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Brønsted acidic ionic liquid as a metal free catalyst for the one-pot synthesis of α-aminonitriles under mild and solvent-free conditions

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ABSTRACT

An efficient, mild and environmentally friendly method was developed for the Strecker reaction to synthesize α-aminonitriles in the presence of methyl imidazolium hydrogen sulfate ([Hmim][HSO_4]) as an efficient catalyst. These syntheses were performed via a one-pot three-component condensation of aldehydes (or ketones), amines, and trimethylsilyl cyanide under mild and solvent free conditions.

***Keywords**: Strecker, α-Amino nitriles, Methyl imidazolium hydrogen sulfate, Solvent free conditions.*

1. Introduction

The Strecker reaction [1,2] is one of the most important multicomponent reactions in organic chemistry for the direct one-pot synthesis of α-aminonitriles. In this reaction three components including a carbonyl compound (generally an aldehyde), an amine and either alkaline metal cyanide or hydrogen cyanide couple together to produce α-amino nitriles, which are highly useful synthons for the synthesis of α-amino acids [3-8] nitrogen-containing heterocycles such as imidazoles and thiadiazoles [9,10]. and other biologically useful molecules [11]. α-Amino acids have the great biological and economical significance because of their widespread use in chemistry and biology. For example, they are the key precursors for the synthesis of proteins and have several applications as the chiral building blocks in the pharmaceutical industry [6-8]. α-Amino nitriles are generally prepared by nucleophilic addition of cyanide anion to imines. A variety of cyanating agents such as HCN, [8] KCN, [12] Et_2AlCN, [13] $(EtO)_2P(O)CN$, [14] and Bu_3SnCN [15] have been reported for Strecker-type reactions under various conditions. However, most of them are found to be hazardous and special caution has to be taken during their use. It has been observed that the use of Me_3SiCN could overcome all these problems as it is safe to handle and is an effective cyanide source. Many catalysts have been used to promote the Strecker reaction using TMSCN. For example, trifluoroethanol [16] $La(NO_3)_3.6H_2O$ or $GdCl_3.6H_2O$, [17] $Fe(CP)_2PF_6$, [18] $Cu(OTf)_2$, [19] cellulose sulfuric acid, [20] K_2PdCl_4, [21] zirconia solid acid, [22] Guanidine hydrochloride, [23] $InCl_3$, [24] Oxalic acid, [25] Silica-bonded S-sulfonic acid, [26] TiO_2, [27] $Zr(HSO_4)_4$ [28] and Gallium grafted TUD-1 [29]. However, many of these catalysts are expensive, moisture sensitive, non-recyclable, require extended reaction times, harsh conditions and also require tedious workup leading to the generation of a large amount of toxic waste.

Recently, the use of ionic liquids (ILs) has been increasing with a very fast rate because of their beneficial properties such as undetectable vapor pressure, non-inflammability, wide liquid range, reusability and high thermal stability [30]. A subdivision of ILs is protic ionic liquids (PILs), which are produced through the combination of a Brönsted acid and a Brönsted base [31]. These acidic ionic liquids have widely been applied in electrochemistry, synthesis of nanostructure materials, reaction media and catalyst. Furthermore, Brönsted acidic ionic liquids can be designed to replace traditional mineral liquid acids such as sulfuric acid and hydrochloric acid in organic synthesis. Although there are various Brönsted acidic ionic liquids applied in organic synthesis [31], the majority of these ionic liquids are

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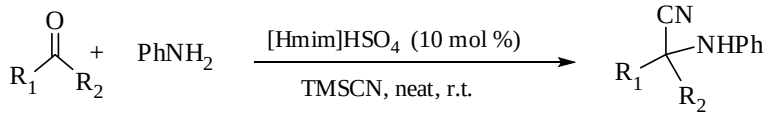


R_1 = aryl, alkyl and R_2= alkyl, H

Scheme 1.

synthesized with a time-consuming and expensive procedure. Methyl imidazolium hydrogen sulfate ([Hmim][HSO_4]) has easily been synthesized and used as an efficient, inexpensive and reusable catalyst in organic synthesis [32-34]. Moreover, the present ionic liquid is halogen free and because of less carbon numbers, this ionic liquid has less toxicity [35]. Therefore, [Hmim][HSO_4] can be introduced as a green ionic liquid.

Herein, we wish to report an efficient method for one-pot three-component synthesis of α-amino nitriles from various carbonyl compounds, anilines and TMSCN in the presence of catalytic amount of [Hmim][HSO_4] under solvent-free conditions at room temperature (Scheme 1).

2. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to the isolated products after purification. The products were characterized by comparison with authentic samples and by spectroscopic data and melting point. All melting points were taken on a Gallenkamp melting apparatus and were uncorrected.

2.1. Preparations of Brönsted acidic ionic liquids (Methylimidazolium hydrogen sulfate [Hmim]HSO_4^-)

1-Methylimidazole (1.59 mL, 20 mmol) and acetonitrile (5 mL) were charged into a 25 mL round-bottom flask. Then, the mixtures were stirred at 0ºC for 1 min. Then, a stoichiometric amount of concentrated sulfuric acid (97%, 1.03 mL) was added drop wise and the mixture stirred for 1 h at 0ºC and then stirred for 2 h at room temperature. The Brönsted acidic ionic liquid was washed repeatedly with ether (2×5 mL) to remove non-ionic residues and dried in vacuum (3.5 g, 97%).

Table 1. Reaction of benzaldehyde, aniline and TMSCN in the presence of different catalytic amount of [Hmim]HSO_4.

Entry	[Hmim]HSO_4 (mol %)	Time(min)	Yield (%)[a]
1	0	3600	Trace
2	5	20	80
3	7	15	82
4	10	10	90
5	15	15	87

[a]The yield refers to the isolated pure product.

2.2. Typical procedure for the preparation of 2-(N-anilino)-2-phenyl acetonitrile

A mixture of benzaldehyde (0.50 g, 5 mmol), aniline (0.45 g, 5 mmol), trimethylsilylcyanide (0.60 g, 6 mmol) and [Hmim][HSO_4] (0.09 g, 10 mol %) was stirred at room temperature. The reaction was followed by TLC (EtOAc/cyclohexane, 1:3). After 15 min, water (15 ml) was added and the reaction mixture was filtrated. The crude product was washed with cold water (2×10 mL) and then recrystallized from ethanol to afford the pure product in 93 % yield (0.97 g).

3. Results and Discussion

Initially, to optimize the reaction conditions, we studied the reaction of benzaldehyde (1 mmol), aniline (1 mmol) and TMSCN (1.2 mmol) as a simple model reaction in the presence of different catalytic amount of [Hmim]HSO_4 at room temperature under solvent-free conditions (Table 1). It was found that 10 mol % of [Hmim]HSO_4 was sufficient to catalyze the reaction efficiently to produce high yield in short reaction time. (Table 1, entry 4). As shown in Table 1, the reaction was not successful in the absence of the catalyst. Using 10 mol % of the catalyst was sufficient to progress the reaction and an increase of the catalyst amount did not improve the yield. Therefore, the catalyst loading was optimized to 10 mol % for further reactions.

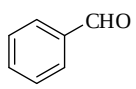
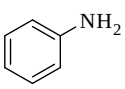
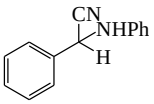
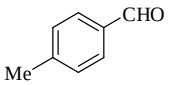
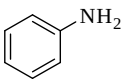
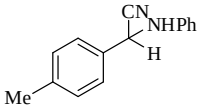
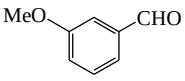
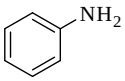
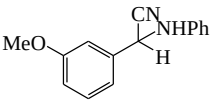
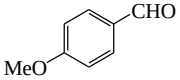
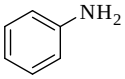
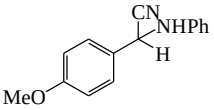
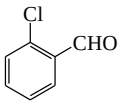
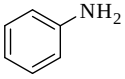
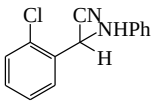
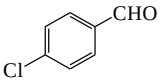
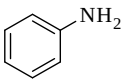
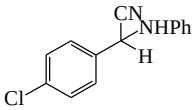
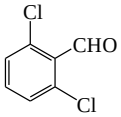
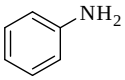
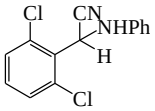
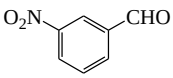
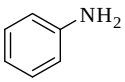
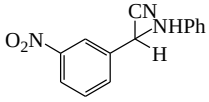
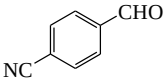
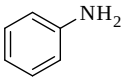
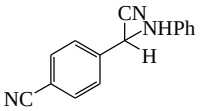
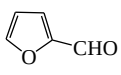
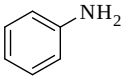
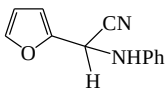
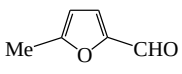
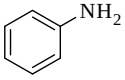
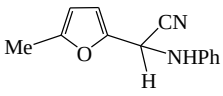
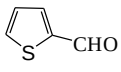
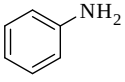
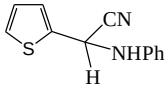
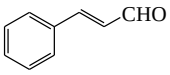
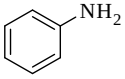
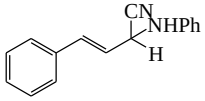
After optimization of the reaction conditions, we studied the generality of this method. Using this procedure, different kinds of aromatic, aliphatic and heterocyclic aldehydes were treated with aniline and TMSCN to produce the corresponding α-amino nitriles under solvent-free conditions in high to excellent yields (Table 2).

