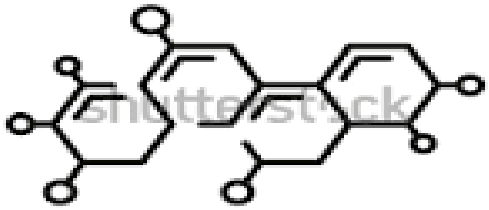
People's Democratic Republic of Algeria
Ministry of Higher Education and Scientific Research
Ibn Khaldoun University - Tiaret

Faculty of Materials Sciences
Chemistry Department

Practical Work

In

Organic Synthesis



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Preface

This laboratory manual has been carefully designed for Master 1 students in Organic Chemistry to provide hands-on experience in the synthesis, purification, and characterization of organic compounds. It serves as a practical complement to the theoretical principles studied in lectures, helping students to connect reaction mechanisms and experimental applications.

Through a series of structured experiments, students will explore the main classes of organic reactions including substitution, addition, elimination, and oxidation–reduction processes as well as more advanced topics related to modern synthetic methodologies.

Particular emphasis is placed on the development of laboratory skills, such as the correct use of glassware, safe handling of reagents and solvents, measurement techniques, and analytical characterization (melting point, TLC, IR, UV–Vis, etc.). The manual also introduces students to essential concepts of reaction optimization, yield calculation, and product analysis.

By completing these experiments, students will gain not only technical competence but also a deeper understanding of the fundamentals of organic synthesis and its importance in research and industrial chemistry. The course ultimately aims to cultivate critical thinking, precision, and a professional approach to laboratory work.

Table content

Symbols Used on Chemical Product Labels

(Chemical Hazard Symbols and Safety Precautions)

Below are the main GHS (Globally Harmonized System) symbols used internationally to identify chemical hazards. Each pictogram is associated with specific hazards and precautionary measures.

Symbol	Meaning / Hazard	Examples of Substances	Precautionary Measures
	Acute toxicity (fatal or harmful if swallowed, inhaled, or absorbed through skin)	Cyanides, methanol	Avoid contact; wear gloves, mask, and eye protection; handle under fume hood
	Flammable substances (solids, liquids, gases); self-heating or emits flammable gas	Ethanol, acetone, hydrogen	Keep away from heat, sparks, and open flames; use explosion-proof equipment
	Explosive or self-reactive materials	TNT, peroxides	Avoid shock, friction, or heat; store separately
	Corrosive to metals, skin, and eyes	Hydrochloric acid, sodium hydroxide	Wear protective gloves and goggles; avoid skin contact

	Carcinogenic, mutagenic, toxic to reproduction, or organ damage	Benzene, formaldehyde	Use in ventilated area; avoid prolonged exposure
	Irritant, sensitizer, or narcotic effects	Ammonia, chloroform	Avoid inhalation and skin contact
	Contains compressed, liquefied, or dissolved gases	Oxygen, nitrogen, propane	Store in well-ventilated area; secure cylinders upright
	Hazardous to aquatic environment	Pesticides, mercury compounds	Avoid release into the environment; dispose properly
	Oxidizing substances; may cause or intensify fire	Hydrogen peroxide, potassium nitrate	Keep away from flammable materials

General Safety Precautions

Working safely in the laboratory is an essential part of scientific training. All students must follow strict safety rules to prevent accidents and ensure a healthy working environment. The following general precautions apply to all laboratory activities:

- Wear appropriate personal protective equipment at all times, including a laboratory coat, safety goggles, and gloves.
- Do not eat, drink, or smoke in the laboratory. Food and beverages are strictly prohibited in all working areas.
- Know the location of emergency equipment such as fire extinguishers, eye-wash stations, safety showers, and first-aid kits.
- Handle chemicals with care. Always read the label and consult the Safety Data Sheet before using any reagent.
- Work in a well-ventilated area or under a fume hood when handling volatile, toxic, or flammable substances.
- Never pipette by mouth. Use a pipette bulb or other appropriate device.
- Avoid direct contact with chemicals and minimize exposure to vapors. Wash your hands thoroughly after completing an experiment.
- Dispose of chemical waste properly. Follow the instructions provided for waste segregation and disposal.
- Label all containers clearly with the chemical name, concentration, and hazard symbols.
- Keep your workspace clean and organized. Spills must be cleaned immediately, and broken glass should be disposed of in special containers.
- Report any accident or injury immediately to the instructor or laboratory supervisor, no matter how minor it seems.
- Never work alone in the laboratory; an instructor or authorized supervisor must always be present.
- Be attentive and cautious. Think before you act prevention is the key to laboratory safety.

TP 1: Acetylation of (D)-Glucose

Objective: To perform the acetylation of D-Glucose to produce glucose pentaacetate, and to understand the mechanism of esterification reactions in carbohydrates.

Principle: Acetylation is a type of reaction in which a hydrogen atom is substituted by an acetyl ($CH_3C=O$) group in a compound. When the hydrogen of hydroxide group is replaced by acetyl group then ester will be formed as a product.

Glucose reacts with acetic anhydride to yield pentaacetate derivatives by acetylating the hydroxyl groups.

Reagents: D-glucose, acetic anhydride, pyridine, ice, ethanol.

Apparatus:

- 50 mL round-bottom flask
- Magnetic stirrer or stirring rod
- Ice bath
- Funnel, filter paper
- Beaker, watch glass

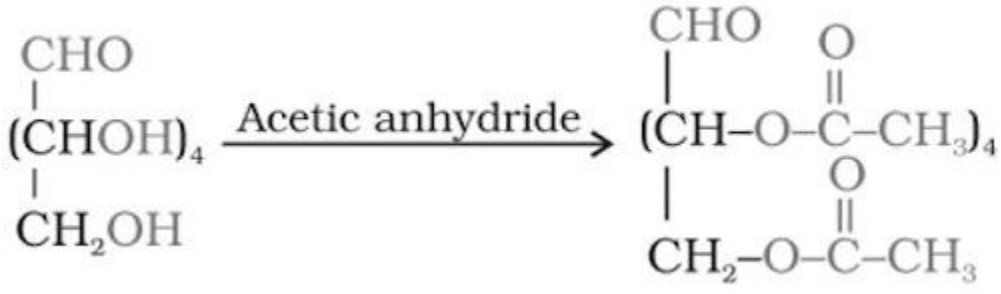
Procedure: To a 50 mL round-bottom flask, 2 g of D-glucose was placed. Then, 10 mL of acetic anhydride was added gradually while stirring. The mixture was cooled in an ice bath, and 1–2 drops of concentrated sulfuric acid were carefully added as a catalyst. The reaction mixture was stirred at room temperature for 15–20 minutes. After completion, the mixture was poured into 50 g of crushed ice to precipitate the acetylated product. The resulting solid product is collected by filtration and purified by recrystallization from ethanol-water. The product was then dried in a desiccator. Finally, the melting point of the obtained acetylated glucose was determined using a melting point apparatus.

Observation:

- Formation of a white crystalline solid.
- Slight vinegar odor due to acetic acid.

Figure: Acetylation of (D)-Glucose steps

Additional information: Glucose is white crystalline solid having a melting point of 146^0C. When the glucose molecule is crystallized with cold water, it forms glucose monohydrate of melting point 86^0C. It is extremely soluble in water, only sparingly soluble in ethanol and insoluble in ether. It is an optically active compound.
Remember acetylation takes place only on the hydrogen which is attached to oxygen. Rate of reaction can vary on different hydroxyl groups. Also remember the acylation and acetylation are two different types of reactions.



Scheme: Chemical reaction of (D)-Glucose's acetylation.

Safety Notes:

- Acetic anhydride and sulfuric acid are corrosive use gloves and goggles.
- Always add acid to the mixture slowly while cooling.

