Monatshefte für Chemie 138, 759–762 (2007)
DOI 10.1007/s00706-007-0675-5
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Lithium Tetrafluoroborate–Catalyzed Solventless Synthesis of α-Aminonitriles

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Received November 3, 2006; accepted March 2, 2007; published online May 31, 2007

Summary. Lithium tetrafluoroborate-catalyzed one-pot, highly efficient, and solvent-free protocol has been developed for the synthesis of α-aminonitriles from aldehydes/ketones, amines, and trimethylsilyl cyanide.

Keywords. Aldehydes; Amines; Trimethylsilyl cyanide; α-Aminonitriles; Lithium tetrafluoroborate.

Introduction

α-Aminonitriles are useful intermediates for the synthesis of aminoacids [1] as well as nitrogen containing heterocycles such as thiadiazoles, imidazoles, *etc.* [2], and they possess a wide range of biological and biochemical properties. As such, they act as enzyme inhibitors, have an effect on the contraction of muscles, are known to inhibit the introduction of gallium into tissues, and are reported to serve as antitumor agents. Some compounds of this class have been proved to be highly effective towards carcinoma and seminoma in clinical experiments and a number of α-aminonitriles do exhibit fungicidal and herbicidal activity [3].

α-Aminonitriles are generally prepared by the nucleophilic addition of cyanide ion to imines (*Strecker* synthesis). Amongst various cyanide ion sources [4] trimethylsilyl cyanide (*TMS*CN) is a safer and more easily handled reagent. The nucleophilic addition of cyanide ion to imines is carried out in the presence of either a base or an acid. However, the use of a *Lewis* acid catalyst is one of the keys to performing this reaction efficiently. Many *Lewis* acid catalysts like the triflates of Sc [5a], Yb [5b], V [5c], and Cu [5d], lithium perchlorate/diethylether [6], iodine [7], and the halides of Ru [8a], Bi [8b], Co [8c], and In [8d] have been successfully used. Quite recently copper triflate [5d] as well as bromodimethylsulfonium bromide [9] have also been reported for the synthesis of α-aminonitriles. However, many *Lewis* acids are prone to undergo decomposition in the presence of nitrogen containing reactants and this sometimes necessitates the use of more than stoichiometric amounts of a *Lewis* acid catalyst [10]. Furthermore, some of these catalysts are expensive [5a–d, 8a, d], toxic [8a, c], need longer reaction time, and are not environmentally benign. Thus, the development of a new, highly rapid, and efficient protocol for the synthesis of α-aminonitriles is desirable.

Lithium tetrafluoroborate is a well-known mild *Lewis* acid catalyst which has received much attention these days. Unlike lithium perchlorate-diethyl ether it is a non-explosive, non oxidizing, as well as non nucleophilic agent and serves as a slow release source of BF_3 [11]. Thus, it provides a convenient procedure to carry out reactions under neutral conditions. It has been used earlier in many organic transformations,

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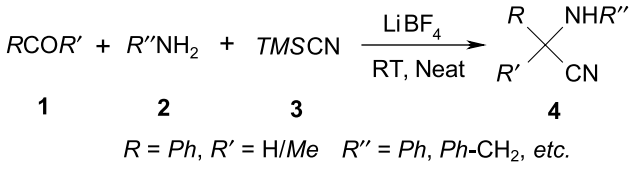

Scheme 1

including the cyanosilylation of ketones [12]. However, to the best of our knowledge it has not been used so far for the synthesis of α-aminonitriles and herein we report the use of lithium tetrafluoroborate as a mild *Lewis* acid catalyst for the synthesis of α-aminonitriles under solvent-free conditions (Scheme 1).

Results and Discussion

A mixture of benzaldehyde (1 equiv.), aniline (1 equiv.), *TMS*CN (1.1 equiv.), and $LiBF_4$ (0.1 equiv.) was stirred at room temperature, when corresponding α-aminonitrile resulted (TLC, IR) in a short reaction time. The structure of the resultant α-aminonitrile was confirmed by spectral studies. The appearance of two singlets in the ^{1}H NMR spectrum at $\delta = 4.03$ and 5.26 ppm clearly indicated the formation of the expected α-aminonitrile **4b**. The reaction conditions were then optimized with respect to the amount of catalyst used, which revealed the non-formation of the desired product in the absence of catalyst and the necessity of 10 mol% catalyst for the completion of the reaction at room temperature. The use of common organic solvents was not found to be beneficial and the best results were obtained under solvent-free conditions.

