Zinc-mediated addition of bromoacetonitrile to carbonyl compounds under solvent-free conditions

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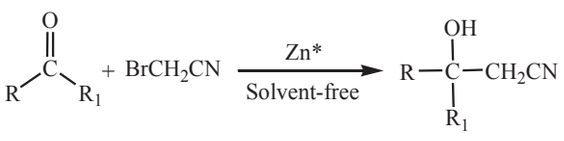
Zinc mediated addition reaction of bromoacetonitrile with aryl aldehydes and ketones produces β-hydroxynitriles under solvent-free conditions. The valuable feature of the methodology are solvent-free and catalyst-free conditions and short reaction times (5 min).

Keywords: zinc, bromoacetonitrile, carbonyl compounds, β-hydroxynitriles, solvent-free conditions

β-Hydroxynitriles are useful building blocks for the synthesis of β-hydroxycarboxylic acids and their derivatives, γ-amino alcohols as well as other important functionalities.[1–3] Typically, β-hydroxynitriles are prepared through the deprotonation of a nitrile followed by addition to an aldehyde or ketone through a nucleophilic attack.[4] The procedure has the disadvantage of being harsh on sensitive acidic functional groups present in the substrate and the facile dehydrations of β-hydroxynitriles usually give the desired products in unsatisfactory yields.[5] To overcome the above problems, the Reformatsky-type reaction is recognised as being a good alternative.[6–8] Some activated metals such as nickel,[9] antimony,[10] tin,[11] indium[12] and SmI_2[13] are reported to promote Reformatsky-carbonyl addition reactions of α-halonitriles. However, there are few examples of satisfactory Reformatsky-type reaction with bromoacetonitriles mediated by zinc. This is due to the relatively low activity and the requirement of strict reaction conditions with zinc. Various methods have been reported to improve the activation of organozinc, such as ultrasound[14,15] and microwave.[16] In our preliminary research, we found that the reactivity of organozinc could be enhanced dramatically in the absence of solvent (THF). We have reported the solvent-free addition reaction of allylzinc bromide and carbonyl compounds.[17] Now we report an efficient addition reaction of bromoacetonitrile with aryl carbonyl compounds mediated by zinc under solvent-free conditions. We found that the reactivity with zinc could be enhanced dramatically in the absence of the solvent THF. The reaction is very fast in all cases with substrates reacting completely in less than 5 min at room temperature.

We now propose that an organozinc compound ($BrZnCH_2CN$) may be formed through the oxidative addition of bromoacetonitrile to zinc, and that nucleophilic addition of this species to carbonyl groups yields the products. The reaction of organozinc reagents always requires strict reaction conditions such as a transition-metal catalyst, N_2 atmosphere, anhydrous solvent, and low temperature. However, our solvent-free reaction is completed in less than 5 min in an open atmosphere at room temperature and does not need any catalyst. The yields are good, and the reaction time is very short. The examples are shown in Scheme 1.



1 **2** **3a-i**

R = C_6H_5, p-F-C_6H_4, p-Cl-C_6H_4, m-CH_3O-C_6H_4, p-CH_3O-C_6H_4, C_6H_5-CH=CH, C_6H_5-CH=C(CH_3), 2-Furyl

R_1 = H, CH_3

Scheme1

Solvent-free conditions play a major role in the reaction. The reaction did not proceed at all in the presence of the solvent THF. The reason is probably that the micro-environment and the higher concentration of reactants in the absence of solvent lead to more favourable kinetics than in solution.

The zinc mediated addition reactions of bromoacetonitrile with a series of aldehydes and ketones under solvent-free conditions are contained in Table 1. The reaction provides good yields in reactions utilising aryl aldehydes and ketones. Aryl aldehydes containing both electron-donating and electron-withdrawing groups in the aromatic rings and heteroaryl aldehydes were found to undergo the conversion smoothly (Table 1, entries 1–5, 8). The corresponding products β-hydroxynitriles were obtained in yields ranging from 74% to 92%. The approach only gave 1, 2-addition for α, β-unsaturated aldehydes, and conjugate addition did not occur (Table 1, entries 6 and 7). Aryl ketones also proceed by a similar reaction, but the yield is lower than with aldehydes. Lower activated aliphatic aldehydes or ketones, unfortunately, did not undergo the addition reactions.

