1st Edition

UNDERSTANDING THE ORGANIC CHEMISTRY

A PRACTICAL APPROACH

Editor

Tahir Farooq (PhD Bergen, Norway)

ISBN 978-969-7818-00-6

Tahir Farooq
Editor

UNDERSTANDING THE ORGANIC CHEMISTRY: A PRACTICAL APPROACH

Tahir Farooq
Editor

UNDERSTANDING THE ORGANIC CHEMISTRY:
A PRACTICAL APPROACH

Editor

Tahir Farooq
Department of Applied Chemistry
Government College University,
Allama Iqbal Road,
Faisalabad, Pakistan.

ISBN 978-969-7818-00-6
Copyright © 2017 by Innovative Scientific Information & Services Network
This published work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now know or hear after developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

Innovative Scientific Information & Services Network
537-B, G.M. abad, Faisalabad, Pakistan
www.isisn.org

Preface and Introduction of the Manual

The manual has been designed to make student understand the basic concepts in organic chemistry with practical approach. The students have always been involved learning about basic chemical reactions with theoretical mechanistic aspects. Students should have learnt about organic oxidations, reductions, nucleophilic and electrophilic additions and substitutions etc. In this manual, the relevant practical activities have been included to make students grasp aforementioned concept on practical basis.

The manual has been divided into following chapters,

- Identification of unknown organic compounds
- Organic synthesis
- Synthetic dyes
- Lab-scale synthesis of heterocyclic compounds

In the first chapter, the students are supposed to learn about different identification tests. The chemistry of each identification test has been well explained mechanistically so the students could comprehend what really happens in the test tube.

The second chapter is meant to make students familiar with basic organic conversions, identification and isolation of products. The students are given comprehensive concepts about the extraction, separation and isolation techniques.

The third chapter has been designed to make students recognize the applied aspects of synthetic organic chemistry. Students are supposed to learn the basic reaction concepts for the synthesis of textile dyes.

The forth chapter explains the lab-scale synthesis of heterocycles in shortest possible time. The students are supposed to learn about handling the sensitive reaction conditions.

Dr. Tahir Farooq

PhD (Bergen, Norway)

Dedicated to my beloved father who couldn’t live long to see me prospering

Table of Contents

Chapter 1

1 Identification of Unknown Organic Compound

Sarosh Iqbal, Tahir Farooq

This chapter has been designed to make students learn about the basic concept involved for the identification of unknown organic compounds. The chapter explains actual reactions of different confirmatory tests happening inside test tube. Indeed, the well-explained systematic scheme aims to enable students to identify any type of unknown organic compound.

1.1 Element Detection in Organic Compounds

The presence of sulphur, nitrogen and halogens is detected by the Lassaigne's test or sodium fusion test in organic compounds.

Theory and Chemistry of Lassaigne's Test:

Generally, the Lassaigne's test or sodium fusion test is employed to detect the presence of nitrogen, sulphur or halogens in a given unknown organic compound. These elements are attached to organic molecules through covalent bonding. So, they should be converted to their ionic forms for proper element detection. For this purpose, the organic compounds are made to fuse with sodium-metal. Subsequently, the aqueous solution extraction of ionic compounds generated during the fusion process is accomplished to perform the relevant confirmatory tests.[1]

The aqueous extract is known as Lassaigne's extract or sodium fusion extract.

Test for the detection of halogens:

Sodium halides are formed when organic compounds are fused with sodium-metal. In aqueous extract, the detection of sodium halide is accomplished with the addition of silver nitrate solution after acidification with dilute nitric acid.

The appearance of a white-curdy precipitation soluble in NH_4OH confirms the presence of chlorine.

$$\mathrm{Na} + \mathrm{Cl} \longrightarrow \mathrm{NaCl}$$

$$\mathrm{NaCl} + \mathrm{AgNO_3} \longrightarrow \mathrm{AgCl} + \mathrm{NaNO_3}$$

While the formation of yellowish-white precipitation with sparing solubility in NH_4OH represents the presence of bromine.

$$\mathrm{NaBr} + \mathrm{Br} \longrightarrow \mathrm{NaBr}$$

$$\mathrm{NaBr} + \mathrm{AgNO_3} \longrightarrow \mathrm{AgBr} + \mathrm{NaNO_3}$$

However, a yellow colored precipitation with no solubility in NH_4OH indicates the presence of iodine.

$$\mathrm{Na} + \mathrm{I} \longrightarrow \mathrm{NaI}$$

$$\mathrm{NaI} + \mathrm{AgNO_3} \longrightarrow \mathrm{AgI} + \mathrm{NaNO_3}$$

Test for the detection of nitrogen:

A water soluble sodium cyanide is formed when an organic compound containing carbon and nitrogen is fused with sodium-metal. With the addition of ferrous sulphate, the sodium cyanide changes to sodium ferrocyanide. Further, a prussian-blue precipitation of ferric ferrocyanide is observed when *in situ* generated ferric reacts with ferrocyanide.

$$\mathrm{Na} + \mathrm{C} + \mathrm{N} \longrightarrow \mathrm{NaCN}$$

$$6\mathrm{NaCN} + \mathrm{FeSO_4} \longrightarrow \mathrm{Na_4[Fe(CN)_6]} + \mathrm{Na_2SO_4}$$

Sodium ferrocyanide

$$\mathrm{Na_4[Fe(CN)_6]} + \mathrm{Fe_3^{+}} \longrightarrow \mathrm{Fe_4[Fe(CN)_6]_3}$$

Ferric Ferrocyanide

Test for the detection of sulphur:

The fusion with sodium-metal converts the sulphur of organic compound into sodium sulphide.

Sodium nitroprusside helps in the identification of sulphide ions.

$$\mathrm{Na} + \mathrm{S} \longrightarrow \mathrm{Na_2S}$$

$$\mathrm{Na_2S} + \mathrm{Na_2[Fe(CN)_5NO]} \longrightarrow \mathrm{Na_4[Fe(CN)_5NOS]}$$

Sodium nitroprusside

Test for the detection of both sulphur and nitrogen:

Organic compound containing both nitrogen and sulphur on fusion with sodium produces sodium thiocyanate. Which subsequently reacts with Fe^{3+} to develop $[Fe(SCN)]^{2+}$, a blood-colored complex.

$$Na + C + N + S \longrightarrow NaSCN$$

$$Fe^{3+} + 2Na \longrightarrow [Fe(SCN)]^{2+}$$

Instead of sodium thiocyanate, the sodium sulphide and sodium cyanide are formed when excess of sodium metal is present in Lassaigne's extract. Under such cases, the aforementioned separate tests are performed for the confirmation of nitrogen and Sulphur.

$$NaSCN + 2Na \longrightarrow NaCN + Na_2S$$

Procedure:

Lassaigne’s Extract Preparation:

Take an ignition tube, add a little amount of organic compound and a small piece of sodium metal. Heat the tube till it turns red hot and plunge it into china dish containing distill water (10 mL). The mixture is made to boil before filtration. The filtrate is used for confirmatory tests.

A small pellet of metallic sodium together with a little of the substance is heated to red hot in an ignition tube. It is then suddenly plunged into about 10ml of distilled water in a china dish. The mixture is boiled well and filtered. The filtrate is used for doing the following tests.

Detection of nitrogen:

Take 1 mL of filtrate and add 1 mL of fresh ferrous sulphate solution and the put the solution to boil. As the solution cools down, 3-4 drops of $FeCl_3$ are added after acidification with dilute hydrochloric acid. The blue-colored precipitates confirm the presence of nitrogen in the given compound.[2]

Detection of chlorine:

Take I mL of filtrate, after the addition of 3-4 drops of dilute nitric acid the solution is made to boil. The $AgNO_3$ solution is added as the filtrate cools down to room temperature. The presence of chlorine is confirmed by the formation of white precipitation. These precipitates are soluble in NH_4OH.[3]

Detection of Sulphur:

Take 1 mL of filtrate and add 2-3 drops of sodium nitroprusside (fresh solution) and the presence of sulphur is confirmed by the formation of brilliant violet color.

1.2 Detection of Functional Groups

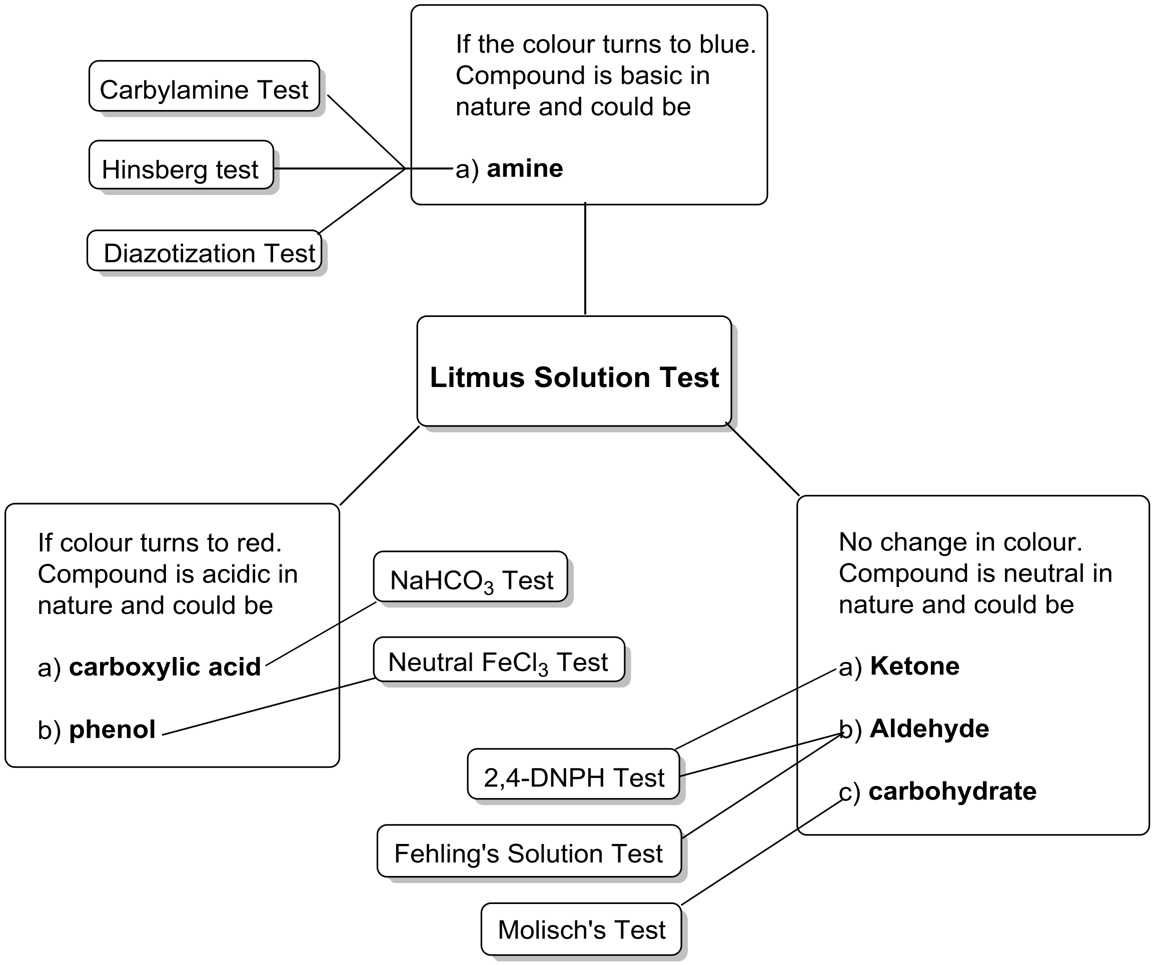
An unknown organic compound could be identified by following under given steps

1) Perform litmus solution test to determine the acidic, basic or neutral nature of given compound.

2) a) If compound happens to be basic then perform relevant identification tests like carbylamines test, hinsberg test and diazotization test.

b) If the compound showed acidic nature then perform relevant identification tests like $NaHCO_3$ test and neutral $FeCl_3$ test.

c) If the compound found to be neutral then perform the relevant identification tests like 2,4-DNPH test, Fehling’s solution test, Molisch’s test



Scheme: Litmus solution test

3) After performing the identification tests, manage to perform bromine-water test or KMnO4 test to determine whether the given compound is saturated or unsaturated in nature.

4) After the identification of class of compound, students are supposed to determine the melting or boiling point of the compound.

5) Finally, match the melting or boiling point of the given compound with the list of the compounds in that particular class. Also, keep in mind the presence of saturation or unsaturation in compound.

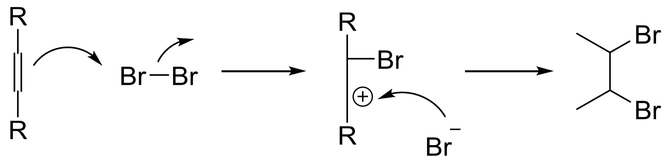
Chemistry of different tests:

Bromine-water Test:

Take 1 mL of bromine water and add 0.1 g of organic compounds into it and shake it well. If the color of solution discharges, it suggests the given compound is unsaturated.

Chemistry of Bromine-water Test:

The Br2 gets add at double bond through electrophilic addition. In doing so, the bond between Br-Br breaks which results in colour disappearance.[4]



Bromine-water Test

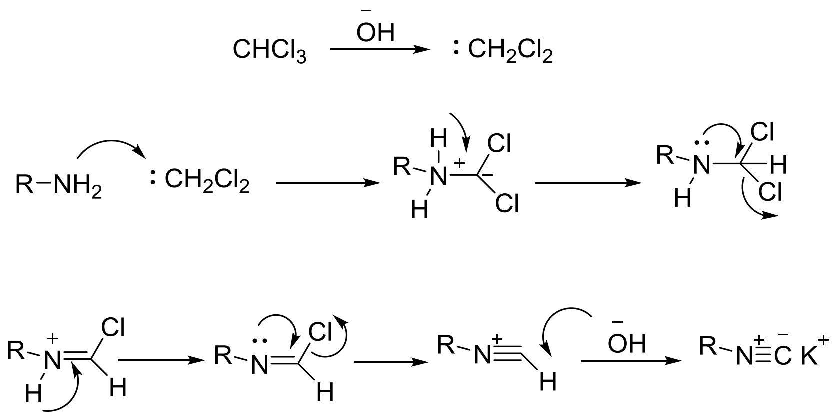
Carbylamine test:

Take 0.5 g of organic compound in 1.5 mL of alcoholic potassium hydroxide then introduce 0.5 mL of chloroform. On heating this mixture, an unpleasant smell suggests the presence of aliphatic amine.

Chemistry of Carbylamine Test:

This test is used to confirm the presence of primary amines.

$$R-NH_2 \xrightarrow[\text{heat}]{CHCl_3,\ KOH} R-\overset{+}{N}\equiv\overset{-}{C} + 3H_2O + 3KCl$$



Chemistry of Carbylamine Test

Hinsberg Test:

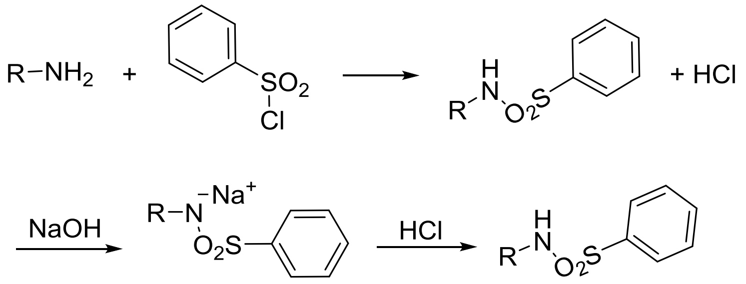
Take 1 mL of 10% NaOH and 1 mL of benzene sulfonyl chloride in a test tube then add 1 mL of organic solution.

P°-amines produce sulphonamides insoluble in HCl but soluble in NaOH.

S°-amines produce corresponding sulphonamides insoluble in NaOH.

T°-amines undergo no reaction.

Chemistry of Hinsberg Test:



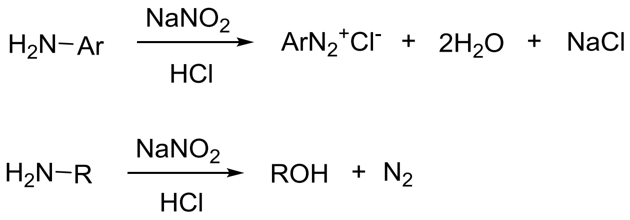
Chemistry of Hinsberg Test

In the presence of NaOH, the *N*-alkylsulphonamides are produced by primary aliphatic amines on reaction with benzene sulfonyl chloride. The sulphonamide contains an acidic hydrogen so dissolves in NaOH to produce corresponding soluble sodium salt. Furthermore, on acidification, sulfonamide precipitates out which are insoluble in HCl.[5]

Diazotisation Test:

Dissolve 0.5 g of organic compound in 2 mL of concentrated HCl then add 3 mL of aqueous $NaNO_2$ *solution. Afterwards, add a solution of 2-nephthol in sodium hydroxide. The appearance of orange colour confirms the presence of primary aromatic amine.*

Chemistry of Diazotisation Test:



$$H_2N{-}Ar \xrightarrow[HCl]{NaNO_2} ArN_2^+Cl^- + 2H_2O + NaCl$$

$$H_2N{-}R \xrightarrow[HCl]{NaNO_2} ROH + N_2$$

Chemistry of Diazotization Test

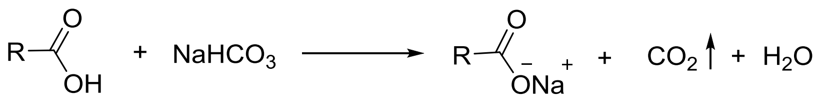
At 0-5°C aromatic primary amines dissolved in HCl reacts with aqueous $NaNO_2$ to produce water soluble diazonium salts. They further react with 2-naphthol to form a characteristic coloured-dye. However, aliphatic primary amines never form stable diazonium salts under such condition. They react with nitrous acid to generate corresponding alcohols and nitrogen which produces foaming.

$NaHCO_3$ Test:

Dissolve 0.1 g of organic compound in 1 mL of $NaHCO_3$ test. The precipitation of different colours confirms the presence of different phenols.[6]

Chemistry of $NaHCO_3$ Test:

In this test, the carboxylic acids are converted into corresponding sodium salts with evolution of carbon dioxide gas.

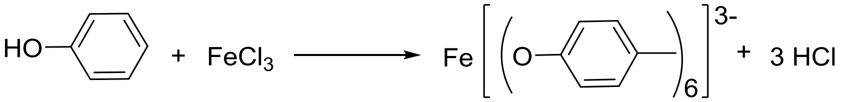


Chemistry of $NaHCO_3$ Test

Neutral $FeCl_3$ Test:

Take 1 mL solution of organic compound (0.1 g of O.C/mL of H_2O *or ethanol) and I mL of neutral ferric chloride solution. The precipitate formation in blue, green, purple or red colours confirm phenolic compound.*

Chemistry of Neutral $FeCl_3$ Test:



Chemistry of Neutral $FeCl_3$ test

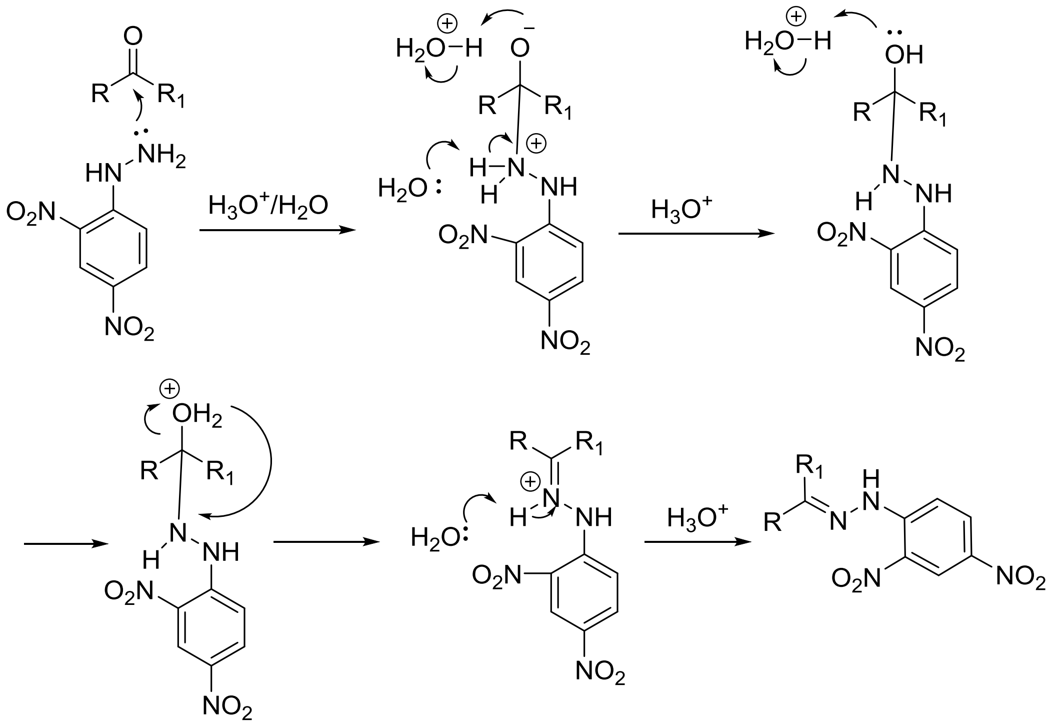
The ferric chloride fabricates a complex with the phenol. This coloured-complex acts as a confirmatory test for different phenols.[2]

2,4-DNPH test

Take 0.1 g of organic compound in a test tube and introduce 3 mL of 2,4-DNPH solution. Shake the tube well and let it stand for at least five minutes. The appearance of yellow or orange yellow precipitates indicates the presence of carbonyl compound (both aldehyde and keone).

Chemistry of 2,4-DNPH test

The presence of carbonyl group could be confirmed by 2,4-DNPH test. The formation of dinitrophenylhydrazone as yellow, orange or red precipitates confirms the presence of carbonyl group. The red precipitates represent aromatic carbonyl compound and aliphatic carbonyls appear as yellow colour.[7] The carbonyl functionality reacts with 2,4-DNPH as under,



Chemistry of 2,4-DNPH test

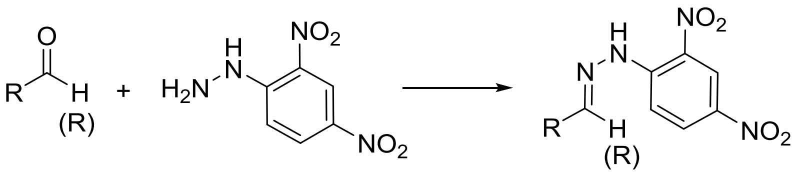


Fig 3. Formation of dinitrophenylhydrazone

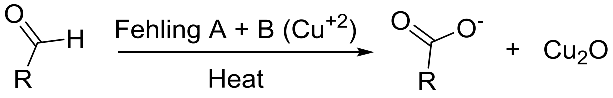
Fehling’s solution test:

Take at least 1 g of organic compound in test tube followed by a gentle addition of 5 mL of fehling’s solution. Then heat this mixture till it boils. The formation of red precipitates identifies the aldehydes.

