



Indium(III) iodide-mediated Strecker reaction in water: an efficient and environmentally friendly approach for the synthesis of α -aminonitrile via a three-component condensation

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ABSTRACT

A mild, efficient and environmentally friendly method has been developed for the synthesis of α -aminonitriles via a three-component condensation of aldehyde, amine and TMSCN in the presence of a catalytic amount of indium(III) iodide in water. The reactions proceeded smoothly at room temperature in water to generate the corresponding products in moderate to excellent yields.

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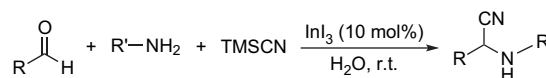
1. Introduction

α -Aminonitriles are significantly important intermediates for the synthesis of a wide variety of amino acids, amides, diamines and nitrogen-containing heterocycles.¹ Among the methods reported for the synthesis of α -aminonitriles, Strecker reaction, which proceeded via the addition of HCN to imine proved to be an effective one for the preparation of α -aminonitrile.² Recently, modified method using one-pot procedure via a three-component condensation of aldehyde, amine and trimethylsilyl cyanide (TMSCN, a promising alternative to HCN and alkali cyanide due to its nature as an effective, safe and easily-handled cyanation reagent) catalyzed by Lewis acids (or protic acids) in conventional organic solvents has been described.³ However, many of these reported methods involve the use of expensive reagents, toxic organic solvent, tedious workup procedure and longer reaction times. Therefore, it is still desirable to develop an efficient and practical method for the Strecker reaction under mild conditions.

In recent decades, water has aroused considerable attention in synthetic community and proved to be a promising solvent in organic synthesis due to its economic, environmentally friendly and polar nature.⁴ In relation to this, significant efforts have been

dedicated to developing organic reactions in water with many inherent advantages over reactions in conventional organic solvents. Therefore, if the Strecker reaction can be developed to operate in water, it will be of practical value and contribute to the area of water chemistry.

More recently, indium(III) compounds have been demonstrated to be mild, efficient and water-tolerant Lewis acids for various organic transformations.⁵ In contrast to classical Lewis acids, which often are required in stoichiometric quantities, indium(III) compounds readily promote a wide variety of organic reactions in catalytic quantities soluble both in organic solvents and in aqueous media. In continuation of our work to apply indium(III) compound as catalyst to organic reactions in water,⁶ herein, we report an efficient and environmentally friendly method for the synthesis of α -aminonitriles catalyzed by indium(III) iodide (InI₃) in water (Scheme 1).



Scheme 1. Strecker reaction in water.

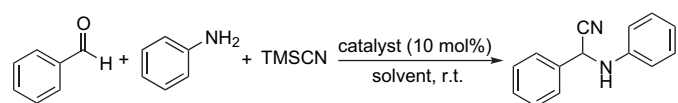
2. Results and discussion

Initial research was focused on the reaction of benzaldehyde, aniline and TMSCN in acetonitrile using different catalysts (10 mol%). As shown in Table 1, the one-pot reaction proceeded

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Table 1
One-pot synthesis of α -aminonitrile using different catalysts



| Entry | Catalyst | Solvent | Time | Yield ^a (%) |
|-------|----------------------|--------------------|--------|------------------------|
| 1 | InF ₃ | CH ₃ CN | 24 h | 94 |
| 2 | InCl ₃ | CH ₃ CN | 24 h | 93 |
| 3 | InBr ₃ | CH ₃ CN | 24 h | 91 |
| 4 | In(OTf) ₃ | CH ₃ CN | 24 h | 93 |
| 5 | In(OH) ₃ | CH ₃ CN | 24 h | 72 |
| 6 | InI ₃ | CH ₃ CN | 24 h | 98 |
| 7 | InI ₃ | — ^b | 10 min | 95 |
| 8 | InI ₃ | H ₂ O | 30 min | 95 (89) ^c |
| 9 | Pyridine | CH ₃ CN | 24 h | 87 |
| 10 | DABCO ^d | CH ₃ CN | 24 h | 89 |
| 11 | DMAP ^e | CH ₃ CN | 24 h | 76 |
| 12 | HMT ^f | CH ₃ CN | 24 h | 67 |
| 13 | MIM ^g | CH ₃ CN | 24 h | 87 |

^a Isolated yield.

