Alinteri J. of Agr. Sci. (2021) 36(1): 323-327
e-ISSN: 2587-2249
info@alinteridergisi.com

http://dergipark.gov.tr/alinterizbd
http://www.alinteridergisi.com/
DOI:10.47059/alinteri/V36I1/AJAS21048

RESEARCH ARTICLE

Strecker Synthesis of α-aminonitriles Facilitated by N-methyl Imidazolium Acetate

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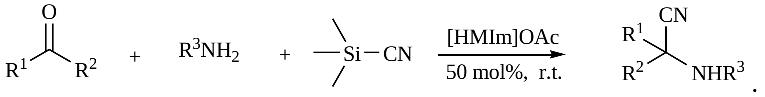
ARTICLE INFO

Article History:
Received: 15.03.2021
Accepted: 15.04.2021
Available Online: 21.06.2021

Keywords:
α-aminonitriles
Strecker Reaction
N-methyl Imidazolium Acetate

ABSTRACT

N-Methyl imidazolium acetate [HMIm]OAc was simply prepared through reaction of *N*-methyl imidazole with acetic acid and it was applied as a media and promoter for Strecker synthesis of *α*-aminonitriles. The three component reaction of a variety of structurally different aldehydes and amines with trimethylsilyl cyanide (TMSCN) in the presence of [HMIm]OAc were evaluated. Reaction of aromatic aldehydes and cinnamaldehyde with either aromatic and aliphatic amines provided the corresponding *α*-aminonitriles in high to excellent isolated yields after short period of time at room temperature.



Please cite this paper as follows:

Madadi, E. (2021). Strecker Synthesis of α-aminonitriles Facilitated by N-methyl Imidazolium Acetate. *Alinteri Journal of Agriculture Sciences, 36*(1): 323-327. doi: 10.47059/alinteri/V36I1/AJAS21048

Introduction

The stepwise formation of particular bonds in target molecules is the most common procedure for the synthesis of organic compounds. Besides the multistep reactions, sequential synthesis of a target molecule in a one-pot three-component reaction of starting materials without changing the reaction conditions, isolating the intermediates, or adding reagents is much more impressive. It is evident that multi-component reactions may allow the minimization of waste generation. Since in comparison with stepwise reactions, the number of energy, adsorbents, reagents, and solvents might decrease significantly that could result in an environmentally and economically favorable production [1].

Interesting components of α-Aminonitriles are particular and bifunctional compounds that have a nitrile and amino group at the same carbon atom. The availability of CN and NH2 functional groups makes α-aminonitriles a crucial versatile building block in agrochemicals, pharmaceuticals, and heterocyclic chemistry.

All these compounds are precious mediators for the synthesis of heterocyclic compounds, 2-diamines, α-amino acids, and different extremely crucial molecules which are complex heterocyclic and carbocyclic [2-4].

Preparation of *α*-aminonitriles through three component Strecker reaction of an aldehyde or ketone, amine and a cyanide source is the most straightforward route [5]. This approach offers high atom economy, and the possibility of incorporating additional functional groups through the choice of the corresponding precursors. Traditionally, HCN, NaCN and KCN were employed as cyanide sources. However, these cyanide sources are yet employed in enantioselective α-aminonitrile synthesis through nucleophilic addition to imines [6,7].

Later, other alternatives such as $(EtO)_2P(O)CN$ [8], Bu_3SnCN [9], Et_2AlCN [10], $K_2[Fe(CN)_6$ [11], Me_3SiCN (TMSCN) [12], acetyl cyanide [13] and acetone cyanohydrine (ACH) [14] were also introduced. Due to the less toxic character of TMSCN, high solubility in organic solvents and relatively safe operation and handling, protocols employing TMSCN as cyanide source are much more appeared in the literature. Methods that are based on trimethylsilyl cyanide (TMSCN)

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often need Lewis acid catalytic or Bronsted systems. Therefore, a vast number of catalysts including homogeneous and heterogeneous acid catalysts [15-21], organo-catalysts [21-24], ionic liquids [25-27] and metal complexes [28-30] have been proposed for this purpose. However, these methods may at least encounter one of the following drawbacks such as the use of expensive reagents, long reaction times, low yields of the products and tedious work-up procedures.