Chemistry of Fehling`s Test

In this test, the specific blue colour of $CuSO_4$ disappears and the formation of red-coloured precipitates of copper oxide confirms the presence of aldehydes. This test usually employed for the confirmation of reducing sugars but not strictly specific for aldehydes.

In fact, fehling`s reagent contains fehling’s A and fehling’s B solutions. Solution A provides $Cu^{+2}$ ions and the second provides OH ions. When an aldehyde is boiled with Fehling`s solution, copper-II is reduced to Copper-I. Further, this copper-I gets converted to Cu_2O and precipitates out in red color.[8]



$$RCHO + 5\,OH^- + 2Cu^{+2} \longrightarrow RCOO^- + Cu_2O + H_2O$$

Chemistry of Fehling's solution test

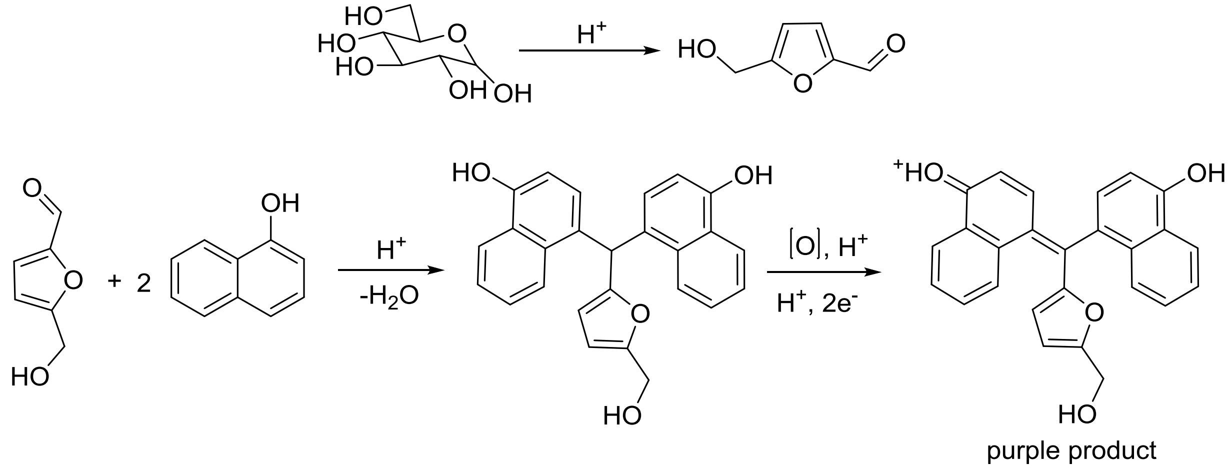
Molisch's test

Into the aqueous solution of organic compound add 2 mL of 1% ethanolic sol. of naphthol. Then add 0.5 mL of con. H_2SO_4*. Red or purple coloured-products confirms the presence of carbohydrates.*

Chemistry of Molisch's test

This test confirms the presence of carbohydrates. Monosaccharides react immediately while disaccharides and polysacchraides react at slow rate.

In this test, the con. H_2SO_4 facilitates the molisch reagent to dehydrates pentoses to respective furfural and hexoses produce 5-hydroxymethyl furfurals. Afterwards, furfurals react with α-naphthol and produce red or purple color.[9]

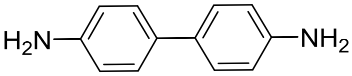


Chemistry of Molisch's test

Model Analysis of Basic Compound

Test/Experiment	Observations	Inferences
Litmus solution test	Litmus solution turns blue	Amine is present
Bromine-water test	Colour of Br_2 disappears	Unsaturated compound
Carbylamine test	Unpleasant smell detected	Primary amine indicated
Diazotization test	Orange colour appears	Primary aromatic amine
Determine the m.p	124 ˚C	Match with the list of amines

Result: From the above it is found that the given compound is basic, unsaturated primary aromatic amine with m.p of 124 ˚C. In the given list of amines, it matches closely with benzidine. So, the given compound may likely be benzidine.

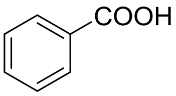


Benzidine
126 °C

Model Analysis of Basic Compound

Test/Experiment	Observations	Inferences
Litmus solution test	Solution turns red	Acidic compound detected
Bromine-water test	Colour of Br_2 disappears	Unsaturated compound
$NaHCO_3$ Test	Gas evolved with effervescences	Carboxylic acid present
Neutal FeCl3 test	No reaction	Phenols are absent
Determination of m.p.	118 ˚C	Match with given list

Result: From the above, it is found that the given compound is an unsaturated carboxylic acid with m.p 118 ˚C. In the given list of carboxylic acids, it closely matches with benzoic acid. So, the given compound may likely be benzoic acid.

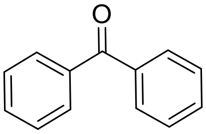


Benzoic acid
120 °C

Model Analysis of Neutral Compound

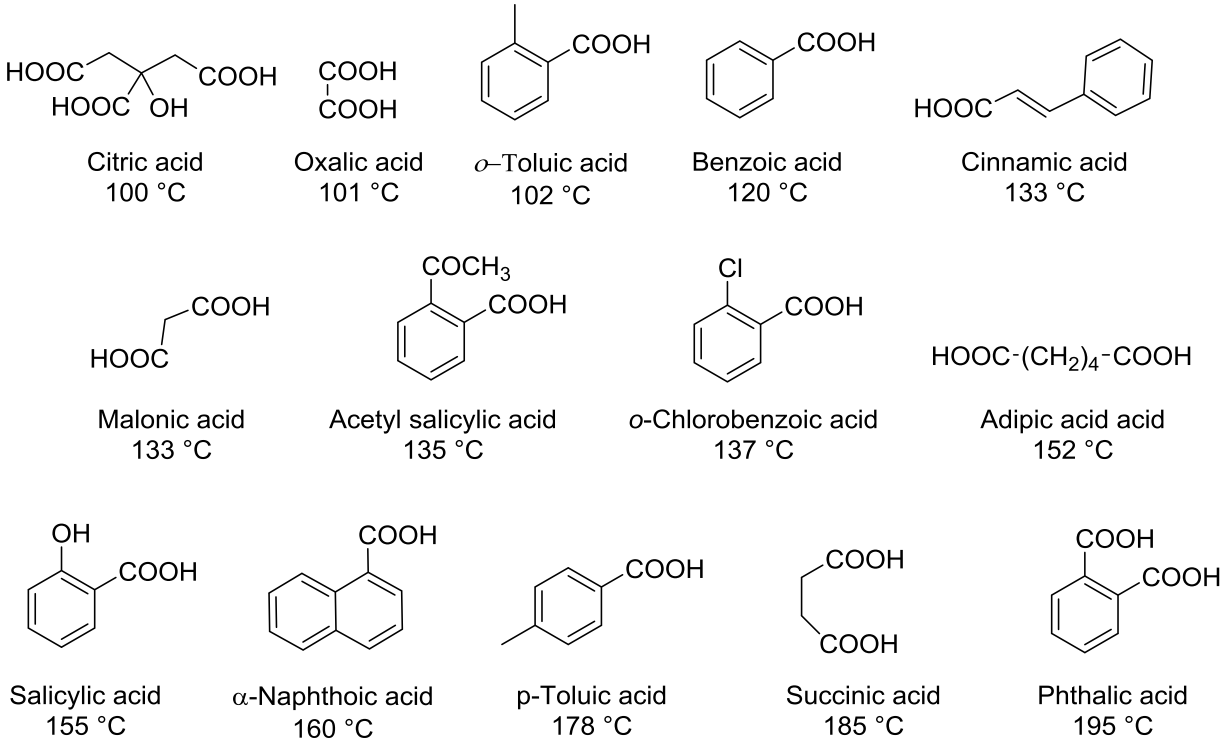
Test/Experiment	Observations	Inferences
Litmus solution test	No change in colour	Neutral compound detected
Bromine-water test	Colour of Br_2 disappears	Unsaturated compound
2,4-DNPH test	Yellow precipates	Carbonyl compound indicated
Fehling solution test	No reaction	Aldehyde absent, ketone present
Determination of m.p.	46 ˚C	Match the m.p. in the given list

Result: From the above, it is found that the given compound is an unsaturated ketone with m.p. 46 ˚C. In the given list of ketones, it closely matches with benzophenone. So, the given compound may likely be benzophenone.



Benzophenone
48 °C

List of Common Carboxylic Acid (Acidic Compounds)



Citric acid
100 °C

Oxalic acid
101 °C

o–Toluic acid
102 °C

Benzoic acid
120 °C

Cinnamic acid
133 °C

Malonic acid
133 °C

Acetyl salicylic acid
135 °C

o-Chlorobenzoic acid
137 °C

Adipic acid acid
152 °C

Salicylic acid
155 °C

α-Naphthoic acid
160 °C

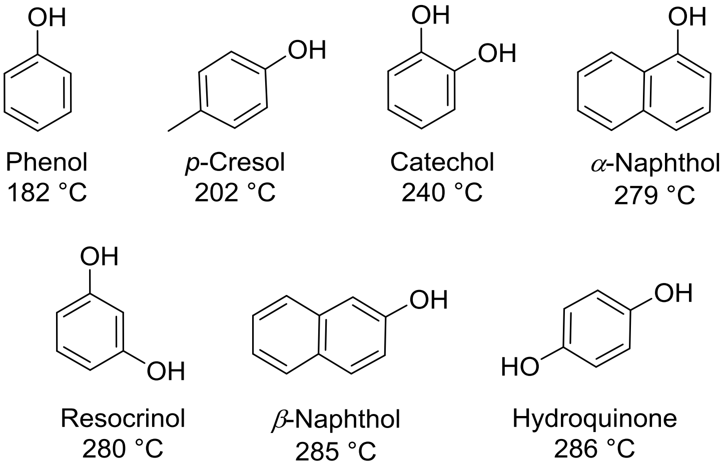
p-Toluic acid
178 °C

Succinic acid
185 °C

Phthalic acid
195 °C

Carboxylic acids with their melting points

List of Common Phenolic compounds (Acidic Compounds)



Phenol
182 °C

p-Cresol
202 °C

Catechol
240 °C

α-Naphthol
279 °C

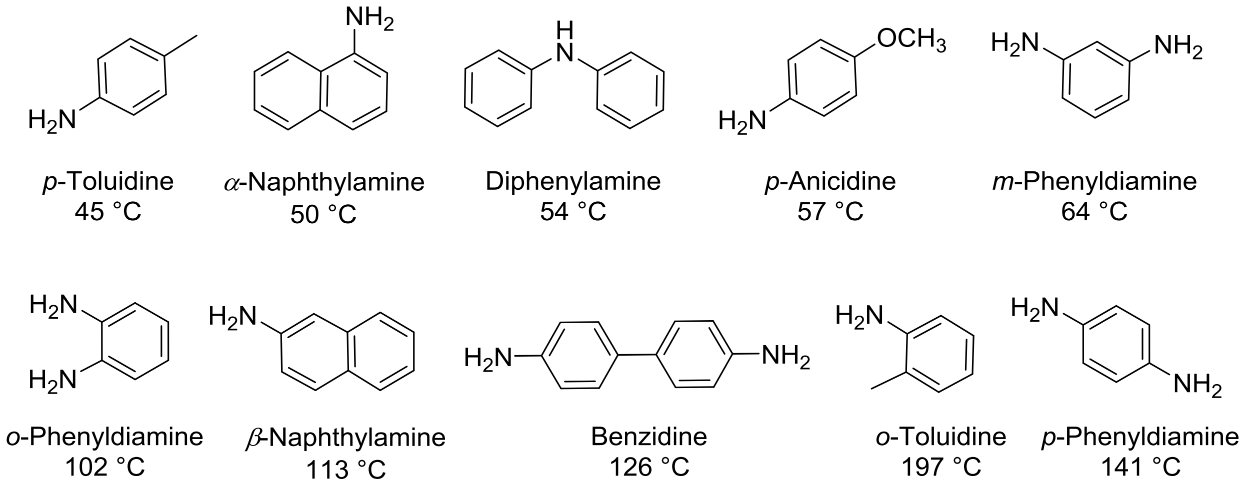
Resocrinol
280 °C

β-Naphthol
285 °C

Hydroquinone
286 °C

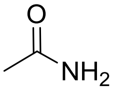
Phenols with their melting points

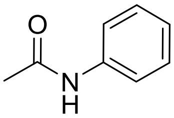
List of Common Amines (Basic Compounds)

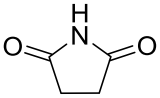


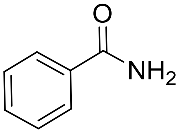
Amines with their melting points

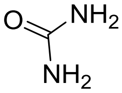
List of Common Amides, Imides and Anilides (Neutral Compounds)

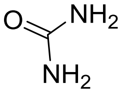

Acetamide
82 °C

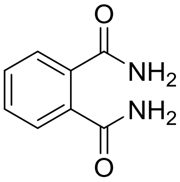

Acetanilide
115 °C

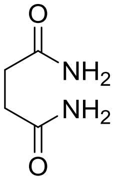

Succinimide
126 °C


Benzamide
128 °C


Urea
132 °C

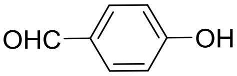

Thiourea
180 °C

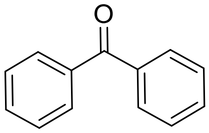

Phthalamide
219 °C

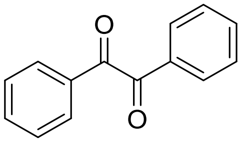

Succinamide
242 °C

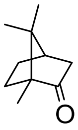
Amides, Imides and Anilides with their melting points

List of Common Aldehyde and Ketones (Neutral Compounds)


p-Hydroxybenzaldehyde
115 °C


Benzophenone
48 °C


Benzil
95 °C


d-Camphor
175 °C

Aldehyde

Ketones

Aldehyde and ketones with their melting point

References:

1. Gilbert, J. C.; Martin, S. F., *Experimental organic chemistry: a miniscale & microscale approach*. Cengage Learning: 2015.
2. Carey, F. A.; Sundberg, R. J., *Advanced organic chemistry: part A: structure and mechanisms*. Springer Science & Business Media: 2007.
3. Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S., *An introduction to modern experimental organic chemistry*. Holt, Rinehart and Winston New York: 1969.
4. Palleros, D. R., *Experimental organic chemistry*. Wiley & Sons: 2000.
5. Harwood, L. M.; Moody, C. J.; Percy, J. M., *Experimental organic chemistry: standard and microscale*. Blackwell science Malden, MA: 1999.
6. Harwood, L. M.; Moody, C. J., *Experimental organic chemistry: principles and practice*. Blackwell: 1989.
7. Roberts, R. M., *Modern experimental organic chemistry*. Saunders College Publishing: 1985.
8. Steyermark, A., *Quantitative organic microanalysis*. Elsevier: 2012.
9. Furniss, B. S., *Vogel's textbook of practical organic chemistry*. Pearson Education India: 1989.

Chapter 2

2 Organic Synthesis

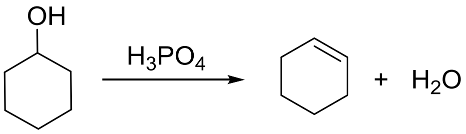
Tahir Farooq, Sarosh Iqbal

This chapter aims to enable the students to apply basic reaction concept to practical synthesis. They are supposed to learn about the handling of reactions under different conditions. Further, students are expected to learn about the modern spectroscopic techniques required for the structure elucidations of reaction products.

2.1 Dehydration

2.1.1 Experiment 1: Preparation of Cyclohexene from Cyclohexanol

Aim: The objective of the following experiment is to synthesize cyclohexene from cyclohexanol.



Dehydration of alcohol to produce alkene

Experimental learning objectives: Students are supposed to learn about

- setting up of a distillation assembly for distillation
- handling of separatory funnel
- aqueous wash and drying of organic phase
- recognize the organic layer in immiscible mixture
- covert an alkene to a corresponding alcohol through dehydration process

In this lab activity, an alcohol will be converted to alkene by dehydration using phosphoric acid as a catalyst.[1]

Procedure:

In a round bottom flask, take 10 g of cyclohexanol (10.6 mL) then slowly add 3 mL of 85% phosphoric acid dropwise. Then you should add 3 boiling chips and heat the round bottom flask gently. You should stop distillation process with the appearance of white fumes in the round bottom flask and subsequent collection of around 10 mL of distillate. Then pour the collected distillate to a separatory funnel of about 50 mL capacity. After shaking leave the funnel for a while, the mixture will get separated in two identifiable layers. Then run off slowly and carefully the lower aqueous layer into a conical flask and keep it aside. The subsequent addition of 10 mL of water in the separatory funnel is called the washing of the cyclohexene with water. Again run off the aqueous layer into initially collected portion. The organic phase is then washed with 10 mL of 10% Na_2CO_3. Again, the aqueous layer is run off the aqueous layer. Final washing with 10 mL of water is repeated. Pour the organic phase into a dry conical flask and add 2 g of calcium chloride, swirl the flask and allow the solution to stand over the drying agent for at least ten more minutes. Afterwards, filter the unpleasant smelling organic phase into a pre-weighed beaker by gravity filtration. Then weigh out the amount of cyclohexene and calculate the percentage yield. The formation of required product could be confirmed by the bromine and permanganate tests.

Mass of cyclohexene expected: ________________ g

No. of moles of cyclohexene expected: ________________

Mass of cyclohexene obtained: ________________ g

No. of moles of cyclohexene obtained: ________________

Percent yield = expected no of moles of product/no. of moles of product obtained X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

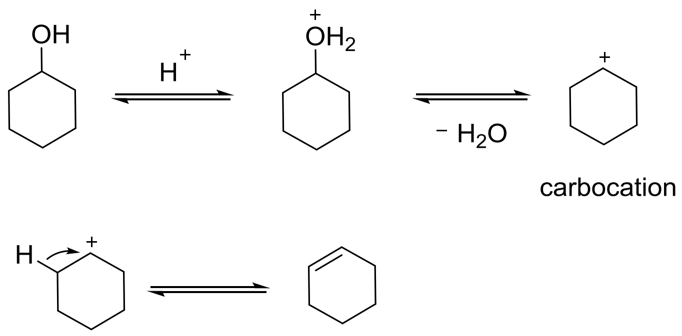
Viva questions:

Why organic layer is washed with water?

The remnants of unreacted alcohol, catalytic phosphoric acid and possible by-products could contaminate the crude product and washing with water helps to eliminate such impurities.

What is the mechanism of the reaction?

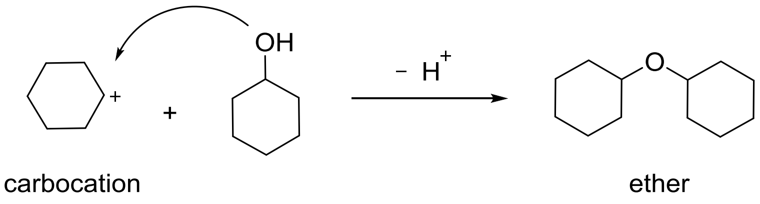
The mechanism of reaction initially comprises the development of a carbocation.



Dehydration of alcohol

What could be the side product of the reaction?

The dicyclohexyl ether could probably be the side product of the reaction.



What could be the confirmatory test for the confirmation of product formation?

The bromination test could confirm the product formation. The decolouration of bromine water confirms the presence of alkene in this case.

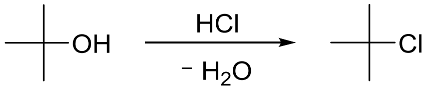
Safety Cautions:

1. Students should be careful while using phosphoric acid to avoid severe skin burns.
2. Bromine also can cause severe skin burns so a cautious handling is required.
3. The exposure to cyclohexanol could become irritating for respiratory system.

2.2 Nucleophilic Substitution

2.2.1 Experiment 2: The preparation of tertiary butyl chloride (2-chloro-2-methylpropane)

Aim: The objective of the following experiment is to synthesize *t*-butyl chloride from *t*-butanol through acid catalyzed SN1 nucleophilic substitution reaction.



Conversion of alcohol to corresponding alkyl halide

Experimental learning objectives: Students are supposed to learn about

- Handling of SN1 nucleophilic substitution reaction
- Aqueous wash and drying of organic product
- Separation of layers
- Conversion of an alcohol to corresponding alkyl halide through nucleophilic substitution

In this lab activity, an alcohol will be converted to corresponding alkyl halide through acid catalyzed nucleophilic substitution reaction.[2]

Procedure:

Take a 100 mL separatory funnel and pour into it 12.4 g of anhydrous *t*-butyl alcohol. Then add 21 mL of hydrochloric acid. Vigorously shake the mixture in separatory funnel for about 20 minutes. Time and again, open the stopcock to release any internal pressure produced in the separatory funnel after each shaking. Afterwards, put the separatory funnel on stand until the appearance of two identifiable layers. Separate the aqueous acidic layer in a beaker. Pour the organic layer into a dry conical flask. For 10-15 minutes, dry the organic layer with 2 g of anhydrous magnesium sulfate and sodium carbonate. Filter the organic layer through filter paper into a pre-weighted beaker. Determine the weight of the *t*-butyl chloride.

Expected mass of *t*-butyl chloride: ________________ g

Expected no. of moles of *t*-butyl chloride: ________________

Actual mass of *t*-butyl chloride: ________________ g

Actual no. of moles of *t*-butyl chloride: ________________

Percent yield = expected no of moles of product/actual no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva questions:

Why hydrochloric acid is added in the *t*-butanol?

Initially, hydrochloric acid protonates the *t*-butanol molecule and helps to generate corresponding carbocation.

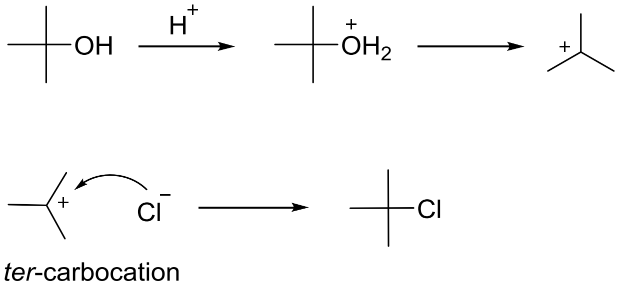
Why sodium carbonate is used?

Sodium carbonate is used to neutralize the extra quantities of hydrochloric acid.

The formation of *t*-butyl chloride follows SN1 or SN2 pathway?

The *t*-butanol generates a stable carbocation. So the reaction follows SN1 pathway.

What is the reaction mechanism?



Nucleophilic substitution reactions (SN_1)

What could be the confirmatory test for the confirmation of product formation?

