# $FeCl_3$: Highly Efficient Catalyst for Synthesis of α-Amino Nitriles

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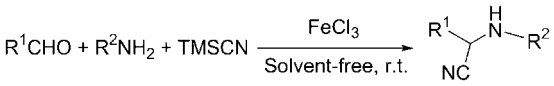
α-Amino nitriles are synthesized by the three-component coupling reaction of aldehydes, amines and trimethylsilyl cyanide using $FeCl_3$ as a solid acid catalyst, under solvent-free conditions in good yields. The catalyst was recovered by simple filtration and was recycled in subsequent reactions.

**Keywords** one-pot, $FeCl_3$, trimethyl silyl cyanide, α-aminonitriles

## Introduction

α-Amino nitriles, are important precursors in the synthesis of natural and unnatural α-amino acids, various nitrogen-containing heterocycles[1] and other biologically useful molecules such as saframycin A.[2] The Strecker reaction, discovered in 1850,[3] has been recognized as the first multicomponent reaction[4] published ever and has a central importance to the life sciences.[5] The three-component coupling of an amine, a carbonyl compound (generally an aldehyde) and either hydrogen cyanide or its alkaline metal cyanides to give α-aminonitriles[6] constitutes an important indirect route in the synthesis of α-amino acids.[7] Some of the Strecker methodologies rely on the use of toxic cyanide derivatives involving harsh reaction conditions, which poses problems to be addressed, particularly when large-scale applications are considered. In order to avoid partially this inconvenience, acetone cyanohydrin, diethylaluminium cyanide, TMSCN, *etc*. have been introduced as cyanide sources in the Strecker reaction, wherein TMSCN is a promising alternative, simplest, safe, easy to handle, most soluble and more effective cyanide ion source for the nucleophilic addition reactions. Many of the Strecker reactions involve the use of expensive reagents, harsh conditions, extended reaction time, and also require tedious workup leading to the generation of a large amount of toxic waste. In order to overcome these problems recently one-pot procedures have been developed for this transformation.[8] In continuation of our work to develop new catalysts for organic transformations,[9] here we report a mild, efficient and environmentally benign method for the preparation of α-aminonitriles from aldehydes, amines and trimethylsilyl cyanide in the presence of $FeCl_3$ as a safe catalyst under solvent-free condition at room temperature (Scheme 1).

**Scheme 1**




## Results and discussion

$FeCl_3$ is an efficient catalyst in modern organic synthesis.[10] It has become the focus of attention in several environmentally friendly and atom-economical organic transformations. Recent reports on $FeCl_3$ catalyzed arylation of benzyl alcohols and benzyl carboxylates,[11] and hydroarylation of styrenes,[12] have highlighted the applications of $FeCl_3$ in organic synthesis. In this contribution, we disclose a simple and practical synthesis of α-aminonitriles catalyzed by $FeCl_3$. Mild reaction conditions and environmentally friendly catalyst make this transformation an attractive option for the straightforward preparation of these compounds. The reaction of aldehydes and amines with TMSCN in the presence of a catalytic amount of $FeCl_3$ (5 mmol%) afforded the corresponding α-aminonitriles under solvent free condition in good yields (Scheme 1, Table 1). The reaction is successful using amines with a variety of aldehydes but not ketones. These three-component coupling reactions proceeded efficiently at room temperature with high selectivity. No cyanohydrin trimethylsilyl ethers (an adduct between an aldehyde and trimethylsilyl cynide) were obtained under these reaction conditions. This is because of the rapid formation and activation of the imines by $FeCl_3$. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields in a relatively short reaction time. This method is equally effective with aldehydes bearing electron withdrawing substituents in the aromatic ring. However, we found that the reaction did not proceed with aliphatic aldehydes.

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**Table 1** Synthesis of $\alpha$-amino nitriles in the presence of $FeCl_3$ as a catalyst

| Entry | 1 | 2 | Product | m.p./℃ | | Time/min | Yield[a]/% |
|---|---|---|---|---|---|---|---|
| | | | | Observed | Found | | |
| 1 | Benzaldehyde | Aniline | **4a** | 75 | 73—74[13] | 15 | 78 |
| 2 | Benzaldehyde | Benzyl amine | **4b** | Oil | oil[14] | 15 | 75 |
| 3 | 4-Methoxybenzaldehyde | Aniline | **4c** | 92—93 | 94—95[13] | 15 | 75 |
| 4 | 4-Methoxybenzaldehyde | Benzyl amine | **4d** | Oil | Oil[15] | 15 | 74 |
| 5 | 4-Methylbenzaldehyde | Aniline | **4e** | 74—76 | 76—78[13] | 15 | 74 |
| 6 | 4-Methylbenzaldehyde | Benzyl amine | **4f** | Oil | Oil[15] | 15 | 74 |
| 7 | 4-Chlorobenzaldehyde | Aniline | **4g** | 110 | 109—112[13] | 10 | 80 |
| 8 | 4-Chlorobenzaldehyde | Benzyl amine | **4h** | Oil | Oil[15] | 10 | 81 |

[a] Yields of isolated products.

