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Concerning the Solvent Effect in the Aldol Condensation

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Summary. Except for the catalyst and the temperature, the nature of the solvent also affects the aldol condensation, favouring α,β-unsaturated carbonyl compounds in alcoholic solvents or β-hydroxyl carbonyl compounds in tetrahydrofuran.

Keywords. Aldol condensation; Solvent; α,β-Unsaturated carbonyl compounds; β-Hydroxyl carbonyl compounds.

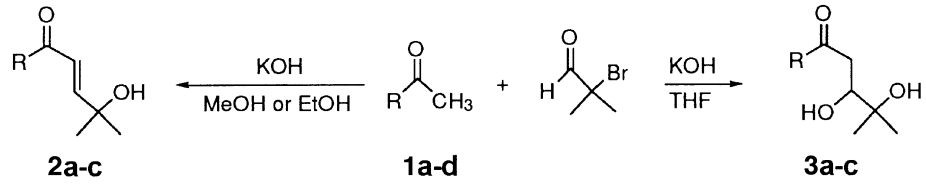
Introduction

The aldol condensation is a common reaction in organic synthesis. It includes reactions producing β-aldols or β-ketols by self-condensation or mixed condensation of aldehydes or ketones as well as reactions affording α,β-unsaturated aldehydes or α,β-unsaturated ketones *via* dehydration of intermediate β-aldols or β-ketols. It may be catalyzed by acids or bases, bases being more frequently employed. The type of product depends on the catalyst as well as on the temperature. Although these dependencies have been thoroughly investigated, the influence of the solvent has raised little attention. Usually, the choice of solvent depends on the solubility of reactants and catalyst. Studies of solvent effects on the aldol condensation have merely dealt with the ratio of 1-condensation to 3-condensation of methyl ketones with aldehydes [1] as well as the kinetics of decomposition of the dimer of acetone [2].

Results and Discussion

It was observed that the solvent can also affect the product type of the aldol condensation, *i.e.* the formation of corresponding β-hydroxyl of α,β-unsaturated carbonyl compounds could be directed by changing the solvent from tetrahydrofuran to ethanol or methanol. Due to the rather similar boiling points of methanol (64.5°C) and *THF* (66°C) and the use of the same catalyst, effects of temperature and catalyst can be excluded in these reactions.

Obviously, non-aqueous protic solvents increase the strength of the catalytic base, thus promoting dehydration of intermediate β-aldols or β-ketols. In the experiments, 2-bromo-2-methylpropanal was reacted with KOH for 2 h to produce



Scheme 1. **2a**: $R = 2,4$-dimethylphenyl; **2b**: $R = 1$-hydroxy-1-(2′-methylphenyl)-ethyl; **2c**: $R = 1$-hydroxy-1-phenylethyl; **3a**: $R = 1$-hydroxy-1-phenylethyl; **3b**: $R = 1$-hydroxy-1-(3′-methylphenyl)-ethyl; **3c**: $R = 1$-hydroxy-1-(4′methyl-2′-(2″-tetrahydropyranoxyl)-phenylethyl

2-hydroxyl-2-methylpropanal [3] which was then reacted *in situ* with the corresponding ketone **1** in an alcoholic solvent to afford α,β-unsaturated ketone derivatives **2a–c**. In *THF*, however, β-hydroxyl ketone derivatives **3a–c** were obtained. The compounds were identified by spectroscopic methods (IR, MS, NMR) and elemental analyses.

Experimental

Melting points were determined on a Kofler microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on Jeol-90Q and Bruker AM 500 instruments; chemical shifts are reported in ppm downfield from *TMS*. MS were measured on a ZAB-2F MS instrument. Elemental analyses agreed with the calculated values for C and H within $\pm 0.4\%$. IR spectra were measured on a Perkin-Elmer-683 infrared spectrometer as CH_2Cl_2 film or KBr pellet. Column chromatography was performed on silica gel 60 with petroleum ether (60–90°C) as eluent. 2-Bromo-2-methylpropanal was prepared according to Ref. [4], ketones **1a–d** according to Refs. [5–7].

Procedure A

2-Bromo-2-methylpropanal (3.3 mmol) was added to a solution of 3.3 mmol KOH in alcoholic solvent (6 cm^3). The mixture was stirred at room temperature for 2 h. Then 3.3 mmol ketone **1** were added, and the resulting mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure; the residue was treated with water (5 cm^3) and extracted with ethyl acetate (3×6 cm^3). The ethyl acetate layer was washed with water (2×3 cm^3), dried over $MgSO_4$, and the ethyl acetate was removed under reduced pressure. The crude product was isolated on silica gel using ethyl acetate/petroleum ether as eluent to give compounds **2**.

E-1-(2′,4′-Dimethylphenyl)-4-hydroxy-4-methyl-2-penten-1-one (**2a**; $C_{14}H_{18}O_2$)

Solvent: methanol; yield: 50%; colorless soil; IR (film): $\nu = 1674$ (C=O) cm^{-1}; MS (EI): $m/z = 219$ ($M^+ + 1$), 200, 185, 159 (100), 145, 133, 105, 77, 59, 43; ^{1}H NMR ($CDCl_3$): $\delta = 1.44$ (s, 6H, 6-$(Me)_2$), 2.38 (s, 3H, Ar-CH_3), 2.43 (s, 3H, Ar-CH_3), 6.67 (d, $J = 17.3$ Hz, 1H, O=CC=CH), 7.0 (d, $J = 8$ Hz, 1H, 5′-ArH), 7.04 (s, 1H, 3′-ArH), 7.36 (d, $J = 17.3$ Hz, 1H, O=CCH=C), 7.39 (d, $J = 8$ Hz, 1H, 6′-ArH) ppm.

