Organic Chemistry for Materials Scientists (MSE 211)
- Lab Course -

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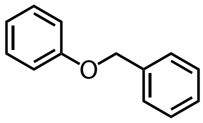
Synthesis and Purification of Benzyl Phenyl Ether

1. Introduction

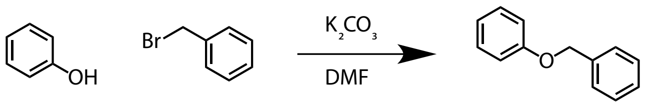


The Williamson ether synthesis is a prime example of a nucleophilic substitution reaction at an sp^3-hybridized carbon. The reaction of O-nucleophiles such as alcohols/alcoholates with organohalides is the most common way to synthesize symmetric or unsymmetrical ethers.
The purpose of this laboratory experiment is the synthesis of benzyl phenyl ether from phenol and benzyl bromide.

See also: *Chapter 4.2* of the class.
Reading Recommendation: *McMurry*, 7th ed., chapters 11.2-11.5, 12.1-12.3 & 18.2; *Clayden*, Chapters 3 (p. 50-56) & 17

2. General Principle of the Synthesis

Benzyl phenyl ether is prepared by the reaction of phenol and benzyl bromide at elevated temperatures. Unreacted starting material is separated by liquid-liquid extraction using water and methyl *tert*-butyl ether (MTBE), the latter containing the target compound. After removal of the organic solvent by distillation, the crude product is recrystallized at temperatures below 0 °C (due to its low melting point).



3. Required Equipment

- A 50 mL round-bottom flask
- A DrySin© with heating plate and magnetic stirrer
- Separating funnel
- Reflux condenser
- Büchner funnel
- Spatula

4. Experimental Procedure

In a 100 mL round-bottom flask, potassium carbonate (40.1 mmol) is suspended in 20 mL of *N,N*-dimethylformamide (DMF). Phenol (18.4 mmol) is added and, subsequently, benzyl bromide (16.7 mmol) is added dropwise. The reaction flask is equipped with a reflux condenser and the reaction mixture is stirred at 120 °C for 30 minutes. After cooling to room temperature, 35 mL of water are added. Then, the mixture is extracted three times with 35 mL of MTBE. The organic phases are combined, and washed twice with 35 mL of water and 35 mL of a saturated aqueous NaCl solution. The MTBE solution is dried over $MgSO_4$ and then the solvent is evaporated using a rotary evaporator.

5. Purification

The crude product is recrystallized from ethanol/water (13 mL/40 mL). For this purpose, it is dissolved in hot ethanol, the respective amount of water is added and the solution is cooled using an acetone/ice/NaCl bath. The crystals are collected and dried in vacuum in a desiccator. The dry crystals are weighed to determine the yield of the reaction.

6. Control of the Purity

6.1 Melting Point Measurement

The melting point of the dry sample is measured and compared with the literature value (35 °C).

6.2 Mass Spectrometry

Interpret the mass spectrum of benzyl phenyl ether: give the exact mass of the compound and assign the fragmentation peak at 91m/z.

Learning Objective: **Liquid-Liquid Extraction**

The different solubility of a compound in different solvents is utilized for the isolation of pure products, for the separation of mixtures, as well as for the separation of impurities, and provides an indispensable method for the work-up of a reaction mixture. The distribution of a dissolved compound in two non-miscible solvents is the basis for solvent extraction.

In equilibrium, the distribution of a compound (A) between two non-miscible solvents (1, 2), often water and an organic solvent, is described by Nernst's distribution law

$$\frac{c(A)_{sol.\ 1}}{c(A)_{sol.\ 2}} = k$$

with $c(A)_{sol.\ 1}$ as the concentration of (A) in solvent 1, $c(A)_{sol.\ 2}$ as the concentration of (A) in solvent 2, and k as distribution coefficient. The ratio of $c(A)_{sol.\ 1}$ and $c(A)_{sol.\ 2}$ is constant at equilibrium and independent of the amount of (A). Thus, a compound can be more completely transferred from solvent 1 into solvent 2, the lower its solubility in 1 and the higher its solubility in 2.
In case of small k, repeated extractions with small solvent volumes give a much better separation than a single extraction with large solvent amounts. A single extraction is therefore often not sufficient.
The exchange of the compound occurs at the phase interface. A large interface accelerates the establishment of the distribution equilibrium. In practice, a large and continuously revolving interface is achieved by shaking of the two phases within a separating funnel for several minutes. A frequent ventilation of the separating funnel must be ensured in order to avoid overpressure, particularly if highly volatile solvents such as diethyl ether are used! The phase separation after extraction takes time, during which the funnel should not be moved.

7. **End of the Manipulation**

1) Benzyl phenyl ether is stored in a glass vial that is labeled with the compound name, student name, and date.

2) All starting materials are put back into the retention trays.

3) The glassware is cleaned, dried, and put back in place:
- Remaining traces of organic chemical compounds (except benzyl bromide) are removed by rinsing the flask with a minimum of solvent (for example acetone), which is subsequently disposed as non-halogenated organic solvent waste.
- Traces of benzyl bromide are dissolved in acetone and disposed as halogen containing organic solvent waste.
- Traces of potassium carbonate are dissolved in water and disposed as basic aqueous waste.
- Being free of any chemical contamination, the dirty glassware is washed with a conventional detergent and rinsed thoroughly. It is then rinsed with deionized water to avoid the presence of limestone. It is possible to dry the glassware with acetone.
- All the glassware used is placed back into its original location. Any defective part is signalled to the assistant.

4) The fume hood is tidied up. All electrical appliances are unplugged. Ventilation and lighting of the hood are switched off.
5) The sink is cleaned.
6) All waste contaminated with chemicals (absorbent paper, etc.) is collected in specific recovery cans, according to the indications of the assistants.

Learning Objective: **Distillation and the Rotary Evaporator**

Distillation is the most versatile method for the purification of liquids, thus being used for the separation from less volatile components and for the separation of mixtures of liquids.

In a closed system, an equilibrium between evaporation and condensation of a compound is established that is characterized by the vapor pressure (p). The relation between p and absolute temperature (T) is given by *Clausius-Clapeyron* equation

$$\ln \frac{p_2}{p_1} = \frac{-\Delta H_{evap}}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

with ΔH_{evap} as the molar heat of evaporation and R the gas constant. The temperature at which p equals the external pressure is the boiling temperature. According to the Clausius-Clapeyron equation, the boiling temperature is decreased at reduced pressure, a principle that is made use of in a rotary evaporator.

The rotary evaporator is particularly used for the fast and mild removal of large solvent amounts. While the temperature of the external heating source is kept constant (40-60 °C), the pressure is adjusted in order to control the boiling temperature. For MTBE, the pressure is adjusted to 500 mbar in order to reduce its boiling temperature appropriately.
During distillation the flask is rotated in the heating bath, which guarantees a large and continuously revolving surface of the liquid to be distilled, overall accounting for a fast evaporation. The vapor is condensed in a condenser and collected in a separated flask. Thus, the liquid is forced to continuously go from its liquid state into the gas phase.

8. To be Addressed in the Protocol

- Give a detailed reaction mechanism including the elementary steps.
- For most Williamson-type ether syntheses the presence of a strong base is required. Give the pKa values of phenol and K2CO3 and explain why a rather weak base is already sufficient for the present reaction.Judge whether the reaction occurs according to S_N1 or S_N2 mechanism. What role does the solvent play?
- Which compounds are separated by the liquid-liquid extraction?
- Be sure you have also completed:
    - Prelab protocol (done **BEFORE** lab)
    - Mass spectrometry peak assignment