Organic Syntheses

A Publication
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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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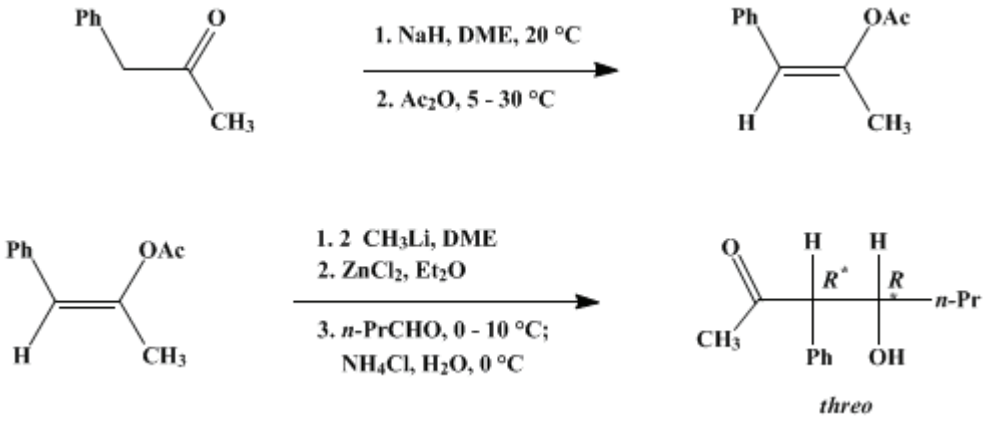
DIRECTED ALDOL CONDENSATIONS: *threo*-4-HYDROXY-3-PHENYL-2-HEPTANONE

[2-Heptanone, 4-hydroxy-3-phenyl-, (*R*,*R*)-]



Submitted by Robert A. Auerbach, David S. Crumrine, David L. Ellison, and Herbert O. House[1].
Checked by Wataru Nagata and Norbuhiro Haga.

1. Procedure

Caution! Since hydrogen is liberated, this preparation should be performed in a hood.

A. 2-*Acetoxy*-trans-1-*phenylpropene*. A dry, 500-ml., three-necked flask is fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a rubber septum, and the apparatus is arranged so that the flask may be cooled intermittently with an ice bath. After the reaction vessel has been flushed with nitrogen (admitted through a hypodermic needle in the rubber septum) a static nitrogen atmosphere is maintained in the reaction vessel for the remainder of the reaction. The flask is charged with 35 g. of a 57% dispersion of sodium hydride (20 g., 0.83 mole) in mineral oil (Note 1). The mineral oil is washed from the hydride with 200 ml. of anhydrous pentane. The supernatant pentane layer is removed with a stainless-steel cannula inserted through the rubber septum (Note 2). The residual sodium hydride is mixed with 250 ml. of anhydrous 1,2-dimethoxyethane (Note 3) before 65 g. (0.48 mole) of phenylacetone (Note 4) is added dropwise and with stirring over 50–60 minutes. During this addition an open hypodermic needle should be inserted in the rubber septum to permit the escape of hydrogen, and intermittent cooling with an ice bath may be necessary to keep the reaction solution from boiling. The resulting mixture is stirred for 3 hours while it is allowed to cool, then the mixture is allowed to stand for approximately 2 hours, permitting the excess sodium hydride to settle. The supernatant liquid is transferred under positive nitrogen pressure through a stainless-steel cannula (Note 2) into a 1-l., three-necked flask containing 108 g. (100 ml., 1.00 mole) of cold (0°), freshly distilled acetic anhydride (b.p. 140°) and fitted with a mechanical stirrer, a thermometer, an ice bath, and a rubber septum into which are inserted a hypodermic needle to admit nitrogen and a cannula to transfer the enolate solution.

