

An efficient one-pot synthesis of α -amino nitriles using ecofriendly Lewis-acidic ionic liquid choline chloride.2ZnCl₂

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ABSTRACT

α -Amino nitriles are synthesized in a one-pot, three-component coupling of aldehydes (or ketones), aniline, and trimethylsilyl cyanide using a catalytic amount of choline chloride.2ZnCl₂ as a bio Lewis acidic ionic liquid. Mild Lewis acidic characteristic of this ionic liquid allows efficient synthesis of α -amino nitriles from acid sensitive aldehydes.

Keywords: Strecker reaction, α -Amino nitriles, Trimethylsilylcyanide, Choline chloride.

1. Introduction

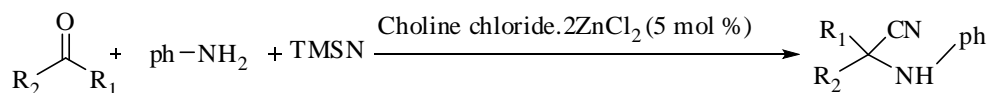
α -Amino nitriles are important intermediates for the preparation of many amino acids [1] and various nitrogen containing heterocycles such as imidazoles, thiadiazoles [2] and other pharmacologically useful molecules like saframycin A [3]. Because of their wide range of applications these compounds have received a great deal of attention in recent years in connection with their synthesis.

Among various methods reported in the literature for the preparation of α -amino nitriles, the most important route for the synthesis of them is the Strecker reaction. In this reaction on mixing aldehyde and amine, Schiff's bases are produced and then by nucleophilic addition of cyanide ion to the imine, α -amino nitriles are formed. Trimethylsilyl cyanide (TMSCN) [4-7] has emerged as the most useful, safest and more effective cyanide source for nucleophilic addition to carbon nitrogen double bond in comparison with hydrogen cyanide [8], potassium cyanide [9] or other cyanide sources [10-13]. For nucleophilic addition of cyanide ion, carbon nitrogen double bond should be polarized and this can be achieved by a suitable acidic catalyst, bronsted acidic or Lewis acidic catalysts. The use of strong bronsted acids frequently leads to the formation of undesirable side products during aqueous workup and decreases the yield of desired products and most Lewis acids generate large amount of toxic waste. Nevertheless,

different Lewis acid catalysts such as lithium perchlorate [14], scandium triflamide [15], vanadyl triflate [16], nickel(II) chloride [17], Fe₃O₄ [18], ruthenium(III) chloride [19], NHC-amidate palladium(II) complex [20], bismuth(III) chloride [21], montmorillonite KSF [22], sulphamic acid [23], guanidine hydrochloride [24] and fluorinated alcohols [25] were used for this reaction. Of course, many of these methods required strong acidic conditions, expensive reagents, long reaction times, harsh experimental conditions and tedious work-up procedures.

With increasing environmental concern, the need for environmentally benign method has become of significant importance. According to the principle of green chemistry, synthetic method should be designed to use substances that exhibit little or no toxicity to human health and environment [26]. In this regard, ionic liquids (ILs) have attracted a lot of attention in recent years and among them room-temperature ionic liquids (RTILs) have been used more widely for synthetic and catalytic applications because of their important attributes such as wide liquid range, negligible vapor pressure, high catalytic activity, excellent chemical and thermal stabilities, potential recoverability, design possibilities, and ease of separation of the products from reactants. In 2001, Abott et al. reported [27] a new class of moisture insensitive IL composed of choline chloride and ZnCl₂ which has been utilized extensively as a Lewis acid catalyst as well as a reaction medium in carrying out Diels–Alder reactions [28], Fischer indole annulations [29], electrolytic deposition [30], O-acetylation of cellulose and

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Scheme 1. The three component Strecker reaction catalyzed by Choline chloride.2ZnCl₂

monosaccharides [31] and protection of carbonyls [32]. The Lewis acidic activity is primarily due to the presence of complex zinc chloride ions, [ZnCl₃]⁻, [Zn₂Cl₅]⁻ and [Zn₃Cl₇]⁻ along with some higher clusters of low intensity as confirmed by FAB mass study [28, 33]. Choline chloride.2ZnCl₂ is ecofriendly, water insensitive, non-corrosive to steel, and relatively inexpensive compared with the imidazolium based ionic liquids. These characteristics made us use this ionic liquid as a recyclable green catalyst and reaction media for synthesizing α -amino nitriles. Herein, we describe a mild and efficient protocol for the synthesis of α -amino nitriles using a catalytic amount of choline chloride.2ZnCl₂ under solvent-free conditions at ambient temperature.