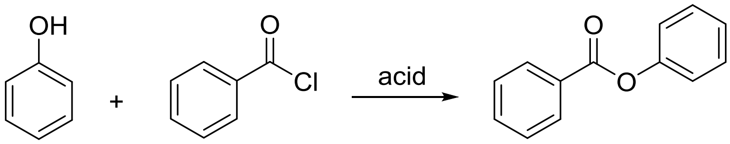
The confirmatory test for alkyl halides could confirm the presence of t-butyl chloride, the required product.

Safety Cautions:

1- Working with hydrochloric acid needs extra care.
2- The *t*-butyl chloride happens to be highly volatile in nature. So, extra care is required to handle it in fume-hood.
3- The aqueous layer should be disposed of properly because of the presence of acid remnants.

2.2.2 Experiment 3: Preparation of the benzoate of phenol

Aim: The objective of the following experiment is to synthesize benzoate from phenol through SN2 nucleophilic substitution reaction.



Nucleophilic substitution reaction of carbonyl compound

Experimental learning objectives: Students are supposed to learn about

- handling of nucleophilic substitution reaction
- aqueous wash and drying of organic product
- recrystallization methods for organic solids
- conversion of a phenol to a corresponding ester through nucleophilic substitutions

In this lab activity, a phenol will be converted to benzoate by base catalyzed nucleophilic substitution reaction.

Procedure:

In a small conical flask add 0.5 g of phenol and 10 mL of 5% sodium hydroxide. Then slowly add 2 mL of benzyl chloride in small fractions. The resultant mixture is shaken violently for few minutes. The solid benzoate gets separate from the mixture after 15 minutes of shaking with occasional cooling in cold water. If no solid separates out from an oily reaction mixture, then the addition of solid sodium hydroxide makes it an alkaline. Which consequently separates out solid required benzoate.

Filter the reaction mixture to collect the solid benzoate and thoroughly wash it with cold water to eliminate undesirable impurities. Recrystallize the product from ethanol. Determine the weight of product.

Expected mass of benzoate: ________________ g

Expected no. of moles of benzoate: ________________

Actual mass of benzoate: ________________ g

Actual no. of moles of benzoate: ________________

Percent yield = expected no of moles of product/actual no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva questions:

Why 5% sodium hydroxide solution is added in the phenol?

Phenol is an acidic compound which loses its proton in the presence of base like sodium hydroxide. Then this phenoxide ion, a nucleophile attacks benzyl chloride which subsequently undergoes nucleophilic substitution reaction to produce benzoate.[3]

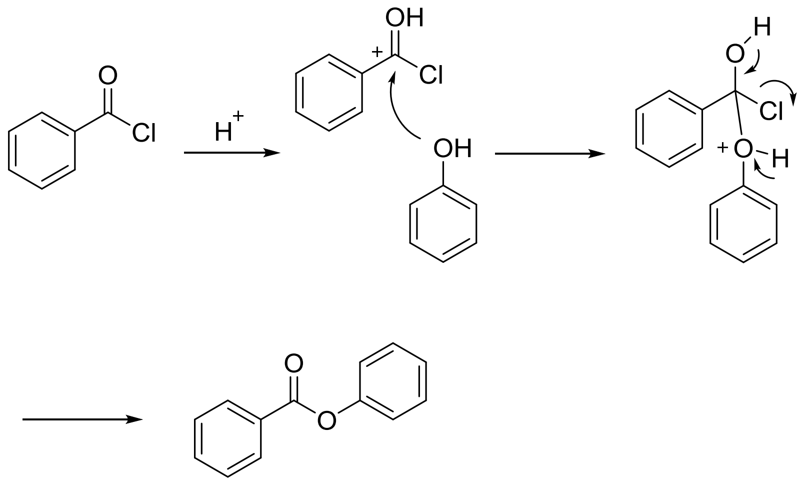
Why crystalline solid is washed with water?

The crystalline solid is washed with water to remove impurities of sodium hydroxide.

The formation of phenyl benzoate follows SN1 or SN2 pathway?

The benzyol chloride is a primary alkyl halide so it follows SN2 pathway.

What is the reaction mechanism?



What could be the confirmatory test for the confirmation of product formation?

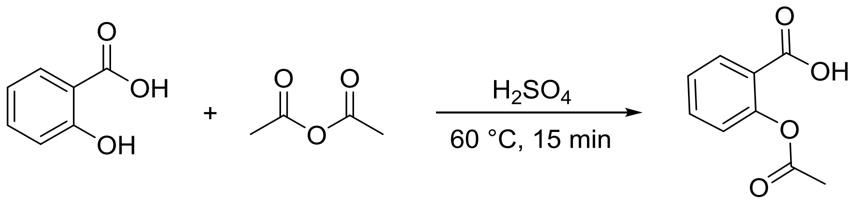
The confirmatory test for esters could confirm the presence of benzoate, the required product.

Safety Cautions:

1- Benzoyl chloride happens to be lachrymatory in nature so extreme care is required for its handling. Better to use it under fume-hood.
2- Phenol is known for its toxicity and can cause skin burns.
3- Sodium hydroxide solution should also be used with safe handling.

2.2.3 Experiment 4: Preparation of aspirin

Aim: The objective of the following experiment is to synthesize aspirin from salicylic acid and acetic anhydride through nucleophilic substitution reaction.



Synthesis of aspirin through nucleophilic substitution reaction of carbonyl compound

Experimental learning objectives: Students are supposed to learn about

- handling of nucleophilic substitution reactions of carbonyl compounds
- aqueous wash and drying of organic product
- recrystalline methods for organic solids
- conversion of a phenol to a corresponding ester through nucleophilic substitutions
- performance of vacuum filtration

In this lab activity, salicylic acid will be converted to aspirin by acid catalyzed nucleophilic substitution reactions of carbonyl compounds.[4]

Procedure:

Take 2 g of salicylic acid and 3 mL of acetic anhydride in a beaker of 50 mL capacity. Afterwards, introduce at least 1 drop of con. sulfuric acid before stirring the mixture. For fifteen minutes stir the mixture by glass rod with continuous heating. Then slowly introduce 30-40 mL of water while swirling the mixture. After that install the set-up to perform vacuum filtration. Determine the mass of crude product received after filtration. Recrystallization is opted to remove the impurities to purify the crude acetylsalicylic acid. The crude filtrate is dissolved in 5 mL of hot ethanol or methanol. Subsequently this solution slowly transferred into 25 mL of hot water. A complete dissolution of crude acetylsalicylic acid is achieved by heating the mixture. Then let the mixture cool down for 10 minutes later put it in ice water. This process results in the formation of crystals of pure acetylsalicylic acid (Aspirin). After recrystallization, the pure solid product is filtered out and air or vacuum dried. Finally, you are supposed to determine the mass of supposedly uncontaminated solid aspirin.

Expected mass of acetylsalicylic acid: ________________ g

Expected no. of moles of acetylsalicylic acid: ________________

Actual mass of acetylsalicylic acid: ________________ g

Actual no. of moles of acetylsalicylic acid: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Why drops of sulfuric acid is added?

Sulfuric acid catalyzes this nucleophilic substitution reaction.

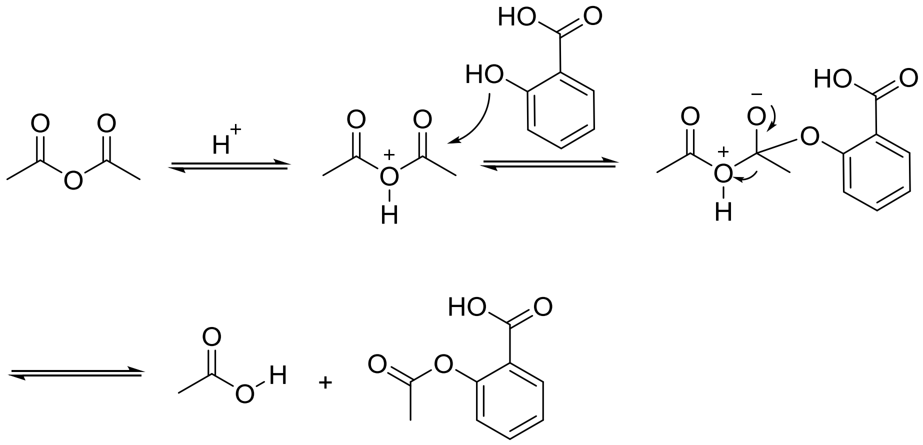
Why crystalline solid is washed with water?

The crystalline solid is washed with water to remove impurities.

The vacuum filtration is used in this process?

The vacuum filtration is employed when filtrate happens to be very viscous.

What is the reaction mechanism?



Synthesis of aspirin

What could be the confirmatory test for the confirmation of product formation?

The confirmatory test for esters could confirm the presence of the required product.

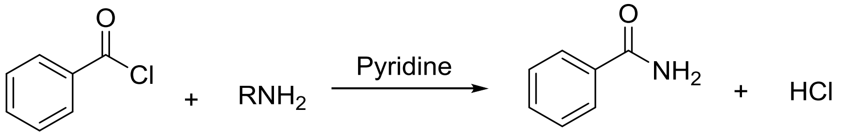
Safety Cautions:

1- Working with sulfuric acid needs extra care.
2- The aqueous layer should be disposed of properly because of the presence of acid remnants
3- Working with vacuum filtration needs extra care otherwise you will lose your product.

2.3 Nucleophilic Substitution Reaction of Carbonyl Compounds

2.3.1 Experiment 5: Synthesis of Benzamide

Aim: The main object of this experimental acidity is to synthesize benzamide from benzoyl chloride through nucleophilic substitution reaction.



Nucleophilic substitution at carbonyl compound

Experimental learning objectives: Students are supposed to learn about

- handling of nucleophilic substitution reactions of carbonyl compounds
- aqueous wash and drying of organic product
- recrystallization methods for organic solids
- conversion of a benzoyl chloride to a corresponding amide through nucleophilic substitutions

In this lab activity, benzoyl chloride reacts with amines through nucleophilic substitution reactions of carbonyl compounds.[5]

Procedure:

In a 50 mL round-bottom flask, take 2 mL of pyridine and add into it 0.15 g of amine and 3 mL of toluene. Add 0.3 mL of benzoyl chloride to the flask. Then a condenser is attached and the mixture is heated for about 20 minutes in boiling water. Cool the mixture to room temperature and transfer into 15 mL water. Then transfer the mixture to a separatory funnel, shake well and let the two layers get separated. The separately collected organic layer is washed with 5 mL of saturated Na2CO3 solution which subsequently dry with anhydrous Na2SO4. After the removal of solvent by evaporation, the benzamide is recrystallized using ethanol or ethanol/water. Finally, find out the mass of the pure benzamide

Expected mass of benzamide: ________________ g

Expected no. of moles of benzamide: ________________

Actual mass of benzamide: ________________ g

Actual no. of moles of benzamide: ________________

Percent yield = Actual no of moles of product/expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Why pyridine is used in this reaction?

Pyridine is a basic compound and acts as a catalyst in this base catalyzed nucleophilic substitution reaction.

How pyridine is removed in this reaction?

The HCl produced in this reaction reacts with pyridine to form pyridinium chloride salt. Which is water soluble so is removed in aqueous layer.

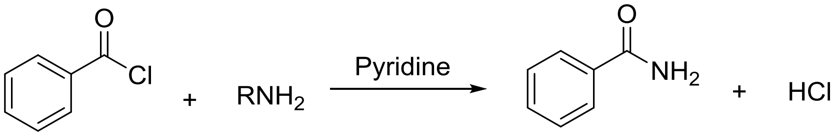
Why organic layer is washed with saturated sodium carbonate solution?

The organic phase is washed with saturated sodium carbonate solution to remove inorganic impurities.

Why crystalline solid is washed with water?

The crystalline solid is washed with water to remove impurities of sodium carbonate.

What is the reaction mechanism?



Nucleophilic substitution at carbonyl compound

What could be the confirmatory test for the confirmation of product formation?

The confirmatory test for esters could confirm the presence of benzoate, the required product.

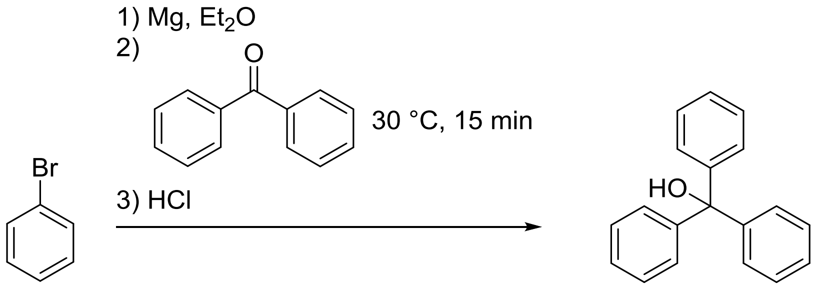
Safety Cautions:

1- The benzoyl chloride is lachrymatory in nature and can cause skin irritation. So, you should be very careful while using it. Better to use it in the fume-hood
2- Pyridine is toxic with unpleasant smell. Use gloves and glasses to protect yourself.
3- The aqueous layer should be disposed of properly because of the presence of pyridine remnants

2.4 Nucleophilic Additions

2.4.1 Experiment 6: Synthesis of Triphenylmethanol

Aim: The objective of the following experiment is to synthesize triphenylmethanol through nucleophilic addition reaction of ketone with Grignard's reagent.



Nucleophilic addition of carbonyl compounds via Grignard's reagent

Experimental learning objectives: Students are supposed to learn about

- handling of nucleophilic addition reactions of carbonyl compounds
- synthesis of Grignard's reagent
- recrystallization methods for organic solids
- conversion of a ketone to a corresponding nucleophilic addition product
- handling of reactions under extremely dry conditions

In this lab activity, benzophenone will be converted to triphenylmethanol through nucleophilic addition reaction of ketone with Grignard's reagent.[4]

Preparation of the Grignard Reagent:

Take a flame-dried round bottom flask of 250 mL capacity fitted with a condenser and a funnel, add 0.9 g of magnesium turnings in it. This glass-assembly again flame dried to remove even minor moisture contents and the condenser fitted with CaCl2 guard to minimize the re-entrance of moisture. As this assembly cools, at room temperature, 4 mL of bromobenzene and 1 mL of ether are introduced into the funnel. Then slowly add the bromobenzene solution into the round bottom flask containing magnesium tunings. The reaction proceeds in the absence of external heat. After few minutes of reaction time, the mixture becomes cloudy in appearance, gets milky and at last darker brown when ether starts boiling. Now, dropwise manage to transfer the remaining bromobenzene solution while ether remain in boiling phase without heating. After the addition of bromobenzene, reaction mixture is refluxed for 20-30 minutes to consume the remaining amounts of magnesium. Afterwards, let the Grignard's reagent cool down.

Step-II Grignard addition reaction – Preparation of Triphenylmethanol:

Prepare a solution of 4.8 g benzophenone in 15 mL of anhydrous ether. Dropwise, introduce this solution to already prepared Grignard reagent. Upon addition, the mixture turns red in color. Then put this mixture on reflux at least for 5 min, in so doing pink colored precipitation starts. The reaction mixture in the round-bottom flask is transferred slowly to a beaker of 250 mL capacity containing 50 mL of 3N HCl and ice. The flask should be rinsed with little amount of ether. Subsequently, pour the reaction mixture to a separatory funnel to extract the organic phase. Which is further washed with water and dried by using sodium sulfate. On rotary evaporator ether is evaporated and the remaining precipitate is filtered off and later dried completely. Find out the final mass of the required triphenylmethanol.

Expected mass of triphenylmethanol: _______________ g

Expected no. of moles of triphenylmethanol: _______________

Actual mass of triphenylmethanol: _______________ g

Actual no. of moles of triphenylmethanol: _______________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Why extra dry conditions are required for synthesis of Grignard's reagent?

Magnesium metal reacts violently with moisture. So, extra moisture free conditions are employed.

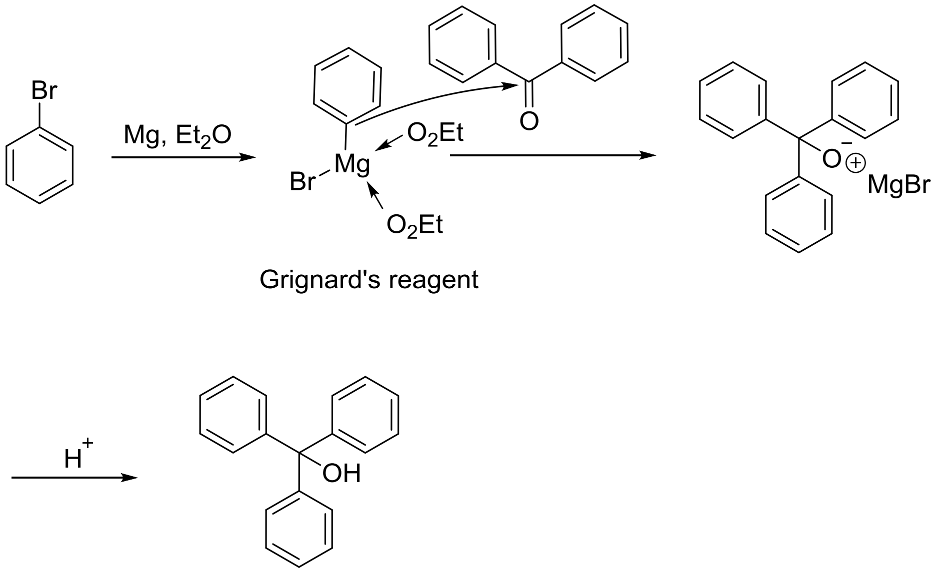
What is the role of $CaCl_2$?

The $CaCl_2$ is used to absorb moisture contents.

What is the role of 3N HCl in this reaction?

The hydrochloric acid provides protons to generate final stable alcoholic product.

What is the reaction mechanism?



Nucleophilic addition of carbonyl compounds via Grignard's reagent

What could be the confirmatory test for the confirmation of product formation?

The confirmatory test for alcohol could confirm the presence of the required product.

Safety Cautions:

1- Working with magnesium metal needs extra care because it can react violently with moisture contents.

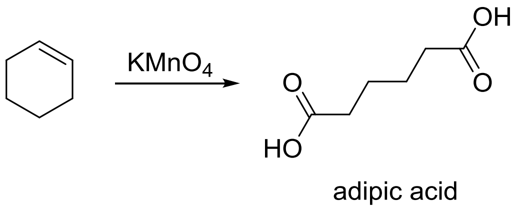
2- The aqueous layer should be disposed of properly because of the presence of acid remnants

3- The Grignard's reagent is very reactive so proper reaction time management is required.

2.5 Oxidation of Organic Compounds

2.5.1 Experiment 7: Preparation of Adipic Acid from Cyclohexene.

Aim: The objective of the following experiment is to oxidize cyclohexene to produce adipic acid.



Oxidation of alkene

Experimental learning objectives: Students are supposed to learn about

- handling of oxidation reactions of organic compounds ……
- use of the oxidizing agent
- recrystallization methods for organic solids
- conversion of an alkene to adipic acid
- handling of vacuum filtration

In this lab activity, the cyclohexene synthesized in one of the previous experiments is oxidized to adipic acid.[6]

Procedure:

Take an Erlenmeyer flask of 250 mL capacity and add 50 mL water, 2 mL of cyclohexene and 8.4 g of potassium permanganate into it. Put on a loose stopcock on the flask, swirl it vigorously for 5 minutes after wrapping with a piece of towel. The flask is supposed to get warm gently. If you find no change in flask temperature, heat the reaction mixture on steam bath. For at least twenty minutes, manage to swirl the flask after short intervals. The reaction yield directly corresponds to mixing of the reactants at this phase. The flask temperature should range between 35° to 40 °C. If you find temperature just around 45 °C, slowly cool it in an ice-water bath. For fifteen minutes, the flask is placed on a steam bath after removing the stopper. Parallelly, a continuous swirling of the flask after short time intervals is required. Take a spot test by withdrawing a little of reaction mixture. The sample of reaction mixture on the tip of a stirring rod is deposited on a filtering paper; the permanganate, if still present becomes visible as a dark purple ring just around the dark brownish spot of MnO2. In this case, 1 mL of methanol is added before heating. Keep repeating this practice till the permanganate colour-band disappears. Subsequently, filter the reaction mixture through aa appropriate Buchner funnel under vacuum. The reaction flask is rinsed with 10 mL of 1% hot NaOH solution and pour it through the filter. Redo the same with the second portion of 10 mL of 1% NaOH solution. Put the filtrate for washings in a beaker of 250 mL maximum capacity, after adding a boiling chip, boil the mixture till the volume of the solution reduces to 10 mL. The solution is cooled in an ice-water bath and a pH of about 1 is attained by dropwise addition of concentrated hydrochloric acid with continuous stirring. dropwise while stirring the solution. Later,3 mL of hydrochloric acid is introduced followed by stirring and put the beaker in the ice bath for 10 minutes for the completion of recrystallization. Finally collect the acid product by vacuum filtration. To purify the product, recrystallize it by putting it in 5 mL of boiling water. Let it cool to room temperature, then for about ten minutes put it in an ice-water. Finally, filter the product by vacuum filtration and let it get dry. Determine the mass of the product and its melting point.

Expected mass of adipic acid: ________________ g

Expected no. of moles of adipic acid: ________________

Actual mass of adipic acid: ________________ g

Actual no. of moles of adipic acid: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

What is the role of KMnO4 in this reaction?

The KmnO4 acts as oxidizing agent for alkene.

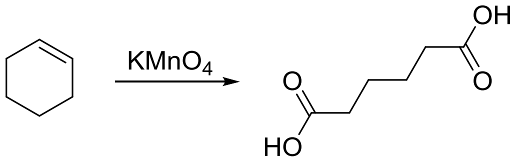
What could be the by-product n this reaction?

In oxidation reactions of organic compounds, carbon dioxide is the usual by-product

Why vacuum filtration is used in this reaction?

The vacuum filtration is used reaction mixtures are viscous and could not be filtered by ordinary filtration.

What is the reaction mechanism?



adipic acid

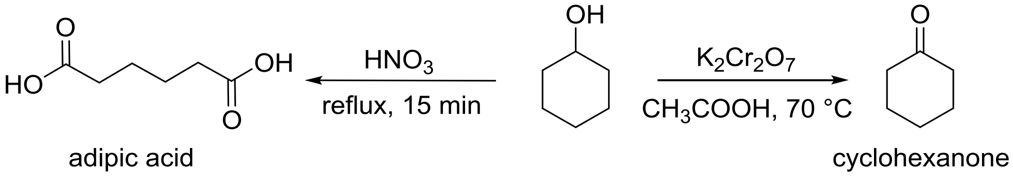
Oxidation of alkene

Safety Cautions:

1. Add concentrated hydrochloric acid to the strongly basic solution very cautiously
2. Potassium permanganate is handled very carefully because it is a strong oxidizing agent.
3. One should avoid of breathing cyclohexene and methanolic vapours.

