An efficient cyanosilylation of aldehydes with trimethylsilyl cyanide catalysed by MgI_2 etherate

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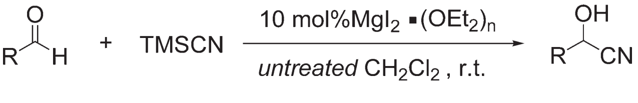
A convenient procedure for the synthesis of cyanohydrins by the addition of trimethylsilyl cyanide to aromatic aldehydes, heteroaromatic aldehydes, aliphatic aldehydes and unsaturated aldehydes catalysed by MgI_2 etherate (MgI_2•$(OEt_2)_n$) in good to excellent yields is described.

Keywords: aldehyde, trimethylsilyl cyanide, cyanohydrins, MgI_2 etherate

Cyanohydrins serve as useful precursors to many important classes of organic compounds (*e.g.*, β-amino alcohols, α-hydroxy aldehydes, and α-hydroxy acids). Consequently, considerable attention has been taken to design efficient methods for their synthesis.[1,2] Among them, the Lewis acid-catalysed cyanosilylation of aldehydes with trimethylsilyl cyanide has been widely used in the construction of the carbon–carbon bond in generating cyanohydrins. Metal halides, such as $AlCl_3$,[3] BF_3,[4] $BiBr_3$,[5] $InBr_3$,[6] $LnCl_3$ (Ln = La, Ce, Sm),[7] $SnCl_4$,[4] $(n\text{-}C_4H_9)_2SnCl_2$ or $(C_6H_5)_2SnCl_2$,[8] $TiCl_4$,[4] ZnI_2,[9] and LiCl[10] are known to be Lewis acid catalysts for the cyanosilylation of aldehydes. Chiral Lewis acid–Lewis base combined catalysts have been successfully applied to the asymmetric reaction.[11,12] However, the traditional methods using Lewis acids such as $AlCl_3$, BF_3•Et_2O and $SnCl_4$ must be carried out under strictly anhydrous conditions, which are difficult to be handled especially on a large scale. Water-tolerant Lewis acids lanthanide triflates are rather expensive. Consequently, the development of less expensive, environmentally benign, and easily handled promoters for the cyanosilylation of aldehydes is still highly desirable.

Due to their abundant, inexpensive and nontoxic character, Lewis acid Mg(II) catalysts have been widely utilised in various organic reactions.[13] In our previous papers,[14,15] we have demonstrated that MgI_2 etherate can efficiently catalyse the allylation of aldehydes with allylstannane and the Clauson–Kass condensation of primary amines with 2,5-dimethoxytetrahydrofuran. In continuation of our research, we now report a simple and efficient procedure for the cyanosilylation of aldehydes with TMSCN catalysed by MgI_2 etherate under mild reaction conditions in good to excellent yields (Scheme 1).



Scheme 1 MgI_2 etherate-catalysed the cyanosilylation of aldehydes with TMSCN.

Results and discussion

We initiated our studies by carrying out the cyanosilylation of benzaldehyde with trimethylsilyl cyanide in the presence of 10 mol% of freshly prepared MgI_2 etherate (1.0 M in Et_2O/benzene 1:2) [16] in untreated CH_2Cl_2 at room temperature. After stirring for 4.0 h, the desired cyanohydrins were obtained in 93% yield. In order to clarify the scope of this reaction, several aldehydes were examined in the presence of 10 mol% MgI_2 etherate. The results were summarised in Table 1. As shown in Table 1, the reaction proceeded smoothly at room temperature and provided good to excellent yields (Table 1, entries 1–9). Of the various aldehydes which were screened, aromatic aldehydes with either electron-donating (Table 1, entries 3–5) or electron-withdrawing groups (Table 1, entries 6–9) afforded the corresponding products in high yields. Moreover, the cyanosilylation of unsaturated aldehydes exclusively provided the 1,2-adduct (Table 1, entry 10). In addition, heteroaromatic aldehydes gave good yields (Table 1, entries 11–13). Aliphatic aldehydes also worked well. It is worth noting that the more sterically hindered pivaldehyde afforded the desired product in good yield. However, electronically deactivated aromatic ketones and aliphatic ketones do not undergo this reaction even after a long time at room temperature (Table 1, entries 16–17) This is due to the lower reactivity of ketones, compared to aldehydes, towards trimethylsilyl cyanide.

