Chapter 1

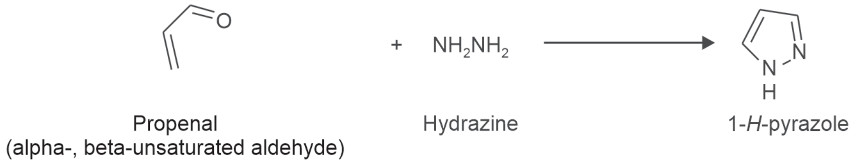
Preparation of Drugs/Intermediates

EXPERIMENT 1.1

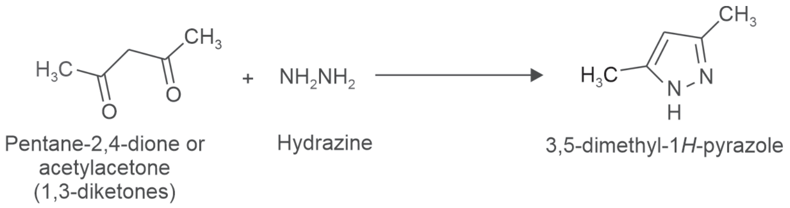
To prepare and submit pyrazole

1.1.1 Theory

Pyrazole is also known as 1,2-diazole and 1*H*-pyrazole. Pyrazoles are synthesized by the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation.



Substituted pyrazoles are prepared by condensation of 1,3-diketones with hydrazine. For example, acetylacetone and hydrazine gives 3,5-dimethyl-1*H*-pyrazole.



Pyrazole is one of the important intermediates used in medicinal chemistry for synthesis of number of drugs, i.e. sildenafil, phenazone, phenylbutazone, mepiprazole, indiplon, surinabant, betazole. Several pesticides, i.e. fungicides, insecticides and herbicides contain pyrazole as nucleus in its structure.

1.1.2 Chemicals required

(a) Sodium hydroxide (0.5 M)	100 ml
(b) Hydrazine sulphate	13 g
(c) Pentane-2,4-dione	10 g

(d) Ether	60 ml
(e) Sodium chloride	q.s. to prepare saturated solution

1.1.3 Procedure

(a) Place around 100 ml of 0.5 M NaOH solution in a 250 ml three necked flask, add hyrazine sulphate (13 g; 0.1 mol) with intermittent stirring. Now equip three necks of the flask with a thermometer, mechanical stirrer and dropping funnel.
(b) Submerge the flask in an ice bath and wait to reach the temperature at 15 °C (at this point, some sodium sulphate may segregate), add 10 g (10.3 ml; 0.1 mol) of acetylacetone (pentane-2,4-dione) from dropping funnel dropwise with constant stirring while keeping the temperature at 15 °C.
(c) After the complete addition of acetylacetone, stir the reaction mixture for around 1 h at 15 °C, resulting in the formation and separation of dimethylpyrazole.
(d) Add around 50 ml of distilled water and stir to dissolve inorganic salts. Transfer the content of flask to a separatory funnel, add around 20 ml of ether and shake the separatory funnel for 2 minutes. Segregate both the layers. Now extract the aqueous layer with 4 × 10 ml fractions of ether. Mix the ethereal extracts and wash it with saturated solution of sodium chloride followed by drying it over anhydrous potassium carbonate. Take out the ether using rotary evaporator while applying vacuum, results in appearance of pale yellow solid. The product so obtained can be recrystallised with light petroleum.

1.1.4 Calculation

The molecular weights of pentane-2,4-dione, hydrazine sulphate, and 3,5-dimethyl-1*H*-pyrazole are 100.13 g, 130.12 g and 96.13 g, respectively.

As per chemical reaction, 100.13 g of pentane-2,4-dione reacts with 130.12 g of hydrazine sulphate to gives 96.13 g of 3,5-dimethyl-1*H*-pyrazole.

Therefore, 10 g of pentane-2,4-dione will give x g of 3,5-dimethyl-1*H*-pyrazole.

$$x = (96.13/100.13) \times 10 = 9.60 \text{ g}$$

Thus, theoretical yield of pentane-2,4-dione = 9.60 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.1.5 Precautions

(a) The temperature condition should be carefully maintained.
(b) Adequate shaking using separatory funnel should be performed.

1.1.6 Physical properties

It is white to yellow crystalline powder with melting point of 68 °C. It is a weak base, with pK_b value 11.5. Its octanol/water partition coefficient is 0.27.

1.1.7 Uses

(a) Pyrazole is used as an intermediate/starting material for preparation of drugs, i.e. a number of pyrazole derivatives are being used for their anticancer (tartrazine, crizotinib), NSAIDs (phenazone, phenylbutazone, ramifenazone, ionazolac, tepoxalin, deracoxib), minor tranquilizer (mepiprazole), antianxiety (indiplon, zaleplon), antiobesity (surinabant, rimonabant), anticoagulant (apixaban), antihistaminic (betazole), antidepressant (fezolamine), anabolic steroid (stanozolol) and male erectile dysfunction (sildenafil) and analgesic (difenamizole) activity.

(b) The pyrazole nucleus is also a part of several pesticides, i.e. fungicides, insecticides and herbicides (examples: fipronil, tebufenpyrad, chlorfenapyr, and fenpyroximate).

1.1.8 Viva voce

(a) What are the reaction conditions required for synthesis of pyrazole?

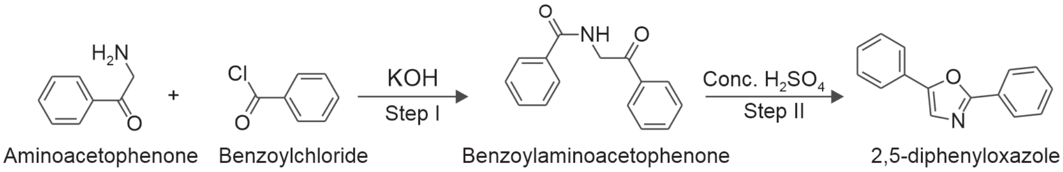
(b) What is the importance of pyrazole nucleus in medicinal chemistry?

EXPERIMENT 1.2

To prepare and submit 1,3-oxazole

1.2.1 Theory

Oxazoles are five membered heterocyclic compounds possessing two hetero atoms, i.e. N and O in their rings.



This synthesis of oxazole from benzoylaminoacetophenone is known as Robert Robinson method.

The oxazole nucleus is a part of several heterocyclic compounds belonging to natural and synthetic compounds. The example of category of drugs containing oxazole nucleus include (i) antibiotics, i.e. flopristin, streptogramin A, griseovirdin, (ii) anticancer drugs, i.e. mubritinib, telomestatin (iii) antidiabetic drugs, i.e. darglitazone and aleglitazar.

1.2.2 Chemicals required

Step I

(i)	Aminoacetophenone hydrochloride	5.14 g
(ii)	Benzoyl chloride	7 g
(iii)	Potassium hydroxide aqueous solution (40%)	q.s.

Step II

(i)	Benzoylaminoacetophenone	1 g
(ii)	Conc. sulphuric acid	5 ml

1.2.3 Procedure

The synthesis of oxazole comprises following two steps:

Step I: Synthesis of benzoylaminoacetophenone

(i) Dissolve aminoacetophenone hydrochloride (5.14 g; 0.03 mol) in distilled water (50 ml). Stir the solution.

(ii) Add benzoyl chloride (7 g; 0.05 mol) followed by addition of adequate aqueous KOH solution (40%) to make the reaction mixture alkaline. The completion of reaction (all the benzoyl chloride reacted), results in solidification of the oil.

(iii) Collect the almost colourless, crystalline product and wash well with water. Remove the oily impurity (if found) using porous porcelain.

(iv) Recrystallize the product using alcohol to obtain needles of the purified product. The melting point of this product is 123 °C.

Step II: Synthesis of 2,5-diphenyloxazole

(i) Dissolve benzoylaminoacetophenone (1 g; 0.004 mol) in conc. sulphuric acid (5 ml) with occasional stirring.

(ii) Warm the solution on water bath for 2 minutes and then pour into water. Filter the precipitate, wash the filtrate with water.
(iii) Recrystallize the product using light petroleum.

1.2.4 Calculation

Step I: Synthesis of benzoylaminoacetophenone

The molecular weights of aminoacetophenone, benzoyl chloride and benzoylaminoacetophenone are 171.62 g, 140.57 g and 239.09 g, respectively.

As per chemical reaction, 171.62 g of aminoacetophenone reacts with 140.57 g of benzoyl chloride to give 239.09 g of benzoylaminoacetophenone.