The amount of catalyst has been optimized to 5 mmol%; however, lesser amount (3 mmol%) would also work with longer reaction time. This method does not require any additives or stringent reaction conditions to proceed.

The synthesis of $\alpha$-amino nitriles was carried out using various common solvents such as $CCl_4$, acetonitrile, methanol, ethylacetate and THF. With using $FeCl_3$ as a catalyst, the highest yield of products was obtained under solvent-free condition. In addition, the time required for completion of the reaction was found to be less in this condition (Table 2).

**Table 2** Synthesis of **4a** with $FeCl_3$ in the presence of different solvent

| Entry | Solvent | Time/min | Yield[a]/% |
|---|---|---|---|
| 1 | $CCl_4$ | 25 | 60 |
| 2 | Acetonitrile | 20 | 67 |
| 3 | Methanol | 20 | 65 |
| 4 | Ethylacetate | 20 | 66 |
| 5 | THF | 20 | 71 |
| 6 | Solvent-free | 15 | 78 |

[a] Yield of isolated products.

Next, we investigated the reusability of $FeCl_3$. At the end of the reaction, the catalyst could be recovered by a simple filtration, washed with methanol and subjected to a second run of the reaction process. To assure that the catalysts were not dissolved in dichloromethane, they were weighed after filteration and before use and reused for the next reaction. The results show that these catalysts are not soluble in dichloromethane.

In Table 3, the comparison of efficiency of $FeCl_3$ in synthesis of **4a** after five times is reported. As shown in Table 3 the first reaction using recovered $FeCl_3$ afforded a similar yield to that obtained in the first run. In the second, third, fourth and fifth runs, the yields were gradually decreased.

In summary, the mild reaction conditions, experimental simplicity, low cost, excellent yield, and the environmentally benign nature are major advantages of this new approach. Some highly toxic and expensive reagents can be avoided. We expected that this green complimentary method would provide a general application in organic synthesis.

**Table 3** Reuse of the $FeCl_3$ for synthesis of **4a**[a]

| Entry | Time/h | Yield[a]/% |
|---|---|---|
| 1 | 1.5 | 78 |
| 2 | 2.0 | 73 |
| 3 | 3.0 | 70 |
| 4 | 4.0 | 68 |
| 5 | 4.5 | 68 |

[a] Isolated yields.

## Experimental

All products are known compounds and were characterized by m.p., IR, $^1$H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. $^1$H NMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions.

### General procedure for the synthesis of $\alpha$-amino nitriles

A mixture of aldehyde (1 mmol), amine (1 mmol), trimethylsilyl cyanide (1 mmol) and $FeCl_3$ (5 mmol%) was stirred vigorously at room temperature for the indicated time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloromethane (10 mL×3), then the solvent was evaporated. The residue was recrystallized from ethanol to give the pure product.

  

### Selected physical data

**4a**: m.p. 75 ℃; IR (KBr) *v*: 3360, 3025, 2950, 2230, 1600, 1500, 1460, 1315, 1140, 995, 750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 4.1 (s, 1H, NH), 5.4 (s, 1H), 6.5—6.8 (m, 5H), 7.1—7.8 (m, 5H); GC/MS (*m*/*z*): 208 ($M^+$).

**4b**: Colorless oil; IR (KBr) *v*: 3400, 2930, 2230, 1650, 1514, 1400, 1108, 1028, 920, 825, 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 1.80 (s, 1H, NH), 3.90 (q, $J$=13.0 Hz, 2H), 4.85 (s, 1H), 6.85 (d, $J$=8.0 Hz, 1H), 7.15 (t, $J$=7.8 Hz, 1H), 7.25—7.40 (m, 6H), 7.45—7.51 (m, 2H); GC/MS (*m*/*z*): 222 ($M^+$).

**4c**: m.p. 92—93 ℃; IR (KBr) *v*: 3380, 3060, 2930, 2240, 1600, 1500, 1455, 1290, 1116,1040, 929, 760; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$: 3.80 (s, 3H), 4.1 (d, $J$=8.1 Hz, 1H), 5.30 (d, $J$=8.1 Hz, 1H), 6.50 (d, $J$=8.1 Hz, 2H), 6.80 (t, $J$=7.9 Hz, 1H), 7.05 (d, $J$=8.0 Hz, 2H), 7.25 (t, $J$=7.9 Hz, 2H), 7.50 (d, $J$=8.0 Hz, 2H); GC/MS (*m*/*z*): 238 ($M^+$).

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