Synthesis of β-Hydroxy Nitriles via Indium-Induced Coupling of Bromoacetonitrile with Carbonyl Compounds

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(Received October 8, 1993)

The organoindium reagent, derived from indium metal and bromoacetonitrile, reacted with carbonyl compounds in the presence of chlorotrimethylsilane to give, after hydrolysis, β-hydroxy nitriles. The coupling proceeded with high chemoselectivity, though the diastereoselectivity was low.

Organoindium reagents have recently been introduced to organic synthesis and proved to be useful in several organic transformations.[1] In particular, allylic indium reagents possess enough reactivity to make new carbon–carbon bonds under mild reaction conditions with high selectivity.[2] Indium enolates are an another type of indium reagents of potential synthetic value. Indium enolates of esters[3] (indium-Reformatsky reagent) and ketones[4] were actually prepared and utilized in the synthesis of β-hydroxy esters and in aldol reactions, respectively. As a further example of indium enolates, this paper describes the preparation and reactions of the organoindium reagent derived from bromoacetonitrile, which, on the reaction with carbonyl compounds, provide a facile route to β-hydroxy nitriles.

Results and Discussion

The reaction of bromoacetonitrile with indium powder smoothly proceeded in tetrahydrofuran (THF) at room temperature to give a colorless solution of organoindium reagent **1**. Although the concrete structure of **1** is not yet established, it was tentatively deduced, by analogy with the corresponding organoindium compound from haloacetate (indium-Reformatsky reagent),[3a] as tribromotris(cyanomethyl)diindium (Chart 1). On the contrary to the smooth reaction of the indium-Reformatsky reagent with carbonyl compounds, **1** did not react with benzaldehyde and the expected β-hydroxy nitrile was not obtained at all. It is known that chlorotrimethylsilane (TMSCl) markedly accelerates the addition of organocuprates to carbonyl compounds.[5] Therefore, we then examined the effects of TMSCl and other additives on this coupling. As is seen from Table 1, TMSCl is the most effective; the reaction proceeded smoothly at room temperature within 2 h to furnish 3-trimethylsiloxy-3-phenylpropanenitrile.[6] After desilylation of the silyl ether, 3-hydroxy-3-phenylpropanenitrile was isolated in 86% yield (Table 2). The reaction is compatible with various functional groups. Thus, 4-nitro- and 4-chlorobenzaldehydes, methyl 4-formylbenzoate, and *p*-anisaldehyde gave good yields of the desired products. In the *p*-anisaldehyde case, considerable amounts of the dehydration products (α,β-unsaturated nitriles) were also isolated. However, aromatic aldehydes with a hydroxyl group or an amino group gave less satisfactory results. Aliphatic aldehydes gave lower yields than aromatic aldehydes.

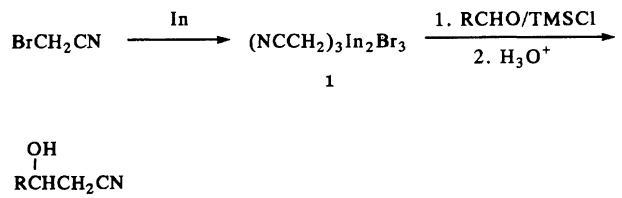


Chart 1.

Table 1. Effect of Additives[a]

Additive	Yield/%
Me_3SiCl	86[b]
Bu^tMe_2SiCl	58[b]
$TiCl_4$	64
$SnCl_4$	34
$BF_3{\cdot}OEt_2$	0
Me_3SiOTf	0

a) All reactions were carried out with benzaldehyde (3 mmol), bromoacetonitrile (6 mmol), indium (4.5 mmol), and an additive (9 mmol) in THF (3 cm^3). b) Yield of desilylated product.