2.5.2 Experiment 8: Synthesis of Cyclohexanone and Adipic Acid from Oxidation of Cyclohexanol

Aim: The objective of the following experiment is to oxidize a cyclohexanol to produce ketone under mild conditions. Secondly, the same is oxidized to carboxylic acid under harsh conditions.



Oxidation of alcohol

Experimental learning objectives: Students are supposed to learn about

- handling of oxidation reactions of organic compounds
- use of the different oxidizing agents
- recrystallization methods for organic solids
- conversion of an alcohol to adipic acid
- find out the difference of oxidation potential of different acids

Part A: In this lab activity, the cyclohexanone will be synthesized from oxidation of cyclohexanol under mild conditions.[7]

Procedure:

Take a 100 mL Erlenmeyer flask add 5 g of potassium dichromate in 20 mL of acetic acid with constant heating. After the completion of dissolution, cool down the mixture in flask by keeping it down under tap water. Then, you should label the flask as solution 1. Afterwards, add 10 mL of cyclohexanol and 5 mL of acetic acid in second Erlenmeyer flask, after stirring the newly introduced mixture cool it for 10 minutes in an ice bath. You are supposed to label this flask as solution 2. Then, at quite a bit slow pace introduce solution 2 into solution 1 with continuous stirring to homogenize the mixture. Then take the flask away from ice bath. Monitor the temperature of the reaction mixture continuously and keep it below 70 ^oC. Use tap water for cooling purpose. When the reaction mixture turns to green and the temperature drops down it indicates the completion of reaction. Pour this reaction mixture into a round-bottom flask. Then introduce at least 35 mL of water and carry out distillation. Take a separatory funnel and pour the distillate in it. Subsequently, proceed to extract the organic layer using 15-20 mL of dichloromethane. Later wash the organic layer with 20 mL of saturated solution of sodium bicarbonate and 10 mL of water. Put in 2 g of anhydrous MgSO4 as dehydrating agent. After drying, filter the organic layer in a round-bottom flask. Afterwards, dichloromethane is evaporated on a rotary evaporator. Finally, determine the mass of pure expected product i.e. cyclohexanone.

Expected mass of cyclohexanone: ________________ g

Expected no. of moles of cyclohexanone: ________________

Actual mass of cyclohexanone: ________________ g

Actual no. of moles of cyclohexanone: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Part B:

Oxidation of cyclohexanol under harsh conditions:

Add nitric acid in a round-bottom flask of 250 mL capacity equipped with a condenser and an additional funnel, start heating lightly till temperature gets closer to boiling. Introduced 5 mL of cyclohexanol in the addition funnel, initially add 2 drops to the flask. Upon this a nitrous vapours are emitted because of vigorous reaction. Add the rest of cyclohexanol dropwise in about one hour. During this addition phase, the temperature of the flask should be maintained near to the boiling point. After addition, the mixture is put to reflux for about 15 minutes then pour the contents into beaker of 100 mL capacity. Cool the mixture to room temperature and then at 0 ^{o}C. Filter the crystals and wash with 10-15 mL of ice water, let the crystals dry. Finally determine the mass of a pure required product i.e. adipic acid.

Expected mass of adipic acid: ________________ g

Expected no. of moles of adipic acid: ________________

Actual mass of adipic acid: ________________ g

Actual no. of moles of adipic acid: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

What is the role of $K_2Cr_2O_7$ in this reaction?

The $K_2Cr_2O_7$ acts as oxidizing agent.

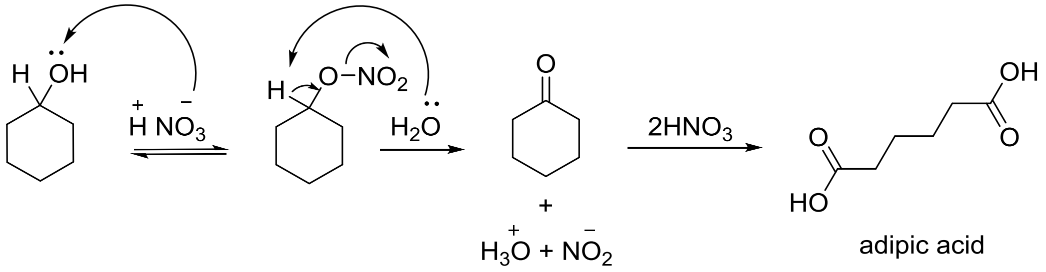
Explain the oxidation of alcohols?

Under mild conditions, the alcohol is converted into ketones and under harsh conditions alcohols are converted into carboxylic acids.

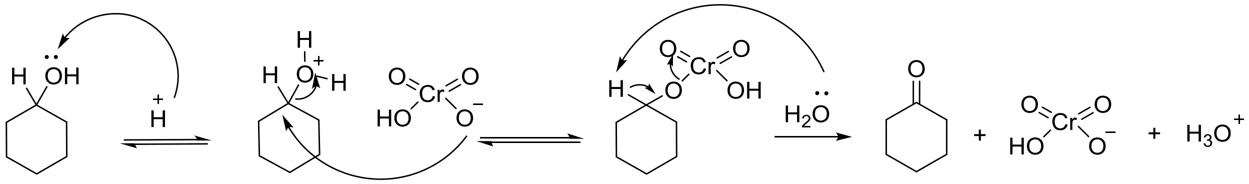
What is the role of anhydrous $MgSO_4$?

The anhydrous $MgSO_4$ acts as dehydrating agent. It removes the water contents from organic extract.

What is the reaction mechanism?



Oxidation of alcohol with HNO_3



Oxidation of alcohol with potassium dichromate

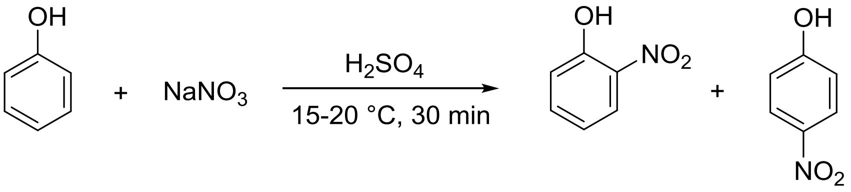
Safety Cautions:

1. Nitric acid should be handled very cautiously.
2. Potassium dichromate is handled very carefully because it is a strong oxidizing agent.
3. One should avoid of breathing cyclohexanol.

2.6 Electrophilic Substitution Reactions

2.6.1 Experiment 9: Nitration of Phenol

Aim: The objective of this experiment is to synthesis *o*-nitrophenol by electrophilic nitration of phenol.



Nitration of phenol, an electrophilic substitution of electrophile

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Steam distillation
- conversion of phenol to *o*-nitrophenol
- find out the difference of oxidation potential of different acids

In this lab activity the phenol undergoes nitration to produce *o*-nitrophenol and p-nitrophenol in excellent yield.[8]

Procedure:

Take a round-bottom flask of 250 mL capacity and add 10 g of sodium nitrate and 20 mL of water and put it in an ice bath. Then add 7 mL of con. sulfuric acid dropwise with extreme cautions. Take 6.5 mL of phenol in 2 mL of water then add dropwise this suspension to reaction mixture with continuous stirring in ice bath. Afterwards, the stirring is continued for next 30 minutes then 100 mL water is added. Then pour the reaction mixture into a separating funnel.

The aqueous layer is separated and the dark oily organic layer is washed again with 100 mL of water.

Flask containing the oily dark organic layer is placed in an external steam distillation setup. Lastly, stop the distillation is supposed to stop when no more product distills out. Filter the product using a Büchner funnel. When the product is completely dried find out its actual mass.

Expected mass of *o*-nitrophenol: ________________ g

Expected no. of moles of *o*-nitrophenol: ________________

Actual mass of *o*-nitrophenol: ________________ g

Actual no. of moles of *o*-nitrophenol: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

What is the role of sulfuric acid in this reaction?

The sulfuric acid acts as catalyst and helps to generate nitronium ion as electrophile.

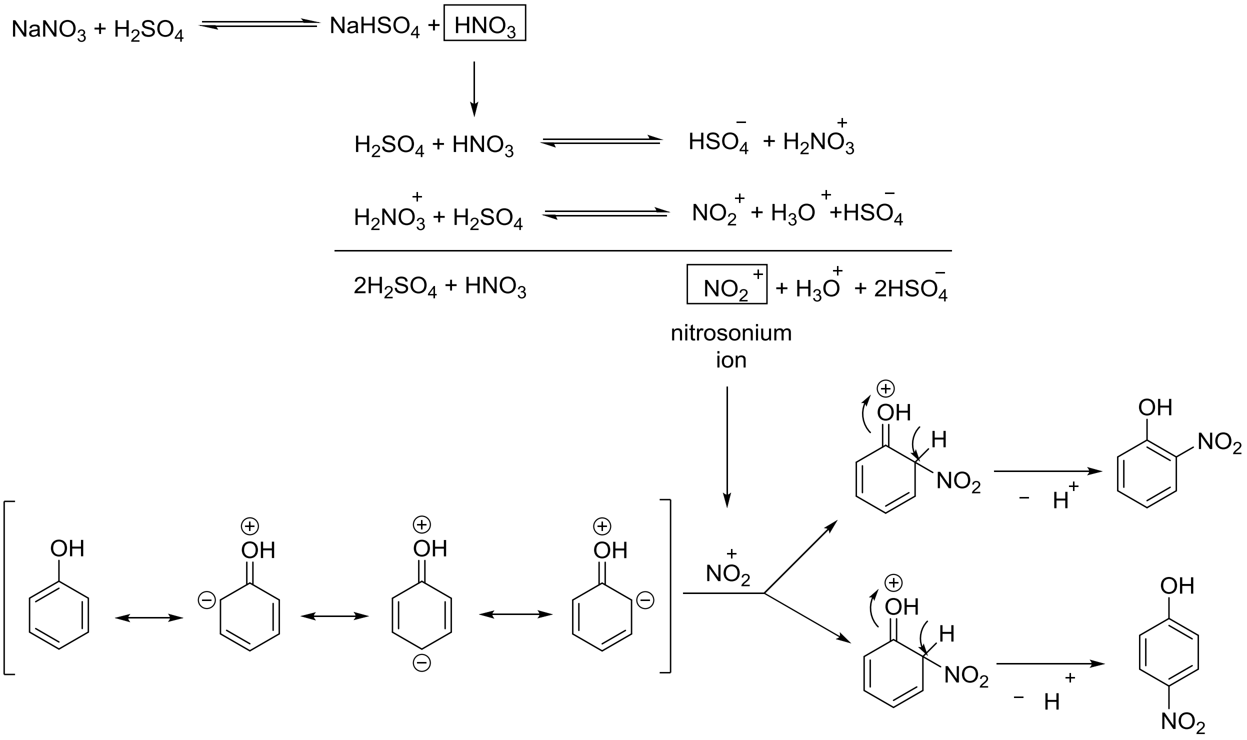
Why benzene undergo electrophilic substitution reaction?

Benzene acts as a saturated system so undergo electrophilic substitution reactions

Why buchner funnel is used for filtration?

Buchner funnel is used for such reaction mixtures which are thick and inseparable by gravity filtration.

What is the reaction mechanism?



$$NaNO_3 + H_2SO_4 \rightleftharpoons NaHSO_4 + \boxed{HNO_3}$$

$$H_2SO_4 + HNO_3 \rightleftharpoons HSO_4^- + H_2NO_3^+$$

$$H_2NO_3^+ + H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + HSO_4^-$$

$$2H_2SO_4 + HNO_3 \quad \boxed{NO_2^+} + H_3O^+ + 2HSO_4^-$$

Nitration of phenol

Safety Cautions:

1. Nitric acid should be handled very cautiously.
2. Con. sulfuric acid should be used with care.
3. One should avoid of breathing phenol.

2.6.2 Experiment 10: Friedel-Crafts Acylation of Benzene

Aim: The main objective of this experiment is to synthesize acetophenone through Friedel-Craft's acylation.

Friede-Craft's acylation

Experimental learning objectives: Students are supposed to learn about

- handling of air/water-sensitive reagents
- controlling of rate of exothermic reactions
- monitoring of reaction progress using thin layer chromatography (TLC)
- purification of products using distillation method

In this experiment, acyl reacts with benzene to produce acetophenone using aluminiuum chloride as catalyst.[9]

Procedure:

Take a round-bottom flask of 100 mL capacity add 0.055 mol of anhydrous aluminum chloride (0.055 mol, 1.1 equiv) and 15 mL of methylene chloride. Further, the flask was equipped with a funnel capped with septum, reflux condenser capped with septum and a septum. This glass-system should be flushed with nitrogen gas, once emitting through the top of condenser and then through the top of the additional funnel. Afterwards, nitrogen should pass through the solution escaping through the condenser again. Use ice-bath to maintain 0 ^{o}C. The solution of acetyl chloride (0.055 mol) in 10 mL of methlyene chloride is added dropwise to additional funnel first and later to aluminum chloride. Subsequently, a solution of aromatic compound (0.50 mol) in 10 mL of methylene chloride is prepared to introduce in the reaction mixture. The addition amount should be controlled so the mixture does not boil wildly. Then the ice-bath is removed and the reaction mixture should attain the room temperature. At room temperature, stir the mixture for 15 minutes more. Then pour this mixture very cautiously into a beaker containing 15 mL hydrochloric acid and 25 g of ice. The mixture should be moved to a separatory funnel to extract organic layer. Methylene chloride should be used to extract aqueous layer. Saturated sodium bicarbonate is used to wash the combine organics and are dried with anhydrous MgSO4. After filtration, the solvent should be evaporated on rotary evaporation. The leftover mixture should be distilled. The unreacted starting material is supposed to distill around 150^{o}C and the products appear over 200^{o} C. Finally, weigh the product.

Expected mass of pure acetophenone: ________________ g

Expected no. of moles of pure acetophenone: ________________

Actual mass of pure acetophenone: ________________ g

Actual no. of moles of pure acetophenone: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

What is meant by electrophiic substitution reactions?

Such organic reactions where one electrophile replaces another electrophile. In general benzene undergoes electrophilic substitution reactions.

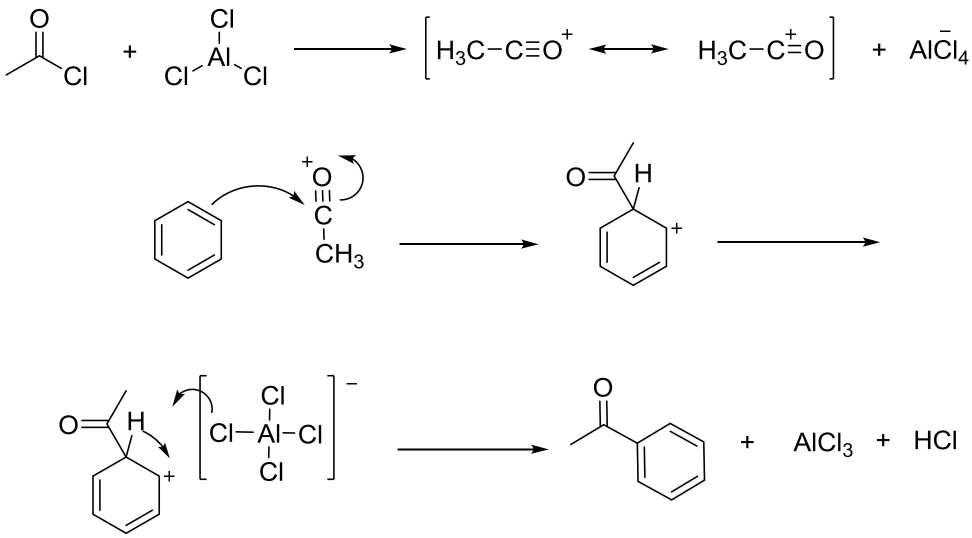
What is meant by the flushing of glassware with argon or nitrogen.

Some synthetic reactions are air/water sensitive. For such reactions, the glassware set-up is flushed with argon or nitrogen to remove air or moisture contents. These reactions are run under inert conditions.

Why organic phase is washed with saturated sodium bicarbonate solution?

The organic layer is washed with saturated sodium bicarbonate solution to remove any remaining acidic impurities.

What is the reaction mechanism?



Friede-Craft's acylation

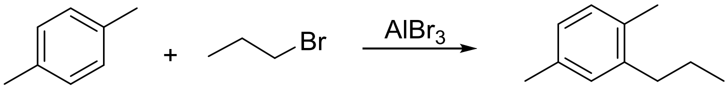
Safety Cautions:

1. Anhydrous aluminum chloride and acyl chloride should be handled very cautously it loses it reactivity in the presence of moisture contents.
2. Hydrochloric acid should be used carefully.

3. You should not wash glassware just before the experiment. The glassware is supposed to be very clean and dry.

2.6.3 Experiment 11: Friedel-Craft's Alkylation

Aim: The main objective of this experiment is to synthesize alkyl substituted benzene through Friedel-Craft's alkytion reaction.[10]



Friede-Craft's acylation

Experimental learning objectives: Students are supposed to learn about

- handling of air/water-sensitive reagents
- controlling of rate of exothermic reactions
- monitoring of reaction progress using thin layer chromatography (TLC)
- purification of products using distillation under reduced pressure

Procedure:

Take a 25 mL round-bottom flask add 0.4 g of anhydrous aluminum chloride. Then flask is fitted with a dropping funnel, a claisen adaptor and a condenser. Later, 6 mL of p-xylene and 4.5 mL of 1-bromopropane is introduced into the dropping funnel. The p-xylene and 1-bromopropane solution is introduced dropwise with great care in about 15 minutes otherwise the reaction becomes rigorous and ice-bath is used cooling purpose. After this addition, stirring should be continued at room temperature for next half an hour.

Afterwards, the reaction mixture is transferred into a 50 mL beaker containing 5 g of ice. The separatory funnel is used to extract organic phase and subsequently washed with brine solution and dried with anhydrous sodium sulfate. Then organic layer is filtered and evaporated. Then crude product is purified with simple distillation and the unreacted 1-bromopropane is collected at its bp 71^{o}C. Then the distillation is performed at reduced pressure and the p-xylene should distill about 30-60 ^{o}C.. The remaining fraction in the distillation flask is the required product. Finally, find out the mass of the product.

Expected mass of pure product: ________________ g

Expected no. of moles of pure: ________________

Actual mass of pure: ________________ g

Actual no. of moles of pure: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

What is meant by electrophilic substitution reactions?

Such organic reactions where one electrophile replaces another electrophile. In general benzene undergoes electrophilic substitution reactions.

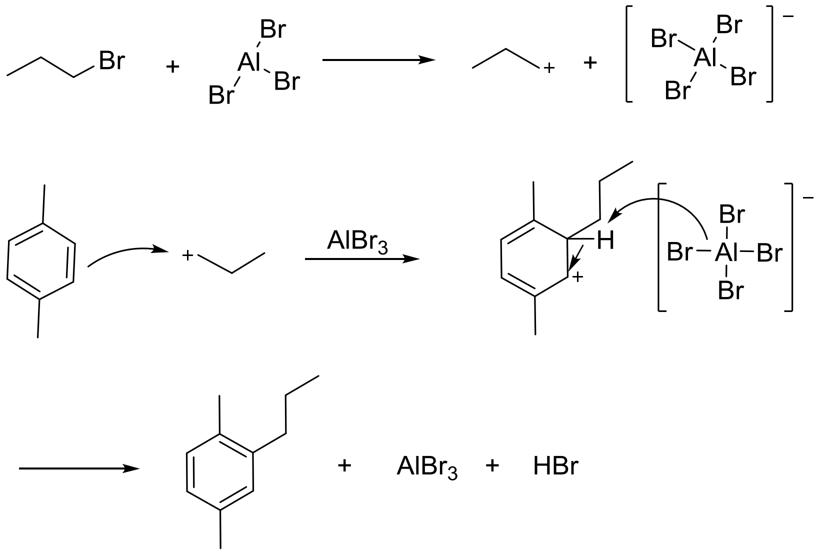
What is meant by the flushing of glassware with argon or nitrogen.

Some synthetic reactions are air/water sensitive. For such reactions, the glassware set-up is flushed with argon or nitrogen to remove air or moisture contents. These reactions are run under inert conditions.

Why organic phase is washed with brine solution?

The organic layer is washed with brine solution to remove any remaining inorganic impurities.

What is the reaction mechanism?



Friede-Craft's acylation

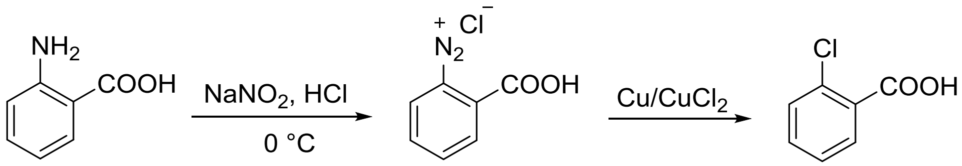
Safety Cautions:

1. Anhydrous aluminum chloride and acyl chloride should be handled very cautiously it loses it reactivity in the presence of moisture contents.
2. The *p*-xylene should be used carefully.
3. You should not wash glassware just before the experiment. The glassware is supposed to be very clean and dry.

2.7 Nucleophilic Substitutions at Benzene

2.7.1 Experiment 12: Synthesis of *o*-Chlorobenzoic Acid

Aim: The objective of this experiment is understanding the nucleophilic substitution reaction at benzene ring. Preparation of aryl halide through the Sandmeyer reaction on the diazonium salt.



Nucleophilic substitution reaction of aromatic compounds

Experimental learning objectives: Students are supposed to learn about

- Handling of nucleophilic reactions at benzene.
- Handling of diazotization reactions
- Understanding of Sandmeyer reactions
- Recrystallization methods for organic solids

Procedure:

Take an Erlenmeyer flask of 100 mL capacity add 4.7 g of CuCl2.2H2O and 20 mL of water, continue stirring to dissolve solid completely. Then introduce 15 mL of con. hydrochloric acid and 3.5 g of Cu-turnings and let it boil for at least 10-15 minutes till the reaction mixture decolorizes. On parallel side, manage to execute the diazotization of anthranilic acid.

Diazotization:

Take second Erlenmeyer flask of the same capacity, put in 10 mL of con. hydrochloric acid, 50 mL of water and introduce 5.5 g of anthranilic acid with continuous heat. After complete dissolution, put the flask in ice-salt bath. Afterwards, a solution of 2.8 g sodium nitrate in 10 mL of water is introduced at slow drop rate to the flask containing mixture of anthranilic acid and the temperature should remain less than zero. Once the addition is over, keep the Erlenmeyer flask in the ice-salt bath.

Sandmeyer reaction:

Take a beaker of 500 mL capacity, introduce into it above prepared CuCl2 solution, maintain the temperature to 0 ^{o}C. Then manage a gradual introduction of diazonium mixture with continuous vigorous stirring for at least 30 minutes. An appearance of foam indicates the emission of nitrogen gas. Later, Then, Büchner funnel is used for filtration followed by washing of the precipitates. At first wash the precipitates three times with 20 cold 8 M nitric acid then with cold water till the filtrate loses colored-impurities to become colorless. The precipitates are dried under vacuum. Perform recrystallization of the crude in 50 mL of water/methanol (9:1) mixture. Again, filter and dry before weighing the mass of pure *o*-chlorobenzoic acid.

