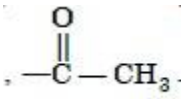
Syntheses of Medicinal Compounds

Acetylation methods:

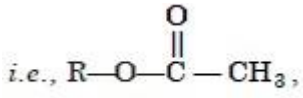
Introduction

The replacement of '*active hydrogen*' of compounds belonging to the class **ROH** (phenols or alcohols), in addition to compounds of the category $\mathbf{RNH_2}$ and $\mathbf{R_2NH}$ (*i.e., primary*- and *secondary*-amines may be acetylated directly, whereby the reactive H-atom is specifically replaced by the **acetyl radical**



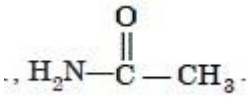
This replacement of an *active hydrogen* by an **acetyl function** is termed as **acetylation**.

In true sense, the acetylation of alcohols and phenols is really regarded as a specific instance of **esterification** by virtue of the fact that the resulting *acetyl derivative*



Is evidently an '*ester*' of acetic acid. Likewise, the primary and secondary amines give rise to the corresponding derivative of the types:

respectively, that may be regarded as *mono*- and *di*-substituted derivatives of **acetamide**

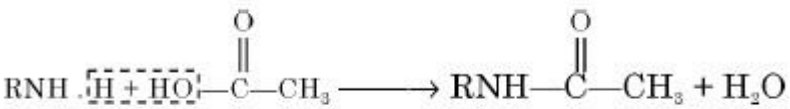


In actual practice, *acetylation* may be accomplished by *two* major procedures:

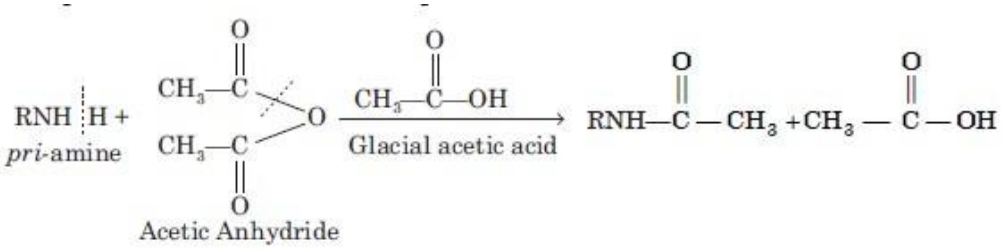
Procedure–I.

Heating with a mixture of Acetic anhydride and Acetic acid :

It has been observed that when a primary or secondary amine is reacted with glacial acetic acid by the application of heat, the corresponding acetyl derivative is obtained ; however, the ensuring reaction is invariably found to be extremely sluggish and slow, as given below:

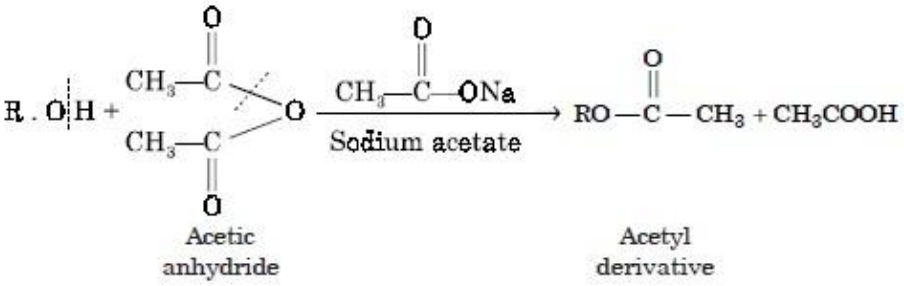


If, acetic anhydride is mixed with glacial acetic acid in equal proportions (1 : 1) the acetylation proceeds with a remarkable rapid and fast manner, as shown below :



This is due to the fact that acetic anhydride is much more reactive than glacial acetic acid alone ; and the presence of the latter helps the reaction to proceed in the forward direction to knock out a mole of acetic acid.

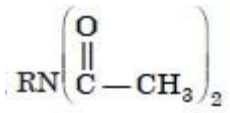
The primary alcohol on being treated with acetic anhydride in the presence of sodium acetate yields the acetyl derivative (an ester) along with a mole of acetic acid as given below :



The role of sodium acetate is to provide enough acetate ions upon dissociation which would carry out the reaction in the forward direction to generate the corresponding acetyl derivative and acetic acid.

Disadvantage of Using Acetic Anhydride. There are *two* main disadvantages observed when acetic anhydride is employed as an acetylating agent, namely :

(*a*) **Formation of traces of Diacetyl Compound.** The primary amines usually forms traces of the corresponding *Diacetyl compound* :



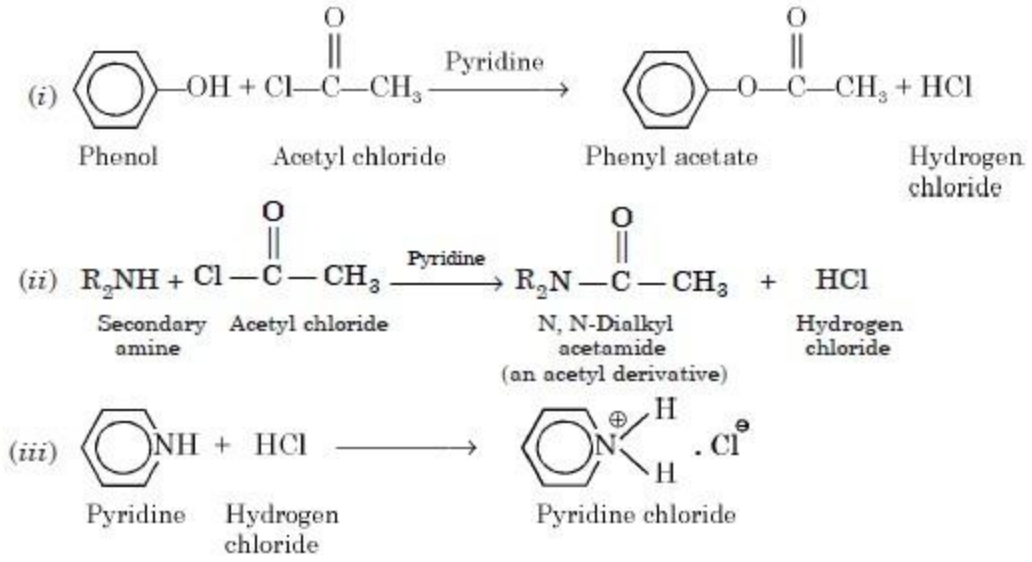
However, the possibilities of this specific secondary acetylation are quite rare and remote. The ultimate recrystallization of the crude product from an aqueous medium shall broadly hydrolyze the Diacetyl derivative back to the mono-acetyl derivative very rapidly.

(*b*) **Addition of a catalyst.** In order to carry out the complete acetylation of *polyhydric chemical entities*, such as : **glucose** and **mannitol**, even pure acetic anhydride is not that useful and effective ; and therefore, the absolute necessity of an appropriate third substance is required as a '**catalyst**', such as : *anhydrous sodium acetate.*

Procedure–II.

Treatment with Acetyl Chloride :

Acetylation may be caused with the help of acetyl chloride specifically smoothly in the presence of **pyridine** which absorbs the hydrogen chloride formed during the course of reaction almost instantaneously as given below :



Uses of Acetylation.

The following are the major uses of *acetylation reaction,* such as :

(1) For the identification and subsequent characterization of hydroxy compounds as well as primary and secondary amines, by preparing their crystalline acetyl derivatives.

Note : The particular aspect is exclusively applicable to the aromatic compounds because the aliphatic compounds are invariably liquid in nature, and also are frequently miscible in an aqueous medium.

(2) For the **protection** of either a *primary-* or a *secondary-amino moiety* in the course of a chemical reaction.

Example. Preparation of *para*-nitroaniline :

The highly active amino function present in aniline is duly protected by acetylating it with acetic anhydride to obtain **acetanilide** and the elimination of a mole of acetic acid. The acetanilide is now subjected to nitration by concentrated sulphuric acid and fuming nitric acid to obtain the *two* products, namely : *para*-nitro acetanilide (~ 90%) and *ortho*-nitro acetanilide (~ 10%).* Finally, the *para*-nitroaniline is obtained by carrying out the hydrolysis of the corresponding *p*-nitro acetanilide with 70% sulphuric acid.

(3) For the preparation of *mono-substituted derivatives* of the *aromatic amines* or *phenols.*

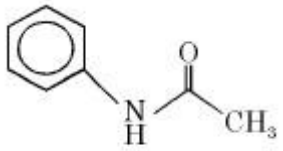
practical lab 1

synthesis of Acetanilide

Theory:

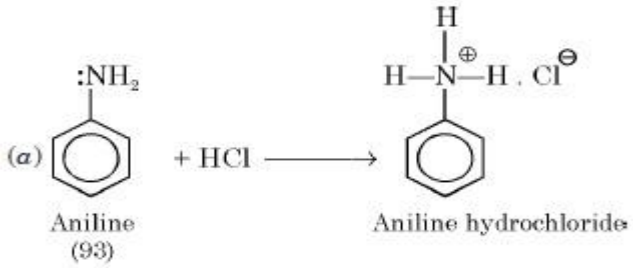
The freshly redistilled aniline, is almost a colourless oily liquid which being practically insoluble in water. Therefore, before carrying out the '**acetylation'** aniline has got to be made soluble in the aqueous medium. It can be accomplished by adding requisite amount of concentrated HCL whereby the highly reactive amino function easily takes up a proton from the dissociation of HCL in water, get protonated to yield aniline hydrochloride that is water-soluble. Subsequently, the soluble form of aniline is reacted with acetic anhydride in the presence of sodium acetate. The acetate ion obtained from the hydrolysis of the salt (sodium acetate) helps to sustain the acetylation reaction in the forward direction to yield acetanilide completely.

Chemical Structure :

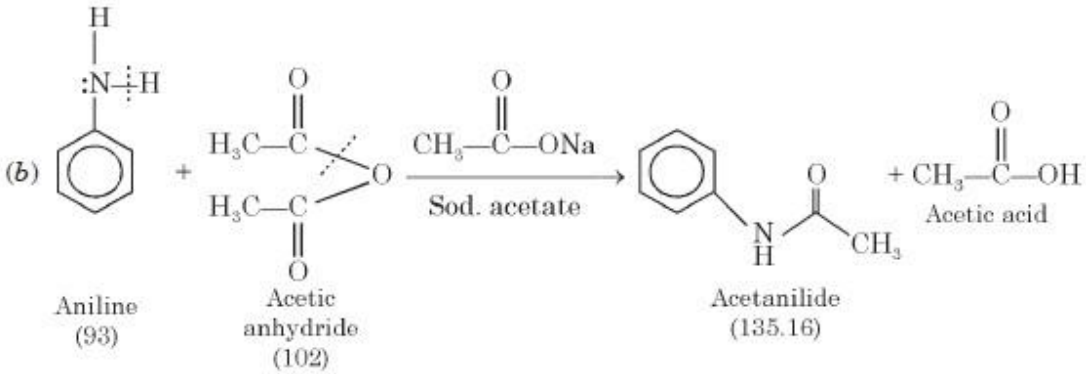


Acetanilide

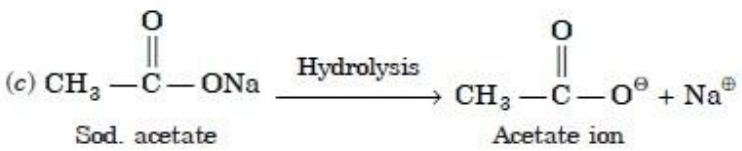
Equations:



Aniline (93) Aniline hydrochloride



Aniline (93) Acetic anhydride (102) Sod. acetate Acetanilide (135.16) Acetic acid



Sod. acetate Acetate ion

Chemicals Required:

1. Aniline : 10 ml (Freshly redistilled to have almost a colourless product) .
2. Acetic anhydride : 13 ml .
3. Sodium acetate (crystalline) : 16.5 g .
4. Concentrated Hydrochloric acid (12 N) : 9 ml.

