was increased to 19% by use of Mg instead of Zn,[4] and to a yield of 65% by use of methylal as solvent.[5]

In the absence of α hydrogens, *i.e.*, when α,α-disubstituted acids are used, the product β-hydroxy acids on heating or on heating with acids will undergo reversal of the condensation[6] or an elimination–decarboxylation to the olefin. In some cases, olefins were obtained from the reaction procedure. Such behavior parallels that found in the β-hydroxyimine products of the directed aldol condensation.[7]

Hamrick and Hauser[8] have effected the condensation of disodio- and dilithiophenylacetate with benzophenone and with cyclohexanone using Na and Li amides in liquid ammonia. The present work offers an extension to other acids and the use of the more convenient butyllithium and tetrahydrofuran.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded by Mr. E. Schoeb on a Beckman IR-9 spectrophotometer. Nmr spectra were taken by Mr. R. B. Scott on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Microanalyses were carried out by Mr. C. E. Childs and his staff.

General Procedure for the Preparation of α-Lithiated Carboxylic Acid Lithium Salts.—Redistilled diisopropylamine (2 molar equiv) and tetrahydrofuran (dried over CaH_2 and run through Woelm basic alumina just prior to use) were introduced into the N_2-swept flask and cooled to 0–5° by an external ice bath. *n*-Butyllithium in heptane solution (Foote Mineral Co.) (2.1 molar equiv) was introduced in a fine steam by means of a syringe and needle through a rubber septum. The mixture was then stirred for 0.25–0.5 hr while still being cooled. A solution of 1 molar equiv of the carboxylic acid in dry tetrahydrofuran was dropped in by means of a second syringe (the surface of the septum should be wiped clean of any lithium hydroxide to prevent possible plugging of the syringe needle). The reaction was kept cold during the acid addition and stirred throughout. Stirring was continued for 0.5 hr with cooling and then at 40–50° (warm water bath) for 1–1.5 hr.

General Procedure for the Reaction of Carbonyl Compound with α-Lithiated Acid Salts.—The solution of the α-lithiated acid salt was cooled in ice and 1 molar equiv or slightly less of the carbonyl compound in tetrahydrofuran solution was dropped in from an addition funnel. The reaction was protected from moisture, kept under N_2, and stirred throughout. After addition was complete, the reaction was stirred for 1 hr and then overnight to room temperature.

Two procedures were used to work up the reaction mixtures.

A. The reaction was cooled in an ice bath and decomposed by the addition of water slowly with stirring. Excess (*ca.* 1 vol) water was added and the heptane layer separated. This was then extracted with water and the combined aqueous solutions were extracted with ether. The aqueous solution and wash were cooled and acidified with 3 *N* hydrochloric acid. The precipitated acid was separated by filtration or by extraction.

B. The reaction was cooled in an ice bath and decomposed by the addition of 1 *N* hydrochloric acid (*ca.* 1 vol) slowly with stirring. The heptane layer was separated and the aqueous layer extracted with ether. The ether–heptane solution was then extracted with 0.1 *N* NaOH solution which was then cooled and acidified with 3 *N* hydrochloric acid. The acid product was then separated by filtration or by extraction into ether.

Where olefins were produced, they were found in the heptane–ether layer (procedure A) or in the ether solution after NaOH extraction (procedure B). In procedure A, the β-hydroxy acid product occasionally appeared in the heptane–ether solution as a salt with diisopropylamine. Procedure B avoided this complication.

The β-hydroxy acids were generally recrystallized from acetonitrile.

Acknowledgment.—The authors are indebted to Dr. P. L. Creger for sharing his experience in the lithiation of carboxylic acids.

---

[4] J. Jacques and C. Weidmann, *Bull. Soc. Chim. Fr.*, 1478 (1958).

[5] J. Cure and M. Gaudemar, *ibid.*, 2471 (1969).

[6] R. L. Shriner, *Org. React.*, **1**, 14 (1942).

[7] G. Wittig and H. D. Frommeld, *Chem. Ber.*, **97**, 3551 (1964).

[8] P. J. Hamrick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **82**, 1957 (1960).

Lithium–Ammonia Reduction of α,β-Unsaturated Acids and β-Keto Acid Methoxymethyl Enol Ethers

James E. Shaw*[1] and Karen K. Knutson

Department of Chemistry, Moorhead State College, Moorhead, Minnesota 56560

Received September 17, 1970

Although reductions of α,β-unsaturated ketones with alkali metals in liquid ammonia have been studied extensively, there are few reported examples of similar reductions of α,β-unsaturated acids to saturated acids[2-4] and no reported reductions of β-keto acid enol ethers. Except for *trans*-cinnamic acid,[4] the unsaturated acids which have been previously reduced are complicated steroid molecules for which steric hindrance could have affected the results of the reduction. We now wish to report that reduction of simple α,β-unsaturated acids with excess lithium in liquid ammonia proceeds cleanly to give high yields of saturated acids as shown in Table I. The yields are highest for those unsaturated acids with more highly substituted double bonds. In the cases of *trans*-cinnamic acid and crotonic acid, some dimeric or polymeric materials appeared to be present in the crude reduction products and are probably due to coupling of anion radical intermediates.