To explore scope and limitations of the catalyst, the protocol was extended towards a variety of aldehydes including an aliphatic aldehyde (**4a**), aromatic aldehydes possessing electron donating groups (**4c**, **4e**, **4f**, **4j**), acid sensitive aldehydes like cinnamaldehyde (**4l**), furfuraldehyde (**4g**), as well as with a range of amines including aliphatic (**4p**), aromatic, aralkyl (**4h**, **4i**), and a secondary amine like morpholine (**4k**, **4m**). In all these cases, the reactions proceeded satisfactorily to furnish corresponding α-aminonitriles in acceptable yields and purity. The protocol was then extended towards ketones as the source of carbonyl compounds. Interestingly, with acetophenone as well as cyclohexanone, although desired α-aminonitriles were obtained with an aromatic amine, they failed to react with benzyl amine, morpholine, as well as piperidine (**4q**, **4r**, **4s**). The results are summarized in Table 1.

In conclusion we have demonstrated that lithium tetrafluoroborate is a highly efficient catalyst for the synthesis of α-aminonitriles in short time under solvent-free conditions.

Table 1. Lithium tetrafluoroborate-catalyzed synthesis of α-aminonitriles

α-Aminonitriles **4**	Aldehyde/ketone **1**	Amine **2**	Time/min	Yield[a]/%
a	Isobutyraldehyde	Aniline	20	86
b	Benzaldehyde	Aniline	12	90
c	4-Methylbenzaldehyde	Aniline	15	82
d	Benzaldehyde	4-methylaniline	15	87
e	3,4-Dimethoxybenzaldehyde	Aniline	20	79
f	4-Chlorobenzaldehyde	Aniline	10	94
g	2-Furaldehyde	Aniline	15	93
h	Benzaldehyde	Benzylamine	15	91
i	4-Chlorobenzaldehyde	Benzylamine	20	95
j	4-Isopropylbenzaldehyde	Aniline	15	84
k	Benzaldehyde	Morpholine	20	96
l	Cinnamaldehyde	Aniline	20	86
m	4-Chlorobenzaldehyde	Morpholine	20	85
n	Acetophenone	Aniline	20	91
o	Cyclohexanone	Aniline	25	88
p	Benzaldehyde	Isopropyl amine	25	72
q	Acetophenone/cyclohexanone	Benzylamine	NR	–
r	Acetophenone/cyclohexanone	Morpholine	NR	–
s	Acetophenone/cyclohexanone	Piperidine	NR	–

[a] Yields refer to pure, isolated products; NR no reaction

Experimental

All the aldehydes, *TMS*CN, and various amines were obtained from Lancaster or Acros and were used without purification. The melting points reported were recorded on a KUMAR melting point apparatus. IR spectra were recorded on a Perkin Elmer-793 instrument. ^{1}H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively, using *TMS* as an internal standard. Chemical shifts are expressed in δ units.

Representative Procedure

A mixture of 2 mmol benzaldehyde (**2a**), 2 mmol aniline (**2b**), 2.2 mmol *TMS*CN and 20 mg lithium tetrafluoroborate (0.20 mmol) was stirred at room temperature for an appropriate time (Table 1). On completion of the reaction (TLC), 20 cm^3 water were added, and the reaction mixture was extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and ether was removed. The residue obtained was filtered through a short column of silica gel to afford pure α-aminonitrile **4b**, which was characterized by spectral methods.

The spectral data of some of the α-aminonitriles are summarized below.

2-Isopropyl-2-(phenylamino)acetonitrile (**4a**, $C_{11}H_{14}N_2$)
Liquid; IR (neat): $\bar{\nu} = 3419$, 3020, 2227 (weak), 1760, 1513, 1373, 1216, 1009, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.17$ (3H, d, $J = 6$ Hz), 1.18 (3H, d, $J = 6$ Hz), 2.16 (1H, septet, $J = 6$ Hz), 4.03 (1H, d, $J = 6$ Hz), 5.26 (1H, brs, $J = 6$ Hz), 6.69 (2H, d, $J = 8$ Hz), 6.84 (1H, t, $J = 8$ Hz), 7.21 (2H, d, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.32$ (CH_3), 19.24 (CH_3), 31.64 [$CH(CH_3)_2$], 52.47 (CH), 113.95 (CN), 118.42, 119.80, 129.39, 144.93 (Ar–Cs) ppm.

2-Phenyl-2-(phenylamino)acetonitrile (**4b**)
Mp 71–73°C (Ref. [13] 73–74°C); IR (KBr): $\bar{\nu} = 3419$, 3020, 2741, 2237 (weak), 1602, 1503, 1311, 1217, 757, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 4.03$ (1H, d, $J = 6$ Hz), 5.26 (1H, d, $J = 6$ Hz), 6.72 (2H, d, $J = 6$ Hz), 6.86 (1H, t, $J = 6$ Hz), 7.23 (2H, d), 7.41 (3H, brs) 7.56 (2H, brs) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 50.36$ (CH), 114.36 (CN), 117.90, 120.46, 127.30, 129.34, 129.62, 134.35, 144.81 (Ar–Cs) ppm.

