

Conjugate Reduction of α,β -Unsaturated Ketones with Amphiphilic Reaction System

Katsumasa NONOSHITA, Keiji MARUOKA, and Hisashi YAMAMOTO*

Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464

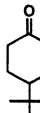
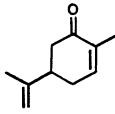
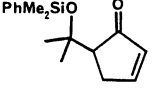
(Received January 16, 1988)

Synopsis. The conjugate reduction of α,β -unsaturated ketones has been effected with amphiphilic reaction system consisting of methylaluminum bis(2,6-di-*t*-butyl-4-alkylphenoxide) and certain complex aluminum hydride reagent.

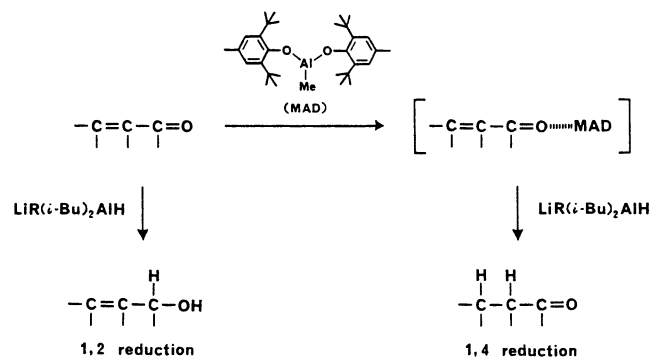
Conjugate reduction of α,β -unsaturated carbonyl compounds is an important synthetic operation and a variety of promising approaches have been developed for this purpose.¹⁾ Those include (1) catalytic hydrogenation of various noble metals;²⁾ (2) electrochemical reductions including dissolving metal reduc-

tions;³⁾ (3) biochemical reductions using microorganisms;⁴⁾ (4) reduction with several transition-metal hydride reagents including those produced in situ from transition-metal compounds and conventional reducing agents;⁵⁾ and (5) reduction with certain aluminum hydride and borohydride type reagents such as L-Selectride.⁶⁾ Here we wish to disclose a conceptually new approach to this transformation based on the amphiphilic reduction, i.e. nucleophilic reduction of electrophilically activated substrate by combining use of exceptionally bulky methylaluminum bis(2,6-di-*t*-

Table 1. Conjugate Reduction of α,β -Unsaturated Ketones^{a)}

Entry	Substrate	Reagent ^{b)}	1,4-Reduction % yield ^{c)}	1,2-Reduction % yield ^{c)}
1		A	68	0
2		A	76	0
3		A	0	74
4		A	93	2
5		A ^{d)}	6	87
6		A ^{e)}	71	15
7		A ^{f)}	52	11
8		A	45	49
9		A	83	0
10	(<i>E</i>)-PhCH=CHC(=O)CH ₃	A	0	99
11	(<i>E</i>)-PhCH=CHC(=O)Ph	A	60	28
12		B	57	12
13		C	51	43
14		D	2	97
15		E	37	61
16	(<i>E</i>)-PhCH=CHC(=O)(<i>o</i> -Tolyl)	A	76	11
17	(<i>E</i>)-PhCH=CHC(=O)(Mesityl)	A	84	0

a) Unless otherwise noted, reduction was carried out at -78°C by adding complex aluminum hydride reagent (2 equiv) in ether to the carbonyl compound (1 equiv)-MAD (2 equiv) complex in toluene. b) Reagent A: MAD/Li(*n*-Bu)(*i*-Bu)₂AlH; B: MAD/Li(*t*-Bu)(*i*-Bu)₂AlH; C: MAD/Li(Me)(*i*-Bu)₂AlH; D: MAD/LiAlH₄; E: MAT/Li(*n*-Bu)(*i*-Bu)₂AlH. c) Isolated yield. d) Use of a toluene solution of Li(*n*-Bu)(*i*-Bu)₂AlH. e) Use of a THF solution of Li(*n*-Bu)(*i*-Bu)₂AlH. f) Each 1 equiv of MAD and Li(*n*-Bu)(*i*-Bu)₂AlH was utilized.



butyl-4-alkylphenoxide) (as Lewis acid) and certain complex aluminum hydride reagent (as nucleophile) as illustrated in Scheme 1.⁷⁾

