INSTITUTE OF CHEMICAL TECHNOLOGY PRAGUE
Faculty of Chemical Technology
Department of Organic Technology

Specialized Laboratory for Drug production
(N111049)
Instructions

Aldol condensation in drug synthesis

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Study program:	*Drug synthesis and production*
Study field:	*Drug production*
Location:	*A67, A68*

CONTENT

1. INTRODUCTION

Aldolisation is reaction between two molecules of an aldehyde or ketone in the formation of new C-C bonds. [1] It is used for the synthesis of organic compounds, particularly specialty chemicals (such as perfumes, medicaments). Bond is formed between the α-carbon of the first component and carbonyl-carbon of the second component. [2] This reaction is called aldolisation due product, which is also both **ald**ehyde and alcoh**ol**. These compounds are therefore generally says **aldols**. If the reaction mixture containing the aldol is heated to a higher temperature leads to its dehydration to an unsaturated aldehyde or ketone with a conjugated system of multiple bonds. In mixtures containing aldol can also occur spontaneous dehydration since it is slightly exothermic reaction. Under these conditions, we are talking about an **aldol condensation**.

Aldol condensation can be catalyzed by acids, but more we are using basic catalysis. [1-3]. Fig. 1 shows a reaction scheme for base-catalyzed aldol condensation, which involves the formation of an enolate (equilibrium reaction). In the next step, the resulting enolate adds to the carbonyl group of the second molecule. The adduct is subsequently protonated by water to β-hydroxycarbonyl compound.

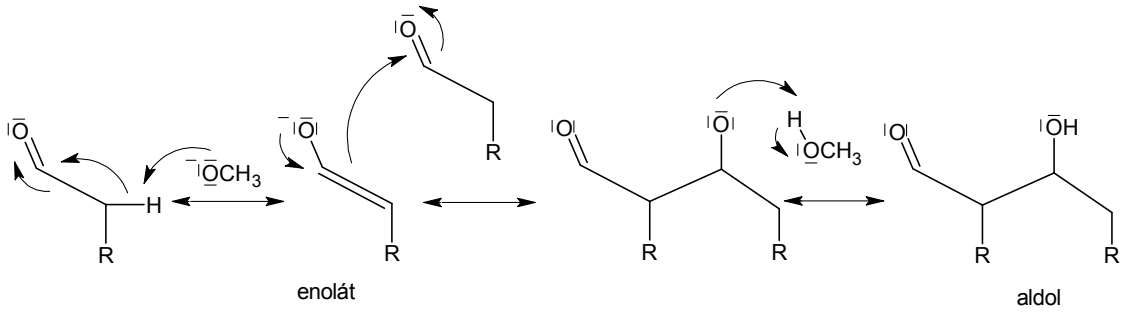

Fig. 1 Scheme by base-catalyzed symmetrical aldol condensation (self-condensation).

This laboratory work is focused on the preparation of 2-methyl-2-pentenal, the prodrug of meprobamate (2-methyl-2-propyl-1,3-propandiolkarbamate). 2-Methyl-2-pentenal is yellowish liquid, which is an important intermediate for production of a substantial number of drugs and pharmaceutical substances. [4] Meprobamate is a sedative hypnotic agent from the group of carbamates. For meprobamate as drug was demonstrated anxiolytic effect. Therefore, meprobamate is often used in the treatment of anxiety disorders, depression and psychiatric disorders weaker. [5]

2. METHOD OF LABORATORY WORK

2.1 Apparatus description

Aldol condensation of propanal to 2-methyl-2-pentenal (Fig. 2) for meprobamate (Fig. 3) synthesis is carried out in a groundglass round bottom flask with the volume of 500 ml and reflux condenser. During condensation the reaction mixture is stirred with a magnetic stirrer. Samples are taken using a syringe.

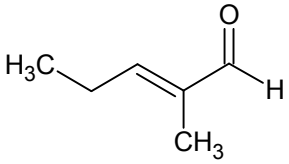

Fig. 2 2-Methyl-2-pentenal.

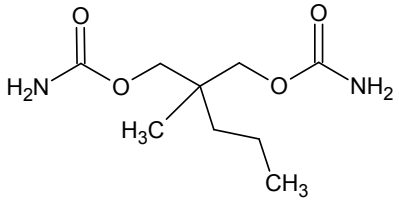

Fig. 3 Meprobamate.

2.2 Experiment description

2.2.1 Aldol condensation

This work is focused on basic symmetrical aldol condensation of propanal. Into the 500ml flask is presented 50 ml of previously weighed propanal, 270 ml of previously weighed solvent (methanol) and 6% (by weight) of basic catalyst (36% solution) relative to the substrate. After adding magnetic stirrer is flask equipped with reflux condenser. The reaction proceeds at room temperature and room pressure. During aldol condensation, the reaction mixture is sampled about 0.2 ml (at suitable intervals of 15, 30, 45, 60, 90, 120, 150,180, 195, 210, 225, 240 min). The obtained samples are neutralized with sulfuric acid (10%), diluted with a solvent in a volume ratio 1:3 (methanol) and centrifuged. The organic phase is analysed using a gas chromatograph.