Procedure:

1. Transfer 10 ml of aniline is a 500 ml beaker and add to it 9 ml of concentrated hydrochloric acid and 25 ml of distilled water. Stir the contents of the beaker thoroughly with a glass rod till the whole of aniline undergoes dissolution.
2.Dissolve in a separate 100 ml beaker 16.5 g of sodium acetate in 50 ml of distilled water.
3. To the clear solution of aniline (1), add 13 ml of acetic anhydride, in small lots at intervals, with constant vigorous stirring until a perfect homogeneous solution is obtained.
4. Immediately pour the solution obtained from (3) into the sodium acetate solution (2). Shake the contents thoroughly with the help of a glass rod and immerse the beaker containing the reactants in an ice-bath.
5. Beautiful shining crystals of **Acetanilide** separate out which may be filtered at the Büchner funnel by applying suction, washed with enough cold water, squeeze out the excess of water by pressing with an inverted glass stopper. Transfer the crude product onto a watch glass with the aid of a stainless-steel spatula and finally dry it in an electric oven previously maintained at 80°C. The yield of crude acetanilide (mp 113– 114°C) is approximately 12 g.

calculation:

Theoretical yield/Practical yield.

The theoretical yield may be calculated from Eq. (*b*) under theory as follows :
93 g of aniline on reacting with 102 g of acetic anhydride yields acetanilide = 135.16 g
10 g of aniline* shall yield acetanilide = 135.16 / 93 × 10 = 14.5 g
Therefore, Theoretical yield of Acetanilide = **14.5 g**
Reported Practical yield = 12 g
Hence, Percentage Practical yield = Practical yield / Theoretical yield × 100
= 12 / 14.5 × 100 = **82.75**

Uses :

(1) It possesses antipyretic and analgesic activities.
(2) It is invariably used in the manufacture of other medicinal *e.g.*, sulphonamide ; besides dyes.
(3) It is also employed as a stabilizer for H_2O_2 solution.
(4) It finds its application as an additive to cellulose ester varnishes.

practical lab 2

Synthesis of salicylic acid

Theory:

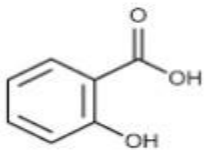
salicylic acid is prepared from methyl salicylate by hydrolysis of ester group with aqueous alkali (NaOH or KOH). Salicylic acid is a monohydroxybenzoic acid, a type of phenolic acid and a beta hydroxy acid. This colorless crystalline organic acid is widely used in organic synthesis and functions as a plant hormone. It is derived from the metabolism of salicin.

There are two types of derivatives of SA depends upon the attack on which group takes place

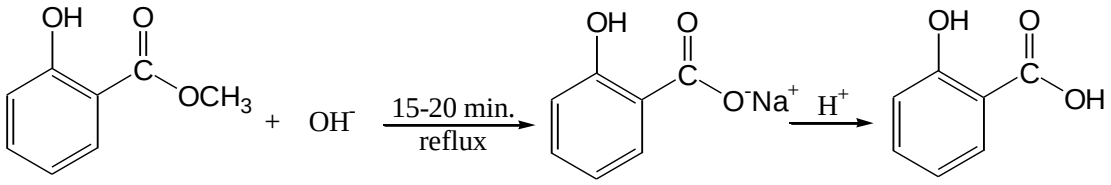
a. Esters of carboxylic acid.
b. Substitution of phenolic groups.

Most of these derivatives are introduced to minimize the gastric disturbances, hemorrhage irritation and undesirable taste.

Chemical structure:

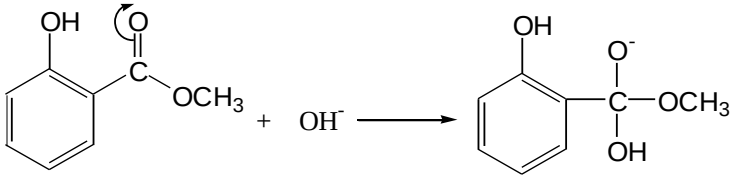


equations:

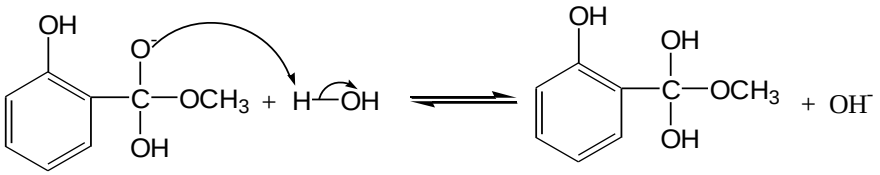


The mechanism:

1. Nucleophilic addition of OH- ion to the carbonyl group:

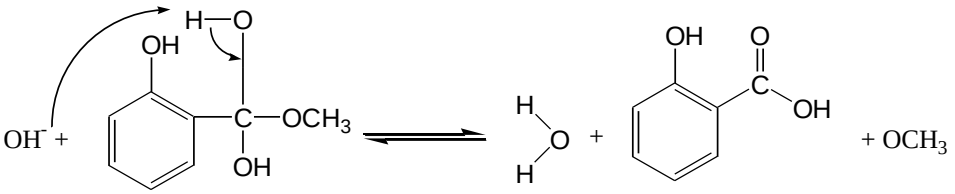


2. *Proton Transfer to anionic form of tetrahedral intermediate:*

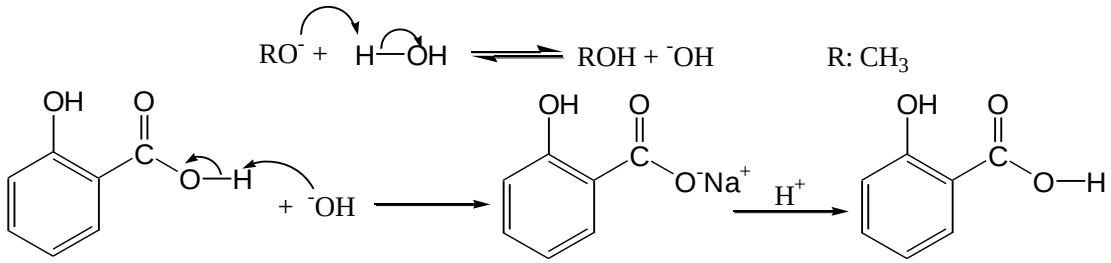


Tetrahedral intermediate

3. *Dissociation of tetrahedral intermediate:*



4. *Proton transfer yields an alcohol and carboxylate anion:*



Sod. salicylate Salicylic acid

Chemicals Required :

Methyl salicylate (0.1 g); 20 % (w/v) aq. Sol. of NaOH; dil. H_2SO_4.

Procedure:

1. Place 5 g of oil of methyl salicylate (0.1 g of Wintergreen) in a 250-ml distilling flask together with 50 ml of 20 % (w/v) aq. Sol. of NaOH.
2. Mix well, the sod. salt of methyl salicylate phenolic group may separate out at this point, but will re-dissolve on heating.
3. Reflux at the boiling point for 15-20 min.
4. Transfer the mixture to a 125-ml beaker, cool and acidify with dil. H_2SO_4 (check acidification by litmus paper).
5. Filter the precipitated SA with suction and dry.

Recrystallization:

Recrystallize from the minimum amount of hot water and weigh the pure SA (white crystals). (MP = 165-157 °C) (M wt = 138 g/mol).

Calculations:

Theoretical yield/Practical yield.

The theoretical yield is usually calculated from the equation under theory as stated under 152 g of methyl salicylate on reacting with 40 g of Sod. Hydroxide yields Salicylic acid = 138 g

∴ 5 g of methyl salicylate shall yield Salicylic acid =152 /138 × 5 = 5.50 g

Hence, Theoretical yield of Salicylic acid = **5.50g**

Reported Practical Yield = ×

Therefore, Percentage Practical Yield = Practical yield / Theoretical yield × 100

Uses :

Salicylic acid has strong antiseptic and germicidal properties; therefore, it's used as preservative material for foods and pharmaceuticals. In addition, it has good treatment of warts, corns and athlete's feet. Internally, although it shows antipyretic and analgesic activities, its salts and derivatives are used for these purposes.

Practical lab 3

Ester Derivatives of Salicylic Acid

Synthesis of aspirin

Theory:

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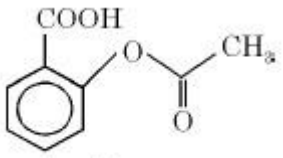
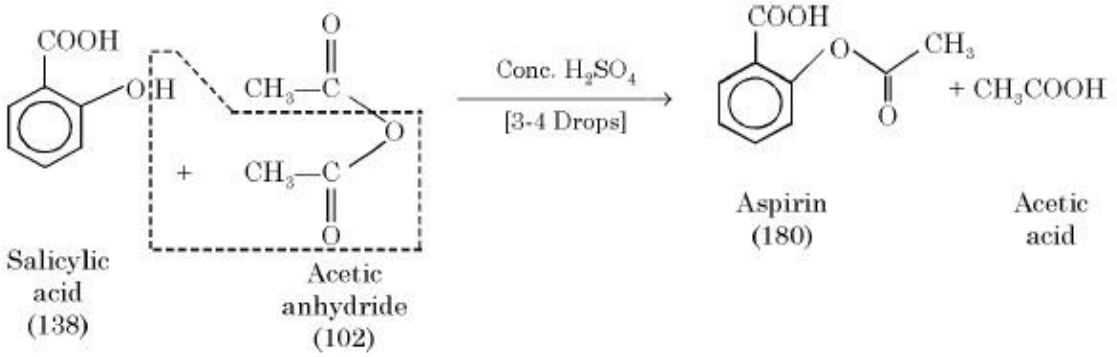
Salicylic acid interacts with acetic anhydride in the presence of a few drops of concentrated sulphuric acid to produce aspirin and a molecule of acetic acid. The purpose of adding conc. sulphuric acid is to aid and augment the process of detaching the acetate ion from acetic anhydride which ultimately gets associated with the H+ ion from the phenolic hydroxy group in salicylic acid to be eliminated as a mole of acetic acid.

Chemical Structure:



Aspirin

Equation:



Salicylic acid (138) | Acetic anhydride (102) | Aspirin (180) | Acetic acid

Chemicals Required :

(1) Salicylic acid : 6 g ; (2) Acetic anhydride : 8.5 ml ; and (3) Conc. Sulphuric acid : 3–4 drops.

Procedure:

The various steps involved are :

1. Weigh 6 g of salicylic acid and transfer to a 100 ml clean and dry conical flask.
2. Add to the flask 8.5 ml of acetic anhydride and 3–4 drops of concentrated sulphuric acid carefully.
3. Mix the contents of the flask thoroughly ; and warm the mixture on a water-bath maintained at 60°C for about 15–20 minutes with frequent stirring.

4. Allow the contents of the flask to cool down to ambient temperature, and pour it in a thin stream into 100 ml of cold water in a 250 ml beaker with constant stirring.
5. Filter the crude product on a Büchner funnel using suction, wash it generously with **cold water**, drain well and dry between the folds of filter paper or in an oven maintained a 90°C. The yield of crude aspirin (mp 133–134°C) is about 7.75 g.

Precautions :

(1) All glass apparatus that are used in the synthesis must be absolutely dry.
(2) Concentrated sulphuric acid should be added very cautiously into the reaction mixture.
(3) The reaction mixture is to be warmed only at 60°C for 20 minutes.

Recrystallization:

Recrystallize the crude product from a mixture of acetic acid and water (1 : 1). The yield of pure colourless aspirin (mp 13.4°C) is 7.25 g

Calculations:

Theoretical yield/Practical yield.

The theoretical yield is usually calculated from the equation under theory as stated under
138 g of salicylic acid on reacting with 102 g of acetic anhydride yields Aspirin = 180 g
∴ 6 g of salicylic acid shall yield Aspirin =180 /138 × 6 = 7.82 g
Hence, Theoretical yield of Aspirin = **7.82 g**
Reported Practical Yield = 7.5 g
Therefore, Percentage Practical Yield = Practical yield / Theoretical yield× 100
= 7.5 / 7.82 × 100 = **95.90**

Uses :

(1) It is used for the relief of minor aches and mild to moderate pain.
(2) It is recommended for arthritis and related arthritic conditions.
(3) It is also indicated for myocardial infarction prophylaxis.
(4) It is employed to reduce the risk of transient ischemic attacks in men.