E-2, 6-Dihydroxy-6-methyl-2-(2′-methylphenyl)-4-hepten-3-one (**2b**; $C_{15}H_{20}O_3$)

Solvent: methanol; yield: 41%; colorless oil; IR (film): $\nu = 1689$ (C=O) cm^{-1}; MS (EI): $m/z = 231$ (M^+-17), 213, 159, 135 (100), 119, 91; ^{1}H NMR ($CDCl_3$): $\delta = 1.26$ (s, 6H, 6-$(Me)_2$), 1.73 (s, 3H, 1-CH_3), 2.16 (s, 3H, Ar-CH_3), 6.14 (d, $J = 15$ Hz, 1H, O=CC=CH), 7.10 (d, $J = 15$ Hz, 1H, O=CCH=C), 7.07–7.28 (m, 3H, 3′-H, 4′-H, 5′-H), 7.38–7.56 (m, 1H, 6′-H) ppm.

E-2,6-Dihydoxy-6-methyl-2-phenyl-4-hepten-3-one (**2c**; $C_{14}H_{18}O_3$)

Solvent: ethanol; yield: 41%; colorless oil; IR (film); $\nu = 1668$ (C=O) cm^{-1}; MS (CI): $m/z = 235$ ($M^+ + 1$), 217 (100), 199, 121, 105; ^1H NMR ($CDCl_3$); $\delta = 1.29$ (s, 6H, 6-$(Me)_2$), 1.79 (s, 3H, 1-CH_3), 6.42 (d, $J = 15$ Hz, 1H, O=C-C=CH), 7.06 (d, $J = 15$ Hz), 1H, O=C-CH=C), 7.20–7.44 (m, 5H, ArH) ppm.

Procedure B

KOH (18 mmol) was added to a solution of 18 mmol 2-Bromo-2-methylpropanal in *THF* (15 cm^3) portions. The mixture was stirred under room temperature for 2 h, 18 mol ketone **1** were added, and the resulting mixture was reacted under reflux for 6 h. The mixture was poured in water (20 cm^3), separated, and the aqueous layer was extracted with ethyl acetate (3×15 cm^3). The organic layers were combined, washed with H_2O, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was isolated on silica gel using ethyl acetate/petroleum ether as eluent to give compounds **3**.

6-Methyl-2,5,6-trihydroxy-2-phenyl-heptan-3-one (**3a**; $C_{14}H_{18}O_4$)

Yield: 45%; white solid; IR (KBr): $\nu = 1714$ (C=O) cm^{-1}; MS (EI): $m/z = 235$ (M^+-17), 217 (M^+-18-17), 199, 191, 173, 121 (100), 105, 91, 77, 71, 59, 43; ^1H NMR ($CDCl_3$): $\delta = 1.07$ (s, 6H, 6-$(Me)_2$), 1.74 (s, 3H, 1-CH_3), 2.30 (dd, $J = 4.6$, 16.2 Hz, 1H, 4-H_a), 2.92 (dd, $J = 4.6$, 9.0 Hz, 1H, 4-H_b), 4.12 (dd, $J = 9.0$, 16.2 Hz, 1H, 5-CH), 7.20–7.44 (m, 5H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.4$ (C-1), 23.5 (C-7, C-7′), 36.7 (C-4), 70.1 (C-5), 80.5 (C-6), 80.8 (C-2), 125.8 (C-2′), 128.1 (C-4′), 128.7 (C-3′), 141.0 (C-1′), 209.3 (C=O) ppm.

6-Methyl-2,5,6-trihydroxy-2-(3′-methylphenyl)-heptan-3-one (**3b**; $C_{15}H_{20}O_4$)

Yield: 38%; colorless oil; IR (film); $\nu = 1716$ (C=O) cm^{-1}; MS (EI): $m/z = 249$ (M^+-17), 231 (100), 217, 213, 199, 159; ^1H NMR ($CDCl_3$): $\delta = 1.07$ (s, 6H, 6-$(Me)_2$), 1.74 (s, 3H, 1-CH_3), 2.33 (s, 3H, $ArCH_3$), 2.25–2.35 (m, 1H, 4-H_a), 2.85–2.95 (m, 1H, 4-H_b), 3.95–4.05 (m, 1H, 5-H), 7.10–7.30 (m, 4H, ArH).

6-Methyl-2,5,6-trihydroxy-2-(4′-methyl-2′-(2″-tetrahydropyranoxyl)-phenyl)-heptan-3-one (**3c**; $C_{20}H_{30}O_6$)

Yield: 35%; colorless oil; IR (film): $\nu = 1724$ (C=O) cm^{-1}; MS (CI): $m/z = 336$ (M^+-15-15), 335 (M^+-15-15-1), 317, 275, 247, 229 (100), 151, 135, 89; MS (EI): $m/z = 275$, 229, 151, 135, 85 (100), 71, 59, 43, 41; ^1H NMR (DMSO-d_6): $\delta = 1.22$ (s, 3H, 7-CH_3), 1.23 (s, 3H, 7a-CH_3), 1.38–1.60 (m, 6H, 3″-CH_2, 4″-CH_2, 5″-CH_2), 1.70 (s, 3H, 1-CH_3), 2.24 (s, 3H, 4′-$ArCH_3$), 2.20–2.60 (m, 1H, 4-H_a), 2.70–3.00 (m, 1H, 4-H_b), 3.35–3.80 (m, 2H, 6″-CH_2), 3.95–4.20 (m, 1H, 5-H), 5.10–5.30 (m, 1H, 2″-H), 6.68 (dd, $J = 2.4$, 8.5 Hz, 1H, 5′-H), 6.92 (d, $J = 2.4$ Hz, 1H, 3′-H), 7.45 (d, $J = 8.5$ Hz, 1H, 6′-H).

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