2.2.2 Atmospheric distillation

During the aldol condensation of propanal are formed except 2-methyl-2-pentenal also byproducts (e.g., 2-methyl-1-pentanol, etc.). The aim of this work is to get the cleanest possible product for hydrogenation, therefore, must be made by atmospheric distillation. For atmospheric distillation is used three-necked 500 ml round bottom flask, into which is inserted boiling stone. Into one neck is located thermometer that reads the temperature of the mixture, the second neck is plugged. The middle neck is deployed downward condenser equipped with a thermometer that reads the temperature of the vapor. Downward condenser is terminated by the flask for collecting the distillate. The flask is heated with a heating mantle always slightly above the boiling point of the individual fractions. The boiling points of some substances bottoms composition are shown in Table 1. All ground-lass connections are tight enough, which ensures lubrication with silicone grease. All fractions are then analyzed by a gas chromatograph.

Table 1 Some compounds boiling points of the distillation mixture after propanal self aldol condensation

Substance	Boiling point [°C]
Methanol	**64.7**
Propanal	**46-50**
2-Methyl-2-pentenal	**137-138**
2-Methyl-1-pentanol	**149**

2.3 Sample analysis

Reaction mixture samples after the self aldol condensation of propanal and subsequent distillation fractions are analysed using a gas chromatograph SHIMADZU GC-17 A equipped with ZB-1 A-1 column (60 m, 0.25 mm diameter, 0.25 μm film). Table 2 summarizes retention times of the potential compounds present in the reaction mixture. Table 3 shows the chromatography analysis conditions of individual samples.

Table 2 Retention times of the potential compounds present in the reaction mixture

Substance	Retention time
Methylalcohol	2.41
Propanal	2.45
2-Methyl-2-pentenal	3.32
2-Methyl-1-pentanol	3.33

Table 3 Chromatographic analysis conditions

Column temperature	80 °C
Time of column temperature	5 min
Temperature rate	10 °C min^{-1}
Ending temperature	250 °C
Time of ending temperature	5 min
Analysis time	34 min
Constant carrier gas flow (He)	5 ml min^{-1}
Inlet pressure	320 kPa
Linear velocity	42 cm s^{-1}
Split	59
Injector temperature	250 °C
Detector temperature	250 °C
Feed	0.2 µl

3. RESULTS

For results evaluation are used Equations 1-3. By Equation 1 is calculated conversion K (%) of compound A, where the values given in square brackets are units, $A0$ is the substrate concentration at the start (time 0) and $A\tau$ is the substrate concentration in the reaction (at time τ).

$$K = \frac{A0[\%] - A\tau[\%]}{A0[\%]}.100 \qquad \textbf{Equation 1}$$

The selectivity S (%) of the catalyst is calculated according to Equation 2, where values given in square brackets are units, $A0$ is the substrate concentration at the start (time 0), $A\tau$ is substrate concentration during the reaction (at time τ) and $B\tau$ is the concentration of the desired product during the reaction (at time τ).

$$S = \frac{B\tau[\%]}{A0[\%] - A\tau[\%]}.100 \qquad \textbf{Equation 2}$$

Yield V (%) of product B was calculated according to Equation 3, where the values given in square brackets are units, $A0$ is the substrate concentration at the start (time 0), $B\tau$ is the product concentration in the reaction (at time τ), M_A is the substrate molar mass and M_B is the product molar mass.

$$V = \frac{B\tau[\%]M_A[gmol^{-1}]}{M_B[gmol^{-1}]A0[\%]} \qquad \textbf{Equation 3}$$

4. TASKS

Before entering the lab A68 for Specialized laboratory I Aldol condensation in drug synthesis you first think about Tasks 1-4.

Task 1: Draw scheme of propanal symmetrical aldol condensation in the presence of basic catalyst.

Task 2: During symmetrical aldol condensation occurs always result in one aldol. During mixed aldol condensation of two different aldehydes or ketones that contain the α-carbon hydrogen atoms produces a mixture of four products. It is possible to perform a mixed aldol condensation of the aldehyde with the ketone to form a single product, but under carefully controlled conditions. Locate and write to the log two conditions so that when at least one of them led to only one reaction product aldol condensation. (Recommended reading: McMurry, J. *Organic Chemistry*, 1st ed. .; VUTIUM: Brno, **2007**.)

Task 3: To the reaction mixture is submitted to 30 g of propanal. Calculate how much must be weighed sodium hydroxide to form a 36% aqueous solution, and simultaneously formed of 6% (by weight) relative to the substrate (propanal). Enter the full exact calculation with computational relations.

Task 4: What atmospheric distillation fraction of the reaction mixture after symmetrical aldol condensation of propanal would be suitable for the subsequent hydrogenation of the 2-methyl- 2-pentenal to 2-methylpentanal?

5. PROTOCOL CONTENT

Protocol to the Specialized Laboratory I Aldol condensation in drug synthesis will include following points:

1) Introduction
2) Aim of work
    i) Answer to Task 1
    ii) Answer to Task 2
3) Short work progress
4) Results and discussion
    i) Answer to Task 3
    ii) Exact sample weight of substrate, catalyst and solvent
    iii) Time dependence of reaction mixture components concentration during aldol condensation (Graph)
    iv) Calculations examples and results for conversion, selectivity and yield of the symmetrical aldol condensation
    v) Table fraction composition of atmospheric distillation
    vi) Answer to Task 4
5) Conclusion
6) List of symbols (if necessary)
7) References

6. REFERENCES

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2. Svoboda, J. a kolektiv. *Organická chemie I*, 1st ed.; ICT Prague, **2000**.
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4. Sharma, S. K.; Parikh, P. A.; Jasra, R. V. *Solvent free aldol condensation of propanal to 2-methylpentenal using solid base catalysts*. J. Mol. Catal. A: Chemical **2007**, 278, 135-144.
5. Lincová, D.; Farghali, H. *Základní a aplikovaná farmakologie*, 2nd ed., GALEN: Prague, **2007**.