Questions:

1. What is the purpose of acetylating D-Glucose?
2. Which functional groups in D-Glucose are protected during acetylation?
3. Why is acetic anhydride commonly used for acetylation reactions?
4. Explain the reason for cooling the reaction mixture in an ice bath before pouring into water.
5. What type of reaction mechanism occurs during the acetylation of hydroxyl groups?
6. Why is recrystallization from ethanol–water necessary after filtration?
7. How can the melting point help in assessing the purity of the product?
8. In the IR spectrum, why does the O–H stretching band disappear after acetylation?
9. What do the IR bands at 1740 cm^{-1} and 1230 cm^{-1} indicate about the product?
10. How would impurities or incomplete acetylation affect the physical and spectroscopic properties of the product?
11. What could happen if excess water is present during the reaction?
12. Suggest another method to confirm the formation of penta-O-acetyl-D-glucose besides IR and melting point.

TP 2: Preparative Thin Layer Chromatography (TLC)

Appliqued on synthetic Aspirin

Introduction: Preparative Thin Layer Chromatography is a technique used to separate and purify small amounts of compounds from a mixture. Unlike analytical TLC, PTLC uses thicker layers of adsorbent and larger sample quantities to allow collection of purified compounds.

Objective:

- To separate components of a mixture using preparative TLC. Principle: Compounds are separated based on their affinity toward stationary and mobile phases.
- To visualize the separated components and determine their Rf values.

Materials:

- Silica gel-coated preparative TLC plates (thicker than analytical TLC, 1–2 mm)
- Sample mixture (organic compound mixture, e.g., dye, natural extract, reaction product)
- Suitable developing solvent or solvent mixture
- Capillary tubes or micropipettes
- TLC chamber (or a glass jar with a lid)
- UV lamp (254 nm or 365 nm) or iodine chamber for visualization
- Scalpel or spatula
- Glass plates or watch glass for collecting scraped silica
- Evaporation setup (rotary evaporator or simple air-drying)
- Salicylic acid and Acetic anhydride
- Concentrated phosphoric acid (85%)(catalyst) and Ethanol
- Ice bath

- Glassware: 50-mL Erlenmeyer flask, graduated cylinder, beaker, Buchner funnel, filter paper
- Salicylic acid standard (for comparison)

Procedure

Synthesis of Aspirin (Acetylsalicylic Acid)

In this experiment, 2g of salicylic acid was weighed and transferred into a 50-mL Erlenmeyer flask. To the flask, 5 mL of acetic anhydride was added, followed by 5 drops of concentrated phosphoric acid as a catalyst. The mixture was gently stirred and heated in a water bath maintained at 75–80°C for 15 minutes. After heating, 2mL of distilled water was cautiously added to decompose any excess acetic anhydride, and the mixture was allowed to stand for 2 minutes. Subsequently, 20mL of distilled water was added, and the flask was swirled to mix. The mixture was then placed in an ice bath for 10 minutes to promote crystallization of aspirin.

The crystalline product was collected by vacuum filtration using a Buchner funnel and washed with cold distilled water to remove impurities. The crude aspirin was transferred to a 50mL Erlenmeyer flask and dissolved in 4mL of ethanol by gentle heating. After complete dissolution, 13mL of cold distilled water was added slowly, and the solution was cooled in an ice bath for 10 minutes to allow recrystallization. The purified aspirin was collected by filtration using a Buchner funnel, transferred to a clean watch glass, and allowed to dry completely. Finally, the dried aspirin was weighed to determine the yield and to analyze by TLC

Analysis by TLC

To analyze the purity of synthesized aspirin and check for the presence of unreacted salicylic acid using TLC.

Plate Preparation:

- Mark the origin line lightly with a pencil about 1–2 cm from the bottom of the PTLC plate.
- Draw a faint line across the plate where the sample spots will be applied.

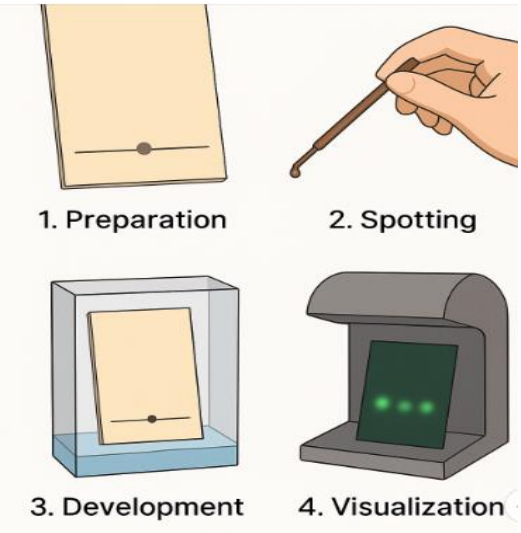


Figure: plate preparation.

Sample Application

- Dissolve the aspirin in a small amount of suitable solvent (ethanol)
- Using a capillary tube, spot a small amount of synthesized aspirin solution on the origin line.
- Spot the salicylic acid standard on the same line for comparison.
- Allow spots to dry before applying additional layers if necessary.
- Transfer the developing solvent (ethyl acetate–hexane (3:1) or chloroform–methanol (9:1))
- into the TLC chamber to a depth of ~0.5 cm.
- Place the TLC plate upright in the chamber, ensuring the spots do not touch the solvent directly.
- Cover the chamber with a lid to saturate it with solvent vapor.
- Allow the solvent to rise until it is ~1–2 cm from the top of the plate.
- Remove the plate and immediately mark the solvent front with a pencil.
- Observe the plate under a UV lamp or in an iodine chamber.
- Mark the positions of separated spots with a pencil.
- Measure the distance traveled by the solvent (solvent front) and the distance traveled by each spot.
- Compare the Rf of the synthesized aspirin to the standard salicylic acid.

- Calculate the R_f values using the formula:

$$R_f = \frac{\text{Distance traveled by spot}}{\text{Distance traveled by solvent front}}$$

Questions

1. What is the purpose of using acetic anhydride in this reaction?
2. Why is concentrated phosphoric acid added as a catalyst?
3. What is the role of water after the reaction is complete?
4. Explain why crystallization occurs when the reaction mixture is cooled in an ice bath.
5. Why is recrystallization necessary after initial filtration?
6. How would the yield of aspirin be affected if the reaction was not heated?
7. What impurities might be present in the crude product, and how are they removed?
8. How can you confirm the purity of the synthesized aspirin without TLC?
9. What is the principle of Thin Layer Chromatography?
10. Why is it important to run a standard (salicylic acid) alongside your sample?
11. How do you calculate the Rf value of a compound?
12. What does it indicate if a spot corresponding to salicylic acid appears in the TLC of the synthesized aspirin?
13. How can TLC help in determining whether the reaction went to completion?
14. Why might you need to adjust the polarity of the developing solvent?
15. Explain why UV light or iodine is used to visualize the spots.
16. What could cause two compounds to have very similar Rf values, and how would you resolve this problem?
17. What factors influence the separation?

TP 3: Column Chromatography

Appliqued on synthetic Aspirin

Introduction: Column chromatography is a technique for separating and purifying compounds based on their polarity and adsorption to a stationary phase. In this experiment, crude aspirin is separated from unreacted salicylic acid and other impurities using a silica gel column.

Objective: To purify synthesized aspirin and separate it from unreacted salicylic acid and other impurities using column chromatography.

Materials:

- Silica gel (stationary phase, 60–200 mesh)
- Crude aspirin
- Solvent system (mobile phase, e.g., ethyl acetate–hexane 3:1 or chloroform–methanol 9:1)
- Glass column (suitable diameter for sample size)
- Cotton or glass wool (to plug the column)
- Beakers or flasks to collect fractions
- TLC plates for monitoring fraction purity
- Capillary tubes or pipettes

Procedure of column chromatography:

Column Packing

- Plug the bottom of the column with a small piece of cotton or glass wool.
- Add silica gel and pack the column carefully, using the chosen solvent to create a slurry for uniform packing.
- Ensure there are no air bubbles or gaps in the silica gel.