Table 2. Synthesis of β-Hydroxy Nitriles[a]

Carbonyl Compound	Yield/%[b]
PhCHO	86
4-$O_2NC_6H_4CHO$	58
4-ClC_6H_4CHO	87
4-$MeO_2CC_6H_4CHO$	77
4-$MeOC_6H_4CHO$	54(19)[c]
2-HOC_6H_4CHO	27
4-HOC_6H_4CHO	Trace
4-$Me_2NC_6H_4CHO$	Trace
n-$C_7H_{15}CHO$	41
PhCH=CHCHO	68
MeCH=CHCHO	18
PhCOMe	16
n-PrCOMe	Trace

a) All reactions were carried out with carbonyl compound (3 mmol), bromoacetonitrile (6 mmol), indium (4.5 mmol), and chlorotrimethylsilane (9 mmol) in THF (3 cm^3). b) Yield of disilylated product. c) Yield of dehydration product.

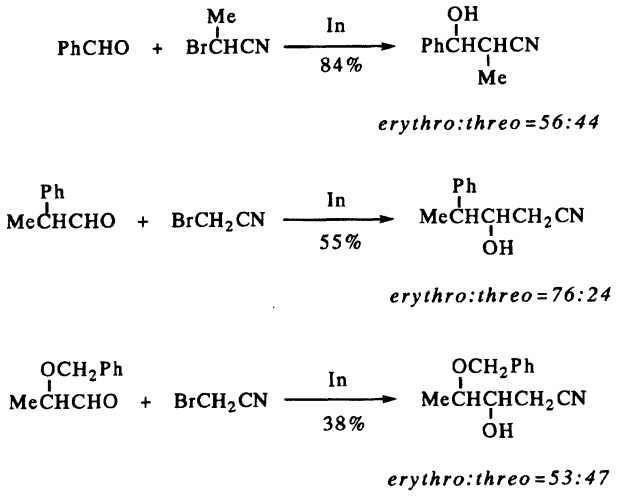
The indium reagent **1** reacts with α,β-unsaturated aldehydes via exclusive 1,2-addition; no conjugate addition was observed. With ketones the yields of the β-hydroxynitriles were only modest. The high chemoselectivity (aldehyde vs. ketone) was demonstrated by the competitive reaction with benzaldehyde and acetophenone; the indium reagent **1** reacted exclusively with benzaldehyde to give a 77% yield of the adduct, whereas acetophenone was recovered unchanged (56%).

In order to examine the streoselectivity of this indium-induced coupling, the following three reactions were carried out (Scheme 1). The reaction of benzaldehyde and 2-bromopropanenitrile gave a high yield (84%) of the cross-coupling product, but the *erythro/threo* ratio was low (56/44). The reaction of 2-phenylpropanal and bromoactonitrile gave moderate diastereoselectivity (76/24). Even with 2-(benzyloxy)propanal, which is capable of reaction by the way of a chelated intermediate, diastereofacial preference was only modest (53/47).

β-Hydroxy nitriles are synthetically important compounds. Zinc-mediated Reformatsky-type reaction of bromoacetonitrile and carbonyl compounds is hitherto the most conventional method for the synthesis of β-hydroxy nitriles. However, its experimental difficulties (e.g. activation of zinc, careful purification of solvent) and the relatively low yields prevent the wide use.[7] Recently some improved methods based on other metals such as activated nickel[8] and antimony[9] were reported. Our indium-induced procedure is still limited in scope (e.g. good yields only with aromatic aldehydes, poor steroselectivity); nevertheless, its high chemoselectivity and experimental simplicity make the method convenient and useful.

Experimental

General. Metlting points were measured on a hot-stage apparatus and are uncorrected. Boiling points refer to bath temperatures during Kugelrohr distillation (Shibata GTO-250RS glass tube oven). Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ on a Hitachi R-90H (90 MHz) or on a Varian XL-200 (200 MHz) spectrometer with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a Varian XL-200 (50 MHz) sepctrometer. For gas chromatography Shimadzu GL-14A (equipped with ULBON HR-1. 50 m×0.25 mm) and Yanaco G-1800 (SE-30, 2 m ×3 mm) gas chromatographs were used. Elemental analysis was performed at Elemental Analysis Center of Kyoto University. Indium powder, stabilized by 0.5% MgO, was obtained from Nacalai Tesque Co., Ltd. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. All reactions were done under argon.



Scheme 1.