2-(4-Methylphenyl)-2-(phenylamino)acetonitrile (**4c**)
Mp 76–78°C (Ref. [13] 76–78°C); IR (KBr): $\bar{\nu} = 3418$, 3020, 2927, 2232 (weak), 1605, 1503, 1216, 1098, 757, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.32$ (3H, s), 3.87 (1H, brs), 5.26 (1H, brs), 6.65 (2H, d, $J = 8$ Hz), 6.79 (1H, t, $J = 8$ Hz), 7.12–7.20 (4H, m), 7.36 (2H, d, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.54$ (CH_3), 50.59 (CH), 114.31 (CN), 118.32, 127.08, 129.11, 129.27, 129.53, 129.88, 133.91, 142.19 (Ar–Cs) ppm.

2-(4-Methylphenylamino)-2-phenylacetonitrile (**4d**, $C_{15}H_{14}N_2$)
Mp 81–83°C; IR (KBr): $\bar{\nu} = 3394$, 3020, 2741, 2232 (weak), 1519, 1215, 759, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.28$ (3H, s), 3.84 (1H, d, $J = 10$ Hz), 5.35 (1H, d, $J = 10$ Hz), 6.66 (2H, d, $J = 8$ Hz), 7.05 (2H, d, $J = 8$ Hz), 7.42 (3H, m), 7.57 (2H, t) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.56$ (CH_3), 50.59 (CH), 114.33 (CN), 118.23, 127.08, 129.10, 129.26, 129.52, 129.87, 133.92, 142.19 (Ar–Cs) ppm.

2-(3,4-Dimethoxyphenyl)-2-(phenylamino)acetonitrile (**4e**, $C_{16}H_{16}N_2O_2$)
Liquid; IR (neat): $\bar{\nu} = 3419$, 3020, 2966, 2236 (weak), 1607, 1504, 1373, 929, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.91$ (1H, s), 3.95 (6H, s), 5.37 (1H, brs), 6.77 (2H, d, $J = 8$ Hz), 6.92 (1H, t, $J = 8$ Hz), 7.06–7.15 (2H, m), 7.26 (1H, d), 7.41 (2H, d, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 49.70$ (CH), 55.80 (OCH_3), 109.86 (CN), 110.98, 113.84, 118.23, 119.44, 119.82, 125.96, 128.86, 129.25, 144.52, 149.45 (Ar–Cs) ppm.

2-(4-Chlorophenyl)-2-(phenylamino)acetonitrile (**4f**)
Mp 109–110°C (Ref. [13] 109–112°C); IR (KBr): $\bar{\nu} = 3369$, 2924, 2854, 2238 (weak), 1603, 1502, 1385, 1218, 1094, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 4.03$ (1H, d, $J = 6$ Hz), 5.33 (1H, d, $J = 6$ Hz), 6.69 (2H, d, $J = 7$ Hz), Hz), 6.87 (1H, t, $J = 7$ Hz), 7.22 (2H, t, $J = 7$ Hz), 7.37 (2H, d, $J = 7$ Hz), 7.48 (2H, d, $J = 7$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 49.60$ (CH), 114.36 (CN), 117.63, 128.61, 129.53, 132.64, 132.58, 135.64, 144.41 (Ar–Cs) ppm.

2-Furyl-2-(phenylamino)acetonitrile (**4g**)
Mp 67–69°C (Ref. [13] 68–70°C); IR (KBr): $\bar{\nu} = 3393$, 3020, 2236 (weak), 1738, 1603, 1523, 1424, 1217, 1018, 770, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 4.13$ (1H, brs), 5.44 (1H, d, $J = 6$ Hz), 6.41 (1H, d, $J = 3$ Hz), 6.57 (1H, d, $J = 4$ Hz), 6.72 (2H, d, $J = 8$ Hz), 6.88 (1H, t, $J = 8$ Hz), 7.25 (2H, t, $J = 8$ Hz), 7.46 (1H, d, $J = 3$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 52.90$ (CH), 114.42 (CN), 105.02, 110.52, 142.10, 152.50 (furan ring Cs), 117.82, 118.65, 129.44, 147.60 (Ar–Cs) ppm.

2-(Benzylamino)-2-phenylacetonitrile (**4h**, $C_{15}H_{14}N_2$)
Liquid; IR (neat): $\bar{\nu} = 3397$, 3020, 2229 (weak), 1661, 1531, 1261, 1216, 1095, 759, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.18$ (1H, brs), 3.94 (2H, AB quartet), 4.71 (1H, s), 7.19–7.82 (10H, m) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 51.90$ (CH), 54.92 (CH_2), 114.75 (CN), 120.36, 127.63, 128.91, 129.36, 131.51, 135.70, 138.50, 142.90 (Ar–Cs) ppm.