Therefore 5.14 g of aminophenone will give x g of benzoylaminoacetophenone.

$$x = (239.09/171.62) \times 5.14 = 7.16 \text{ g}$$

Thus, theoretical yield of benzoylaminoacetophenone = 7.16 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

Step II: Synthesis of 2,5-diphenyloxazole

The molecular weights of benzoylaminoacetophenone and 2,5-diphenyloxazole are 239.09 g and 221.25 g, respectively.

As per chemical reaction, 239.09 g of benzoylaminoacetophenone reacts with conc. H_2SO_4 (around 500 ml) to give 221.25 g of 2,5-diphenyloxazole.

Therefore 1 g of benzoylaminoacetophenone will give x g of 2,5-diphenyloxazole.

$$x = (221.25/239.09) \times 1 = 0.92 \text{ g}$$

Thus, theoretical yield of 2,5-diphenyloxazole = 0.92 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.2.5 Precautions

Perform the reaction in fume cupboard as even a short exposure to benzoyl chloride can cause skin and eye irritation. The inhalation of benzoyl chloride should be avoided.

1.2.6 Physical properties

It occur as yellowish powder. Its melting point is 73 °C and octanol/water coefficient is 4.67.

1.2.7 Uses

Some of well known drugs possessing oxazole moiety in their structure includes darglitazone (antidiabetic drug) and aleglitazar (antidiabetic drug), mubritinib (anticancer drug), ditazole (a platelet aggregation inhibitor), oxaprozin (NSAIDs drug) and telomestatin (anticancer drug). Several antibiotics also contain an oxazole ring, i.e. flopristin, streptogramin A, griseovirdin and calcinomycin.

1.2.8 Viva voce

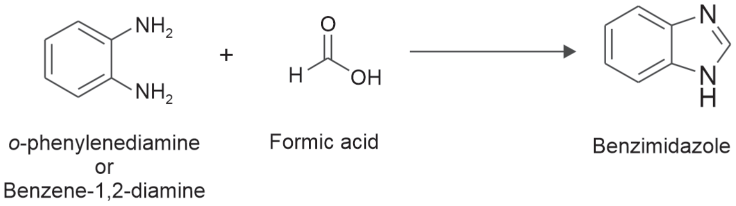
(i) How would you synthesize diphenyloxazole?
(ii) What is the medicinal importance of oxazole nucleus?
(iii) What are the precautions to be considered while dealing with benzoyl chloride?

EXPERIMENT 1.3

To prepare and submit benzimidazole

1.3.1 Theory

Benzimidazole is also known as 1*H*-benzimidazole. When a benzene ring is fused to an imidazole ring through its 4,5-bond, a benzimidazole ring is formed. The simplest way to prepare benzimidazole is cyclization reaction of *o*-phenylenediamine with formic acid.



1.3.2 Chemicals required

(a) *o*-phenylenediamine	6.75 g
(b) 90% formic acid	4 ml
(c) Sodium hydroxide solution (10%)	q.s.
(d) Activated charcoal	1 g

1.3.3 Procedure

(a) In a 100 ml round bottom flask, take *o*-phenylenediamine (6.75 g; 0.06 mol) and add 4.3 g (4 ml; 0.85 mol) of 90% formic acid. After mixing the content, heat the reaction mixture on water bath (at 100 °C) for around 2 h.

(b) Cool the reaction mixture and add sodium hydroxide solution (10% w/v) gradually, with constant stirring until reaction mixture is just alkaline to litmus paper.

(c) Filter the separated crude benzimidazole and wash it two times with an ice-cold water (2 × 10 ml).

(d) Dissolve the crude benzimidazole in 100 ml of boiling water, add 1 g of decoloring charcoal then boil for 10 minutes and filter it while hot. The cooling of filtrate to around 10 °C results in appearance of pure benzimidazole. Filter and dry the product.

1.3.4 Calculation

The molecular weights of *o*-phenylenediamine, formic acid and benzimidazole are 108.14 g, 46.03 g and 118.14 g, respectively.

As per chemical reaction, 108.14 g of *o*-phenylenediamine reacts with 46.03 g of formic acid to give 118.14 g of benzimidazole.

Therefore 6.75 g of *o*-phenylenediamine will give x g of benzimidazole.

$$x = (118.14/108.14) \times 6.75 = 7.37 \text{ g}$$

Thus, theoretical yield of benzimidazole = 7.37 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.3.5 Precautions

(a) *o*-phenylenediamine (white to brownish crystalline solid) should be carefully dealt as it may cause nose and throat irritation on breathing/exposure and may cause asthma like allergy.
(b) Be sure that crude benzimidazole is completely digested with decoloring carbon in the last step.

1.3.6 Physical properties

It is a colourless solid with melting point of 170 to 172 °C. It is soluble in water (2010 mg/L). It is freely soluble in alcohol, sparingly soluble in ether and practically insoluble in benzene, petroleum ether.

1.3.7 Uses

Benzimidazole is used as an intermediate for synthesis of several drugs, i.e. albendazole (anthelmintic), mebendazole (anthelmintic) and thiabendazole (anthelmintic), astemizole (antihistaminic), bezitramide (analgesic), candesartan (antihypertensive), domperidone (antiemetic), Irtemazole (uricosuric), lansoprazole (antiulcer), milenperone (antipsychotic), marivavir (antiviral), omeprazole (antiulcer), pimobendan (cardiotonic), rabeprazole (antiulcer), carbendazim (fungicide), etc.

1.3.8 Viva voce

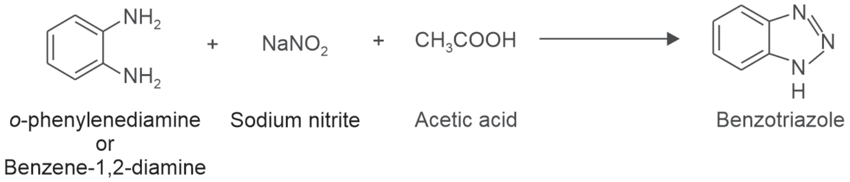
(a) What is the purpose of using activated charcoal in the last step of benzimidazole synthesis?
(b) What will be the product, if we use acetic acid instead of formic acid during synthesis of benzimidazole?
(c) Name various drugs in which benzimidazole ring is present?

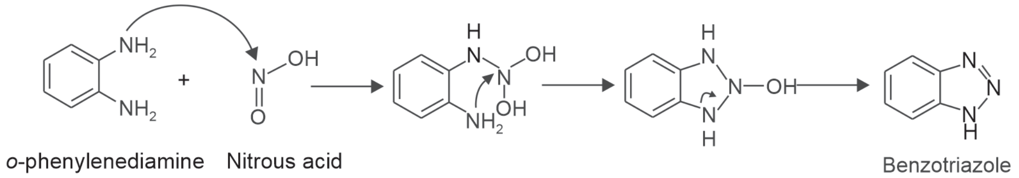
EXPERIMENT 1.4

To prepare and submit benzotriazole

1.4.1 Theory

It is a bicyclic heterocyclic system comprising three nitrogen atoms and fused benzene ring. The reaction between *o*-phenylenediamine and nitrous acid (generated on reaction of sodium nitrite with glacial acetic acid) results in the formation of benzotriazole.





1.4.2 Chemicals required

(a) *o*-phenylenediamine	2.16 g
(b) Glacial acetic acid	2.3 ml
(c) Sodium nitrite	1.5 g
(d) Decolouring charcoal	q.s.

1.4.3 Procedure

(a) Prepare a mixture of glacial acetic acid (2.3 ml; 0.04 mol) and 10 ml of water in a 100 ml beaker and add *o*-phenylenediamine (2.16 g, 0.02 mol) to it. The content of beaker may be slightly heated to facilitate the dissolution of *o*-phenylenediamine to prepare a clear solution.

(b) Cool the solution to 15 °C, add 10 ml of sodium nitrite (1.5 g, 0.022 mol) solution prepared in water with adequate stirring. The temperature of reaction mixture reaches to about 85 °C (within 2–3 minutes), then starts to cool with simultaneous change in colour from dark red to pale brown. After sometime, temperature of reaction mixture reaches to 25–40 °C then chill it using ice-water bath for 25–30 minutes. Filter the separated out pale brown solid, wash with ice-cold water (3 × 30 ml portions).

(c) Dissolve the crude product in about 40 ml of boiling water. Add decolouring charcoal and filter it. Allow the filtrate to cool to about 50 °C. Add some crystals of the crude benzotriazole (for seeding, so that better and faster crystals could form), then chilling in an ice-bath results in separation of pale straw coloured needles of benzotriazole. It can be recrystalized from benzene.

1.4.4 Calculation

The molecular weights of *o*-phenylenediamine, sodium nitrite and benzotriazole are 108.14 g, 69.00 g and 106.11 g, respectively.

