



Ionic liquid-promoted dehydration of aldoximes: a convenient access to aromatic, heteroaromatic and aliphatic nitriles

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ABSTRACT

A simple and convenient procedure for the synthesis of nitriles by dehydration of aldoximes using an ionic liquid, 1-pentyl-3-methylimidazolium tetrafluoroborate, [pmim]BF₄ under organic solvent-free condition, has been developed. A variety of aromatic, heteroaromatic and aliphatic aldoximes are converted to the corresponding nitriles. The ionic liquid is recovered and reused for subsequent reactions.

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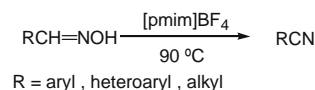
The organic nitriles are of much importance in organic synthesis as these are versatile intermediates in the synthesis of amines, carboxylic acids, esters and ketones which are useful raw materials for pharmaceuticals, agrochemicals and dyes.¹ The cyano moiety is also present in numerous bioactive molecules.² The classical method for the synthesis of alkyl cyanide involves nucleophilic substitution of an alkyl halide with metal cyanides,^{1a} whereas aromatic nitriles are produced by the Sandmeyer reaction and ammoxidation.³ However, these methods are associated with the use of NaCN/KCN/metal cyanides, which are in general highly poisonous, and heavy metal cyanides such as zinc cyanide which leaves residue of heavy metal salts. This is not desirable in the context of a clean environment. Dehydration of aldoximes to nitriles is one of the cleanest routes avoiding inorganic cyanides. Many methods have been developed for this transformation⁴ and some of the recently reported procedures involve Pd(OAc)₂/PPh₃ in CH₃CN,^{4a} benzotriazole phosphonium hexafluorophosphate derivative/DBU in CH₂Cl₂,^{4b} *N*-chlorosuccinimide/pyridine in CH₃CN,^{4c} DMF at 135 °C,^{4d} tungsten–tin mixed hydroxide in *o*-xylene at 149 °C,^{4e} diethylchlorophosphate in toluene,^{4f} molecular sieves under flash vacuum pyrolysis,^{4g} ZnO/CH₃COCl,^{4h} chlorosulfonic acid in toluene,⁴ⁱ dimethylthiocarbonate/Et₃N in dioxane,^{4j} diethylchlorophosphate in CHCl₃,^{4k} zeolite under microwave irradiation,^{4l} AlCl₃·6H₂O/KI/H₂O/CH₃CN,^{4m} Preyssler's anion, [NaP₅W₃₀O₁₁₀]¹⁴⁻,⁴ⁿ Burgess reagent^{4o} and thionyl chloride^{4p} as dehydrating agents. Among these, only a few are catalytic,^{4a,e,n} and most of them use stoichiometric amounts of reagents.^{4b–d,f,h–k,m,o,p} In general,

all these procedures are quite satisfactory; however a majority of them are restricted to the reactions of aromatic aldoximes. The aliphatic aldoximes are addressed by a few methods.^{4e,i,j,h,f}

Moreover, many of them involve hazardous organic solvents and toxic chemicals, and require long reaction times. Thus, alternative procedures with more general applicability, considerably faster reaction and environmentally friendly conditions are still in demand.

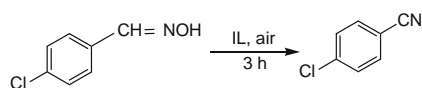
The ionic liquids having low volatility and unique catalytic activity have received considerable attention as eco-friendly solvents as well as catalysts^{5a,b} and reagents^{5f–h} in the context of green synthesis.^{5a} As a part of our continued efforts to explore the potential of ionic liquids for useful reactions,^{5c–e} we report here the dehydration of aldoximes by an inexpensive and easily accessible ionic liquid, 1-pentyl-3-methylimidazolium tetrafluoroborate, [pmim]BF₄ in the absence of any organic solvent and additive (Scheme 1).

To optimize the reaction conditions and find the right ionic liquid, a few experiments were carried out with different ionic liquids at varied temperatures, as illustrated in Table 1. It was found that the reaction using [pmim]BF₄ at 90 °C provided the best yield (Table 1, entry 3). The analogous ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF₄ also gave



Scheme 1.

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Table 1
Standardization of reaction conditions

Entry	IL	Equiv of IL	Temp (°C)	Yield ^a (%)
1	[pmim]BF ₄	1	25	10 ^b
2	[pmim]BF ₄	1	60	45 ^b
3	[pmim]BF₄	1	90	88
4	[pmim]BF ₄	0.5	90	40 ^b
5	[pmim]BF ₄	0.75	90	65 ^b
6	[bmim]BF ₄	1	90	82
7	[pmim]Br	1	90	0 ^c
8	[pmim]OH	1	90	0 ^d

^a Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ¹H and ¹³C NMR).

