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Remarkably Selective Reduction of the α,*β*-Carbon−Carbon Double Bond in Highly Activated α,*β*,*γ*,*δ*-Unsaturated Alkenes by the $InCl_3$−$NaBH_4$ Reagent System

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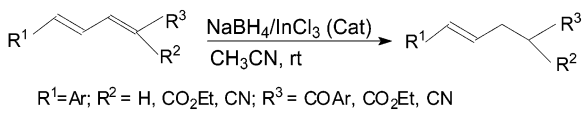
Abstract: A combination of sodium borohydride and a catalytic amount of indium(III) chloride in acetonitrile reduces exclusively the α,*β*-carbon−carbon double bond in α,*β*,*γ*,*δ*-unsaturated diaryl ketones, dicarboxylic ester, cyanoester, and dicyano compounds.

The selective reduction of one functional group in molecules containing a number of other similar reducible functionalities is a challenging problem in organic synthesis. The reduction of α,*β*,*γ*,*δ*-unsaturated carbonyl compounds is very complicated because of the presence of three reducible positions. A literature survey shows a few isolated examples,[1−5] and no general study was found. The Birch reduction with lithium and ammonia of an α,*β*,*γ*,*δ*-unsaturated steroidal ketone produces a *β*,*γ*-unsaturated ketone.[1] In another report, hydrogenation with Ni−Al_2O_3 under very controlled conditions reduces the *γ*,*δ*-unsaturated double bond while the presence of Pb or Cd reduces the α,*β*-one.[2] The reduction of the α,*β*-double bond is also observed using triallylsilane in the presence of either rhodium[3] or platinum[4] catalyst. The reduction of α,*β*,*γ*,*δ*-unsaturated carboxylic ester by trialkylsilane in the presence of Wilkinson's catalyst provides *β*,*γ*-unsaturated ester from acyclic molecules, whereas in cyclic strained compounds the α,*β*-double bond is reduced.[5]

The reduction by indium metal has attracted considerable current attention because of its remarkable efficiency for selective reduction in multifunctional molecules.[6] Very recently, indium hydrides, formed in situ from the combination of indium halides and metal hydrides, have shown great promise as practical and better alternatives to the existing reducing agents.[7] As a part of our continued interest in indium-mediated reactions,[6e−j,7e,8] we have discovered that the indium(III) chloride−sodium borohydride reagent system selectively reduces the α,*β*-carbon−carbon double bond in highly activated α,*β*,*γ*,*δ*-unsaturated alkenes (Scheme 1).

SCHEME 1



R^1=Ar; R^2 = H, CO_2Et, CN; R^3 = COAr, CO_2Et, CN

The experimental procedure is very simple. The α,*β*,*γ*,*δ*-unsaturated alkene was stirred with a solution of sodium borohydride and a catalytic amount of indium(III) chloride (15 mol %) in anhydrous acetonirile at room temperature for a period of time required to complete the reaction (monitored by TLC). The reaction mixture was then diluted with ether (technical grade, 98%), and the product was isolated by extraction followed by purification through column chromatography. It has been observed that quenching of the reaction mixture with water leads to reduction of the keto-carbonyl by the excess hydride reducing agent present to the extent of 2−5%. However, when the reaction was quenched with commercial ether, which usually contains traces of water, reduction of ketone functionality was arrested.

A wide variety of α,*β*,*γ*,*δ*-unsaturated diaryl ketones, dicarboxylic esters, cyanoesters, and dicyano compounds underwent exclusive reduction of the α,*β*-carbon−carbon double bond to provide the corresponding *γ*,*δ*-unsaturated derivatives in high yields. The results are summarized in Table 1. Several sensitive groups such as Cl, OBn, OMe, and methylenedioxy remained unaffected. However, this selective reduction is observed only in highly activated alkenes as listed in Table 1. The corresponding monocarboxylic ester does not undergo any reduction, and aryl alkyl ketone leads to partial reduction. In a comparative study, an α,*β*,*γ*,*δ*-unsaturated diaryl ketone (entry 1) on treatment with sodium borohydride in methanol for 10 h produces the corresponding alcohol without any reduction of the double bonds whereas hydrogenation over palladium−charcoal in ethanol furnishes the saturated alcohol. On the other hand, lithium aluminum hydride leads to a mixture of reduced products.

Although the mechanism of this reduction is not very clear, it may be speculated that chloroindium hydride (Cl_2InH), formed by the combination of sodium borohydride and indium(III) chloride,[7c] might be the active species.

