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Environmentally Friendly Room Temperature Strecker Reaction: One-Pot Synthesis of α-Aminonitriles in Ionic Liquid

M.M. Mojtahedi*, M.S. Abaee and H. Abbasi
Chemistry & Chemical Engineering Research Center of Iran, P.O.Box 14335-186, Tehran, Iran

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A three component efficient and facile procedure is developed for the synthesis of α-aminonitriles from aromatic and aliphatic aldehydes, amines, and trimethylsilyl cyanide in 1-butyl-3-methyl-1*H*-imidazolium perchlorate ([bmim][ClO_4]) ionic liquid as the reaction medium at room temperature. Excellent yields are obtained in this one-pot procedure with short reaction times and the ionic liquid medium reused several times in a row.

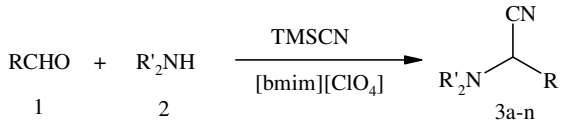
Key words: Ionic liquids, Strecker reaction, α-Aminonitriles, Imminium ions

INTRODUCTION

Three component combinations of aldehydes, amines, and cyanide, known as the Strecker reaction [1], facilitate the formation of α-aminonitriles [2], which are equivalent synthones to imminium moieties [3] and acyl anions [4]. These compounds are very versatile intermediates for the synthesis of α-aminoacids [5,4b], 1,2-diamines [6], amides [7], and various nitrogen containing heterocycles such as thiadiazoles and imidazoles [8]. Many modifications to the original procedure have been developed to enhance the efficiency of this reaction [9]. However, because of the reversible nature of the process, these modifications still suffer from certain drawbacks such as tedious workup and difficulties associated with the separation of the products from unreacted starting materials and cyanohydrin by-products.

Recent progress such as development of one-pot procedures for aminative cyanation of carbonyl compounds [10], use of Lewis acidic conditions [11], and employment of new cyanating reagents, especially trimethylsilyl cyanide (TMSCN) [12,1a], have contributed outstanding elaborations to the Strecker reaction. However, use of expensive reagents and strong acidic conditions, long reaction times, deactivation and decomposition of the catalytic systems and production of toxic disposals are still among deficiencies of many of these methods. Thus, development of efficient, clean, and environmentally benign methodologies for the synthesis of the title structures are still in demand. Recent advancement in designing smooth and environmentally safe synthetic transformations has given extremely important position to ionic liquids as alternative recyclable media for organic reactions [13]. Among various ionic liquids, those based on 1-butyl-3-methyl-1*H*-imidazolium moiety have shown great potential as eco-friendly catalytic systems for room temperature organic transformations [14]. In continuation of our previous experiences on the development of environmentally safe reactions [15], we would like to introduce the first procedure for [bmim][ClO_4] promoted combination of aldehydes, amines, and TMSCN leading to the synthesis of α-aminonitriles via imminium ion intermediates. The procedure has successfully incorporated both aromatic and aliphatic aldehydes (Scheme 1).

*Corresponding author. E-mail: m_mojtahedi@yahoo.com



Scheme 1

EXPERIMENTAL

Typical experimental procedure: A mixture of aldehyde (2 mmol) and amine (5 mmol) in 1.5 ml [bmim][ClO_4] [16] was stirred at room temperature for 15 minutes. TMSCN (2 mmol) was added to this mixture and stirring continued for another 10-15 min until TLC and IR experiments showed completion of the reaction. The product was extracted three times by 10 ml portions of diethyl ether and the combined etheral phases were washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the product was purified by column chromatography over silica gel, if necessary using EtOAc/hexane as an eluent. Products were characterized by their NMR, IR, and mass spectra.

Selected Spectral Data

(4-Methoxy-phenyl)-piperidin-1-yl-acetonitrile (3c). ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 1.22-1.50 (m, 6H), 2.25-2.50 (m, 4H), 3.65 (s, 3H), 4.61 (s, 1H), 6.77 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H); ^{13}C NMR (80 MHz, $CDCl_3$): δ (ppm) 23.7, 25.5, 50.4, 54.9, 61.9, 113.7, 115.5, 125.3, 128.7, 159.5; MS: m/z 230 (M^+), 204, 146, 121, 84; IR (neat) ν 2224, 1513, 1250 cm^{-1}.

Piperidin-1-yl-thiophen-2-yl-acetonitrile (3d). ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 1.47-1.75 (m, 6H), 2.45-2.70 (m, 4H), 4.91 (s, 1H), 6.80-7.32 (m, 3H); ^{13}C NMR (80 MHz, $CDCl_3$): δ (ppm) 23.7, 25.5, 50.7, 58.5, 114.7, 126.5, 126.7, 137.8; MS: m/z 206 (M^+), 122, 97, 84; IR (neat) ν 3107, 2937, 2368, 1442 cm^{-1}.

(4-Chloro-phenyl)-pyrrolidin-1-yl-acetonitrile (3g). ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 1.59-1.88 (m, 4H), 2.42-2.59 (m, 4H), 4.91 (s, 1H), 7.20 (d, J = 7 Hz, 2H), 7.38 (d, J = 7 Hz, 2H); ^{13}C NMR (80 MHz, $CDCl_3$): δ (ppm) 23.3, 50.0, 58.5, 115.6, 128.6, 128.7, 132.7, 134.5; MS: m/z 220 (M^+), 221, 222, 150, 125, 109; IR (neat) ν cm^{-1} 2968, 2360, 1598, 1092.

