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Short communication

Lanthanum(III) nitrate hexahydrate or gadolinium(III) chloride hexahydrate catalyzed one-pot synthesis of α-amino nitriles☆

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Abstract

A simple, convenient and general method has been developed for the synthesis of α-aminonitriles by a one-pot three component condensation of aldehydes, amines and trimethyl silyl cyanide in acetonitrile in the presence of a catalytic amount of $La(NO_3)_3{\cdot}6H_2O$ or $GdCl_3{\cdot}6H_2O$.

Keywords: Aldehyde; Amine; Trimethylsilyl cyanide; Lanthanum nitrate hexahydrate; Gadolinium chloride; α-Aminonitriles

1. Introduction

The addition of cyanide anion to imines (the Strecker reaction) [1] provides one of the most important and straight forward method for the synthesis of α-aminonitriles, which are useful intermediates for the synthesis of amino acids [2] and nitrogen containing heterocycles such as thiadiazoles and imidazoles, etc. [3]. The classical Strecker reaction usually carried out in aqueous solution and the work-up procedure is also tedious. Thus several modifications of Strecker reaction have been reported using a variety of cyanide reagents [4], such as diethyl phosphorocyanidate and α-trimethlysiloxy nitriles, as well as catalysts [5] such as $InCl_3$, $BiCl_3$, montmorillonite KSF clay, $Sc(OTf)_3$, bromodimethyl sulfonium bromide under various reaction conditions. The use of trimethylsilyl cyanide is a safer and more effective cyanide anion source for the nucleophillic addition reactions of imines under mild conditions [6]. However, many of these methods involve the use of expensive reagents, harsh conditions, extended reaction times, and also require tedious work-up leading to the generation of a large amount of toxic waste. Further more many of these catalysts are deactivated or sometimes decomposed by amines and water that exist during imine formation. In order to overcome these problems recently one-pot procedures have been developed for this transformation [5c,d,e,f].

In continuation of our work to develop new catalysts for organic transformations [7], here we report mild, efficient and environmentally benign two catalysts [8] for the preparation of α-aminonitriles from carbonyl compounds, amines and trimethylsilyl cyanide in presence of $La(NO_3)_3{\cdot}6H_2O$ or $GdCl_3{\cdot}6H_2O$ in acetonitrile at room temperature (Scheme 1).

In a typical general procedure, a mixture of aldehyde, amine and trimethylsilyl cyanide in acetonitrile was stirred in presence of $La(NO_3)_3{\cdot}6H_2O$ or $GdCl_3{\cdot}6H_2O$. The reaction proceeded smoothly at room temperature to afford the corresponding α-aminonitrile in high yields. The reaction was monitered by TLC. After completion of reaction acetonitrile was removed and extracted into ethyl acetate (3×10 mL). The crude extract was purified on a silica gel column using EtOAc:hexane (1:9) as eluent to afford pure α-aminonitrile. Similarly a variety of aldehydes were coupled with various amines and trimethylsilyl cyanide in a one-pot operation by this method to produce α-aminonitriles in 90–96% yields. The plausible mechanism of the reaction is given in Scheme 2.

The results are summarized in Table 1. It was found that various aldehydes, in general, including aromatic, aliphatic, conjugated and heterocyclic units participates readily in this procedure. Similarly aromatic, aliphatic primary amines and cyclic secondary amines like morpholine are readily coupled. The longer reaction times for aliphatic amines can be attributed

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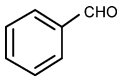
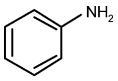
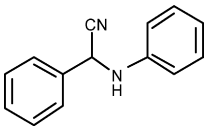
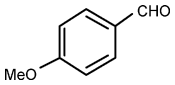
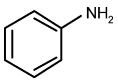
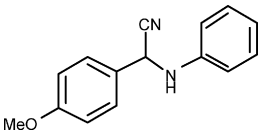
Table 1
$La(NO_3)_3 \cdot 6H_2O$ or $GdCl_3 \cdot 6H_2O$ catalyzed synthesis of α-aminonitriles with TMSCN

