(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

(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

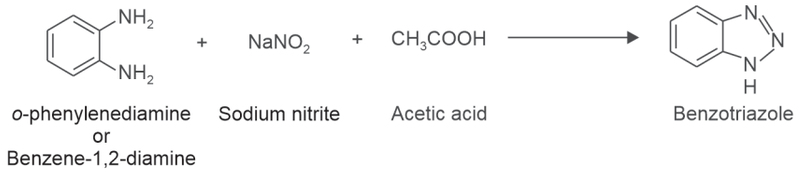
(i) How would you synthesize diphenyloxazole?
(ii) What is the medicinal importance of oxazole nucleus?
(iii) What are the precautions to be considered while dealing with benzoyl chloride?

EXPERIMENT 1.4

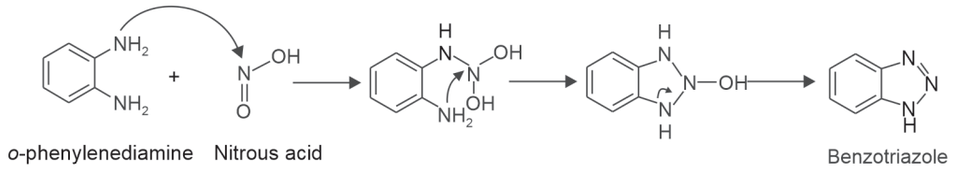
To prepare and submit benzotriazole

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.



o-phenylenediamine or Benzene-1,2-diamine | Sodium nitrite | Acetic acid | Benzotriazole



o-phenylenediamine | Nitrous acid | 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.

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.

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