Tests on Aspirin:

1. Test with Bicarbonate

Acetylsalicylic acid molecules still contain the organic acid group (carboxyl) and will react with sodium bicarbonate to release carbon dioxide gas:

$$H^+ + HCO_3^- \rightarrow H_2O + CO_2$$

Add a very small portion of your aspirin (crude or purified) to a test tube. Add also a small portion of sodium bicarbonate. Add a small amount of water and note the evolution of carbon dioxide. This test indicates only that aspirin is an acid; it is not a specific test for aspirin.

2. Test with Iron (III)

If the synthesis of aspirin has not been effective, or is aspirin has decomposed with time, then free salicylic acid will be present. This would be harmful if ingested. The standard United States Pharmacopoeia test for the presence of salicylic acid is to treat the sample in question with a solution of iron(III). If salicylic acid is present, the phenolic functional group (-OH) of salicylic acid present.

Set up four test tubes in a rack. To the first test tube, add a small quantity of pure salicylic acid as a control. To the second and third test tubes, add very small portions of your crude and purified aspirin, respectively. Add 5 mL of distilled water to each test tube, and stir to mix. Add 8-10 drops of iron(III) chloride (ferric chloride) solution. The appearance of a pink or purple color in you aspirin o the commercial table sample indicates the presence of salicylic acid.

3. Melting point determination

After the crude and purified aspirin samples have dried for a week, determine their melting points by the capillary method described in Experiment 4. Compare the observed melting points with the literature value.

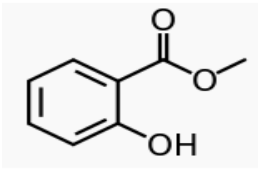
Practical lab 4

Preparation of Methyl Salicylate

Theory:

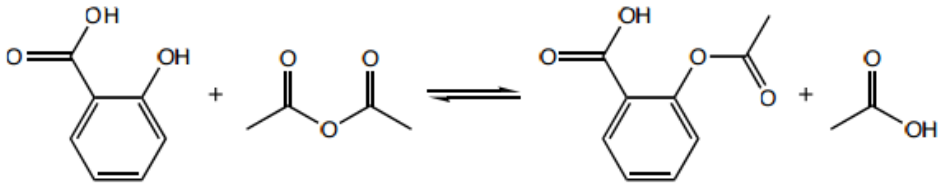
The second common ester of salicylic acid that is used as a drug is methyl salicylate. When salicylic acid is heated with methyl alcohol, the carboxyl group of salicylic acid is esterified producing a strong-smelling liquid ester (methyl salicylate).

Insert illustration of salicylic acid+ methyl alcohol → methyl salicylate + water.



Methyl Salicylate M. wt :152.15 gm/mol

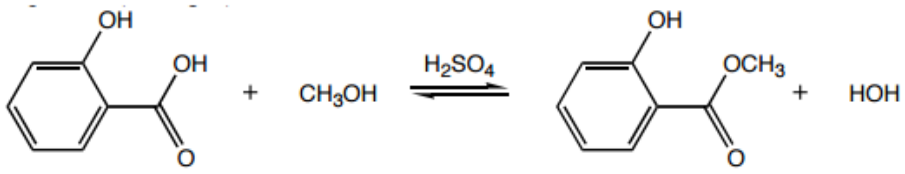
In the General Chemistry Laboratory, you took advantage of the nucleophilicity of the phenolic OH on salicylic acid and the electrophilicity of acetic anhydride to form acetylsalicylic acid (aspirin) .



salicylic acid acetic anhydride

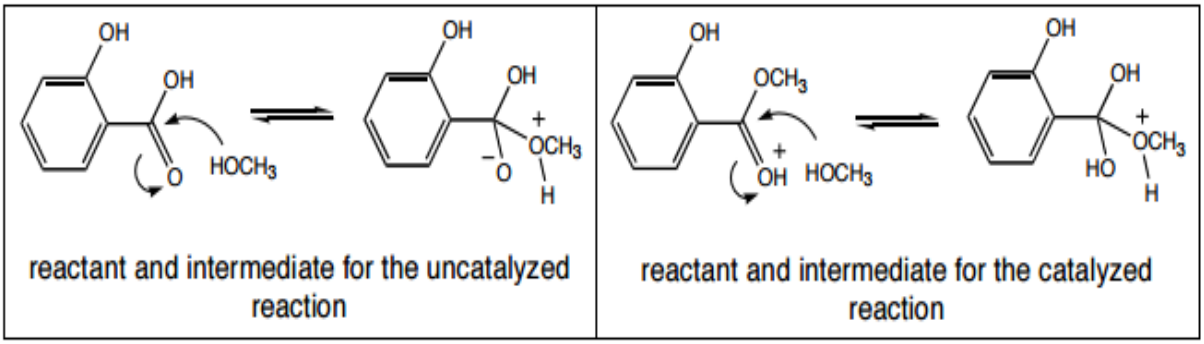
However, salicylic acid also has an electrophilic carbon atom as part of its carboxylic acid functional group. Thus, salicylic acid can react with nucleophilic molecules like methanol in addition to reacting with electrophilic molecules like acetic anhydride. The reaction of a carboxylic acid with an alcohol, an esterification, its analogues, amidation for example, and the reverse reactions, ester hydrolysis for example, are essential to life as we know it. Today's reaction, the reaction of salicylic acid with methanol, is not a vitally important reaction, but it does produce an interesting product never the less.

Esters often have interesting aromas associated with them. For example, many of the flavors that wines develop are formed when alcohols and carboxylic acids in the wine combine to form esters. The reaction that we will be doing is interesting for at least two reasons. Firstly, for the reaction to proceed at an appreciable rate, we must add an acid catalyst. Secondly, the reaction is an equilibrium reaction and particular effort must be made to drive the reaction to completion .



By protonation the carbonyl (C=O), the carbonyl carbon becomes more electrophilic. Additionally, since the intermediate for the catalyzed reaction is not zwitter ionic, as it is in the un catalyzed reaction ,the transition state that leads to the intermediate is lower in energy for the catalyzed reaction as compared to the un catalyzed reaction. The acid catalyst also lowers the activation energy for the elimination of water from the intermediate. While the addition of the acid gets the reaction going, it cannot drive the equilibrium towards the products. Instead, this reaction will be driven to completion by the addition of excess methanol. Alternative methods for driving the reaction to completion include the removal of water from the reaction.

Scheme 1



Chemicals Required:

0.65 g salicylic acid, 2.0 mL methanol, 0.75 mL concentrated sulfuric acid, 1 mL CH_2Cl_2
1 mL 5% sodium bicarbonate solution.

Procedure:

Formation of methyl salicylate

1. Place 0.65 g of salicylic acid, 2.0 mL methanol, and a spin vane in a 5-mL conical flask.
2. Stir the mixture until the salicylic acid dissolves.
3. Place the conical flask in an aluminum block on a stirring hotplate, and, while stirring, slowly, and in small portions, add 0.75 mL of concentrated sulfuric acid to the salicylic acid–methanol solution.
4. Attach the 5-mL conical flask to a water-cooled condenser, cap the condenser with a drying tube that has been loosely packed with $CaCl_2$.
5. Gently boil the solution for 75 minutes (maintain the temperature of the aluminum block at approximately 80 °C).

Isolation of methyl salicylate:

6. After the solution cools to room temperature, add 1 mL of CH_2Cl_2, to the reaction mixture
7. Shake the resulting suspension (with venting)
8. Allow the layers to separate, and transfer the organic layer, which contains your product, to another container.
9. Repeat steps 5, 6 and 7 twice more.
10. Add 1 mL of an aqueous 5% sodium bicarbonate solution to the combined CH_2Cl_2 extracts
11. Mix the solutions together, allow the solvents to separate, and transfer the organic layer to a clean, dry flask.
12. Dry the CH_2Cl_2 solution with anhydrous sodium sulfate.
13. Evaporate the CH_2Cl_2 using a warm water bath and a gentle stream of compressed air. Determine the mass of your product, and obtain an IR spectrum your product, methyl salicylate.
14. Obtain a copy of an IR spectrum of salicylic acid. Note the smell of your product.

Calculations:

Theoretical yield/Practical yield:

The theoretical yield is usually calculated from the equation
Practical Yield = x
Therefore, Percentage Practical Yield = Practical yield / Theoretical yield× 100

Uses:

- in high concentrations as a rubefacient and analgesic in deep heating liniments to treat joint and muscular pain.

- in low concentrations (0.04% and under) as a flavoring agent in chewing gum and mints.
- providing fragrance to various products and as an odor-masking agent for some organophosphate pesticides
- to clear plant or animal tissue samples of color, and as such is useful for microscopy and immunohistochemistry when excess pigments obscure structures or block light in the tissue being examined. This clearing generally only takes a few minutes, but the tissue must first be dehydrated in alcohol.
- as a transfer agent, to produce a manual copy of an image on a surface.
- in small amounts, to lower the freezing point of glacial acetic acid for transport.
- a simulant or surrogate for the research of chemical warfare agent sulfur mustard, due to its similar chemical and physical properties.

- an antiseptic in Listerine mouthwash .

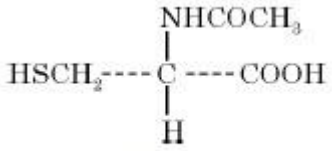
Practical lab 5

Synthesis of acetylcystiene

Theory:

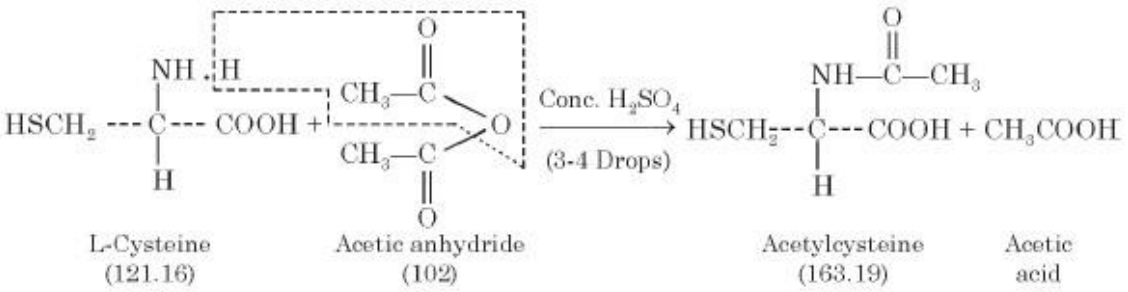
L-Cysteine is directly acetylated with acetic anhydride in the presence of a few drops of concentrated sulphuric acid to produce acetyl cysteine and a mole of acetic acid The H_2SO_4 present helps in the abstraction of one H-atom from the amino function of L-cysteine to form one mole of acetic acid.

Chemical Structure :



Acetylcysteine

Equation:



Chemicals Required:

(1) L-Cysteine : 5.4 g ; (2) Acetic anhydride : 9.0 ml ; (3) Conc. Sulphuric acid : 3–4 drops.

Procedure:

Follow the underlying steps sequentially :

1. Weigh 5.4 of L-cysteine and transfer to a 100 ml conical flask.
2. Add to the flask 9 ml of acetic anhydride and 3 to 4 drops of concentrated sulphuric acid carefully.
3. Mix the contents of the flask intimately, and warm the mixture over a water-bath maintained at 60°C for about 20 minutes with intermittent stirring.
4. Allow the contents of the flask to attain room temperature, and pour the contents in a thin stream right into 100 ml of cold water in a 250 ml beaker with frequent stirring with a glass rod.
5. Filter the crude product on a Buchner funnel using suction, wash it generously with

cold water, drain well and dry the product in an oven maintained at 80°C. The yield of crude acetyl cysteine (mp 106–110°C) is approximately 5.9 g.

Precautions :

(1) All glass apparatus used in the above synthesis should be perfectly dry.

(2) Addition of 3–4 drops of concentrated sulphuric acid must be done very carefully.

(3) The reaction mixture is to be warmed at 60°C for a duration of 20 minutes only.

Recrystallization;

The crude product may be Recrystallize from a mixture of rectified spirit and water (1 : 1). The yield of pure white, crystalline powder (mp 106–109.5°C) is 5.75 g.