2. Experimental

All chemical reagents were purchased from Merck and were used without further purification. ¹H-NMR spectra were recorded on a Bruker 500 spectrometer using TMS as an internal standard in CDCl₃ and FT-IR spectra were obtained as KBr pellets on a JASCO 680-PLUS spectrophotometer. Melting points were determined with a Gallenkamp melting apparatus and are uncorrected.

2.1. General procedure for the preparation of choline chloride.2ZnCl₂

Choline chloride salt (5 mmol) was mixed with zinc chloride (10 mmol) and heated to almost 150 °C in air with stirring until a clear colourless liquid was obtained.

2.2. General procedure for the preparation of α -amino nitriles

A mixture of aromatic aldehyde or ketone (1 mmol), aniline (1 mmol), trimethylsilyl cyanide (1.2 mmol, 0.15 ml) and choline chloride.2ZnCl₂ ionic liquid (5 mol% or 10 mol%) was stirred vigorously at room temperature (or at 50 °C for some compounds) for an appropriate amount of time. After completion of the reaction, as indicated by TLC, 10 ml water was added to the mixture and the product was extracted with ethylacetate (3×10 ml). The organic layer was concentrated under vacuum and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethylacetate–hexane) to afford pure α -amino nitriles. All compounds are known and their ¹H NMR, ¹³C NMR and IR were consistent with the assigned structures and were compared with those reported in the literature [5, 20, 35-40] except for 2-anilino-2-(4-nitro phenyl) propanitrile.

2.3. 2-anilino-2-(4-nitro phenyl) propanitrile (Table 2, Entry 12)

A mixture of 0.165 g (1 mmol) 4-nitroacetophenone, 0.09 mL (1 mmol) aniline, 0.15 mL (1.2 mmol) trimethylsilyl cyanide, 0.041 g (0.1 mmol) choline chloride.2ZnCl₂ was stirred vigorously at 50 °C for 1 minute. Then 10 ml water was added to the mixture and the product was extracted with ethylacetate (3×10 ml). The organic layer was dried over anhydrous MgSO₄ and concentrated under vacuum. The product was obtained as a yellow solid, m.p 148-150 °C. IR (KBr, cm⁻¹): 3381, 3072, 3005, 2938, 2846, 2226, 1604, 1521, 1509, 1497, 1347, 1316, 1263, 1176, 1099, 853, 744, 690. ¹H NMR (400 MHz, CDCl₃, ppm) δ : 2.0 (3H, s), 4.2 (1H, s), 6.5 (2H, d, *J* = 10.7 Hz), 6.87 (1H, t, *J* = 9 Hz), 7.16 (2H, t, *J* = 11.1 Hz), 7.86 (2H, d, *J* = 11 Hz), 8.29 (2H, d, *J* = 11 Hz). ¹³C NMR (100 MHz, CDCl₃, ppm) δ : 33.07, 56.76, 115.7, 119.7, 120.66, 124.64, 126.19, 129.26, 142.62, 147.04, 148.13. Anal. Calcd for C₁₅H₁₃N₃O₂: C, 67.4; H, 4.9; N, 15.72. Found: C, 66.33; H, 4.32; N, 15.74.

3. Results and discussion

Choline chloride.2ZnCl₂ is a mild bio Lewis acidic ionic liquid that has been used effectively in organic synthesis, which encouraged us to use it in synthesis of α -amino nitriles. It can be readily prepared by mixing choline chloride and ZnCl₂ in 1:2 molar ratio and heating the resulted mixture in an oil bath at 150 °C until a transparent liquid is formed [27].

The reaction of 4-chlorobenzaldehyde with aniline and TMS-CN was investigated at room temperature using different amounts of choline chloride.2ZnCl₂ as a model reaction to optimize the amount of catalyst. As can be seen in Table 1, the reaction did not proceed completely without the catalyst even after 24 hours and since the reaction time

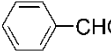
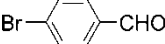
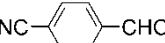
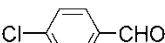
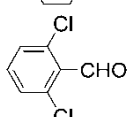
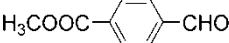
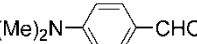
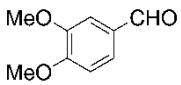
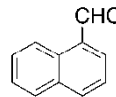


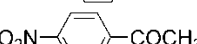
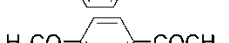
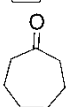

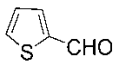
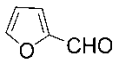
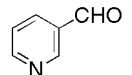
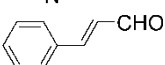
Table 1. Condensation of 4-chloro benzaldehyde, aniline and TMS-CN in the presence of different amounts of choline chloride.2ZnCl₂^a

Entry	Mol% of catalyst	Reaction time (min)	Yield (%) ^b
1	No catalyst	24 h	<5
2	3	2	95
3	5	1.3	99
4	7	1.3	99
5	10	2.75	97
6	20	3	97

^aReaction conditions; 4-chloro benzaldehyde (1 mmol), aniline (1 mmol), TMS-CN (1.2 mmol), room temperature.