The enolate solution is added slowly with cooling and vigorous stirring so that the temperature of the reaction mixture remains below 30°. After all the supernatant enolate solution has been transferred, the residual slurry of sodium hydride is washed with an additional 50-ml. portion of anhydrous 1,2-dimethoxyethane (Note 3); these washings are also added to the acetic anhydride solution. The resulting viscous mixture is stirred at room temperature for an additional 30 minutes and poured cautiously into a mixture of 500 ml. of pentane, 500 ml. of water, and 130 g. (1.54 moles) of sodium hydrogen carbonate. When hydrolysis of the excess acetic anhydride and neutralization of the acetic acid are complete, the pentane layer is separated, and the aqueous phase is extracted with 100 ml. of pentane. The combined

pentane solutions are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. Distillation of the residual orange liquid through a 20–30-cm. Vigreux column (Note 5) provides 61.7–80.6 g. (73–95%) of 2-acetoxy-*trans*-1-phenylpropene, b.p. 82–89° (1 mm.), n_D^{25} 1.5320–1.5327 (Note 6).

B. threo-4-*Hydroxy*-3-*phenyl*-2-*heptanone*. A dry, 500-ml., three-necked flask is fitted with a Teflon®-coated magnetic stirring bar, a gas-inlet tube equipped with a stopcock, a low-temperature thermometer, and a rubber septum and mounted to permit the use of an external cooling bath. The apparatus is flushed with nitrogen, and a static nitrogen atmosphere is maintained in the reaction vessel throughout the reaction. After 10–20 mg. of 2,2'-bipyridyl has been added to the reaction flask as an indicator, an ethereal solution containing 0.412 mole of halide-free methyllithium (Note 7) is added to the reaction flask with a hypodermic syringe or stainless-steel cannula inserted through the rubber septum. The diethyl ether is removed under reduced pressure (Note 8) while the flask is warmed to 40° with a water bath, the reaction vessel is refilled with nitrogen, and 120 ml. of anhydrous 1,2-dimethoxyethane is added (Note 3). The resulting purple solution is cooled to −10 to −20° with a 2-propanol–dry ice bath before 35.2 g. (0.200 mole) (Note 9) of 2-acetoxy-*trans*-1-phenylpropene is added from a hypodermic syringe dropwise and with stirring over 15 minutes while the temperature of the reaction mixture is kept in the range −20 to +10°. The resulting red-brown solution is stirred for an additional 10 minutes at −10 to 0° before 285 ml. of an ethereal solution containing 0.202 mole of anhydrous zinc chloride (Note 10) is added to the cold (−10 to +10°) reaction mixture from a hypodermic syringe dropwise and with stirring over 10 minutes. The reddish-yellow cloudy reaction mixture (Note 11) is stirred at 0° for 10 minutes before 14.50 g. (0.2014 mole) of freshly distilled butyraldehyde (Note 12) is added rapidly (30 seconds) and with stirring to the cold (−5 to +10°) reaction mixture. After the mixture has been stirred at 0–5° for 4 minutes, it is poured with vigorous stirring into a cold (0–5°) mixture of 500 ml. of 4 *M* ammonium chloride and 200 ml. of ether. The ether layer is separated, and the aqueous phase is extracted with two 200-ml. portions of ether. The combined organic solutions are washed successively with two 100-ml. portions of 1 *M* ammonium chloride and with two 50-ml. portions of saturated aqueous sodium chloride, and the combined aqueous washings are extracted with an additional 100-ml. portion of ether. The combined ether solutions are dried over anhydrous magnesium sulfate and concentrated under reduced pressure (water aspirator) with a rotary evaporator, removing the solvents and residual 1,2-dimethoxyethane. The residual liquid, which may crystallize on standing (Note 13), is triturated with 50 ml. of pentane, and the crystalline solid that separates is collected on a filter. The filtrate is concentrated under reduced pressure and again triturated with pentane, yielding an additional crop of the crude product. The combined crops of the crude *threo*-aldol product total 26.2–28.4 g. (64–69%), m.p. 57–62°. The crude product is recrystallized from 125–150 ml. of hexane. After the solution has been cooled to 0°, 21.3–24.1 g. of the *threo*-aldol product is collected as white needles, m.p. 71.5–72.5° (Note 14). The mother liquors are concentrated and cooled, separating additional fractions of the product (0.5–0.8 g.), m.p. 71–72°. The total yield of the *threo*-aldol product is 22.1–24.6 g. (53–60%).