Entry	Aldehyde	Amine	Product[a]	Catalyst[b]	Time (h)	Yield[c] (%)
1				i	1	96
				ii	1	94
2				i	1	98
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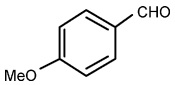
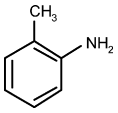
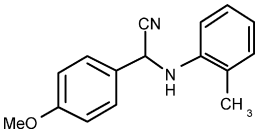
3				i	1	94
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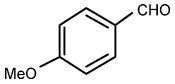
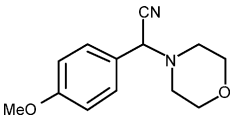
4				i	3	72
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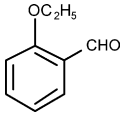
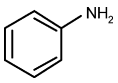
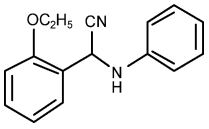
5				i	1	96
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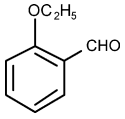
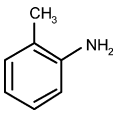
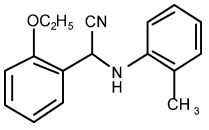
6				i	1	94
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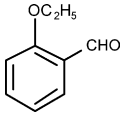
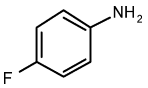
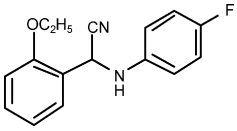
7				i	1	94
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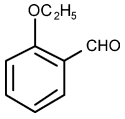
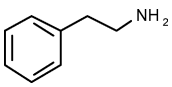
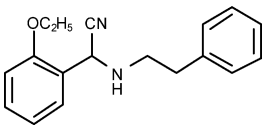
8				i	2.5	78
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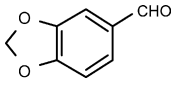
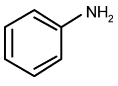
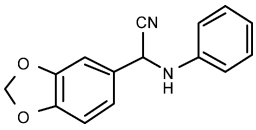
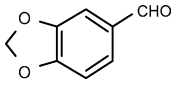
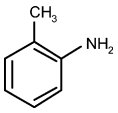
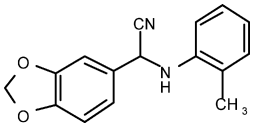
9				i	1	98
				ii	1	96
10				i	1	98
				ii	1	95

Table 1 (*Continued*)