Expected mass of pure *o*-chlorobenzoic acid: ________________ g

Expected no. of moles of pure *o*-chlorobenzoic acid: ________________

Actual mass of pure *o*-chlorobenzoic acid: ________________ g

Actual no. of moles of pure *o*-chlorobenzoic acid: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

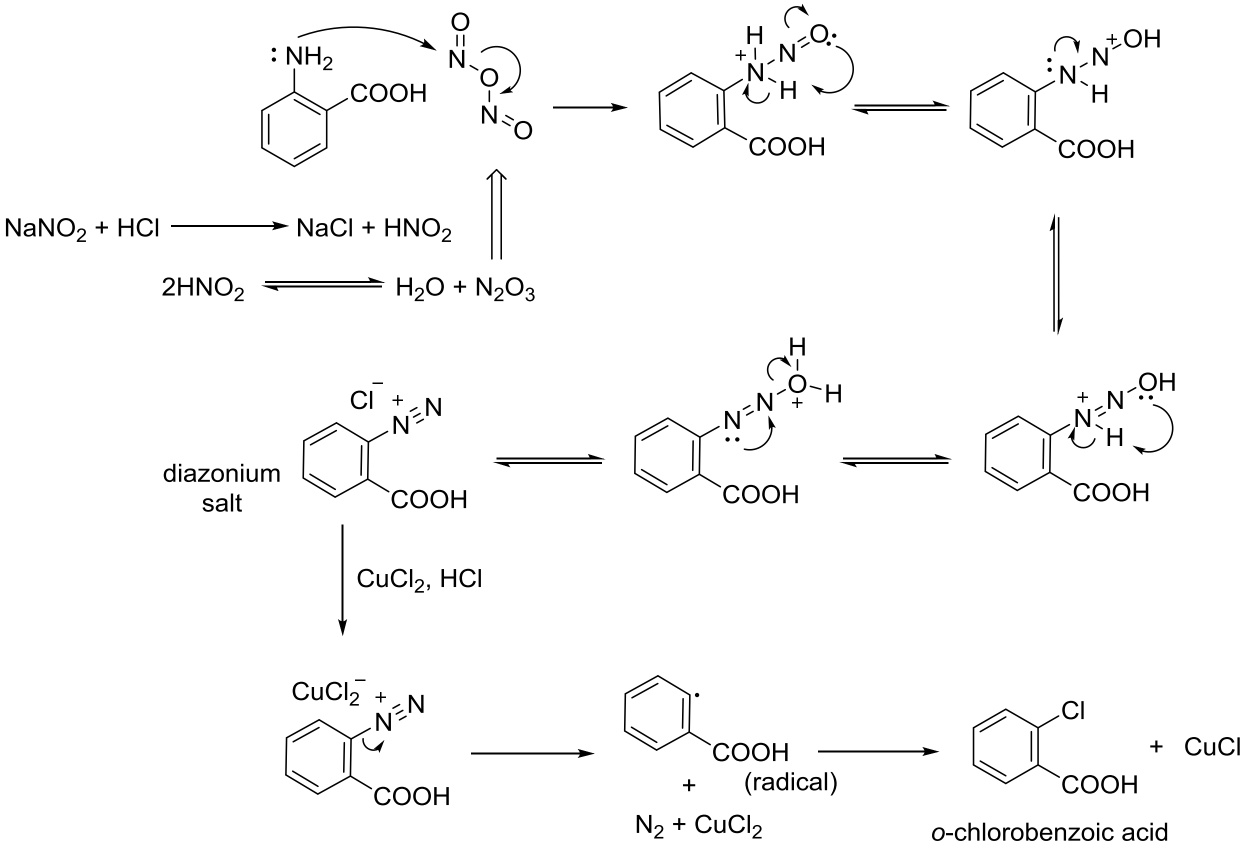
What is meant by nucleophilic substitution reaction?

Such organic reactions where one nucleophile is replaced by another nucleophile.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts.

What is the reaction mechanism?



Nucleophilic substitutions at aromatic ring

Safety Cautions:

1. Nitric acid should be handled very cautiously.

2. Concentrated sulfuric acid should be used with care.

3. Use anthranilic acid with care.

References:

1. Afonso, C. A.; Candeias, N. R.; Simão, D. P.; Trindade, A. F.; Coelho, J. A.; Tan, B.; Franzén, R., *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*. Royal Society of Chemistry: 2016.
2. Gilbert, J. C.; Martin, S. F., *Experimental organic chemistry: a miniscale & microscale approach*. Cengage Learning: 2015.
3. Schore, N. E., *Study Guide and Solutions Manual: For Organic Chemistry*. Macmillan: 2002.
4. Lehman, J. W., *Operational Organic Chemistry: A Problem-Solving Approach to the Laboratory Course*. Prentice Hall: 2009.
5. Wills, M., Advanced Practical Organic Chemistry. *Synthesis* **1995,** *1995* (06), 727-728.
6. Vinod, T.; Craine, L. E., *Lab Manual for Organic Chemistry: A Short Course, 13th*. Cengage Learning: 2011.
7. Leonard, J.; Lygo, B.; Procter, G., *Advanced practical organic chemistry*. CRC press: 2013.
8. Pedersen, S.; Myers, A., *Understanding the Principles of Organic Chemistry: A Laboratory Course, Reprint*. Nelson Education: 2010.
9. Sharp, J. T., *Practical organic chemistry: a student handbook of techniques*. Springer Science & Business Media: 2012.
10. Roberts, R. M., *Modern experimental organic chemistry*. Saunders College Publishing: 1985.

Chapter 3

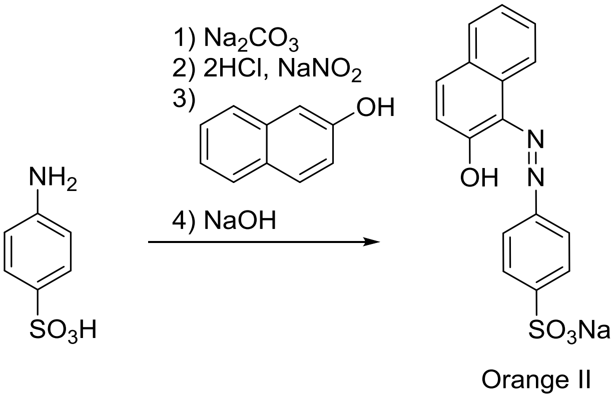
3 Synthetic Dyes

Tahir Farooq

This chapter has been designed to make students apply their theoretical knowledge for purpose-based practical synthesis. Through the learning of this chapter, the students are expected to transform their chemical thinking into product development. This chapter highlights the utility of basic reaction concepts for the construction of complex dye molecules.

3.1 Experiment 1: Synthesis of Orange II Dyes from Sulfanilic Acid and 2-Naphthol

Aim: The main objective of this lab activity to synthesize Orange II, an azo dye, using sulfanilic acid and 2-naphthol.[1]



Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines
- Azo-dye synthesis under basic conditions
- Suction filtration

Procedure:

Formation of the diazonium salt

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of sulfanilic acid. This mixture could be heated to achieve complete dissolution of sulfanilic acid. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 250 mL capacity and add 5mL of cold 3M NaOH solution to dissolve 0.9g of 2-naphthol. Afterwards, the diazotized sulfanilic acid suspension is added into the 2-naphthol solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time. Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. The transfer the filtrate to a beaker and add 12 mL water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Let the filtrate cool down to 80^{o} C and add 20-25 mL of ethanol to pure crystals of the product. The cooled mixture is foltered and then dry. The product crystallizes as a dihydrate complex (i.e. C16H11N2O4SNa. 2H2O) so calculate the yield accordingly. On heating at 120^{o}C, water of hydration gets removed and the product becomes fiery red in appearance.

Expected mass of pure Orange II: _______________ g

Expected no. of moles of pure Orange II: _______________

Actual mass of pure Orange II: _______________ g

Actual no. of moles of pure Orange II: _______________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment sulfanilic acid undergo diazotization.

Why diazonium salts are used as suspensions?

Dry diazonium salts are explosive. So, they are used in suspension form.

How sulfanilic acid exists in solution?

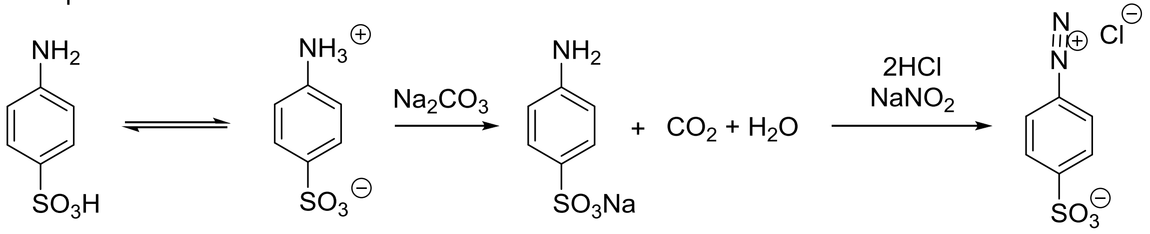
In aqueous solution, sulfanilic acid found to exist in the form of zwitter ion.

What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

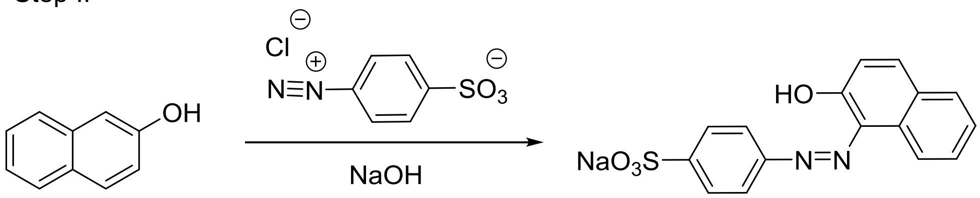
What is the reaction mechanism?

Step I



Diazotization of sulfanilic acid

Step II



Coupling of diazonium salt with 2-naphthol

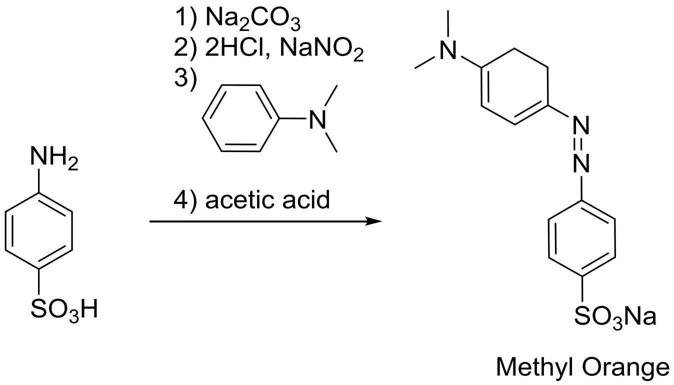
Safety Cautions:

1. Hydrochloric acid should be handled very cautiously.
2. Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.

3. You are supposed to neutralize the acid washings with alkali or base before disposing them in the sink.

3.2 Experiment 2: Synthesis of Methyl Orange from Sulfanilic Acid and *N,N*-Dimethylaniline

Aim: The main objective of this lab activity to synthesize Methyl Orange, an azo dye using sulfanilic acid and *N,N*-dimethylaniline.[2]



Synthesis of Methyl Orange

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines

- Azo-dye synthesis under acidic conditions
- Suction filtration

Procedure:

Formation of the diazonium salt

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of sulfanilic acid. This mixture could be heated to achieve complete dissolution of sulfanilic acid. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 50 mL capacity and add 0.6 mL of acetic acid to dissolve 0.8 mL of *N*,*N*-dimethylaniline. Afterwards, the diazotized sulfanilic acid suspension is added into the 2-naphthol solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time. Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. The transfer the filtrate to a beaker and add 12 mL water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Cool and dry the filtrate. Recrystallize the product in water.

Expected mass of pure Methyl Orange: ________________ g

Expected no. of moles of Methyl Orange: ________________

Actual mass of pure Methyl orange: ________________ g

Actual no. of moles of pure Methyl orange: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment sulfanilic acid undergo diazotization.

Why diazonium salts are used as suspensions?

Dry diazonium salts are explosive. So, they are used in suspension form.

How sulfanilic acid exists in solution?

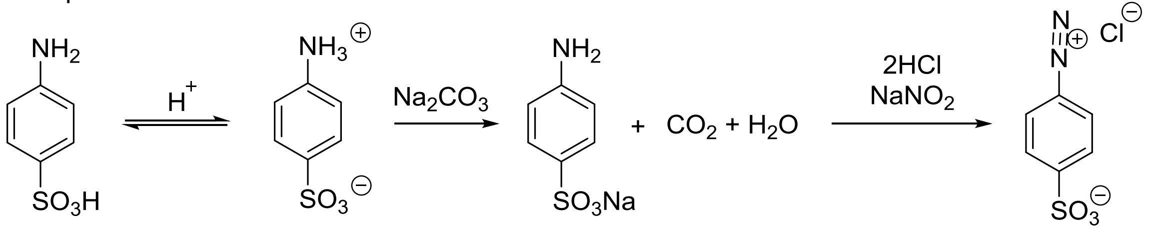
In aqueous solution, sulfanilic acid found to exist in the form of zwitter ion.

What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

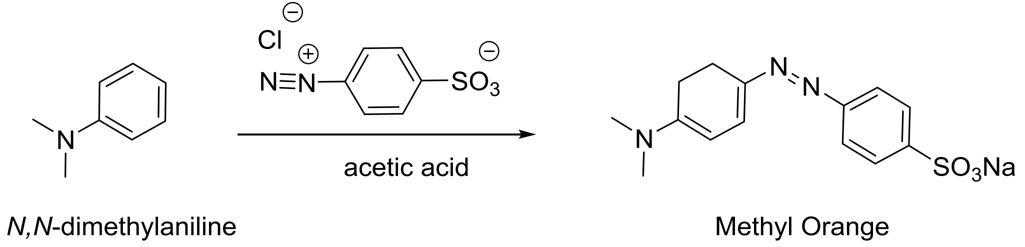
What is the reaction mechanism?

Step I



Diazotization of sulfanilic acid

Step II



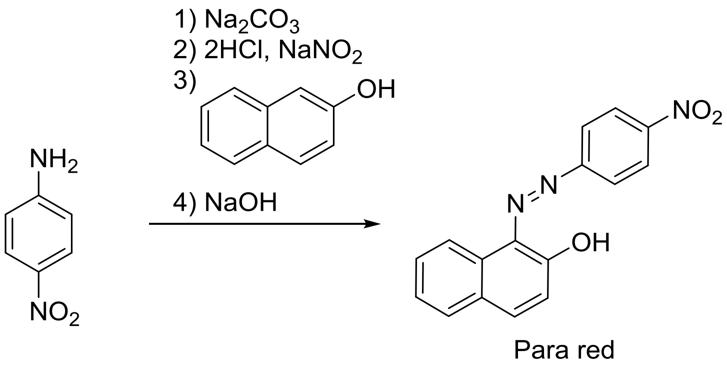
Coupling of diazonium salt with *N,N*-dimethylaniline

Safety Cautions:

1- One should be careful as *N,N*-dimethylaniline is an irritant.
2- Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.
3- Sodium nitrite is an oxidizing agent and could be very toxic.

3.3 Experiment 3: Synthesis of Para Red Dye from *para*-Nitroaniline and 2-Naphthol

Aim: The main objective of this practical activity is to synthesize Para Red dye from para-Nitroaniline and 2-naphthol.[3]



Synthesis of para red from *para*-nitoaniline and 2-naphthol

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines
- Azo-dye synthesis under basic conditions
- Suction filtration

Procedure:

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of p-nitroaniline. This mixture could be heated to achieve complete dissolution of p-nitroaniline. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 250 mL capacity and add 5mL of cold 3M NaOH solution to dissolve 0.9g of 2-naphthol. Afterwards, the diazotized p-nitroaniline suspension is added into the 2-naphthol solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time.

Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. The transfer the filtrate to a beaker and add 12 mL water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Let the filtrate cool down to 80^o C and add 20-25 mL of ethanol to pure crystals of the product. The cooled mixture is foltered and then dry. On heating at 120^{o}C, water of hydration gets removed and the product becomes fiery red in appearance.

Expected mass of para red dye: ________________ g

Expected no. of moles of para der dye: ________________

Actual mass of para red dye: ________________ g

Actual no. of moles of para red dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment para-nitroaniline undergo diazotization.

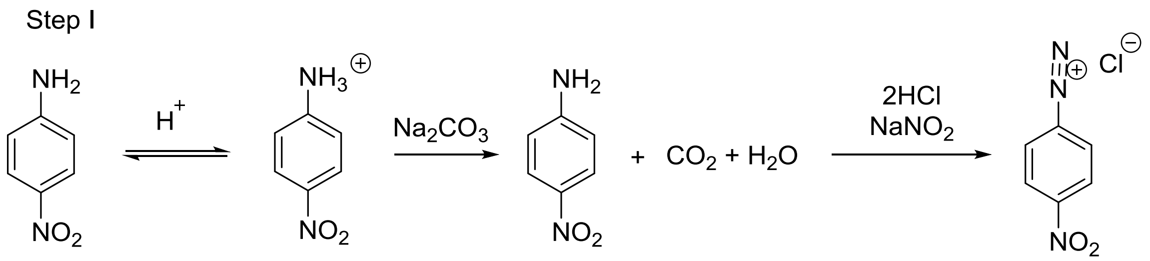
Why diazonium salts are used as suspensions?

Dry diazonium salts are explosive. So, they are used in suspension form.

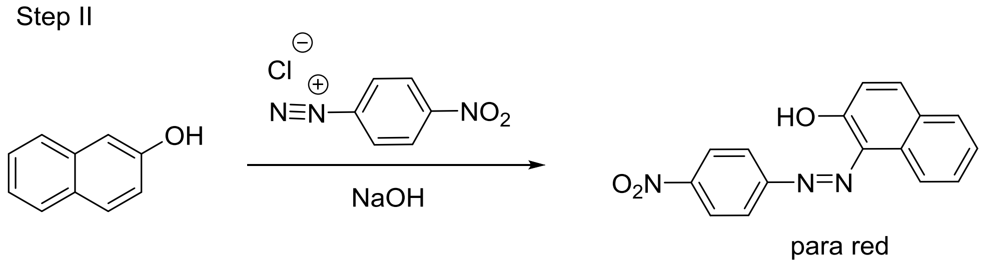
What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

What is the reaction mechanism?



Diazotization of *para*-nitoaniline



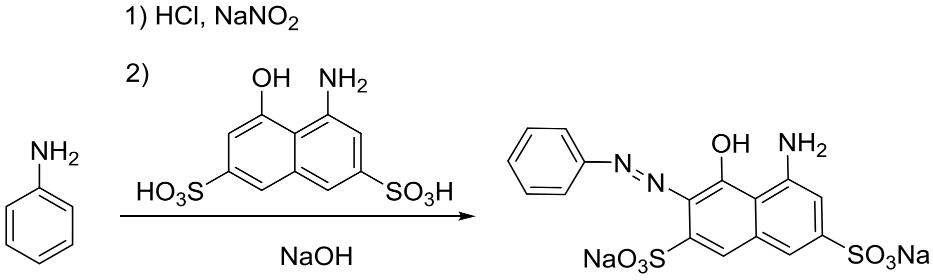
Coupling of diazonium salt with 2-naphthol

Safety Cautions:

1- Para-nitroaniline is very toxic so should be handled with extreme care
2- 2-naphthol is categorized as carcinogen.
3- Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.
4- Para red is also a suspected carcinogen so needs extra working care.
5- Sodium nitrite is an oxidizing agent and could be very toxic.

3.4 Experiment 4: Synthesis of Azo-Dyes Using H-acid and Aniline

Aim: The main objective of this practical activity is to synthesize azo dye using H-acid as coupling agent in basic medium.[4]



Synthesis of a dye from H-acid under basic conditions

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines
- Azo-dye synthesis under basic conditions
- Suction filtration

Procedure:

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of aniline. This mixture could be heated to achieve complete dissolution of p-nitroaniline. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 250 mL capacity and add 5mL of cold 3M NaOH solution to dissolve 0.9g of H-acid. Afterwards, the diazotized p-nitroaniline suspension is added into the 2-naphthol solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time. Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. Then transfer the filtrate to a beaker and add 12 mL of water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Let the filtrate cool down to 80^{o} C and add 20-25 mL of ethanol to pure crystals of the product. The cooled mixture is filtered and then dried. On heating at 120^{o}C, water of hydration gets removed and the product becomes fiery red in appearance.

Expected mass of dye: ________________ g

Expected no. of moles of dye: ________________

Actual mass of dye: ________________ g

Actual no. of moles of dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment aniline undergoes diazotization.

Why diazonium salts are used as suspensions?

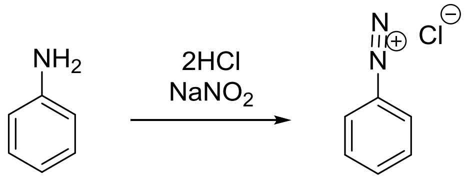
Dry diazonium salts are explosive. So, they are used in suspension form.

What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

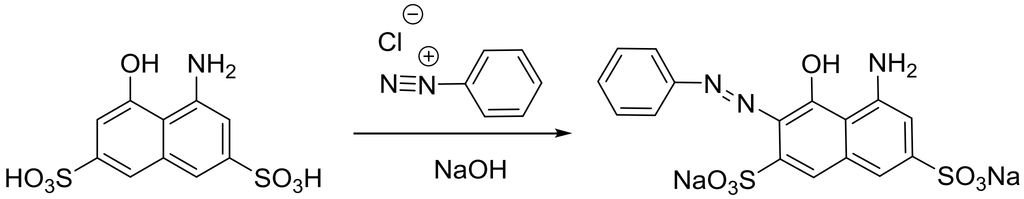
What is the reaction mechanism?

Step I



Diazotization of aniline

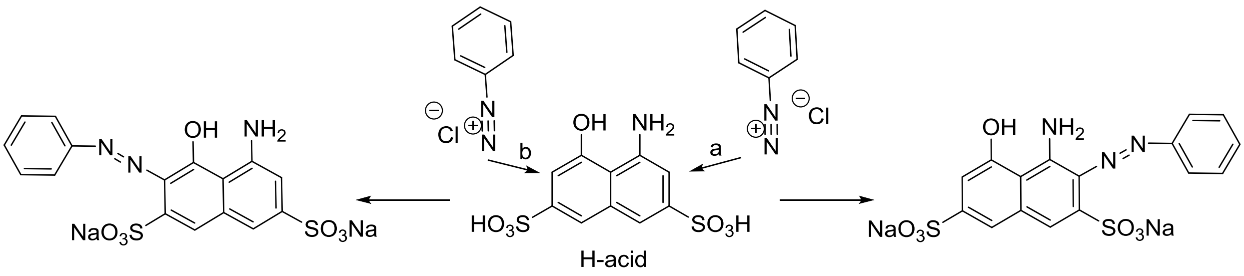
Step II



Coupling of diazonium salt with H-acid under basic conditions

How the coupling occurs on H-acid in acidic medium?