Calculations:

Theoretical yield/Practical yield:

The theoretical yield is calculated from the equation as given below :

121 g of L-Cysteine on reacting with 102 g of acetic anhydride yields acetyl cysteine = 163 g

$\therefore$ 5.4 g of L-cysteine shall yield acetyl cysteine $= 163 / 121 \times 5.4 = 7.27$ g

Hence, Theoretical yield of Acetyl cysteine = **7.27 g**

Actual Practical yield = 5.9 g

Therefore, Percentage Practical yield = Practical yield / Theoretical yield $\times$ 100

$= 5.9 / 7.27 \times 100 =$ **81.15**

Uses :

(1) It reduces the viscosity of pulmonary secretions and facilitate their removal.

(2) It is most effective in 10% to 20% solutions with a pH of 7 to 9 ; and is mostly employed either by **direct instillation*** or by **acerosol nebulization**.**

(3) Administration of N-Acetyl cysteine (NAC) appears to reduce symptomatology associated with *influenza* and *influenza-like* episodes.

(4) Oral supplementation with NAC might be a prudent recommendation for smokers or individuals constantly exposed to second-hand smoke.

(5) NAC is the **antidote of choice** for acetaminophen (*i.e.*, paracetamol) overdose or poisoning.

(6) NAC seems to have some clinical usefulness as a **chelating agent** in the therapy of *heavy-metal poisoning.* (NAC effectively chelates Au, Ag and Hg.)

(7) NAC may have a beneficial therapeutic effect on ocular symptoms of **Sjogren's Syndrome**.

Practical lab 6

Synthesis of paracetamol

Theory:

Many preparative methods have since been described for the synthesis of paracetamol, mostly employing the acetylation of *para*-aminophenol with acetic anhydride as indicated above. However, a number of *other routes of synthesis* have also been discovered and used commercially,

(*a*) **Phenol—**is converted to *para*-nitrosophenol and then reduced and acetylated.

(*b*) **Late sixties—**a single-step synthesis from **nitrobenzene** to *para*-aminophenol was *patented*.

(*c*) **Late seventies—**observed a new entrant to the field using a process starting from **mono chlorobenezene** followed by *nitration, hydrolysis* and *acetylation*.

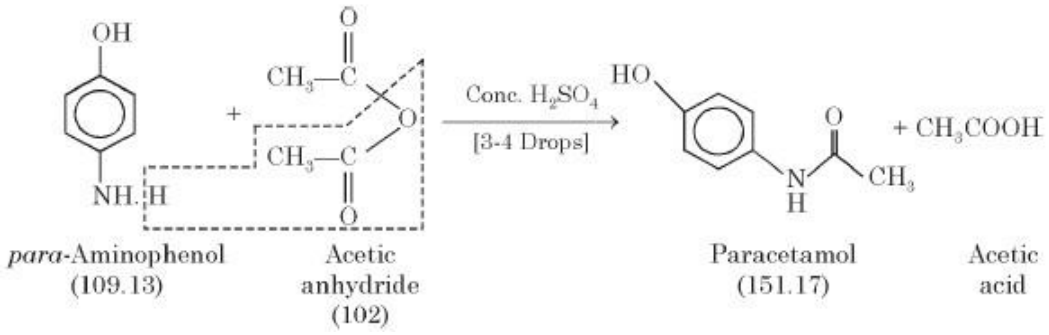
(*d*) **Mid-eighties—**saw an altogether '*new route of synthesis*' starting from **phenol**, but employing an **innovative technology** *via* **4-hydroxyacetophenone** followed by a *rearrangement* to **paracetamol**.

(*e*) **Paracetamol—**synthesis by one-step *Pd-La/C catalytic hydrogenation* and *acylation**. Here, *para*-nitro phenol is used as a starting material. The optimal reaction conditions are as follows : reaction temperature 140°C, reaction pressure 0.7 MPa and reaction time 2 hours. The yield of paracetamol is up to 97%.

Chemical Structure:

Paracetamol

Equation:



para-Aminophenol (109.13) | Acetic anhydride (102) | Paracetamol (151.17) | Acetic acid

Chemicals Required:

para-Aminophenol : 6 g ; Acetic anhydride : 6.5 ml ; Concentrated Sulphuric acid : 4 drops.

Procedure:

The various steps are enumerated as under :

1. Weigh 6 g of *para*-aminophenol and transfer to a 100 ml thoroughly cleaned and dried conical flask.
2. Add to the flask 6.5 ml of acetic anhydride and 3–4 drops of concentrated sulphuric acid **cautiously**.
3. The contents of the flask may be mixed thoroughly. Warm the mixture on a water bath previously maintained at 60°C for about 20–25 minutes with constant stirring.
4. Allow the contents of the flask to attain room temperature, and pour it directly into a beaker having 100 ml of cold water (with a few chips of crushed ice) and stir it vigorously.
5. The crude product obtained in (4) is filtered onto a Büchner funnel using suction, wash it with plenty of **cold water**, drain well and dry the product either between the folds of filter paper and air-dry it or dry it in an electric oven maintained at 100°C.

The yield of crude paracetamol (169–170.5°C) is approximately 6.8 g.

Precautions:

(1) All glass apparatus which are used in the synthesis must be perfectly dry.
(2) Concentrated sulphuric acid should always be added with great caution.
(3) To complete the reaction mixture it must be warmed at 60°C for 20–25 minutes.

Recrystallization:

Dissolve the crude product in 70% (*v/v*) ethanol and warm it to 60°C ; add 2 g of powdered animal charcoal (decolorizing carbon). Filter and concentrate the filtrate over a water-bath. Allow it to cool and large monoclinic crystals will separate out.

The yield of the pure paracetamol (mp 169–170.5°C) is 6.5 g.

Calculations:

Theoretical yield/Practical yield

109 g of *p*-Aminophenol on acetylation with 102 g of acetic anhydride yields Paracetamol = 151 g

6 g of *p*-Aminophenol shall yield Paracetamol = $151 / 109 \times 6 = 8.31$ g

Hence, Theoretical yield of Paracetamol = **8.31 g**

Reported Practical yield = 6.8 g

Therefore, Percentage Practical yield = $\text{Practical yield} / \text{Theoretical yield} \times 100$

$= 6.8 / 8.31 \times 100 =$ **81.82**

Uses:

(1) It is an effective *antipyretic* and *analgesic* ; the former activity *i.e.*, **antipyresis** is caused by acting on the hypothalamic heat-regulating centre, whereas the latter action

i.e., **analgesia** by elevating the pain-threshold.

(2) It is also found to be useful in diseases accompanied by pain, discomfort, and fever, for instance : the common cold and other viral infections.

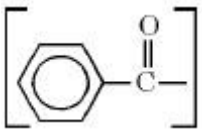
(3) It is also effective in a wide spectrum of *arthritic* and *rheumatic* conditions involving *musculoskeletal pain* as well as the pain caused due to headache, dysmenorrhea*, myalgias,** and neuralgias.***

(4) Unlike aspirin, paracetamol **does not antagonize** the effects of *uricosuric agents*.

Benzoylation methods

Introduction:

The insertion of a benzoyl moiety instead of the active hydrogen atom present in hydroxyl (—OH), primary amino (—NH2) or secondary amine function (> NH) is usually termed as the '**Benzoylation Reaction**'. Interestingly, this particular reaction essentially bears a close resemblance to the phenomenon of '*Acetylation*', except that in this specific instance the reagent employed is '**benzoyl chloride**' which reacts in the presence of **Pyridine** or *Sodium hydroxide* and NOT benzoic anhydride (as in the case of '*acetylation*').



Schotten-Baumann Reaction:

In the Schotten-Baumann method of benzoylation, the hydroxyl or amino compound (or a salt of the latter) is either suspended or dissolved in an excess of freshly prepared *10%* (*w*/*v*) *aqueous sodium hydroxide solution*, together with a *small excess of benzoyl chloride* (*i.e.*, nearly 10% more than the theoretical quantity), and the resulting mixture is shaken vigorously in ambient conditions. It has been observed that under these experimental parameters '**benzoylation**' proceeds smoothly. Thus, the solid benzoylated product, which being insoluble in the aqueous medium, gets separated briskly. Simultaneously, the NaOH solution hydrolyses the excess of benzoyl chloride present in reaction mixture, thereby resulting into the formation of **sodium chloride** and **sodium benzoate**, which being water soluble remain in solution

.

Advantages of Benzoylation over Acetylation:

There are, in fact, *two* major advantages of benzoylation over acetylation, namely :

(*a*) *First*, generally the benzoyl derivatives are obtained as crystalline solids having comparatively **higher melting points** than the corresponding acetyl derivatives ;mbesides, possessing **lower solubilities** in a wide range of solvents.

(*b*) *Secondly*, the benzoyl derivatives may be prepared rapidly and conveniently in **aqueous medium**, as compared to the 'acetylation' carried out in acetic anhydride, acetyl chloride, and glacial acetic acid ; in addition to the fact that *benzoyl chloride* undergoes hydrolysis rather extremely slowly and sluggishly.

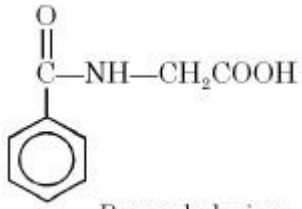
Practical lab 7

Synthesis of Benzoyl Glycine

Theory:

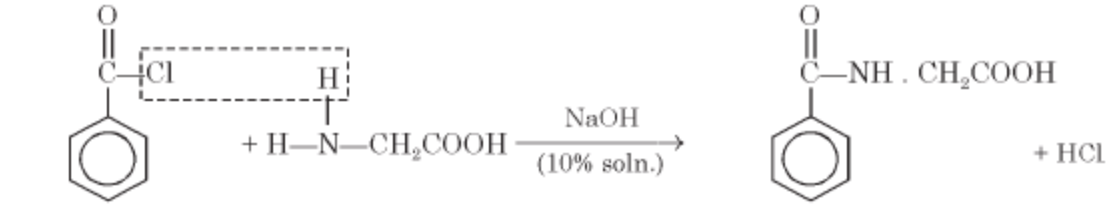
Glycine (*i.e.*, α-aminoacetic acid) interacts with one mole of benzoyl chloride, in the presence of 10% (*w*/*v*) NaOH solution, to yield benzoyl glycine with the elimination of one mole of HCl. The excess of 10% NaOH solution serves two purposes, namely : *first*, to remove the un reacted benzoyl chloride and *secondly*, the HCl eliminated reacts with NaOH to yield NaCl. Interestingly, both sodium benzoate and sodium chloride are water-soluble, whereas the desired product benzoyl glycine being insoluble may be separated easily.

Chemical Structure:



Benzoyl glycine

Equation:



Benzoyl chloride (135.5) | Glycine (75.07) | Benzoyl glycine (179.18)

Chemicals Required:

Glycine 5 g ; Sodium hydroxide solution 10% (*w*/*v*) : 50 ml ; Benzoyl chloride : 10.8 g (9.0 ml) ; Carbon tetrachloride : 20 ml ; Conc. Hydrochloric acid : 5 ml .

Procedure:

The various steps involved are as follows :

1.Dissolve 5 g (0.33 mol) of glycine in 50 ml of 10% NaOH solution contained in a 250 conical flask.

2.Transfer 10.8 g (9 ml, 0.385 mol) of benzoyl chloride in approximately five equal lots to the above solution (1).

3.Stopper the 250 ml flask securedly with a rubber-cork and shake the contents vigorously after each addition unless and until all the benzoyl chloride has virtually reacted.

4. Pour the contents of the flask to a 250 ml beaker and rinse the flask with a little water.
5. Add a few grams of crushed-ice into the solution and acidify the contents by adding concentrated hydrochloric acid drop wise and carefully with constant stirring until the mixture is acid to Congo red paper (pH 5.0 Red ; pH 3.0 Blue-Violet).
6. Collect the resulting crystalline precipitate of benzoyl glycine, which is contaminated with a small amount of benzoic acid, on a Büchner funnel, wash with cold water and drain well by the help of an inverted glass stopper.
7. Transfer the solid into a beaker containing 20 ml of carbon tetrachloride, cover it with a clean water-glass, and boil it gently over an electric water-bath for 10 minutes (bp CCl_4 76.7°C). Thus, it will extract any benzoic acid which may have been produced during the course of reaction (FUME CUPBOARD).
8. The resulting mixture is allowed to cool slightly, filter under gentle suction and wash the crude product on the filter with 10-20 ml of CCl_4. The yield of the crude benzoyl glycine (mp 185–186.5°C) is 9.2 g.

