

# GaCl<sub>3</sub> CATALYZED EFFICIENT ONE POT SYNTHESIS OF $\alpha$ -AMINO NITRILES

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## ABSTRACT

*$\alpha$ -Amino nitriles are synthesized in a one pot three component coupling of aldehydes, amines and trimethylsilyl cyanide using catalytic amount of GaCl<sub>3</sub> at ambient temperature.*

**Key words:** Strecker nitriles, gallium(III) chloride, trimethylsilyl cyanide.

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## INTRODUCTION

Strecker reaction<sup>1</sup> is an important reaction of organic chemistry yielding valuable synthons  $\alpha$ -amino nitriles which are of great importance to synthetic chemists. They occupy a unique position in organic syntheses as they are starting materials for several amino acids,<sup>2</sup> a variety of nitrogen heterocycles like thiadiazoles,<sup>3</sup> imidazoles<sup>4</sup> and other biologically significant molecules like saframycin A.<sup>5</sup> Over and above all these applications in heterocyclic preparations, discovery of Bruylants reaction<sup>6</sup> placed these nitriles at very prestigious position as they are also used as starting materials for the synthesis of a group of short-acting opioid analgetics.<sup>7</sup> Conventional Strecker reaction employed KCN as cyanide source in aqueous solution which had several drawbacks like high toxicity of KCN and produced highly alkaline reaction mixture which severely affected substrates and thus limited the scope of this reaction. These limitations and importance of this reaction in organic synthesis, several variants as cyanide source were investigated, some of these are; diethyl phosphorocyanidate,<sup>8</sup>  $\alpha$ -trimethylsilyloxy nitriles,<sup>9</sup> acetone cyanohydrin<sup>10</sup> and trimethylsilyl cyanide<sup>11</sup> etc. Out of these non-alkali metal cyanide variants trimethylsilyl cyanide has emerged as most useful as well as safer and more effective cyanide source and to facilitate its addition to carbon-nitrogen double bonds in Schiff bases, acids like H<sub>2</sub>SO<sub>4</sub> and its derivatives SiO<sub>2</sub>:H<sub>2</sub>SO<sub>4</sub>,<sup>12a</sup> NH<sub>2</sub>SO<sub>3</sub>H<sup>12b</sup> were used. Also use of Lewis acids such as Zn halides,<sup>12c</sup> InCl<sub>3</sub>,<sup>12d</sup> La(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O or GdCl<sub>3</sub>.6H<sub>2</sub>O<sup>12e</sup> in this reaction have been reported. Because of certain limitations and drawbacks in already reported additives *viz.* some of them are very strong acid/ hazardous and some are expensive, further exploration are of current interest in finding more convenient protocol. We and others<sup>13</sup> have been investigating the use of gallium and its salts in many chemical transformations including selective protection of aldehydes, Biginelli, Reformatsky, Pechmann, Grignard and Barbier reactions. These successful applications and several advantage of gallium(III) halides as mild Lewis acids prompted authors to explore its use in Strecker reaction which has not been explored earlier and this is subject of present communication. In continuation to our studies on gallium and its salts in organic synthesis<sup>13a,13b</sup> and to provide facile and efficient process, we report the use of gallium(III) chloride, a mild Lewis acid catalyst in one pot synthesis of  $\alpha$ -amino nitriles using aldehydes, amines and trimethylsilyl cyanide at room temperature (Scheme 1).

## EXPERIMENTAL

**General Remarks:** Melting points were determined in open capillaries and were compared with authentic samples.  $^1\text{H}$  NMR spectra were recorded in FT-NMR-AL300 spectrometer using tetramethylsilane (TMS) as internal standard. IR spectra were obtained with a Perkin-Elmer 237B infra red spectrometer.  $\text{GaCl}_3$  used was commercial grade and used without further purification.

**General procedure for the synthesis of  $\alpha$ -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 was added anhydrous  $\text{GaCl}_3$  (5 mol%). Stirred the resulting solution for time indicated in Table 1. After completion of reaction (vide TLC), evaporated excess of acetonitrile under reduced pressure. Extracted residue with diethyl ether (3 x 20 mL). Washed organic layer with saturated solution of  $\text{NaHCO}_3$  (2 x 20 ml), brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Evaporation of solvent gave crude product which was purified by recrystallization with benzene:pet. ether mixture to affords  $\alpha$ -amino nitriles.

