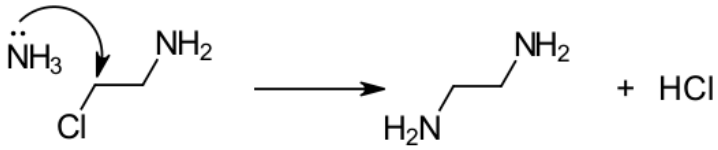


Figure 41: Undesired reaction - formation of ethanediamine

To prevent the side reaction, the terminal chlorine should be added at the end. This can be done via the same method as conversion of alcohol to bromide.

Conditions and yield
The conditions are same as conversion of alcohol to bromide, except with concentrated HCl. It typically gives a 90% yield. (Vogel & Furniss, 1989, p.556)

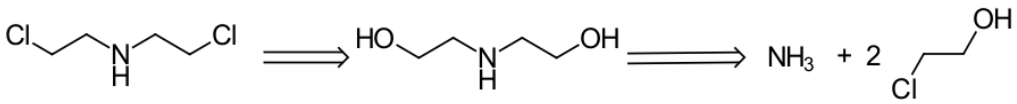


Figure 42: Correct retrosynthesis of bis(2-chloroethyl)amine

The next step is formation of diethanolamine by S_N of 2-chloroethanol by NH_3.
As all reagents are soluble or miscible in water, aqueous NH_3 can be used.

Conditions and yield
The yield of diethanolamine depends on the stoichiometry of reactants. From literature, a yield of about 40% can be obtained at a NH_3:2-chloroethanol ratio of 6:1 and refluxing. (Nygaard & Diguilio, 1998)

Precautions

NH_3 is safe, but 2-chloroethanol is acutely toxic if swallowed or touched. Therefore, it should also be made *in situ* before forming bis(2-chloroethyl)amine.

Like other amine formation reactions, there will be a mixture of primary, secondary, tertiary, and quaternary amines. These can be separated by fractional distillation but it would need high temperatures above 200^oC. Instead, fractional crystallization is more feasible. The primary, secondary, and tertiary amines have melting points of 10.5^oC, 28^oC, and 21^oC respectively. ("PubChem Compound Database", n.d.)

The next step is synthesis of 2-chloroethanol. It is produced industrially from ethylene oxide and HCl. (Miao, 2009) However, the former is extremely toxic and carcinogenic. ("Safety and Hazards: Ethylene Oxide — OSHA", n.d.)

A better method is the electrophilic addition of ethylene using HOCl.

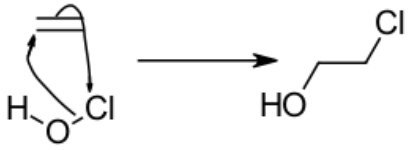


Figure 43: Formation of 2-chloroethanol from ethylene

Hypochlorous acid is formed as chlorine dissolves in water, according to the following equation:

$$Cl_2 + H_2O \rightleftharpoons HCl + HOCl$$

As for ethylene, it can be produced by dehydration of ethanol. This is easily done by passing gaseous ethanol over heated Al_2O_3. (Clark, 2015a) The ethylene can then be bubbled into HOCl to form 2-chloroethanol solution. The rest of the reaction can be done in this solution without separation of toxic substances.

8.3 Synthesis scheme of 1-(2,3-dichlorophenyl)piperazine

In summary, 1-(2,3-dichlorophenyl)piperazine can be synthesized according to the scheme below:

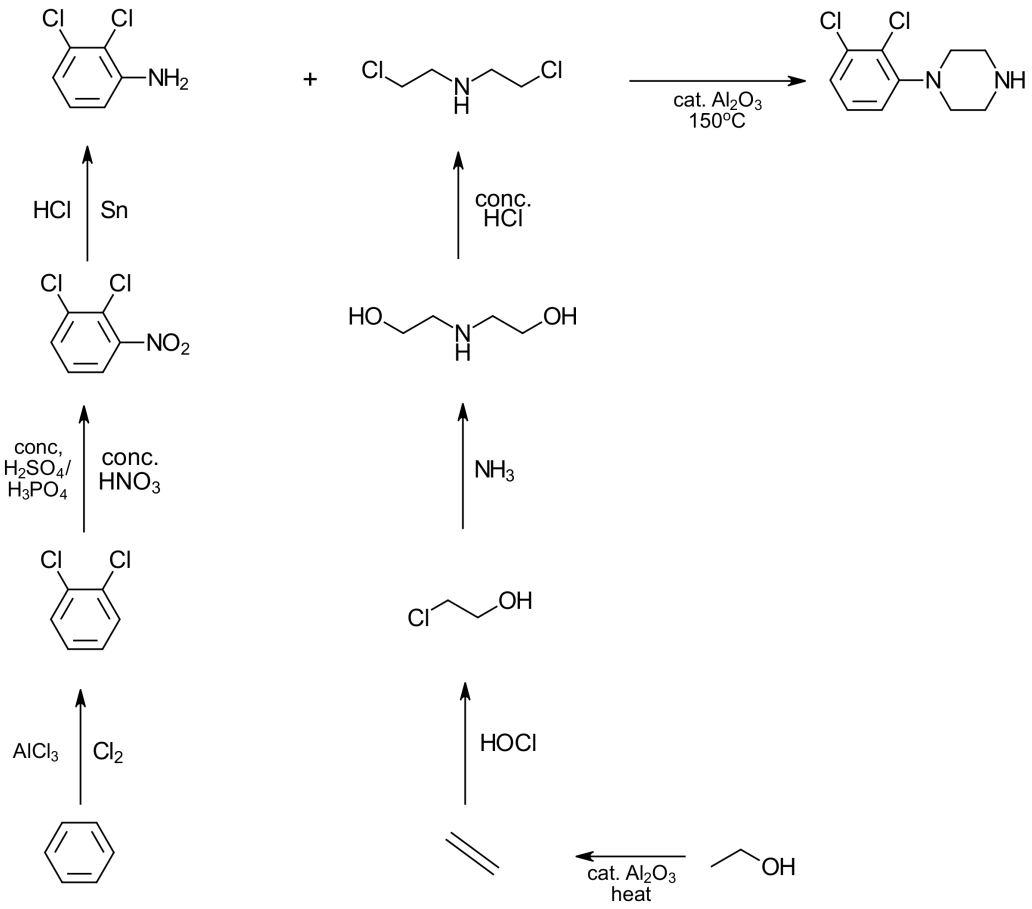


Figure 44: Synthesis of 1-(2,3-dichlorophenyl)piperazine

9 Overall total synthesis of Aripiprazole

From the above results, we can conclude that all reagents and catalysts necessary for a theoretical total synthesis of Aripiprazole can be made from common reagents.
Organic reagents:

- Succinic acid
- Butanoic acid
- Benzene
- Lactic acid
- Ethanol

Inorganic reagents:

- K_2CO_3
- NH_3
- $LiAlH_4$
- Cl_2
- Sn
- $SOCl_2$
- Na_2S
- $NaNO_2$
- HBr
- HCl
- HNO_3
- H_2SO_4

Catalysts:

- Al_2O_3
- $AlCl_3$
- $Ca_3(PO_4)_2$

Some steps can be done without purification, and some reagents generated *in situ* to prevent exposure to harmful substances. For other steps, standard precautions are needed.

10 Cost comparison for synthesis of Aripiprazole

After the scheme is mapped out, an approximate cost of lab synthesis can be calculated based on yields.
The standard for comparison is the price of Aripiprazole in the US. It varies from 0.41 to 1.5 USD per milligram. ("Aripiprazole Prolonged Release Suspension for Injection", 2017)
This calculation makes several assumptions, both for ease of calculation, and the fact that it can vary depending on the experimenter, their environment, or precise procedure:

- Ignore cost of solvents, equipment, electricity, inorganic catalysts, waste neutralization and disposal
- Yield is similar to that listed in literature
- For processes without literature-provided yield, it is assumed to be 100%
- Synthesis scale does not affect yield