Indium-Mediated Reactions of Bromoactonitriles with Carbonyl Comounds. The following reaction of bromoacetonitrile and 4-nitrobenzaldehyde is representative. To a suspension of indium powder (525 mg, 4.5 mmol) in THF(3 cm^3), bromoacetonitrile (0.42 cm^3, 6.0 mmol) was added and the mixture was stirred at 0 °C for 10 min and then at room temperature for another 10 min. 4-Nitrobenzaldehyde (453 mg, 3.0 mmol) and chlorotrimethylsilane (1.1 cm^3, 9.0 mmol) were successively added, and the whole mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. Diluted hydrochloric acid (1 mol dm^{-3}, 60 cm^3) was added and the mixture was stirred for 30 min. The product was extracted several times with ether (400 cm^3), and the extracts were washed with saturated aqueous sodium hydrogencarbonate and then with brine. After being dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was column chromatographed on silica gel with dichloromethane as an eluent to yield 3-hydroxy-3-(4-nitrophenyl)propanenitrile (332 mg, 58%). Other reactions were similarly carried out and the products were isolated by column chromatography or Kugelrohr distillation.

3-Hydroxy-3-phenylpropanenitrile. Colorless oil; bp 200 °C/3.5 Torr (1 Torr=133.322 Pa) (lit,[10] bp154—155 °C/1 Torr); ^{1}H NMR (90 MHz) δ=2.41 (1H, br s, OH), 2.75 (2H, d, J=6.0 Hz, CH_2), 5.04 (1H, t, J=6.0 Hz, CH), and 7.39 (5H, s, Ph).

3-Hydroxy-3-(4-nitrophenyl)propanenitrile. Yellow crystals; mp 119°C (EtOH)(lit,[11] mp 118—120 °C ($CHCl_3$); ^{1}H NMR (200 MHz) δ=2.73 (1H, d, J=5.0 Hz, OH), 2.82 (2H, d, J=5.0 Hz, CH_2), 5.20 (1H, q, J=5.0 Hz, CH), 7.63 (2H, d, J=10.0 Hz, Ar), and 8.27 (2H, d, J=10.0 Hz, Ar).

3-(4-Chlorophenyl)-3-hydroxypropanenitrile. Colorless oil;[12] bp 250 °C/3.6 Torr; ^{1}H NMR (90 MHz) δ=2.42 (1H, br s, OH), 2.76 (2H, d, J=6.0 Hz, CH_2), 5.02 (1H, t, J=6.0 Hz, CH), and 7.26 (4H, s, Ar).

Methyl 4- (2- Cyano- 1- hydroxyethyl)benzoate. Colorless crystals; mp 95—96 °C (EtOH); IR (KBr) 3460, 2260, 1712, 1440, 1288, 1118, and 1062 cm^{-1}; ^{1}H NMR (200 MHz) δ=2.50 (1H, d, J=5.0 Hz, OH), 2.80 (2H, d, J=5.0 Hz, CH_2), 3.93 (3H, s, OMe), 5.11 (1H, q, J=5.0 Hz, CH), 7.49 (2H, d, J=10.0 Hz, Ar), and 8.07 (2H, d, J=10.0 Hz, Ar). Found C, 64.18; H, 5.41%. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40%.

3- Hydroxy- 3- (4- methyoxyphenyl)pronanenitrile. Colorless oil; bp 200 °C/2.9 Torr (lit,[13] bp 173 °C/4 Torr); ^{1}H NMR (90 MHz) δ=2.36 (1H, br s, OH), 2.77 (2H, d, J=6.0 Hz, CH_2), 3.77 (3H, s, OMe), 4.98 (1H, t, J=6.0 Hz, CH), 6.91 (2H, d, J=9.0 Hz, Ar), and 7.32 (2H, d, J=9.0

Hz, Ar).

