MgI_2 etherate-catalysed Strecker reaction: a facile and efficient synthesis of α-aminonitriles from aldimines and trimethylsilyl cyanide

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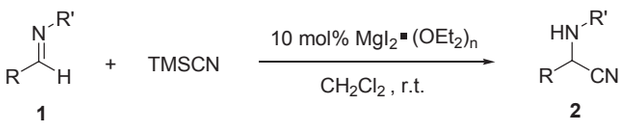
A mild and efficient procedure for the synthesis of α-aminonitriles is achieved by treatment of aldimines with trimethylsilyl cyanide catalysed by MgI_2 etherate.

Keywords: aldimines, trimethylsilyl cyanide, Strecker, MgI_2 etherate

The Strecker synthesis is one of the most atom-economical methods for the synthesis of α-amino acids, and the intermediate α-aminonitriles are also very useful precursors for the synthesis of various nitrogen-containing heterocycles.[1] The first stage of the classical Strecker synthesis is the reaction of KCN with an imine to yield an α-aminonitrile. Several modifications of this nucleophilic addition reaction have been reported using a variety of cyanating agents such as Bu_3SnCN,[2] Et_2AlCN,[3] EtOCOCN,[4] $K_2[Fe(CN)_6]$[5] and $(EtO)_2P(O)CN$.[6] The use of trimethylsilyl cyanide (TMSCN) is a promising alternative cyanation reagent for nucleophilic addition reactions, due to its nature as an effective, easily-handled, relatively safe and one of the simplest and highly soluble cyanide ion sources.

Recently, many methods for the synthesis of α-aminonitriles from imines with TMSCN have been developed in the presence of various Lewis acid catalysts, such as $Fe(CP)_2PF_6$,[7] $RhI_3•H_2O$,[8] Ga $(OTf)_3$,[9] $GaCl_3$,[10] Pr $(OTf)_3$,[11] $NiCl_2$,[12] $RuCl_3$,[13] InI_3,[14] $BiCl_3$,[15] $GdCl_3•H_2O$,[16] Cu $(OTf)_2$,[17] $CeCl_3$[18] and $FeCl_3$.[19] However, the traditional methods using Lewis acids must be carried out under strictly anhydrous conditions, which can be problematical especially if carried out on a large scale. Water-tolerant Lewis acids such as lanthanide triflates are rather expensive. From these viewpoints, the development of less expensive, environmentally benign, and easily handled promoters for cyanation of aldimines is still highly desirable.

MgI_2 etherate is easily prepared, inexpensive and more easily handled than other metal halides such as $InCl_3$, $TiCl_4$ and $SnCl_4$. To the best of our knowledge, there is no report of the use of MgI_2 etherate as a mild catalyst for cyanation. In continuation of our research, we now describe a simple cyanation of aldimines to α-aminonitriles with TMSCN catalysed by MgI_2 etherate under mild reaction conditions in good to excellent yields (Scheme 1).



R = aryl, heteroaryl; R' = alkyl, aryl

Scheme 1

Results and discussion

Initially, we prepared a variety of aldimines derived from aromatic aldehydes and alkyl and aryl-amines. We carried out our initial studies into the cyanation of an aldimine employing the product of condensation of benzaldehyde and aniline, **1a** (R, R' = Ph). When a solution of **1a** (R, R' = Ph) and 10 mol% of MgI_2 etherate in CH_2Cl_2 at room temperature was treated with TMSCN and stirred for 3 h, the desired α-aminonitrile was obtained in 95% yield. Encouraged by these results, a variety of aldimines were subjected to similar reaction conditions. The results are summarised in Table 1. Cyanation of aldimines **1b**, **1c** and **1d**, prepared from benzaldehyde and, respectively, 4-methyl-, 2-methyl and 4-methoxyaniline, produced the corresponding α-aminonitriles **2b**–**d** in nearly quantitative yield (Table 1, entries 2–4). Furthermore, the cyanation of imine **1e**, prepared from benzaldehyde and benzylamine, also worked well and gave the desired product in good yield (Table 1, entry 5). Four aldimines **1f–i**, the products of condensation of aniline with variously substituted benzaldehydes, also gave excellent yields of the corresponding products, **2f–i** (Table 1, entries 6–9). Moreover, the reaction of heteroaryl imines **1j**–**m**, also proceeded in good yields (Table 1, entries 10–13). In addition, the use of benzylamine as the imine component was examined and the cyanation products **2n–o** were obtained in good yields (Table 1, entries 14 and 15). As can be seen, the use of an aromatic amine as the imine component gave, in general, better results than the use of a benzylamine. The reaction of TMSCN with a chiral imine catalysed by MgI_2 etherate was also studied (Table 1, entry 16). The cyanation with a chiral imine employing the *R*-l-phenyl-ethylamine auxiliary afforded **2p** with moderate stereoselection in excellent yield. The procedure could not be applied to ketimines, for it was found that neither (**1**; Me for H; R, R' = Ph) nor (**1**; Me for H; R = 4-$NO_2C_6H_4$, R' = 4-$MeOC_6H_4$) reacted with TMSCN in the presence of MgI_2 etherate.