Precautions:

(1) The addition of benzoyl chloride to the alkaline mixture of glycine must be carried out slowly and that too under different stages.
(2) Continuous shaking of the above mixture be done till the whole of benzoyl chloride has reacted.
(3) It is necessary to render the resulting mixture to acidic conditions with Congo Red paper.

Recrystallization:

Recrystallize the dried crude product from 100 ml of boiling distilled water with the addition of 1–2 g of powdered decolorizing carbon (activated carbon), if necessary, filter through a hot-water funnel and allow to crystallize. Collect the benzoyl glycine on a Büchner funnel under suction and dry the pure product in an oven maintained at 110°C. The yield is 8.8 g (mp 186.5-187°C).

Calculations:

Theoretical yield/Practical yield:

The theoretical yield is calculated from the equation under theory as given below :
75.07 g of Glycine on reaction with 135.5 g of Benzoyl chloride
yields Benzoyl glycine = 179.18 g
∴ 5 g of Glycine shall yield Benzoyl glycine = $179.18 / 75.07 \times 5 = 11.9$ g
Hence, Theoretical yield of Benzoyl glycine = **11.9 g**
Reported Practical yield = 8.8 g
Therefore, Percentage Practical yield = Practical yield / Theoretical yield × 100
$= 8.8 / 11.9 \times 100 =$ **73.9**

Uses:

Conjugation with amino acids is an important route in the conjugation of drug and xenobiotic carboxylic acids for elimination. These amino acid conjugates are usually less toxic than their precursor acids and hence, are excreted readily into the urine and bile.

Practical lab 8

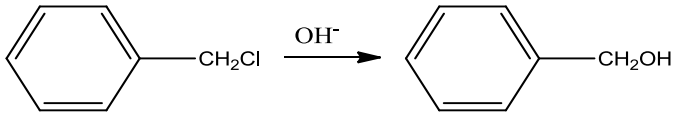
Canizzaro Reaction

benzoic acid and benzyl alcohol

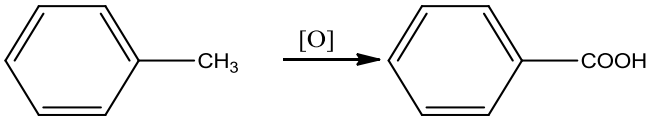
Theory:

Both benzoic acid and benzyl alcohol can be prepared in laboratory by Canizzaro reaction by the action of sodium or potassium hydroxide on benzaldehyde.

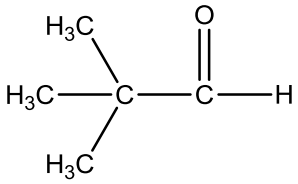
Benzyl alcohol can be prepared by the hydrolysis of benzyl chloride with sodium hydroxide.



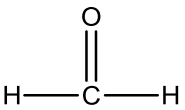
Benzoic can be prepared by the oxidation of toluene using oxidizing agent.



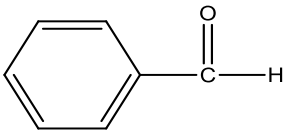
Examples for some compounds to interact by Canizzaro reaction are



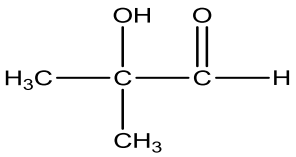
Trimethyl acetaldehyde,



Formaldehyde,

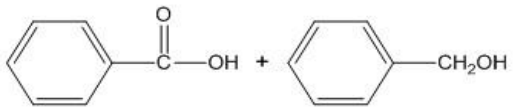


Benzaldehyde



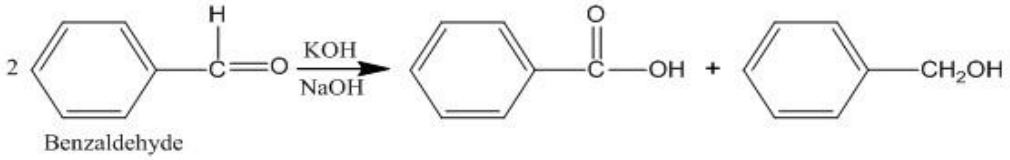
α-hydroxy-3-isobutyraldehyde

chemical structure



Benzoic acid **Benzaldehyde**

Equation:



Chemical required:

Benzaldehyde 7.3 ml**;** KOH 7.2ml.

Procedure:

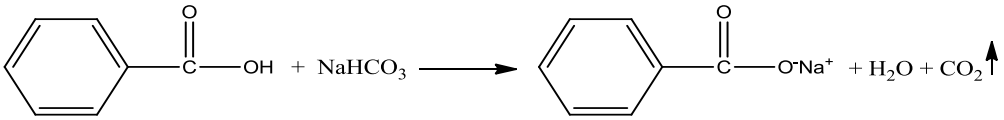
1. Wash the reagent bottle.
2. Put 7.2 g of KOH.
3. Add 7 ml tap water.
4. Cool the solution (Canizzaro reaction is exothermic).
5. Add 7.3 ml of benzaldehyde.
6. Shake 15 min until thick white emulsion formed.
7. Allow the mixture above to stand to the next lab by which time the reaction should have been completed.

Properties of benzyl alcohol

1. Colorless to very fine yellow (due to oxidation) oily liquid.
2. Immiscible with water, miscible with organic solvents like ether.
3. Boiling point is 204-207 ºC.

Properties of benzoic acid

1. White crystalline plates or needles.
2. Sparingly soluble in water, soluble in hot boiled water.
3. Volatile with steam (so can be purified by sublimation).
4. Reacts with sod. bicarbonate to give CO_2 gas.



5. Melting point is 121-123 ºC.

Uses

Both alcohols and organic acids are well known for their biological actions.

1. Antibacterial properties.
2. Preservatives for food and pharmaceutical local application as antiseptics.

Benzyl alcohol has some local anesthetic properties, it is useful as antipruretic and is the reason for its inclusion in some dental remedies and injectable in pharmaceutical preparations intended for local application, benzyl alcohol has been used up to 10 % in ointments as antipruretic and to prevent secondary infections.

In injectable, it is included in many painful IM injectable, both as a preservative and as a local anesthetic. On the other hand, benzoic acid is used as a food preservative as a free acid, or in the form of sodium salt, also used externally in form of lotions, ointments, mouth washes, etc.

Practical lab 9

Separation of benzoic acid and benzyl alcohol

Procedure:

1. Take the reagent bottle obtained in lab. 1 and add just sufficient water (about 30 ml) to complete dissolve the potassium benzoate. Shaking with stirrer to completely dissolve the pot. benzoate, transfer to a separatory funnel.
2. Wash the reagent bottle with about 10 ml of ether to complete dissolving of benzyl alcohol remaining in the reagent bottle.
3. Add everything in the reagent bottle to the separatory funnel. Shake well for 5 min and leave for few minutes for settling.
4. It will be separated into 2 layers: aqueous later which contains benzoic acid as pot. benzoate and ethereal layer which contains benzyl alcohol and unreacted benzaldehyde.
5. Take the ethereal layer and shake twice with 3-ml portions of saturated solutions of sod. bisulfate $NaHSO_3$ to remove any excess or unreacted benzaldehyde.
6. Separate the oily liquid from the aqueous $NaHSO_3$ solution. Wash this oily liquid with 5 ml of 10 % Na_2CO_3 to ensure complete removal of the bisulfate solution.

$$Na_2CO_3 + 2NaHSO_3 \longrightarrow CO_2\uparrow + H_2O + 2NaSO_3$$

ex. sod. bisulfite -in ether layer — sod. sulfite

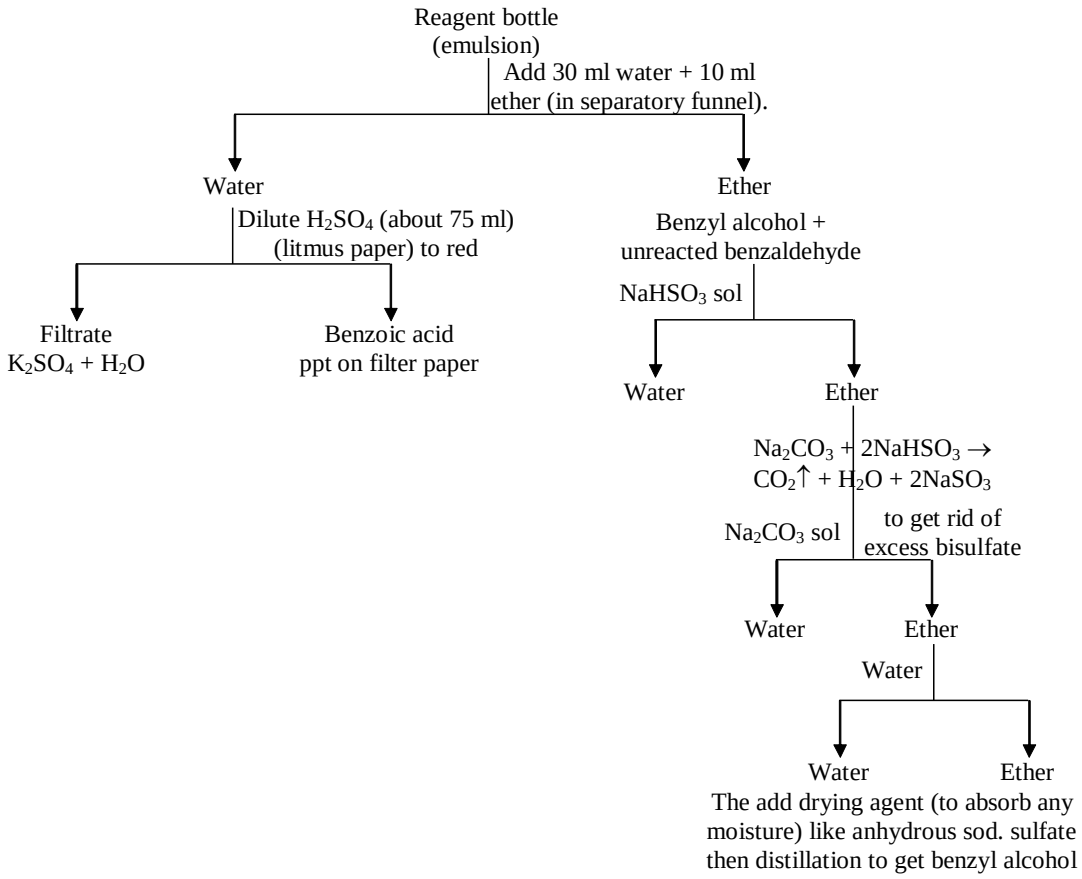
7. Wash with 5 ml of water. Separate the oily liquid once more and dry over anhydrous sod. sulfate (or calcium chloride) to absorb any moisture (act as drying agents).

There are other compounds used as drying agents as: anhydrous magnesium sulfate $MgSO_4$ or anhydrous pot. carbonate K_2CO_3.

8. Pour the watery layer into dilute H_2SO_4 (about 75 ml) and check with litmus paper till convert to red color (acidic solution) leading to formation of white ppt of benzoic acid.
9. Cool and filter the ppt by filter paper to get benzoic acid.

$$Ar\text{-}COO^-K^+ + H_2SO_4\ (dil) \rightarrow Ar\text{-}COOH + KHSO_4$$

We prevent excess dilute H_2SO_4 to avoid dissolving of benzoic acid (like dissolve like)



Recrystallization of benzoic acid

Procedure:

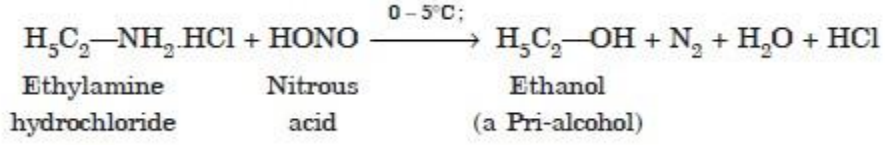
Benzoic acid can be purified by recrystallization from water because of its high solubility in hot water and poor solubility in cold water, the avoidance of organic solvents for the recrystallization makes this experiment particularly safe. Other possible recrystallization solvents include acetic acid (anhydrous or aqueous), benzene, petroleum ether, and a mixture of ethanol and water.