As per chemical reaction, 108.14 g of *o*-phenylenediamine reacts with 69.00 g of sodium nitrite to give 106.11 g of benzotriazole.

Therefore, 2.16 g of *o*-phenylenediamine will give x g of benzotriazole.

$$x = (106.11/108.14) \times 2.16 = 2.11 \text{ g}$$

Thus, theoretical yield of benzotriazole = 2.11 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.4.5 Precautions

(a) The proper maintaining of temperature condition is required for better yield and purity of the product.
(b) The pure benzotriazole can be obtained on using purified *o*-phenylenediamine as in general *o*-phenylenediamine possesses coloured impurities.

1.4.6 Physical properties

It is a white to brown coloured crystalline powder with MP 99–100 °C. Its other properties are as follows: density: 1.36 g/cm^3; water solubility: 2 g/100 ml; pKa: 8.2 and UV absorbance: 286 nm.

1.4.7 Uses

(a) One of benzotriazole based anticancer drug is available in market, i.e. 4,5,6,7-tetrabromobenzotriazole (TBB) possessing highly selective inhibition against protein kinase CK2. Vorozole, another benzotriazole analogue is in clinical trial as anticancer agent.
(b) It is used as an intermediate for the manufacturing of drugs in bulk in drug industry.
(c) Its non-pharmaceutical application, i.e. it is an effective corrosion inhibitor for copper and its alloys by preventing undesirable surface reactions.

1.4.8 Viva voce

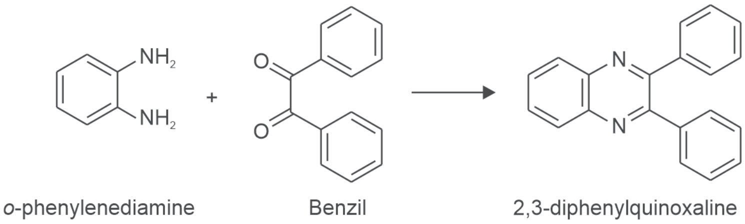
(a) Why different temperature conditions are required during synthesis of benzotriazole?
(b) Give name of one market available drug based on benzotriazole nucleus.
(c) Why pure crystals of benzotriazole is added during its recrystallization?

EXPERIMENT 1.5

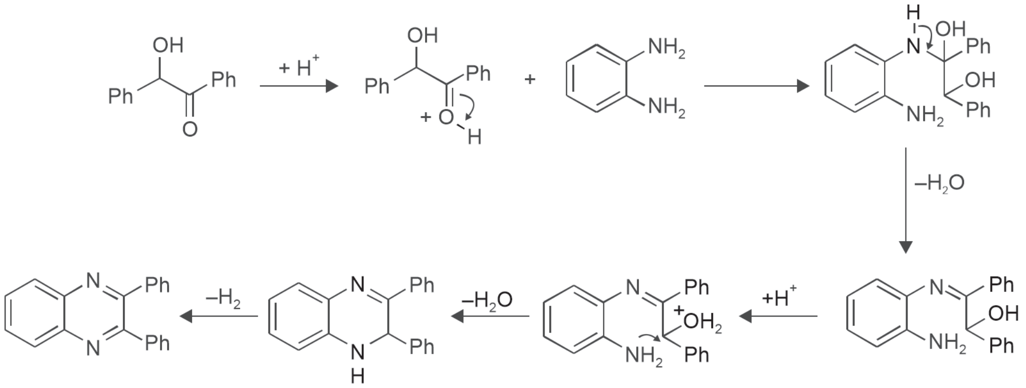
To prepare and submit 2,3-diphenyl quinoxaline using conventional method

1.5.1 Theory

It involves condensation of an aryl 1,2-diamine (ex: *o*-phenylenediamine) with a 1,2-dicarbonyl compound or α-diketones (ex: benzil) by heating results in formation of 2,3-diphenylquinoxaline.



Reaction mechanism



1.5.2 Chemicals required

(a) Benzil	2.1 g
(b) *o*-pheynlenediamine	1.1 g
(c) Rectified spirit	20 ml

1.5.3 Procedure

(a) Dissolve benzil (2.1 g; 0.01 mol) in 10 ml of rectified spirit by warming it.
(b) Prepare a solution of *o*-phenylenediamine (1.1 g; 0.01 mol) in 10 ml of rectified spirit.
(c) Add *o*-pheynlenediamine solution to benzil solution and warm it using water bath for 25 to 30 minutes.
(d) Add water to the reaction mixture until a slight cloudiness persists. Now cool and filter the crude product. Recrystallize it using ethanol.

1.5.4 Calculation

The molecular weights of *o*-phenylenediamine, benzil and 2,3-diphenyl quinoxaline are 108.14 g, 210.23 g and 282.34 g, respectively.

As per chemical reaction, 210.23 g of benzil reacts with 108.14 g of *o*-phenylenediamine to give 282.34 g of 2,3-diphenyl quinoxaline.

Therefore, 2.1 g of benzil will give x g of 2,3-diphenyl quinoxaline.

$$x = (282.34/210.23) \times 2.1 = 2.82 \text{ g}$$

Thus, theoretical yield of 2,3-diphenyl quinoxaline = 2.82 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.5.5 Precautions

(a) *o*-phenylenediamine (white to brownish crystalline solid) should be carefully dealt as it may cause nose and throat irritation on breathing/exposure and responsible for asthma like allergy.
(b) The glasswares should be completely dried.

1.5.6 Physical properties

The melting point is 125–127 °C. Solvent system comprising petroleum ether and ethylacetoacetate in the ratio of 9 : 1 can be used for thin layer chromatography of 2,3-diphenyl quinoxaline.

1.5.7 Uses

It is used as an intermediate for manufacturing of drugs in drug industry. It is one of the intermediates being employed for synthesis of new drugs as part of drug discovery process.

1.5.8 Viva voce

Explain the principle and reaction mechanism involved in synthesis of 2,3-diphenylquinoxaline.

To prepare and submit 2,3-diphenyl quinoxaline using green chemistry approach

There are several approaches (methods) for synthesis of 2,3-diphenyl quinoxaline using green chemistry. Some of them are described below.

Approach I

Preparation of 2,3 diphenyl quinoxaline without using catalyst in sonicator.

Procedure

Prepare a separate solution of 2.1 g (0.01 mol) of benzil and 1.1 g (0.01 mol) of *o*-phenylenediamine in 8 ml of rectified spirit using sonicator. A slight increase in temperature can be used to facilitate the dissolution. Now, mix both the solutions in a beaker and sonicate the reaction mixture for 15 min at 60 °C. Add enough distilled water, allow to cool for 10–15 min. Filter, dry and recrystallize the product so obtained using ethanol.

Approach II

Preparation of 2,3-diphenyl quinoxaline using oxalic acid as catalyst in sonicator.

Procedure

Prepare a separate solution of 2.1 g (0.01 mol) of benzil and 1.1 g (0.01 mol) of *o*-phenylenediamine in 8 ml of rectified spirit using sonicator. A slight increase in temperature can be used to facilitate the dissolution. Now, mix both the solutions in a beaker containing a suitable catalyst and sonicate the reaction mixture for 5–10 min at 60 °C. Add enough distilled water, allow to cool for 10–15 min. Filter the product. Extract the filtrate two times with 30 ml of $CHCl_3$. Separate the aqueous layer (containing oxalic acid), evaporate it to obtain pure oxalic acid. Oxalic acid is the catalyst in this reaction and after its recovery, it can be used again for next identical reaction. The other catalysts, i.e. $ZnCl_2$, $CoCl_2$, $Ni(OAc)_2$, $Mn(OAc)_2$ can also be employed instead of oxalic acid in this procedure.

Approach III

Preparation of 2,3-diphenyl quinoxaline with later addition of *para*-toluene sulphonic acid (*p*-TSA) under sonication (using ethanol as solvent).

Procedure

Dissolve 2.1 g (0.01 mol) of benzil and 1.1 g (0.01 mol) of *o*-phenylenediamine in 5 ml of ethanol in a flat bottom flask. Add 0.034 g (0.002 mol) of *p*-TSA to reaction mixture followed by sonication for 8 min. Pour the reaction mixture on crushed ice and stir for 10 min. Filter the crude product, wash with distilled water and dry it. Recrystallize the product using ethanol.

Approach IV

Preparation of 2,3-diphenyl quinoxaline with earlier addition of *p*-TSA under sonication (using ethanol as solvent).

Procedure

Place 2.1 g (0.01 mol) of benzil, 1.1 g (0.01 mol) of *o*-phenylenediamine and 0.034 g (0.002 mol) of *p*-TSA in a flat bottom flask. Add 5 ml of ethanol to dissolve them, stir the reaction mixture for 10 min. Filter the crude product, wash with distilled water and dry it. Recrystallize the product using ethanol.