The reaction times for 2-chloro benzaldehyde and 2,6-dichloro benzaldehyde were longer than the others which may be due to the steric effect of *ortho*-substituents (Table 2, entries 5 and 7).

The reaction conditions were mild enough to perform these reactions with acid sensitive aldehydes such as furfuraldehyde, 5-methyl furfural, thiophen-2-carbaldehyde and cinnamaldehyde (Table 2, entries 10-13).

In this area of research, a few studies on Strecker reaction with ketones have been reported in the literature [16,18,24]. In the present study, we examined the condensation of ketones with aniline and TMSCN in the presence of 10 mol% of [Hmim]HSO_4 under solvent-free conditions at 50 °C (Table 2, entries 15-20). In comparison with aldehydes, the reactions proceeded in longer times to produce the

Table 2. Synthesis of α-amino nitriles from various aldehydes and ketones in the presence of catalytic amount of [Hmim]HSO_4 under solvent-free conditions.[a]

Entry	Aldehyde/ ketone	Amine	Product	Time (min)	Yield (%)
1				15	93
2				20	91
3				25	90
4				25	89
5				30	84
6				25	87
7				120	82
8				25	88
9				25	85
10				10	84
11				10	87
12				10	86
13				30	83

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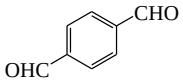
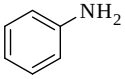
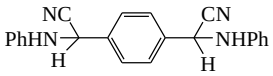
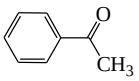
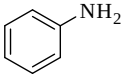
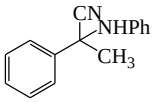
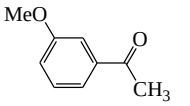
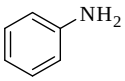
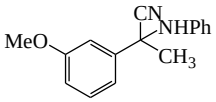
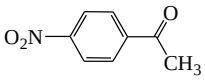
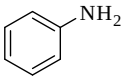
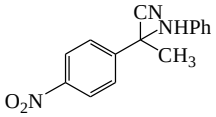
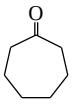
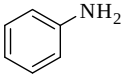
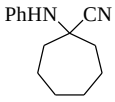
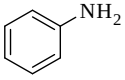
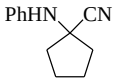
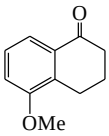
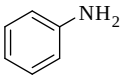
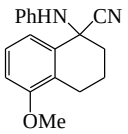
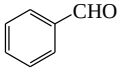
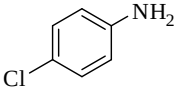
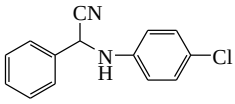
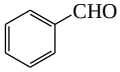
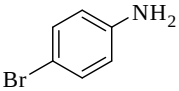
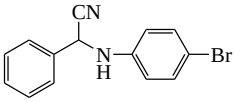
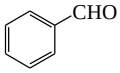
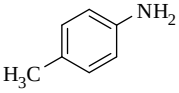
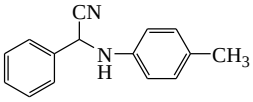
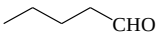
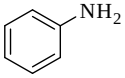
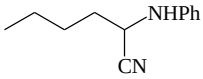
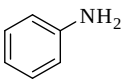
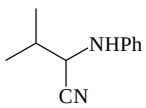
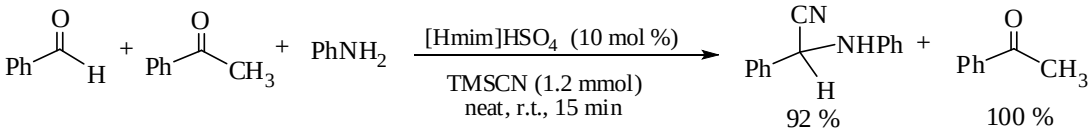
14 [b]				30	80
15 [c]				35	85
16 [c]				35	82
17 [c]				35	89
18 [c]				40	87
19 [c]				40	88
20 [c]				40	86
21				35	86
22				30	88
23				30	87
24				90	91
25				90	88