3-Hydroxy-3-(2-hydroxyphenyl)propanenitrile. Pale yellow crystals; mp 101—102 °C (hexane); IR (KBr) 3360, 2265, 1616, 1460, 1348, 1234, 1054 and 752 cm^{-1}; ^1H NMR (200 MHz) δ=1.69 (1H, br s, OH), 2.86 (1H, dd, J=2.7, 8.1 Hz, CH_2), 2.94 (1H, dd, J=3.9, 8.1 Hz, CH_2), 5.22 (1H, dd, J=3.9, 6.6 Hz, CH), 6.74 (1H, br. s, $C_6H_4O\underline{H}$), and 6.80—7.33 (4H, m, Ar). Found: C, 65.77; H, 5.65%. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.65%.

3-Hydroxydecanenitrile. Colorless oil; bp 200 °C/2.9 Torr; IR (neat) 3450, 2945, 2860, 2255, 1722, 1464, 1082, 848, and 722 cm^{-1}; ^1H NMR (90 MHz) δ=0.88 (3H, t, J=5.7 Hz, Me), 1.30 (12H, m, CH_2), 2.48 (2H, d, J=6.0 Hz, CH_2), 2.76 (1H, br. s, OH), and 3.92 (1H, t, J=5.7 Hz, CH). Found: C, 70.31; H, 11.25%. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31%.

3-Hydroxy-5-phenyl-4-pentenenitrile. Colorless oil; bp 150 °C/3.9 Torr (lit,[8] bp 143 °C/0.41 Torr); ^1H NMR (90 MHz) δ=2.10 (1H, br s, OH), 2.70 (2H, d, J=6.0 Hz, CH_2), 4.64 (1H, q, J=6.0 Hz, CH), 6.23 (1H, dd, J=6.0, 16.2 Hz, PhCH=C$\underline{H}$), 6.74 (1H, d, J=16.2 Hz, PhC$\underline{H}$=CH), and 7.33 (5H, m, Ar).

3-Hydroxy-4-hexenenitrile. Colorless oil; bp 150 °C/24 Torr (lit,[14] bp 84—85 °C/10 Torr); ^1H NMR (90 MHz) δ=1.76 (3H, d, J=6.0 Hz, Me), 1.94 (1H, br. s, OH), 2.57 (2H, d, J=6.0 Hz, CH_2), 4.40 (1H, q, J=6.0 Hz, CH), and 5.70 (2H, m, MeC$\underline{H}$=C$\underline{H}$).

3-Hydroxy-3-phenylbutanenitrile. Colorless oil; bp 150 °C/3.7 Torr (lit,[10] bp 150—151 °C/4 Torr); ^1H NMR (90 MHz) δ=1.78 (3H, s, Me), 2.26 (1H, br s, OH), 2.82 (2H, s, CH_2), and 7.44 (5H, m, Ar).

3-Hydroxy-2-methyl-3-phenylpropanenitrile. *Erythro/threo* mixture (56/44 by ^1H NMR); colorless oil;[15] bp 150 °C/14 Torr; ^1H NMR (200 MHz) δ=1.28 (1.32H, dd, J=3.2, 6.4 Hz, Me of *threo*), 1.31 (1.68H, dd, J=3.2, 6.4 Hz, Me of *erythro*), 2.19 (1H, br. s, OH), 2.95 (0.44H, quin, J=3.6 Hz, C$\underline{H}$Me of *threo*), 3.05 (0.56H, quin, J=3.0 Hz, C$\underline{H}$Me of *erythro*), 4.76 (0.44 H, d, J=3.6 Hz, C$\underline{H}$OH of *threo*), 4.86 (0.56H, d, J=3.0 Hz), C$\underline{H}$OH of *erythro*), 7.42 (2.80H, s, Ph of *erythro*). and 7.43 (2.20H, s, Ph of *threo*).