### Representative spectral data:

Phenyl(phenylamino)acetonitrile (**3a**): M.p. 72-73 °C, Lit<sup>12</sup> M.p. 72-73 °C; IR (KBr): 3340, 2240.  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.51-7.39 (m, 3H), 7.30 (t,  $J$  = 7.9 Hz, 2H), 7.02 (t,  $J$  = 7.9 Hz, 1H), 6.92 (d,  $J$  = 7.9 Hz, 2H), 6.72 (d,  $J$  = 7.9 Hz, 2H), 5.39 (s, 1H), 4.03 (br s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 146.7, 136.5, 130.4, 129.9, 128.8, 128.2, 127.2, 122.7, 117.2, 51.2.

(4-chlorophenyl)(phenylamino)acetonitrile (**3d**): M.p. 109-111 °C, Lit<sup>12</sup> M.p. 109-112 °C; IR (KBr): 3351, 2239.  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.55 (d,  $J$  = 7.8 Hz, 2H), 7.40 (d,  $J$  = 8.1 Hz, 2H), 7.16 (t,  $J$  = 7.9 Hz, 2H), 7.01 (t,  $J$  = 8.1 Hz, 1H), 6.69 (d,  $J$  = 7.8 Hz, 2H), 5.40 (s, 1H) 4.10 (br s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 145.2, 136.2, 133.2, 130.1, 129.3, 128.3, 122.2, 119.2, 115.2, 113.8, 52.2.

(benzylamino)(phenyl)acetonitrile (**3h**): Colorless oil.<sup>12</sup> IR (KBr): 3319, 2235.  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.54-7.44 (m, 2H), 7.39-7.30 (m, 6H), 7.20 (t,  $J$  = 7.9 Hz, 1H), 6.90 (d,  $J$  = 7.9 Hz, 1H), 4.81 (s, 1H), 3.94 (AB, q,  $J$  = 13.4 Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 140.2, 139.2, 137.9, 136.2, 135.2, 130.2, 129.5, 128.7, 127.9, 116.4, 51.8.

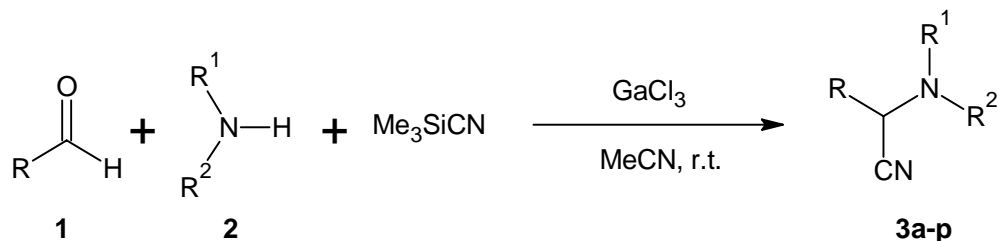
Morpholin-4-yl(phenyl)acetonitrile (**3n**): M.p. 68-70 °C, Lit<sup>12</sup> M.p. 68-70 °C; IR (KBr): 2232.  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.48-7.29 (m, 5H), 4.82 (s, 1H), 4.78 (t,  $J$  = 4.5 Hz, 4H), 2.57 (t,  $J$  = 4.5 Hz, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 133.2, 130.7, 129.5, 129.2, 128.5, 116.5, 72.2, 62.3 53.4.

## RESULTS AND DISCUSSION

In initial experiments, equimolar amount of benzaldehyde, aniline and trimethylsilyl cyanide in presence of anhydrous  $\text{GaCl}_3$  in acetonitrile were stirred at room temperature for 30 minutes to afford 2-(*N*-anilino)-2-phenylacetonitrile **3a** in 95 % yield.