Diazotization and coupling reactions

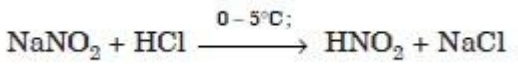
[A] Diazotization Reactions:

There exists a marked and pronounced difference between the *aliphatic amines* and the *primary aromatic amines* ; whereby the former reacts with **cold aqueous nitrous acid (HNO2)** to give rise to the formation of the corresponding *primary alcohol* as the major product of reaction ; and the latter under identical experimental parameters exclusively results into the formation of *benzenediazonium chloride* (salt), sometimes also termed as *diazo-benzene chloride* as illustrated below :

(*a*) **Ethylamine (an aliphatic amine)**

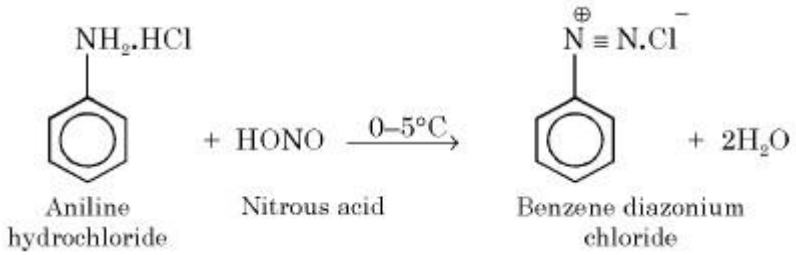


In the above reaction HNO2 (*i.e.,* nitrous acid) is generated by the interaction of sodium nitrite and dilute HCl as given below :



Nitrous acid is highly unstable and extremely volatile in nature ; therefore, the above reaction is invariably carried out between 0–5°C so that the HNO2 generated instantly is fully utilized in the diazotization process. In this particular instance the two atoms of nitrogen escape out of the reaction mixture as nitrogen gas (N2) leaving behind the primary aliphatic alcohol (*i.e.,* ethanol) in the reaction mixture.

(*b*) **Aniline (an aromatic primary amine)**

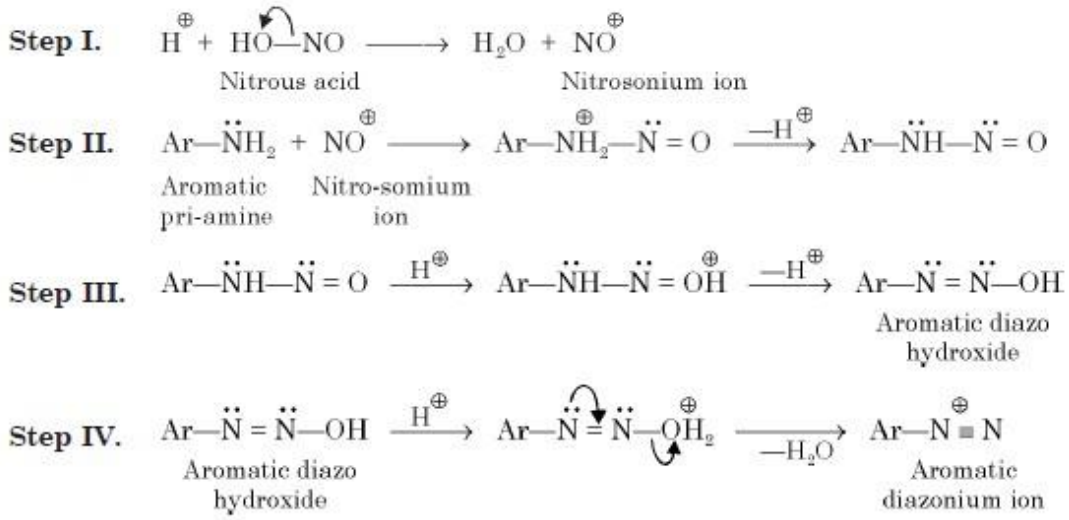


In the aforesaid reaction, aniline first-gets solubilized as its hydrochloride (*i.e.,* aniline hydrochloride) in aqueous medium ; thereafter, it undergoes diazotization with nitrous acid 0–5°C yielding the *benzene diazonium chloride* (salt) plus liberating *two* moles of water.

It is pertinent to mention here that the +ve charge usually resides on the N-atom *nearer to the aromatic ring* as shown above by virtue of the fact that the said N-atom is deficient in electrons (*i.e.,* N-atom has only four valancies out of five) ; and the second N–atom away from the benzene nucleus has all the three valancies duly satisfied. (**Note.** *N atom has two valancies 3 and 5).*

Mechanism:

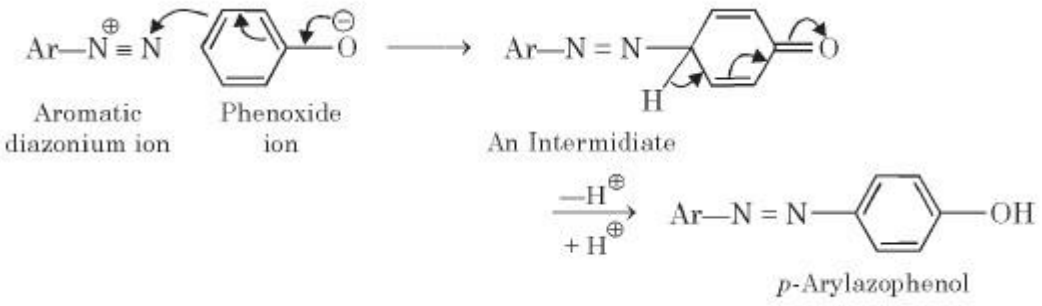
The formation of the *diazonium ion* by the interaction of **nitrous acid** and **aromatic primary amine** is usually accomplished by means of the following *four* sequential steps



[B] Coupling Reactions:

The **coupling reaction** is defined as—'An electrophilic substitution reaction involving the diazonium ion that eventually reacts at the position of greatest electron availability, *i.e.*, the position either *ortho*-or *para*-to the electron releasing amino or phenoxy functions'.
It has been observed that usually the **diazonium salt** couples at a vacant *para*-position, but in case this position is not available free, coupling invariably takes place at *ortho*position.

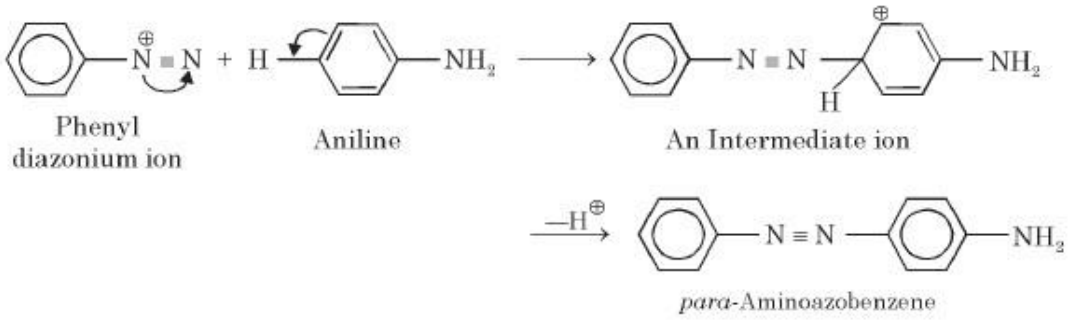
1. **Coupling Reaction with Phenoxy Function :**



The interaction between aromatic diazonium ion and the peroxide ion undergo several proto tropic shifts to give rise to a coupled intermediate product, which further affords intramolecular rearrangement to yield *para*-arylazophenol.

2. **Coupling Reaction with Amino Function :**

The reaction between phenyl diazonium ion and aniline results into the formation of an intermediate ion, which upon loss of a proton yields the coupled product *p*-aminoazo-benzene.



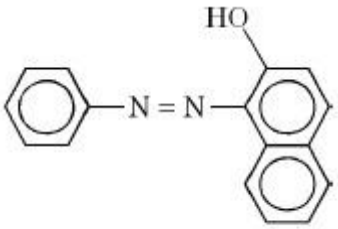
Practical lab 10

Synthesis of Phenyl-azo-β-Naphthol

Theory:

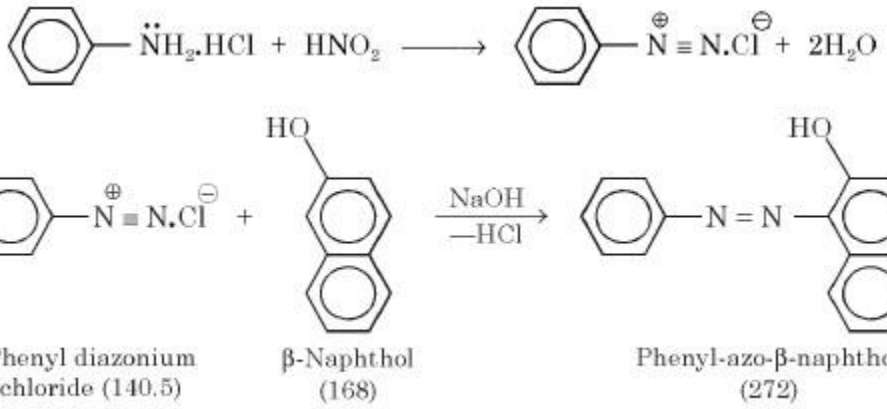
Phenyl diazonium chloride is obtained first by the diazotization of aniline with nitrous acid as explained earlier, which on coupling with β-Naphthol in the presence of NaOH solution yields the desired coupled product phenyl-azo-β-Naphthol. A mole of HCl is eliminated which instantly reacts with NaOH from the medium to produce NaCl and H2O. Importantly, both diazotization and coupling reactions are required to be carried out between 0-5°C.

Chemical Structure:



Phenyl-azo-β-naphthol

Equation:



Chemicals Required:

Aniline (freshly distilled) : 4.0 g ; Hydrochloric acid conc. (12 N) : 12.8 ml ; β-Naphthol : 6.24 g ; Sodium hydroxide solution [10% (w/v)] : 40 ml ; Sodium nitrite (pure) : 3.2 g ;

Procedure:

1. In a 250 ml beaker dissolve 4.0 g (3.92 ml ; 0.054 mol) of aniline in 12.8 ml conc. HCl and dilute it with 12.8 ml distilled water. Cool the contents of the beaker in an ice bath with frequent stirring till it attains a temperature between 0-5°C. [One may observe that the

freshly distilled oily aniline has completely dissolved in the aqueous medium as aniline hydrochloride.]

2. Meanwhile, dissolve separately 3.2 g sodium nitrite in 15 ml water and chill the solution also in the same ice-bath (0–5°C).

3. Diazotize the aniline solution (1) by the addition of sodium nitrite solution (2) in small lots (2 ml) at a time in intervals with vigorous stirring with a glass rod taking care that the temperature of the reaction mixture must not exceed beyond 5°C at any cost. (If required 10-15 g of crushed ice may be added into the reaction mixture to ensure proper chilling while diazotization is on).

4. After the complete addition of sodium nitrite solution, it is required to test the reaction mixture for the presence of free nitrite by taking out a drop of it and immediately placing it on KI-starch paper that will distinctly turn blue in the presence of free nitrous acid. (It may be noted that by using good quality sodium nitrite and adding 10% excess than the theoretical value one may ascertain completion of diazotization reaction).

5. Dissolve 6.24 g (0.054 mol) β-Naphthol separately in a 250 ml beaker in 40 ml of sodium hydroxide solution, and cool the Naphthol-solution in an ice-bath (0-5°C).

6. Cautiously and slowly add the cold diazonium salt solution to the β-Naphthol solution with vigorous constant stirring. Special care must be taken for not allowing the temperature of the reaction mixture rise beyond 5°C. If need be, crushed ice should be added in between while the coupling-reaction proceeds.