^b Solvent-free condition.

^c With catalyst loading of 5 mol %.

^d DABCO=1,8-diazabicyclo[5.4.0]undec-7-ene.

^e DMAP=4-*N,N*-dimethylamino pyridine.

^f HMT=hexamethylenetetramine.

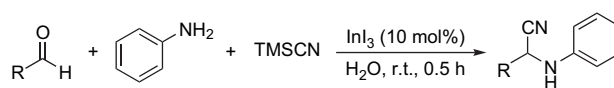
^g MIM=1-methyl imidazole.

efficiently in the presence of various indium(III) compounds at room temperature. Among the various catalysts used, InI₃ proved to be the best one and 98% yield of the corresponding product was afforded (entry 6, Table 1). In the meantime, employing InI₃ as catalyst, it was found that the three-component reaction could also take place efficiently in water or under solvent-free condition to furnish the desired product both in 95% yields within a short reaction time of 30 min (entries 7 and 8, Table 1). Considering the advantages provided by using water as reaction solvent, following reactions were carried out in water. In addition, it was worthy of noting that the one-pot reaction could also work well in acetonitrile in the presence of different nitrogen-containing organocatalysts, good yields were obtained when utilizing pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DABCO) and 1-methyl imidazole (MIM) as catalysts (entries 9, 10 and 13, Table 1).

In the following work, a series of α -aminonitriles were synthesized by using different aldehydes, amines and TMSCN in the presence of InI₃ (10 mol%) in water. As shown in Table 2, all aldehydes could react effectively with aniline and TMSCN in water catalyzed by InI₃ to afford the corresponding products with excellent yields of 81–97%. The catalytic system also worked well with acid sensitive heterocyclic aldehydes such as 5-methyl-furaldehyde, 2-thiophenecarboxaldehyde and 3-pyridinecarboxaldehyde to generate the corresponding products with good yields of 93%, 97% and 83% (entries 8, 9 and 10, Table 2). Even for α,β -unsaturated aldehyde, a good yield of the desired product (81%) was obtained without observing the formation of other side products (Table 2, entry 7).

Encouraged by above results, we continued our task to explore the reactivity of different amines with benzaldehyde and TMSCN under similar reaction conditions. As shown in Table 3, all aromatic amines could efficiently undergo reactions with benzaldehyde and TMSCN to give the products in excellent yields (entries 1–4, Table 3). When it came to aliphatic amines such as benzyl amine, pyrrolidine and morpholine, relatively slow reaction rate occurred due to the unstable nature of the formed aliphatic imines in the presence of water (entries 5–7, Table 3). However, if the reaction time was prolonged to 10 h, moderate to good yields of the desired products could be obtained.

Table 2
One-pot synthesis of α -aminonitrile in water^a



| Entry | Aldehyde | Yield ^b (%) |
|-------|----------|------------------------|
| 1 | | 91 |
| 2 | | 95 |
| 3 | | 90 |
| 4 | | 93 |
| 5 | | 93 |
| 6 | | 92 |
| 7 | | 81 |
| 8 | | 93 |
| 9 | | 97 |
| 10 | | 83 |

^a The reactions were operated at room temperature for 0.5 h catalyzed by InI₃ in water.

^b Isolated yield.

The three-component condensation is proposed to proceed via two-step reactions. Firstly, InI₃ serves as a Lewis acid to promote the formation of imine, which derived from the condensation of aldehyde and amine. Then the formed imine is further activated by InI₃ to produce a more electrophilic C=N intermediate, which facilitates the following attack of TMSCN to the carbon–nitrogen double bond, and thus forms the desired product α -aminonitrile after hydrolysis with water.

3. Conclusion

In summary, we have developed a mild, efficient and environmentally friendly method for the synthesis of α -aminonitriles via a three-component condensation of aldehydes, amines and TMSCN catalyzed by a catalytic amount of water-stable Lewis acid InI₃ in water. This method is quite general and it works well with a wide variety of aldehydes and amines at room temperature. The mild reaction conditions, short reaction time, good yields, the simplicity

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