Protic ionic liquids (PILs) have all beneficial characteristics of ionic liquids, as well as the possibility of being synthesized easily [31,32]. Through a stoichiometric reaction between Brønsted bases and certain Brønsted acids, protic ionic liquids could be obtained. Various stable salts could be achieved by combinations of Brønsted acids and bases. Anyway, only when there is a complete proton transfer from acid to base, a true ionic liquid could be obtained. This could be achieved when the difference between pKa values of the precursor acids and bases is greater than 8-10 [ΔpKa = pKa(base)-pKa(acid)] [33]. Recently, we have reported catalytic applications of some protic ionc liquids in organic transformation [34-36]. Herein, we introduce the catalytic application of *N*-methyl-imidazolium acetate as a protic ionic liquid for three component strecker reaction of aldehydes, amines and TMSCN.

Experimental

Chemicals were either prepared in our laboratory or were purchased from Merck and Aldrich chemical companies. The progress of the reactions was followed by thin-layer chromatography (TLC) using silica gel GF_{254} plates. Using a JASCO FT-IR 4600 spectrophotometer, IR spectra were recorded. Moreover, by means of Bruker Avance DPX 500 MHz spectrometers, 1H and 13C NMR spectra were recorded by using TMS as an internal standard. By means of the Cole-Parmer Electrothermal IA9200 melting point apparatus, melting points were measured while are uncorrected.

Preparation of N-methyl Imidazolium Acetate

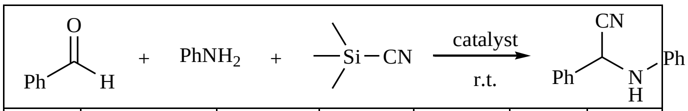
N-methyl imidazole (1.59 mL, 20 mmol) was added to a round-bottomed flask containing CH2Cl2 (10 mL). While the reaction mixture stirred, acetic acid (1.14 mL, 20 mmol) was added drop by drop for 10 minutes at room temperature and then was allowed to stir for 3 hours. Next, the solvent was evaporated and *N*-methyl imidazolium acetate was obtained in a quantitative yield as a colorless liquid. ^1H NMR (500 MHz, $CDCl_3$), δ(ppm): 1.92 (s, 3H), 3.59 (s, 3H), 6.80 (s, 1H), 6.94 (s, 1H), 7.56 (s, 1H), 12.16 (s, 1H); IR (neat): 3444, 3121, 1714 cm^{-1}.

Three component Strecker synthesis of *α*-aminonitriles, a typical procedure: To a round bottomed flask, benzaldehyde (0.1 mL, 1.0 mmol), aniline (0.09 mL, 1.0 mmol), TMSCN (0.15 mL, 1.2 mmol) and [HMIm]OAc (0.07 g, 50 mol%) were added respectively and then the prepared mixture was stirred at room temperature. After 5 minutes, through monitoring by TLC the reaction was completed and then cooled. Then by filtration, the product was precipitated and separated which provided pure 2-phenyl-2-(phenylamino) acetonitrile as a white solid (Table 2, entry 1). The catalyst was also recovered by evaporation of EtOH under reduced pressure. 2-phenyl-2-(phenylamino) acetonitrile: mp 76–78 °C, ^1H NMR (500 MHz; $CDCl_3$): δ= 4.15 (br s, 1H, NH), 5.45 (s, 1H, CH), 6.8 (d, *J* = 8 Hz, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 7.3 (t, *J* = 7.5 Hz, 2 H), 742-7.51 (m, 3H), 7.58–7.65 (m, 2H); IR (KBr): 3337, 3030, 2940, 2236 cm^{-1}.

