October 1989 Notes *Chem. Pharm. Bull.* **37**(10) 2817—2818 (1989) 2817

Reductive Deoxygenation of α,β-Unsaturated Ketones *via* Cyanophosphates by Lithium in Liquid Ammonia

Ryuji Yoneda, Hirotaka Osaki, Shinya Harusawa, and Takushi Kurihara*

Osaka University of Pharmaceutical Sciences, 2-10-65, Kawai, Matsubara, Osaka 580, Japan. *Received March 20, 1989*

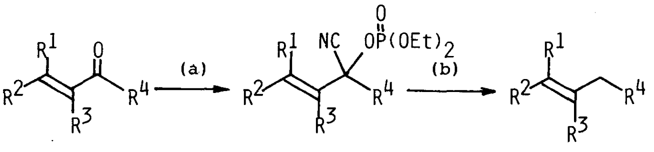
A new method for deoxygenation of α,β-unsaturated ketones *via* cyanophosphates by lithium metal in liquid ammonia is described.

Keywords reductive deoxygenation; diethyl phosphorocyanidate; lithium cyanide; cyanophosphate; lithium; liquid ammonia; α,β-unsaturated ketone

Reductive deoxygenation of a carbonyl to a methylene group is an important procedure in organic synthesis, and various methods have been developed for this transformation.[1] These methods generally work well with saturated or aryl ketones and aldehydes.[2] The major deoxygenation method for α,β-enones known so far is the so-called Mozingo reaction, which involves the formation of a thioacetal or thioketal and desulfurization with an excess of Raney nickel or metal in liquid ammonia,[3] but some isomerized or reduced olefin may be formed in the reduction step in the former case.[2] Meanwhile, we have reported that cyanohydrin *O*-diethyl phosphates (cyanophosphates), which can be prepared readily from a variety of carbonyl compounds with diethyl phosphorocyanidate (DEPC) and lithium cyanide (LiCN), are versatile synthetic intermediates.[4] Our continuing investigations in this area have now resulted in the development of a new method for deoxygenation of α,β-enones *via* cyanophosphates. The results are presented here.

Although the reductive deoxygenation of alkyl phosphates[5] and reductive decyanation[6] of allyl and tertiary nitriles by the use of liquid ammonia or ethylamine with an alkali metal in the presence of a proton source have been investigated, little is known about reductive cleavage of cyanophosphates under these conditions. From this point of view, we became interested in metal–ammonia reduction of cyanophosphate.

Treatment of cholestan-3-one with DEPC (3 mol eq) and LiCN (3 mol eq) in tetrahydrofuran (THF) afforded the crude cyanophosphate. Without purification, reduction of the cyanophosphate with lithium metal (Li) (10 mol eq) in freshly distilled liquid ammonia containing *tert*-butyl alcohol (1.2 mol eq) gave no deoxygenated product, but a complex mixture of products was obtained. On the other hand, cholest-4-en-3-one (**1A**) was successively converted to cholest-4-ene (**3A**) in quantitative yield *via* cyanophosphate (**2A**) under the conditions as described above. A steroidal enone (**1B**) with a methoxymethyl ether (MOM) group at the 17-position was also deoxygenated through the above reaction sequence, giving the corresponding 4-ene steroid (**3B**) in 80% yield. Cyclic or acyclic enones with an isolated double bond such as (−)-carvone (entry C) and α-ionone (entry D) were also successively converted to (−)-limonene (**3C**) and the corresponding CH_2 compound (**3D**), respectively, in excellent yields.

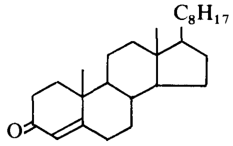
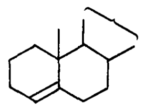
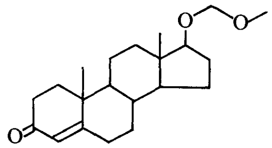
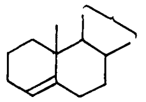
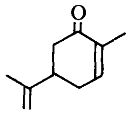
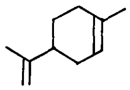
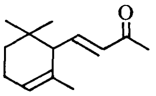
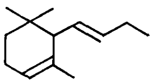
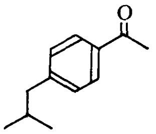
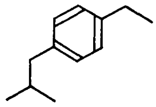


1 **2** **3**

(a): DEPC/LiCN in THF/5—30 min
(b): Li/liq. NH_3/*tert*-BuOH/0.5—2 h

Chart 1

Table I. Reductive Deoxygenation of α,β-Unsaturated Ketones *via* Cyanophosphates

Entry	Carbonyl compd. (**1**)	Product (**3**)$^{a)}$	Yield (%)
A			99
B			80
C			96
D			99
E			89

a) Reaction time for reduction: entries A, B = 30 min; entry C = 1.5 h; entries D, E = 2 h.

It has been reported that metal–ammonia reduction of monoaromatic ketones such as acetophenone in the presence of a proton source proceeds in three ways: dimerization, nuclear reduction, and carbonyl carbon reduction.[7] However, the present method was applicable to 4-isobutylacetophenone (entry E) to yield 4-isobutylethylbenzene (**3E**) in 89% yield *via* cyanophosphate (**2E**).

Consequently, cyanophosphorylation followed by Li-

liquid ammonia reduction in the presence of *tert*-butyl alcohol was found to provide a useful method for deoxygenation of an α,β-enone without isomerization or reduction of the double bond.

