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Tin-mediated Organic Reactions: a Practical Method for the Synthesis of β-Hydroxynitriles and β-Hydroxyketones†

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In the presence of chlorotrimethylsilane, the tin mediated addition of bromoacetonitrile or α-bromacetophenone to aldehydes in THF gives β-hydroxynitriles or β-hydroxyketones in moderate to good yields.

Organic reactions promoted by metals have aroused much interest in recent years.[1] Among many types of applied metals, tin plays an important role, not only for its low cost but also for its availability. Most work has been directed to the reaction of allylic halides which give, in general, good yields and selectivity towards aldehydes and ketones.[2–5] A few other publications refer to reactions of α-bromoketones and α-bromoesters.[6] Such reactions proceed through an allylic tin intermediate or a divalent tin enolate species. Reports also indicated that many reactions could be accelerated by either sonication or the presence of water.[7,8] These significant studies provided a convenient method for the synthesis of homoallyl alcohols and other important compounds. It is anticipated that metallic tin will have a more widespread use in organic synthesis.

In view of the fact that the cyano group is becoming increasingly valuable in many applications, and that many very useful inversions can be derived from it, the production of cyano group-containing compounds *via* effective methods is especially important. We have reported a tin-mediated reaction for the synthesis of β-aminonitriles,[9] and it was proposed that the reaction proceeded through an organotin intermediate. Now we report a simple and convenient procedure for the synthesis of β-hydroxynitriles mediated by tin (Scheme 1).

$$\underset{\mathbf{1}}{\mathrm{RCHO}} + \mathrm{BrCH_2CN} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{Sn,\ TMSCl,\ THF}} \underset{\mathbf{2}}{\mathrm{RCH(OH)CH_2CN}}$$

Scheme 1

The results are listed in Table 1. Commercial tin powder was employed without any activation and reactions were performed in THF. The addition of bromoacetonitrile to aldehydes occurred slowly at room temperature, but required 5 h. Water did not promote reaction whereas when 1 equivalent of chlorotrimethylsilane (TMSCl) was added most reactions were accelerated and were complete within 2 h. The action of TMSCl on the aldehyde may lead to an active intermediate,[10] and accelerate the reaction. The reaction was found to be general and applicable to aromatic or aliphatic aldehydes and proceeded *via* an exclusive 1,2-addition to α,β-unsaturated aldehydes; conjugate addition did not occur (Table 1, entry 7). Addition to ketones did not occur even at higher temperatures. Under the present reaction conditions, no further reduction products were observed. Although it is, as yet, not clear, we propose that an organotin compound ($BrSnCH_2CN$) is formed through the oxidative addition of bromoacetonitrile to tin; and that nucleophilic addition of this species to aldehydes gives the products.

Table 1 Addition of bromoacetonitrile or α-bromoacetophenone to aldehydes

Entry	R	t/h	T/°C	Product	Yield[a] (%)
1	Ph	2	r.t.	**2a**	76
2	p-ClC_6H_4	1.5	r.t.	**2b**	81
3	p-BrC_6H_4	1.5	r.t.	**2c**	83
4	p-MeC_6H_4	2	r.t.	**2d**	68
5	p-CNC_6H_4	2	r.t.	**2e**	78
6	p-$MeOC_6H_4$	2.5	r.t.	**2f**	54
7	PhCH=CH	1.5	r.t.	**2g**	70
8	n-C_7H_{15}	2.5	r.t.	**2h**	43
9	Ph	2	0	**3a**	68
10	p-ClC_6H_4	1.5	0	**3b**	72
11	p-MeC_6H_4	2	0	**3c**	55
12	n-C_7H_{15}	3	−10	**3d**	65

[a] Isolated yields based on aldehydes

During our continuous investigation on the exploration of new synthetic reactions using metallic tin, we also found that the reaction of α-bromoacetophenone with aldehydes gave β-hydroxyketones (Scheme 2).

$$\underset{\mathbf{1}}{\mathrm{RCHO}} + \mathrm{BrCH_2COPh} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{Sn,\ TMSCl,\ THF}} \underset{\mathbf{3}}{\mathrm{RCH(OH)CH_2COPh}}$$

Scheme 2

The reaction took place under similar conditions as the reaction of bromoacetonitrile above. Use of lower temperatures led to higher yield and if TMSCl was not added, the reaction was rather sluggish and also the reduction product acetophenone would be generated. In the presence of TMSCl, this side reaction was reduced and the corresponding aldols were produced with moderate yields.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 683 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL FX-90Q spectrometer with TMS as an internal standard.

Typical Experimental Procedure.—Aldehyde **1** (1 mmol) was added to a mixture of bromoacetonitrile or α-bromoacetophenone (1.2 mmol) and metallic tin (1 mmol) in THF (10 ml) under nitrogen atmosphere. After stirring at 0 °C or room temperature for 10 min, TMSCl (1 mmol) was added. The reaction mixture was stirred at the appropriate temperature for the time listed in Table 1 before a 5% HCl solution was added. The product was extracted several times with diethyl ether. After being dried over anhydrous Na_2SO_4, the solvent was evaporated *in vacuo* and the residue was column chromatographed on silica gel with diethyl ether–light petroleum (bp 30–60 °C) as eluent to yield the corresponding product (**2** or **3**).