7. A red color develops and crystals of crude phenyl-azo-β-Naphthol separate out. Allow the reaction mixture to stand for 30-40 minutes with stirring in between so as to complete the reaction. Filter the red product in a Buchner funnel using suction, and wash the same with ice-cold water. Drain the water by pressing with an inverted glass-stopper.

The yield of crude product mp 129-130°C is 9.5 g..

Precautions:

(1) Aniline should be dissolved in aqueous HCl and cooled to 0-5°C.

(2) Good quality of $NaNO_2$ must be used ; and about 10% extra amount actually employed from the theoretical amount.

(3) The solution of β-Naphthol in 10% (w/v) aqueous NaOH is made and chilled to 0-5°C.

(4) The coupling reaction is carried out in an ice-bath only because heat is generated during the course of reaction.

Recrystallization:

The crude product (9.5 g) may be Recrystallize from approximately 100-110 ml glacial acetic acid, and filter the deep red crystals with suction, wash with a little ethanol (or methylated spirit) to get rid of any residual glacial acetic acid. Finally dry the pure crystallized product upon filter paper. The yield of pure phenyl-azo-1-naphthol mp 130.5-131°C is 9.1 g.

Uses:

(1) It is used as an important and useful stain for various pathological objects.

(2) It also finds its application as a biological stain.

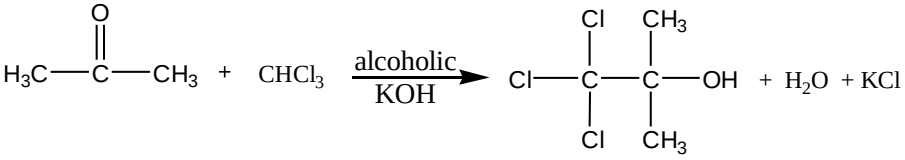
Practical lab 11

synthesis Chlorobutanol

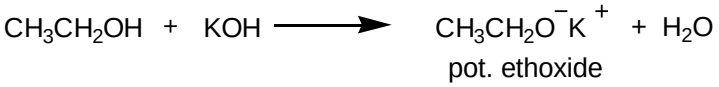
Theory:

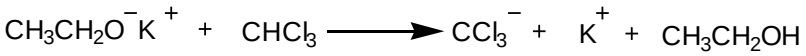
Chlorobutanol is formed by the simple nucleophilic addition of chloroform and acetone, this reaction is base driven by potassium or sodium hydroxide.

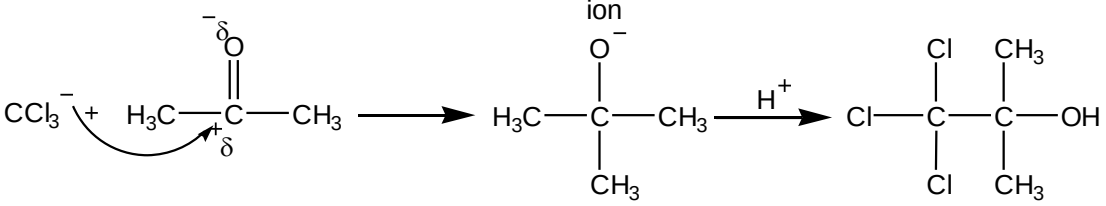
Alcoholic KOH is used in order to accelerate the reaction towards formation of Chlorobutanol.



Mechanism of reaction:







$K^+ + Cl^- \rightarrow KCl$ (white ppt)

The source of Cl^- came from dissociation of another chloroform molecule.

Firstly, we obtain white ppt of KCl, we must get rid of it by filtration then we must evaporate alcohol to obtain Chlorobutanol.

Chemicals Required:

Acetone 50gm ;chloroform 20gm;KOH 3.5gm:ethanol.

Procedure:

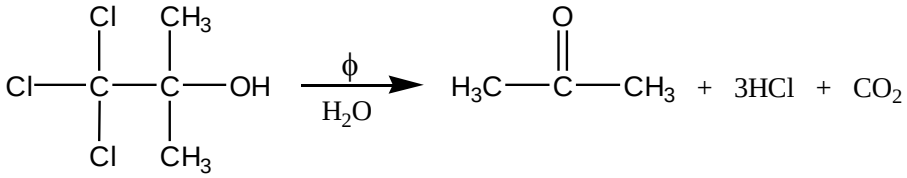
1. In a dry conical flask about 500 ml put 50 g of acetone with 20 g of chloroform.
2. Cool the mixture.
3. Alcoholic solution is prepared from dissolving 3.5 g of KOH in the minimum amount of ethanol (rectified spirit).
4. Add Alcoholic solution in step 3 to the mixture of step 2.
5. Filter the precipitated KCl and wash it twice with small portions of acetone.
6. Evaporate in water bath.

7. Recrystallize from the mixture of water and ethanol.

Physical properties:

It is white crystalline powder found in two forms: anhydrous and hydrated, also it has characteristic camphor-like odor and taste. The melting point is 95-99 C and boiling point is 167 C

It is freely soluble in alcohol (1:1) slightly soluble in cold water (1:125) and more soluble in boiling water but such high temperature may lead to hydrolysis of Chlorobutanol.



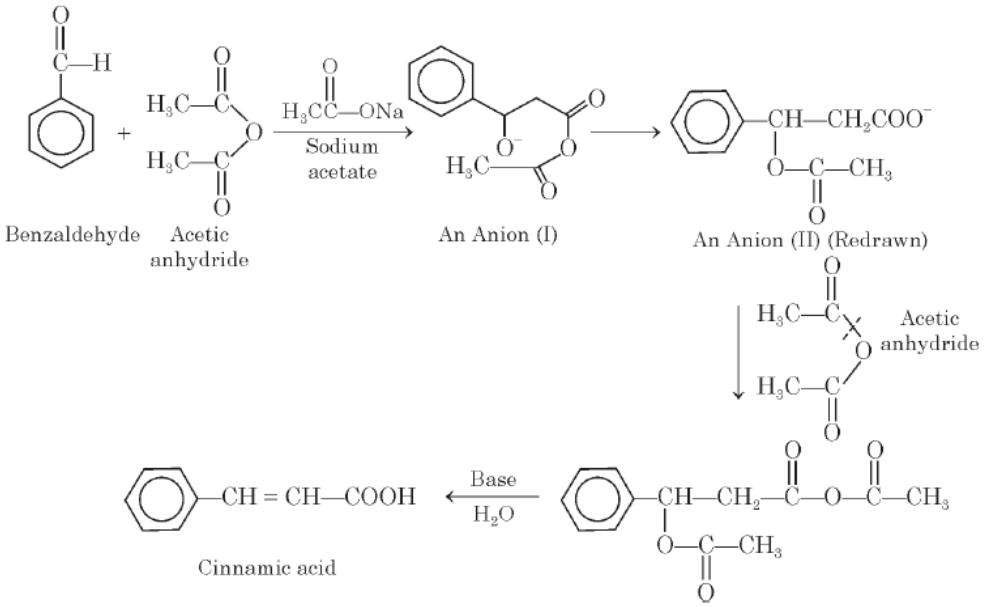
So it must be Recrystallize from water/alcohol mixture. Water is not good solvent for recrystallization and often hydro alcoholic mixtures are used for this purpose.

Uses:

1. Bacteriostatic use as preservatives in many injectable, ophthalmic and intranasal preparations.
2. Sedative, hypnotic and in motion sickness.
3. Local anesthetic in many painful IM injections and dental preparations.

Perkin Reaction:

The formation of α, β-unsaturated carboxylic acid by '*Aldol Condensation*', *viz*., of aromatic aldehydes and acid anhydrides in the presence of an alkali salt of the acid is known as the **Perkin Reaction.***

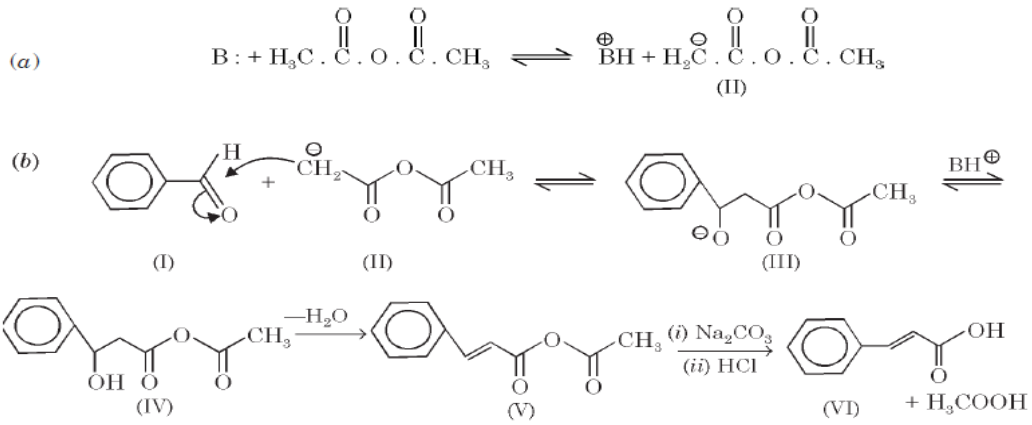


*

The above discourse of the **Perkin Reaction** is self-explanatory in which benzaldehyde and acetic anhydride interacts to form an anion (I) that undergoes molecular rearrangement to give another anion (II). The resulting restructured anion (II) reacts with acetic anhydride to form an intermediate which subsequently undergoes hydrolysis in the presence of a base to give rise to the formation of an α, β-unsaturated carboxylic acid

Mechanism of Perkin reaction:

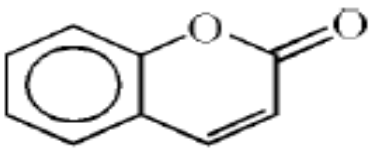
The mechanism of the reaction, which is of the Aldol-type may be expatiated with the help of the following equations (*a*) and (*b*) respectively.



Practical Lab 12

Coumarin

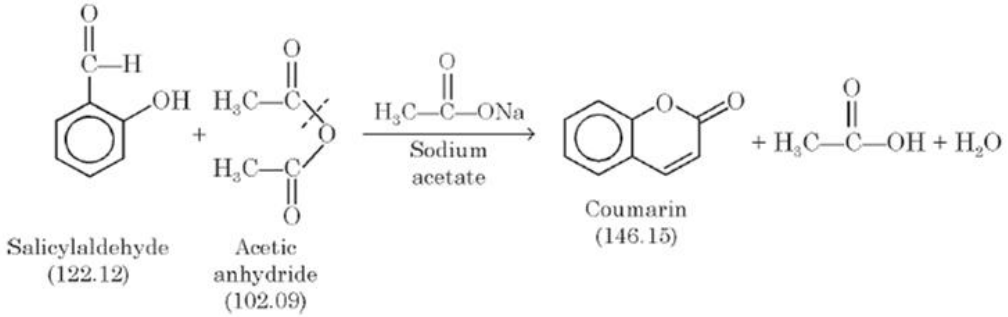
Chemical Structure:



Coumarin

Theory:

The interaction between benzaldehyde and acetic anhydride in the presence of sodium acetate results into the formation of the heterocyclic pyran ring to give coumarin in addition to a mole each of acetic acid and water as products of reaction.



Chemicals Required:

Salicylaldehyde : 8 g ; Acetic Anhydride : 20 ml ; Fused and finely powdered Sodium Acetate : 10 g ; Sodium Carbonate : q.s. ; and Activated Animal Charcoal : 2 g ;

Procedure:

The following steps may be adopted in a methodical manner as stated under :

(1) Transfer 8 g salicylaldehyde, 10 g fused sodium acetate and 20 ml acetic anhydride in a 250 ml round-bottomed flask duly installed with an air reflux condenser the top-end of which should be provided with a $CaCl_2$-guard tube.
(2) Heat the mixture in an oil-bath for a duration of 6 hours between 180-190°C.
(3) Cool the contents of the flask and subject it to steam distillation, so as to get rid of the un reacted salicylaldehyde completely, and discard the distillate.
(4) Add to the resulting residue in the flask solid Na_2CO_3 slowly and carefully until the solution is rendered alkaline to litmus paper.
(5) Chill the contents of the flask in an ice-bath when the desired product coumarin gets separated. Filter it in a Buchner funnel, wash with a little spray of cold water, drain well and dry it in filter paper folds.
The yield of the crude product is 4.3 g mp 68–69°C

. Precautions:

(1) Always use freshly fused and finely powdered sodium acetate in the Perkin Reaction.
(2) The heating of the reaction mixture in an oil-bath should be steady and gentle foa period of
6 hours at a stretch preferably.
(3) After removal of the un reacted salicylaldehyde by steam distillation the residual product must be made alkaline carefully by adding solid Na2CO3 to litmus paper.
(4) A small amount of activated decolorizing carbon powder may be used while recrystallizing
the crude product.