All but three of the 16 α-aminonitriles that were synthesised were characterised by comparison of melting point, if a solid, and ^1H NMR with literature data. The three new compounds, **2j**, **2k** and **2l** were additionally characterised by HRMS analysis.

To examine the halide anion effect, halogen analogues of MgI_2 etherate, $MgCl_2$ etherate and $MgBr_2$ etherate were compared under similar reaction conditions were found to be less effective. Probably, the greater reactivity of MgI_2 etherate can be attributed to the dissociative character of the iodide counterion and the greater Lewis acidity of the $[MgI]^+$ species.

In conclusion, we have shown for the first time that MgI_2 etherate can be used in the Strecker reaction for the synthesis of α-aminonitriles from aldimines and TMSCN. This catalytic reaction enables cyanation to be carried out under essentially neutral conditions at room temperature in good to excellent yields. The study of asymmetric Strecker reactions catalysed by MgI_2 etherate is on-going in our lab.

Experimental

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 °C) were used. ^1H NMR spectra were taken on a Bruker AM-500 spectrometer with TMS as an internal standard in $CDCl_3$. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. Melting points were measured on a BUCHI B-540 and uncorrected.

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Table 1 Yields of α-aminonitriles **2a–p** from aldimines **1a–p** treated with TMSCN catalysed by 10 mol% MgI_2• $(OEt_2)_n$ [a]

Entry	Aldimine	R	R'	Time/h	Product[b]	Yield/%[c]
1	**1a**	Ph	Ph	3	**2a**	97
2	**1b**	Ph	4-MeC_6H_4	2	**2b**	94
3	**1c**	Ph	2-MeC_6H_4	3	**2c**	99
4	**1d**	Ph	4-$MeOC_6H_4$	1	**2d**	94
5	**1e**	Ph	Bn	4	**2e**	80
6	**1f**	4-$MeOC_6H_4$	Ph	4	**2f**	92
7	**1g**	4-MeC_6H_4	Ph	3	**2g**	99
8	**1h**	4-BrC_6H_4	Ph	2	**2h**	95
9	**1i**	3-$NO_2C_6H_4$	Ph	2	**2i**	94
10	**1j**	2-thiophenyl	4-$MeOC_6H_4$	2	**2j**	85
11	**1k**	2-Thiophenyl	4-FC_6H_4	3	**2k**	83
12	**1l**$_4$	2-Furfuryl	4-Meoc_6h	3	**2l**	87
13	**1m**	4-Methylthiazolyl	4-Meoc_6h_4	3	**2m**	86
14	**1n**	4-BrC_6H_4	Bn	2	**2n**	97
15	**1o**	2-Thiophenyl	Bn	4	**2o**	84
16	**1p**	Ph	*R*-C_6H_4CH (Me)	2	**2p**	86[d] (*dr*=72:28)

[a]The reaction was carried out by addition of TMSCN (0.6 mmol) to aldimine (0.5 mmol) and 10 mol% MgI_2• $(OEt_2)_n$ in CH_2Cl_2 at room temperature.
[b]All products were identified by their ^{1}H NMR spectra.
[c]Yields of products isolated by column chromatography.
[d]The ratio of *dr* value was determined by ^{1}H NMR analysis.

FT-IR spectra were recorded on a Bruker Tensor 27 spectrometer. HRMS were determined on a Waters GCT Premier spectrometer. All starting materials and reagents were purchased from Sigma-Aldrich.

Synthesis of α-aminonitriles; typical procedure

Freshly prepared MgI_2 etherate (0.05 mmol) was added to a stirred solution of benzylideneaniline **1a** (0.5 mmol) in CH_2Cl_2 (5 mL) at room temperature. After stirring for 10 min, a solution of TMSCN (0.6 mmol) was added dropwise *via* a syringe. The resulting homogeneous reaction mixture was stirred at room temperature for 3.0 h and quenched by saturated $NaHCO_3$ aqueous solution. Extractive work-up with ethyl acetate and chromatographic purification of the crude product on silica gel gave the aminonitriles **2a** in 97% yield.