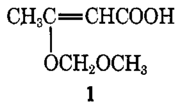
TABLE I

REDUCTION OF VARIOUS α,β-UNSATURATED ACIDS TO SATURATED ACIDS

α,β-Unsaturated acid	% yield of corresponding saturated acid[a]
1-Cyclohexenecarboxylic acid	94
1-Cyclopentenecarboxylic acid	82
Cyclohexylideneacetic acid	93
trans-Cinnamic acid[b]	65
α-Methylcinnamic acid	95
Crotonic acid	73
3-Methylcrotonic acid	92
2-Dodecenoic acid	70

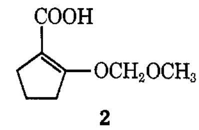
[a] Isolated yield, product recrystallized or distilled. [b] For a previous reduction, see ref 4.

The lithium–ammonia reduction of two other α,β-unsaturated acids, acetoacetic acid methoxymethyl enol ether (1) and 2-cyclopentanonecarboxylic acid



$$\underset{\displaystyle OCH_2OCH_3}{CH_3C}{=}CHCOOH$$

1



2

---

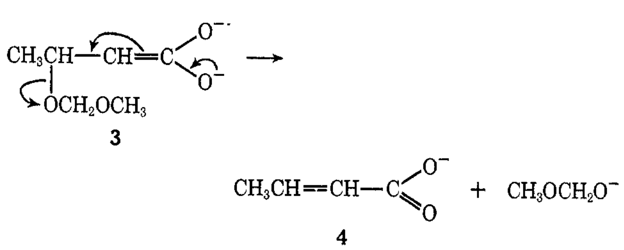
[1] Author to whom correspondence should be directed.

[2] G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Sarett, *J. Amer. Chem. Soc.*, **76**, 1715 (1954).

[3] F. Sondheimer, W. McCrae, and W. G. Salmond, *ibid.*, **91**, 1228 (1969).

[4] R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597, 2601 (1970).

methoxymethyl enol ether (2), were also investigated. These α,β-unsaturated acids should exhibit a "double" reduction[4-6] to the saturated acids since the enol ether group should be eliminated from the initial enolate anion intermediate **3** as in the case of **1** to give a new α,β-unsaturated acid **4** which then can also be reduced.



Reduction of **1** and **2** gave butanoic acid and cyclopentanecarboxylic acid in yields of 78 and 79%, respectively. These yields are close to those obtained for the reduction of crotonic acid and 1-cyclopentenecarboxylic acid (Table I) and demonstrate that elimination of the enol ether leaving group is an efficient process.

Acids **1** and **2** were prepared by alkaline hydrolysis of the previously synthesized[4] β-keto ester methoxymethyl enol ethers. The procedure of converting a β-keto ester to its methoxymethyl enol ether followed by hydrolysis to the β-keto acid methoxymethyl enol ether and then reduction to the saturated acid appears to be a reasonable method for converting the ketone carbonyl of a β-keto ester to a methylene group since the overall yields for the three-step sequence are about 50%.

Experimental Section[7]

General Procedure for Reduction of the α,β-Unsaturated Acids.—A solution of 25 mmol of the α,β-unsaturated acid in 75 ml of anhydrous ether was rapidly added to a magnetically stirred, dark blue solution of 695 mg (0.100 g-atom) of lithium in 175 ml of anhydrous ammonia under argon. After being stirred for 30 min at the liquid ammonia boiling point (−33°), the blue reaction mixture was carefully quenched by slow addition of 20 g of ammonium chloride. Then 125 ml of ether was added, and the Dry Ice–isopropyl alcohol condenser was replaced by a sodium hydroxide drying tube. After evaporation of the ammonia overnight, the reaction mixture was acidified with 6 *N* hydrochloric acid. Often more water was added to get all inorganic salts in solution. The solution was extracted twice with ether, and the combined ether extracts (250 ml) were washed three times with 40-ml portions of saturated sodium chloride solution and then dried over sodium sulfate. Evaporation of the ether under reduced pressure gave the crude saturated acid. In the case of a crystalline saturated acid, the crude product always crystallized at room temperature or in a freezer. Recrystallization from pentane–ether gave the yields shown in Table I. The recrystallized acid gave the proper melting point and also an infrared spectrum identical with that of authentic saturated acid. In the case of a liquid acid, the crude product was distilled under reduced pressure to give the yields shown in Table I. The distilled acid gave the proper boiling point and refractive index and gave an infrared spectrum identical with that of authentic saturated acid. In the case of crotonic acid, an unidentified white solid remained after distillation of the reduction product which probably was dimeric or polymeric material. An unidentified white crystalline product was also found upon recrystallization of the reduction product of *trans*-cinnamic acid.