Sample Loading

- Dissolve crude aspirin in a minimum amount of solvent (ethanol).

- Carefully apply the solution to the top of the packed column without disturbing the silica.
- Allow the sample to adsorb onto the top of the silica gel.

Elution

- Begin elution with the chosen solvent system (ethyl acetate–hexane 3:1 or chloroform–methanol 9:1)
- Collect eluate in small fractions (e.g., 5–10 mL per fraction).
- Monitor the progress of separation using analytical TLC. Spot each fraction and compare with standard aspirin and salicylic acid.

Fraction Combination

- Combine fractions containing pure aspirin as identified by TLC.
- Evaporate the solvent under reduced pressure or by air-drying to obtain purified aspirin.

Analysis

- Check the melting point of purified aspirin (expected ~135°C).
- Optional: confirm purity with IR spectroscopy (ester C=O ~1750 cm^{-1}, phenolic O–H absent).

Notes

- Use a solvent system that gives good separation between aspirin and salicylic acid.
- TLC is crucial to monitor which fractions contain the desired compound.

Figure

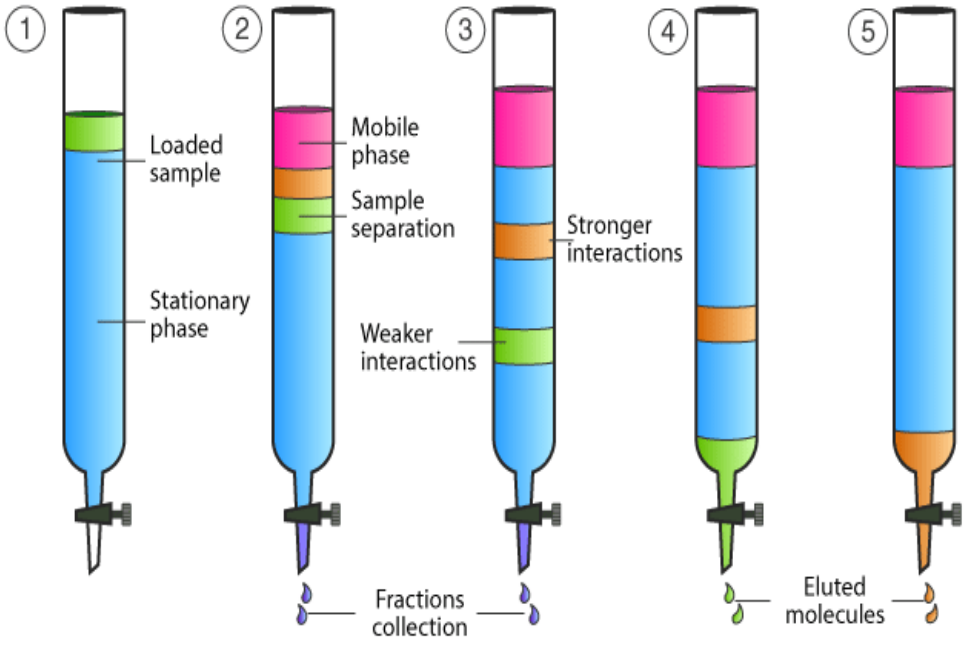


Figure: Column Chromatography steps.

Questions:

1. What is the principle behind column chromatography?
2. How does the polarity of a compound affect its movement through the column?
3. Why is silica gel commonly used as the stationary phase in column chromatography?
4. Explain the role of the mobile phase in separating compounds.
5. How does column chromatography differ from TLC?
6. Why is it important to pack the column carefully without air bubbles?
7. What could happen if the sample is overloaded on the column?
8. Why is it necessary to collect fractions instead of one bulk elution?
9. How do you decide which fractions to combine?
10. Why should the solvent be added slowly to the column?
11. How can TLC be used to monitor the purity of the fractions?
12. What would you expect to see on TLC if unreacted salicylic acid is present?
13. How can the melting point help confirm the purity of the final aspirin product?

14. Which IR signals would confirm the presence of aspirin and the absence of unreacted salicylic acid?

15. Suggest an alternative method to purify aspirin if column chromatography is not available.

16. How could you improve the separation between aspirin and salicylic acid if they are very close in polarity?

17. Why might some aspirin still remain in the silica gel after elution

18. How could the choice of solvent system affect the resolution of the separation?

TP 4: Distillation of Aniline

Objective: The objective of this experiment is to purify aniline by simple or fractional distillation based on the difference in boiling points between aniline and its possible impurities. Distillation is one of the most common separation and purification techniques used in organic chemistry for liquid compounds.

Through this experiment, students will:

- Understand the principle of distillation and the role of vapor–liquid equilibrium.
- Learn how to assemble and operate a distillation apparatus safely.
- Observe the relationship between boiling point and purity of a compound.
- Gain practical experience in measuring temperature, collecting distillate fractions, and evaluating product purity.

Principle: Distillation separates liquids based on differences in boiling points. Reagents: Crude aniline, drying agents.

Procedure:

1. Place crude aniline in a round-bottom flask.
2. Heat gently using a heating mantle.
3. Collect the fraction boiling around 184 °C.
4. Dry and store in a sealed container.

Observations: Clear colorless distillate obtained.

Questions:

1. What is the main principle of distillation? Explain how the difference in boiling points allows the separation of liquid mixtures.

2. Why is aniline distilled under reduced pressure (vacuum distillation) rather than at atmospheric pressure? Discuss the reasons related to boiling point, decomposition, and safety.

3. What is the boiling point of pure aniline at 1 atm? Compare your experimental value with the literature value and comment on any difference.

4. What is the function of the thermometer in the distillation apparatus? At which point should the thermometer bulb be positioned?

5. What is the role of the condenser in the setup? Explain why cold water must circulate in a specific direction (from bottom to top).

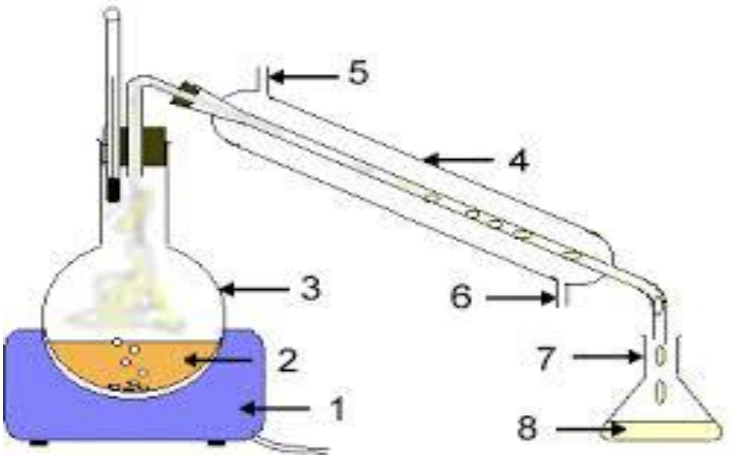
6. What precautions should be taken when heating aniline? Mention the safety risks associated with aniline (toxicity, flammability) and the appropriate protective measures.

7. How can you determine whether the distillate is pure? Suggest analytical techniques that can be used to assess purity (e.g., boiling point, refractive index, IR spectroscopy).

8. What would happen if the distillation were performed too rapidly? Describe the effect on separation efficiency and purity of the collected product.

