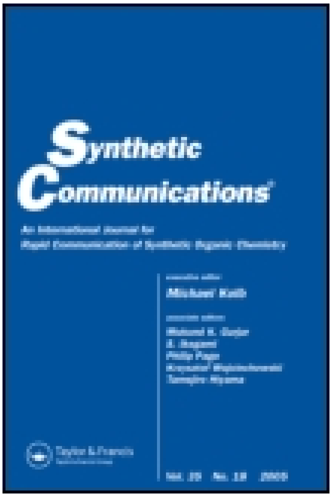

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LiBr: A Mild Lewis Acid Catalyst for Efficient One-Pot Synthesis of α-Amino Nitriles

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Abstract: α-Amino nitriles are synthesized in a one-pot, three-component coupling of aldehydes, amines, and trimethylsilyl cyanide using a catalytic amount of LiBr at ambient temperature.

Keywords: LiBr, Strecker nitriles, trimethylsilyl cyanide

The addition of cyanide to imine is the most common strategy to prepare α-amino nitriles, which serve as important synthons in synthetic organic chemistry. Because of their wide range of applications, these compounds have received a great deal of attention in recent years in connection with their synthesis. Because alkali cyanides are well-known poisons and they also produce highly alkaline reaction conditions that are not tolerated in many cases, particularly when conjugated aldehydes are used,[1] and instead solvolyzed by-products are produced, clearly some improvements were necessary. Therefore, to overcome these problems, some alternative cyanide transferring agents have been used such as diethyl phosphorocyanidate,[2] α-trimethylsiloxy nitriles,[3] acetone cyanohydrin,[4] and trimethylsilyl cyanide (TMSCN).[5] Out of these nonalkali metal cyanide variants, trimethylsilyl cyanide has emerged as the most useful, safest, and more effective cyanide source for nucleophilic addition to carbon-oxygen or carbon–nitrogen double bonds. It is worth mentioning here that in aprotic solvents, it almost produces neutral conditions. Invariably on mixing aldehyde and amine, Schiff's bases are produced, which are

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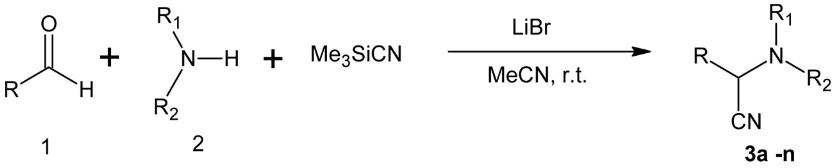


Scheme 1.

used in situ, and TMSCN addition occurs. Evidently this process requires polarization of the C = N bond to facilitate nucleophilic attack of cyanide from TMSCN, and this is achieved by using a suitable Lewis acid and other additives.[6] Several of these already reported methods suffer from drawbacks such as expensive catalyst systems, long reaction times, harsh reaction conditions, low product yields and so on. Moreover, the use of strong acids such as H_2SO_4 frequently leads to the formation of undesirable side products during aqueous workup, which in turn decrease the yield of desired products. Therefore, there is still need to search for a mild, inexpensive, and ecofriendly catalyst for the synthesis of α-amino nitriles. We and others[7] have been using LiBr as a mild Lewis acid in many chemical transformations, including Biginelli condensation, Ehrlich–Sachs reaction, Friedel–Crafts reaction, and preparation of acylals and xanthenes. In most of these reported reactions, LiBr is almost neutral[8] and also does not form any corrosive or harsh by-products during aqueous workup, unlike strong and expensive catalysts. Herein, we report the catalytic use of mild Lewis acid LiBr in an one-pot coupling of aldehydes, amines, and trimethylsilyl cyanide at room temperature leading to a synthesis of α-amino nitriles (Scheme 1). In a typical case, benzaldehyde (2 mmol), aniline (2 mmol), trimethylsilyl cyanide (2 mmol), and LiBr (0.2 mmol, 10 mol%) were stirred in acetonitrile (15 mL) at room temperature for 50 min to afford α-amino nitrile in 92% yield. Similarly, other aldehydes and amines were reacted with trimethylsilyl cyanide at room temperature using a catalytic amount of LiBr to obtain corresponding α-amino nitriles in 75–92% yields.

A variety of aromatic, conjugated, and heterocyclic aldehydes have been reacted with amines and TMSCN at room temperature to obtain α-amino nitriles (Table 1). Secondary amines such as morpholine, piperidine, and pyrrolidine have also been employed along with aromatic amines. The reaction completes within 50–85 min, and 10 mol% of catalyst is enough to facilitate the reaction to completion. The use of a large amount of catalyst did not improve the yields or reduce the reaction time. When the reaction is conducted without the addition of LiBr, there was no significant formation of α-amino nitriles even after several hours.

Table 1. LiBr-mediated synthesis of α-amino nitriles

Compound[a]	Aldehyde	Amine	Time (min)	Yield (%)[b]
3a	Benzaldehyde	Aniline	50	92
3b	4-Methylbenzaldehyde	Aniline	55	90
3c	4-Methylbenzaldehyde	Benzyl amine	55	86
3d	Benzaldehyde	4-chloroaniline	50	84
3e	Benzaldehyde	4-Anisidine	65	89
3f	Benzaldehyde	Benzyl amine	70	92
3g	4-Methylbenzaldehyde	4-Chloroaniline	55	82
3h	4-Methoxybenzaldehyde	Aniline	60	80
3i	Cinnamaldehyde	Aniline	80	83
3j	Furfural	Benzyl amine	85	78
3k	Benzaldehyde	Pyrrolidine	75	76
3l	Benzaldehyde	Morpholine	70	84
3m	Cinnamaldehyde	Piperidine	80	79
3n	Cinnamaldehyde	Morpholine	85	75

[a] The products were characterized by comparison of their melting points and spectral (IR, ^{1}H NMR) data with those of authentic samples.