The high coordinating ability of the magnesium (II) towards the oxygen atom of the carbonyl moiety is presumably responsible for the effective activation of the aldehydic carbonyl. To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgCl_2$ etherate and $MgBr_2$ etherate were compared under parallel reaction conditions (10 mol % of catalyst) in the cyanosilylation reaction of aryl aldehydes with TMSCN, respectively. $MgCl_2$ etherate and $MgBr_2$ etherate were less effective in terms of substrate conversion yield and gave moderate yields. Apparently, the unique reactivity of MgI_2 etherate is attributed to the dissociative character of iodide counter-ion and a more Lewis acidic cationic $[MgI]^+$ species. All the compounds were characterised by their ^1H NMR spectra and by comparison with known compounds.

In conclusion, we have demonstrated the unique reactivity of MgI_2 etherate in the cyanosilylation of aromatic aldehydes,

Table 1 The cyanosilylation of aldehydes with trimethylsilyl cyanide catalysed by MgI_2•$(OEt_2)_n$[a]

Entry	R	Time/h	Product[b]	Yield/%[c]
1	Ph	4	**1a**	93
2	β-Naphthyl	4	**1b**	94
3	4-MeC_6H_4	5	**1c**	92
4	3-MeC_6H_4	4	**1d**	93
5	4-$MeOC_6H_4$	4	**1e**	93
6	4-$NO_2C_6H_4$	2	**1f**	98
7	4-FC_6H_4	3	**1g**	95
8	2-ClC_6H_4	4	**1h**	94
9	2-BrC_6H_4	4	**1i**	96
10	(*E*)-PhCH=CH	5	**1j**	86
11	2-Furyl	5	**1k**	88
12	3-Me-2-thiophenyl	5	**1l**	83
13	2-Indolyl	4	**1m**	88
14	CH_3CH_2	5	**1n**	90
15	$(CH_3)_3C$	5	**1o**	88
16	4-$NO_2C_6H_4COCH_3$	12	NA[d]	NR[e]
17	Cyclopentanone	12	NA	NR

[a] The reaction was carried out by addition of aldehyde and trimethylsilyl cyanide catalysed by 10 mol% of MgI_2•$(OEt_2)_n$ at room temperature in untreated CH_2Cl_2.
[b] All products were identified by their ^1H NMR spectra.
[c] Yields of products isolated by column chromatography.
[d] NA, Not available.
[e] NR, No reaction.

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heteroaromatic aldehydes, unsaturated aldehydes and aliphatic aldehydes with TMSCN. This catalytic reaction enables the cyanosilylation to be carried out under essentially neutral conditions in untreated CH_2Cl_2 at room temperature in good to excellent yields. Further investigation on the catalytic reactivity of MgI_2 etherate in other C–C bond forming reactions is underway.

Experimental

Silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 °C) were used for product purification by flash column chromatography. ^{1}H NMR spectra were taken on a Bruker AM-500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. The reactions monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. All compounds were identified by ^{1}H NMR and are in good agreement with those reported.

Synthesis of cyanohydrins; typical procedure

A stirred benzaldehyde solution of (5 mmol) in CH_2Cl_2 (20 mL) was treated with freshly prepared MgI_2 etherate (0.5 mmol) at room temperature, followed by the addition of a solution of trimethylsilyl cyanide (6 mmol) in CH_2Cl_2 (10 mL) via a syringe. The resulting reaction mixture was stirred at r.t. for 4.0 h and quenched with saturated $Na_2S_2O_3$ aqueous solution. Extractive workup with CH_2Cl_2 and chromatographic purification of the crude product on silica gel gave the 2-phenyl-2-hydroxyacetonitrile in 93% yield.

2-Phenyl-2-hydroxyacetonitrile (**1a**):[17] Pale yellowish oil, $R_f = 0.36$ (33% EtOAc in petroleum ether), δ_H 4.45 (br s, 1H), 5.48 (s, 1H), 7.42–7.43 (m, 3H), 7.48-50 (m, 2H).

2-Naphthalene-2-hydroxyacetonitrile (**1b**):[18] Pale yellowish oil, $R_f = 0.66$ (33% EtOAc in petroleum ether), δ_H 3.06 (br s, 1H), 6.19 (s, 1H), 7.51–7.54 (m, 1H), 7.57–7.61 (m, 1H), 7.63–7.66 (m, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.94–7.97 (m, 2H), 8.16 (d, J = 8.5 Hz, 1H).

