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COMMUNICATION

A Convenient Reagent for the Conversion of Aldoximes into Nitriles and Isonitriles

Wei Zhang,[a] Jin-Hong Lin,[a] Pengfei Zhang,*[b] and Ji-Chang Xiao*[a]

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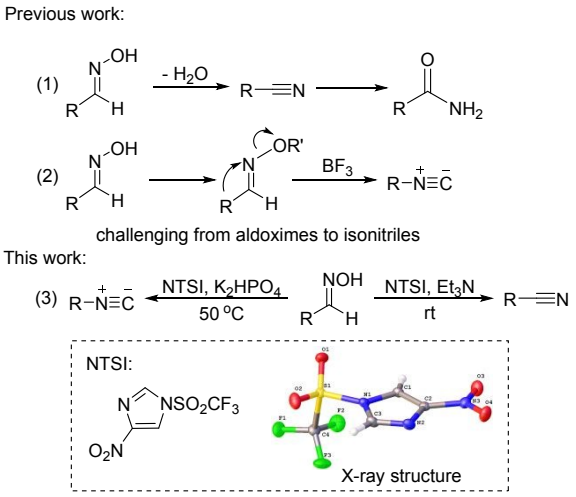
For the dehydroxylation of aldoximes with 4-nitro-1-((trifluoromethyl)sulfonyl)-imidazole (NTSI), slight modifications of reaction conditions resulted in significantly different reactions paths to provide either nitriles or isonitriles. The challenging conversion of aldoximes into isonitriles was achieved under mild conditions.

It is well known that reaction conditions play an important role in organic conversions and may determine reaction paths. If slight modifications of reaction conditions could result in completely different reaction paths to provide different useful products, the transformations may deserve much attention. Dehydroxylation of aldoximes has found widespread applications in organic synthesis since it may deliver nitriles[1] or provide amides[2] via the first formation of nitriles followed by a hydrolysis[3] (Scheme 1, eq 1). A migration of the substituent *anti* to the hydroxyl unit from the carbon to the nitrogen atom may be involved in the dehydroxylation of oximes, but the oximes which can undergo this rearrangement are limited to ketoximes.[4] For the dehydroxylation of aldoximes, the direct elimination of the proton in the CH=N moiety to afford nitriles is preferred, and thus this rearrangement usually does not occur.[2b] Although a previous example for the dehydroxylation of aldoximes have shown that the migration process may proceed to give isonitriles, the transformation suffers from a tedious two-step procedure and the need for isolation of the first-step products (eq 2).[5] Interestingly, we found that slight modifications of the reaction conditions could significantly change the reaction paths to furnish different products, nitriles and isonitriles, for the dehydroxylation of aldoximes with 4-nitro-1-((trifluoromethyl)sulfonyl)-imidazole (NTSI) (eq 3). The substituent migration was involved for the formation of isonitriles under mild conditions.



Scheme 1 The conversion of aldoximes into nitriles and isonitriles

The dehydroxylation reagent, NTSI, could be easily prepared by a reaction of nitro-imidazole with trifluoromethanesulfonic anhydride at room temperature (See supporting Information). The side product was removed by filtration, and the pure NTSI was obtained as a solid simply by concentration under vacuum to remove the solvent. Compared with the similar compound without a NO_2 substituent, a reagent which has to be purified by distillation and is usually used to convert phenols into aryl triflates,[6] NTSI may show wider application due to the convenient operations for its isolation and its higher electrophilic reactivity enhanced by the electron-withdrawing NO_2 group. Although both nitrile **2-1** and isonitrile **3-1** were produced in the dehydroxylation of aldoxime **1-1** with NTSI in most cases (Table 1), the base and the reaction solvent were found to be crucial for the respective reaction path. The use of CH_3CN as the solvent favoured the formation of nitrile **2-1**

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, China. Email: jchxiao@sioc.ac.cn.
[b] NHC Key Laboratory of Cancer Proteomics, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, 410008, China. Email: zhangpf690421@csu.edu.cn.
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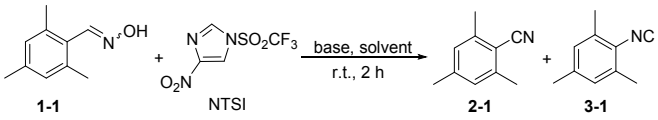
irrespective of whether an organic or inorganic base was used (entries 1-6). Whereas isonitrile **3-1** was obtained in 38% yield in CH_3CN by using K_2HPO_4 as the base (entry 5). The conversion into nitrile **2-1** occurred rapidly, and was finished within 10 min to give a high yield (entry 7). The conditions for the generation of isonitrile **3-1** was further screened (entries 8-14). A brief survey of the reaction solvents (entries 8-11) revealed that in CH_3NO_2 nitrile **2-1** could be suppressed and isonitrile **3-1** was obtained in 35% yield (entry 11). Prolonging the reaction time and elevating the reaction temperature increased the yield of isonitrile to 72% yield (entry 13). ^{13}C NMR analysis could easily distinguish the isonitrile structure from the nitrile structure. Two unique triplet signals were observed for the isonitrile (δ = 167 ppm and δ = 124 ppm), corresponding to the N≡C carbon and the C-(N ≡ C) carbon, respectively (See Supporting Information and the references therein).