Approach V

Preparation of 2,3-diphenyl quinoxaline using *p*-TSA in sonicator (using distilled water as solvent).

Procedure

Place 2.1 g (0.01 mol) of benzil, 1.1 g (0.01 mol) of *o*-phenylenediamine and 0.034 g (0.002 mol) of *p*-TSA in a flat bottom flask. Add 10 ml of distilled water to dissolve them, stir the reaction mixture for 20 min. Filter the crude product, wash with distilled water and dry it. Recrystallize the product using ethanol.

Advantages

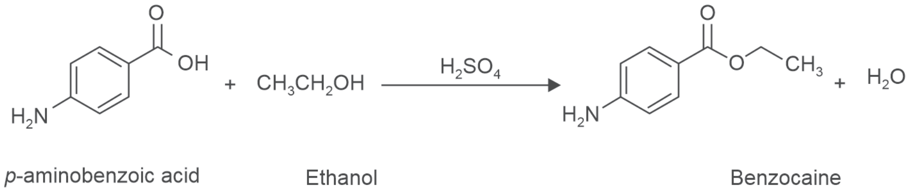
The green chemistry approach has many advantages over conventional method of synthesis including good yield, short reaction time, low cost, simple experimental procedures, pollution free and safer to medicinal chemist.

EXPERIMENT 1.6

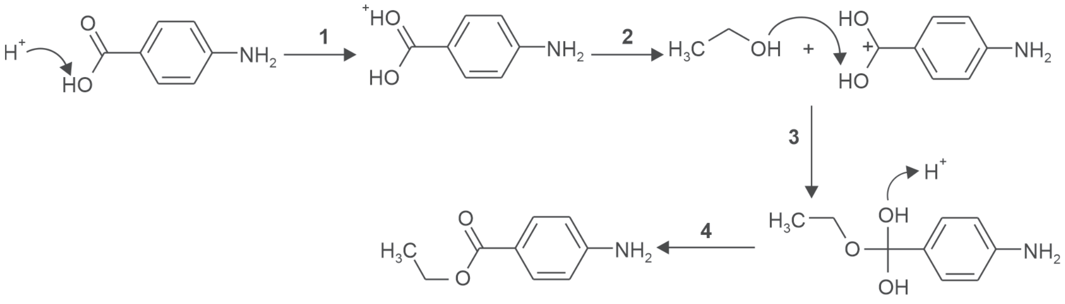
To prepare and submit benzocaine

1.6.1 Theory

The synthesis of benzocaine is based on fisher esterification reaction. The carboxylic group of *p*-amino benzoic acid reacts with hydroxyl group of ethanol in the presence of sulphuric acid to form corresponding ester, i.e. benzocaine. Here sulphuric acid is used as catalyst as well as dehydrating agent.



The mechanism of reaction follows four steps namely (1) protonation of carboxylic acid by acid catalyst, (2) nucleophilic attack of the alcohol, (3) transfer of proton, (4) loss of water and loss of proton to give benzocaine.



1.6.2 Chemicals required

(a) *p*-aminobenzoic acid	1.25 g
(b) Ethyl alcohol	10 ml
(c) Concentrated H_2SO_4	1.0 ml
(d) 10% Na_2CO_3	q.s.
(e) Methylene chloride	10 ml

1.6.3 Procedure

(a) Place 1.25 g of *p*-aminobenzoic acid in a round bottom flask equipped with magnetic stirrer. Add 10 ml of ethyl alcohol followed by addition of 1.0 ml of concentrated H_2SO_4 dropwise with continuous stirring to the reaction mixture.

(b) The precipitate that forms on the addition of sulfuric acid should dissolve when the solution is heated. Reflux the reaction mixture with stirring for 1 h.

(c) Cool to room temperature. Neutralize the reaction mixture with dropwise addition of 10% Na_2CO_3 until the pH is approximately 8.

(d) Extract with two 5 ml portions of methylene chloride. Wash the combined methylene chloride layers with two 10 ml portions of distilled water.

(e) Dry the methylene chloride solution over anhydrous sodium sulfate. Filter into a clean flask containing a boiling stone. Evaporate methylene chloride using the rotary evaporator resulting in the formation of a whitish residue. The crude product so obtained can be recrystallized using a solvent pair, ethyl alcohol and water. Other solvent system, i.e. petroleum ether and acetone in the ratio of 9.5 : 0.5 can also be used for recrystallization.

1.6.4 Calculation

The molecular weights of *p*-aminobenzoic acid and benzocaine are 137.14 g and 165.19 g, respectively.

As per chemical reaction, 137.14 g of *p*-aminobenzoic acid reacts with ethanol in the presence of H_2SO_4 to give 165.19 g of benzocaine.

Therefore 1.25 g of *p*-aminobenzoic acid will give *x* g of benzocaine.

$$x = (165.19/137.14) \times 1.25 = 1.50 \text{ g}$$

Thus, theoretical yield of benzocaine = 1.50 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.6.5 Precautions

(a) Be cautious during neutralization of reaction mixture with dropwise addition of 10% Na_2CO_3 until the pH is approximately 8. Be careful at this step as gas evolution is vigorous.
(b) Be completely sure that neutralization is complete and confirm that pH has reached to 8.
(c) Care should be taken during separation of the products as at pH = 8, product is in deprotonated state and the unreacted reagent is soluble in water. At this stage product is not soluble in water so it can be filtered. At pH = 8, product is soluble in organic solvent (ether), so liquid-liquid extraction could be performed for its separation.
(d) Sulphuric acid is intensely caustic, if acid gets onto skin, immediately wash with plenty of water.

1.6.6 Physical properties

Benzocaine is an odourless, white, rhombohedric crystal with density of 1.17 g/cm^3. It is sensitive to light exposure and to temperatures above 30 °C. It is sparingly soluble in water; it is more soluble in dilute acids and completely soluble in ethanol and chloroform. Its melting point is 88–90 °C.

1.6.7 Uses

(a) Benzocaine is a local anesthetic commonly used as a topical pain reliever. It is the active ingredient in many over-the-counter analgesic ointments.
(b) It is also used as a lubricant and topical anesthetic on intratracheal catheters, nasogastric and endoscopic tubes and urinary catheters.
(c) It is also combined with antipyrine to form otic drops to relieve ear pain and remove earwax.
(d) It is used as a key ingredient in numerous pharmaceuticals especially over the counter throat lozenges. Some condoms are designed to prevent premature ejaculation. It acts to desensitize the penis and allowing an erection to be maintained.

1.6.8 Viva voce

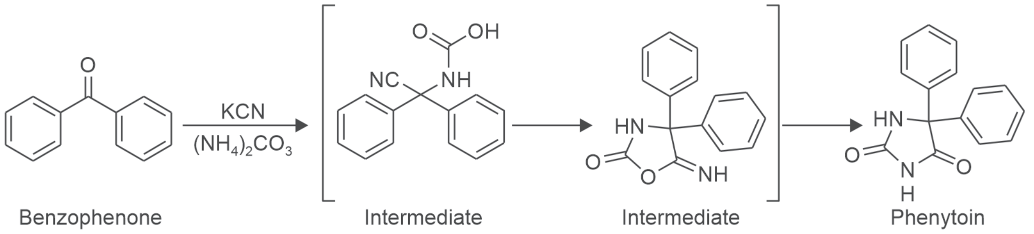
(a) What is the purpose of the sulphuric acid for this reaction? Is the acid consumed during the synthesis?
(b) How would you confirm that benzocain has formed?

EXPERIMENT 1.7

To prepare and submit phenytoin

1.7.1 Theory

Phenytoin is also known as 5,5-diphenyl hydantoin. It can be synthesized by two different methods. The first involves a base catalyzed addition of urea to benzil followed by a benzilic acid rearrangement to form phenytoin. This method is known as the *Biltz synthesis of phenytoin*.



The second method involves the reaction of benzophenone with sodium cyanide in the presence of ammonium carbonate followed by the simultaneous cyclization of the resulting product (carboxyaminonitrile) and its rearrangement under the reaction conditions to form phenytoin.