Acetoacetic Acid Methoxymethyl Enol Ether (1).—Ethyl acetoacetate (15.6 g, 0.120 mol) was converted to 21.5 g of crude ethyl acetoacetate methoxymethyl enol ether as previously described.[4] To 21.5 g of the crude methoxymethyl enol ether was added a solution of 49.2 g (1.23 mol) of sodium hydroxide in 170 ml of water and 85 ml of ethanol. The mixture was rapidly stirred under nitrogen for 17 hr at room temperature. The reaction mixture was then cooled in ice water and was acidified with 6 *N* hydrochloric acid to pH 3–4. The mixture was immediately extracted twice with ether, and the combined ether extracts (500 ml) were washed four times with saturated sodium chloride, dried over sodium sulfate, and evaporated under reduced pressure at room temperature. The acid crystallized upon evaporation. Recrystallization at temperatures of 25° or below from ether–pentane gave 10.8 g (62% overall from the β-keto ester) of **1** as white crystals: mp 104–105° (lit.[8] mp 105°); ir ($CHCl_3$) 1687 (C=O) and 1612 cm^{-1} (C=C); nmr ($CDCl_3$) τ −1.56 (s, 1 H), 4.71 (s, 1 H), 4.90 (s, 2 H), 6.49 (s, 3 H), and 7.64 (s, 3 H).

2-Cyclopentanonecarboxylic Acid Methoxymethyl Enol Ether (2).—After 6.24 g (40.0 mmol) of 2-carbethoxycyclopentanone was converted to 8.20 g of crude 2-carbethoxycyclopentanone methoxymethyl enol ether as previously described,[4] the crude enol ether was added to a solution of 16.4 g (0.41 mol) of sodium hydroxide in 70 ml of water and 35 ml of ethanol, and this solution was stirred for 17 hr at room temperature under nitrogen. Work-up was similar to that described for acetoacetic acid methoxymethyl enol ether. The yield of acid **2** after recrystallization from ether–pentane at temperatures of 25° or below was 3.85 g (56% overall from the β-keto ester) of white crystals: mp 108.5–110.5°; ir ($CHCl_3$) 1716 (C=O) and 1631 cm^{-1} (C=C); nmr ($CDCl_3$) τ −0.71 (s, 1 H), 4.84 (s, 2 H), and 6.47 (s, 3 H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.78; H, 7.03. Found: C, 55.69; H, 7.14.

Reduction of Acetoacetic Acid Methoxymethyl Enol Ether (1).—A solution of 4.38 g (30 mmol) of acetoacetic acid methoxymethyl enol ether in 75 ml of anhydrous ether was rapidly added to a magnetically stirred solution of 1.46 g (0.210 g-atom) of lithium in 200 ml of anhydrous ammonia under argon. After being stirred for 30 min at the liquid ammonia boiling point (−33°), the blue reaction mixture was carefully quenched by slow addition of 20 g of ammonium chloride. The remainder of the procedure was the same as that described under the general procedure above. The yield of distilled butanoic acid was 2.06 g (78%): bp 74–78° (20 mm); $n^{20}{}_D$ 1.3993 (lit.[9] $n^{20}{}_D$ 1.3991). The infrared spectrum of the product was identical with that of authentic butanoic acid.

Reduction of 2-Cyclopentanonecarboxylic Acid Methoxymethyl Enol Ester (2).—A solution of 4.30 g (25 mmol) of 2-cyclopentanonecarboxylic acid methoxymethyl enol ether in 150 ml of anhydrous ether was rapidly added to a magnetically stirred solution of 1.21 g (0.175 g-atom) of lithium in 200 ml of anhydrous ammonia under argon. After being stirred for 30 min, the blue reaction mixture was carefully quenched by slow addition of 20 g of ammonium chloride. The remainder of the procedure was identical with that described under the general procedure given above. The yield of distilled cyclopentanecarboxylic acid was 2.26 g (79%): bp 106–110° (12 mm) [lit.[9] bp 106–108° (12 mm)]; $n^{20}{}_D$ 1.4531 (lit.[9] $n^{20}{}_D$ 1.4532). The infrared spectrum was identical with that of authentic cyclopentanecarboxylic acid.

Registry No.—**1**, 27808-89-5; **2**, 27808-90-8; 1-cyclohexenecarboxylic acid, 636-82-8; 1-cyclopentenecarboxylic acid, 1560-11-8; cyclohexylideneacetic acid, 1552-91-6; *trans*-cinnamic acid, 621-82-9; α-methylcinnamic acid, 1199-77-5; crotonic acid, 3724-65-0; 3-methylcrotonic acid, 541-47-9; 2-dodecenoic acid, 4412-16-2.

Acknowledgment.—We wish to thank the Minnesota State College Board for financial support.

---

(5) D. S. Watt, J. M. McKenna, and T. A. Spencer, *J. Org. Chem.*, **32**, 2674 (1967).

(6) M. Vandewalle and F. Compernolle, *Bull. Soc. Chim. Belges*, **76**, 43 (1967).

(7) Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 237B spectrometer and were calibrated with the polystyrene band at 1603 cm^{-1}. Nmr spectra were determined with a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard. Microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn.

(8) J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 2106 (1909).

(9) "Handbook of Chemistry and Physics," 45th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1964.