9. Differentiate between simple distillation and fractional distillation. In which case is each method more appropriate?

10. Give the glassware used in the distillation montage.



11. Explain why aniline may darken during distillation. What causes this change, and how can it be minimized?

TP 5: Solvent Purification

Objectives:

1. Understand the importance of solvent purity for organic reactions (water, peroxides, dissolved gases, stabilizers).
2. Learn and perform common solvent purification techniques: simple distillation, fractional distillation, drying with molecular sieves, and drying with sodium/benzophenone (for ethers/THF) under inert atmosphere.
3. Learn safe handling, storage, and disposal of purified solvents.
4. Compare methods in terms of practicality, dryness achievable, and hazards.
5. Develop good laboratory practice for working with anhydrous and oxygen-free solvents.

Important safety note: some procedures (e.g., sodium/benzophenone drying, distillation under reduced pressure, use of Schlenk techniques) involve hazardous reagents and operations. These must be carried out only under the direct supervision of an experienced instructor and with appropriate training, PPE, and safety equipment.

Theoretical background

Why purify? Many reagents/catalysts are moisture or oxygen-sensitive (organometallics, anionic polymerizations, catalysts). Trace water, peroxides, or oxygen can quench reagents, cause side-reactions, or give poor reproducibility.

Main contaminants: water, dissolved oxygen, stabilizers (e.g., BHT), peroxides (ethers), particulate impurities.

Drying principles:

(a) chemical drying reactive reagents (e.g., Na, CaH_2) react with water;

(b) physical drying removal of water by azeotropic distillation (Dean–Stark) or by adsorption (molecular sieves);

(c) degassing removal of dissolved gases by freeze–pump–thaw or inert gas sparging.

Choosing a method: consider solvent type (protic/aprotic, peroxide-forming), required dryness (ppm H_2O), safety, time, and available equipment.

Required Materials & Reagents

Common solvents to purify (examples): tetrahydrofuran (THF), diethyl ether, dichloromethane (DCM), toluene, hexane, methanol, ethanol, acetonitrile.

Drying agents & chemicals: activated 3Å or 4Å molecular sieves (powder or beads), anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4) (for drying small volumes), sodium metal, benzophenone (for sodium/benzophenone ketyl), calcium hydride (CaH_2), sodium/potassium alloy (NaK) only if trained and permitted.

Equipment: round-bottom flasks, distillation head, fractionating column (Vigreux or packed), condenser, heating mantle/oil bath, thermometer, Schlenk line or inert gas manifold, septa, Schlenk flasks, vacuum pump (for reduced pressure distillation), cannula/needle transfer apparatus, rubber tubing, gas regulators, ice bath, drying oven (for molecular sieves activation).

Analytical: Karl Fischer titrator (for accurate water content), or simple check methods (e.g., anhydrous indicator such as sodium/benzophenone color, or GC).

Procedures

A- General precautions and preparation

1. Inspect solvent bottles for visible impurities, cloudiness, or peroxides (particularly ethers). If peroxide risk exists, test or discard appropriately.

2. Choose purification method appropriate to solvent and intended use. For most sensitive work, use molecular sieves or sodium/benzophenone for ethers/THF; for many routine needs, freshly distilled solvent or molecular-sieve-dried solvent suffices.

3. Label all purified solvent containers clearly: solvent name, method of purification, date, dryness indicator (if any), initials.

B-Drying by activated molecular sieves (recommended general method)

Overview: Safe, versatile, suitable for many solvents (toluene, THF, Et_2O, DCM, hexane, acetonitrile). Gives dryness ~ <50 ppm depending on sieve and contact time.

Activation of sieves: Heat 3Å or 4Å sieves in oven at 200–300 °C (per manufacturer) under vacuum or dry N_2 for several hours. Cool in desiccator.

Procedure (small scale, e.g., 100–500 mL):

1. Place activated molecular sieves (3–4 Å, approx. 10–20% w/v; e.g., 10–20 g per 100 mL solvent) into a dry, oven-dried bottle or flask under inert atmosphere or in a glovebox.

2. Add solvent by syringe or cannula to minimize air contact. Cap or seal the container.

3. Stir or leave standing for at least 12–24 hours (longer for lower water content). For very dry solvent, contact for 48 h or more and use freshly activated sieves.

4. Decant or cannula-transfer the solvent to a clean, dry container; avoid transferring sieves. Optionally filter through a dried plug (cotton/oven-dried filter) under inert gas.

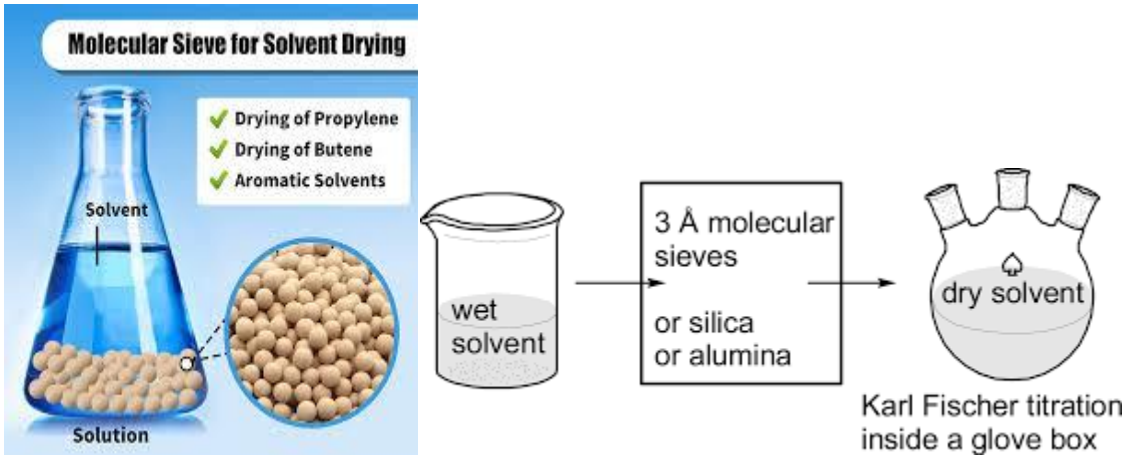


Figure: Sieve for solvent drying.

C — Drying by sodium/benzophenone ketyl (for ethers and THF)

Overview: Produces essentially anhydrous, oxygen-free ether/THF. Sodium reduces benzophenone to a deep blue/purple ketyl radical; color indicates dryness and absence of oxygen. Highly effective but hazardous.

Procedure (typical small-scale ~100–500 mL):

1. Set up a flame-dried, 3-neck round-bottom flask fitted with a reflux condenser, septum, and inert gas inlet. Ensure a good inert atmosphere (N_2 or Ar).

2. Add a clean piece of sodium metal (washed of mineral oil; handle with tweezers) and a few crystals of benzophenone to the flask. (Use minimal sodium just enough to form ketyl; instructor to advise quantities.)

3. Under inert gas, add dry or non-dry solvent slowly to the flask (do not add to sodium exposed to air). Stir and gently heat (reflux) until solution turns deep blue or purple (formation of benzophenone ketyl). Continue reflux for ~1–2 h to ensure dryness and degassing.

4. Cool under inert atmosphere. Transfer solvent via cannula to a dry, evacuated receiver or Schlenk flask. Store under inert gas over activated molecular sieves for long term.