^b Besides product, the reaction mixture contains unreacted starting material.

^c The reaction mixture contains unreacted starting material (aldoxime) only without any product.

^d The reaction mixture contains unreacted starting material (aldoxime) and the corresponding aldehyde in 1:1 ratio.

comparable results. However, for our own convenience, [pmim]BF₄ has been used. The reaction using a basic ionic liquid, 1-methyl-3-pentylimidazolium hydroxide did not proceed at all.

Several aldoximes were subjected to dehydration by this procedure⁶ using [pmim]BF₄ to produce the corresponding nitriles. The results are summarized in Table 2. Both electron-donating and electron-withdrawing group-substituted aromatic aldoximes provided uniformly good results. The vinyl aldoximes such as cinnamyl and acrolyl aldoxime (Table 2, entry 11) also underwent dehydration without any difficulty. Thus, this protocol provides an easy access to conjugated nitriles. This procedure is also compatible with heteroaryl (Table 2, entry 16) and aliphatic aldoximes (Table 2, entries 13–15).

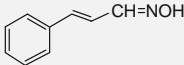
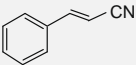


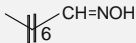

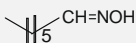

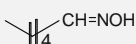

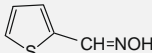
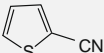
Although ionic liquids have been reported to catalyze Beckmann rearrangement of ketoximes efficiently,⁷ their use for dehydration of aldoximes is rather scarce.⁸ Only two reactions of aromatic aldoximes have been demonstrated using a complex task-specific ionic liquid bearing a sulfonyl chloride moiety.^{8a} This ionic liquid is not readily available and its preparation involves a number of steps and expensive chemicals. In another report,^{8b} dehydration of aldoximes was carried out using a combination of

Table 2
Dehydration of aldoximes to nitriles by [pmim]BF₄

Entry	Aldoxime	Time (h)	Product	Yield ^a (%)	Ref.
1		4		86	4d
2		3		88	11
3		3		90	4e
4		4		84	4a
5		4		82	4e
6		5		82	4e
7		5		80	4e
8		4		82	4k
9		5		75	12
10		5		78	4a

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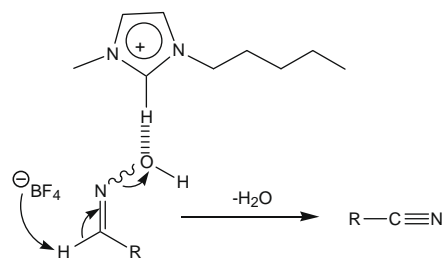
Table 2 (continued)

Entry	Aldoxime	Time (h)	Product	Yield ^a (%)	Ref.
11		5		76	4a
12		5		75	14
13		4		86	13
14		6		90	4f
15		7		76	4g
16		5		75	4d

^a Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ¹H and ¹³C NMR).

AlCl₃/[bmim]Br in xylene under microwave irradiation. The use of AlCl₃ is not very desirable as it entails environment pollution. Our procedure using a very common and readily accessible⁹ ionic liquid [pmim]BF₄ or [bmim]BF₄ without any organic solvent and co-catalyst possesses distinct advantages over the other two. Moreover, the reactions are relatively fast (3–7 h) and the yields (isolated) are quite high (75–90%). The ionic liquid works here as a catalyst as well as a reaction medium. The reaction is also effective using 75 mol % of ionic liquid; however, the reaction is relatively slow. This procedure is also more general as it is compatible with aromatic, heteroaromatic as well as aliphatic aldoximes, and a variety of functionalities such as Cl, Br, NO₂ and OH. The ionic liquid was recovered after the reaction and recycled for three runs without any appreciable loss of efficiency.

Although we do not have any experimental data regarding the mechanism of this reaction, we propose a reaction pathway as outlined in Scheme 2. The ionic liquid, [pmim]BF₄ facilitates the dehydration process through co-ordination of its 2-carbon-H with –OH of aldoxime,¹⁰ followed by abstraction of H⁺ by BF₄[–]. Here BF₄[–] acts as a base rather than as a nucleophile. When [pmim]OH is used, OH[–] being a stronger nucleophile attacks the sp² hybridized



Scheme 2.

carbon of the oxime (C=N bond) leading to the formation of the corresponding aldehyde (Table 1, entry 8). Br[–] is effective neither as a base nor as a strong nucleophile as OH[–], thus producing neither nitrile nor aldehyde (Table 1, entry 7).