1.7.2 Chemicals required

Benzophenone	5 g
Ammonium carbonate	8 g
Potassium cyanide	2 g
Ethanol (60% v/v)	50 ml
Sodium hydroxide solution (2 M)	q.s.
Hydrochloric acid (6 M)	q.s.
Ethanol (90% v/v)	300 ml

1.7.3 Procedure

(a) Place benzophenone (5 g; 0.5 mol), potassium cyanide (2 g; 0.61 mol), ammonium carbonate (8 g; 0.66 mol) and 50 ml ethanol (60% v/v) in a round bottom flask. Shake the reaction mixture to dissolve the contents.
(b) Reflux the reaction mixture for approx 10 h without any disturbance.
(c) Concentrate the reaction mixture under vacuum.
(d) Acidify the reaction mixture with litmus paper and hydrochloric acid (6 M).
(e) Chill the reaction mixture to obtain crude product, filter and wash it with cold distilled water.
(f) Add 10–20 ml of sodium hydroxide solution (2 M) to dissolve any residue of unreacted benzophenone and filter.
(g) Again cautiously add hydrochloric acid to filterate for precipitation of phenytoin sodium. The crude phenytoin can be purified using ethanol.

1.7.4 Calculation

The molecular weights of benzophenone and phenytoin are 182.21 g and 252.26 g, respectively.

As per chemical reaction, 182.21 g of benzophenone reacts with potassium cyanide in the presence of ammonium carbonate to give 252.26 g of phenytoin.

Therefore 5 g of benzophenone will give x g of phenytoin.

$$x = (252.26/182.21) \times 5 = 6.92 \text{ g}$$

Thus, theoretical yield of phenytoin = 6.92 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.7.5 Precautions

(a) Potassium cyanide is a highly poisonous substance so due precautions should be considered while handling it.
(b) The process of acidification should be carefully performed to receive optimum yield of the product.

1.7.6 Physical properties

It is a white powder with MP 295–298° C. Its solubility profile is as follows: 1 g dissolve in 60 ml ethanol or 30 ml acetone. It is soluble in alkali hydroxide while insoluble in water.

1.7.7 Uses

(a) Phenytoin sodium is a commonly used anticonvulsant drug. It is used for the treatment and management of various types of seizure, i.e. generalized tonic-clonic seizures (grandmal), complex partial seizures.
(b) It is also used as an antiarrhythmic drug for the treatment of paroxysmal atrial tachycardia and digitalis induced cardiac arrythmias.

1.7.8 Viva voce

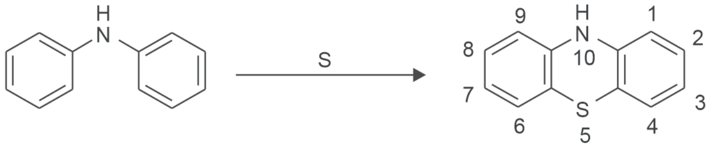
(a) What is use of sodium hydroxide solution in the synthesis of phenytoin?
(b) How would you handle potassium cyanide in lab?
(c) How would you synthesize phenytoin?

EXPERIMENT 1.8

To prepare and submit phenothiazine

1.8.1 Theory

The other names of phenothiazine are thiodiphenylamine; 2,3,5,6-dibenzo-1,4-thiazine and dibenzoparathiazine.



Diphenylamine Phenothiazine

One of the common methods for the synthesis of phenothiazine involves reaction of diphenylamine with a sulphur in the presence of hexamine and aluminium trichloride.

1.8.2 Chemicals required

(a) Diphenylamine	1.69 g
(b) Sulphur	0.32 g
(c) Hexamine	20 mg
(d) Aluminium trichloride	30 mg
(e) Acetone	50 ml

1.8.3 Procedure

(a) Place a solution of diphenylamine (1.69 g, 0.01 mol) in 50 ml acetone in a round bottom flask fitted with reflux condenser. Add sulphur (0.32 g, 0.02 mol), hexamine (20 mg) and $AlCl_3$ (30 mg) to it.

(b) Reflux the reaction mixture for around 10 hours. Cool and pour the reaction mixture into beaker containing sufficient crushed ice with stirring results in the formation of precipitate. Filter the precipitate so obtained, wash with water and dry in oven.

(c) The product can be recrystallized using *n*-butanol.

1.8.4 Calculation

The molecular weights of diphenylamine and phenothiazine are 169.22 g and 199.27 g, respectively.

As per chemical reaction, 169.22 g of diphenylamine reacts with sulphur in the presence of aluminium trichloride to give 199.27 g of phenothiazine.

Therefore, 1.69 g of diphenylamine will give *x* g of phenothiazine.

$$x = (199.27/169.22) \times 1.69 = 1.99 \text{ g}$$

Thus, theoretical yield of phenothiazine = 1.99 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.8.5 Precaution

The intermittent TLC should be performed to confirm the formation of product and to avoid excessive heating of reaction mixture.

1.8.6 Physical properties

Pure phenothiazine is a light yellow crystalline solid with melting point of 180–181 °C. It gets oxidized easily and converts to bluish-green powder. Its solubility profile is as follows.

- Almost insoluble in water, slightly soluble in ethanol and soluble in organic solvents.
- It is slight bitter in taste.

1.8.7 Uses

(a) Phenothiazine is a lead compound in medicinal chemistry for the synthesis of various bioactive compounds. This nucleus is present in various antipsychotic and antihistaminic drugs. It is also used as an anthelmintic and insecticide. Its derivatives are useful as urinary antiseptics and tranquilisers.
(b) Some of the most commonly used antipsychotic drugs are derivatives of phenothiazine. They are employed for the treatment of schizophrenia, psychotic depression and the manic phase of manic-depression. The examples of frequently used phenothiazine antipsychotics include chlorpromazine, prochlorperazine, perphenazine and thioridazine.
(c) The phenothiazine antipsychotics (prochlorperazine and chlorpromazine) are also used for the treatment of nausea, vomiting and hiccups.

1.8.8 Viva voce

(a) What is the importance of phenothiazine in medicinal chemistry?
(b) What are physical properties of phenothiazine?

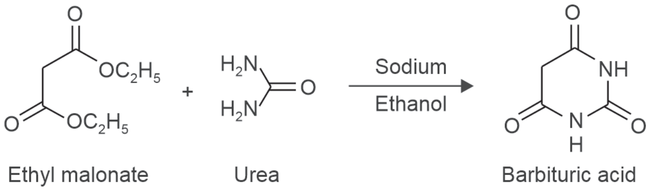
EXPERIMENT 1.9

To prepare and submit barbituric acid

The derivatives of barbituric acid are collectively known as barbiturates. Examples of barbiturates include allobarbital, phenobarbital, amobarbital, butabarbital, pentobarbital, secobarbital, etc.

1.9.1 Theory

Barbituric acid can be synthesized by condensation reaction between ethyl malonate and urea.



1.9.2 Chemicals required

(a) Sodium	2.3 g
(b) Diethyl malonate	15.2 ml
(c) Urea	6 g
(d) Absolute ethanol	100 ml
(e) Conc. hydrochloric acid	q.s.

1.9.3 Procedure

(a) Place sodium (2.3 g; 0.1 mol) in a 500 ml round bottom flask equipped with reflux condenser. Now place the flask in an ice-bath and add slowly (preferably in parts) around 50 ml of absolute ethanol.

(b) Once the reaction between sodium and ethanol is complete, add diethyl malonate (16 g/15.2 ml; 0.1 mol) with adequate stirring, subsequently add urea solution (6 g, 0.1 mol) prepared in 50 ml hot absolute ethanol.

(c) Shake the reaction mixture adequately. Fit calcium guard-tube to the top of reflux condenser. Reflux at temperature of 110 °C for around 7 hours using oil bath results in appearance of white solid product.

(d) Add 100 ml of hot water and conc. hydrochloric acid with stirring until solution is acidic. Filter this almost clear solution and place it in refrigerator overnight.

(e) Filter the product so obtained, wash with cold water and dry it at 100 °C till the evaporation of moisture.

1.9.4 Calculation

The molecular weights of ethyl malonate, urea and barbituric acid are 160.17 g, 60.06 g and 128.09 g, respectively.

As per chemical reaction, 160.17 g of ethyl malonate reacts with 60.06 g of urea to give 128.09 g of barbituric acid.

Therefore, 16 g of ethyl malonate will give x g of barbituric acid.

$$x = (128.09/160.17) \times 16 = 12.79 \text{ g}$$

Thus, theoretical yield of barbituric acid = 12.79 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.9.5 Precautions

(a) Place the flask in an ice bath while adding ethanol to sodium to carry out the reaction smoothly.
(b) The glassware to be used should be clean and completely dry.

1.9.6 Physical properties

- It is an odourless powder with melting point of 245 °C.
- It is soluble in water.
- Its octanol-water partition coefficient is –1.47.
- The formation of product can be confirmed using TLC with solvent system comprising ethanol and chloroform in the ratio 8 : 1.

1.9.7 Uses

(a) Barbiturates are widely employed for the treatment of severe nervous insomnia, some forms of epilepsy and certain psychological diseases.
(b) The commonly used barbiturates for insomnia are phenobarbital, pentobarbital, amobarbital, secobarbital and sodium thiopental.

