Perustöiden II synteesit

Perustyöt II:ssa tehdään itsenäisesti viisi synteesiä, kaasukromatografiatyö sekä luonnonaineen eristys. Opiskelijalle määrätään joko 1. tai 2. paketti.

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Reduction on a microscale – the stereochemistry of commercial 2,6-dimethylcyclohexanone

The isomer ratio of a commercial ketone (2,6-dimethylcyclohexanone) is determined by means of hydride reduction and GC analysis. Reference: Garner, C. M. *Journal of Chemical Education* 1993, 70, A310.

Before you start with this laboratory work, study the use of a gas chromatograph, the use and cleaning procedures of microliter syringe.

**Reagents**
- 1 μL of ketone mixture
- 15 drops of methanol
- A tiny granule of 10-40 mesh NaBH₄

**Equipment**
- Small test tube
- 10 μL syringe
- Gas chromatograph

**NOTE! THE SYRINGE MUST BE WASHED THOROUGHLY AFTER EVERY INJECTION!!!**

**Determination of the ketone isomer ratio**
First, the ketone isomer ratio of 2,6-dimethylcyclohexanone (Aldrich) is determined by capillary GC using the program set from 50 °C to approximately 80 °C at 3 °C/min. 1 μL of standard solution (1 μL of ketone in 2-3 mL of hexane) is injected with the microliter syringe. The standard solution is already diluted.
The reduction of the ketone
1 μL of commercial, undiluted ketone is dissolved in 15 drops of methanol in a small test tube, a tiny granule (the tip of a spatula - not more than a few milligrams) of 10-40 mesh (granule size) sodium borohydride is added, and the liquid is swirled until the solid dissolves. Let the reaction mixture stand for 5 minutes. Then 0.5 mL of saturated aqueous sodium bicarbonate and 1-2 mL of hexane are added, and the vial is capped and shaken vigorously for a few seconds. After the layers separate (the organic phase should be clear), a 10 μL syringe is used to sample about 1 μL of the upper organic phase (not the lower water layer!) for GC analysis using the same conditions as above. In the end wash the syringe several times with distilled water and finally with ethyl acetate.

Analysis by GC

Check separate notes on how to use the gas chromatograph and how to select the method.
Column: 15 m x 0.32 mm x 0.25 μm NB-54

The following samples have to be examined by gas chromatography:
1. Pure hexane to see impurities contained in the system.
2. The determination of the isomer ratios of the commercial ketone.
3. The determination of the %-ratios of the reduction products.

Work report

Examine the reaction equations above and make conclusions about the composition of the starting material and the product mixture.

Sorbic acid, \textit{trans-hexa-2,4-dienoic acid}

\begin{center}
\begin{tikzpicture}
    \node[draw,shape=circle] (A) at (0,0) {\text{\O}};
    \node[draw,shape=circle] (B) at (1.5,0) {\text{\O}};
    \node[draw,shape=circle] (C) at (0,1.5) {\text{\O}};
    \node[draw,shape=circle] (D) at (1.5,1.5) {\text{\O}};
    \node[draw,shape=rectangle] (E) at (2.5,0) {\text{\O}};
    \node[draw,shape=rectangle] (F) at (4,0) {\text{\O}};
    \draw (A) -- (B) -- (C) -- (D) -- (E) -- (F);
\end{tikzpicture}
\end{center}

Hünig-Märkl-Sauer 5.4.1
Reagents
6.0 g malonic acid
4.0 g crotonaldehyde
6.0 g pyridine

Equipment
round-bottomed flask
reflux apparatus
suction filtration apparatus

Procedure
Place 4.0 g (4.6 mL) of crotonaldehyde (b.p. 101-103 °C), 6.0 g of malonic acid and 6.0 g (6.1 mL) of pyridine (b.p. 113-115 °C) in a 100 mL round-bottomed flask, attach a reflux condenser and heat to reflux for 3 hours. At the end of this period the vigorous evolution of carbon dioxide will have ceased. Cool the mixture in ice and cautiously acidify it by adding an ice-cold solution of 2 mL of conc. sulphuric acid in 5 mL of water with stirring. Check the acidity with pH-paper (pH 2), add more acid if needed. Most of the sorbic acid separates immediately; a more complete separation is achieved by cooling the solution in ice for 3-4 hours. Filter the acid with a Büchner funnel and wash it with a little ice-cold water.

Isolation and purification
Recrystallize from boiling water; the maximum recovery of purified acid is achieved by leaving the solution in a refrigerator overnight and then filtering (yield: 31 %).

Product characterization
Record the IR spectrum and the melting point of the pure product.

Questions
1. What are the safety precautions in handling crotonaldehyde?
2. How do you choose the solvent for the recrystallisation?