2-Phenyl-2-(phenylamino)acetonitrile (**2a**):[20] White solid, m.p. 74–75 °C [lit.[20] 74–76 °C]; IR (KBr): 3369, 2234, 1604, 1490, 1240, 1120 cm^{-1}; ^{1}H NMR: δ_H 4.27 (d, *J*=8.4 Hz, 1H), 5.46 (d, *J*=8.5 Hz, 1H), 6.83 (d, *J*=7.9 Hz, 2H), 6.97–6.70 (m, 1H), 7.33–7.36 (m, 1H), 7.50–7.51 (m, 3H), 7.63–7.65 (m, 2H).

2-Phenyl-2-(4-methylphenylamino)acetonitrile (**2b**):[21] White solid, m.p. 103–105 °C [lit.[21] 104–106 °C]; IR (KBr): 3375, 2245, 1614, 1590, 1256, 1128 cm^{-1}; ^{1}H NMR: δ_H 3.14 (s, 3H), 3.98 (d, *J*=8.6 Hz, 1H), 5.42 (d, *J*=8.7 Hz, 1H), 6.7 (d, *J*=8.4 Hz, 2H), 7.11 (d, *J*=8.3 Hz, 1H), 7.47–7.48 (m, 3H), 7.61–7.63 (m, 2H).

2-Phenyl-2-(2-methylphenylamino)acetonitrile (**2c**):[22] Light yellow solid, m.p. 71–73 °C [lit.[22] 72–73 °C]; IR (KBr): 3419, 2236, 1615, 1580, 1250, 1127 cm^{-1}; ^{1}H NMR: δ_H 2.26 (s, 3H), 4.18 (d, *J*=8.4 Hz, 1H), 5.55 (d, *J*=8.3 Hz, 1H), 6.97–7.02 (m, 2H), 7.28 (d, *J*=7.5 Hz, 1H), 7.33–7.36 (m, 1H), 7.55–7.59 (m, 3H), 7.74–7.75 (m, 2H).

2-Phenyl-2-(4-methoxyphenylamino)acetonitrile (**2d**):[23] Dark green solid, m.p. 68–70 °C; IR (KBr): 3379, 2224, 1519, 1492, 1240, 1100 cm^{-1}; ^{1}H NMR: δ_H 3.76 (s, 3H), 5.34 (d, *J*=10 Hz, 1H), 6.75–6.76 (m, 2H), 6.84–6.85 (m, 2H), 7.43–7.69 (m, 2H).

*2-Phenyl-2-(benzylamino)acetonitrile (***2e**):[20] Colourless oil, IR (KBr): 3363, 2232, 1612, 1501, 1450, 1260 cm^{-1}; ^{1}H NMR: δ_H 4.02–4.05 (m, 1H), 5.02 (d, *J*=10.0 Hz,1H), 7.07–7.09 (d, *J*=10.0 Hz, 1H), 7.26–7.40 (m, 2H), 7.42–7.45 (m, 3H), 7.52–7.54 (m, 5H).

2-(4-Methoxyphenyl)-2-(phenylamino)acetonitrile (**2f**):[20] Yellow solid, m.p. 70–71 °C [lit.[20] 69–71 °C]; IR (KBr): 3359, 2130, 1504, 1480, 1220, 1150 cm^{-1}; ^{1}H NMR: δ_H 3.85 (s, 3H), 4.04 (d, *J*=8.2 Hz, 1H), 5.37 (d, *J*=8.2 Hz, 1H), 6.79–6.80 (d, *J*=7.9 Hz, 2H), 6.91–6.94 (m, 1H), 6.98 (d, *J*=8.8 Hz, 2H), 7.28–7.31 (m, 2H), 7.52–7.53 (m, 2H).

2-(4-Methylphenyl)-2-(phenylamino)acetonitrile (**2g**):[20] White solid, m.p. 94–95 °C [lit.[20] 95–96 °C]; IR (KBr): 3345, 2213, 1524, 1490, 1140 cm^{-1}; ^{1}H NMR: δ_H 2.44 (s, 3H), 4.07 (d, *J*=8.3 Hz, 1H), 5.40 (d, *J*=8.3 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 2H), 6.92–6.95 (m, 1H), 7.29–7.33 (m, 4H), 7.51 (d, *J*=8.1 Hz, 2H).

2-(4-Bromophenyl)-2-(phenylamino)acetonitrile (**2h**):[20] Light yellow solid, m.p. 86–87 °C [lit.[20] m.p. 87–88 °C]; IR (KBr): 3340, 2234, 1604, 1490, 1240, 1120 cm^{-1}; ^{1}H NMR: δ_H 4.08 (d, *J*=5.0 Hz, 1H), 5.40 (d, *J*=5.0 Hz, 1H), 6.76 (m, 2H), 6.91–6.94 (m, 1H), 7.26–7.29 (m, 3H), 7.47–7.49 (m, 2H), 7.58–7.60 (m, 2H).