Similarly other aldehydes were coupled with a variety of amines and trimethylsilyl cyanide in presence of catalytic amount of  $\text{GaCl}_3$  to furnish racemic  $\alpha$ -amino nitriles **3b-3p** in 80-96 % yields (Table 1). A variety of aromatic, conjugated and heterocyclic aldehydes have been reacted with amines and TMS-CN at room temperature to obtain  $\alpha$ -amino nitriles (Table 1). Secondary amines such as morpholine, piperidine, pyrrolidine have also been employed along with aromatic

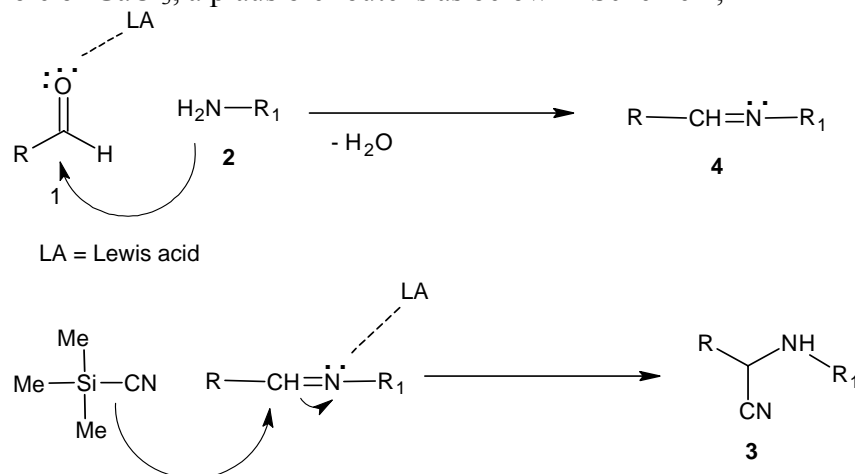
amines. When the present procedure was extended to ketones it was not fairly good as formation of intermediate Schiff's base from hindered carbonyl compound is very slow.



### Scheme-1

The reaction completes within 30-50 minutes and 5 mol % of catalyst is enough to facilitate the reaction to completion. The use of large amount of catalyst did not improve the yields or reduce the reaction time. When the reaction is conducted without the addition of  $\text{GaCl}_3$  there was no significant formation of  $\alpha$ -amino nitriles even after several hours. It is worth mentioning here in present reaction, the formation of any ring ruptured dyes was not observed.<sup>14</sup> Certainly, during Schiff's base formation  $\text{GaCl}_3$  did not rupture the furan ring as the furan ring is very much sensitive to acids as well as bases.

Further utility and superiority of present protocol is demonstrated using conjugated aldehydes, where no double bond migration is observed rather normal nitriles are obtained. These results are in contrast to previous reports where double bond migrates to conjugate with cyanide.<sup>15</sup> It is worth mentioning here that in conjugated systems double bond migrated, if nitriles are heated for few minutes or allowed to stand at room temperature for a long time. Regarding the role of  $\text{GaCl}_3$ , a plausible route is as below in Scheme 2;



### Scheme-2: Plausible role of $\text{GaCl}_3$

$\text{GaCl}_3$  activates the aldehydes thus help in formation of imine **4** which involves the loss of water molecule. The catalyst binds to the electron rich position on nitrogen in imine **4** which results in the polarization of  $\text{C}=\text{N}$  bond and thus facilitates cyanide ion attack on to azomethine carbon resulting in the formation of  $\alpha$ -amino nitriles.

### CONCLUSION

In conclusion, the present protocol employing catalytic amount of  $\text{GaCl}_3$ , is an efficient, mild and one pot strategy for the preparation of  $\alpha$ -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. The present protocol is also free of any hazardous by-product formation during aqueous work-up which is serious drawback in some already reported procedures.