3-*Hydroxy*-3-*phenylpropanenitrile* (**2a**). Colorless oil. IR 3385, 3010, 2238, 1540 cm^{-1}. ^1H NMR δ 2.50 (br, 1 H), 2.72 (d, $J = 5.8$ Hz, 2 H), 5.02 (t, $J = 5.8$ Hz, 1 H), 7.33 (s, 5 H).

3-*Hydroxy*-3-(4-*chlorophenyl*)*propanenitrile* (**2b**). Colorless oil. IR 3384, 3022, 2241, 1540 cm^{-1}. ^1H NMR δ 2.42 (br, 1 H), 2.70 (d, $J = 6.0$ Hz, 2 H), 5.10 (t, $J = 6.0$ Hz, 1 H), 7.20 (m, 4 H).

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3-*Hydroxy*-3-(4-*bromophenyl*)*propanenitrile* (**2c**). Colorless oil. IR 3398, 3019, 2243, 1530 cm^{-1}. ^{1}H NMR δ 2.42 (br, 1 H), 2.68 (d, $J = 6.0$ Hz, 2 H), 5.06 (t, $J = 6.0$ Hz, 1 H), 7.25 (m, 4 H).

3-*Hydroxy*-3-(4-*methylphenyl*)*propanenitrile* (**2d**). Colorless oil. IR 3370, 3025, 2235, 1545 cm^{-1}. ^{1}H NMR δ 2.28 (s, 3 H), 2.52 (br, 1 H), 2.73 (d, $J = 5.4$ Hz, 1 H), 5.08 (t, $J =$ Hz, 1 H), 7.35 (m, 4 H).

3-*Hydroxy*-3-(4-*cyanophenyl*)*propanenitrile* (**2e**). Mp 84 °C (lit,[11] 84.5 °C). IR 3430, 3042, 2240, 2225 cm^{-1}. ^{1}H NMR δ 2.32 (br, 1 H), 2.72 (d, $J = 6.2$ Hz, 1 H), 5.15 (t, $J = 6.2$ Hz, 1 H), 7.23 (m, 4 H).

3-*Hydroxy*-3-(4-*methylphenyl*)*propanenitrile* (**2f**). Colorless oil. IR 3402, 3010, 2240, 1523 cm^{-1}. ^{1}H NMR δ 2.36 (br, 1 H), 2.75 (d, $J = 6.0$ Hz, 2 H), 3.68 (s, 3 H), 5.01 (t, $J = 6.0$ Hz, 1 H), 7.22 (m, 4 H).

3-*Hydroxy*-5-*phenylpent*-4-*enenitrile* (**2g**). Colorless oil. IR 3390, 3021, 2235, 1528 cm^{-1}. ^{1}H NMR δ 2.28 (br, 1 H), 2.70 (d, $J = 6.2$ Hz, 2 H), 4.52 (m, 1 H), 6.38 (dd, $J = 6.0$, 15.8 Hz, 1 H), 6.85 (d, $J = 15.8$ Hz, 1 H), 7.40 (m, 5 H).

3-*Hydroxydecanenitrile* (**2h**). Colorless oil. IR 3420, 2935, 2250, 1460 cm^{-1}. ^{1}H NMR δ 0.8–1.38 (m, 15 H), 2.48 (d, $J = 6.0$ Hz, 2 H), 2.65 (br, 1 H), 3.88 (m, 1 H).

3-*Hydroxy*-1,3-*diphenylpropan*-1-*one* (**3a**). Mp 47 °C (lit.,[12] 44–46 °C). IR 3535, 1670, 1210, 750 cm^{-1}. ^{1}H NMR δ 3.35 (d, $J = 6.0$ Hz, 2H), 3.43 (br, 1H), 5.10–5.43 (m, 1H), 7.10–8.00 (m, 10H).

3-*Hydroxy*-3-(4-*chlorophenyl*)-1-*phenylpropan*-1-*one* (**3b**). Mp 96 °C (lit,[12] 96–96.5 °C). IR 3465, 1668, 1210, 752, 685 cm^{-1}. ^{1}H NMR δ 3.32 (d, $J = 5.8$ Hz, 2 H), 3.76 (br, 1 H), 5.12–5.38 (m, 1 H), 7.35 (m, 7 H), 7.86 (m, 2 H).

3-*Hydroxy*-3-(4-*methylphenyl*)-1-*phenylpropan*-1-*one* (**3c**). Mp 46 °C (lit,[12] 47–48 °C). IR 3470, 1685, 1210, 750 cm^{-1}. ^{1}H NMR δ 2.30 (s, 3 H), 3.31 (d, $J = 6.0$ Hz, 2 H), 3.64 (br, 1 H), 5.10–5.40 (m, 1 H), 7.01–7.98 (m, 9 H).

3-*Hydroxy*-1-*phenyldecanone* (**3d**). Mp 47 °C (lit,[13] 48 °C). IR 3425, 1672, 1024, 745 cm^{-1}. ^{1}H NMR δ 0.80–1.38 (m, 15 H), 2.85 (br, 1 H), 3.10 (d, $J = 6.0$ Hz, 2 H), 4.10–4.27 (m, 1 H), 7.20–8.02 (m, 5 H).

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