In conclusion, we have developed an ionic liquid-promoted efficient procedure for the dehydration of aldoximes to nitriles under organic solvent-free condition in an aerobic atmosphere. The simplicity in operation, general applicability, relatively fast reaction, high yields and recyclability of ionic liquid up to three runs make this protocol an attractive alternative.

Acknowledgements

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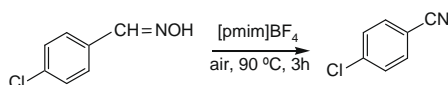
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.069.

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Table 3
Recyclability of ionic liquids



No. of cycles	Yield (%)	Amount of recovered ionic liquid (mg)
1 ^a	88	192
2 ^b	82	144
3 ^b	75	123
4 ^b	68	93

^a One millimolar (156 mg) of oxime was taken in 1 mmol (240 mg) of [pmim]BF₄.

^b The aldoximes were taken in proportionate molar ratio of the recovered ionic liquids.

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 - Representative experimental procedure for dehydration of aldoximes. Conversion of benzaldoxime (mixture of cis and trans isomers) to benzonitrile (Table 2, entry 1): A mixture of benzaldoxime (121 mg, 1 mmol) and [pmim]BF₄ (240 mg, 1 mmol) ([bmim]BF₄ may also be used) was stirred at 90 °C in an aerobic atmosphere for 4 h (monitored by TLC). After the reaction was over, the reaction mixture was extracted with ether (3 × 10 mL), and the ether extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent left the crude product which was purified by column chromatography over silica gel (hexane/ether 95:5) to afford pure benzonitrile (89 mg, 86%). The ¹H and ¹³C NMR data of this compound are in good agreement with the reported data.^{4d}
The ionic liquid, left after extraction of the product was dried under vacuum and reused for subsequent reactions. The details are outlined in Table 3. This procedure was followed for all the reactions listed in Table 2. All the products are known compounds and were identified by comparison of their spectroscopic data (IR, ¹H NMR and ¹³C NMR) with those reported (See references in Table 2). Spectroscopic characterization data (IR, ¹H NMR and ¹³C NMR) of a few selected compounds are provided below as ready reference.
Benzonitrile (Table 2, entry 1): colourless liquid; IR (neat): 3065, 2230, 1599, 1491, 1446, 1288 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.49–7.43 (m, 3H), 7.34–7.29 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 132.57, 131.80 (2C), 128.90 (2C), 118.57, 112.04.
4-Hydroxy-3-methoxybenzonitrile (Table 2, entry 8): Solid; mp 90 °C; IR (KBr): 3363, 3228, 2228, 1603, 1520, 1371, 1283 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.19 (d, J = 8.1 Hz, 1H), 7.07 (s, 1H), 6.93 (d, J = 8.1 Hz), 6.44 (br s, 1H), 3.90 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 150.18, 146.91, 126.77, 119.35, 115.62, 115.09, 102.98, 55.96.
2-Naphthalenecarbonitrile (Table 2, entry 10): colourless liquid; IR (neat): 3433, 3062, 2226, 1626, 1593, 1361, 1273 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 8.00 (s, 1H), 7.73–7.68 (m, 3H), 7.50–7.39 (m, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 134.59, 134.09, 132.18, 129.18, 129.06, 128.39, 128.05, 127.67, 126.27, 119.28, 109.29.
(E)-3-Phenylprop-2-enitrile (Table 2, entry 11): colourless liquid; IR (neat): 3366, 3060, 2218, 1697, 1618, 1494, 1207 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.34 (br s, 5H), 7.29 (d, J = 16.7 Hz, 1H), 5.79 (d, J = 16.6 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 150.64, 133.60, 131.33, 129.21 (2C), 127.50 (2C), 118.33, 96.40.
1-Heptanonitrile (Table 2, entry 14): colourless liquid; IR (neat): 3016, 2959, 2932, 2860, 2247, 1462, 1427, 1379, 1115 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 2.24 (t, J = 6 Hz, 2H), 1.59–1.50 (m, 2H), 1.39–1.31 (m, 2H), 1.24–1.22 (m, 4H), 0.81 (t, J = 6 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 119.56, 30.66, 28.05, 25.09, 22.09, 16.76, 13.61.
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