[a]The yields refer to the isolated pure products which were characterized from their spectral data by comparison with authentic samples.
[b]The molar ratio of terephthaldialdehyde/aniline/ TMSCN is 1:2:2.4.
[c]The reaction was carried out at 50 ºC.

corresponding α-amino nitriles from ketones. Furthermore, the reaction of benzaldehyde with other aromatic amines such as 4-chloroaniline, 4-bromoaniline or 4-methylaniline was respectively studied under the same reaction conditions. It was found that the corresponding α-amino nitriles were produced in high yields and short reaction times (Table 2,



Scheme 2.

entries 21-23). Moreover, the present method was suitable for the conversion of aliphatic aldehydes to their corresponding α-amino nitriles in high yields and short reaction times (Table 2, entries 24, 25). Finally, using the present catalyst, the reaction of benzaldehyde with TMSCN and aliphatic amines such as benzyl amine or butyl amine was studied under solvent-free conditions at room temperature. It was observed that the corresponding α-amino nitriles were obtained in low yields after 3 h. It may be due to the higher basicity of the aliphatic amines.

To show the chemoselectivity of this method, we studied the competitive reaction for the synthesis of α-amino nitrile from benzaldehyde in the presence of acetophenone using catalytic amount of $[Hmim]HSO_4$ under solvent-free conditions. As shown in Scheme 2, benzaldehyde was selectively converted to its corresponding α-amino nitrile and the starting ketone was intact.

To show the merit of the present work in comparison with those already reported, we compared the results of the synthesis of 2-(*N*-anilino)-2-phenyl acetonitrile from benzaldehyde, aniline and TMSCN with a number of catalysts. As shown in Table 3, $[Hmim]HSO_4$ can act as an effective catalyst with respect to reaction time and yield. Moreover, using solvent-free conditions, metal-free catalyst, easy and simplified procedure can make this method be attractive in this area of research. Furthermore, the present ionic liquid is halogen free and because of less carbon numbers, this ionic liquid has less toxicity.

Finally, the reusability of the present catalyst was also studied so that after each run, water was added to the reaction mixture and the product was filtered. To recycle the catalyst, all the water added for filtering and washing the product, was collected and washed with CH_2Cl_2 (3×10 mL) to remove organic impurities. Then water was evaporated and the catalyst was dried at 65 °C under reduced pressure for 2 h. It was found that the catalyst could be employed three times, although its activity gradually decreased Table 3 (entries 13-15).

4. Conclusion

In summary, we developed a mild, efficient and a more environmentally friendly method for the synthesis of α-aminonitriles via a three-component condensation of aldehydes (or ketones), amines and TMSCN catalyzed by a catalytic amount of $[Hmim]HSO_4$. Using an inexpensive

Table 3. Synthesis of 2-(*N*-anilino)-2-phenyl acetonitrile by different catalysis.

Entry	Catalyst (mol %)	TMSCN (mmol)	Solvent	Time (h)	Yield (%)	Ref
1	$Cu(OTf)_2$	TMSCN (1)	CH_3CN	6	89	19
2	$Fe(CP)_2PF_6$ (5)	TMSCN (1.3)	-	0.33	94	18
3	Trifluoroethanol (1 mL)	TMSCN (1)	-	2	97	16
4	SO_4^{2-}/ZrO_2(100 mg)	TMSCN (1.2)	THF	1.5	93	22
5	K_2PdCl_4 (10)	TMSCN (1.3)	H_2O	0.2	95	21
6	Oxalic acid (10)	TMSCN (2)	-	1	97	25
7	$La(NO_3).6H_2O$ (10)	TMSCN (1.2)	CH_3CN	1	96	17
8	Cellulose sulfuric acid (0.05 g)	TMSCN (1.2)	CH_3CN	0.75	97	20
9	$InCl_3$ (30)	KCN(1.5)	THF	6	75	24
10	Guanidine hydrochloride (3)	TMSCN (1.1)	CH_3OH	1	94	23
11	Gallium grafted TUD-1	TMSCN (1.3)	-	0.5	95	29
12	Catalyst-free	TMSCN (1.03)	CH_3CN	17.5	92	36
13	$[Hmim]HSO_4$ (10) (first run)	TMSCN (1.2)	-	0.25	93	-
14	$[Hmim][HSO_4]$ (10) (2nd run)	TMSCN (1.2)	-	0.25	87	-
15	$[Hmim][HSO_4]$ (10) (3rd run)	TMSCN (1.2)	-	0.25	81	-

and non-toxic catalyst, mild reaction conditions, short reaction times, high yields, the simplicity of the reaction procedure and easy work-up were the notable advantages of this method.

Acknowledgments

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