Recrystallization:

Dissolve the crude coumarin in 250-300 ml of boiling water and add to it 1-1.5 g of decolorizing carbon. Filter at the pump and concentrate the filtrate over a water bath till its volume becomes almost 1/3 rd its original volume. Keep it in the refrigerator overnight when beautiful crystals of pure coumarin shall separate out.

The yield of the pure coumarin is 4.0 g mp 68.5-70°C.

Theoretical Yield/Practical Yield:

The theoretical yield is calculated from the equation under theory as given below :
122.12 g of Salicylaldehyde on reacting with 102.09 g of Acetic
Anhydride yields Coumarin = 146.15 g
∴ 8 g of Salicylaldehyde shall yield Coumarin $= 146.15 / 122.12 \times 8 = 9.57$ g
Hence, Theoretical yield of Coumarin = **9.57 g**

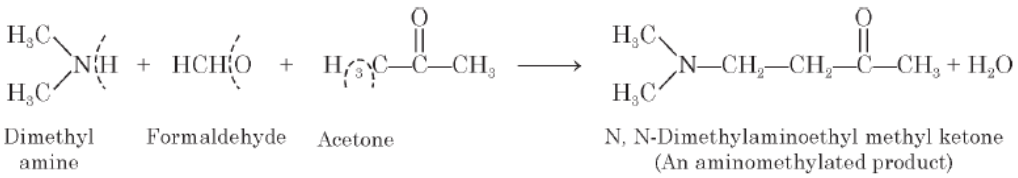
Reported Practical yield = 4.3 g
Therefore, Percentage Practical yield = Practical yield / Theoretical yield x100
= 4.3 / 9.57 x100 = **44.93**

Uses:

(1) It is used mostly as a flavoring agent in pharmaceutical preparations *i.e.*, as pharmaceutical
aid.
(2) Many structural analogues of 'coumarin' may be employed as anticoagulants.

Mannich Reaction:

The reaction of compounds having an active hydrogen atom with non-enolizable aldehydes
and ammonia or primary or secondary amines to give rise to the formation of amino ethylated product exclusively is commonly known as the **Mannich Reaction**; and the product is invariably termed as the **Mannich Base**, as depicted below:



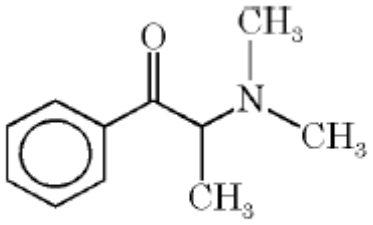
Explanation. The active H-atom of the methyl function in acetone, the H-atom of the secondary amine (dimethy amine) and the O-atom of the aldehyde (formaldehyde) gets eliminated as one mole of water. Thus, the resulting amino methylated product essentially possesses an additional methylene (—CH_2—) moiety. In other words, in all Mannich reactions the carbon-chain shall be increased by **one** due to the —CH_2— methylene function forming a part of the Mannich Base.

In general, the Mannich bases are scantly water soluble ; therefore, they are mostly employed as their respective hydrochlorides which are fairly water soluble.

practical lab 13

Metamfepramone

Chemical structure



Metamfepramone

Theory:

Acetophenone (120.15) | Paraformaldehyde | Dimethylamine hydrochloride (81.58) | Metamfepramone hydrochloride [salt] (213.75)

Acetophenone reacts with dimethylamine hydrochloride along with one mole of formaldehyde (obtained from **para formaldehyde** which is polymerized formaldehyde) to yield the corresponding salt metamfepramone hydrochloride plus a mole of water. Most of the Mannich reactions, it is a practice to make use of the hydrochloride salt of the secondary amine, so that the reaction moves faster in the solubilized conditions ; and the resulting condensed product, with an additional methylene linkage (—CH_2—) is also obtained as its HCL salt.

Chemicals Required:

Dimethylamine hydrochloride : 6.6 g ; Para formaldehyde : 2.5 g ; Acetophenone : 7.5 ml ; Acetone : 75 ml ; Rectified spirit : 25 ml ;Ethanol : 10 ml.

Procedure:

The various steps followed are as given below :

(1) Transfer 6.6 g dimethylamine hydrochloride, 2.5 g para formaldehyde, and 7.5 ml acetophenone into a 250 ml round-bottom flask fitted with a reflux condenser.

(2) Add to the flask 10 ml of ethanol and a few drops of acetophenone, and shake the contents thoroughly.

(3) Reflux the reaction mixture on an electric water bath for a duration of 2 hours until it becomes perfectly clear and homogeneous. In case, any residue still appears, filter it and discard the same.

(4) Add to the resulting clear filtrate 50 ml acetone and keep it in a refrigerator overnight.

when the salt of the Mannich base *i.e.*, metamfepramone hydrochloride gets separated.

(5) Filter the solid residue in a Büchner funnel under suction, wash with a spray of 4–5 ml acetone and dry in the folds of filter paper.
The yield of the crude product is 9.7 g having mp ranging between 201–203°C.

Precautions:

(1) All the reagents used in the condensation Mannich reaction should be preferably free from any moisture, whatsoever.
(2) After refluxing the reaction mixture for 2 hours, any solid residue appearing must be discarded immediately by simple filtration under suction.
(3) The product may be either air dried or within the folds of filter paper conveniently.

Recrystallization:

The crude product may be Recrystallize by dissolving the same in minimum quantity of a mixture of rectified spirit and acetone (1 : 5) when pure metamfepramone hydrochloride is obtained as crystals having mp 202–204°C and yield 9.3 g.

Theoretical Yield/Practical Yield:

The theoretical yield is calculated from the equation under theory as follows :
120.15 g of Acetophenone on interacting with **81.58** g of Dimethylamine hydrochloride yields Metamfepramone HCl = **213.75 g**
∴ 7.75 g* of Acetophenone shall yield Metamfepramone HCl $= 213\ 75 / 120\ 15 \times 7.75 =$ **13.79g**
Hence, Theoretical yield of Metamfepramone HCl = **13.79 g**
Reported Practical yield **= 9.7** g
Therefore, Percentage Practical yield $= (practical\ yield)/(Theoretical\ yield) \times 100$
=9. $70/13.79 \times 100 = 70.34$

Uses:

(1) It is reported to be a sympathomimetic agent used as the hydrochloride in the treatment of *hypotension.*
(2) It is also employed in preparations for the relief of the symptoms of the *common cold.*
(3) It was *formerly* used as an *anorectic agent***

. * The d_{15}^{15} of Acetophenone is 1.033.
** **Anorectic Agent.** An agent that decreases the appetite appreciably.

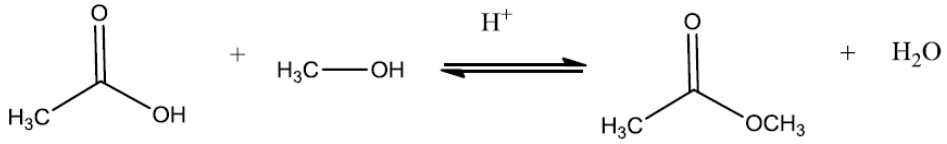
Practical Lab 14

Preparation of Methyl Benzoate

Theory:

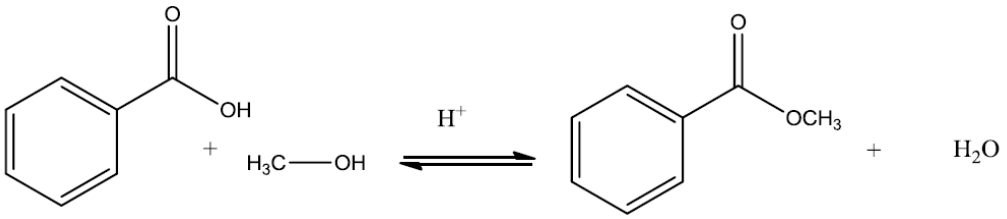
The ester group is an important functional group that can be synthesized in a number of different ways. The low-molecular-weight esters have very pleasant odors and indeed are the major components of the flavor and odor aspects of a number of fruits. Although the natural flavor may contain nearly a hundred different compounds, single esters approximate the natural odors and are often used in the food industry for artificial flavors and fragrances.

Esters can be prepared by the reaction of a carboxylic acid with an alcohol in the presence of a catalyst such as concentrated sulfuric acid, hydrogen chloride, *p*-toluenesulfonic acid, or the acid form of an ion exchange resin:



This Fischer esterification reaction reaches equilibrium after a few hours of refluxing. The position of the equilibrium can be shifted by adding more of the acid or of the alcohol, depending on cost or availability. The mechanism of the reaction involves initial protonation of the carboxyl group, attack by the nucleophilic hydroxyl, a proton transfer, and loss of water followed by loss of the catalyzing proton to give the ester.

In this experiment you will prepare methyl benzoate by reacting benzoic acid with methanol using sulfuric acid as a catalyst. Since this is a reversible reaction, it will reach an equilibrium that is described by the equilibrium constant, Keq .



For this experiment, you will isolate the product, methyl benzoate, and any unreacted benzoic acid. Using this data, you will calculate the equilibrium constant for the reaction (see calculation section below).

Chemicals Required:

0.1 mol benzoic acid**,** 40 mL methanol**,** 3.0 mL methanol ,50mL methylene chloride, 20 mL 5% sodium carbonate

Procedure :

A. Reflux

1. Add 0.1 mole of benzoic acid to a 100 mL round bottom flask.
2. Add 40 mL of methanol
3. Add 3.0 mL of concentrated sulfuric acid
4. Mix all reactants and add boiling stones
5. Attach a water cooled reflux condenser
6. Reflux for one hour

B. Separation

1. Cool the mixture to room temperature
2. Decant the mixture into a separatory funnel
3. Rinse the round bottom flask with 10 mL of methylene chloride into the funnel
4. Add 40 mL of methylene chloride and 40 mL of water to the funnel
5. Extract the methyl benzoate into the methylene chloride layer by shaking
6. Separate the organic and aqueous phases

C. Washing (do not discard any materials during this step)

1. Wash the organic layer with 20 mL of R. I. water
2. Wash the organic layer with 20 mL of 5% sodium carbonate
3. Repeat step 2
4. Wash the organic layer with water
5. Drain the organic layer into a dry Erlenmeyer flask and dry with magnesium sulfate
6. The aqueous layer from the **sodium carbonate wash** should be acidified with concentrated HCl. When this aqueous material is made strongly acidic with hydrochloric acid, un reacted benzoic acid may be observed. The un reacted benzoic acid should precipitate. Remove the solvent by vacuum filtration. Collect and dry the solid benzoic acid and let it air-dry until the next lab period. You will need this weight for the K_{eq} calculations.

D. Distillations

1. Transfer the dried product (minus the solids) and methylene chloride to a round bottom flask large enough to accommodate the total volume
2. Attach a three way adapter and short condenser and thermometer
3. Distill off the solvent, methylene chloride.
4. Transfer the residue from step 3 into a pre weighed container. If needed, transfer the residue from step 3 to a small round bottom flask as possible, reattach the adapter and condenser and thermometer and distill the product into a pre weighed container

E. Analysis

1. Determine the actual yield of the product and the un reacted (recovered) benzoic acid.
2. Determine the refractive index of the product
3. Obtain an IR spectrum of the product (reference spectrum are at the end of this document)
4. Calculate Keq
5. Calculate theoretical yield and determine % yield .

Calculations

Calculation of the % Yield based upon amount of benzoic acid that is consumed:

$$\% \text{ yield} = \frac{(\text{moles methyl benzoate obtained})(100)}{(\text{Initial moles benzoic acid})}$$