Results and Discussions

In order to investigate Strecker synthesis of *α*-aminonitriles first, 4-*N*, *N*-dimethylaminopyridinium acetate (DMAP. HOAc) and *N*-methyl imidazolium acetate (NMIm. HOAc) were prepared through neutralization reaction of 4-*N*,*N*-dimethylaminopyridine and *N*-methyl imidazole with acetic acid. Then the Strecker three-component synthesis of α-aminonitriles was investigated in the presence of these protic ionic liquids. For initial screening, treatment of benzaldehyde and aniline as representative substrates was investigated. The results are summarized in Table 1. A control experiment was performed in the presence of any promoter. Neither under solvent-free conditions nor in ethanol the reaction proceeds to completion (Table 1, entries 1-3). Further experiments were conducted to show the effect of ionic liquids (Table 1, entries 4-6). The best result was obtained in *N*-methyl imidazolium acetate in 50 mol %.

Table 1. Optimization of the reaction conditions[a]

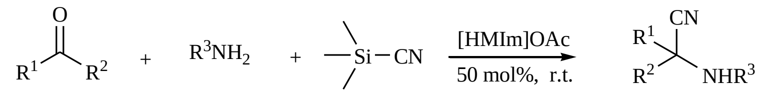


Entry	Catalyst	Catalyst (mol%)	TMSCN (mmol)	Solvent	Time (min)	Yield %
1	no catalyst	0	1	neat	30	60
2	no catalyst	0	1.2	neat	30	70
3	no catalyst	0	1.2	EtOH	30	60
4	DMAP.HOAc	20	1.2	CH_2Cl_2	60	70
5	NMIm.HOAc	20	1.2	neat	5	70
6	NMIm.HOAc	50	1.2	neat	5	100

[a] Reactions were achieved using equal molar ratios of benzaldehyde and aniline.

Under optimized conditions, the generality and scope of the reaction were studied for various amines, aldehydes, and acetophenone (Table 2). Cinnamaldehyde and aromatic aldehydes were replaced with benzylamine and anilines to afford the corresponding α-aminonitriles in high to excellent yields during short reaction times (Table 2, entries 1-13). As expected, reaction of acetophenone, aniline and TMSCN was sluggish under operation conditions (Table 2, entry 14).

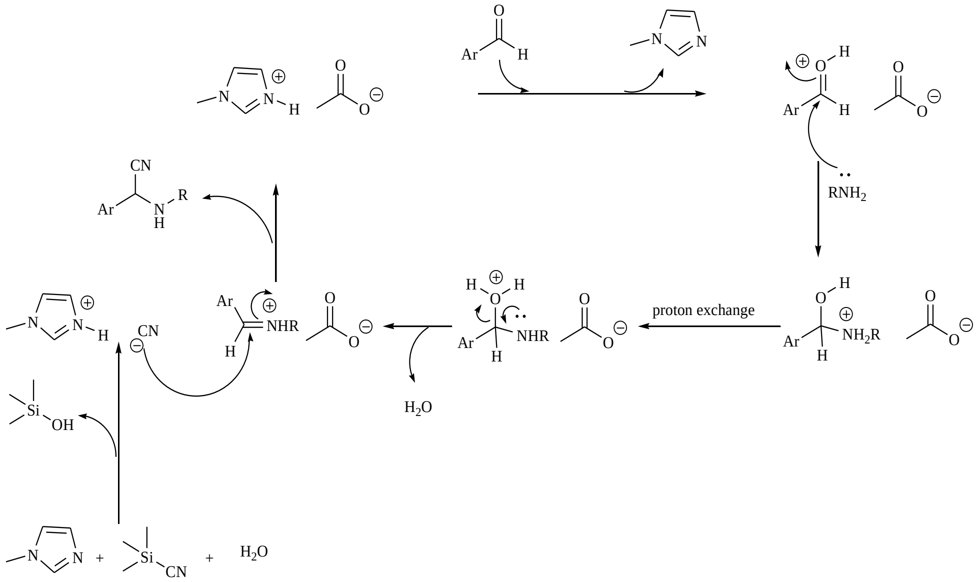
Table 2. Generality and substrate scope for Strecker synthesis [a]



