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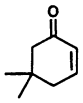
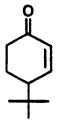
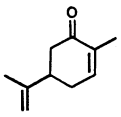
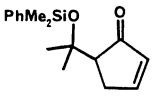
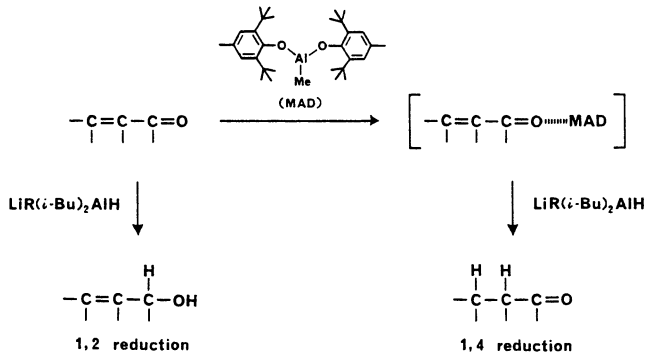
Synopsis. The conjugate reduction of α,β-unsaturated ketones has been effected with amphiphilic reaction system consisting of methylaluminum bis(2,6-di-*t*-butyl-4-alkylphenoxide) and certain complex aluminum hydride reagent.

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 reductions;[3] (3) biochemical reductions using microbioorganisms;[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	(*E*)-PhCH=CHC(=O)CH_3	**A**	0	99
11	(*E*)-PhCH=CHC(=O)Ph	**A**	60	28
12		**B**	57	12
13		**C**	51	43
14		**D**	2	97
15		**E**	37	61
16	(*E*)-PhCH=CHC(=O)(*o*-Tolyl)	**A**	76	11
17	(*E*)-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)$_2$AlH; **B**: MAD/Li(*t*-Bu)(*i*-Bu)$_2$AlH; **C**: MAD/Li(Me)(*i*-Bu)$_2$AlH; **D**: MAD/$LiAlH_4$; **E**: MAT/Li(*n*-Bu)(*i*-Bu)$_2$AlH. c) Isolated yield. d) Use of a toluene solution of Li(*n*-Bu)(*i*-Bu)$_2$AlH. e) Use of a THF solution of Li(*n*-Bu)(*i*-Bu)$_2$AlH. f) Each 1 equiv of MAD and Li(*n*-Bu)(*i*-Bu)$_2$AlH was utilized.



Scheme 1.

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 (Li(n-Bu)(i-Bu)$_2$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 Li(n-Bu)(i-Bu)$_2$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 Li(n-Bu)(i-Bu)$_2$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 Li(n-Bu)(i-Bu)$_2$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 Li(n-Bu)(i-Bu)$_2$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, Li(n-Bu)(i-Bu)$_2$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 ^{1}H 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-A 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, Li(R)(i-Bu)$_2$AlH (1 mmol) in ether (2 ml) (prepared in another flask from DIBAH and RLi (R =n-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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H NMR (CCl_4) δ=0.92—2.85 (m, 11H), 0.97 (d, J=6 Hz, trans CHC$\underline{H}_3$), 1.02 (d, J=6 Hz, cis CHC$\underline{H}_3$), 1.75 (s, 3H, CH_3-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—95 °C (Kugelrohr bath temp, 5 Torr (1 Torr≈133.322 Pa)); IR (neat) 3325, 3090, 2925, 1650, 1450, 1040, 895, 815 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.13—2.60 (m, 8H), 1.70 (s, 3H, CH_3-C=C), 2.94 (br s, 1H), 3.70—4.30 (m, 1H), 4.65 (s, 2H), 5.36 (br s, 1H). Anal. ($C_{10}H_{16}O$) C, H.

3,5-Dimethylcyclohexanone: IR (neat) 2965, 2885, 1720, 1455 cm^{-1}; ^{1}H 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}; ^{1}H 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. ($C_{15}H_{14}O$) 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. ($C_{16}H_{16}O$) 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 ($C_{18}H_{20}O$) C, H.

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