Boric acid catalysed synthesis of α-aminonitriles by a three-component reaction at room temperature

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A simple, efficient, and cost-effective method has been developed for the one-pot, three-component condensation reaction of trimethylsilyl cyanide, aldehydes and aromatic amines using boric acid as a heterogeneous solid acid catalyst, under solvent-free conditions. α-Aminonitriles were synthesised relatively quickly in good yields at room temperature.

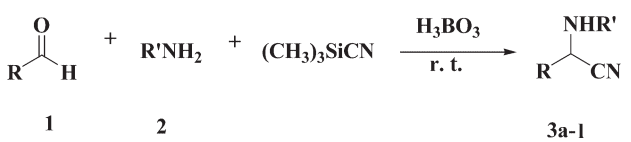
Keywords: α-aminonitriles, boric acid, trimethylsilyl cyanide, solvent-free conditions

α-Aminonitriles are not only versatile intermediates for the synthesis of α-amino acids,[1] and various nitrogen containing heterocycles,[2,3] such as imidazoles and thiadiazoles but also show a valuable dual reactivity, which has a wide range of synthetic applications.[4] In addition, the α-aminonitrile moiety has been found to occur in saframycin A, a natural product with anti-tumour activity, and in phtalascidin, a synthetic analogue, which exhibits even greater potency.[5] The Strecker reaction,[6] provides one of the most important methods for the synthesis of α-aminonitriles. Numerous modifications have been made to the original Strecker reaction, using a variety of cyanating agents such as hydrogen cyanide, sodium or potassium cyanide, Bu_3SnCN, bis(dialkylamino)cyanobora nes, diethylphosphorocyanidate, and trimethylsilyl cyanide (TMSCN).[7–11] TMSCN is a safer, more effective, and more easily handled anion source compared to others. The efficiency of the reaction has been increased by the use of various catalysts.[7–19]

However, these methodologies show varying degrees of success as well as limitations due to the use of toxic organic solvents, expensive catalysts, prolonged reaction times, and the requirement for special apparatus, or harsh reaction conditions. Thus, there is a need for an alternative route for the production of α-aminonitriles, which overcomes these limitations.

Following our systematic studies directed towards the development of practical, safe, and environmentally-friendly procedures for one-pot multi-component reactions,[20–23] we have developed the first procedure for a boric acid promoted reaction of aldehydes, amines, and TMSCN leading to the synthesis of α-aminonitriles under solvent-free conditions at room temperature (Scheme 1).

Boric acid (H_3BO_3) is a useful and environmentally-benign catalyst which can effectively promote organic reactions such as the aza-Michael addition,[24] the Mannich reaction,[25] and the synthesis of alkylidene bisamides.[26] It has been utilised by our group for the synthesis of dibenzoxanthenes,[20] α-aminophosphonates,[21] and dihydroquinazolinones.[22] It offers milder conditions relative to common mineral acids. Boric acid is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture. Hence, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst for the synthesis of α-aminonitriles.



1 **2** **3a-l**

Scheme 1

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To optimise the reaction conditions, treatment of benzaldehyde and aniline with TMSCN was used as a model reaction. Reactions under different conditions and with various molar ratios of substrates in the presence of boric acid revealed that boric acid gave the corresponding α-aminonitrile in 88% yield in 10 min under solvent-free conditions at room temperature.

To show the generality of the present method the optimised system was utilised for the synthesis of other α-aminonitrile derivatives. Various examples illustrating this novel and general method for the synthesis of α-aminonitriles are summarised in Table 1.

Various functionalities present in the aryl aldehydes, such as chloro, fluoro and methyl groups as well as arylamines such as chloro, bromo and methylaniline were tolerated under these conditions at room temperature (Table 1).

The catalytic system also worked well with aliphatic aldehydes to generate the corresponding products with good yields (entries 11 and 12, Table 1). Even with an α,β-unsaturated aldehyde, a good yield of the desired product (80%) was obtained without the formation of other side products (Table 1, entry 12).

To illustrate the need of boric acid for these reactions an experiment was conducted in the absence of boric acid. The yield in this case was about 10% after 1 hour. Obviously, the boric acid is an important component of the reaction.

All products were identified by ^{1}H NMR, ^{13}C NMR and IR spectroscopic methods and the results were confirmed by comparison with those available in the literature. Table 2 compares the features of the previously reported procedures with those of the present methodology for the reaction of benzaldehyde, aniline and trimethylsilyl cyanide.

In conclusion this paper describes a convenient and efficient process for the synthesis of α-aminonitriles by a one-pot reaction of trimethylsilyl cyanide, aldehydes and aromatic amines in the presence of boric acid at room temperature under solvent-free conditions. This method offers some advantages in terms of simplicity of performance, short reaction times, solvent-free condition, low cost, and it follows along the line of green chemistry. The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture.

Experimental

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. IR spectra were run on a Shimadzu IR spectroscopy. The ^{1}H and ^{13}C NMR was run on Bruker Avance 300 (300 MHz). Melting points were recorded on an Electrothermal type 9100 melting point apparatus in open capillary tubes and are uncorrected.

Synthesis of α-aminonitriles **3a–l**; *general procedure*

A mixture of the aldehyde (2 mmol), boric acid (0.2 g), amine (2.4 mmol) and trimethylsilyl cyanide (2.4 mmol) was stirred at room temperature for the appropriate time indicated in Table 1.