2. Notes

1. The submitters used a 57% dispersion of sodium hydride in mineral oil obtained from Alfa Inorganics, Inc., and the checkers used a 50% dispersion of sodium hydride in mineral oil obtained from Metal Hydrides, Inc.
2. As a stainless-steel cannula was not available, the checkers made a minor modification in the operation without any trouble. They transferred the supernatant pentane and the solution of the sodium enolate using a Luer-lock hypodermic syringe with a stainless-steel needle preflushed with nitrogen, sweeping the apparatus with nitrogen during this operation.
3. The submitters distilled 1,2-dimethoxyethane (b.p. 83°) from lithium aluminum hydride immediately before use. The checkers distilled from sodium hydride immediately before use.
4. The submitters used a commercial sample of phenylacetone obtained from Aldrich Chemical Company, Inc.; the checkers used material of the same grade obtained from Maruwaka Chemical Industries Ltd. (Japan) without further purification.
5. The checkers used a 15 × 1 cm., unpacked, vacuum-jacketed column instead of Vigreux column for the distillation.
6. The results of GC analysis of the products made by the submitters are as follows: On a 3-m. GC

column, packed with silicone fluid QF_1 supported on Chromosorb P, and heated to 190°, the product exhibits peaks at 5.8 minutes corresponding to 2–3% phenylacetone, at 7.5 minutes corresponding to 97–98% of the enol acetate (*cis* and *trans* isomers not resolved), and at 8.0 minutes corresponding to a trace (<1%) of 3-phenyl-2,4-pentanedione. On a second, 7-m. GC column, packed with silicone fluid DC-710 on Chromosorb P and heated to 190°, the product exhibits peaks at 21.0 minutes corresponding to phenylacetone, at 39.0 minutes corresponding to the *trans*-enol acetate (97–98% of the product), and at 42.2 minutes corresponding to the *cis*-enol acetate (2–3% of the product). The checkers used a 45 m. × 0.25 mm. stainless-steel column (Golay type) coated with Apiezon L, heated to 150° and swept with helium at 1.5 kg./cm.[2] The product exhibits peaks at 5.5 minutes corresponding to phenylacetone (2–3% of product), at 14.2 minutes corresponding to the *trans*-enol acetate (91–92% of the product), and at 15.8 minutes corresponding to the *cis*-enol acetate (5–6% of the product). The product has IR absorption (CCl_4) at 1765 (enol ester C=O) and 1685 cm^{-1} (enol ester C=C) with UV maxima (95% C_2H_5OH) at 248.5 nm (ε 18,000) and 325 nm (ε 415) and ^1H NMR peaks (CCl_4) at δ 2.01 (partially resolved m, 6H, CH_3CO and vinyl CH_3), 5.82 (partially resolved m, 1H, vinyl C*H*), and 7.0–7.4 (m, 5H, C_6H_5). The mass spectrum of the product has a parent ion at *m/e* 176 with abundant fragment peaks at *m/e* 134, 91, 45, 43, and 39.

7. The submitters used an ether solution of halide-free methyllithium, purchased from Foote Mineral Company, while the checkers prepared the compound from methyl chloride and lithium metal in ether according to the literature.[2] The solution was standardized before use by the titration procedure described in *Org. Synth.*, **Coll. Vol. 6**, 121 (1988). The checkers observed that use of a halide-containing ether solution of methyllithium resulted in a considerable decrease in yield of the product, principally due to difficulty in following the subsequent procedure described in the text.

8. A convenient apparatus for evacuating the reaction vessel and refilling it with nitrogen is described in *Org. Synth.*, **Coll. Vol. 6**, 121 (1988).

9. If the violet color of the reaction solution is completely discharged, indicating that all the methyllithium has been consumed, addition of the enol acetate should be stopped at that point. The actual concentration of enolate anion in the solution can be calculated from the amount of enol acetate added.