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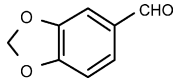
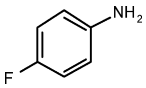
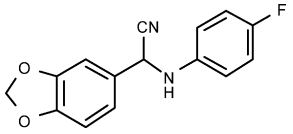
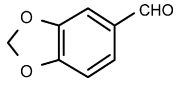
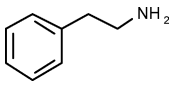
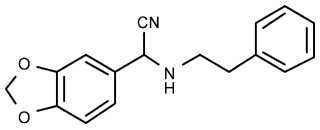
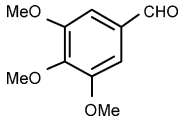
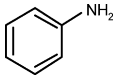
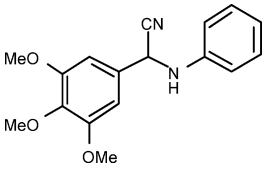
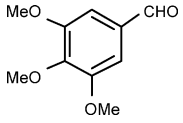
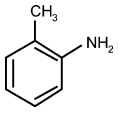
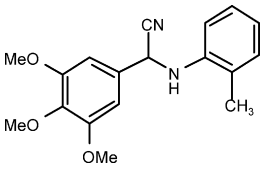
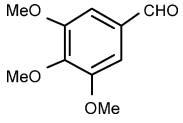
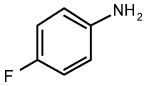
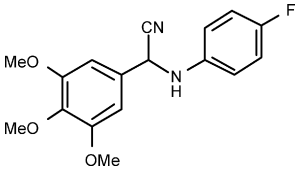
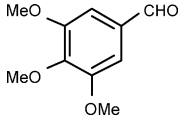
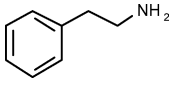
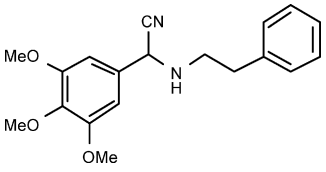
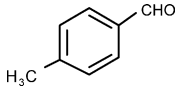
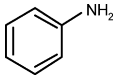
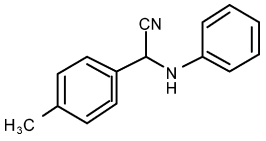
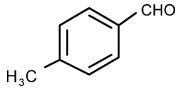
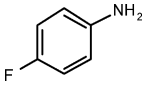
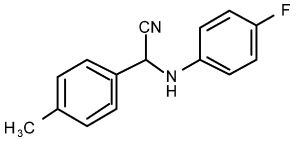
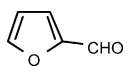
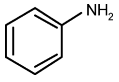
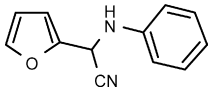
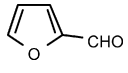
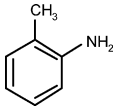
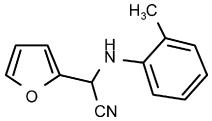
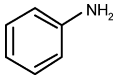
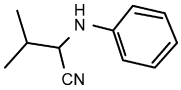
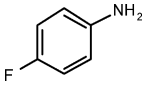
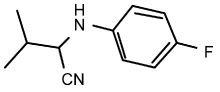
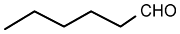
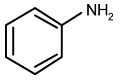
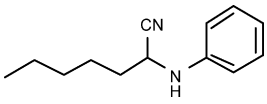
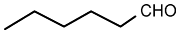
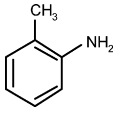
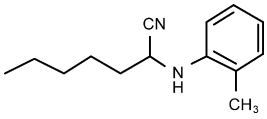
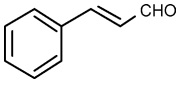
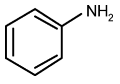
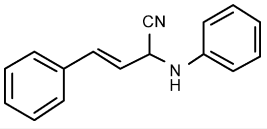
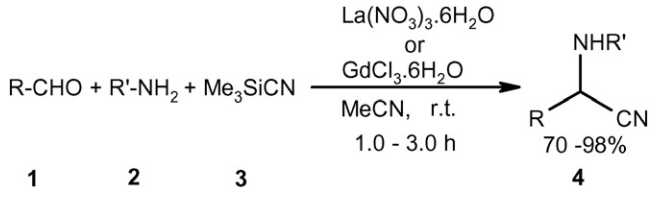
11				i ii	1 1	96 94
12				i ii	2.5 2.5	78 76
13				i ii	1 1	98 95
14				i ii	1 1	96 94
15				i ii	1 1	96 95
16				i ii	2.5 2.5	75 72
17				i ii	1 1	93 92
18				i ii	1 1	92 90
19				i ii	1 1	94 93
20				i ii	1 1	94 91

Table 1 (*Continued*)

Entry	Aldehyde	Amine	Product[a]	Catalyst[b]	Time (h)	Yield[c] (%)
21				i ii	1 1	92 90
22				i ii	1 1	92 88
23				i ii	1 1	90 88
24				i ii	1 1	94 90
25				i ii	1 1	94 92

[a] All products were characterized by m.p., ^{1}H NMR and mass spectral data.
[b] Catalyst: i, $La(NO_3)_3{\cdot}6H_2O$; ii, $GdCl_3{\cdot}6H_2O$.
[c] Yields refer to pure isolated products after chromatography.



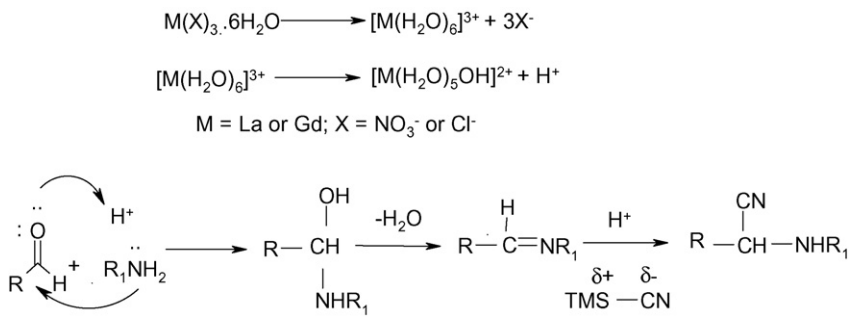
Scheme 1.