Now, barbiturates are being substituted with safer drugs such as benzodiazepine due to their susceptibility for addiction and decreased effect over prolonged use.

1.9.8 Viva voce

(a) Give example of drugs that belongs to the category ‘barbiturates’.
(b) Name the chemicals required for the synthesis of barbituric acid.

EXPERIMENT 1.10

To prepare and submit sulphanilamide

1.10.1 Theory

The synthesis of sulphanilamide from acetanilide comprises three steps. In the first step acetanilide is treated with an excess of chlorosulphonic acid to give *p*-acetamidobenzene sulphonyl chloride. Later reacts with ammonia to give *p*-acetamidobenzene sulphonamide. In the last step, sulphonamide forms on hydrolysis of acetamidobenzene sulphonamide.

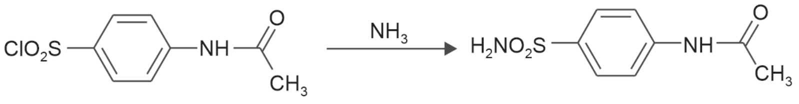
Step I

Chlorosulphonation (electrophilic aromatic substitution reaction) is used to introduce chlorosulphonyl group *para* to acetamide group in acetanilide. Sulphonic acid (initially formed substitution product) converts to *p*-acetamidobenzene sulphonyl chloride in the presence of excess of chlorosulfonic acid with formation of sulphuric acid as the co-product.

Acetanilide   Chlorosulphonic acid   *p*-acetamidobenzene sulphonyl chloride

Step II

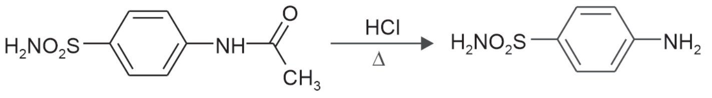
para-acetamidobenzene sulphonyl chloride is subjected to treatment with aqueous ammonia to form corresponding sulphonamide.



p-acetamidobenzene sulphonyl chloride   *p*-acetamidobenzene sulphonamide

Step III

The acidic hydrolysis is carried out to remove acetamide group of *para*-acetamidobenzene sulphonamide without affecting the sulphonamide group, which is much lesser susceptible to hydrolysis. At last, sulphanilamide is isolated with neutralization of acidic hydrolysis solution using sodium carbonate.



p-acetamidobenzene sulphonamide   *p*-aminobenzene sulphonamide (sulphanilamide)

1.10.2 Chemicals required

Step I

(a) Chlorosulphonic acid	25 ml
(b) Acetanilide	10 g

Step II

(a) *p*-acetamidobenzene sulphonyl chloride	as received from step I
(b) Concentrated ammonia solution with specific gravity 0.88	35 ml
(c) Dilute sulphuric acid	q.s.

Step III

(a) *p*-acetamidobenzene sulphonamide	as received from step II
(b) Concentrated HCl	5 ml
(c) Sodium carbonate	8 g
(d) Decolouring carbon	q.s.

1.10.3 Procedure

Step I

Preparation of *p*-acetamidobenzene sulphonyl chloride

(a) Place chlorosulphonic acid (25 ml) in a three necked round bottom flask (equipped with mechanical stirrer and a dropping funnel).
(b) Cool the flask in an ice-bath and add dry acetanilide (10 g, 0.074 mol) through third neck in portions with continuous stirring.
(c) Connect the top of reflux condenser to a gas trap to absorb the liberated HCl gas. Warm the reaction mixture on water bath at 60 °C for 10 to 15 minutes.
(d) Pour the content of flask in to ice cold water (300 ml) resulting in precipitation of product.
(e) Filter, wash with cold water and drain well the crude product which can be used for next step. If required, the crude product can be recrystallized using chloroform or mixture of benzene and acetone.

Step II

Preparation of *p*-acetamidobenzene sulphonamide

(a) Place crude *p*-acetamidobenzene sulphonyl chloride in a 250 ml conical flask.
(b) Add ammonia solution (35 ml concentrated ammonia solution with specific gravity of 0.88 + 35 ml distilled water) with proper mixing.
(c) Heat the reaction mixture at 80–90 °C using water bath for 10 minutes.
(d) Cool the reaction mixture and acidify with dilute sulphuric acid until reaction mixture is just acidic to congo red paper.
(e) Filter the separated product, wash and drain well. For the next step, this product may be used as such, if required it may be recrystallized using distilled water. The melting point of this product is 218 °C.

Step III

Preparation of *p*-aminobenzene sulphonamide (sulphanilamide)

(a) Place crude *p*-acetamidobenzene sulphonamide in a round bottom flask. Add dilute HCl (5 ml conc. HCl + 15 ml distilled water) and reflux the reaction mixture for 20–25 minutes.
(b) Now keep watching that there should be no solid product separation on cooling, if so it indicate for incomplete reaction and it requires further heating for some time.
(c) Add decolouring carbon and heat the reaction mixture to boiling and filter it.
(d) Cool the clear solution obtained. Add sodium carbonate (8 g) in small portions with stirring till solution do not show acidic test by litmus paper, i.e. at last solution should be normal.
(e) Cool the reaction mixture in an ice-bath and filter the product so obtained. It can be recrystallized from alcohol.

1.10.4 Calculation

The molecular weights of acetanilide and sulphanilamide are 135.17 g and 172.2 g, respectively.

Therefore 10 g of acetanilide will give x g of sulphanilamide.

$$x = (172.2/135.17) \times 10 = 12.73 \text{ g}$$

Thus, theoretical yield of sulphanilamide = 12.73 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.10.5 Precautions

(a) Perform step I in fume cup board, as excess of chlorosulphonic acid reacts vigorously with water.
(b) Chlorosulphonic acid is corrosive and irritant. Avoid its contact with skin and eyes and do not inhale it.
(c) Step II, should be performed in fume cupboard, as ammonia has pungent smell.

1.10.6 Physical properties

It is a white powder with melting point of 164–165 °C. Its water solubility is 7500 mg/L (at 25 °C) and it is sensitive to light. Its octanol–water partition coefficient is 0.82. Its 0.5% aqueous solution has pH of 5.8 to 6.1.

1.10.7 Uses

(a) Sulphanilamide is a sulphonamide antimicrobial agent.
(b) It is the basic structure present in many sulpha drugs, i.e. sulphadiazine, sulfadoxine, sulphathiazole, sulphamethoxazole, sulphapyrazine, etc.
(c) It is used to treat vaginal yeast infections in which it reduces vaginal burning, itching and discharge.

1.10.8 Viva voce

(a) What are the precautions to be taken while handling chlorosulphonic acid?

(b) Name the intermediate products when acetanilide is used as starting material for synthesis of sulphanilamide.

(c) Why sodium carbonate is used in step III during synthesis of sulphanilamide from acetanilide?

EXPERIMENT 1.11

To prepare and submit 7-hydroxy-4-methylcoumarin

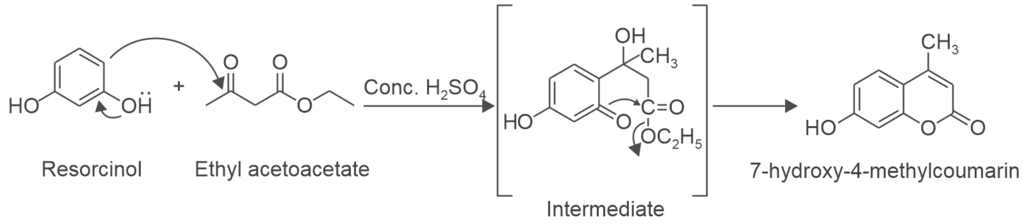
1.11.1 Theory

7-hydroxy-4-methylcoumarin is also known as hymecromone, 4-methylumbelliferone, 7-hydroxy-4-methyl-2*H*-1-benzoppyran, 7-hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran.

A condensation reaction comprises a chemical reaction in which two molecules or moieties unite to form one single molecule, with the loss of a small molecule.

The synthesis of 7-hydroxy-4-methylcoumarin is an example of **Pechman condensation**, discovered by the German chemist Hans von Pechmann. The Pechmann condensation comprises coumarins synthesis from a phenol and a carboxylic acid or ester containing β-carbonyl group. The condensation is performed in the presence of Lewis catalysts under acidic conditions. The mechanism involves an esterification/transesterification accompanied by attack of the activated carbonyl ortho to the oxygen to give the new ring. Dehydration is the final step in this reaction.