3-Hydroxy-4-phenylpentanenitrile. *Erythro/threo* mixture (76/24 by ^1H NMR and GLC); colorless oil; bp 150 °C/3.9 Torr; IR (neat) 3450, 2976, 2250, 1600, 1412, 1078, 1050, and 1022 cm^{-1}; ^1H NMR (200 MHz) δ=1.39 (0.72H, d, J=2.1 Hz, Me of *threo*), 1.43 (2.28H, d, J=2.1 Hz, Me of *erythro*), 1.99 (1H, br. s, OH), 2.38 (0.48H, d, J=3.6, 8.4 Hz, C$\underline{H}_2$ of *threo*), 2.42 (1.52H, d, J=2.4, 8.4 Hz, C$\underline{H}_2$ of *erythro*), 2.90 (0.76H, quin, J=2.1 Hz, PhC$\underline{H}$ of *erythro*), 2.96 (0.24H, quin, J=2.1 Hz, PhC$\underline{H}$ of *threo*), 3.93—4.08 (1H, m, C$\underline{H}$OH), and 6.91—7.69 (5H, m, Ph); ^{13}C NMR δ=17.1 (Me, *threo*), 17.2 (Me, *erythro*), 23.2 (CH_2, *erythro*), 24.1 (CH_2, *threo*), 44.5 (CHMe, *erythro*), 45.3 (CHMe, *threo*), 71.2 (CHOH, *erythro*), 71.8 (CHOH, *threo*), 117.9 (CN, *erythro*), 118.0 (CN, *threo*), 126.9 (Ph), 127.0 (Ph), 127.2 (Ph), 127.9 (Ph), 128.3 (Ph), 128.5 (Ph), 141.2 (ipso of Ph, *threo*), and 142.5 (ipso of Ph, *erythro*). Found: C, 75.19; H, 7.58%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48%.

3-Hydroxy-4-benzyloxypentanenitrile. *Erythro/threo* mixture (47/53 by ^1H NMR); pale yellow oil; bp 200 °C/3.9 Torr; IR (neat) 3460, 2250, 1456, 1148, 1078, 1030, 742, and 702 cm^{-1}; ^1H NMR (200 MHz) δ=1.23 (1.59H, dd, J=2.7, 6.0 Hz, Me of *erythro*), 1.25 (1.41H, dd, J=2.7, 6.0 Hz, Me of *threo*), 2.09 (1H, br. s, OH), 2.59 (0.94H, dd, J=3.3, 6.0 Hz, C$\underline{H}_2$CN of *threo*), 2.60 (1.06H, dd, J=3.3, 6.0 Hz, C$\underline{H}_2$CN of *erythro*), 3.63 (1H, d quin , J=4.7, 6.0 Hz, MeC$\underline{H}$), 3.79 (0.47H, dq, 5.3, 6.0 Hz, C$\underline{H}$CH$_2$CN of *threo*), 3.91 (0.53H, dq, J=5.3, 6.0 Hz, C$\underline{H}$CH$_2$CN of *erythro*), 4.46 (0.47H, dd, J=9.3, 12.0 Hz, OC$\underline{H}_2$Ph of *threo*), 4.47 (0.53H, dd, J=9.3, 12.0 Hz, OC$\underline{H}_2$Ph of *threo*), 4.47 (0.53H, dd, J=9.3, 12.0 Hz, OC$\underline{H}_2$Ph of *erythro*), 4.67 (0.53H, dd, J=6.0, 12.0 Hz, OC$\underline{H}_2$Ph of *erythro*), 4.70 (0.47H, dd, J=6.0, 12.0 Hz, OC$\underline{H}_2$Ph of *threo*), and 7.31 (5H, s, Ph); ^{13}C NMR δ=14.7 (Me, *threo*), 14.9 (Me, *erythro*), 21.7 (CH_2), 70.1 (OCH_2, *threo*), 70.7 (OCH_2, *erythro*), 75.5 (CHOH, *threo*), 76.2 (CHOH, *erythro*), 117.6 (CN, *threo*), 118.0 (CN, *erythro*), 127.5 (ph), 127.6 (Ph), 128.2 (Ph), 137.4 (ipso of Ph, *erythro*), and 137.6 (ipso of Ph, *threo*). Found: C, 70.44; H, 7.31%. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37%.

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6) Recently, Lipshutz demonstrated that TMSCl acts as a Lewis base in cuprate conjugate addition.[5] This is consistent with our finding that only the chlorine-containing additives are effective, though cuprate and the indium reagent **1** are different in scope (e.g. 1,4- vs. 1,2-addition to α,β-unsaturated carbonyls, see text).

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