Reaction of carvone with lithium butyl(diisobutyl)-aluminum hydride ($\text{Li}(n\text{-Bu})(i\text{-Bu})_2\text{AlH}$) was reported to give 1,2-reduction product solely.⁸⁾ However, initial complexation of carvone with methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (abbreviated to MAD) in toluene and subsequent treatment with $\text{Li}(n\text{-Bu})(i\text{-Bu})_2\text{AlH}$ in ether at -78°C resulted in total reversal of selectivity, producing 1,4-reduction product almost exclusively in 93% yield. The initial hydride transfer from $\text{Li}(n\text{-Bu})(i\text{-Bu})_2\text{AlH}$ to MAD followed by reduction of the resulting bulky hydride with the enone seems to be unlikely, since treatment of carvone with a pre-mixture of MAD and $\text{Li}(n\text{-Bu})(i\text{-Bu})_2\text{AlH}$ at -78°C gave result (88% of 1,2 adduct and 8% of 1,4 adduct) close to that in the sole addition of $\text{Li}(n\text{-Bu})(i\text{-Bu})_2\text{AlH}$. Some other examples are listed in Table 1, which revealed the following characteristic features. The α,β -unsaturated ketone possessing the sterically less demanding carbonyl moiety, even when combined with MAD, is readily susceptible toward the 1,2-hydride attack (Entries 3 and 10). The similar tendency was observed in the conjugate addition of RLi to the enone in the presence of MAD,^{7d)} although the present conjugate reduction exhibited better 1,4-selectivity. Among various nucleophilic aluminum hydride reagents examined, $\text{Li}(n\text{-Bu})(i\text{-Bu})_2\text{AlH}$ would be most suitable in view of selectivity (Entries 11–14) and the ready availability.³⁾ The choice of solvents profoundly affects the selectivity. For example, in the MAD-mediated reduction of carvone, ether as solvent was found to be satisfactory, but use of toluene resulted in the predominant 1,2-reduction (Entry 5). Methylaluminum bis(2,4,6-tri-*t*-butylphenoxide) (MAT) lowered 1,4 selectivity (Entry 15).

Experimental

The IR spectra were determined on a Hitachi 260-10 spectrometer. The ^1H NMR spectra were recorded on a JNM-PMX 60 spectrometer, using TMS (tetramethylsilane) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; m, multiplet; br, broad. The microanalyses were performed at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. Analytical gas-liquid phase chromatography (GLC) was performed on

Gasukuro Kogyo Model 370 instruments with a flame-ionization detector and a capillary column of PEG-HT (0.25×25,000 mm) using nitrogen as carrier gas. Ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl. Toluene was dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4-Å Molecular Sieves. All experiments were carried out under an argon atmosphere. Purification of the product was carried out by column chromatography on silica gel Fuji-Davison BW-300.

Preparation of α,β -Unsaturated Ketones. 6-Methyl-2-cyclohexen-1-one and 4-*t*-butyl-2-cyclohexen-1-one were prepared by selenenylation-selenoxide elimination sequence according to Reich's method.⁹⁾ 5,5-Dimethyl-2-cyclohexen-1-one was prepared by reduction of enol ether of 5,5-dimethyl-1,3-cyclohexanedione with LiAlH_4 and subsequent acid hydrolysis. 5-(1-Dimethylphenylsiloxy-1-methylethyl)-2-cyclopenten-1-one was derived from aldol reaction of 2-cyclopenten-1-one lithium enolate (generated with LDA) with acetone followed by silylation with Me_2PhSiCl and NEt_3 . 1-(2-Methylphenyl)-3-phenyl-2-propen-1-one and 3-phenyl-1-(2,4,6-trimethylphenyl)-2-propen-1-one were prepared by aldol condensation according to the literature procedure.¹⁰⁾

General Procedure. To a solution of 2,6-di-*t*-butyl-4-methylphenol (441 mg, 2 mmol) in toluene (5 ml) was added a 2 mol cm^{-3} hexane solution of Me_3Al (0.5 ml, 1 mmol) and the resulting colorless solution was stirred at room temperature for 1 h. After cooling to -78°C , enone (0.5 mmol) was added at -78°C , and after 5 min, $\text{Li}(\text{R})(i\text{-Bu})_2\text{AlH}$ (1 mmol) in ether (2 ml) (prepared in another flask from DIBAH and RLi ($\text{R} = n\text{-Bu}$, *t*-Bu, and Me) at 0°C for 10 min) was transferred to the enone-MAD complex by cannula. The mixture was stirred at -78°C for 15 min, poured into 10% HCl, extracted with ether, and dried over Na_2SO_4 . Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane as eluant) gave the saturated ketone and/or the unsaturated alcohol depending on the enone substrates, hydride reagents, and reaction conditions.