^bIsolated products.

Table 2. The Strecker reaction of TMSCN, aniline and various aldehydes and ketones catalyzed by choline chloride.2ZnCl₂^a.

Entry	Aldehyde/Ketone	Reaction time (min)	Yield (%) ^b	m.p °C (lit.) [ref]
1		3	87	76-78 (81-83)[5]
2		10	94	88-91(86-88)[5]
3		1	96	112-116 (118-121)[35]
4		1.3	99	108-110 (110-112)[36]
5		8	92	68-71 (73-76)[35]
6		0.5	92	114-116
7		1.5	88	103-107 (108-112)[37]
8		1	93	144-146 (134-136)[38]
9		4	92	99-101 (97-98)[39]
10 ^c		30	89	71-74 (72-74)[5]
11 ^c		35	92	93-95 (92-94)[5]
12 ^c		1	95	148-150
13 ^c		60	89	113-115 (115-116.5)[20]
14 ^c		140	75	79-81 (83-86)[35]
15 ^c		140	70	48-50 (51-54)[35]
16		4	89	100-102 (98-100)[36]
17 ^d		120	93	67-69 (68-69)[36]
18 ^d		180	82	79-84 (74-83)[20]
19		0.5	85	118-121 (118-120)[5]

^aReaction conditions; aldehyde or ketone (1 mmol), aniline (1 mmol), TMSCN (1.2 mmol), room temperature.^bIsolated products.^c10 mol% choline chloride.2ZnCl₂ at 50 °C.^d10 mol% choline chloride.2ZnCl₂.

and yield for 7 mol% of catalyst was the same as that of 5 mol%, the latter was chosen as the optimum amount. As a result, different derivatives of benzaldehyde were reacted in the presence of 5 mol% choline chloride.2ZnCl₂ with TMSCN and aniline to afford the corresponding α -amino

nitriles up to 99% yield. Since ZnCl₂ is a weak Lewis acid, it was necessary to use 10 mol% of ionic liquid and 50 °C heat for ketones and benzaldehydes with electron donating substituents in order to make them react (see Table 2).

The compounds with electron donating substituents on benzaldehyde reacted with aniline as well as electron withdrawing ones, although harsher reaction conditions and longer time were needed for electron donating substituents such as methyl and methoxy. The steric hindrance did not affect the reaction rate very much (see Entry 5). Even conjugated aldehyde, cinnamaldehyde, effectively reacted with aniline and TMSCN under these conditions in a very short time with remarkable yield (Entry 19). It is worth mentioning here that in conjugated systems, the double bond migrates if nitriles are heated for a few minutes or allowed to stand at room temperature for a long time [34]. We also did not observe the formation of 1,4-addition products.

In addition to different benzaldehyde derivatives, this reaction was also tested with cyclic and acyclic ketones and it was observed that in contrast to weak Lewis acidity nature of ionic liquid, these reactions proceeded in a reasonable range of time with high yields. 4-methoxyacetophenone and 4-nitroacetophenone were tested as sample acyclic ketones and showed the same substituent effect as benzaldehydes (Entry 12 and Entry 13). Among cyclic ketones, cyclopentanone and cycloheptanone were chosen but the yields were less in comparison with benzaldehydes or acetophenones. The most important feature of this ionic liquid is its application in the synthesis of α -amino nitriles using acid sensitive aldehydes such as furfuraldehyde, thiophen carbaldehyde and pyridine carbaldehyde, which can be polymerized under strong acidic conditions. These compounds were readily used under weak Lewis acidity characteristic of this ionic liquid without any polymerization and made the corresponding α -amino nitriles in relatively high yields. No cyanohydrin trimethylsilyl ether (an adduct between an aldehyde and trimethylsilyl cyanide) was obtained under these reaction conditions. The tendency of this ionic liquid for water absorption resulted in rapid formation and activation of the imines or iminium salts. At the end of reaction, choline chloride.2ZnCl₂ ionic liquid can be readily removed from reaction media by washing the organic phase with water.

4. Conclusion

In conclusion, a novel, efficient and environmentally benign method for the synthesis of α -amino nitriles using the Lewis acidic IL, choline chloride.2ZnCl₂, as catalyst was reported. The advantage of this method is that using mild Lewis acidic characteristic of IL, different derivatives of benzaldehyde, cyclic and acyclic ketones and especially acid sensitive aldehydes were used and yielded the corresponding α -amino nitriles efficiently. This IL is inexpensive and easy to prepare compared to imidazolium based ILs and as the IL is moisture insensitive, there is no need to remove water produced during the reactions.

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