Table 1 Optimization of The Reaction Conditions[a]



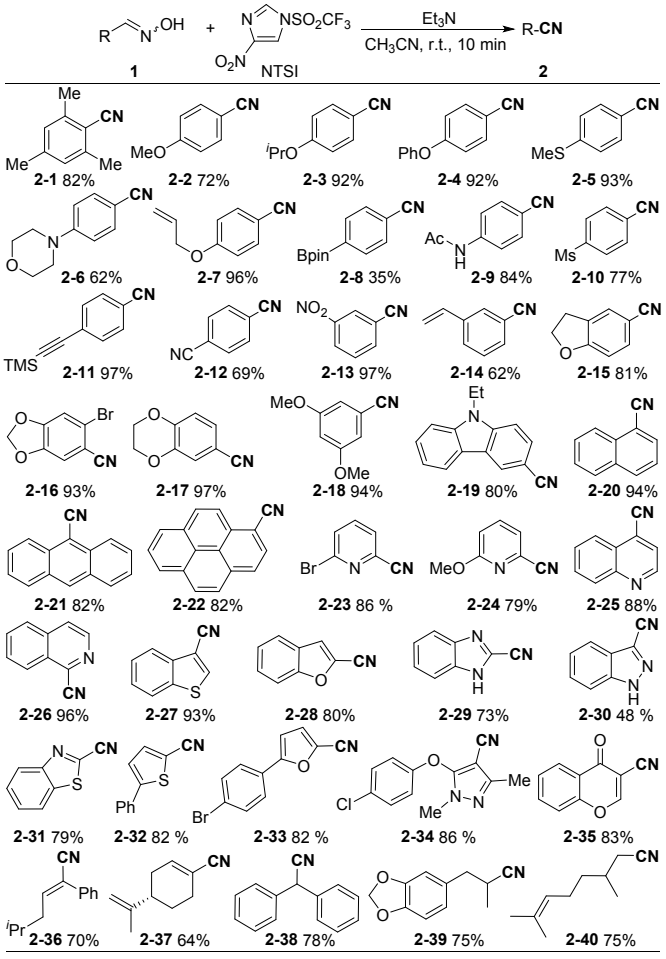
1-1 NTSI 2-1 3-1

entry	base	solvent	yield (%)[b]	
			2-1	**3-1**
1	Et_3N	CH_3CN	86	12
2	pyridine	CH_3CN	58	20
3	Na_2CO_3	CH_3CN	48	37
4	KF	CH_3CN	38	30
5	K_2HPO_4	CH_3CN	45	38
6	Na_2HPO_4	CH_3CN	trace	trace
7[c]	**Et_3N**	**CH_3CN**	**87**	**12**
8	K_2HPO_4	Acetone	32	28
9	K_2HPO_4	EA	40	20
10	K_2HPO_4	THF	43	22
11	K_2HPO_4	CH_3NO_2	trace	35
12[d]	K_2HPO_4	CH_3NO_2	7	46
13[de]	**K_2HPO_4**	**CH_3NO_2**	**8**	**72**
14[df]	K_2HPO_4	CH_3NO_2	13	64

[a]Reaction conditions: **1-1** (0.2 mmol), NTSI (1.2 equiv), base (2.0 equiv), solvent (2.0 mL), under N_2, 2 h; EA = Ethyl Acetate; THF = Tetrahydrofuran; [b]The yields were determined by ^1H NMR spectroscopy by using CH_2Br_2 as an internal standard; [c]The reaction time was 10 min; [d]The reaction time was overnight; [e]The reaction temperature was 50 °C; [f]The reaction temperature was 70 °C.