2-(Benzylamino)-2-(4-chlorophenyl)acetonitrile (**4i**, $C_{15}H_{13}ClN_2$)
Liquid; IR (neat): $\bar{\nu} = 3401$, 3020, 2229 (weak), 1635, 1553, 1422, 1219, 1994, 772, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.98$ (1H, brs), 3.94 (2H, AB quartet), 4.74 (1H, s), 7.14–7.89 (9H, m) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 48.60$ (CH), 52.10 (CH_2), 117.26 (CN), 127.32, 128.29, 129.16, 129.79, 130.82, 132.16, 134.13, 138.75 (Ar–Cs) ppm.

2-(4-Isopropylphenyl)-2-(phenylamino)acetonitrile (**4j**, $C_{17}H_{18}N_2$)
Liquid; IR (neat): $\bar{\nu} = 3420$, 3020, 2966, 2236 (weak), 1607, 1504, 1373, 1219, 929, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.31$ (6H, d, $J = 8$ Hz), 2.99 (1H, septet, $J = 8$ Hz), 5.41 (1H, s), 6.81

(2H, d, $J = 8$ Hz), 6.93 (1H, t, $J = 8$ Hz), 7.29–7.37 (5H, m), 7.55 (2H, d, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 28.87$ (CH_3), 33.83 [**C**H(CH_3)$_2$], 49.79 (CH), 113.87 (CN), 118.23, 119.86, 127.10, 127.15, 129.31, 131.08, 144.55, 150.18 (Ar–Cs) ppm.

2-(Morpholino)-2-phenylacetonitrile (**4k**)
Mp 69–71°C (Ref. [8a] 69–71°C); ^{1}H NMR ($CDCl_3$): $\delta = 2.50$–2.65 (4H, m), 3.60–3.80 (4H, m), 4.81 (1H, s), 7.30–7.70 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 50.22$ (CH), 61.80 ($2 \times$ N–CH_2), 66.38 ($2 \times$ O–CH_2), 114.92 (CN), 128.24, 129.63, 130.10, 132.90 (Ar–Cs) ppm.

2-Cinnamyl-2-(phenylamino)acetonitrile (**4l**)
Mp 114–116°C (Ref. [13] 117–119°C), IR (KBr): $\bar{\nu} = 3419$, 3019, 2232 (weak), 1602, 1501, 1217, 928, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.86$ (1H, brs), 5.33 (1H, s), 6.74 (2H, d, $J =$ 8 Hz), 6.93 (1H, dd, $J = 16$, 2 Hz), 7.21–7.50 (10H, m) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 47.72$ (CH), 114.24 (CN), 117.56, 120.23, 120.81, 1226.80, 128.70, 129.45, 130.15, 133.178, 134.90, 144.27 (=CH, Ar–Cs) ppm.

2-Phenyl-2-(phenylamino)propionitrile (**4n**, $C_{15}H_{14}N_2$)
Mp 146–148°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.98$ (3H, s), 4.3 (1H, bs), 6.7 (2H, d, $J = 8$ Hz), 6.79 (1H, t, $J = 8$ Hz), 7.15 (2H, t, $J = 8$ Hz), 7.38 (3H, m), 7.62 (2H, d, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.38$ (CH_3), 57.07 (C–CH_3), 115.58 (CN), 119.76, 120.61, 124.71, 128.41, 128.85, 129.07, 139.71, 143.30 (Ar–Cs) ppm.

2-Cyclohexyl-2-(phenylamino)acetonitrile (**4o**, $C_{13}H_{16}N_2$)
^{1}H NMR ($CDCl_3$): $\delta = 1.28$–1.36 (1H, bs), 1.60–1.74 (6H, m), 1.76–1.82 (2H, m), 2.28–2.38 (2H, m), 6.86–6.96 (3H, m, $J = 8$ Hz), 7.4 (2H, t, $J = 8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 22.22$ (CH_2), 24.88 (CH_2), 36.57 (CH_2), 54.32 (C–NH), 117.35 (CN), 120.34, 121.08, 129.03, 143.35 (Ar–Cs) ppm.

2-(Isopropylamino)-2-phenylacetonitrile (**4p**, $C_{11}H_{14}N_2$)
^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (6H, d, $J = 7$ Hz), 3.27 (1H, m), 4.64 (1H, s), 7.30–7.50 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ 20.82 (CH_3), 21.70 (CH_3), 47.52 [CH(CH_3)$_2$], 52.63 (CH), 119.43 (CN), 127.81, 129.31, 129.43, 136.10 (Ar–Cs) ppm.

Acknowledgements

One of the authors (*UVD*) thanks UGC, New Delhi for financial assistance [F.30-72/2004(SR)]. *TST* and *SDM* thank UGC authorities for the research Fellowships.

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