Under acidic conditions, the diazonium ion couples at ortho to amine and while in basic conditions the coupling occurs ortho to hydroxyl group.



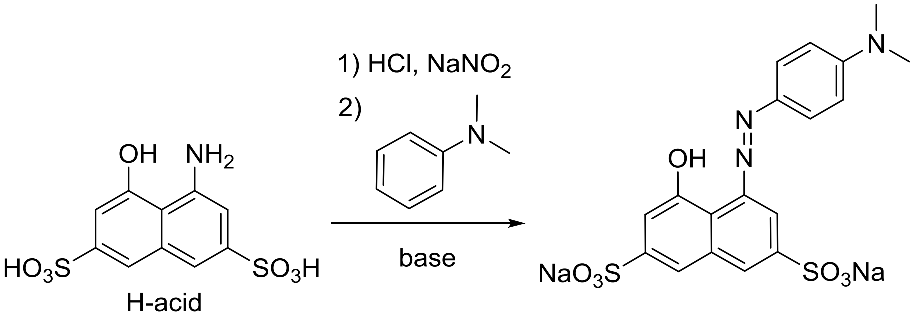
a) coupling under acidic conditions
b) coupling under basic conditions

Safety Cautions:

1- Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.
2- Aniline is also a suspected carcinogen so needs extra working care.
3- Sodium nitrite is an oxidizing agent and could be very toxic.

3.5 Experiment 5: Synthesis of Azo-Dyes Using H-acid and *N,N*-Dimethylaniline

Aim: The main objective of this practical activity is to synthesize an azo dye using diazonium salt of H-acid and *N,N*-dimethylaniline as coupling agent in basic medium.[5]



Synthesis of a dye from H-acid under acidic conditions

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines
- Azo-dye synthesis under basic conditions
- Suction filtration

Procedure:

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of H-acid. This mixture could be heated to achieve complete dissolution of H-acid. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 250 mL capacity and add 5mL of cold 3M NaOH solution to dissolve 0.9g of *N,N*-dimethylaniline. Afterwards, the diazotized H-acid suspension is added into the 2-naphthol solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time. Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. Then transfer the filtrate to a beaker and add 12 mL of water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Let the filtrate cool down to 80^o C and add 20-25 mL of ethanol to pure crystals of the product. The cooled mixture is filtered and then dried. On heating at 120^oC, water of hydration gets removed and the product becomes dry.

Expected mass of dye: ________________ g

Expected no. of moles of dye: ________________

Actual mass of dye: ________________ g

Actual no. of moles of dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment H-acid undergoes diazotization.

Why diazonium salts are used as suspensions?

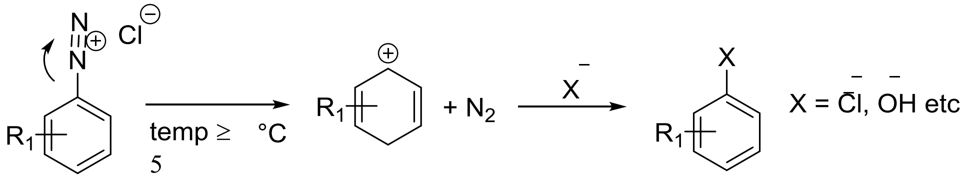
Dry diazonium salts are explosive. So, they are used in suspension form.

What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

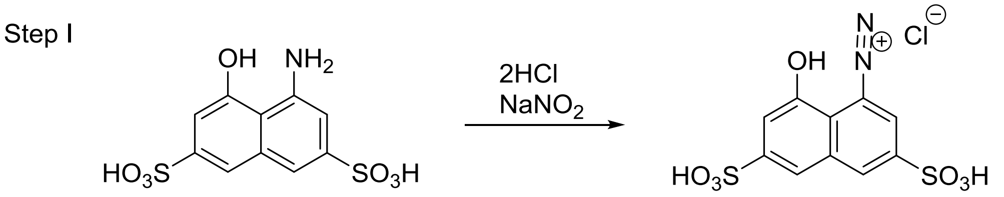
Why temperature should be kept to 0 C for diazotization step.

The diazonium salts are unstable at higher temperature. If the temperature raises over 5 C, the diazonium ion could lose the nitrogen and the remaining aromatic ring could be attacked by nucleophile to generate by products.

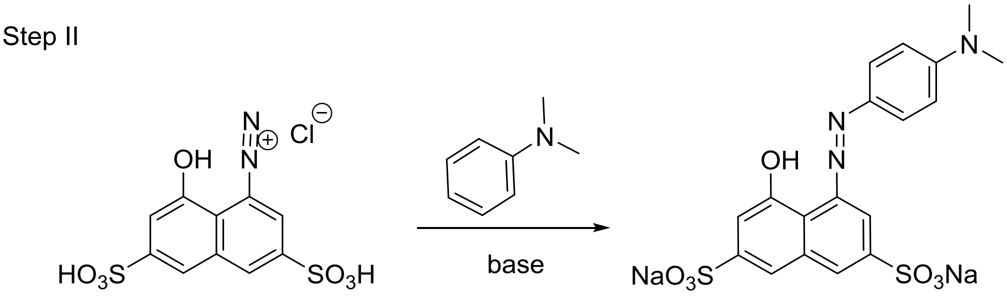


Destable diazonium salts

What is the reaction mechanism?



Diazotization of H-acid



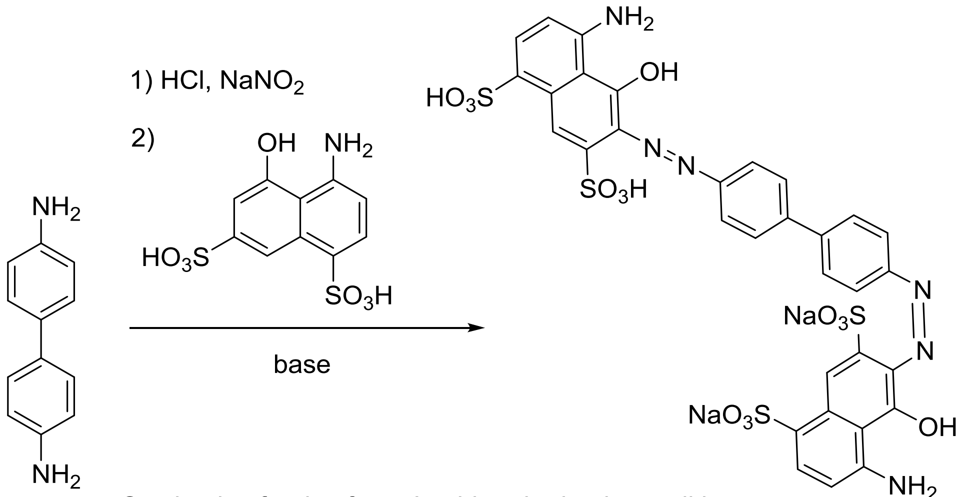
Coupling of diazonium salt with H-acid

Safety Cautions:

1- Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.
2- N,N-dimethylaniline is an irritant with carcinogenic effects.
3- Sodium nitrite is an oxidizing agent and could be very toxic.

3.6 Experiment 6: Synthesis of Azo-Dyes from J-acid and Benzidine

Aim: The main objective of this practical activity is to synthesize azo dye from benzidine and J-acid.[6]



Synthesis of a dye from J-acid under basic conditions

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines
- Azo-dye synthesis under basic conditions

Procedure:

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of benzidine. This mixture could be heated to achieve complete dissolution of benzidine. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 250 mL capacity and add 5mL of cold 3M NaOH solution to dissolve 0.9g of J-acid. Afterwards, the diazotized benzidine suspension is added into the J-acid solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time. Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. Then transfer the filtrate to a beaker and add 12 mL of water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Let the filtrate cool down to 80^{o} C and add 20-25 mL of ethanol to pure crystals of the product. The cooled mixture is filtered and then dried. On heating at 120^{o}C, water of hydration gets removed and the product becomes dry.

Expected mass of dye: ________________ g

Expected no. of moles of dye: ________________

Actual mass of dye: ________________ g

Actual no. of moles of dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment J-acid undergoes diazotization.

Why diazonium salts are used as suspensions?

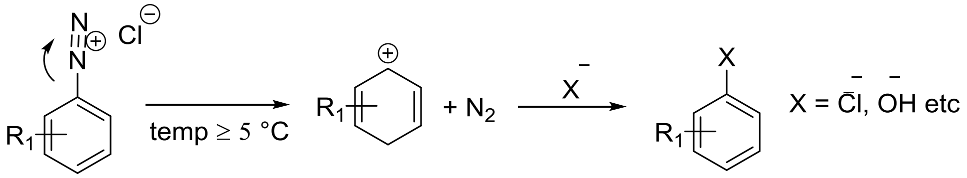
Dry diazonium salts are explosive. So, they are used in suspension form.

What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

Why temperature should be kept to 0 ˚C for diazotization step.

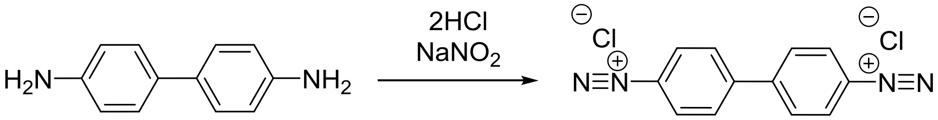
The diazonium salts are unstable at higher temperature. If the temperature raises over 5 ˚C, the diazonium ion could lose the nitrogen and the remaining aromatic ring could be attacked by nucleophile to generate by products.



Destable diazonium salts

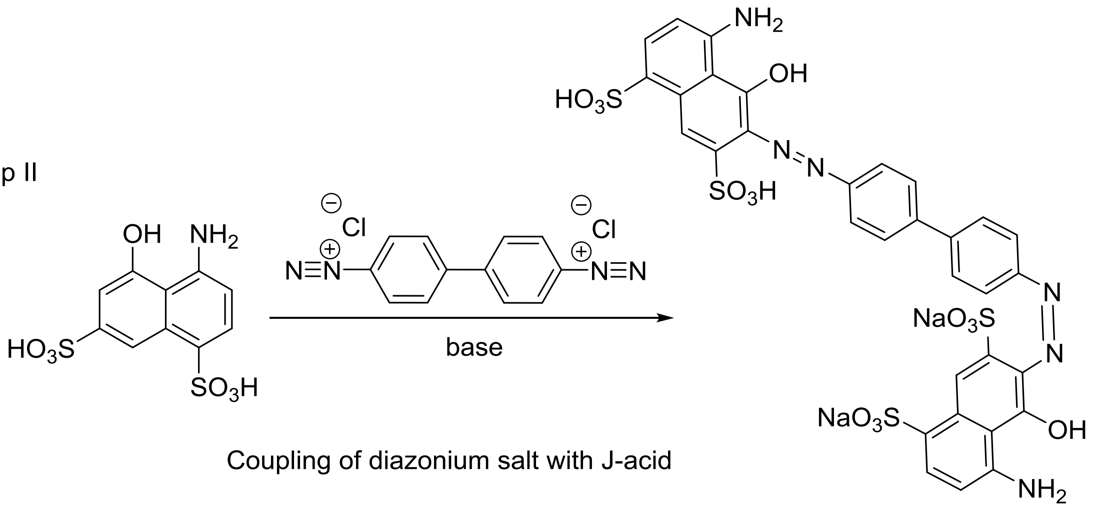
What is the reaction mechanism?

Step I



Diazotization of benzidine

Step II



Coupling of diazonium salt with J-acid

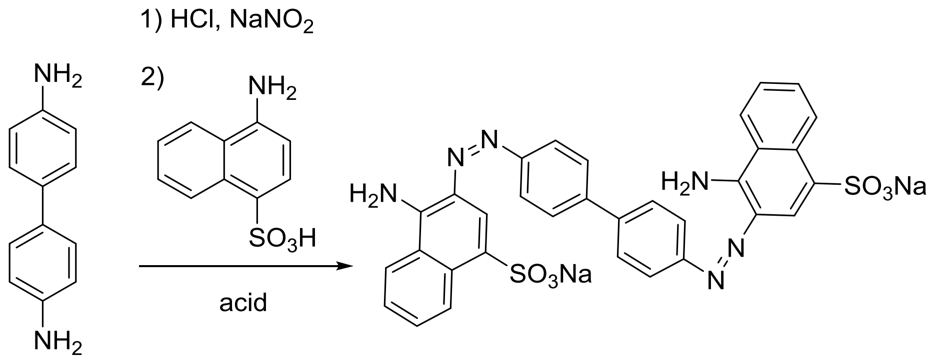
Safety Cautions:

1- Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.

2- Benzidine is also a potential carcinogen so needs extra working care.
3- Sodium nitrite is an oxidizing agent and could be very toxic.

3.7 Experiment 7: Synthesis of Congo Red as Direct dye

Aim: The main objective of this practical activity is to synthesize a direct dye called congo red from benzidine and naphthionic acid.[7]



Synthesis of congo red, a direct dye

Experimental learning objectives: Students are supposed to learn about

- Electrophilic substitution reactions of aromatic compounds
- Generation of electrophiles
- Diazotization of aromatic amines
- Azo-dye synthesis under acidic conditions
- Suction filtration

Procedure:

Take an Erlenmeyer flask of 50 mL capacity, add 12 mL of 2.5% Na2CO3 and then introduce 1.2g of benzidine. This mixture could be heated to achieve complete dissolution of benzidine. Tap water is used for cooling purpose. Subsequently, 0.47g of sodium nitrite is added with continuous vigorous stirring. Then put this flask into ice containing beaker. At around 0 ˚C, add dropwise 1.3 mL of concentrated hydrochloric acid with continuous stirring. Stir the mixture for about 5 minutes. The diazo product is not isolated and is further used as a suspension. Take a beaker of 250 mL capacity and add 5mL of cold 3M HCl solution to dissolve 0.9g of naphthionic acid. Afterwards, the diazotized benzidine suspension is added into the naphthionic acid solution with continuous stirring for next 10 minutes. Then introduce 2.5g of NaCl to decrease the solubility of dye-product. Heat the dye mixture for 10-15 minutes. Then cool it to room temperature and put it in ice jacket again but stirring should continue all the time. Then use Buchner funnel to filter the dye and use sodium chloride solution for rinsing the beaker. The product is supposed to dry slowly and contains at least 20% NaCl. Then transfer the filtrate to a beaker and add 12 mL of water and let it boil till the water evaporates. Perform suction filtration using Buchner funnel. Let the filtrate cool down to 80^{o} C and add 20-25 mL of ethanol to pure crystals of the product. The cooled mixture is filtered and then dried. On heating at 120^{o}C, water of hydration gets removed and the product becomes dry.

Expected mass of dye: ________________ g

Expected no. of moles of dye: ________________

Actual mass of dye: ________________ g

Actual no. of moles of dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Explain diazotization reactions.

Such reactions in which primary amines are converted into diazonium salts. In fact, primary amines undergo oxidation and produce diazonium electrophile. In this experiment benzidine undergoes diazotization.

Why diazonium salts are used as suspensions?

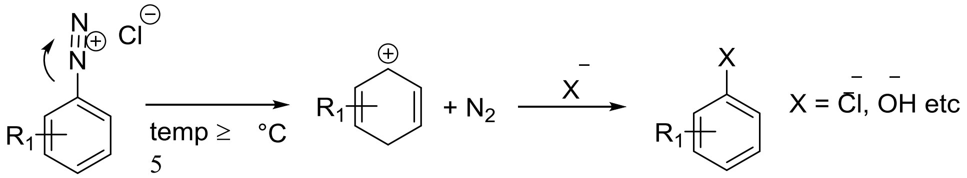
Dry diazonium salts are explosive. So, they are used in suspension form.

What is meant by suction filtration?

The filtration with the help of suction pump is called suction filtration.

Why temperature should be kept to 0 °C for diazotization step.

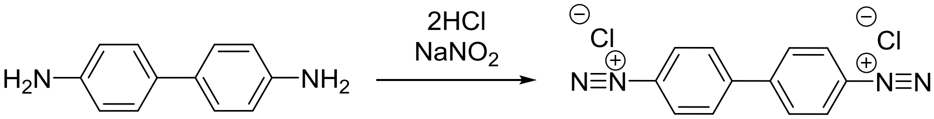
The diazonium salts are unstable at higher temperature. If the temperature raises over 5 °C, the diazonium ion could lose the nitrogen and the remaining aromatic ring could be attacked by nucleophile to generate by products.



Destable diazonium salts

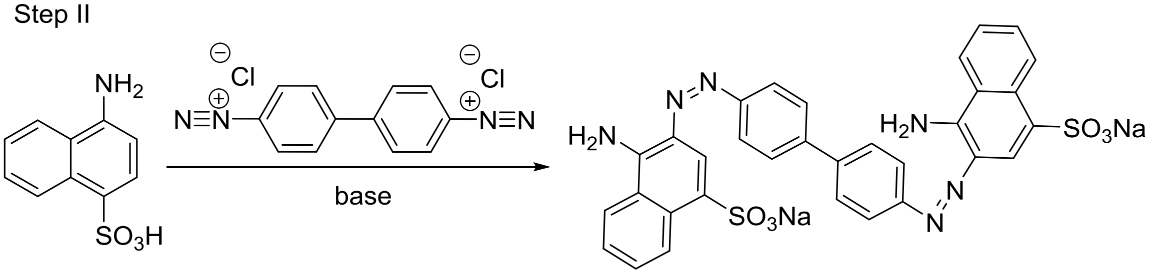
What is the reaction mechanism?

Step I



Diazotization of benzidine

Step II



Coupling of diazonium salt with naphthionic acid

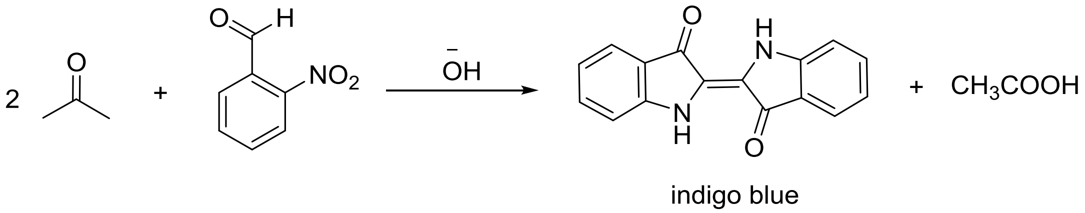
Safety Cautions:

1- Diazonium salts are very reactive so avoid skin contact. They are also explosive when get dry.
2- Benzidine is also a potential carcinogen so needs extra working care.

3- Sodium nitrite is an oxidizing agent and could be very toxic.

3.8 Experiment 8: Synthesis of Indigo Vat Dye

Aim: The main objective of this practical activity is to synthesize naturally occurring indigo as a vat dye.[8]



Synthesis of indigo vat dye

Experimental learning objectives: Students are supposed to learn about

- Synthesis of naturally occurring vat dyes
- Reaction at reflux
- Insoluble dyes
- Reduction and oxidation of indigo dyes
- Use of reducing agents

Procedure:

In round-bottom flask of 25 mL capacity add 6 mL of acetone and then introduce 0.75 g of *o*-nitrobenzaldehyde. Reflux the mixture after attaching a reflux condenser on the flask.

Make 5 mL of 12 M sodium hydroxide solution and in portions through condenser and the reflux should continue for next 30 minutes. Afterwards, cool the flask and add 15 mL of water. Put the reaction mixture in an ice bath next for 10 minutes. Filter the solid using Buchner funnel, use water and a little of acetone to wash dark bluish precipitate and let it air dry. Finally, weigh out the dried product.

Expected mass of pure indigo: ________________ g

Expected no. of moles of pure indigo: ________________

Actual mass of pure indogo: ________________ g

Actual no. of moles of pure indigo: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

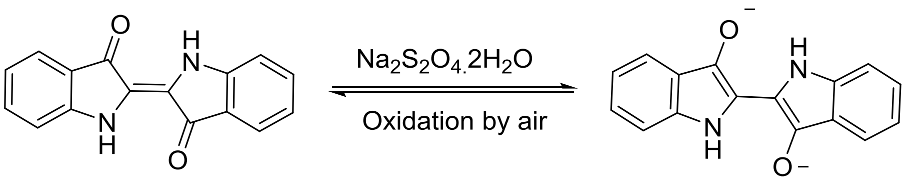
What is the natural source of indigo dye?

Naturally, indigo dye is extracted from the plant Indigoferae sumatrana.

Is indigo dye applied directly?

Indigo is water insoluble and could not be applied as dye. Using sodium dithionite first it is reduced to a water soluble ionic form called leucoindigo. On reduction, the indigo becomes colourless or pale yellow on reduction. The water-soluble form is referred to as a vat dye.

In the vat, after the dye got attach on the surface of fabric, the fabric is washed and dried in air. Then oxygen manages to oxidize slowly the leucoindigo to its original insoluble molecular form. Consequently, the fabric changes its color from yellow to green first and then to blue with passage of time.

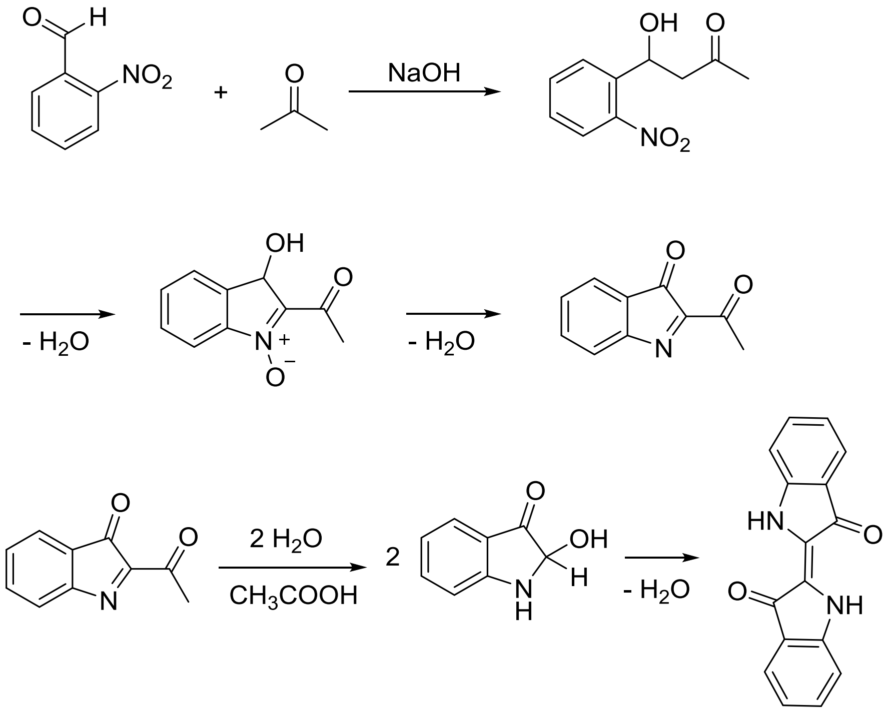


indigo blue

pale yellow

Indigo dye as vat dye

What is the reaction mechanism for the synthesis of indigo dye?