2-Methylcyclohexanone: IR (neat) 2940, 2870, 1715, 1450 cm^{-1} ; ^1H NMR (CCl_4) δ =0.97 (d, J =7 Hz, 3H), 1.03–2.70 (m, 9H).

3,3-Dimethylcyclohexanone: IR (neat) 2950, 2875, 1705, 1450 cm^{-1} ; ^1H NMR (CCl_4) δ =0.96 (s, 6H), 1.17–2.40 (m, 6H), 2.05 (s, 2H).

4-*t*-Butyl-2-cyclohexen-1-ol: IR (neat) 3325, 3010, 2950, 2850, 1645, 1060, 735 cm^{-1} ; ^1H NMR (CCl_4) δ =0.87 (s, 9H), 1.01–2.20 (m, 5H), 3.16 (br s, 1H), 3.78–4.25 (m, 1H), 4.60 (s, 2H).

5-Isopropenyl-2-methylcyclohexanone: IR (neat) 3100, 2925, 2850, 1720, 1640, 1450, 890 cm^{-1} ; ^1H NMR (CCl_4) δ =0.92–2.85 (m, 11H), 0.97 (d, J =6 Hz, trans CHCH_3), 1.02 (d, J =6 Hz, cis CHCH_3), 1.75 (s, 3H, $\text{CH}_3\text{-C=C}$), 4.70 (s, 2H). GLC analysis showed the cis/trans ratio to be 14:86. t_R (trans)=14.2 min, t_R (cis)=15.2 min at 90°C .

5-Isopropenyl-2-methyl-2-cyclohexen-1-ol: Bp $90\text{--}95^\circ\text{C}$ (Kugelrohr bath temp, 5 Torr (1 Torr $\approx$ 133.322 Pa)); IR (neat) 3325, 3090, 2925, 1650, 1450, 1040, 895, 815 cm^{-1} ; ^1H NMR (CCl_4) δ =1.13–2.60 (m, 8H), 1.70 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.94 (br s, 1H), 3.70–4.30 (m, 1H), 4.65 (s, 2H), 5.36 (br s, 1H). Anal. ($\text{C}_{10}\text{H}_{16}\text{O}$) C, H.

3,5-Dimethylcyclohexanone: IR (neat) 2965, 2885, 1720, 1455 cm^{-1} ; ^1H NMR (CCl_4) δ =0.66–2.50 (m, 8H), 1.03 (br d, 6H). GLC analysis indicated the cis/trans ratio to be 1:99. t_R (trans)=8.6 min, t_R (cis)=9.7 min at 70°C .

3,5-Dimethyl-2-cyclohexen-1-ol: IR (neat) 3360, 2930, 1675, 1455, 1380, 1035 cm^{-1} ; ^1H NMR (CCl_4) δ =0.50–2.73 (m, 9H), 1.67 (s, 3H), 4.03 (br s, 1H), 5.16–5.73 (m, 1H).

2-(1-Dimethylphenylsiloxy-1-methylethyl)cyclopentanone:

IR (neat) 2970, 1715, 1635, 1445, 1415, 1370, 1265, 1190, 1005, 815 cm^{-1} ; ^1H NMR (CCl_4) δ =0.28 (s, 6H), 1.25 (s, 6H), 1.48—2.41 (m, 7H), 6.98—7.61 (m, 5H). This product was spectroscopically identical with authentic sample which was prepared by aldol reaction of cyclopentanone lithium enolate (generated with LDA) with acetone followed by silylation with Me_2PhSiCl and NEt_3 .

(E)-4-Phenyl-3-buten-2-ol: IR (neat) 3325, 3020, 2975, 1650, 1490, 1455, 1060, 965, 745, 690 cm^{-1} ; ^1H NMR (CCl_4) δ =1.27 (d, J =6 Hz, 3H), 3.53 (s, 1H), 4.33 (quintet, J =6 Hz, 1H), 5.86—6.66 (m, 2H), 7.13 (s, 5H).

1,3-Diphenyl-1-propanone: IR (neat) 3040, 2945, 1690, 1595, 1580, 1490, 1450, 1205, 750, 690 cm^{-1} ; ^1H NMR (CCl_4) δ =2.54—3.55 (m, 4H), 6.83—8.04 (m, 5H), 7.11 (s, 5H).