In conclusion, zinc-mediated solvent-free nitrile aldol reaction provides an alternative method for introducing a nitrile into a carbonyl compound. The method here has the following advantages: solvent-free, short reaction time (5 min), mediated by cheap metallic zinc, without another catalyst, adaptability to a wide variety of aryl aldehydes and ketones, high yield and environmentally benign.

Experimental

IR spectra were measured using an Alpha Centauri FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra (400 MHz) were recorded in $CDCl_3$ using a Bruker AC-E 400 MHz spectrometer. HRMS was performed on an APEX II FT-ICR. Purification of products was performed *via* flash chromatography with 200–400 mesh silica gel [petroleum ether (bp 60–90 °C) : ethyl acetate, 10 : 1]. The chemicals were obtained from commercial sources.

Synthesis of **3a–i***; general procedure*

In a dried round-bottom flask fitted with magnetic bar and dropping funnel, zinc powder (0.39 g, 6 mmol) was activated [18] and aromatic aldehydes or ketones (4 mmol) were added. After this step, bromoacetonitrile (5 mmol) was added dropwise over 2 minutes and then the reaction was stirred for 5 minutes at room temperature. After complete conversion, saturated aqueous ammonium chloride was poured into the mixture and the mixture was stirred for 5 minutes. Ethyl ether was added to the reaction mixture and the organic layer was

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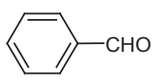
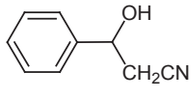
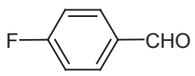
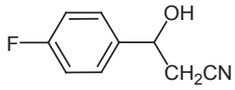
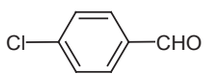
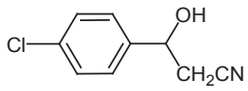
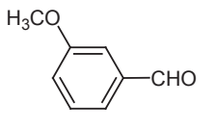
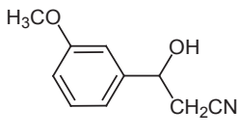
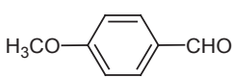
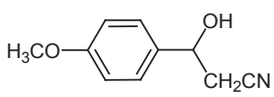
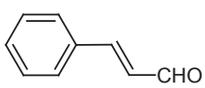
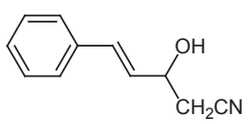
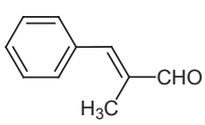
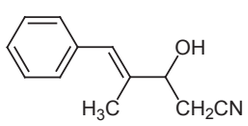
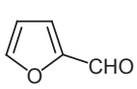
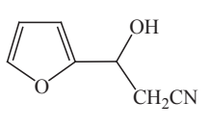
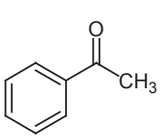
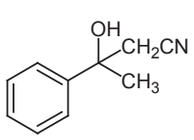
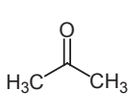
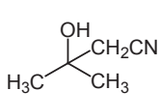
Table 1 Zinc-mediated solvent-free addition reaction of bromoacetonitrile to carbonyl compounds[a]

Entry	Substrate	Product[b]		Yield/%[c]
1			**3a**	85
2			**3b**	92
3			**3c**	88
4			**3d**	74
5			**3e**	83
6			**3f**	74
7			**3g**	76
8			**3h**	71
9			**3i**	62
10			**3j**	0
11	$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2CHCH_2CN$ OH	**3k**	0

[a]Reaction conditions: activated zinc powder (6 mmoL), aldehydes or ketones (4 mmoL), and bromoacetonitrile (5 mmoL) at room temperature for 5 min.
[b]All products were characterised by IR, ^{1}H NMR and ^{13}C NMR.
[c]Isolated yield.

separated. The organic extracts were dried over anhydrous $MgSO_4$. The residue was purified by flash chromatography on silica gel to obtain an oily product. All the isolated products were characterised by IR, ^{1}H NMR and ^{13}C NMR. The physical and spectra data of the compounds **3a–i** are as follows.