Experimental

All melting points are uncorrected. Proton and carbon-13 nuclear magenetic resonance (^{1}H- and ^{13}C-NMR) spectra were taken with a Varian Gemini-200 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded with a Hitachi M-80 spectrometer. For column chromatography, SiO_2 (Merck Art 7734 and 9385) was used.

General Method for Deoxygenation of α,β-Unsaturated Ketones A typical procedure for obtaining cholest-4-ene (**3A**) is as follows: LiCN (50 mg, 1.5 mmol) was added to a solution of cholest-4-en-3-one (**1A**) (193 mg, 0.5 mmol) and DEPC (155 mg, 1.5 mmol) in THF (5 ml) under ice cooling, and the mixture was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was extracted with EtOAc–hexane (1 : 1) (50 ml) and H_2O (10 ml). The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the crude cyanophosphate. Then, a solution of the cyanophosphate, thus obtained, and *tert*-BuOH (45 mg, 0.6 mmol) in THF (5 ml) was added to a solution of Li (34 mg, 5 mmol) dissolved in freshly distilled liquid NH_3 (10 ml). After stirring for 30 min, the reaction was quenched by the addition of NH_4Cl (2.0 g) and the ammonia was allowed to evaporate. The residue was diluted with H_2O (10 ml) and extracted with Et_2O (50 ml × 2). The extract was washed with brine, dried over $MgSO_4$, and then evaporated to give cholestene (**3A**) (183 mg, 99%), mp 74—77 °C (from acetone), $[\alpha]_D^{25}$ +66 (c=0.1, $CHCl_3$) (lit.[8] mp 80—83 °C, $[\alpha]_D$ +66 (c= 1.0, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$) δ: 5.24 (1H, br s, C_4-H). ^{13}C-NMR ($CDCl_3$) δ: 119.0 (d, C-4), 145.5 (s, C-5).

17β-Methoxymethoxyandrost-4-ene (3B) Yield, 80%, mp 42—43 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, s, C_{18}-CH_3), 0.99 (3H, s, C_{19}-CH_3), 3.33 (3H, s, OCH_3), 3.48 (1H, t, J=8 Hz, C_{17}-H), 4.60 (2H, s, OCH_2O), 5.28 (1H, br s, =CH). MS m/z: 318 (M^+). High resolution (HR)-MS m/z Calcd for $C_{21}H_{34}O_2$: 318.2557. Found: 318.2546. *Anal.* Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.14; H, 10.80.

Limonene (3C) Yield, 96%. ^{1}H- and ^{13}C-NMR spectra were identical with those of an authentic sample.[9]

3-(1-Butenyl)-2,4,4-trimethylcyclohexene (3D) Yield, 99%. ^{1}H-NMR ($CDCl_3$) δ: 0.78 and 0.85 (each 3H, each s, C–CH_3), 0.96 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.56 (3H, q, J=2.0 Hz, =C–CH_3), 5.18 (1H, ddt, J=15, 9.5, 1.5 Hz, $C\underline{H}$=CH-CH_2), 5.34 (1H, br, C_2-H), 5.40 (1H, m, CH=C$\underline{H}$–CH_2). ^{13}C-NMR ($CDCl_3$) δ: 14.33 (q), 22.04 (q), 23.30 (t), 25.85 (t), 27.20 (q), 27.63 (q), 31.99 (t), 32.07 (s), 54.69 (d), 120.74 (d), 130.30 (d), 134.08 (d), 135.40 (s). MS m/z: 177 (M^+). HR-MS m/z Calcd for $C_{13}H_{21}$: 177.1659. Found: 177.1639.

4-Isobutylethylbenzene (3E) Yield, 89%. ^{1}H-NMR $CDCl_3$) δ: 1.91 [6H, d, J=5 Hz, $CH(CH_3)_2$], 1.25 (3H, t, J=7.5 Hz, CH_2CH_3), 1.86 [1H, m, $C\underline{H}(CH_3)_2$], 2.45 (2H, d, J=7 Hz, $CHCH_2$), 2.63 (2H, q, J=7.5 Hz, CH_2CH_3), 7.09 (4H, m, Ar-H). MS m/z: 162 (M^+).

Acknowledgement This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientists, Japan, (to R.Y).

References and Notes

1) C. K. Lau, C. Dufresne, P. C. Belanger, S. Pietre, and J. Scheigetz, *J. Org. Chem.*, **51**, 3038 (1986), and references cited therein.
2) J. F. Staddart, "Comprehensive Organic Chemistry," Vol. 1, Pergamon Press, 1979, p. 1081.
3) *a*) R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Am. Chem. Soc.*, **80**, 4604 (1958); *b*) J. Gutzwiller and C. Djerassi, *Helv. Chim. Acta*, **49**, 2108 (1966).
4) *a*) For a review, see T. Kurihara, S. Harusawa, and R. Yoneda, *Yuki Gosei Kagaku Kyokai Shi*, **46**, 1164 (1988); *b*) R. Yoneda, S. Harusawa, and T. Kurihara, *J. Chem. Soc.*, *Perkin Trans. 1*, **1988**, 3163.
5) R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, **1969**, 2145.
6) *a*) P. G. Arapakos, *J. Am. Chem. Soc.*, **89**, 6794 (1967); *b*) J. A. Marshall and R. Bierenbaum, *J. Org. Chem.*, **42**, 3309 (1977).
7) M. Narisada and F. Watanabe, *J. Org. Chem.*, **38**, 3887 (1973).
8) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).
9) *a*) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," John Wiley & Sons, New York, 1972, 400; *b*) C. J. Pouchert and J. R. Cambell, "The Aldrich Library of NMR Spectra," Vol. 1, Aldrich Chemical Company Inc., 1974, p. 45.