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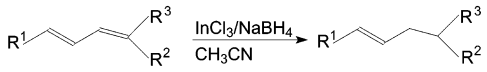
TABLE 1. Reduction of Activated α,β,γ,δ-Unsaturated Alkenes by $InCl_3/NaBH_4$



entry	R^1	R^2	R^3	time(min)	yield(%)[a]
1	C_6H_5	H	C_6H_5-C=O	60	91
2	C_6H_5	H	*p*(Me)-C_6H_4-C=O	60	89
3	C_6H_5	H	*p*(Cl)-C_6H_4-C=O	50	89
4	C_6H_5	H	*p*(OBn)-C_6H_4-C=O	70	87
5	*m*(OMe)-C_6H_4	H	*p*(Me)-C_6H_4-C=O	90	85
6		H	*p*(Me)-C_6H_4-C=O	75	86
7	C_6H_5			90	77
8	C_6H_5	CO_2Et	CO_2Et	90	89
9	C_6H_5	CN	CO_2Et	60	86
10		CN	CO_2Et	80	83
11	C_6H_5	CN	CN	45	97
12	*m*(OMe)-C_6H_4	CN	CN	70	95

[a] The yields refer to those of pure isolated products characterized by spectroscopic data (IR and ^1H and ^{13}C NMR) and elemental analysis.

In conclusion, the indium(III) chloride−sodium borohydride reagent system provides a unique method for selective (exclusive) reduction of the α,β-carbon−carbon double bond in highly activated α,β,γ,δ-unsaturated alkenes which is not achievable by conventional nucleophilic hydride reducing agents. Certainly, this demonstrates the potential of indium hydride and to the best of our knowledge this constitutes the first general method of such selective reduction by a simple reagent. We believe, this procedure will find useful applications in organic synthesis.

Experimental Section

General Methods. Acetonitrile was distilled over phosphorus pentoxide and stored over molecular sieves (4 Å). The α,β,γ,δ-unsaturated alkenes were prepared by standard methods.[9] IR spectra were taken as thin films. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 75 MHz, respectively.

General Procedure for Reduction. Representative Procedure for the Reduction of 1,5-Diphenylpent-2,4-diene-1-one (Entry 1). To a stirred solution of indium(III) chloride (30 mg, 0.135 mmol) and sodium borohydride (56 mg, 1.5 mmol) in dry acetonitrile (3 mL) was added a solution of 1,5-diphenylpenta-2,4-dien-1-one (234 mg, 1 mmol) in acetonitrile (1 mL) at room temperature under nitrogen. Stirring was continued for another 1 h (monitored by TLC), and the reaction mixture was quenched with ether (technical grade, 98%) (10 mL). The whole mixture was then stirred for another 5 min. After the mixture settled, the supernatant organic layer was decanted and the residual semisolid mass (inorganic part) was further extracted by washing with ether. The combined ether extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product which was purified by column chromatography over silica gel to furnish the pure 1,5-diphenylpent-4-en-1-one (215 mg, 91%) as a viscous liquid: IR 1683, 1651, 1596 cm^{-1}; ^1H NMR δ 7.99 (d, *J* = 7.23 Hz, 2H), 7.21−7.57 (m, 8H), 6.48 (d, *J* = 15.84 Hz, 1H), 6.17 (dt, *J* = 15.84, 6.87 Hz, 1H), 3.16 (t, *J* = 7.53 Hz, 2H), 2.64−2.71 (m, 2H); ^{13}C NMR δ 199.8, 137.9, 137.3, 133.5, 131.2, 129.6, 129.1 (2C), 128.9 (2C), 128.5 (2C), 127.5, 126.5 (2C), 38.7, 27.9. Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.35; H, 6.77.

This procedure is followed for the reduction of all the substrates listed in Table 1. Spectroscopic (IR and ^1H and ^{13}C NMR) and analytical data for all products are presented below in order of their entries in Table 1.

(4′-Methylphenyl)-5-phenylpent-4-en-1-one (entry 2): IR 1681, 1651, 1606 cm^{-1}; ^1H NMR δ 7.91 (d, *J* = 8.13 Hz, 2H), 7.21−7.38 (m, 7H), 6.48 (d, *J* = 15.87 Hz, 1H), 6.32 (dt, *J* = 15.87, 6.75 Hz, 1H), 3.13 (t, *J* = 7.50 Hz, 2H), 2.63−2.70 (m, 2H), 2.42 (s, 3H); ^{13}C NMR δ 199.4, 144.2, 137.9, 134.8, 131.1, 129.8 (2C), 128.9 (2C), 128.8, 128.5 (2C), 127.5, 126.5 (2C), 38.5, 28.0, 22.0. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.24. Found: C, 86.41; H, 7.23.