due to the stability of the intermediate imines. The amount of catalyst has been optimized to 10 mmol%; however, lesser amount (5 mmol%) would also work with longer reaction times. Further, the ketones did not yield any product under these reaction conditions. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields in a short reaction time. No undesired side product (such as cyanohydrin trimethylsilyl ether, an adduct between the aldehyde and trimethylsilyl cyanide) was observed because of the rapid formation of the imine intermediate.

In conclusion that the present procedure using lanthanum(III) nitrate hexahydrate or gadolinium(III) chloride hexahydrate provides an efficient synthesis of α-aminonitriles by a one-pot three component coupling of carbonyl compound, amine and TMSCN. The salient features of this methodology are: general applicability to different types of aldehydes and amines, using cheap and commercially available reagents, short reaction times, and high yields of products. Finally this report provides environmentally benign chemical processes.

2. Experimental

General procedure for the preparation of α-aminonitriles. To a mixture of benzaldehyde (1 mmol), aniline (1 mmol) and



Scheme 2.

TMSCN (1.2 mmol) in acetonitrile (5 mL) was stirred in presence of lanthanum nitrate or gadolinium chloride (10 mmol%) at room temperature for 1 h. After completion of reaction, as monitered by TLC, the solvent was evaporated; water was added and extracted into ethyl acetate (3×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude adduct was purified on silica gel column eluting with ethyl acetate, hexane (1:9) to afford the pure desired α-aminonitrile (96% yield).

The spectral (^{1}H NMR and MS) data of some selected compounds are given below:

2-(N-anilino)-2-(4-methoxyphenyl)acetonitrile (***4.2***, *entry 2*). Colourless crystal (98%); m.p. 61–63 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.3$ Hz, 2H), 7.21 (m, 2H), 6.92 (d, $J = 9.1$ Hz, 3H), 6.84 (m, 1H) 6.72 (d, $J = 9.1$ Hz, 2H), 5.32 (d, $J = 8.3$ Hz, 1H), 3.98 (broad s, 1H), 3.78 (s, 3H); EIMS: *m/z* 238 (M^+).

2-(N-o-toloudino)-2-(2-ethoxyphenyl)acetonitrile (***4.6***, *entry 6*). Yellow crystal (96%); m.p. 69–72 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22–7.44 (m, 4H), 6.85–6.98 (m, 4H), 5.42 (d, $J = 8.9$Hz, 1H), 4.20 (broad s, 1H), 4.12 (m, 2H), 2.12 (s, 3H), 1.48 (t, 3H); EIMS: *m/z* 266 (M^+).

2-(N-2-phenyl ethyl amino)-2-piperonylacetonitrile (***4.12***, *entry 12*). Yellow crystal (94%); m.p. 83–86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22–7.44 (m, 5H), 6.82–6.88 (m, 3H), 5.94 (s, 2H), 4.62 (s, 1H), 3.18 (broad s, 1H), 2.98 (m, 2H), 2.82 (m, 2H), EIMS: *m/z* 280 (M^+).

2-(N-4-flouro anilino)-2-(3,4,5-trimethoxyphenyl)acetonitrile (***4.15***, *entry 15*). Yellow solid (94%); m.p. 75–77°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.08 (m, 2H), 6.82 (s, 2H), 6.64 (m, 2H), 5.30 (d, $J = 6.8$Hz, 1H), 3.98 (broad s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), EIMS: *m/z* 316 (M^+).

2-(N-4-fluoro anilino)-2-isopropylacetonitrile (***4.22***, *entry 22*). Brown solid (96%); m.p. 53–56 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.85 (m, 2H), 6.64 (m, 2H), 3.92 (s, 1H), 3.68 (broad s, 1H), 2.26 (m, 1H), 1.20 (dd, 6H); EIMS: *m/z* 192 (M^+).

Acknowledgements

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