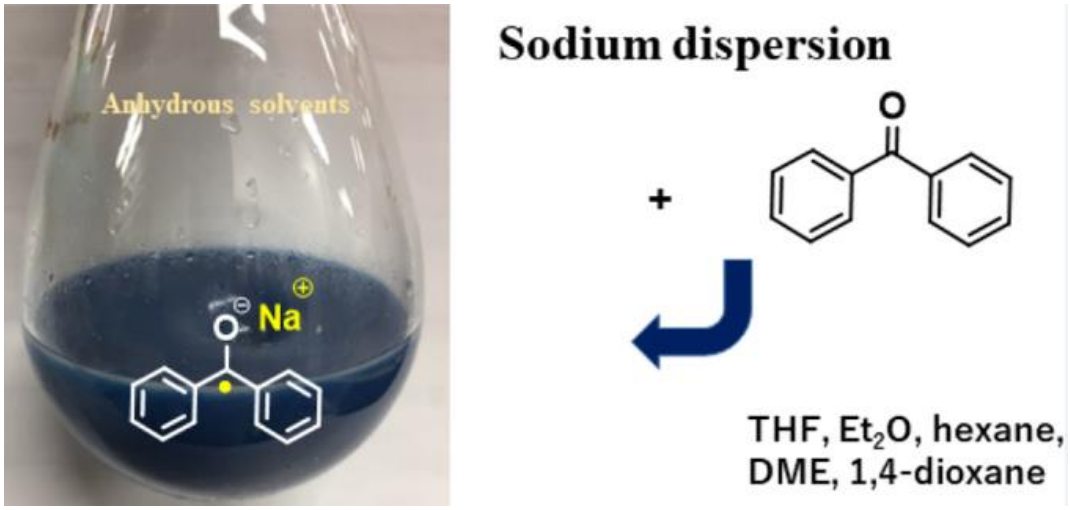


Figure: Drying solvent by sodium/benzophenone ketyl

D — Drying with calcium hydride (CaH_2) / sodium sulfate / $MgSO_4$ (for routine drying)

CaH_2 (for chlorinated solvents, ethers):

1. Add CaH_2 (approx. 0.5–2% w/v; check supplier guidance) to solvent in a dry flask under inert atmosphere.

2. Stir at room temperature for several hours to overnight. CaH_2 reacts with water to evolve H_2; allow gas to vent safely.

3. Decant or filter off CaH_2 under inert atmosphere. Optionally distill to further purify.

$MgSO_4$ / Na_2SO_4 (for small samples):

Drying salts are used to remove residual traces of water from small volumes after workup. Add anhydrous drying agent, swirl, filter, and collect solvent. Not suitable to achieve very low ppm H_2O.

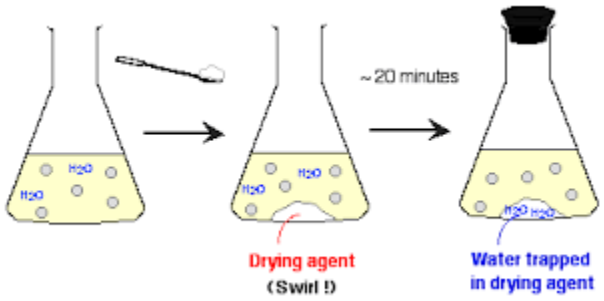


Figure: Drying with calcium hydride (CaH_2)

E — Distillation (simple or fractional distillation)

Use: Remove high-boiling impurities, stabilizers; combine with drying for high purity.

general Procedure:

1. Assemble appropriate distillation apparatus (round-bottom flask, fractionating column if needed, condenser, receiver). Use boiling chips or stir bar.

2. If solvent contains peroxides (ethers), test prior to distillation. If present, remove peroxides chemically (consult instructor) or avoid distilling.

3. Heat gradually using an oil bath; monitor temperature. Collect fractions corresponding to the solvent boiling point. For vacuum distillation, reduce pressure to lower boiling point and avoid decomposition.

4. For very dry solvent, combine with sodium/benzophenone trap and distill under inert gas directly into a dry receiver.

F — Degassing (removing dissolved gases — oxygen, N_2)

Freeze–pump–thaw (small volumes):

1. Place solvent in a Schlenk tube, immerse in liquid N_2 until frozen.

2. Connect to vacuum and evacuate headspace; backfill with inert gas. Repeat freeze–pump–thaw cycle 3 times. Final backfill with inert gas.

Sparging with inert gas: Bubble dry argon or nitrogen through solvent for 20–60 minutes.

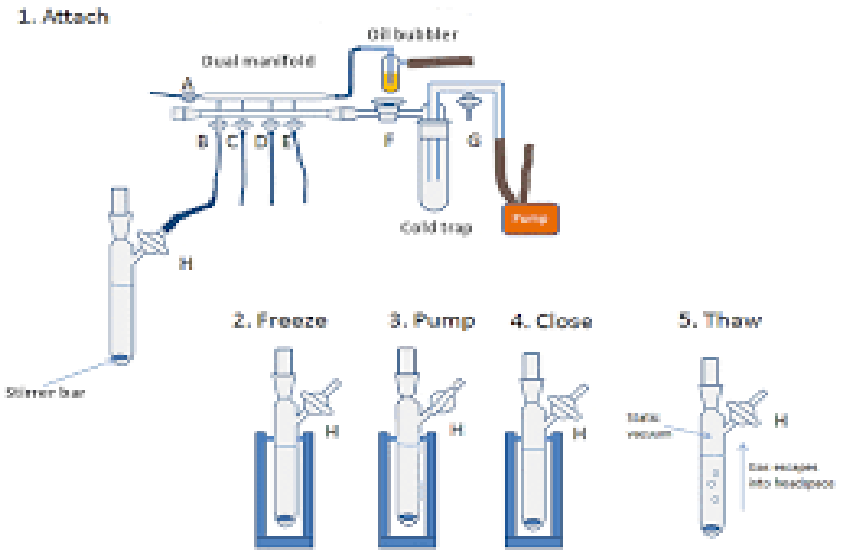


Figure: Degassing steps (removing dissolved gases-oxygen, N_2)

Questions

1. What is the purpose of solvent purification in organic chemistry?
2. Which types of impurities are commonly found in commercial solvents?
3. Why is moisture problematic for many organic reactions?
4. What is the difference between drying a solvent and distilling a solvent?
5. How does the polarity of a solvent affect the choice of purification method?
6. What factors determine the choice of a drying agent for a specific solvent?
7. Why are molecular sieves considered highly effective for drying solvents?
8. What is the principle behind chemical drying agents such as $CaCl_2$ or $MgSO_4$?
9. How does particle size affect the efficiency of a drying agent?
10. In what situations is fractional distillation preferred over simple distillation?
11. What physical property allows distillation to separate impurities from solvents?
12. Why are some solvents purified through reflux with drying agents?
13. Why are inhibitors sometimes removed from solvents before use?
14. Why must some solvents be protected from light or air during storage?
15. What are peroxide-forming solvents, and why do they require special attention?
16. How does improper storage affect the quality of purified solvents?
17. How does solvent purity influence reaction yields and selectivity?
18. Why is anhydrous solvent needed in reactions involving strong nucleophiles?
19. How does solvent purification impact analytical techniques like NMR?

TP 6: Wittig Reaction

Objective:

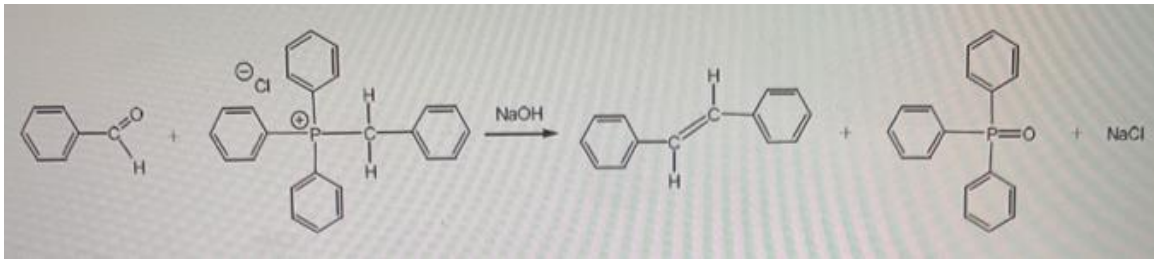
1. To understand the principle of the Wittig reaction, an important method for the synthesis of alkenes.
2. To prepare an alkene by reacting a carbonyl compound (aldehyde or ketone) with a phosphonium ylide
3. To learn the preparation and handling of phosphonium salts and ylides.
4. To practice purification and characterization techniques such as recrystallization or distillation and melting point determination or IR/NMR spectroscopy.