1-(4′-Chlorophenyl)-5-phenylpent-4-en-1-one (entry 3): IR 1680, 1651, 1589 cm^{-1}; ^1H NMR δ 7.91 (d, *J* = 8.52 Hz, 2H), 7.43 (d, *J* = 8.52 Hz, 2H), 7.17−7.38 (m, 5H), 6.46 (d, *J* = 15.87 Hz, 1H), 6.27 (dt, *J* = 15.87, 6.75 Hz, 1H), 3.15 (t, *J* = 7.23 Hz, 2H), 2.61−2.68 (m, 2H); ^{13}C NMR δ 198.5, 139.9, 137.7, 135.6, 131.3, 129.8 (2C), 129.3 (2C), 129.2, 128.9 (2C), 127.5, 126.4 (2C), 38.6, 27.8. Anal. Calcd for $C_{17}H_{15}ClO$: C, 75.41; H, 5.58. Found: C, 75.36; H, 5.60.

1-(4′-Benzyloxyphenyl)-5-phenylpent-4-en-1-one (entry 4): IR 1679, 1649, 1601 cm^{-1}; ^1H NMR δ 7.88 (d, *J* = 8.13 Hz, 2H), 7.19−7.46 (m, 10H), 6.98 (d, *J* = 8.13 Hz, 2H), 6.43 (d, *J* = 15.87 Hz, 1H), 6.22 (dt, *J* = 15.87, 6.69 Hz, 1H), 5.07 (s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.55−2.61 (m, 2H); ^{13}C NMR δ 199.1, 158.7, 138.0, 137.4, 130.7, 130.5, 129.1 (2C), 129.0 (2C), 128.9, 128.4, 127.9 (2C), 127.8 (2C), 127.6, 126.4 (2C), 115.1 (2C), 70.5, 38.7, 27.8. Anal. Calcd for $C_{24}H_{22}O_2$: C, 88.36; H, 6.79. Found: C, 88.22; H, 6.78.

1-(4′-Methylphenyl)-5-(3′-methoxyphenyl)pent-4-en-1-one (entry 5): IR 1681, 1651, 1604 cm^{-1}; ^1H NMR δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.18−7.27 (m, 3H), 6.74−6.95 (m, 3H), 6.44 (d, *J* = 15.87 Hz, 1H), 6.28 (dt, *J* = 15.87, 6.63 Hz, 1H), 3.81 (s, 3H), 3.09 (t, *J* = 7.50 Hz, 2H), 2.61−2.68 (m, 2H), 2.40 (s, 3H); ^{13}C NMR δ 199.3, 160.2, 144.2, 139.4, 134.8, 131.0, 129.8, 129.7, 129.6 (2C), 128.8 (2C), 119.1, 111.8, 111.7, 55.5, 38.5, 27.9, 22.0. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.21; H, 7.12.

5-(3′,4′-Dioxymethylenephenyl)-1-(4′-methylphenyl)pent-4-en-1-one (entry 6): IR 1681, 1651, 1606, 1600, cm^{-1}; ^1H NMR δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 1 Hz, 1H), 6.70−6.77 (m, 2H), 6.36 (d, *J* = 15.78 Hz, 1H), 6.10 (dt, *J* = 15.78, 6.87 Hz, 1H), 5.93 (s, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.57−2.64 (m, 2H), 2.41 (s, 3H); ^{13}C NMR δ 199.5, 148.3, 147.1, 144.2, 134.8, 132.4, 130.6, 129.7 (2C), 128.6 (2C), 127.9, 120.8, 108.6, 105.9, 101.2, 38.6, 27.9, 22.0. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.46; H, 6.05.

3-Phenyl-1-(α-tetralonyl)prop-2-ene (entry 7): IR 1681, 1651, 1598 cm^{-1}; ^1H NMR δ 7.75 (d, *J* = 7.77 Hz, 1H), 7.09−7.41 (m, 8H), 6.39 (d, *J* = 15.81 Hz, 1H), 6.18 (dt, *J* = 15.81, 7.44 Hz, 1H), 2.35−2.94 (m, 3H), 2.15−2.22 (m, 2H), 1.76−1.90 (m, 2H); ^{13}C NMR δ 199.8, 144.5, 137.8, 133.6, 132.9, 132.5, 129.1, 128.9 (2C), 128.4, 127.5, 127.0, 126.5, 126.4 (2C), 48.0, 33.7, 29.1, 28.6. Anal. Calcd for $C_{19}H_{18}O$: C, 86.98; H, 6.91. Found: C, 86.79; H, 6.87.