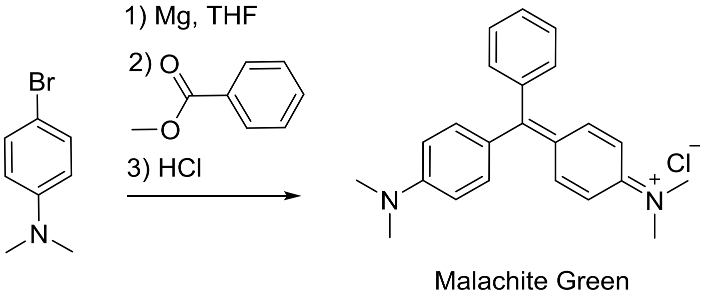
Synthesis of indigo vat dye

Safety Cautions:

1- You are supposed to handle the 2-nitrobenzaldehyde with extreme care because of its hazardous nature. It could act as an irritant with moderate toxicity.
2- Acetone should be used cautiously as it is highly flammable, irritant and hazardous.
3- One should use sodium dithionite cautiously – hazardous. Moderate toxicity, slightly corrosive, irritant.[9]

3.9 Experiment 9: Synthesize Malachite Green as Cationic Dyes

Aim: The main objective of this experimental activity is to synthesize cationic dye using Grignard's reagent and 4-bromo-*N*,*N*-dimethylaniline.[10]



Synthesis of cationic dye Malachite green

Experimental learning objectives: Students are supposed to learn about

- handling of air/water-sensitive Grignard's reagents
- synthesis of cationic dyes
- monitoring of reaction progress using thin layer chromatography (TLC)
- controlling of the exothermic reactions.

Procedure:

Making the Grignard reagent

In a beaker of 50 mL capacity, take 2.5 g of 4-bromo-*N*,*N*-dimethylaniline, 0.4 g of Mg tunings in 30 mL dry THF and 2-3 small crystals of iodine. This solution should be covered with parafilm. A drying tubing containing anh. $CaCl_2$ should be attached to the condenser. A sort of extra dryness is required for Grignard's reagent as they lose reactivity after contact with moisture.

Take a flask of 50 mL capacity and attach to it condenser equipped with drying tube. Remove the condenser for a while and add the above mixture into the flask. Add magnesium tunings to the reaction mixture. Using water bath, maintain the temperature of the reaction mixture around 75

˚C. Let the mixture reflux for next 30 minutes at least. With the passage of time, the reaction mixture changes its colour from dark blackish to a typical grey, the usual appearance of Grignard's reagents. Afterwards, the flask is supposed to cool to room temperature by keeping it under tap water.

In a small vial, take 0.2 g of methyl benzoate and then introduce 1 mL of THF in it. Then add this solution to Grignard's reagent with the help of Pasteur pipette. The addition should be dropwise with continuous swirling of the flask. After the completion of addition, put the mixture to reflux for 5 minutes. Then as the reaction mixture cools to room temperature, pour it into a beaker of 100mL capacity. With continuous stirring, add 5mL of 5% HCl solution.

Expected mass of malachite green dye: ________________ g

Expected no. of moles of malachite green dye: ________________

Actual mass of malachite green dye: ________________ g

Actual no. of moles of malachite green dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Why malachite green dye is called cationic dye?

If you look at the structure of malachite green, the presence of positive charge at nitrogen make it a cationic dye.

Why anhydrous $CaCl_2$ is used in dry tubing?

The anhydrous $CaCl_2$ is used to remove moisture contents.

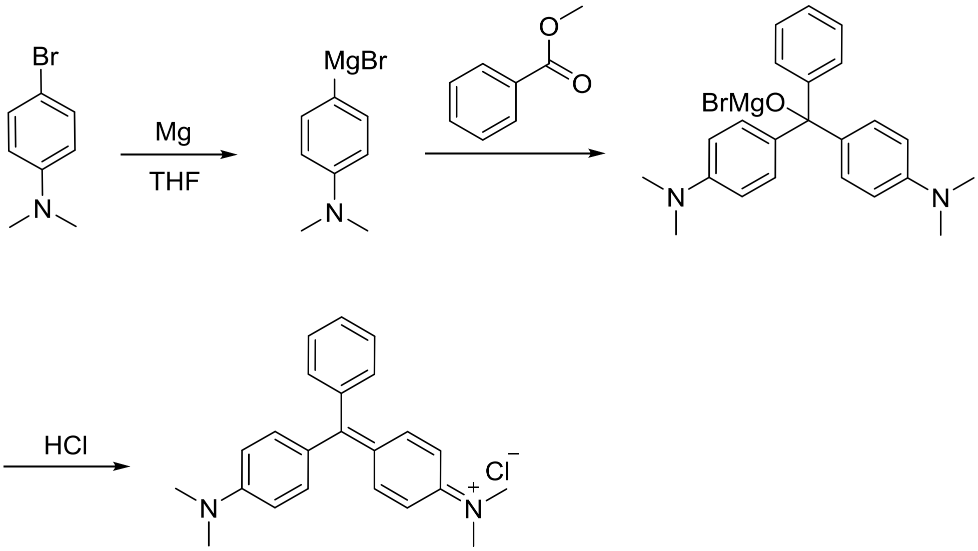
Why bubbling is observed when 5% HCl is added in the mixture?

When hydrochloric acid reacts with remaining magnesium tunings, bubbling is observed due to the emission of hydrogen gas.

Why the reaction is run under extremely dry conditions?

The Grignard's reagent is moisture sensitive. To avoid its inactivity the reaction is supposed to run under extremely dry conditions.

What is the reaction mechanism?



Malachite Green

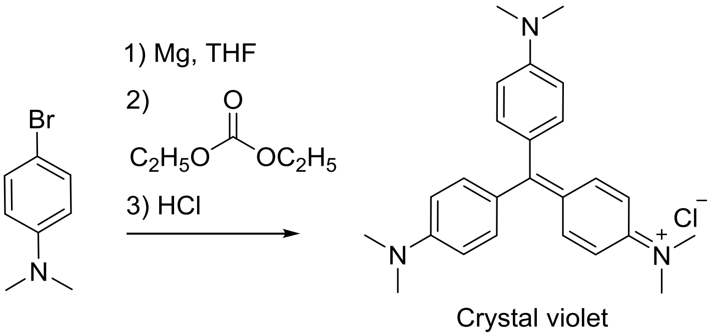
Synthesis of cationic dye Malachite green

Safety Cautions:

1- Magnesium reacts with moisture very violently, so one should be very careful.
2- The 4-Bromo-*N*,*N*-dimethylaniline is an irritant so keep it away from eyes and skin etc.
3- The dye could itself stain clothing and skin.
4- One should use THF carefully due to its hazardous nature.

3.10 Experiment 10: Synthesis of Cationic Dye Crystal Violet

Aim: The main objective of this practical activity is to synthesize cationic dye crystal violet using Grignard's reagent and diethyl carbonate.



Synthesis of cationic dye Crystal violet

Experimental learning objectives: Students are supposed to learn about

- handling of air/water-sensitive Grignard's reagents
- synthesis of cationic dyes
- monitoring of reaction progress using thin layer chromatography (TLC)
- controlling of the exothermic reactions.

Procedure:

Making the Grignard reagent

In a beaker of 50 mL capacity, take 2.5 g of 4-bromo-*N*,*N*-dimethylaniline, 0.4 g of Mg tunings in 30 mL dry THF and 2-3 small crystals of iodine. This solution should be covered with parafilm. A drying tubing containing anh. $CaCl_2$ should be attached to the condenser. A sort of extra dryness is required for Grignard's reagent as they lose reactivity after contact with moisture.

Take a flask of 50 mL capacity and attach to it condenser equipped with drying tube. Remove the condenser for a while and add the above mixture into the flask. Add magnesium tunings to the reaction mixture. Using water bath, maintain the temperature of the reaction mixture around 75 ˚C. Let the mixture reflux for next 30 minutes at least. With the passage of time, the reaction mixture changes its colour from dark blackish to a typical grey, the usual appearance of Grignard's reagents. Afterwards, the flask is supposed to cool to room temperature by keeping it under tap water.

In a small vial, take 0.3 g of diethyl carbonate and then introduce 1 mL of THF in it. Then add this solution to Grignard's reagent with the help of Pasteur pipette. The addition should be dropwise with continuous swirling of the flask. After the completion of addition, put the mixture to reflux for 5 minutes. Then as the reaction mixture cools to room temperature, pour it into a beaker of 100mL capacity. With continuous stirring, add 5mL of 5% HCl solution.

Expected mass of crystal violet dye: ________________ g

Expected no. of moles of crystal violet dye: ________________

Actual mass of crystal violet dye: ________________ g

Actual no. of moles of crystal violet dye: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Why crystal violet dye is called cationic dye?

If you look at the structure of crystal violet, the presence of positive charge at nitrogen make it a cationic dye.

Why anhydrous $CaCl_2$ is used in dry tubing?

The anhydrous CaCl2 is used to remove moisture contents.

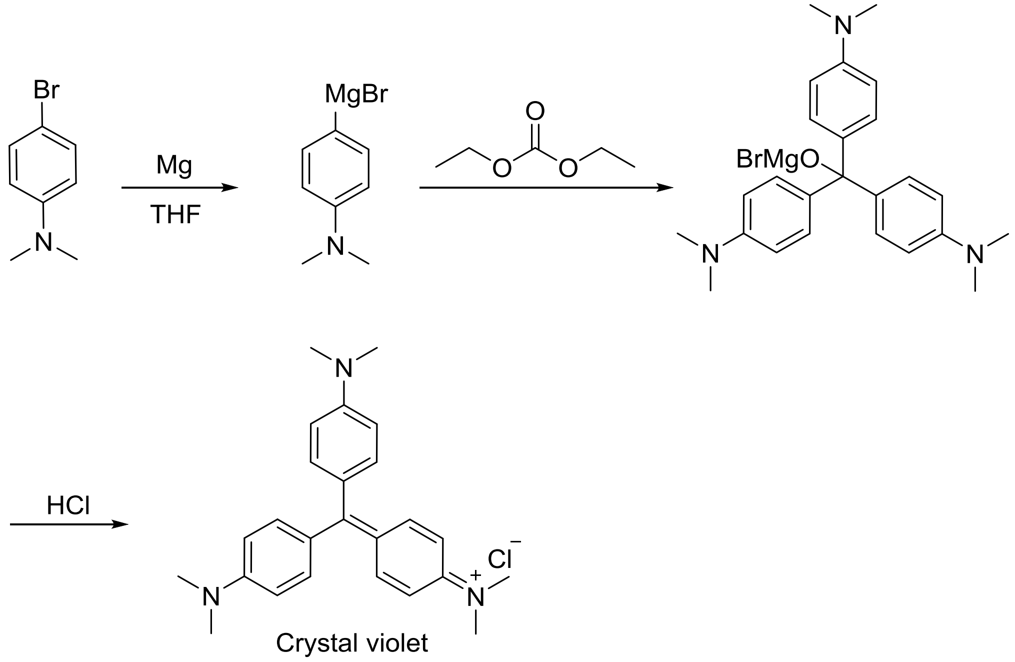
Why bubbling is observed when 5% HCl is added in the mixture?

When hydrochloric acid reacts with remaining magnesium tunings, bubbling is observed due to the emission of hydrogen gas.

Why the reaction is run under extremely dry conditions?

The Grignard's reagent is moisture sensitive. To avoid its inactivity the reaction is supposed to run under extremely dry conditions.

What is the reaction mechanism?



Synthesis of cationic dye Crystal violet

Safety Cautions:

1- Magnesium reacts with moisture very violently, so one should be very careful.
2- The 4-Bromo-*N*,*N*-dimethylaniline is an irritant so keep it away from eyes and skin etc.
3- The dye could itself stain clothing and skin.
4- One should use THF carefully due to its hazardous nature.

References:

1. Christie, R. M., *Colour chemistry*. Royal Society of Chemistry: 2001.
2. Afonso, C. A.; Candeias, N. R.; Simão, D. P.; Trindade, A. F.; Coelho, J. A.; Tan, B.; Franzén, R., *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*. Royal Society of Chemistry: 2016.
3. Griffiths, J., *Developments in the chemistry and technology of organic dyes*. Blackwell Science Inc: 1984; Vol. 7.
4. Hunger, K., *Industrial dyes: chemistry, properties, applications*. John Wiley & Sons: 2007.
5. Kim, S.-H., *Functional dyes*. Elsevier: 2006.
6. Lubs, H. A., *Chemistry of Synthetic Dyes and Pigments*. Reinhold Publishing Corporation.; New York: 1955.
7. Shah, K. M., *Handbook of synthetic dyes and pigments*. Multi-tech Publishing Company: 1998.
8. Zollinger, H., *Color chemistry: syntheses, properties, and applications of organic dyes and pigments*. John Wiley & Sons: 2003.
9. Reife, A.; Reife, A.; Freeman, H. S., *Environmental chemistry of dyes and pigments*. John Wiley & Sons: 1996.
10. Leonard, J.; Lygo, B.; Procter, G., *Advanced practical organic chemistry*. CRC press: 2013.

Chapter 4

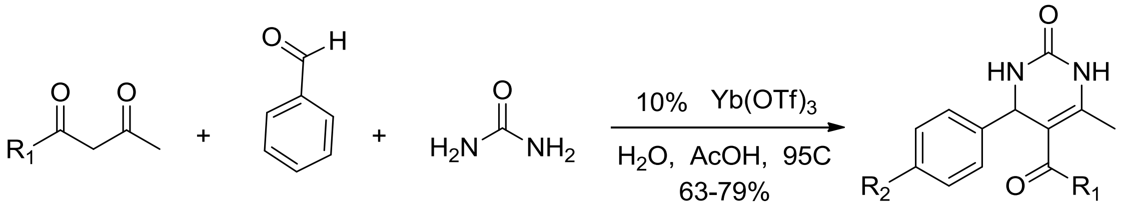
4 Lab-scale Synthesis of Heterocyclic Compounds

Tahir Farooq, Sarosh Iqbal

This chapter has been designed to make students familiar with the lab scale synthesis of heterocycles with wide ranging applications. Students are expected to apply the basic reaction concepts for the construction of complex molecular architectures. Further, students are supposed to learn about handling of sensitive reaction conditions.

4.1 Experiment 1: Preparation of Dihydropyrimidine Derivatives

Aim: The objective of this experiment is to synthesize dihydropyrimidine derivatives by Biginelli condensation.[1]



Experimental learning objectives: Students are supposed to learn about

- Multi-component reactions
- Biginelli condensations
- Lab-scale heterocyclic reactions
- Pyrimidines and dihydromyrimidines

Procedure:

Take about 10 mL of acetic acid and water (3:1) and add 1,3-dicarbonyl compound (2 mmol), urea (2 mmol) and aryl aldehyde (1 mmol). Then add 0.1 equiv. of ytterbium-(III) triflate hydrate into the reaction flask. Put the reaction flask in an oil bath and heat it for 15 min at 95 ºC. Then the oil bath is removed and the reaction flask is allowed to cool to room temperature. Afterwards, the precipitates of the product are recovered by pouring the flask contents into the ice-cold water. The filtered precipitates (simple or vacuum filtration) are washed with ice-cold water and toluene (2-3 mL). The toluene is used to remove remnants of acetic acid. Depending on the R_1 and R_2, the product, dihydropyrimidine is orange, yellow or white solid. When the product is completely dried find out its actual mass.

Expected mass of product: ________________ g

Expected no. of moles of product: ________________

Actual mass of product: ________________ g

Actual no. of moles of product: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva Questions:

What is the role of ytterbium-(III) triflate hydrate in this reaction?

In this reaction, the ytterbium-(III) triflate hydrate acts as catalyst.

Why precipitates are washed with ice-cold water and toluene?

The precipitates of the product are washed with toluene to remove the remnants.

The vacuum filtration is used in this process?

The vacuum filtration is employed when filtrate happens to be very viscous.

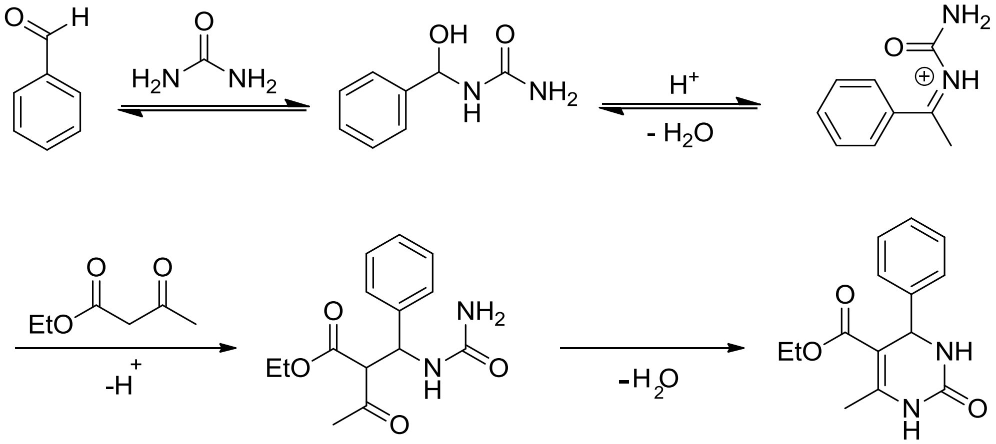
What is the importance of dihydropyrimidine derivatives?

Dihydropyrimidines are an important part of many biologically potent natural and synthetic molecules. They act as building blocks of important drugs.

Explain the reaction between benzaldehyde and urea.

The reaction between benzaldehyde and urea is an example of nucleophilic addition reaction resulting in the formation of corresponding enamine.

What is the reaction mechanism?

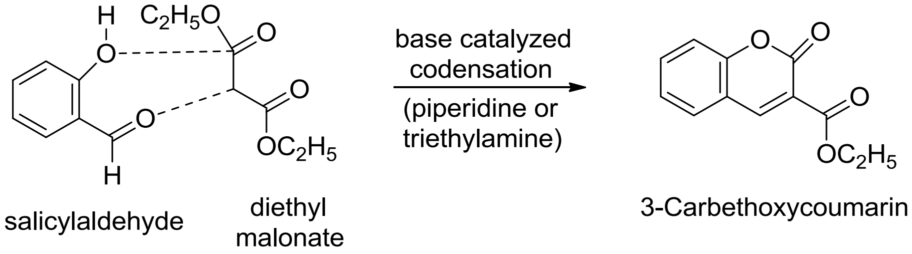


Safety measures:

4- Aryl aldehydes should be handled with care they could cause irritation.
5- The 1,3-dicarbonyl compounds could cause rashes on skin so should be used properly.
6- The aqueous layer should be disposed of properly because of the presence of pyridine remnants

4.2 Experiment 2: Synthesis of 3-Carbethoxycoumarin

Aim: The objective of this lab activity is to prepare 3-carbethoxycoumarin involving diethyl malonate and salicylaldehyde through aldol condensation mechanism.[2]



Experimental learning objectives: Students are supposed to learn about

- Aldol condensation reactions
- Base-catalyzed reactions
- Lab-scale heterocyclic reactions
- Refluxing the reactants
- *O*-heterocycles like coumarins

Procedure:

Take a round-bottom flask of 25 mL capacity, add into it 1.7 mL diethyl malonate and 1.1 mL salicylaldehyde. After putting the flask on stirring, piperidine (20 drops), ethanol (4 mL) and glacial acetic acid (4 drops) are added before connecting water condenser. The reaction mixture is refluxed for two hours with continuous stirring. Afterwards, the reaction mixture is allowed to cool to room temperature and then put it in ice bath till the crystalline solid precipitates out. Using Buchner funnel, the solid is filtered out by vacuum filtration. To purify the crystals, recrystallization is performed with 95% ethanol. When the product is completely dried find out its actual mass.

Expected mass of product: ________________ g

Expected no. of moles of product: ________________

Actual mass of product: ________________ g

Actual no. of moles of product: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva Questions:

What is the role of piperidine in this reaction?

The piperidine acts as a base and catalyzes this reaction. Other inorganic bases like NaOH or KOH are not used as they are very strong bases.

What is meant by reflux?

Reflux means reaction in a boiling solvent. Such reactions require high energy to proceed.

Why recrystallization is performed?

Recrystallization is done to remove impurities from the desired product.

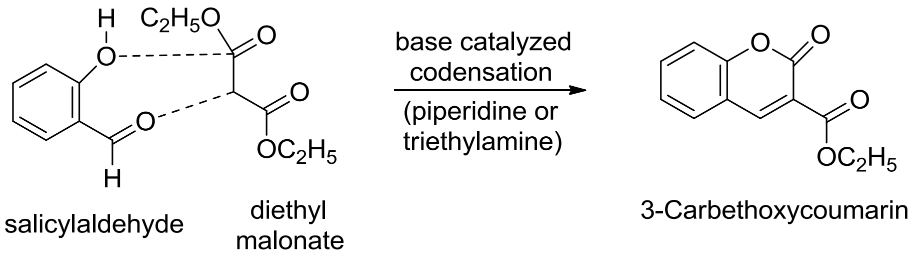
Why water condenser is used in this reaction?

Glass condenser condenses the vapours and help them to get back into reaction flask.

Write about importance of coumarins?

Coumarins are the central structures in many natural and synthetic anti-HIV, antibacterial and anticancer drugs.

Write reaction mechanism for this reaction?

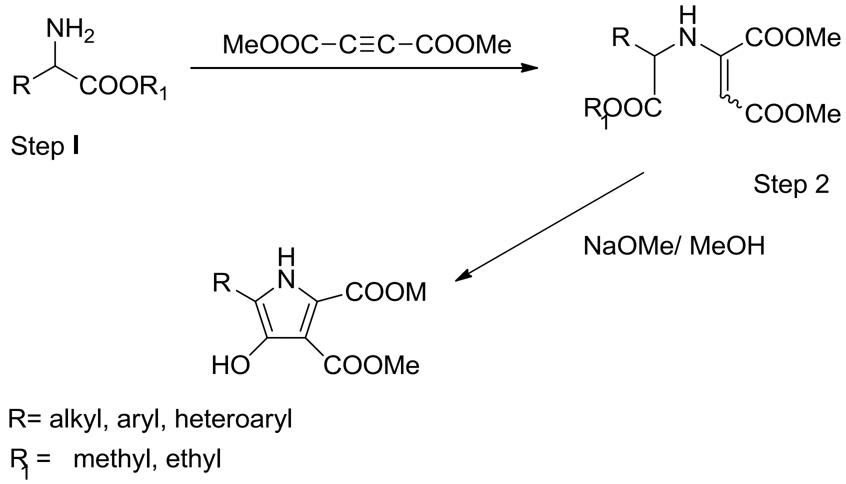


Safety Measures:

1- Piperidine is toxic, so one should be very careful while handling it.
2- Salicylaldehyde is irritant and toxic in nature.
3- Glacial acetic acid is corrosive.