Theoretical Background

The Wittig reaction, discovered by Georg Wittig (Nobel Prize, 1979), is a key organic transformation that converts a carbonyl compound ($R_2C=O$) into an alkene ($R_2C=CR'_2$) using a phosphonium ylide.

Reagents: Benzaldehyde, triphenylphosphonium bromide, base (NaOH or NaH), solvent (THF or ethanol).

Glassware and equipment: 100 mL round-bottom flask, Magnetic stirrer and hotplate, Reflux condenser, Separatory funnel, Ice bath, Filter paper, Büchner funnel, Distillation or recrystallization apparatus, IR/NMR spectrometer (for analysis)



Scheme: General reaction of Wittig reaction

Procedure (Example: Synthesis of Stilbene)

Preparation of the Ylide

Place 2 g of benzyltriphenylphosphonium chloride in a 100 mL round-bottom flask and Add 20 mL of ethanol and stir until the solid dissolves. Add 10 mL of 10% aqueous NaOH solution and stir vigorously for 15–20 minutes. The ylide ($Ph_3P=CHPh$) forms as a yellow suspension. Separate the organic phase, dry it with anhydrous Na_2SO_4, and use immediately.

Reaction with Carbonyl Compound

To the ylide solution, add 1.0 mL (1.0 eq) of benzaldehyde and stir and reflux the mixture gently for 30–45 minutes under inert atmosphere (N_2). Cool the mixture and pour it into 50 mL of cold water.

Isolation of Product

Collect the solid product by filtration and wash with cold ethanol or water. Dry under vacuum or air.

Purification

Recrystallize the crude product from ethanol or hexane then measure the melting point and compare with literature data for trans-stilbene.

Observations

- Formation of a yellow ylide suspension during base treatment.
- Precipitation of solid product (stilbene) upon cooling and addition to water.
- IR spectrum shows disappearance of the C=O band (~1700 cm^{-1}) and appearance of C=C stretching (~1600 cm^{-1}).

Questions

1. What is the role of triphenylphosphine in the Wittig reaction?

2. Why must the reaction be carried out under anhydrous conditions?

3. What differences are observed between stabilized and unstabilized ylides?

4. How can you distinguish between E- and Z- alkenes by NMR spectroscopy?

5. Suggest another example of a compound that can be synthesized using the Wittig reaction.

6. Calculate the obtained yield.

7. Compare melting point with literature value (e.g., trans-stilbene: 124–125 °C).

8. What is the Wittig reaction and what type of product does it typically form?

9. What functional group is transformed during a Wittig reaction?

10. What is a phosphonium ylide in the context of the Wittig reaction?

11. Describe the key steps involved in the Wittig reaction mechanism.

12. What intermediate is formed when a carbonyl compound reacts with an ylide?

13. How does the formation of the oxaphosphetane intermediate influence the reaction outcome?

14. How does the structure of the ylide affect the stereochemistry of the resulting alkene?

15. Why do stabilized ylides often give E-alkenes while non-stabilized ylides give Z-alkenes?

16. What factors determine whether a Wittig reaction proceeds efficiently?

17. How can the Wittig reaction be used to extend the carbon chain of a molecule?

18. Give an example of how the Wittig reaction is used in organic synthesis planning.

19. How does the reactivity of ketones compare to that of aldehydes in the Wittig reaction?

TP 7: Synthesis of Bis-Hydrazines

Objectives:

- Comprendre les principes de formation des liaisons –C=N–NH– ou –CONHNH conduisant à des bis-hydrazones / bis-hydrazides.
- Illustrer sur un exemple modèle la stratégie synthétique, la logique de protection/déprotection (si applicable) et les méthodes analytiques employées pour identifier et caractériser le produit.
- Sensibiliser aux risques associés aux dérivés de l'hydrazine et aux bonnes pratiques de sécurité en laboratoire.
- To prepare bis-hydrazine derivatives from hydrazine and di-carbonyl compounds. Principle: Hydrazine reacts with aldehydes or ketones to form hydrazones or bis-hydrazones.

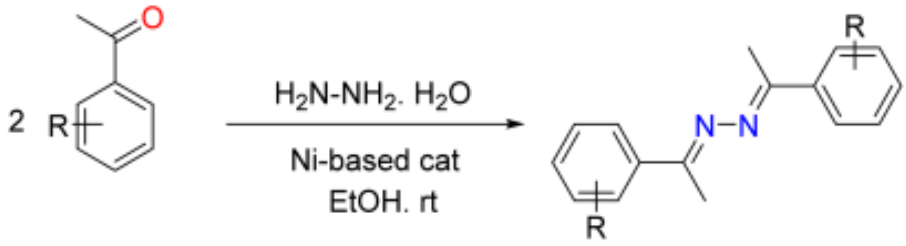
Reagents: Hydrazine hydrate ($NH_2NH_2 \cdot H_2O$), Glyoxal (OHC–CHO) or Benzil (PhCO–COPh), Solvent: Ethanol (as a mild polar solvent)

Amount and montage: Benzil: 5.0 mmol (≈1.08 g), Hydrazine hydrate (80%): 6.0 mmol (≈0.30–0.40 mL depending on concentration) — typically 1.1–1.5 equiv, Ethanol: 15–20 mL, Reflux setup (condenser), magnetic stirrer

Procedure:

1. A mixture of acetophenone (2.08 mmol) in ethanol (15 mL) was stirred with hydrazine hydrate (1 mmol), and then a Ni-based heterogeneous catalyst was added to the mixture with a small amount. The reaction mixture was stirred at room temperature until solidified. The precipitated product was filtered, washed with water, dried, and then crystallized from ethanol to give of ketazines in less than 3 h.
4. Monitor reaction by TLC.
6. Dry the solid under vacuum.
7. recrystallize from ethanol/ethyl acetate.

General equation



Scheme: Synthesis of Bis-Hydrazines

Questions

1. Draw the mechanism of condensation of a dialdehyde with a monosubstituted hydrazine leading to a bis-hydrazone, showing the electron-pushing arrows for the addition step and the subsequent elimination of water.
2. Explain the effect of an acid versus a base catalyst on the rate of hydrazone formation and on the reaction equilibrium.
3. Propose a protection/deprotection strategy if selective substitution on only one of the hydrazine functional groups is desired.
4. Using a set of fictitious spectroscopic data (IR, ^{1}H NMR, HRMS provided in the appendix**),** determine whether the product is a bis-hydrazone or a bis-hydrazide, and justify your answer.
5. Discuss the health hazards and waste management measures associated with hydrazine derivatives.
6. Design an enrichment/purification protocol (without numerical values) for a poorly soluble product, including the choice of solvent and the method.
7. Propose two possible applications of the synthesized bis-hydrazine (e.g., in materials, metal coordination, or medicinal chemistry), and explain why its functional groups are useful.

TP 8: Conversion of Alcohols into Iodides

Objective: To prepare alkyl iodides from alcohols.

Principle: Alcohols react with iodine and red phosphorus or with KI and H_2SO_4 to yield alkyl iodides.