Morpholin-4-yl-phenyl-acetonitrile (3i). ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 2.48-2.54 (m, 4H), 3.57-3.70 (m, 4H), 4.73 (s, 1H), 7.35-7.60 (m, 5H); ^{13}C NMR (80 MHz, $CDCl_3$): δ (ppm) 49.7, 62.1, 72.1, 115.0, 127.3, 128.5, 128.7, 132.3.

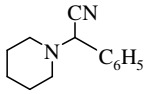
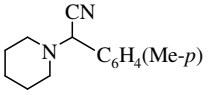
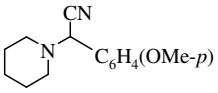
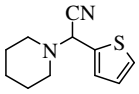
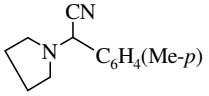
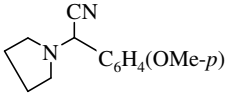
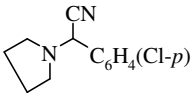
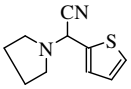
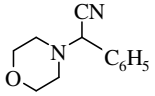
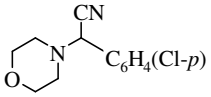
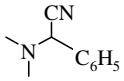
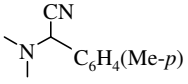
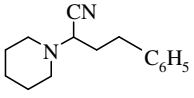
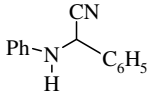
RESULTS AND DISCUSSION

The initial experiment was carried out by reacting a benzaldehyde and piperidine mixture with TMSCN in a [bmim][CLO_4] ionic liquid at room temperature (Table 1). Formation of the imminium intermediate was detected by IR monitoring during the reaction course [17]. TLC showed complete disappearance of the aldehyde and formation of **3a** (entry 1). Control experiments illustrated the catalytic role of the reaction medium. In the absence of the ionic liquid, reactions conducted in THF, dichloromethane, or under neat conditions resulted in the formation of less than 20% of the desired product after several hours. Similar reactions using other aromatic aldehydes and cyclic amines were conducted under the same conditions. Consequently, products **3b**-**3j** were all easily obtained in 90-97% yield in less than 40 min (entries 2-10).

The procedure was further explored using acyclic amines. Reactions between *N*-trimethylsilyldimethylamine ($TMSNMe_2$) with benzaldehyde (Table 1, entry 11) or with *p*-methylbenzaldehyde (entry 12) resulted in rapid formation of products **3k** (96%) or **3l** (88%), respectively. The use of aliphatic aldehydes was also successfully examined by conducting a reaction between 3-phenylpropanaldehyde and piperidine (entry 13) leading to formation of **3m** (85%). Applicability of the procedure for aromatic amines was attempted next using a reaction between aniline and benzaldehyde. As a result, **3n** was formed in 86% yield (entry 14). All products were identified by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopic methods and the results were confirmed by comparison with those available in the literature. Table 2 compares the features of the previously reported procedures with those of the present methodology for products **3i** and **3n**.

In summary, we have demonstrated the first efficient and environmentally friendly use of [bmim][CLO_4] ionic liquid as the catalytic recyclable media for three-component conversion of aldehydes, amines, and TMSCN to α-aminonitriles at room temperature. The versatility of the reaction, production of pure isolated compounds, easy procedure and work up, without the

Table 1. Room Temperature [bmim][ClO_4] Ionic Liquid Promoted Synthesis of α-Aminonitriles

Entry	Aldehyde	Amine	Product		Yield (%)[a]
1	C_6H_5CHO	piperidine		**3a**	95
2	(*p*-Me)C_6H_4CHO	piperidine		**3b**	94
3	(*p*-OMe)C_6H_4CHO	piperidine		**3c**	93
4	2-thiophen-CHO	piperidine		**3d**	93
5	(*p*-Me)C_6H_4CHO	pyrrolidine		**3e**	92
6	(*p*-OMe)C_6H_4CHO	pyrrolidine		**3f**	97
7	(*p*-Cl)C_6H_4CHO	pyrrolidine		**3g**	90
8	2-thiophen-CHO	pyrrolidine		**3h**	91
9	C_6H_5CHO	morpholine		**3i**	92
10	(*p*-Me)C_6H_4CHO	morpholine		**3j**	90
11	C_6H_5CHO	$TMSNMe_2$		**3k**	96
12	(*p*-Me)C_6H_4CHO	$TMSNMe_2$		**3l**	88
13	$C_6H_5CH_2CH_2CHO$	piperidine		**3m**	85
14	C_6H_5CHO	aniline		**3n**	86

[a]Isolated yields.

Table 2. Comparison of the Present and other Available Methodologies

Reactants	Conditions	Solvent	Product	Yield (%)	Reference
Benzaldehyde + Morpholine	[bmim][ClO_4], 0.5 h	-	**3i**	92	This work
	$BiCl_3$, 7 h	CH_3CN	**3i**	89	[11a]
	Silica sulfuric acid, 9 h	CH_2Cl_2	**3i**	81	[11l]
	I_2, 2 h	CH_3CN	**3i**	78	[11b]
	$NiCl_2$, 12 h	CH_3CN	**3i**	74	[11h]
	$LiClO_4$	-	**-**	NR[a]	[11e]
Benzaldehyde + Aniline	[bmim][ClO_4], 0.5 h	-	**3n**	86	This work
	$BiCl_3$, 10 h	CH_3CN	**3n**	84	[11a]
	Silica sulfuric acid, 6 h	CH_2Cl_2	**3n**	88	[11l]
	Montmorillonite, 3.5 h	CH_2Cl_2	**3n**	90	[10]
	I_2, 1 h	CH_3CN	**3n**	94	[11b]
	$NiCl_2$, 12 h	CH_3CN	**3n**	92	[11h]

[a]No reaction.

use of extra additives or Lewis acids are other advantages of the present method.

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