10. To prepare an ethereal solution of anhydrous zinc chloride (m.p. 283°), the submitters placed 50.0 g. (0.369 mole) of pulverized zinc chloride, obtained from either Mallinckrodt Chemical Works or Fisher Scientific Company, in a 1-l., round-bottomed flask, and the vessel was evacuated to about 1 mm. pressure. The flask was heated strongly with a burner with swirling until as much of the solid as practical had been melted. The evacuated flask was cooled and shaken *(Caution! Perform this operation behind a safety shield in a hood and with heavy gloves to protect the operator's hands in case the flask should implode)* to break up the large lumps of zinc chloride. This fusion under reduced pressure should be repeated three times. To the resulting anhydrous zinc chloride was added 500 ml. of anhydrous diethyl ether, freshly distilled from lithium aluminum hydride. The mixture was refluxed for 3 hours under a static nitrogen atmosphere and allowed to stand until the undissolved solid had settled. The resulting supernatant solution was transferred with a stainless-steel cannula under positive nitrogen pressure (Note 2) into a second dry flask or Schlenk tube capped with a rubber septum. Aliquots of this solution, diluted with aqueous ammonia, can be titrated with standard EDTA solution to a Erichrome Black T endpoint to determine the zinc content.[3] Alternatively, the chloride ion concentration of aliquots can be determined by a Volhard titration. Typical values found for these ether solutions are 0.73 *M* in zinc ion and 1.38 *M* in chloride ion, or 0.69–0.73 *M* in zinc chloride. If the final solution is significantly less concentrated than 0.7 *M* in zinc chloride, it is probable that the dehydration of the solid zinc chloride was not complete. In this event, the submitters recommend that a fresh solution of zinc chloride be prepared with more attention to the initial dehydration of the solid zinc chloride. The checkers used pulverized zinc chloride, obtained from Wako Pure Chemical Industries Ltd. (Japan).

11. The white precipitate that separates is a part of the lithium chloride formed in the reaction mixture. Separation of the material is not necessary.

12. The submitters used a commercial grade of butyraldehyde from Eastman Organic Chemicals; the checkers used butyraldehyde of the same grade from Wako Pure Chemical Industries Ltd. (Japan) and distilled it before use, b.p. 72–74°.

13. The ^1H NMR spectrum (C_6D_6) of the crude product exhibits benzylic CH doublets at δ 3.42 (J = 5.3 Hz., attributable to 4–10% of the *erythro* aldol isomer) and 3.58 (J = 9.4 Hz., attributable to 90–96% of the *threo*-aldol isomer). This mixture may be separated by chromatography on acid-washed silicic acid,

permitting the isolation of both the *threo* and the *erythro* diastereoisomers.[4]
14. The *threo*-hydroxy ketone exhibits IR absorption (CCl_4) at 3540 (associated OH) and 1705 $cm.^{-1}$ (C=O) with a series of weak (ε 300 or less) UV maxima (95% C_2H_5OH) in the region 240–270 nm as well as a maximum at 286 nm (ε 345). The ^1H NMR spectrum (CCl_4) of the product shows resonance at δ 0.6–1.9 [m, 7H, $(CH_2)_2CH_3$], 2.03 (s, 3H, CH_3CO), 3.35 (s, 1H, O*H*), 3.65 (d, J = 9.5 Hz., 1H, benzylic C*H*), 4.0–4.4 (m, 1H, C*H*O), and 7.1–7.5 (m, 5H, C_6H_5). The mass spectrum of the product exhibits the following relatively abundant peaks: *m/e* (relative intensity), 206 (M^+, 0.1), 188 (8), 146 (20), 135 (26), 134 (100), 117 (52), 92 (48), 91 (76), 65 (31), 44 (36), and 43 (60).

3. Discussion

The present procedures illustrate general methods for the use of preformed lithium enolates[5] as reactants in the aldol condensation[4] and for quenching alkali metal enolates in acetic anhydride, forming enol acetates with the same structure and stereochemistry as the starting metal enolate.[6] The aldol product, *threo*-4-hydroxy-3-phenyl-2-heptanone, has been prepared only by this procedure.