4.3 Experiment 3: Synthesis of Tetrasubstituted Pyrrole

Aim: The objective of this lab activity is to synthesize tetrasubstituted pyrrole through simple and rapid two-step lab-scale method.[2]



Experimental learning objectives: Students are supposed to learn about

- Two-step reactions
- Reaction monitoring by TLC
- Lab-scale heterocyclic reactions
- Amino acid transformations
- *N*-heterocycles like pyrrole

Procedure:

Take 25 mL of water in a round-bottom flask, add 2.57 g of L-phenylalanine ethyl ester chloride. The mixture is cooled to 0 ºC in an ice bath. For its neutralization, a solution of 0.4 g of NaOH in 15 mL of water is used. Then the solution is extracted with diethyl ether (15 mL ×3). The anhyd. sodium sulfate is used to dry organic phase. The L-phenylalanine ethyl ester is obtained as colorless oil after solvent evaporation. The amount of the product is calculated immediately and used as such for further reaction steps.

Take methanol 10 mL in a round-bottom flak and add L-phenylalanine ethyl ester (1.8 g) and stir the mixture 0 ºC. Then add dropwise dimethyl acetylenedicarboxylate (1.4 g) and continue stirring for one hr. After evaporating the reaction mixture, enamine as pale-yellow oil is obtained. This product is dissolved in methanol (5 mL) and a fresh solution of sodium methoxide (0.2 g in 5 mL methaol) is added dropwise. The reaction mixture is stirred for half hour at room temperature. Then precipitates of sodium salt of hydroxypyrrole are formed, dissolve them in water (10 mL). Further, the mixture is neutralized with 10% CH_3COOH (10 mL) to achieve precipitates of pyrrole. The filtrate is washed with methanol. When the product is completely dried find out its actual mass.

Expected mass of product: ________________ g

Expected no. of moles of product: ________________

Actual mass of product: ________________ g

Actual no. of moles of product: ________________

Percent yield = actual no of moles of product/ expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva Questions:

What happens in the first step of the reaction?

In the first step, dimethyl acetylenedicarboxylate reacts with α-amino acid ester to produce enamine product.

What is the role of sodium methoxide in this reaction?

Sodium methoxide acts as a catalyst in step two, the cyclization process.

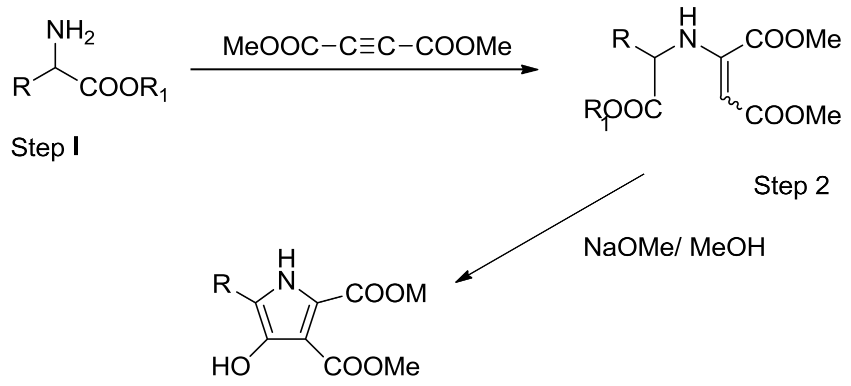
What kind of reaction happens in step II?

In second step of the reaction, the enamine undergoes dieckmann like condensation.

What is the importance of tetra-substituted pyrrole?

They are the important part of many drugs and biologically active molecules. They have also been used as precursors in polymer industry.[3]

What is the mechanism of this reaction?



R= alkyl, aryl, heteroaryl

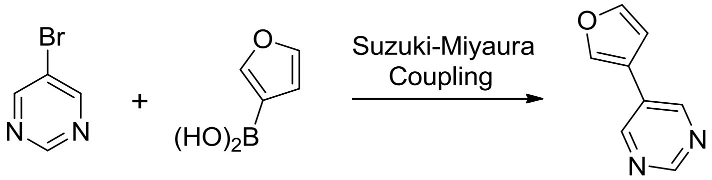
R_1 = methyl, ethyl

Safety Measures:

1- Sodium methoxide should be used very cautiously.
2- To avoid fire hazards, the reaction should be performed in well ventilated place.
3- The reagents should be used with great care.

4.4 Experiment 4: Nickle-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction

Aim: The aim of this lab activity is to synthesize heterocycles using nickle-catalyzed Suzuki-Miyaura cross-coupling reaction.[4]



Experimental learning objectives: Students are supposed to learn about

- Transiition metal catalyzed reactions
- Cross-coupling reaction
- Reaction monitoring by TLC
- Suzuki-Miyaura reactions
- Green chemistry
- Advance reactions of alkyl halides

Procedure:

Take a round-bottom flask of 25 mL capacity and add *ter*-amyl alcohol into it. After putting it on stirring, add 5-bromopyrimidine (2 mmol), boronic acid (2.2 mmol) and K3PO4 (1 mol %) as catalyst. The stirring is continued for next 30 min then the temperature is raised to 80 ºC for one hour. The progress of the reaction is monitored by using TLC. After the completion of reaction, the product is extracted by using ethylacetate (15 mL × 3) and brine solution. The crude product is received by evaporating the solvent on rotary evaporator. The product is purified by flash column chromatography using silica gel and suitable solvent system. When the product is completely dried find out its actual mass.

Expected mass of product: ________________ g

Expected no. of moles of product: ________________

Actual mass of product: ________________ g

Actual no. of moles of product: ________________

Percent yield = actual no of moles of product / expected no. of moles of product X 100

Advice:

Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva Questions:

What is meant by transition metals?

Elements included in d and f block of the periodic table are referred as transition metals. The elements in the f block are referred as inner shell transition metals.

What are cross-coupling reactions?

They are such reactions in which hydrocarbon fragments are coupled with the help of transition metal catalysts.[5]

What is meant by green chemistry?

The reactions which involve environment friendly reactants, solvent and or reaction conditions.

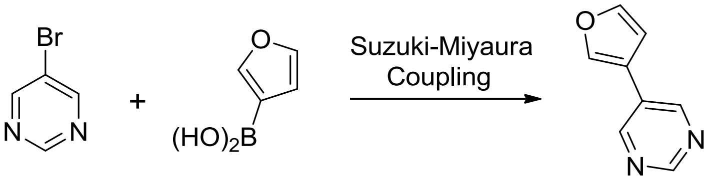
What is the role of amyl alcohol in this reaction?

The amyl alcohol acts as green solvent in this reaction and making it a green reaction.[6]

What could be the other possible reactions for cross-coupling?

They could be Friedel Craft’s alkylation and the reactions involving Grignard’s reagents.

Write the mechanism of this reaction?

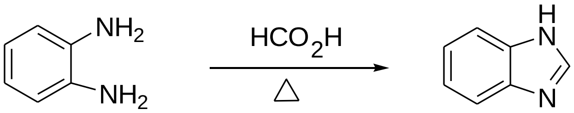


Safety Measures:

1. Ter-amyl alcohol should be used with care as it can cause irritation on skin and eyes.
2. Bromopyridine is also an irritant should be used with care.
3. Ethyl acetate is a flammable so use it carefully while extracting the product.

4.5 Experiment 5: Synthesis of Benzimidazole

Aim: The aim of this lab activity is to synthesize benzimidazole from *o*-phenylenediamine and formic acid.[7]



Experimental learning objectives: Students are supposed to learn about

- Reaction monitoring by TLC
- Suction filtration
- High energy reactions
- Flash column chromatography

Procedure:

Take a round-bottom flask of 100 mL capacity, add 5.5 g of *o*-phenylenediamine and 90% formic acid (10 mL). After connecting the condenser, heat the reaction mixture at 100 ºC for at least thirty minutes. Then cool the mixture to room temperature and add ammonium hydroxide (10 mL) to achieve precipitation of the product. Wash the precipitates with cold water after filtration using Buchner funnel and suction pump. The product is purified by flash column chromatography using silica gel and suitable solvent system. When the product is completely dried find out its actual mass.

Expected mass of product: ________________ g

Expected no. of moles of product: ________________

Actual mass of product: ________________ g

Actual no. of moles of product: ________________

Percent yield = actual no of moles of product / expected no. of moles of product X 100

Advice:

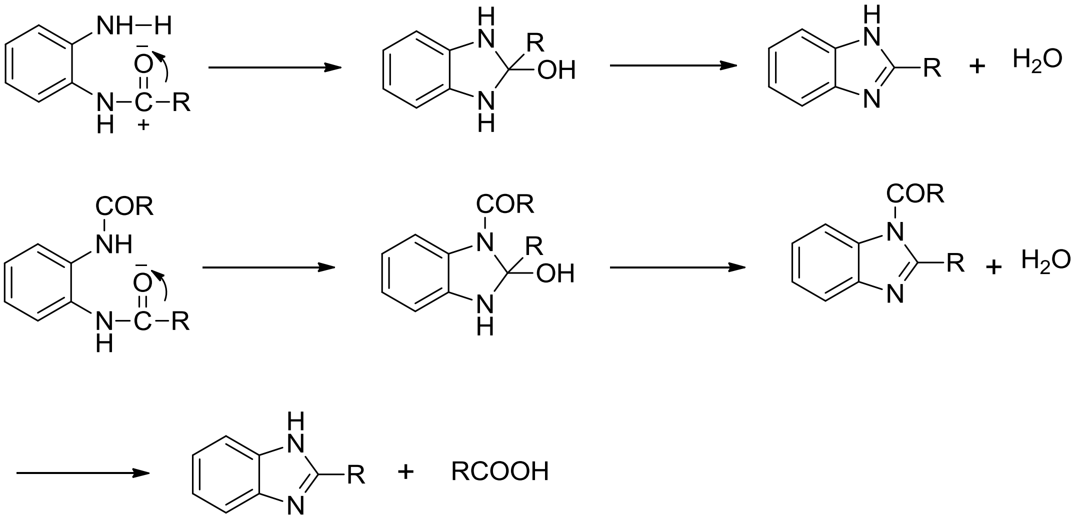
Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva Questions:

What is the role of formic acid in this reaction?

Formic acid is a reagent in this reaction. You need a stoichiometric amount for a successful reaction.

Explain the reaction mechanism.



Why Buchner funnel and suction pump is used for filtration?

Buchner funnel and suction pump is used in such cases when the filtrate is thick and viscous. The simple gravity based filtration becomes hard-task in such cases.

What sort of reaction produces the benzimidazole as product?

The reaction follows the nucleophilic substitution pattern.[8]

Why reactants are heated at 100 ºC for 30 minutes?

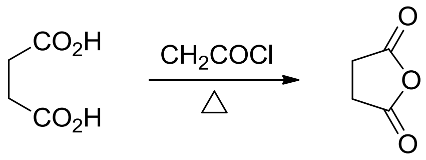
The reactants require high thermal and kinetic energy for reaction. So, the reaction mixture is heated at at 100 ºC for 30 minutes.

Safety Measures:

1- The *o*-phenylenediamine is an irritant and could produce burn on the skin
2- Formic acid should be handled with care otherwise could cause skin blistering and redness of eyes.
3- Benzimidazole is a combustible product, should be handled with care.

4.6 Experiment 6: Synthesis of Succinic Anhydride

Aim: The main objective of this lab activity is to synthesize *O*-heterocyclic compound (Succinic Anhydride) from succinic anhydride.[9]



Experimental learning objectives: Students are supposed to learn about

- Reactions at reflux
- Reaction monitoring by TLC
- Lab-scale *O*-heterocyclic synthesis
- Foamy reactions
- High-energy reaction
- Reactions involving cyclization of reactants

Procedure:

Take a two-neck round bottom flask of 1 L capacity, add acetyl chloride (230 g, 3 mole) and succinic acid (116 g, 1 mole). A reflux condenser is attached with the reaction flask. Reflux the reaction mixture for about one-and-half hour. The progress of the reaction is monitored using TLC. As the reaction completes, let the flask to cool to room temperature and then put it in the ice-bath. The product separates out as fine crystals, separate them using Buchnner funnel. The crystals are washed with ether (50 mL × 2) to remove the presence of impurities. When the product is completely dried find out its actual mass.

Expected mass of product: ________________ g

Expected no. of moles of product: ________________

Actual mass of product: ________________ g

Actual no. of moles of product: ________________

Percent yield = actual no of moles of product / expected no. of moles of product X 100

Advice:

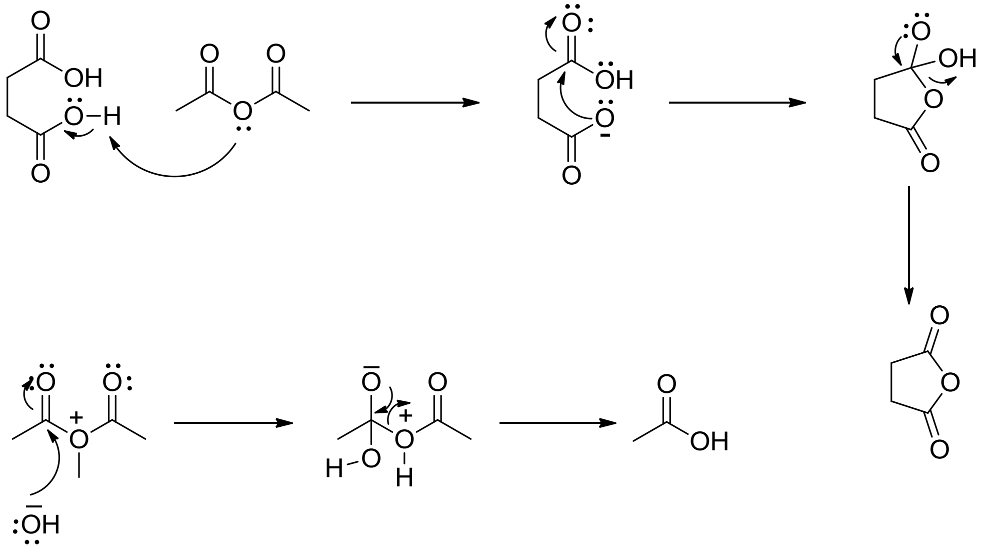
Students should draw the IR spectra of both reactant and product to understand the distinctive functional group absorptions.

Viva Questions:

What is the melting point of succinic anhydride?

The melting point of pure succinic anhydride is 118 ºC.

What is the mechanism of the reaction?



Why reaction mixture is refluxed?

The reactants require high thermal and kinetic energy for reaction. So, the reaction mixture is refluxed in such reactions.

Mention any use of succinic anhydride?

It is frequently used as acylating agent.

What is the IUPAC name of succinic anhydride?

The IUPAC name of succinic acid anhydride is oxolane-2,5-dione.

Safety Measures:

1- Exposure to succinic anhydride could cause respiratory tract irritation.
2- Acetyl chloride is highly flammable, toxic fumes could cause shortness of breath.
3- Exposure to succinic acid could cause irritation on of skin and eyes.

References:

1. Eicher, T.; Hauptmann, S.; Speicher, A., *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*. John Wiley & Sons: 2013.
2. Husson, H., *Asymmetric Synthesis of Nitrogen Heterocycles*. John Wiley & Sons: 2009.
3. van der Plas, H. C.; Katritzky, A. R., *Advances in heterocyclic chemistry*. Elsevier: 1999; Vol. 74.
4. Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V., *Handbook of heterocyclic chemistry*. Elsevier: 2010.
5. Roberts, R. M., *Modern experimental organic chemistry*. Saunders College Publishing: 1985.
6. Ono, N., *The nitro group in organic synthesis*. John Wiley & Sons: 2003; Vol. 9.
7. Larock, R. C., Comprehensive organic transformations; a guide to functional group preparations/; by Richard C. Larock. **1999**.
8. Newkome, G. R.; Paudler, W. W., *Contemporary heterocyclic chemistry: syntheses, reactions and applications*. Wiley-Interscience: 1982.
9. Li, J. J., *Name reactions in heterocyclic chemistry*. John Wiley & Sons: 2004; Vol. 3.

5 Appendices

5.1 Getting Ready for Laboratory

5.1.1 Laboratory's rules

1. Students are supposed to wear lab coats in every laboratory activities/experiments even during the demonstration and discussion time.

2. Students should prepare relevant notices or note important points before begin with practical work.

3. Students should not eat, drink and smoke in the laboratory.

4. Except lab note book other must not be placed on practical performance table and or area.

9. Students should not leave the laboratory during the practical performance.

10. Students should use pipettes to apply liquid reagents.

11. Students should use spatula to apply solid reagents.

12. Students should not remove reagents from their proper places on reagent tables.

13. Students should use every tool according to its helpful utility.

14. Students before leaving should clean fume hood, weighing balance, washing stand, table and seat.

15. Students should record and write experiment's number, procedure, chemical and physical properties of materials used in the experiment, the reaction mechanisms, chemical and physical properties of the reactants, theory, procedure and results in their lab note books.

16. Students should hand over the completed lab not books before the next experiment schedule.

17. Students are supposed to obey the instructions without any exemption.

5.2 Introduction to the laboratory

5.2.1 Laboratory Safety

Safety Equipment

Safety equipment are installed in the laboratory to avoid any undesirable accident. Such safety equipment must include at least

An eye wash

A safety shower

Fire extinguishers

Hoods

First-aid kit

Eye Wash: The eyewash with a water stream is used to flush irritating and hazardous chemicals from the eye. In case of eye accident, the eye is supposed to kept open and the student must use the eyewash for 15 minutes at least. Considering the gravity of the eye condition, student should move to the doctor for real time eye-examine and proper treatment.

Safety Shower: The main purpose of safety shower is to extinguish firing clothes and at certain times could be used for whole body wash in case of huge chemical spill incidents. However, in case of clothing catches fire, possibly the best option would be to lay down and roll. One should never run for shower with clothes on fire, it could maximize the flames. Contaminated clothes preferably be removed because they could put you in serious troubles.

Fire Extinguishers: In the laboratory, the flammable materials are used quite often. Any undesirable accident could create dangerous threats to human life. To avoid such uninvited situations, several fire extinguishers are supposed to be placed in the laboratory premises. Students should know about their location and learn about their proper use.

Hoods: The modern laboratories are well equipped with built in hoods. If possible, student should perform all experimental activities in a fume-hood. In a fume-hood the well aerated ventilation system manages to draw the chemical fumes produced during an experimental activity away from the students. In modern organic laboratories, the chemical reactions are always performed in fume-hoods.

First Aid Kits: Indeed, the first aid kits are used in case of minor accidental injuries. Students should immediately use first aid kits for cuts and bums. The minor cuts should be avoided to get contact with chemical residues because such nasty interaction could lead to serious issues. In case of accidental bums an Immediate flush with cold water could reduce the severity of hurt. However, in case of worse conditions, students should instantly consult a doctor.

Personal Protective Equipment: Students are supposed to wear proper clothing during their laboratory hours. The proper clothing should comprise the safety items like safety goggles, lab coats, gloves and proper shoes etc. Lab coats are specially designed to take them off instantly in cases of chemical spill or under unavoidable circumstances of fire. The students are supposed to wear cotton-made lab coats instead of synthetic materials. Because synthetic materials could melt and get incorporated into the burns. Further, they could get dissolve in organic solvents consequently put you in serious troubles. The students should not allowed eat, drink or smoke in the laboratory premises. Student should put on disposable gloves when dealing with acidic, basic and toxic reagents.

Safe handling of Laboratory Equipment: Heat sources like heating mantles, steam baths and Gas burners are routinely used equipment in the laboratory. Each source should be handled carefully with proper precautionary measure. Quite high temperature could be attained quickly with these devices and never be let unattended. Such equipments should be positioned just outside the hood where the solvent vapor concentrations are very low hence the danger of ignition is minimal. The volatile and easily ignitable materials should be kept away to avoid serious ignition hazards.

Waste Disposal: At the end of every experimental activity in laboratory, the spent organic solvents, solid chemical residues and by products need to be disposed of properly. The appropriate disposal of all types of wastes is as important as the other parts of an experiment. For safety purposes, the students should clean spilled chemicals soon after they occur. The aqueous, halogenated and non-halogenated solvent wastes should be disposed of in properly labelled containers. The solid wastes should be kept separately to dispose them of appropriately because they could react with other spills. Students should not combine unknown waste residues produce from different chemical reactions because violent reactions could result from such mixtures. The spilled acidic and basic materials should be neutralized before the final rinse or clean-up operation.

Good Laboratory Practices: Students should not bring any type of food and drinks during working hours in the laboratory. Food materials and beverages can get contaminated easily with toxic vapors in the laboratory. Serious sort of poisoning has been observed in such cases of carelessness. Smoking should be strictly banned in the laboratory. Smoking poses serious threats of ignition hazards because of the presence of ignitable chemicals in the laboratory.

Finally, students are exposed to several chemical reagents, inorganic and organic solvents during experimental activities. Because of direct handling they could get retain under the finger nails on the hands. So, students should wash their hands to ensure the removal of such toxic materials before they leave the laboratory otherwise they could serious threats.

Dr. Farooq got his doctoral degree in synthetic medicinal chemistry from the University of Bergen, Norway under the supervision of Dr. Bengt Erik Haug and Dr. Leiv K. Sydnes (former President of IUPAC). He has a strong background in synthetic chemistry with a solid grip on modern synthetic techniques. He holds a comprehensive hand-on expertise on modern techniques like GC, GC-MS, HPLC (both analytical and preparative instruments), NMR (1D and 2D techniques).

The author is interested to introduce books and lab manuals on organic chemistry, advanced analytical instruments and modern spectroscopic techniques for undergraduate and postgraduate students. Especially for those who are beginners in such fields. The introduction of this laboratory manual is an example of such much-anticipated efforts in near future.

This lab manual is designed to polish student's basic concepts in synthetic organic chemistry. They are supposed to apply the ever-explained reaction mechanisms on practical basis. They should learn to execute various reactions under sensitive reaction conditions. The color chemistry chapter has been introduced to make student apply their knowledge on industrial applications.

The author welcomes sane suggestions and or healthy criticism for the perfection of this manual.

Dr. Sarosh Iqbal is a Synthetic Medicinal Chemist who got her doctoral degree from H.E.J Research Institute of Chemistry, International Center for Chemical & Biological Sciences, University of Karachi, Pakistan in 2014. During her doctoral study, she was awarded a prestigious Commonwealth split-Ph.D. scholarship tenable at University of Oxford, Oxford, UK. (2012-2013) and gained expertise in polymer chemistry. During her educational career she has won many awards and honors, for instance, distinction in B.S (2007); M.Phil (course work) (2009); 85 %ile in international (Subject) GRE (2010) (A record breaking marks). She joined Government College University, Faisalabad in 2014 as an Assistant professor. Her area of research includes synthesis of medicinally important compounds and modification of polymers..

ISBN 978-969-7818-00-6