### ACKNOWLEDGEMENTS

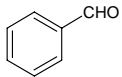
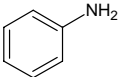
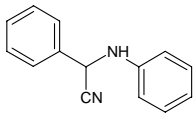
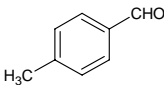
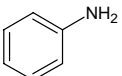
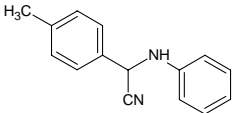
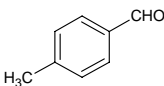
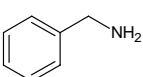
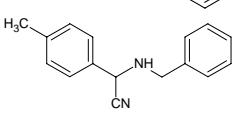
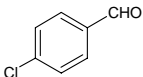
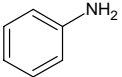
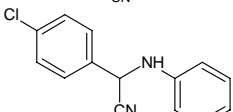
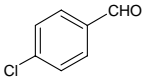
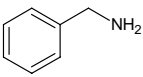
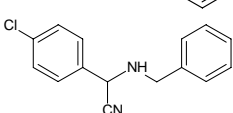
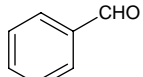
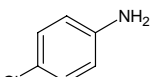
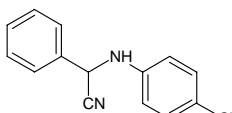
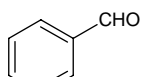
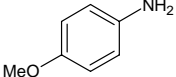
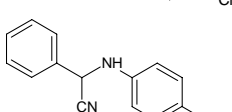
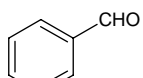
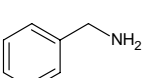
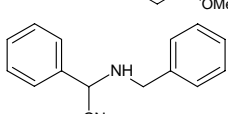
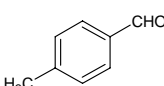
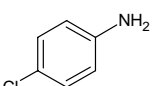
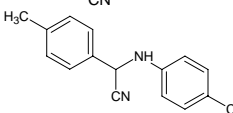
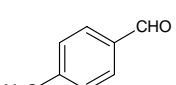
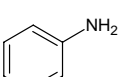
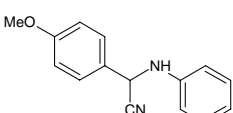
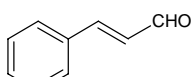
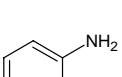
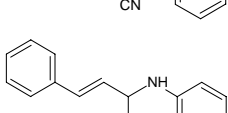
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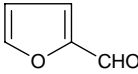
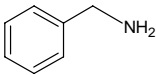
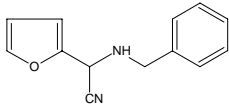
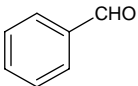

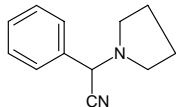
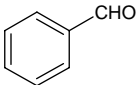
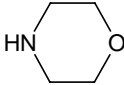
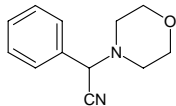
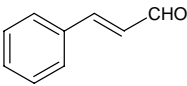
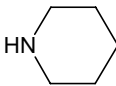
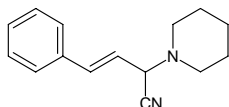
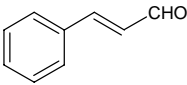
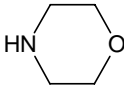
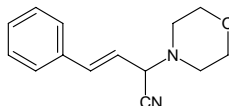
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**Table-1: GaCl<sub>3</sub> mediated synthesis of  $\alpha$ -amino nitriles.**

Compd.	Aldehydes	Amines	Products <sup>a</sup>	Time (min.)	Yields (%) <sup>b</sup>
3a				30	95
3b				35	92
3c				35	90
3d				30	96
3e				40	89
3f				45	87
3g				40	92
3h				35	96
3i				45	84
3j				40	85
3k				40	84

<b>3l</b>				45	82
<b>3m</b>				50	82
<b>3n</b>				45	84
<b>3o</b>				45	83
<b>3p</b>				45	80

<sup>a</sup>The products were characterized by comparison of their melting points and spectral (IR, <sup>1</sup>H NMR) data with those of authentic samples, <sup>b</sup> Isolated yields after recrystallization.

**Table-2:** Comparison of the effect of catalysts in the synthesis 2-(*N*-anilino)-2-phenylacetonitrile

<b>3a</b>				
<b>Catalyst</b>	<b>Amount of catalyst (mol %)</b>	<b>Time (min)</b>	<b>Yield (%)</b>	<b>Reference</b>
InCl <sub>3</sub>	30	300	73	12d
KSF-clay	>100	270	87	12f
RuCl <sub>3</sub>	20	20	74	12g
GaCl <sub>3</sub>	5	30	95	Present study

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RJC-242)