Cinnamyl alcohol, trans-3-phenyl-2-propen-1-ol

Reagents
12.6 mL cinnamaldehyde
1.9 g NaBH₄

Equipment
Erlenmeyer flask
magnetic stirrer
separatory funnel
distillation apparatus

Procedure
Add a few drops of 2 M NaOH¹ to 30 mL of methanol followed by 12.6 mL of cinnamaldehyde. Cool the mixture in an ice-bath and add 1.9 g NaBH₄ in small portions using a spatula into the stirred mixture.² Continue to stir the mixture for a further 15 min.

Isolation and purification
Rinse the reaction mixture with 130 mL water into a separatory funnel and extract three times with 50 mL ether. Wash the combined ether extracts with 50 mL water and dry with Na₂SO₄, filter into a preweighed flask and evaporate the ether with the rotary evaporator. Determine the weight of the crude product and distill it using oil pump vacuum and an vacuum distillation apparatus. The boiling point range is about 70 -100°C/0.01 mmHg. The product may solidify once it has been purified. It is therefore wise to use a solid state distillation apparatus. If a normal distillation apparatus is used, the product may solidify in the condenser and has to be melted. The yield of the product is 92%.

Product characterization
Determine the melting point and run IR and NMR spectra of the purified product.

Questions
Answer the following questions which are related to the text in the procedure section.
1. What is the effect of NaOH in the reaction mixture?
2. What may be observed?
4-Bromoacetanilide

![Chemical structure of 4-Bromoacetanilide](image)

4-Bromoacetanilide is used as a starting material for 4-bromoaniline.


Preparation of acetanilide (N-Phenylacetamide)

**Reagents:**
- 2 ml of aniline
- 3.2 ml of acetic anhydride

**Equipment:**
- 250 ml erlenmeyer flask
- Magnetic stirring apparatus
- Suction filtration apparatus

**Procedure**
Aniline (2 ml) and water (100 ml) are mixed and stirred in an erlenmeyer flask. Add to this heterogeneous mixture 6 M HCl (6-10 ml) until the pH is ca. 1.¹ The resulting homogenous solution is cooled in an ice bath and acetic anhydride (3.2 ml) is added followed by solid NaHCO₃ until the pH is ca. 6¹ evolution of CO₂ has ceased (requires 4-6 g of NaHCO₃).

**Isolation**
The precipitated product is filtered with a Büchner funnel and washed with a little ice-cold water. Let the product dry in a desiccator overnight.

**Product characterization**
Run a TLC from your product and aniline (1:2 EtOAc : CH₂Cl₂). Determine the melting point and run IR spectrum.

¹. Check with pH paper
p-Bromoacetanilide

**Reagents**
- 3.0 g of acetanilide
- 5.4 g of NaBr
- 20 ml of EtOH (95%)
- 15 ml of acetic acid
- 11.6 ml of NaClO (ca. 14%)

**Equipment**
- 100 ml round-bottomed flask
- Magnetic stirring apparatus
- Suction filtration apparatus
- Recrystallization apparatus

**Procedure**
Place previously made acetanilide (3.0 g) and NaBr (5.4 g) in a 100 ml round-bottomed flask. Add ethanol (20 ml) and acetic acid (15 ml) and stir the mixture in an ice bath until the temperature of the mixture is <5 °C. Add 14% NaClO (11.6 ml) and stir 1 minute in an ice bath. Remove the ice bath and stopper the flask with a cork and allow the reaction to warm up to room temperature over 15 minutes. Cool the reaction in an ice bath and quench the reaction by adding 10% sodium thiosulfate solution to remove any unreacted bromine. Add 40 ml of 2 M NaOH.

**Isolation and purification**
The precipitated product is filtered with a Büchner funnel and recrystallized from ethanol. Calculate the yield starting from aniline.

**Product characterization**
Determine the melting point and run IR spectrum.

**Questions**
1. What may be observed?
2. What may be observed?
3. Why is the amine group of aniline protected as an amide before bromination?
4. Why are these two reactions good examples of green chemistry procedures?
4-Bromoaniline

Reagents:
2.4 g of 4-bromoacetanilide
30 ml of ethanol (95%)
30 ml of 2 M HCl

Equipments:
reflux apparatus
magnetic stirrer
separatory funnel
suction filtration apparatus

Procedure
Dissolve 4-bromoacetanilide (2.4 g) in 30 ml of ethanol in a 100 ml round-bottomed flask. Add 2 M HCl (30 ml) and reflux the mixture. The reaction time needed is checked with TLC at hourly intervals (eluent 2:1 CH₂Cl₂:EtOAc).¹

Isolation and purification
Cool the solution in an ice-bath and make the solution basic by adding 2 M NaOH.² The mixture is extracted three times with 20 mL of diethyl ether. The organic phase is washed three times with water and dried with Na₂SO₄ and the solvent is evaporated. The crude product is recrystallized from aqueous EtOH.

Product characterization
Determine the melting point and run IR spectrum.