While this means that it does not accurately reflect a real-world process, it still provides an approximate ballpark.
If a reagent is available for household use (such as lactic acid), prices are found from Amazon. For other lab reagents, their prices are found from Sigma-Aldrich. The detailed calculation is shown in the appendix.
Synthesizing 1g of Aripiprazole would require 29.758 USD, or 0.03 USD per mg, less than 1/13th of the minimum price in the US. Therefore, it is theoretically feasible to synthesize Aripiprazole in an amateur laboratory with common reagents.
It must be kept in mind that apart from synthesis, drug manufacturing has many other processes such as quality control, optimization, and industrial adaptation. Therefore, this is simply a theoretical demonstration and not a legitimate reason to change the market cost of Aripiprazole.

11 Conclusion

From this literature-based investigation, I devised a route to synthesize the schizophrenia treatment Aripiprazole in a common laboratory. Its approximate theoretical cost would be lower than market price. While it does not reflect actual cost, it is still a meaningful demonstration of the capabilities of organic chemistry.

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A Calculation of synthesis cost

All prices were retrieved in February 2021. Chemicals available for households are found on Amazon, others are found on Sigma-Aldrich.

A.1 1g of aripiprazole

Molar mass of aripiprazole = 448.39g
Number of moles in 1g = 2.23 mmol
The microwave synthesis step has a 45% yield
n(1,4-dibromobutane)=n(DCP)=n(7-HQ) = 2.23/0.45 = 4.96 mmol
n(tetra-n-butylammonium bromide) = 0.1×n(7-HQ) = 0.496 mmol
n(K_2CO_3) = 17.4 mmol
m(DMF) = 0.1 × m(1,4-dibromobutane + DCP + 7-HQ + K_2CO_3) = 3.81 mg
Cheapest price for dimethylformamide on Sigma-Aldrich: 671.19 USD/8L
Potassium carbonate is available as a food ingredient.
Cheapest price on Amazon: 20 USD/kg
Price of K_2CO_3 and DMF used in final step: 0.048 USD

A.2 Cost of synthesizing 1,4-dibromobutane

Cost of bromination:
Yield of bromination of 1,4-butanediol = 91%
n(1,4-butanediol) = 4.96/0.91 = 5.45 mmol
n(HBr) = 3 × n(1,4-butanediol) × 2 = 32.8 mmol
Cheapest price of conc. HBr on Sigma-Aldrich: 126.48 USD/L
Price of HBr in bromination of 1,4-butanediol: 0.469 USD

Cost of reduction:
Yield of reduction of succinic acid is assumed to be 100%
n(Succinic acid) = n(1,4-butanediol) = 5.45 mmol
n($LiAlH_4$) = 4 × n(Succinic acid) = 21.8 mmol
Succinic acid is available in pill form as a dietary supplement.
Cheapest price on Amazon: 1.66 USD/g
Cheapest price of $LiAlH_4$ on Sigma-Aldrich: 0.952 USD/g

Price of reagents in 1,4-dibromobutane synthesis: 2.324 USD

A.3 Cost of synthesizing 7-hydroxy-3,4-dihydro-2(1H)-quinolinone

Yield of 7-HQ formation = 60%
n(3-aminophenol) = n(3-chloropropanoyl chloride) = 4.96/0.6 = 8.27 mmol

A.3.1 Cost of synthesizing 3-aminophenol

Cost of making 3-aminophenol from 3-nitroaniline
Yield of reduction of 3-nitrophenol is assumed to be 100%
n(Tin) = 8.27 × 3 = 24.81 mmol
Yield of 3-nitrophenol from 3-nitroaniline = 65%
Ignoring cost of water and dilute HCl
n(m-nitroaniline) = n($NaNO_2$) = 12.7 mmol
Cheapest price of $NaNO_2$ on Sigma-Aldrich: 0.12 USD/g
Cheapest price of tin on Amazon: 63.9 USD/kg
Price of converting 3-nitroaniline to 3-aminophenol: 0.293 USD