(E)-1,3-Diphenyl-2-propen-1-ol: Bp 200—205 °C (Bath temp, 7 Torr); IR (neat) 3350, 3035, 2870, 1600, 1580, 1495, 1450, 1070, 1030, 965, 745, 695 cm^{-1} ; ^1H NMR (CCl_4) δ =3.12 (br s, 1H), 5.11 (d, J =6 Hz, 1H), 5.87—6.68 (m, 2H), 6.94—7.72 (m, 10H). Anal. ($\text{C}_{15}\text{H}_{14}\text{O}$) C, H.

1-(2-Methylphenyl)-3-phenyl-1-propanone: Bp 170—175 °C (Bath temp, 4 Torr); IR (neat) 3060, 3025, 2930, 1685, 1600, 1575, 1490, 1450, 745, 695 cm^{-1} ; ^1H NMR (CCl_4) δ =2.34 (d, J =7 Hz, 3H), 2.70—3.53 (m, 4H), 6.53—8.06 (m, 4H), 7.12 (s, 5H). Anal. ($\text{C}_{16}\text{H}_{16}\text{O}$) C, H.

(E)-1-(2-Methylphenyl)-3-phenyl-2-propen-1-ol: IR (neat) 3325, 3030, 2935, 2870, 1600, 1585, 1495, 1460, 1450, 1075, 1015, 970, 755, 695 cm^{-1} ; ^1H NMR (CCl_4) δ =2.16 (s, 3H), 3.73 (br s, 1H), 5.25 (m, 1H), 5.86—6.70 (m, 2H), 6.83—7.60 (m, 9H).

3-Phenyl-1-(2,4,6-trimethylphenyl)-1-propanone: Bp 185—190 °C (Bath temp., 4 Torr); IR (neat) 3045, 2935, 1705, 1615, 1500, 1455, 1235, 855, 755, 700 cm^{-1} ; ^1H NMR (CCl_4) δ =2.03 (s, 6H), 2.20 (s, 3H), 2.90 (s, 4H), 6.63 (s, 2H), 7.08 (s, 5H). Anal. ($\text{C}_{18}\text{H}_{20}\text{O}$) C, H.

References

- 1) Reviews: a) C. Sc. A. Hajós, "Complex Hydrides and Related Reducing Agents in Organic Synthesis," Elsevier, New York (1979); b) M. Hudlický, "Reductions in Organic Chemistry," John Wiley & Sons, New York (1984).
- 2) a) M. Freifelder, "Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary," John Wiley & Sons, New York (1978); b) P. N. Rylander, "Hydrogenation Methods", Academic Press, New York (1985).
- 3) a) H. O. House, "Modern Synthetic Reactions," Benjamin, Menlo Park (1965); b) M. M. Baiser, "Organic Electrochemistry," Dekker, New York (1973).
- 4) a) A. Kergomard, M. F. Renaud, and H. Veschambre, *J. Org. Chem.*, **47**, 792 (1982); b) J. C. Gramain, A. Kergomard, M. F. Renard, and H. Veschambre, *ibid.*, **50**, 120 (1985).
- 5) a) E. Keinen and N. Greenspoon, *Tetrahedron Lett.*, **26**, 1353 (1985); b) T. Tsuda, T. Hayashi, H. Satomi, T. Kawamoto, and T. Saegusa, *J. Org. Chem.*, **51**, 537 (1986) and references cited therein.
- 6) J. M. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194 (1976).
- 7) Amphiphilic Reactions in Organic Synthesis: a) Y. Matsumura, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **23**, 929 (1982); b) K. Maruoka, T. Itoh, and H. Yamamoto, *J. Am. Chem. Soc.*, **107**, 4573 (1985); c) K. Maruoka, M. Sakurai, and H. Yamamoto, *Tetrahedron Lett.*, **26**, 3853 (1985); d) K. Maruoka, K. Nonoshita, and H. Yamamoto, *ibid.*, **28**, 5723 (1987); e) K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *J. Am. Chem. Soc.*, in press.
- 8) S. Kim and K. H. Ahn, *J. Org. Chem.*, **49**, 1717 (1984).
- 9) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
- 10) E. P. Kohler and H. M. Chadwell, *Org. Synth.*, Coll. Vol. **1**, 78 (1932).