1. How is the reaction followed by TLC? How do you prepare the sample for TLC?
2. Check with pH paper.
**1-Phenyl-1-butanol**

![Chemical Structure](image)


**Reagents**
- 1.5 g of magnesium
- 5.7 mL of n-propyl bromide
- 5.1 mL of benzaldehyde

**Equipment**
- reflux apparatus
- addition funnel
- separation/extraction
- distillation apparatus (normal and reduced pressure)

**Procedure**
The reaction starts with the preparation of a Grignard reagent from n-propyl bromide. Note that any moisture hinders the start of the reaction. Therefore all the reagents, solvents and equipment have to be absolutely dry. First prepare enough dry ether according to instructions (eg. T. Simonen: Orgaanisen kemian työmenetelmistä ja työturvallisuudesta sekä orgaanisesta analytiikasta, p. 130 - in Finnish. Also note the safety instructions for the handling of sodium, p. 147).

Mg-turnings should always be kept in a desiccator. Dry the glassware in the oven and protect it from dampness by using CaCl₂ tubes.

**Preparation of Grignard reagent**
Prepare the Grignard reagent from 1.5 g of magnesium turnings, 5.7 mL of dry, freshly distilled n-propyl bromide (bp. 71°C) and 22.5 mL abs. ether. Place the turnings and some of the ether into a flask. Dissolve n-propyl bromide in dry ether and transfer the solution into an addition funnel. Without stirring, add about 1/10 of the n-propyl bromide solution to the reaction flask. If the reaction does not start immediately (which it usually does with alkyl bromides), slight warming or the addition of a catalyst (eg. a crystal of iodine) can help. A sign that the reaction has started is that the reaction mixture turns dimly grey and, as the reaction is exothermic, the ether starts to boil. Once the reaction has started, the rest of the n-propyl bromide is slowly added in such a way that the reaction mixture does not boil too vigorously. When all of the n-propyl bromide has been added, stirring continues for about 15 minutes at room temperature. The reaction mixture is refluxed for additional 20 minutes.
solution of freshly distilled benzaldehyde (5.1 mL, 178-9°C) in abs. ether (25 mL) is slowly added under stirring at room temperature to the Grignard reagent in such a manner that a gentle reflux is maintained. When the addition is complete, the reaction mixture is heated under reflux for one hour.

**Isolation and purification**

The reaction mixture is cooled with ice water and saturated NH₄Cl (63 mL) is slowly added until two clear phases appear. The organic phase is separated and the aqueous layer is extracted with ether (2 x 25mL). The combined organic phases are successively washed with saturated NaHSO₃ (6.5 mL), saturated NaHCO₃ (6.5 mL) and water (2 x 13 mL), and dried over MgSO₄. The solvent is distilled off in normal pressure and the product is distilled under reduced pressure with a water aspirator (72-74°C/3.5 mmHg). The yield of the product is 80%.

**Product characterization**

Record the boiling point in vacuo, measure the refractive index and run an IR spectrum of the product.

**Questions**

1. Why does benzaldehyde contain benzoic acid after a long period of storage?
2. What do you observe during addition?
3. The reaction mixture can be stirred over night at room temperature, if necessary.
4. Why is NH₄Cl added?
5. Why is NaHSO₃ solution used?
6. Which drying agents can be used and which cannot?
Isolation of eugenol, the fragrant components of cloves

![Structure of Eugenol](image.png)

Clove are dried flower buds of the evergreen tropical tree *Eugenia aromatica*, a native of Southeast Asia, and are known to have been used in cooking by the Chinese over 2000 years ago, being valued for inhibiting putrefaction of meet with which they were cooked. This property and their pungent odor are due largely to a single component, eugenol, which makes up the bulk of the "oil of cloves" that is obtained by steam distillation of the flower buds. Other applications for eugenol include its use in dental preparations, perfumery and an insect attractant.

Reference: Durst & Gokel: *Experimental Organic Chemistry*.

**Reagents**
- 105 mL dichloromethane
- 60 mL 5% NaOH solution
- 5% HCl solution
- Anhydrous sodium sulphate

**Procedure**
Place 10 g of cloves in a 250 mL round bottomed flask, followed by 100 mL water. Steam distill the mixture keeping the internal volume at about 100 mL. Continue the distillation until no oily material can be seen in the condenser.

**Isolation and purification**
Transfer the oily distillate to a separatory funnel and extract with 2x25 mL of dichloromethane. Extract the dichloromethane layer with 3x20 mL of 5% sodium hydroxide (heat evolved). Combine the basic aqueous layers and wash once with 15 mL of dichloromethane. Transfer the aqueous basic layer to a 200 mL beaker and slowly acidify with 5% hydrochloric acid (care! heat evolved!). Extract the aqueous layer with 2x20 mL of dichloromethane. Wash the combined organic layers with 10 mL of water. Dry the organic layer over anhydrous granular sodium sulphate, filter into a pre-weighed flask and remove the solvent on the rotary evaporator. Record the yield of product.

**Product characterization**
Check the purity of the product with gas chromatograph.