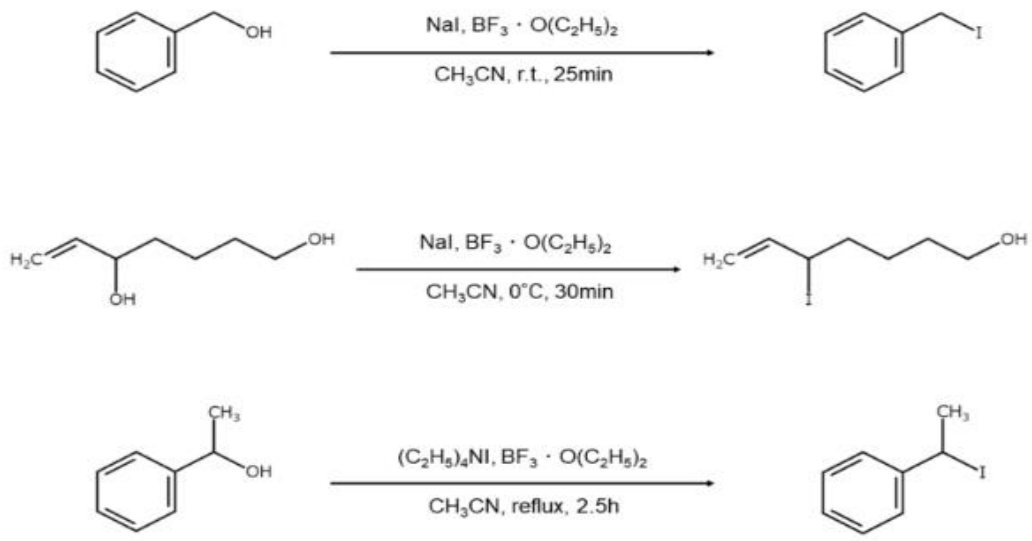
Reagents: Alcohol (e.g., ethanol), red phosphorus, iodine.

Methods with strong protonic acids

Reacting an alcohol and an alkali iodide under the presence of a strong protonic acid generates high yields of iodoalkanes. Such methods are widely used owing to a low occurrence of side reactions. The reaction mechanism differs depending on the structure of the reactant alcohol. When a primary or secondary alcohol is used, protonation with an acid generates oxonium ion intermediates ($[ROH_2]^+$), which undergo an SN2 attack by iodine ions, resulting in a product with inversed stereochemistry. Conversely, caution should be taken when using tertiary alcohols as alkene generation through elimination reactions and the isomerization of carbon skeletons readily occur due to an SN1 mechanism in the reaction via stable carbocations.

Methods that use $BF_3O(C_2H_5)_2$

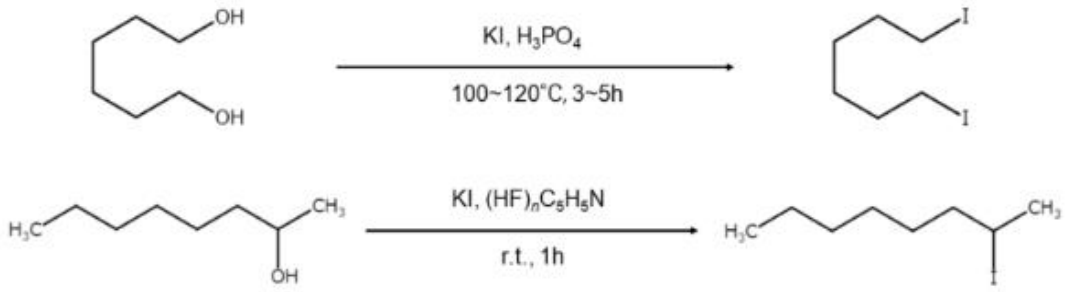
Some proposed methods use $BF_3O(C_2H_5)_2$ as a reagent. In contrast to tertiary, ally, and benzyl alcohols that rapidly convert into iodides, primary and secondary alcohols will slow the reaction, making them useful when targeting the partial iodination of a polyhydric alcohol.



Scheme: Reactions that use $BF_3O(C_2H_5)_2$

Other improved methods

There are promising proposals for improved methods that effectively apply an extensive range of aliphatic and alicyclic alcohols to achieve high yields without isomerization or racemization. For example, some methods use certain combinations with the alcohol, such as with KI-phosphate, NaI chlorotrimethylsilane, and KI-pyridine/polyhydrofluoric acid.



Scheme: Reactions that used KI

Procedure:

1. In a dry round-bottom flask, add the alcohol (e.g., ethanol, 10 mmol).
2. Add a small amount of red phosphorus (≈0.3 equiv).

3. Add iodine crystals (1.5 equiv) slowly with stirring at room temperature.

4. The mixture turns dark brown (formation of PI_3 in situ).

5. Heat gently (40–60 °C) until the brown color fades, indicating the conversion is complete.

6. Cool, add water carefully, and extract the product with ether or dichloromethane.

7. Wash, dry (Na_2SO_4), and distill to obtain the alkyl iodide.

Equation

$$3\ C_2H_5OH + PI_3 \rightarrow 3\ C_2H_5I + H_3PO_3$$

Mechanism

- Protonation of –OH → formation of better leaving group (H_2O).
- I^- acts as a nucleophile and substitutes water (SN1 or SN2 mechanism depending on substrate).

Questions

1. Write the balanced chemical equation for the conversion of an alcohol (e.g., ethanol) into the corresponding iodide using phosphorus and iodine.

2. How is phosphorus triiodide (PI_3) formed in situ in this reaction?

3. Write the stepwise mechanism of the transformation of ethanol into ethyl iodide using PI_3.

4. Why does the hydroxyl group (–OH) need activation before substitution?

5. Is the mechanism SN1 or SN2? Justify depending on the type of alcohol (primary, secondary, tertiary).

6. What is the role of each reagent (P, I_2, alcohol)?

7. Describe the color changes observed during the experiment.

8. Why is it necessary to cool the reaction mixture before adding water?

9. Why must the reaction be carried out in a dry flask?

10. What happens if the alcohol is tertiary? (possible elimination, side reactions)

11. How can the purity of the product be verified (mention physical constant and analytical test)?

12. Compare the use of “HI” and “P/I_2” for converting alcohols to iodides. Which is milder?

13. What are the advantages of the “PPh_3/I_2” method compared to “P/I_2”?

14. Give an industrial or synthetic application of alkyl iodides.

15. Explain why alkyl iodides are more reactive than bromides or chlorides in nucleophilic substitution reactions.

16. Calculate the theoretical yield of alkyl iodide expected from 1 g of ethanol (show steps).

17. Calculate the percentage yield if 0.95 g of ethyl iodide was obtained.

18. Determine the limiting reagent in your experimental mixture (given molar amounts).

19. List the main safety hazards of hydriodic acid, iodine, and red phosphorus.

TP 9: Tosylation Reaction

Objective:

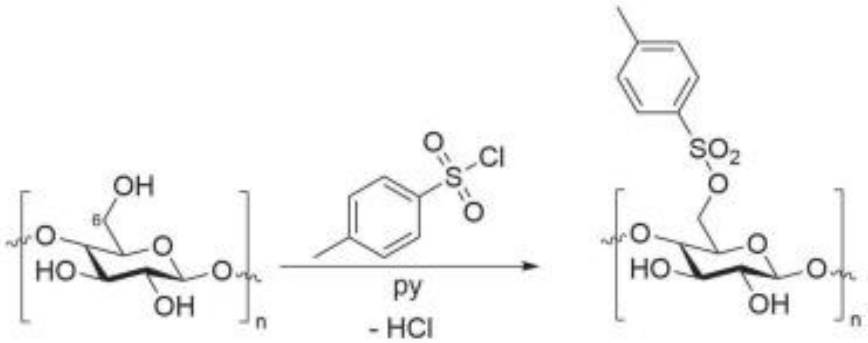
- To convert an alcohol (R–OH) into its corresponding tosylate ester (R–OTs) using p-toluenesulfonyl chloride (TsCl).
- To understand how tosylation activates the –OH group, making it a better leaving group in nucleophilic substitution reactions.
- To observe the reaction conditions, purification, and identification of the tosylate product.

Reaction Principle: Alcohols have a poor leaving group (–OH). Tosylation converts it into a sulfonate ester (–OTs), which is an excellent leaving group for further substitution or elimination reactions.