2-(3-Nitrophenyl)-2-(phenylamino)acetonitrile (**2i**):[20] Yellow oil; IR (KBr): 3260, 2220, 1600, 1499, 1219 cm^{-1}; ^{1}H NMR: δ_H 4.50 (s, 1H), 5.56 (s, 1H), 6.68–6.70 (m, 1H), 6.78 (dd, *J*=6.0, 7.8 Hz, 3H), 7.26–7.29 (m, 3H), 6.96 (t, *J*=7.5 Hz, 1H), 7.16–7.19 (m, 1H), 7.29 (dd, *J*=7.5, 8.4 Hz, 2H), 7.61 (t, *J*=8.0 Hz, 1H).

2-(Thiophen-2-yl)-2-(4-methoxyphenylamino)acetonitrile (**2j**): Yellow oil; IR 3362, 2349, 1612, 1556, 1491, 1313, 1160 (KBr): cm^{-1}; ^{1}H NMR: δ_H 3.81 (s, 3H), 4.43 (d, *J*=10.0 Hz, 1H), 5.61 (d, *J*=10.0 Hz, 1H), 6.84–6.91 (m, 2H), 6.91–6.93 (m, 2H), 7.09 (dd, *J*=5.0, 10.0 Hz, 1H), 7.38–7.42 (m, 2H). HRMS (EI) calcd for $C_{13}H_{12}N_2OS$: 244.0670, found for $[M]^+$: 244.0653.

2-(Thiophen-2-yl)-2-(4-fluorophenylamino)acetonitrile (**2k**): Yellow oil; IR (KBr): 3364, 2261, 1644, 1590, 1502, 1227, 1151 cm^{-1}; δ_H 4.82 (d, *J*=10 Hz, 1H), 5.71 (d, *J*=5.0 Hz, 1H), 6.97–7.00 (m, 2H), 7.40 (d, *J*=5.0 Hz, 2H), 7.43 (d, *J*=5.0 Hz, 1H), 7.76–7.79 (m, 2H). HRMS (EI) calcd for C12H9FN2S: 232.0470, found for $[M]^+$: 232.0454.

2-(Furan-2-yl)-2-(4-methoxyphenylamino)acetonitrile (**2l**):[24] Brown solid, m.p. 93–95 °C [lit.[23] 94–95 °C]; IR (KBr): 3362, 2251, 1600, 1556, 1490, 1310, 1141 cm^{-1}; ^{1}H NMR: δ_H 3.83 (s, 3H), 5.47 (d, *J*=10.0 Hz, 1H), 6.48 (m, 2H), 6.61 (d, *J*=10.0 Hz, 2H), 6.84 (d, *J*=10.0 Hz, 2H), 6.91 (d, *J*=10.0 Hz, 1H).

2-(4-Methylthiazol-5-yl)-2-(4-methoxyphenylamino)acetonitrile (**2m**): Yellow oil; IR (KBr): 3325, 2249, 1602, 1504, 1440, 1248, 1172 cm^{-1}; ^{1}H NMR: δ_H 2.49 (s, 3H), 3.73 (s, 3H), 5.47 (d, *J*=10.0 Hz, 1H), 6.74–6.82 (m, 4H). HRMS (EI) calcd for $C_{13}H_{13}N_3OS$: 259.0779, found for $[M]^+$: 259.0761.

2-(4-Bromophenyl)-2-(benzylamino)acetonitrile (**2n**):[25] Light yellow oil; IR (KBr): 3332, 2221, 1600, 1503, 1431, 1240, 1212 cm^{-1}; ^{1}H NMR: δ_H 3.95 (d, *J*=15.0 Hz, 2H), 4.80 (s, 1H), 7.26–7.35 (m, 7H), 7.35–7.60 (m, 2H).

2-(Thiophen-2-yl)-2-(benzylamino)acetonitrile (**2o**):[22] Light yellow oil; IR (KBr): 3374, 2251, 1602, 1592, 1502, 1222, 1121 cm^{-1}; ^{1}H NMR: δ_H 3.89 (d, *J*=15.0 Hz, 2H), 5.13 (s, 1H), 7.01–7.09 (m, 2H), 7.32–7.49 (m, 6H).

2-Phenyl-2-((R)-1-phenylethylamino)acetonitrile (**2p**):[26] Colourless oil; IR (KBr): 3360, 2233, 1602, 1500, 1460, 1240 cm^{-1}; ^1H NMR: δ_H 1.43–1.46 (m, 3H), 1.89 (s, 1H), 4.02 (d, J = 10.0 Hz, 1H), 4.72 (s, 1H), 7.36–7.50 (m, 10 H).

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