Table 1 Synthesis of α-aminonitriles using boric acid as catalyst

Entry	R	R′	Product	Time/min	Yield/%	M.p. /°C	Lit. M.p./°C
1	Ph	Ph	**3a**	10	88	80–82	80–82[7]
2	4-FC_6H_4	Ph	**3b**	15	85	98–100	98–100[9]
3	4-ClC_6H_4	Ph	**3c**	10	85	110–112	109–112[12]
4	2,4-$Cl_2C_6H_3$	Ph	**3d**	20	70	117–119	115–117[7]
5	4-$CH_3C_6H_4$	Ph	**3e**	10	82	76–77	76–78[12]
6	Ph	4-BrC_6H_4	**3f**	15	75	90–93	91–93[7]
7	Ph	3,4-$(CH_3)_2C_6H_3$	**3g**	15	85	92–94	92–94[7]
8	Ph	2-$CH_3C_6H_4$	**3h**	15	90	70–72	72–73[12]
9	4-ClC_6H_4	4-$CH_3C_6H_4$	**3i**	25	82	84–86	84–85[11]
10	4-FC_6H_4	2-ClC_6H_4	**3j**	15	75	96–98	95–97[12]
11	$CH_3(CH_2)_8$	Ph	**3k**	30	77	Oil	Oil[12]
12	*trans*-PhCH=CH	Ph	**3l**	30	80	117–119	117–119[18]

Table 2 Comparison of efficiency of various catalysts in the synthesis of α-aminonitriles[a]

Conditions	Time/h	Yield/%	Ref.
Silica-based scandium (III) interphase	14	94	8
Montmorillonite KSF, CH_2Cl_2	3.5	90	12
$BiCl_3$, CH_3CN	10	84	13
Silica sulfuric acid, CH_2Cl_2	6	88	14
$NiCl_2$, CH_3CN	12	92	15
$RhCl_3.3H_2O$, CH_3CN	1	86	16
[bmim][ClO_4]	0.5	86	17
H_3BO_3	10 min	88	This work

[a] Times and yields refer to the reaction of benzaldehyde, aniline and TMSCN.

The progress of reactions was monitored by TLC (ethyl acetate/n-hexane=1/6). After completion of the reaction, the reaction mixture was diluted with water and extracted with chloroform, dried over Na_2SO_4, and the solvents were removed under reduced pressure to give, in many cases, the pure α-aminonitrile. In some cases, the residue was purified by short column chromatography on silica gel eluting with ethyl acetate/n-hexane to afford pure products.

2-(N-Anilino)-2-phenylacetonitrile (**3a**): Pale yellow crystalline solid; ^{1}H NMR(300 MHz, $CDCl_3$) δ 3.96 (br, 1H), 5.36 (s, 1H), 6.72 (d, *J* = 7.3 Hz, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 2H), 7.41–7.49 (m, 3H, ArH),7.55–7.61 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 50.3, 114.2, 118.2, 120.3, 127.3, 129.3, 129.5, 129.6, 134.0, 144.7; IR (neat) υ 3336, 3028, 2930, 2236, 1598, 1514, 1445, 1282, 1155, 996, 752 cm^{-1}.

2-(N-Anilino)-2-(4-chlorophenyl)acetonitrile (**3c**): White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (br, 1H), 5.36 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.88 (t, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.4, 135.4, 132.4, 129.5, 129.4, 128.5, 120.4, 117.9, 114.3, 49.5; IR (KBr,): υ 3405, 2927, 2239, 1600, 1515, 1457, 1272, 1161, 1098, 791 cm^{-1}.

2-(N-Anilino)-2-(4-methylphenyl)acetonitrile (**3e**): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 4.15 (d, *J* = 8.0 Hz, 1H), 5.40 (d, *J* = 8.0 Hz, 1H), 6.81–6.95 (m, 3H), 7.28–7.35 (m, 4H), 7.51 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.7, 139.3, 130.9, 129.8, 129.4 , 127.0, 119.9, 118.3, 114.0, 49.7, 21.0; IR (KBr): υ 3306, 2923, 2851, 2225, 1691, 1575, 1462, 1216, 1141, 1017, 940, 765 cm^{-1}.

2-(N-4-Bromoanilino)-2-phenylacetonitrile (**3f**): Pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (br, 1H), 5.33 (s, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 7.28–7.54 (m, 7H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.6, 133.4, 132.2, 129.5, 129.3, 127.1, 117.9, 115.7, 112.1, 50.0; IR (neat): υ 3348, 3021, 2236 cm^{-1}.

2-(N-2-Methylanilino)-2-phenylacetonitrile (**3h**): Pale yellow solid; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 3.83 (br, 1H), 5.45 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.2Hz, 2H), 7.40–7.50 (m, 3H), 7.50 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 143.4, 134.7, 131.3, 130.0, 129.8, 127.9, 127.7, 124.1, 120.4, 118.9, 112.2, 50.7, 17.8; IR (KBr): υ 3365, 2935, 2857, 2237, 1605, 1517, 1461, 1275, 1035, 791 cm^{-1}.

2-(N-2-Chloroanilino)-2-(4-fluorophenyl)acetonitrile (**3j**): White crystalline solid; ^{1}H NMR ($CDCl_3$): δ 4.66 (d, *J* = 8.1 Hz, 1H), 5.45 (d, *J* = 8.1 Hz, 1H), 6.91–6.95 (m, 2H), 7.15–7.35 (m, 4H), 7.59–7.69 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.3, 136.0, 135.5, 132.4, 130.0, 129.8, 128.5, 127.7, 120.5, 117.8, 114.2, 49.5; IR (KBr): υ 3410, 2931, 2230, 1610, 1520, 1461, 1269, 1051, 790 cm^{-1}.

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