In Pechman reaction, when simple phenols are used as starting material, yield is quite good while the reaction conditions required are harsh. With highly activated phenols such as resorcinol, the reaction can be executed under much milder conditions. This provides a useful route to umbelliferone derivatives. The reaction for preparation of 7-hydroxy-4-methylcoumarin is as follows.



1.11.2 Chemical required

Resorcinol	4 g
Ethyl acetoacetate	5.6 g
Concentrated sulphuric acid	18.75 ml
Sodium hydroxide (aqueous solution 10% w/v)	q.s.
Hydrochloric acid (6 N)	q.s.
Methylated spirit	30 ml

1.11.3 Procedure

The various consequetive steps involved in the synthesis of 7-hydroxy-4-methylcoumarin are as follows.

(a) Prepare a solution by dissoving resorcinol (4 g, 0.036 mol) into ethyl acetoacetate (5.6 g, 0.043 mol) by stirring with a clean glass rod in a 100 ml conical flask.

(b) Place 18.75 ml of concentrated sulphuric acid in a flat bottomed flask and cool the flask using crushed ice bath so as to maintain the temperature less than 10 °C. Now add resorcinol solution to the flat bottomed flask containing conc. sulphuric acid slowly with continuous stirring. Further continue the stirring for about 30–40 minutes for completion of the reaction.

(c) Pour the reaction mixture into a 500 ml beaker containing plenty of crushed ice with vigorous stirring. This results in separation of the 7-hydroxy-4-methylcoumarin.
(d) Filter the crude product on buchner funnel under suction. Wash the product with excess of cold distilled water, drain and dry well.
(e) Recrystallization: The crude 7-hydroxy-4-methylcoumarin is dissolved in cold sodium hydroxide solution (10%) and reprecipitated with dilute hydrochloric acid. The residue so obtained is recrystallized with methylated spirit.

1.11.4 Calculation

The molecular weights of resorcinol, ethyl acetoacetate and 7-hydroxy-4-methylcoumarin are 110.1 g, 130.14 g and 194.18 g, respectively.

As per chemical reaction, 110.1 g of resorcinol reacts with ethyl acetoacetate to give 194.18 g of 7-hydroxy-4-methylcoumarin.

Therefore, 4 g of resorcinol will give *x* g of 7-hydroxy-4-methylcoumarin.

$$x = (194.18/110.1) \times 4 = 7.05 \text{ g}$$

Thus, theoretical yield of 7-hydroxy-4-methylcoumarin = 7.05 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.11.5 Precautions

(a) Strictly maintain the temperature below 10 °C during the whole experiment.
(b) The addition of resorcinol solution to concentrated sulphuric acid should be done very slowly in small lots and with continuous stirring.

1.11.6 Physical properties

It has melting point 194–195 °C. Blue fluorescence is obtained in mixture of alcohol and water. It has UV_{max} of 221, 251 and 322.5 nm in methanol respectively. It is soluble in acetic acid and methanol while practically insoluble in cold water. It is slightly soluble in chloroform and ether.

1.11.7 Uses

(a) It increases bile excretion from liver so it is used as cholerectic.
(b) It is also utilized as antispasmodic, i.e. prevent or alleviate involuntary sudden movement or muscular contraction.

1.11.8 Viva voce

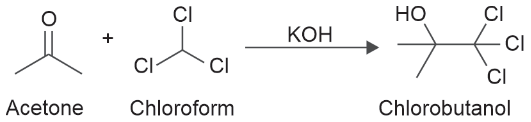
(a) Explain Pechman condensation.
(b) What is the role of conc. sulphuric acid in the preparation of 7-hydroxy-4-methylcoumarin?

EXPERIMENT 1.12

To prepare and submit chlorobutanol

1.12.1 Theory

Chlorobutanol is also known as trichloro-2-methyl-2-propanol. It is synthesized by the reaction of chloroform and acetone under the catalytic influence of potassium or sodium hydroxide.



1.12.2 Chemicals required

(a) Acetone	45 ml
(b) Chloroform	5 ml
(c) Potassium hydroxide	1 g

1.12.3 Procedure

(a) Place acetone (45 ml) in a round bottom flaks. Cool the flask in an ice-bath and add chloroform (5 ml; 7.45 g) and mix the content of flask using a glass rod.
(b) Add powdered potassium hydroxide (1 g) in small portions while proper mixing the reaction mixture.
(c) Stir the content of flask at –5 °C for two hours.
(d) Filter the resulting suspension and remove excess of acetone using distillation from the filtrate.
(e) Pour the yellowish oily residue so obtained in ice-cold water (100 ml), which results in the precipitation of white crystalline product, i.e. chlorobutanol.
(f) Filter the product, drain and dry it using vacuum desiccator. It can be recrystallized using water.

1.12.4 Calculation

The molecular weights of chloroform and chlorobutanol are 119.38 g and 177.46 g, respectively.

As per chemical reaction, 119.38 g of chloroform in the presence of acetone and KOH gives 177.46 g of chlorobutanol.

Therefore 7.45 g of chloroform will give x g of chlorobutanol.

$$x = (177.46/119.38) \times 7.45 = 11.07 \text{ g}$$

Thus, theoretical yield of chlorobutanol = 11.07 g.
Practical yield = …………… g.
% yield = [(Practical yield)/(Theoretical yield)] × 100

1.12.5 Precautions

(a) All the glassware should be completely dry for satisfactory completion of the reaction.
(b) It is required to maintain the temperature conditions as mentioned in procedure.
(c) Chlorbutanol is a skin irritant and a severe eye irritant so it should be dealt carefully.

1.12.6 Physical properties

- It is a white crystalline powder with camphor-like odour.
- Melting point is 78.4 °C.
- It is soluble in chloroform, alcohol, volatile oils, glycerol, ether and acetone.
- It is soluble in hot water but insoluble in cold water.
- Its octanol–water partition coefficient is 2.03.
- It is to be stored in a cool place, away from sunlight.

1.12.7 Uses

(a) It is used as preservative, sedative, hypnotic and weak local anaesthetic agent.
(b) It is employed generally as a preservative in ophthalmic drops.
(c) It has been the part of formulation of various cosmetic and pharmaceutical products (especially parenteral products) because of their antibacterial and antifungal properties.

1.12.8 Viva voce

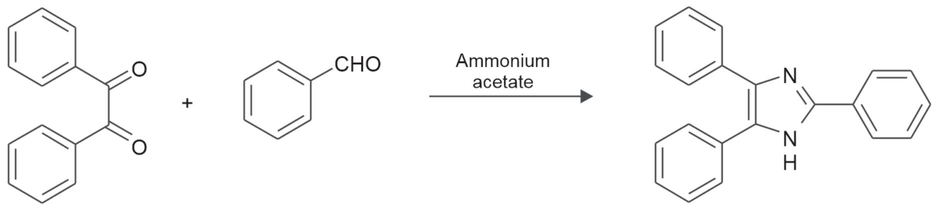
(a) Why NaOH or KOH is used in the synthesis of chlorobutanol?
(b) What are the uses of chlorobutanol?

EXPERIMENT 1.13

To prepare and submit triphenyl imidazole

1.13.1 Theory

Benzoin on reaction with benzaldehyde in the presence of ammoniun acetate (source of ammonia) forms triphenyl imidazole.



Benzoin Benzaldehyde Triphenyl imidazole

1.13.2 Chemicals required

Method I

Benzoin	5 g
Benzaldehyde	5 ml
Ammonia	q.s.

Method II

Benzil	2.10 g
Benzaldehyde	1.3 ml
Ammonium acetate	3.08 g
Sulphanilic acid	1.73 g
Ethanol	20 ml

Method III

Benzil	5.25 g
Benzaldehyde	2.65 ml
Ammonium acetate	10.02 g
Acetic acid	100 ml

1.13.3 Procedure

Method I

(a) Place benzoin (0.023 mol, 5 g) in a round bottom flask and add benzaldehyde (0.05 mol, 5 ml) and few drops of ammonia.
(b) Shake the flask and reflux the reaction mixture for 4 h.
(c) Cool, filter and dry the product so obtained. Recrystallize the product using ethanol.

Method II

(a) Place benzil (2.10 g, 10 mmol) in a round bottom flask (equipped with reflux condenser) and add benzaldehyde (1.3 ml, 10 mmol) with adequate shaking.

(b) Add ammonium acetate (3.08 g, 40 mmol) and sulphanilic acid (1.73 g, 10 mmol) as catalyst in the presence of ethanol (20 ml).

(c) Reflux the reaction mixture at 80 °C for 2 h.

(d) Cool to room temperature and pour on ice-cold water (50 ml) results in the formation of solid precipitate. Filter, wash with cold water and recrystallize with ethanol.