Reagents

Alcohol (e.g., ethanol, 5 mmol) , p-Toluenesulfonyl chloride (TsCl), Solvent and base, Ethyl acetate, water, HCl (1 M), $NaHCO_3$, Na_2SO_4 , Pyridine,

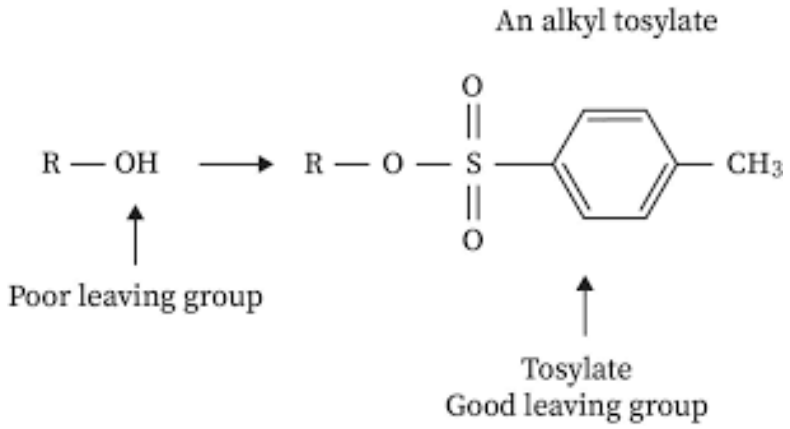
Procedure1: tosylation of Ethylcellulose: Cellulose (cel)(0.2 g) was mixed with an excess of p -toluene sulfonic acid chloride (2.35 g, 0.0123 mol) in dry pyridine (7.5 mL). The mixture was stirred for ≈24 h. To stop the reaction, 15 mL of ice-cold H_2O/aceton (1:1, v/v) was slowly added. The toslyated cellulose (cel-OTs) is subsequently washed with H_2O and then stored in tetrahydrofurane (THF).



Scheme: Tosylation Reaction

Procedure2: Synthesis of Tosylate from Alcohol

In a dry 50 mL round-bottom flask, dissolve the alcohol (5 mmol) in 10 mL of dry pyridine. Cool the solution in an ice bath (0–5 °C), then add TsCl (1.15 g, 6 mmol) portionwise with stirring. Maintain the reaction at 0–5 °C for 15–20 minutes, after which the mixture is allowed to warm to room temperature and stirred for an additional 1–2 hours. Upon completion, pour the reaction mixture into 50 mL of ice-cold water and extract the product with ethyl acetate (3 × 20 mL). The combined organic extracts are washed successively with 1 M HCl (to remove pyridine), saturated $NaHCO_3$ solution (to neutralize acids), and distilled water. Finally, the organic layer is dried over anhydrous Na_2SO_4, filtered, and the solvent is removed under reduced pressure to obtain the tosylate product.



Scheme: Synthesis of Tosylate from Alcohol

Questions

1. Write the complete mechanism of the tosylation reaction.

2. What is the role of pyridine (or triethylamine) in the reaction?

3. Why is the reaction carried out under anhydrous (dry) conditions?

4. Why must the mixture be cooled during the addition of TsCl?

5. How can you confirm the formation of the tosylate product (spectroscopically or chemically)?

6. Why are tosylates better leaving groups than hydroxides?

7. Give an example of a nucleophilic substitution reaction using the tosylate obtained.

8. Compare tosylation with mesylation and triflation reactions (similarities/differences).

9. Can tertiary alcohols be tosylated easily? Why or why not?

10. Suggest a method to convert the tosylate back to the original alcohol.

11. Calculate the theoretical yield of alkyl tosylate expected from 1.0 g of alcohol.

12. If 1.05 g of tosylate was obtained, calculate the percentage yield.

13. What are the main safety hazards associated with pyridine and TsCl?

14. How should waste containing TsCl and pyridine be disposed of properly?

TP 10: Selective Protection of Monoalcohols and Diols

Objective of the Experiment

- To understand the concept of protecting groups in organic synthesis.
- To learn how to selectively protect one hydroxyl group in a molecule containing one or more alcohol functions.
- To perform the protection of a monoalcohol or selective protection of a diol using a silylating reagent (e.g., TBDMS-Cl) or an acetal-forming reagent (e.g., acetone + acid catalyst).
- To study selectivity, reactivity, and reversibility of protection reactions.

Theoretical Background

Purpose of Protection

In molecules containing multiple reactive functional groups (e.g., –OH, –COOH, $–NH_2$), it is often necessary to protect one functional group while performing a reaction on another.

Protection temporarily masks the functional group, preventing it from reacting.

Common Protecting Groups for Alcohols

Type of Protection	Reagent	Product	Deprotection
Silyl protection	TBDMS-Cl + base	R–O–$Si(CH_3)_2tBu$	TBAF or acid hydrolysis
Acetylation	Ac_2O + base	R–O–$COCH_3$	Hydrolysis (NaOH, H_2O)
Acetal/ketal formation(for diols)	Acetone + acid catalyst	Cyclic acetal (1,3-dioxolane)	Acid hydrolysis (H^+, H_2O)

Selectivity in Diols

In a molecule containing two –OH groups (e.g., ethylene glycol, 1,2-butanediol, glycerol), selective protection depends on:

- Steric hindrance (primary OH reacts faster than secondary).
- Intramolecular formation(1,2- or 1,3-diols can form stable cyclic acetals with carbonyls).

Reaction conditions (temperature, reagent ratio, catalyst).

Example Reactions

Protection of Ethanol (Monoalcohol)

$$CH_3CH_2OH + TBDMS{-}Cl \xrightarrow{Et_3N} CH_3CH_2O{-}Si(CH_3)_2tBu + HCl$$

1. In a dry 50 mL round-bottom flask, dissolve the alcohol in 10 mL dry DCM under nitrogen.

2. Add triethylamine and cool to 0 °C (ice bath).

3. Add TBDMS–Cl slowly with stirring.

4. Allow the mixture to warm to room temperature and stir for 2 –3 hours.

5. After completion, wash the mixture with water, then with 1 M HCl, $NaHCO_3$ solution, and brine.

6. Dry the organic layer over Na_2SO_4, filter, and evaporate the solvent.

7. Purify the product by distillation or chromatography.

Selective Protection of 1,2-Ethanediol

$$HOCH_2CH_2OH + (CH_3)_2C=O \xrightarrow{p\text{-}TsOH} (CH_2O)_2C(CH_3)_2 + H_2O$$

Procedure:

1. In a 50 mL round-bottom flask, mix ethylene glycol and acetone.

2. Add a catalytic amount of p-TsOH.

3. Reflux under anhydrous conditions (use Dean-Stark or molecular sieves) for 2–3 hours, then monitor by TLC.

5. After completion, neutralize with $NaHCO_3$, filter off salts, and remove solvent under reduced pressure.

6. Distill to obtain the cyclic acetal product.

Questions

1. Draw the detailed mechanism for the protection of an alcohol with TBDMS–Cl.

2. Explain why a base (triethylamine) is required.

3. Write the mechanism of cyclic acetal formation from ethylene glycol and acetone.

4. Why is water removal essential during acetal formation?

5. What type of reaction is the deprotection step (acid- or base-catalyzed hydrolysis)?

6. In a molecule with both a primary and secondary alcohol, which one reacts faster with TBDMS–Cl? Why?

7. Can you selectively protect only one hydroxyl group of glycerol? How?

8. Why is silyl protection preferred in multistep synthesis involving bases or nucleophiles?

9. What determines whether a 1,2-diol or 1,3-diol will form a five- or six-membered cyclic acetal?

10. Compare the stability of TBDMS, TMS, and TIPS protecting groups.

11. How can you confirm (by IR or NMR) that the protection is complete?

12. Give an example of a subsequent reaction that can be performed safely after protecting the –OH group.

13. Describe how the protecting group can be removed after the desired transformation.

14. What would happen if the reaction was performed in the presence of water?

15. Suggest another method for protecting diols besides acetal formation.

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