2-(4-Methylphenyl)-2-hydroxyacetonitrile (**1c**):[19] Pale yellowish oil, $R_f = 0.28$ (20% EtOAc in petroleum ether), δ_H 2.39 (s, 3H), 4.38 (br s, 1H), 5.44 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H).

2-(3-Methylphenyl)-2-hydroxyacetonitrile (**1d**):[19] Pale yellowish oil, $R_f = 0.26$ (20% EtOAc in petroleum ether), δ_H 2.41 (s, 3H), 3.26 (br s, 1H), 5.49 (s, 1H), 7.25–7.36 (m, 4H).

2-(4-Methoxyphenyl)-2-hydroxyacetonitrile (**1e**):[20] Yellowish oil, $R_f = 0.14$ (30% EtOAc in petroleum ether), δ_H 3.79 (s, 3H), 5.41 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H).

2-(4-Nitrophenyl)-2-hydroxyacetonitrile (**1f**):[17] Yellowish oil, $R_f = 0.17$ (20% EtOAc in petroleum ether), δ_H 5.71 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 8.32 (d, J = 8.8 Hz, 1H).

2-(4-Fluorophenyl)-2-hydroxyacetonitrile (**1g**):[20] Yellowish oil, $R_f = 0.23$ (20% EtOAc in petroleum ether), δ_H 3.51 (br s, 1H), 5.53 (s, 1H), 7.12–7.16 (m, 2H), 7.50–7.53 (m, 2H).

2-(2-Chlorophenyl)-2-hydroxyacetonitrile (**1h**):[21] Pale yellowish oil, $R_f = 0.41$ (20% EtOAc in petroleum ether), δ_H 4.64 (br s, 1H), 5.83 (s, 1H), 7.31–7.35 (m, 2H), 7.37–7.39 (m, 1H), 7.66–7.70 (m, 1H).

2-(2-Bromophenyl)-2-hydroxyacetonitrile (**1i**):[22] Pale yellowish oil, $R_f = 0.34$ (33% EtOAc in petroleum ether), δ_H 4.24 (br s, 1H), 5.82 (s, 1H), 7.28 (t, J = 1.0 Hz, 1H), 7.41 (t, J = 1.0 Hz, 1H), 7.60 (d, J = 1.0 Hz, 1H), 7.71 (d, J = 1.0 Hz, 1H).

4-Phenyl-2-hydroxy-3-butenenitrile (**1j**):[23] Yellowish oil, $R_f = 0.21$ (20% EtOAc in petroleum ether), δ_H 4.23 (br s, 1H), 5.12 (d, J = 6.0 Hz, 1H), 6.20 (dd, J = 6.0, 16.0 Hz, 1H), 6.83 (d, J = 16.0 Hz, 1H), 7.25–7.40 (m, 5H).

2-Furyl-2-hydroxyacetonitrile (**1k**):[20] Yellowish oil, $R_f = 0.27$ (20% EtOAc in petroleum ether), δ_H 4.60 (br s, 1H), 5.54 (s, 1H), 6.38 (dd, J = 1.8, 3.2 Hz, 1H), 6.61 (dd, J = 1.6, 3.6 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H).

2-(3-Methylthiophene)-2-hydroxyacetonitrile (**1l**):[24] Yellowish oil, $R_f = 0.24$ (20% EtOAc in petroleum ether), δ_H 2.31 (s, 3H), 3.79 (br s, 1H), 5.71 (s, 1H), 6.87 (d, J = 5.0 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H).

2-(2-Indolyl)-2-hydroxyacetonitrile (**1m**):[20] Brownish oil, $R_f = 0.23$ (33% EtOAc in petroleum ether), δ_H 4.43 (br s, 1H), 5.47 (s, 1H), 7.33–7.68 (m, 5H).

2-Hydroxy-butanenitrile (**1n**):[22] Pale yellowish oil, $R_f = 0.18$ (33% EtOAc in petroleum ether), δ_H 1.15 (t, J = 7.5 Hz, 3H), 1.84–1.90 (m, 2H), 4.42 (t, J = 6.6 Hz, 1H).

2-Hydroxy-3,3-dimethylbutanenitrile (**1o**):[18] Pale yellowish oil, $R_f = 0.54$ (33% EtOAc in petroleum ether), δ_H 1.08 (s, 9H), 4.12 (s, 1H).

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