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The Combination of 1-Butyl-3-methylimidazolium Bromide and Trichloro(trifluoromethanesulfonato)titanium(IV) as a New Protocol for the Synthesis of Aryl Nitriles

Jalil Noei,[*] Ahmad Reza Khosropour,[†,*] and Arsalan Mirjafari[‡]

Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr 63519, Iran. [*]E-mail: noei0655@yahoo.com
[†]Catalysis Division, Department of Chemistry, Faculty of Science, University of Isfahan, Isfahan 81746-73441, Iran
[*]E-mail: khosropour@ui.ac.ir
[‡]Department of Chemistry, University of South Alabama Mobile, Alabama 36688-0002,USA
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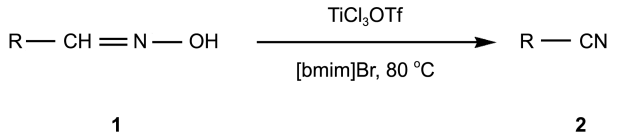
Nitriles are one of the most important precursors in organic synthesis. These compounds are used for the preparation of esters,[1] amides,[1,2] carboxylic acids,[1,3] amines[1,4] and thioamides.[5] Nitriles have also found widespread application in preparation of heterocycles as tetrazoles.[6]

The classical method for the synthesis of alkyl nitriles is the reaction of alkyl halides with highly toxic metal cyanide *via* a nucleophilic pathway. However, this reaction induces one-carbon homologation. Recently, Togo and co-workers reported the conversion of alkyl halides into corresponding nitriles with retention of the number of carbon atoms by molecular iodine and DIH.[7] Nitriles can also be obtained by the direct transformation of alcohols,[8] aldehydes,[9] carboxylic acids[10] and aldoxime ethers,[11] dehydration of amides,[12] oxidation of primary amines[13] and reduction of primary aliphatic nitro compounds.[14] The dehydration of aldoximes is one of the most fundamental methods for the synthesis of nitriles. These reactions can be catalyzed by common reagents such as acid anhydrides,[15] organic acids,[16] strong mineral acids (H_2SO_4, $ClSO_3H$),[17] NBS/pyridine,[18] bromodimethylsulfonium bromide (BDMS),[19] triflyl-imidazole[20] and ion exchangers.[21] Similarly, transition metal catalysts such as $PtCl_4(EtCN)_2$,[22] $[RuCl_2(p\text{-cymene})]_2$,[23] $(HO)ReO_3$,[24] $Ga(OTf)_3$,[25] W–Sn hydroxide,[26] $Cu(OAc)_2$,[27] and $Pd(OAc)_2$/PPh_3[28] have been reported. Recently, Ranu and co-workers used the ionic liquids for synthesis of nitriles.[29] In this report oximes converted into corrosponding nitriles by $[pmim]BF_4$ at 90 °C in 3 to 7 hours. However, the use of this conditions has problems such as high temperature and relatively long time. Probably, the combination of a catalyst with ionic liquid will have better results. To the best of our knowledge, the conversion of oximes into nitriles in ionic liquids using transition metal catalyst has never been reported.



1 **2**

Scheme 1

We wish to report a convenient new protocol for synthesis of nitriles through the dehydration of aldoximes by $TiCl_3OTf$ as a transition metal catalyst in [bmim]Br as a ionic liquid at 80 °C (Scheme 1).

In our initial investigation the reaction of 4-methoxybenzaldoxime to 4-methoxybenzonitrile was selected as a model system to optimize reaction parameters. Next, we investigated the influence of different ionic liquids and solvents. As shown in Table 1, applying [bmim]Br (1.5 molar equiv.) showed the best result.

Table 1. Influence of ionic liquid or solvent on the synthesis of 4-methoxybenzonitrile[a]

Entry	IL or Solvent	Time (min)	Yield (%)[b]
1	$[bmim]BF_4$	60	50
2	$[bmim]PF_6$	60	55
3	[bmim]OTf	60	58
4	[bmim]Cl	60	65
5	[bmim]Br	60	82
6	CH_3CN	60[c]	10
7	$CHCl_3$	60[c]	15
8	CH_2Cl_2	60[c]	15

[a]Oxime: 1 mmol, Catalyst: 10 mol %, T: 70 °C. [b]Isolated yields. [c]Reflux.