The methods previously used to obtain single aldol products (or their dehydrated derivatives) from reactants where several aldol products are possible[7] include the reaction of bromozinc enolates, from α-bromoketones, with aldehydes;[8] the reaction of bromomagnesium enolates, from either α-bromoketones, ketones and bromomagnesium amides or sterically hindered Grignard reagents, with aldehydes;[9,10] and the reaction of α-lithio derivatives of imines with aldehydes or ketones.[11] Like the present procedure, each of these methods relies upon trapping the intermediate β-keto alkoxide derivative as a metal chelate in an aprotic reaction solvent. The present procedure increases the versatility of the aldol condensation by utilizing the variety of specific lithium enolates that can be generated from unsymmetrical ketones.[5] In this procedure the lithium enolate is treated successively with anhydrous zinc chloride and an aldehyde, forming the zinc(II) chelate of a β-keto alkoxide. The optimum quantity of zinc chloride is that amount required to form zinc(II) salts of all strong bases in the reaction mixture. Thus, 1 mole of zinc chloride should be added for each mole of lithium enolate (and accompanying lithium *tert*-butoxide) formed from an enol acetate as in the present example. If the lithium enolate is formed from the ketone and lithium diisopropylamide or from a trimethylsilyl enol ether and methyllithium, then 0.5 mole of zinc chloride should be used for each mole of lithium enolate. The optimum reaction solvent is either ether or ether–1,2-dimethoxyethane mixtures, with a reaction temperature of −10 to +10° and a reaction time of 2–5 minutes. Longer reaction times and higher reaction temperatures may lead to a variety of by-products resulting from polycondensation and dehydration. The aldol products are efficiently isolated by *adding the reaction mixtures* to a cold (0–5°), aqueous solution of ammonium chloride followed by rapid separation of the aldol products. Since many of the aldol products are especially prone to epimerization, dehydration, or reversal of the aldol condensation, they should not be exposed to strong acids or strong bases. Mixtures of stereoisomeric aldol products with similar physical properties can usually be separated by chromatography on acid-washed silicic acid.[4,12]

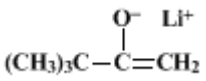
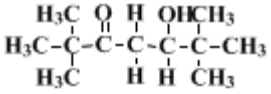
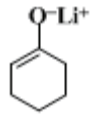
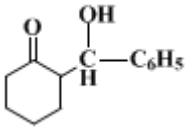
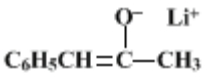
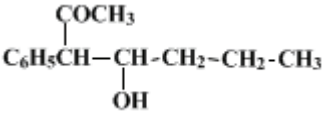
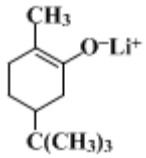
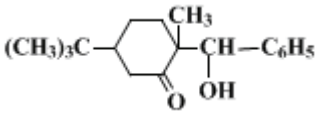
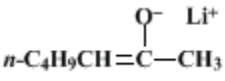
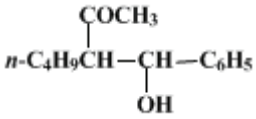
In several cases (including the present example) where diastereoisomeric aldol products are possible, there is a preference for the formation of the *threo*-diastereoisomer. This stereochemical preference presumably arises because the six-membered cyclic zinc chelate of the *threo*-isomer can exist in a chair conformation with both substituents in equatorial positions. Table I summarizes the results obtained from several aldol condensations performed by the present procedure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 277

TABLE I
[4]DIRECTED ALDOL CONDENSATIONS WITH PREFORMED LITHIUM ENOLATES IN THE PRESENCE OF ZINC CHLORIDE

Enolate	Aldol Product	Yield, %	Stereoisomer ratio, *threo/erythro*

		82	—
		76	4/1
		80	9/1
		84	2/1[a]
		80	1/1

[a] The aldol product contained 70% of isomers with an axial α-hydroxybenzyl substituent.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

threo-4-Hydroxy-3-phenyl-2-heptanone

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

methyl chloride (74-87-3)

zinc (7440-66-6)

butyraldehyde (123-72-8)

zinc chloride (7646-85-7)

hydride

Pentane (109-66-0)

phenylacetone (103-79-7)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

Methyllithium (917-54-4)

silicic acid (7699-41-4)

Lithium chloride (7447-41-8)

1,2-dimethoxyethane (110-71-4)

helium (7440-59-7)

2,2'-bipyridyl (366-18-7)

lithium diisopropylamide (4111-54-0)

3-phenyl-2,4-pentanedione (5910-25-8)

EDTA (60-00-4)

lithium tert-butoxide (1907-33-1)

2-Acetoxy-trans-1-phenylpropene (19980-44-0)

2-Heptanone, 4-hydroxy-3-phenyl-, (R,R)- (42052-62-0)