Cost of making 3-nitroaniline from dinitrobenzene:
Yield of selective reduction of dinitrobenzene = 60%
Price of aqueous ethanol solvent is ignored
n(dinitrobenzene) = 12.7/0.6 = 21.2 mmol
n(Na_2S) = 21.2 × 1.9 = 40.3 mmol
n(Na) = 80.6 mmol
n(S) = 40.3 mmol
Cheapest price of Na_2S on Sigma-Aldrich = 12.2 USD/g
Cheapest price of S on Sigma-Aldrich = 0.167 USD/g
Cheapest price of Na on Sigma-Aldrich = 0.952 USD/g
Ignoring the price of triethylamine, it is much cheaper to synthesize Na_2S in the lab
Price of Na_2S for selective reduction = 1.98 USD

Cost of dinitration of benzene:
Volumes of acids required retrieved from Vogel & Furniss, pp.854-856
Yield of first nitration = 80%
Yield of second nitration = 70%
n(Benzene) = 21.2/(0.8 × 0.7) = 37.9 mmol
Volume of conc. H_2SO_4 required = (42mL / 122 mmol) × 37.9 = 13mL
Volume of conc. HNO_3 required = (30mL / 122 mmol) × 37.9 = 9.3mL
Cheapest price for benzene on Sigma-Aldrich: 83.6 USD/L
Cheapest price for conc. HNO_3 on Sigma-Aldrich: 305.3 USD/L
Cheapest price for conc. H_2SO_4 on Sigma-Aldrich: 41.2 USD/L

Total price of benzene dinitration = 3.66 USD

Price of reagents in 3-aminophenol synthesis: 5.933 USD

A.3.2 Cost of synthesizing 3-chloropropanoyl chloride

Cost of making 3-chloropropanoyl chloride from 3-chloropropanoic acid
Yield of chlorination of 3-chloropropanoic acid = 80%
n(3-chloropropanoic acid) = n($SOCl_2$) = 8.27/0.8 = 10.34 mmol
$SOCl_2$ can be made in many ways. For convenience, it is assumed that it is purchased.
Cheapest price of $SOCl_2$ on Sigma-Aldrich: 172 USD/L
Price of $SOCl_2$ for chlorination = 0.129 USD

Cost of hydrochlorination of acrylic acid
Yield of hydrochlorination = 95%
n(Acrylic acid) = 10.34/0.95 = 10.88 mmol
n(HCl) = 4 × 10.88 = 43.52 mmol
Cheapest price of conc. HCl on Sigma-Aldrich: 32.1 USD/L
Price of HCl for hydrochlorination = 0.122 USD

Cost of dehydration of lactic acid
Yield of dehydration = 70%
n(Lactic acid) = 10.88/0.7 = 15.5 mmol
Lactic acid is available as a food additive.
Cheapest price of lactic acid on Amazon: 16.6 USD/L
Price of lactic acid for dehydration = 0.019 USD
Price of reagents for 3-chloropropanoyl chloride synthesis: 0.27 USD

Price of 7-hydroxy-3,4-dihydro-2(1H)-quinolinone synthesis: 6.2 USD

A.4 Cost of synthesizing tetra-n-butylammonium bromide

Cost of quaternary ammonium formation
Yield of TBAB is assumed to be 100%
n(TBAB) = 0.496 mmol = n(NH3 (in ethanol))
n(1-bromobutane) = 0.496 × 4 = 1.984 mmol
Cheapest price of 2M ammonia in ethanol on Sigma-Aldrich: 399 USD/L
Price of ammonia in TBAB formation = 0.099 USD

Cost of 1-bromobutane formation from 1-butanol
Yield of bromination = 91%
n(1-butanol) = 2.18 mmol
n(HBr) = n(1-butanol) × 3 = 6.54 mmol
Price of HBr for bromination (unit price given above) = 0.0935 USD

Cost of reduction of butyric acid:
Yield of reduction is assumed to be 100%
n(Butyric acid) = 2.18 mmol
n($LiAlH_4$) = 2 × 2.18 = 4.36 mmol
Butyric acid is available as a dietary supplement
Cheapest price for butyric acid on Amazon: 1.28 USD/g
Price of reducing butyric acid = 0.403 USD