3-Hydroxy-3-phenylpropanenitrile (**3a**): Oil,[11,12] IR (υ/cm^{-1}): 3387, 3012, 2245, 1538; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.40–7.26 (m, 5H), 5.04–5.01 (t, J = 6.4 Hz, 1H), 2.76–2.74 (d, 2H), 2.57(br s, 1H, OH) ^{13}C NMR (100 MHz, $CDCl_3$): 140.9, 128.9, 128.8, 125.5, 117.3, 69.9, 27.9.

3-(4-Fluorophenyl)-3-hydroxypropanenitrile (**3b**): Oil,[19] IR (υ/cm^{-1}): 3407, 3025, 2243, 1541; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.38–7.05 (m, 4H), 5.00 (t, J = 6.0 Hz, 1H), 3.15 (br s, 1H, OH), 2.73–2.71(d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.9, 161.5, 136.8, 136.7, 127.4, 127.3, 117.2, 115.8, 115.6, 69.2, 27.9.

3-(4-Chlorophenyl)-3-hydroxypropanenitrile (**3c**): Oil,[11,12,19] IR (υ/cm^{-1}): 3385, 3024, 2241, 1547; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.39–7.26 (m, 4H), 5.05–5.00 (q, J = 6.0 Hz, 1H), 2.79–2.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 134.6, 129.1, 126.9, 117.0, 69.3, 27.9.

3-Hydroxy-3-(3-methoxyphenyl)propanenitrile (**3d**): Oil,[19] IR (υ/cm^{-1}): 3406, 3016, 2233, 1517, 1431; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.32–7.26 (m, 1H), 6.94 (s, 2H), 6.89–6.86 (t, 1H), 4.99–4.97 (t, J = 4.0 Hz, 1H), 3.84–3.79 (t, 3H), 2.80 (br s, 1H, OH), 2.74–2.73(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.9, 142.7, 129.9, 117.7, 117.3, 114.2, 111.1, 69.9, 55.3, 27.9.

3-Hydroxy-3-(4-methoxyphenyl)propanenitrile (**3e**): Oil,[11] IR (υ/cm^{-1}): 3401, 3012, 2243, 1523; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.35–7.26 (m, 2H), 6.94–6.91 (q, 2H), 5.02–4.99 (t, J = 6.4 Hz, 1H), 3.82 (s, 3H), 2.82–

2.71 (m, 2H), 2.32 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): 159.9, 133.1, 126.8, 117.3, 114.3, 69.9, 55.3, 27.9.

3-Hydroxy-5-phenylpent-4-enenitrile (**3f**): Oil,[11,12,19] IR (υ/cm^{-1}): 3398, 3019, 2236, 1529; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.57–7.25 (m, 5H), 6.72–6.84 (d, 1H), 6.26–6.20 (t, 1H), 4.64–4.60(q, J = 5.6 Hz, 1H), 2.73–2.61 (m, 2H), 2.51(br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): 135.5, 132.9, 128.7, 128.4, 127.9, 126.7, 117.2, 68.6, 26.3.

3-Hydroxy-4-methyl-5-phenylpent-4-enenitrile (**3g**): Oil, IR (υ/cm^{-1}): 3402, 3014, 2238, 1526; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.37–7.23 (m, 5H), 6.64 (s, 1H), 4.54–4.53(t, J = 6.0 Hz, 1H), 2.70–2.67 (q, 2H), 2.48 (br s, 1H, OH), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 136.6, 136.4, 128.9, 128.2, 127.6, 127.0, 117.4, 73.2, 24.6, 13.2; HRMS calcd for $C_{12}H_{13}NO[M+H]^+$: 188.1075, found: 188.1079.

3-(Furan-2-yl)-3-hydroxypropanenitrile (**3h**): Oil,[19] IR (υ/cm^{-1}): 3405, 2236, 1612, 1518, 1H NMR (400 MHz, $CDCl_3$, TMS): 7.42–7.40(m, 1H), 6.39–6.36 (m, 2H), 5.05–5.02 (t, J = 6.0 Hz, 1H), 3.13 (br s, 1H, OH), 2.91–2.88 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): 152.8, 142.8, 116.9, 110.5, 107.4, 63.7, 24.8.

3-Hydroxy-3-phenylbutanenitrile (**3i**): Oil,[12] IR (υ/cm^{-1}): 3408, 3027, 2249, 1516; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 7.49–7.26 (m, 5H), 2.87–2.77 (q, 2H), 2.42 (br s, 1H, OH), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.5, 128.7, 127.9, 117.3, 72.4, 33.6, 29.1.

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