Table 2. Influence of catalyst and temperature on the synthesis of 4-methoxybenzonitrile

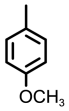
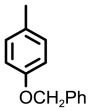
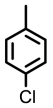
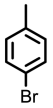
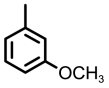
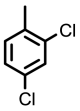
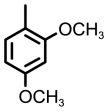
Entry	Equiv of catalyst	Temp (°C)	Time (min)	Yield (%)[a]
1	0	80	60	20
2	0.1	70	30	64
3	0.15	70	30	75
4	0.2	70	30	75
5	0.15	60	15	40
6	0.15	70	15	72
7	0.15	80	15	95
8	0.15	90	15	94

[a]Isolated yields.

The reaction was also optimized with respect to molar equiv. of $TiCl_3(OTf)$ and appropriate temperature. The results are recorded in Table 2. On the basis of the experiments performed, we obtained the best results with 0.15 molar equiv of $TiCl_3(OTf)$ at 80 °C (Table 2, entry 7).

Next, we decided to assess the generality of this transformation and subjected a variety of aldoximes to the optimized reaction conditions. The results are summarized in Table 3. The reaction was successful when there were electron-donating or electron-withdrawing substituents and heterocyclic substrates. We observed electronic effects: for example, aldoximes with electron-donating groups (Table 3, entries 1-2) reacted rapidly, while the presence of electron-withdrawing group (Table 3, entries 3-6) decreased the reactivity, requiring longer reaction times. Stric effects were also effective so the presence of an *o*-substituent or *o*,*p*-substituents reduced the reaction rate (Table 3, entries 7-10). Moreover, heterocyclic aldoximes such as 2-furylaldoxime, 4- or 2-pyridylaldoxime (Table 3, entries 13-15) displayed relatively high reactivity under these conditions.

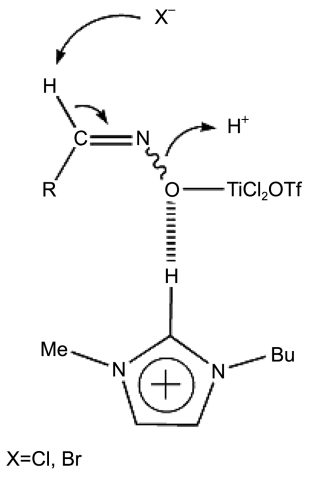
Table 3. Synthesis of aryl nitriles from aryl aldoximes in the presence of $TiCl_3(OTf)$ in [bmim]Br

Entry	R	Product	Time (min)	Yield (%)[a]
1		**2a**	15	95
2		**2b**	20	96
3		**2c**	60	96
4		**2d**	50	93
5		**2e**	60	92
6		**2f**	120	88
7		**2g**	120	91
8		**2h**	120	87
9		**2i**	180	83
10		**2j**	120	93
11		**2k**	40	90
12		**2l**	30	95
13		**2m**	60	94
14		**2n**	30	88
15		**2o**	40	93

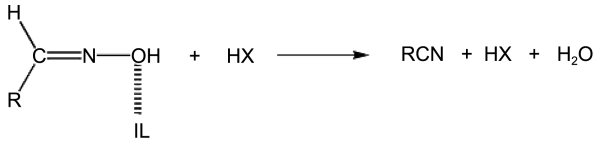
Although the mechanism of the reaction are not known exactly, we propose a reaction pathway considering our results and older articles.[29,30] Both catalyst and ionic liquid affected in this reaction. The reaction didn't make good progress in the absence of either of them (Table 2, entry 1 and Table 1, entries 6-8). Presumbly, in the first step, the replacement of one or more of the chlorine atoms of $TiCl_3(OTf)$ occurs, then interaction between intermediate and ionic liquid facilates the dehydration of intermediate (Scheme 2).

The generated HX can catalyze dehydration of the aldoxime through its continuous generation with assistance of the ionic liquid, which justifies the catalytic behavior of this system (Scheme 3).

In summary, an efficient new method for the synthesis of various aryl nitriles from aryl aldoximes was described. The method gave excellent yields, short reaction times and easy work-up.



Scheme 2



Scheme 3

Experimental

Typical Procedure for the synthesis of 4-chlorobenzonitrile. To a mixture of 4-chlorobenzaldoxime (1 mmol) in [bmim]Br (1.5 mmol), $TiCl_3(OTf)$ (0.15 mmol, 45.7 mg) was added. The reaction mixture was stirred at 80 °C for 1 h. On completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ice-water (10 mL). The mixture was extracted with ether (3 × 5 mL), and the organic layers were combined and washed with brine. After drying ($MgSO_4$) and concentration *in vacuo*, the residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 5:1 as eluent) to afford the pure product in 96% yield.

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