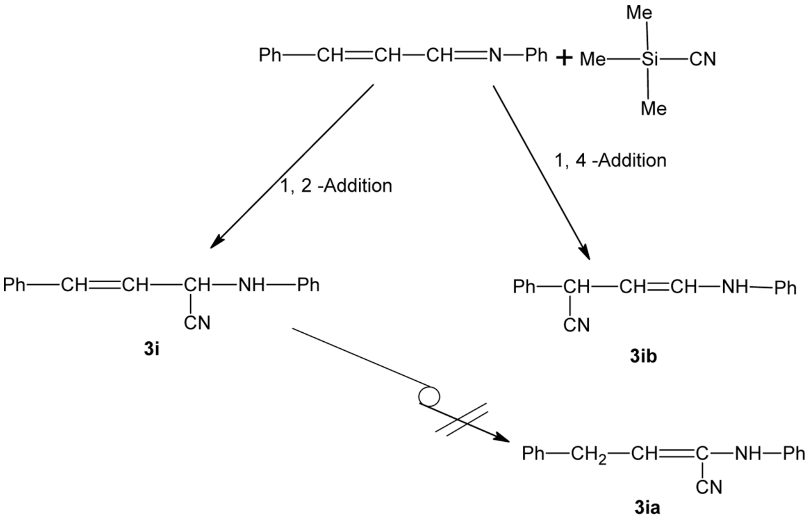
[b] Isolated yields after recrystallization.

Further utility and superiority of the present protocol is demonstrated using conjugated aldehydes, where no double bond migration **3ia** is observed (4); rather normal nitriles **3i, m,** and **n** are obtained (Scheme 2). These results are in contrast to previous reports where the double bond migrates to conjugate with cyanide.[9] It is worth mentioning here that in conjugated systems, the double bond migrates if nitriles are heated for a few minutes or allowed to stand at room temperature in solution for a long time. We also did not observe the formation of 1,4-addition products **3ib**.[10]

In conclusion, the present protocol employing a catalytic amount of LiBr is an efficient, mild, and one-pot strategy for the preparation of α-amino nitriles. The time required is less, and products are obtained in excellent yields. The present procedure is fairly general as a number of aromatic, conjugated, and heterocyclic aldehydes are coupled with primary, secondary, and aromatic amines and trimethylsilyl cyanide at room temperature.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from a commercial source and used without further purification. IR spectra were recorded in KBr discs on a Perkin-Elmer 240 C analyzer. ^{1}H NMR spectra were recorded on



Scheme 2.

Varian Gemini 300 (300-MHz) spectrometer using TMS as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

General Procedure for Preparation of α-Amino Nitriles

To a stirred solution of aldehyde (2 mmol), amine (2 mmol), and trimethylsilyl cyanide (2 mmol) in acetonitrile (15 mL) at room temperature, anhydrous LiBr (10 mol%) was added. The resulting solution was stirred for the time indicated in Table 1. After completion of the reaction (TLC), the excess of acetonitrile evaporated under reduced pressure. Residue was extracted with diethyl ether (3 × 20 mL). The organic layer was washed with saturated solution of $NaHCO_3$ (2 × 20 ml) and brine, then dried over anhydrous Na_2SO_4. Evaporation of solvent gave a crude product, which was purified by recrystallization with benzene–pet. ether mixture to afford α-amino nitriles.

Representative Spectral Data

2-(*N*-Anilino)-2-Phenylacetonitrile (**3a**)

Mp 72–73°C IR (KBr): 3340, 2240 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$ (m, 2H), 7.30 (t, 3H), 7.25 (t, $J = 7.9$ Hz, 2H), 6.92 (t, $J = 7.6$ Hz, Hz, 1H), 6.72 (d, $J = 7.9$ Hz, 2H), 5.39 (s, 1H), 4.03 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.7$, 136.5, 130.4, 129.9, 128.8, 128.2, 127.2, 122.7, 117.2, 51.2.

2-(*N*-Anilino)-2-(4-Methylphenyl)acetonitrile (**3b**)

IR (KBr): 3345, 2242 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J = 8.0$ Hz, 2H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.25–7.35 (m, 2H), 7.12 (t, $J = 7.9$ Hz, 1H), 6.92 (t, $J = 8.0$ Hz, 2H), 5.45 (s, 1H) 4.02 (br s, 1H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 142.3$, 137.7, 134.3, 129.8, 129.2, 128.4, 123.4, 120.3, 118.1, 112.2, 50.6.

2-Phenyl-2-(*N*-Pyrrolidino)acetonitrile (**3k**)

Colorless oil. IR (KBr): 2229 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$–7.42 (m, 2H), 7.40–7.29 (m, 3H), 4.48 (s, 1H), 2.72–2.60 (m, 4H), 1.90–1.69 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 135.6$, 129.6, 129.1, 128.3, 117.8, 110.4, 60.3 52.3.

2-(*N*-Morpholino)-2-Phenylacetonitrile (**3l**)

Mp 68–70°C IR (KBr): 2232 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.29 (m, 5H), 4.78 (t, $J = 4.5$ Hz, 4H), 2.57 (t, $J = 4.5$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 133.2$, 130.7, 129.5, 129.2, 128.5, 116.5, 72.2, 62.3 53.4.

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