Entry	R^1	R^2	R^3	Time (min)	Isolated Yield %
1	Ph	H	Ph	5	97
2	4-OCH$_3$-C$_6$H$_4$-	H	Ph	5	72
3	4-CH$_3$-C$_6$H$_4$-	H	Ph	5	74
4	PhCH=CH-	H	Ph	5	65
5	Ph	H	PhCH$_2$	5	77
6	4-CH$_3$-C$_6$H$_4$-	H	PhCH$_2$	5	80
7	3-OCH$_3$-C$_6$H$_4$-	H	PhCH$_2$	15	80
8	Ph	H	4-CH$_3$-C$_6$H$_4$-	15	98
9	4-CH$_3$-C$_6$H$_4$-	H	4-CH$_3$-C$_6$H$_4$-	5	72
10	4-OCH$_3$-C$_6$H$_4$-	H	4-CH$_3$-C$_6$H$_4$-	40	77
11	Ph	H	3-OCH$_3$-C$_6$H$_4$-	40	63
12	4-CH$_3$-C$_6$H$_4$-	H	3-OCH$_3$-C$_6$H$_4$-	5	75
13	4-OCH$_3$-C$_6$H$_4$-	H	3-OCH$_3$-C$_6$H$_4$-	5	75
14	Ph	CH$_3$	Ph	12 h	20

[a] Reaction conditions: aldehyde (1 mmol), amine (1 mmol), TMSCN (1.2 mmol), [HMIm]OAc 50 mol%, r.t., neat.

The Hammett acidity function (H_0) of *N*-methyl-imidazolium acetate was calculated by the method reported by Thomazeau [37]. It was found 2.03 and was in the range of the Hammett acidity functions (H_0) of some examined Bronsted acidic ionic liquids reported by Riisager et al. [38]. According to Yus's proposal for Strecker synthesis of *α*-aminonitriles [39] and Bronsted acidic nature of *N*-methyl imidazolium acetate, a plausible reaction mechanism for Strecker synthesis of *α*-aminonitriles using *N*-methyl imidazolium acetate as promoter is shown in Scheme 1.



Scheme 1. A possible reaction mechanism for the synthesis of α-aminonitriles that is catalyzed by N-methylimidazolium acetate

The efficiency of [NMImH][OAc] as a Bronsted acidic ionic liquid in comparison with the previously reported catalysts has also been shown in Table 3.

Table 3. Comparison of the efficiency of N-methyl imidazolium acetate with some other catalysts reported for the Strecker reaction of benzaldehyde, aniline and TMSCN

Entry	Cat.	Solvent, Temp., Time	Yield %	Ref.
1	InI$_3$ (10 mol%)	Water, r.t., 30 min	95	15
2	Fe$_3$O$_4$@ZrO$_2$/SO$_4^{2-}$ (100 mg)	EtOH, r.t., 30 min	95	20
3	Chitosan (6 mg)	Neat, r.t., 10 min	95	23
4	Formic acid (30 μL)	EtOH, r.t., 5 min	99	24
5	MgI$_2$.(Et$_2$O)$_n$ (10 mol%)	Neat, r.t., 30 min	95	30
6	[NMImH][OAc] (50 mol%)	Neat, r.t., 5 min	87	This work

Conclusion

In conclusion, we have demonstrated a facile green protocol for one-pot three component synthesis of α-aminonitriles using imidazolium based ionic liquid as a reaction media and catalyst. It is noteworthy that the catalyst was simply recovered by evaporation of ethanol. Simple practical operations, achievement of the reaction at ambient temperature, easy workup procedure, the application of environmentally benign, and reusable catalysts are magnificent features of this method.

Acknowledgments

We are appreciative of the financial support received from the Research Council of the Behbahan Khatam Alanbia University of Technology.

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