Method III

(a) Dissolve benzil (5.25 g, 25 mmol), benzaldehyde (2.65 g, 25 mmol) and ammonium acetate (10.02 g, 130 mmol) in 100 ml acetic acid in a 250 ml round bottom flask.

(b) Reflux the content of flask using oil bath for 1 h with sufficient stirring.

(c) Cool to room temperature and filter it. Add 500 ml distilled water to filtrate and collect the precipitate under suction. Neutralize the filtrate with ammonium hydroxide. It results in the further formation of precipitate, filter it.

(d) Combine both the precipitates and recrystallize using aqueous ethanol.

1.13.4 Calculation

The molecular weights of benzoin, benzaldehyde and triphenyl imidzole are 210.23 g, 106.12 g and 296.37 g, respectively.

As per chemical reaction, 210.23 g of benzoin reacts with benzaldehyde to give 296.37 g of triphenyl imidazole.

Therefore 5 g of benzoin will give x g of triphenyl imidazole.

$$x = (296.37/210.23) \times 5 = 7.04 \text{ g}$$

Thus, theoretical yield of triphenyl imidazole = 7.04 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.13.5 Precautions

(a) Avoid contact of benzaldehyde with eyes and skin. Store it in a tightly closed container and avoid its inhalation.

(b) Ammonia is a corrosive reagent. Use eye, skin and face protection while using it. Its exposure can lead to blindness, lung damage.

1.13.6 Physical properties

It is an off-white powder with melting point range of 274–278 °C. It is soluble in methanol and insoluble in water.

1.13.7 Uses

(a) The compounds containing imidazole moiety possess several pharmacological properties and perform crucial function in processes occurring in biological system. The example of drugs containing imidazole include omeprazole, flumazenil, cimetidine.

(b) Triarylimidazole compounds have received noteworthy attention due to their importance in numerous biological activities. It is also being employed for synthesis of other medicinal compounds.

1.13.8 Viva voce

(a) What is the difference among several methods used for synthesis of triphenyl imidazole?

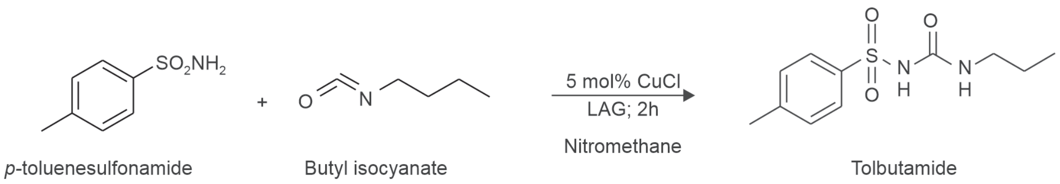
(b) Explain medicinal importance of triphenyl imidazole.

EXPERIMENT 1.14

To prepare and submit tolbutamide

1.14.1 Theory

The synthesis of tolbutamide involves addition reaction of *p*-toluenesulphonamide and butyl isocyanate. The below mentioned reaction involves use of CuCl as catalyst along with liquid assisted grinding (LAG) using ball mill. This mechanochemical method for the synthesis of tolbutamide is being widely used.



1.14.2 Chemicals required

(a)	*p*-toluenesulphonamide	8.55 g
(b)	*n*-butyl isocyanate	4.95 g
(c)	Nitromethane	q.s.

1.14.3 Procedure

(a) Place *p*-toluenesulphonamide (8.55 g; 0.05 mol) and *n*-butyl isocyanate (4.95 g; 0.05 mol) in a suitable container for grinding using ball mill.

(b) Add 5 mol % of CuCl (as catalyst) and nitromethane (as grinding liquid) and run the ball mill for two hours. Nitromethane is being used here for assisting the grinding process, this method is known as liquid assisted grinding (LAG) method.

(c) Remove the catalyst from crude reaction mixture by milling it for a few minutes with aqueous sodium salt of EDTA. Dry the product.

1.14.4 Calculation

The molecular weights of *p*-toluenesulphonamide, butyl isocyanate and tolbutamide are 171.22 g, 99.13 g and 256.32 g, respectively.

As per chemical reaction, 171.22 g of *p*-toluenesulphonamide reacts with butyl isocyanate to give 256.32 g of tolbutamide.

Therefore 8.55 g of *p*-toluenesulphonamide will give x g of tolbutamide.

$$x = (256.32/171.22) \times 8.55 = 12.79 \text{ g}$$

Thus, theoretical yield of tolbutamide = 12.79 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.14.5 Precautions

Standard operating procedure should be followed while using ball mill.

1.14.6 Physical properties

It occur as a white crystalline powder with melting point of 128.5 to 129.5 °C. Its water solubility is 109 mg/L at 37 °C. It is soluble in chloroform, ethanol while insoluble in water. It is freely soluble in dimethyl carbonate. Its log *P* (octanol–water coefficient) value is 2.32.

1.14.7 Uses

Tolbutamide is a first-generation antidiabetic drug used in the treatment of type-2 diabetes. It belongs to sulphonyl urea class. It is used together with diet and exercise to treat diabetes.

1.14.8 Viva voce

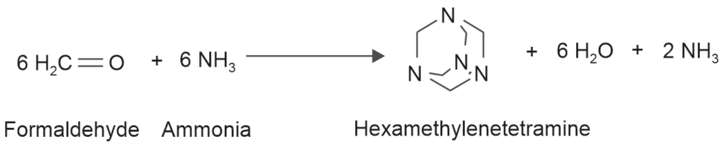
(a) What are the reagents employed for preparation of tolbutamide?
(b) What is the use of CuCl during preparation of tolbutamide?
(c) What do you mean by LAG method?

EXPERIMENT 1.15

To prepare and submit hexamine

1.15.1 Principle

Hexamine is also known as hexamethylenetetramine, methenamine, formin or urotropin. It can be synthesized from reaction of formaldehyde with excess of ammonia either in aqueous media or vapour phase.



1.15.2 Chemicals required

(a) Formaldehyde solution (37%)	2.36 g
(b) Ammonium hydroxide (20%)	3.5 g
(c) Ethanol	q.s.

1.15.3 Procedure

(a) Place 37% formaldehyde solution (2.16 ml; 2.36 g) in a round bottom flask and add 20% ammonium hydroxide solution (3.5 g). It is important to note that density of formaldehyde solution (37%) is 1.09 g/ml.
(b) Allow the reaction mixture to stand for 5–6 h. Add more ammonia if necessary. Filter the solution and evaporate under vacuum resulting in the formation of crystals.
(c) Wash the crystals with ethanol. The product can be recrystallized with water or ethanol.

1.15.4 Calculation

The molecular weights of formaldehyde, ammonia and hexamine are 30.03 g, 17.03 g and 140.18 g, respectively.

As per chemical reaction, 30.03 g of formaldehyde will give 140.18 g of hexamine.

Therefore 2.36 g of formaldehyde will give x g of hexamine.

$$x = (140.18/30.03) \times 2.36 = 11 \text{ g}$$

Thus, theoretical yield of hexamine = 11 g.

Practical yield = …………… g.

% yield = [(Practical yield)/(Theoretical yield)] × 100

1.15.5 Precautions

The experiment should be performed in fume cupboard. Protective gloves of neoprene rubber and safety glasses with side shields should be used during this experiment. Hexamine should not be stored near ignition point as it possesses inflammable property.

1.15.6 Physical properties

It is a white crystalline compound with slight amine odour. Its melting point is 280 °C. It is highly soluble in water and polar organic solvents. Its solubility in water is 874 g/L. The pH of 10% aqueous solution is in between 8 to 9. It sublimes in vacuum at 280 °C.

1.15.7 Uses

(a) Its mandelic acid salt (i.e. methenamine mandelate) is employed for the treatment of urinary tract infection. At acidic pH, the salt decomposes to formaldehyde and ammonia. It is important to mention that formaldehyde possesses bactericidal properties and the mandelic acid adds to this property. Methenamine is used for treatment of excessive sweating and concomitant odour (in the form of cream and spray).
(b) It is a multipurpose reagent in organic/medicinal chemistry for synthesis of various intermediates. It is employed in several known reaction, i.e. Delepine reaction (preparation of amines from alkyl halides), Duff reaction (formylation of arenes) and the Sommelet reaction (conversion of benzyl halides to aldehydes).
(c) Other important applications include manufacture of plastics, paints, foundry resins, textiles, plywood, laminated sheets, cement, fertilizers, pesticides, solid fuel tablets (does not produce smoke while burning), etc. It is base component to produce RDX and other explosives.

1.15.8 Viva voce

(a) What are the chemicals required for the synthesis of hexamine?
(b) What are the precautions to be considered while storing hexamine?
(c) Enumerate applications of hexamine.
(d) How methenamine mandelate works in urinary tract infection?