Price of tetra-n-butylammonium bromide synthesis: 0.596 USD

A.5 Cost of synthesizing 1-(2,3-dichlorophenyl)piperazine

Yield of DCP formation = 70%
n(2,3-dichloroaniline) = n(bis(2-chloroethyl)amine) = n(DCP)/0.7 = 7.09 mmol

A.5.1 Cost of synthesizing 2,3-dichloroaniline

Cost of making 2,3-dichloroaniline from 2,3-dichloronitrobenzene
Yield of reduction of 2,3-dichloronitrobenzene is assumed to be 100%
Ignoring price of dilute HCl
n(2,3-dichloronitrobenzene) = 7.09 mmol
n(Tin) = 7.09 × 3 = 21.27 mmol
Price of tin used in reduction (unit price given above) = 0.161 USD

Cost of nitrating 1,2-dichlorobenzene
Quantities of acids required retrieved from Neumann et al.
Yield of nitration = 15%
n(1,2-dichlorobenzene) = 7.09/0.15 = 47.27 mmol
n(H_2SO_4) = 28.9 mmol
n(H_3PO_4) = 98.34 mmol
n(HNO_3) = 53.5 mmol
Cheapest price for conc. H_3PO_4 on Sigma-Aldrich: 634.84 USD/L
Unit prices for other acids are listed above
Price of acids in nitration of 1,2-dichlorobenzene = 4.12 USD

Cost of dichlorinating benzene
Yield of dichlorination = 35%
Cost of catalyst is neglected, as it varies depending on apparatus and production method
n(benzene) = 47.27/0.35 = 135.1 mmol
n(Cl_2) = 2 × n(benzene) = 270.2 mmol
Price of benzene is provided above
Chlorine can be made in many ways. For this calculation, it is assumed to be made from $KMnO_4$ and HCl.
Cheapest price for $KMnO_4$ on Sigma-Aldrich: 132.3 USD/kg
Price for conc. HCl is provided above.
Price for making 1,2-dichlorobenzene = 9.20 USD

Price of reagents in 2,3-dichloroaniline synthesis: 13.48 USD

A.5.2 Cost of synthesizing bis(2-chloroethyl)amine

Cost of making bis(2-chloroethyl)amine from diethanolamine
Yield of chlorination of diethanolamine = 90%
n(Diethanolamine) = 7.09/0.9 = 7.88 mmol
n(HCl) = 3 × 7.88 = 23.64 mmol
Price of conc. HCl is provided above.
Price of HCl for chlorination of diethanolamine = 0.0651 USD

Cost of making diethanolamine
Yield of diethanolamine = 40%
n(2-chloroethanol) = 7.88/0.4 = 19.7 mmol
n(NH_3 (aq)) = 19.7 × 6 = 118.2 mmol
Aqueous ammonia is commonly used as cleaning solution
Cheapest price for aqueous ammonia (10%): 100 USD/L
Price of ammonia for diethanolamine formation = 6.313 USD

Cost of making 2-chloroethanol
Yield is assumed to be 100%
Cost of water in HOCl formation is ignored, and all chlorine is assumed to be dissolved
n(Ethene) = n(HOCl) = n(Cl_2) = 19.7 mmol
Price for $KMnO_4$ and HCl for Cl_2 production is calculated above.
Price of HOCl for 2-chloroethanol production = 0.599 USD

Cost of dehydrating ethanol
Yield is assumed to be 100%
Cost of Al_2O_3 is neglected, as it can vary depending on apparatus
n(Ethanol) = 19.7 mmol
Cheapest price of absolute ethanol on Amazon: 114.8 USD/L
Price of ethanol for dehydration = 0.132 USD

Price of reagents in bis(2-chloroethyl)amine synthesis: 7.11 USD

Price of 1-(2,3-dichlorophenyl)piperazine synthesis: 20.59 USD

Price of 1g of Aripiprazole = 29.758 USD