1-Diethylcarboxy-4-phenylbut-3-ene (entry 8): IR 1732 cm^{-1}; ^1H NMR δ 7.34 (m, 5H), 6.47 (d, *J* = 15.84 Hz, 1H), 6.15 (dt, *J* = 15.84, 7.17 Hz, 1H), 4.23 (q, *J* = 7.20 Hz, 4H), 3.49 (t,

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J = 7.47 Hz, 1H), 2.81 (m, 2H), 1.25 (t, J = 7.20 Hz, 6H); ^{13}C NMR δ 169.3 (2C), 137.4, 133.2, 128.9 (2C), 127.8, 126.6 (2C), 125.9, 61.8 (2C), 52.4, 32.6, 14.5 (2C). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.41; H, 7.22.

1-Cyano-1-ethylcarboxy-4-phenylbut-3-ene (entry 9): IR 2256, 1745 cm^{-1}; ^{1}H NMR δ 7.18−7.42 (m, 5H), 6.58 (d, J = 15.75 Hz, 1H), 6.17 (dt, J = 15.75, 7.20 Hz, 1H), 4.27 (q, J = 7.20 Hz, 2H), 3.62 (t, J = 6.81 Hz, 1H), 2.82 (dd, J = 7.17, 7.11 Hz, 2H), 1.30 (t, J = 7.20 Hz, 3H); ^{13}C NMR δ 165.9, 136.7, 135.4, 129.0 (2C), 128.3, 126.8 (2C), 122.8, 116.5, 63.3, 38.3, 33.7, 14.4. Anal. Calcd for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.10. Found: C, 73.29; H, 6.48; H, 6.14.

1-Cyano-1-ethylcarboxy-4-(3′,4′-dioxymethylenephenyl)-but-3-ene (entry 10): IR 2255, 1743 cm^{-1}; ^{1}H NMR δ 6.89 (s, 1H), 6.71−6.80 (m, 2H), 6.48 (d, J = 15.69 Hz, 1H), 6.01 (dt, J = 15.69, 6.81 Hz, 1H), 5.95 (s, 2H), 4.28 (q, J = 7.20 Hz, 2H), 3.62 (t, J = 6.87 Hz, 1H), 2.79−2.83 (m, 2H), 1.30 (t, J = 7.20 Hz, 3H); ^{13}C NMR δ 165.8, 148.4, 147.2, 134.9, 131.1, 122.8, 121.5, 116.0, 109.7, 108.6, 101.5, 63.4, 38.4, 35.9, 14.4. Anal. Calcd for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.75; H, 5.44; N, 5.01.

1,1-Dicyano-4-phenylbut-3-ene (entry 11): IR 2258, 1649 cm^{-1}; ^{1}H NMR δ 7.25−7.43 (m, 5H), 6.69 (d, J = 15.75 Hz, 1H), 6.17 (dt, J = 15.75, 7.41 Hz, 1H), 3.80 (t, J = 6.60 Hz, 1H), 2.88 (dd, J = 7.62, 6.63 Hz, 2H); ^{13}C NMR δ 137.5, 136.0, 129.2 (2C), 129.0, 127.1 (2C), 120.3, 112.7 (2C), 34.6, 23.8. Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.37. Found: C, 79.01; H, 5.42; N, 15.25.

1,1-Dicyano-4-(3′-methoxyphenyl)but-3-ene (entry 12): IR 2258, 1648, 1593 cm^{-1}; ^{1}H NMR δ 7.24−7.31 (m, 1H), 6.99 (d, J = 7.59 Hz, 1H), 6.97 (s, 1H), 6.83−6.84 (m, 1H), 6.76 (d, J = 15.72 Hz, 1H), 6.16 (dt, J = 15.72, 7.35 Hz, 1H), 3.79−3.83 (m, 4H), 2.88 (dd, J = 7.14, 6.84 Hz, 2H); ^{13}C NMR δ 160.3, 137.5, 137.3, 130.0, 120.5, 119.7, 115.2, 112.5 (2C), 112.4, 55.7, 34.6, 23.7. Anal. Calcd for $C_{13}H_{12}N_2$: C, 73.56; H, 5.69; N, 13.19. Found: C, 73.48; H, 5.57; N, 13.06.

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