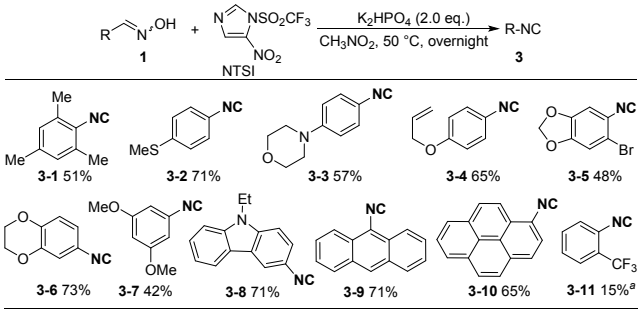
With the optimal conditions in hand (Table 1, entry 7), we then investigated the substrate scope of the conversion into nitriles. As shown in Scheme 2, this process could be extended to a wide range of aryl (**2-1** ~ **2-22**), heteroaryl (**2-23** ~ **2-34**), alkenyl (**2-35** ~ **2-37**) and alkyl (**2-38** ~ **2-40**) aldoximes. All reactions proceeded very fast and a reaction time of 10 min gave moderate to high yields. Electron-rich, -neutral, and -deficient aryl aldoximes could all be transformed smoothly, indicating that substituent electronic effects have no obvious impact on this transformation. This protocol could be applied to the synthesis of various heteroaryl nitriles (**2-23** ~ **2-34**). A variety of functional group could be tolerated, such as vinyl, Bpin, amide, silyl, nitro, cyanide, Ms (CH_3SO_2), halide, and carbonyl groups. The compatibility of Bpin (**2-8**), sivl (**2-11**) and halide (**2-16**, **2-23**, **2-33** and **2-34**) groups with these conditions may allow for further coupling reactions of these CN-containing products.

Since nitriles are widely present as key structural motifs in biologically active molecules and have emerged as versatile intermediates in synthetic chemistry,[7] significant efforts have been devoted to the development of efficient methods for the incorporation of a nitrile group into organic molecules.[8] Cyanation is apparently one of the most straightforward strategies, and a large number of cyanation approaches have been developed.[9] But the most commonly used reagents, including TMSCN[10], KCN[11] and CuCN[12], are highly toxic and are prone to hydrolysis to generate hazardous HCN gas. We have previously shown that the combination of difluorocarbene and ammonia could act as a CN^- source for cyanation.[13] The transformation from aldoximes is also a convenient strategy since aldoximes could be easily prepared. It has been reported that the conversions of aldoximes into nitriles could proceed smoothly under the catalysis of various transition metals,[14] such as palladium[15] and copper[16]. However, a high reaction temperature (80 °C or higher) is usually needed. Compared with the previous methods, the protocol is attractive due to the mild conditions and the rapid reaction rate.



Scheme 2 The conversions of aldoximes into nitriles. Reaction conditions: substrate **1** (0.5 mmol), NTSI (0.6 mmol), Et_3N (1.0 mmol) in CH_3CN (2 mL) at room temperature for 10 min. Isolated yields are shown.

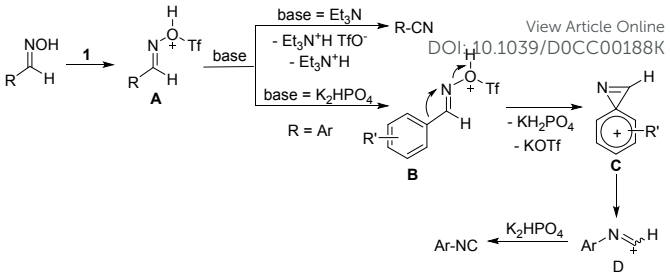
We further investigated the substrate scope of the conversion into isonitriles by using K_2HPO_4 as the base. As shown in Scheme 3, moderate to good yields were obtained in most cases. Because of its substantial sublimation, product **3-1** was isolated in a lower yield (51%) compared with its NMR yield (72% shown in Table 1, entry 13). The electronic effect of the substituent had a strong impact on the reactions of aryl aldoximes. Electron-donating groups are favourable, but an electron-withdrawing group would suppress this conversion (**3-11**). Unlike the conversion into nitriles, the transformation into isonitriles could not be extended to alkyl aldoximes.



Scheme 3 The conversion of aldoximes to isonitriles. Reaction conditions: substrate **1** (0.5 mmol), NTSI (0.6 mmol), K_2HPO_4 (1.0 mmol) in CH_3NO_2 (2 mL) at 50 °C for overnight. Isolated yields are shown. [a]The yield of product **3-11** was a ^{19}F NMR yield by using CF_3CH_2OH as an internal standard.

Isonitriles are commonly found in naturally occurring compounds,[17] and have served as important intermediates due to the dual nucleophilic and electrophilic character of the isonitrile group.[18] Many methods for the synthesis of isonitriles have been developed, such as direct isocyanation,[19] dehydration of formamides,[20] and carbylamine reaction of primary amines with a dihalocarbene[21]. The transformation from aldoximes is a promising approach for the synthesis of isonitriles, but it is a challenging task since the direct conversion into nitriles is preferred over the substituent migration. In our protocol, this reaction proceeds smoothly by using suitable reagents.

Irrespective of whether Et_3N or K_2HPO_4 is used as the base, the first step is to form the N-OTf intermediate **A** (Scheme 4). The generation of the N-OTf moiety increases the acidity of the proton in CH=N group, and thus the elimination of this proton can readily occur to provide nitriles by using Et_3N (pKa of Et_3N^+H is 10.75) as the base. However, K_2HPO_4 (pKa of $H_2PO_4^-$ is 7.21) is not basic enough for deprotonation, and thus a migration would occur.[4] The anchimeric assistance of the aryl group[22] favours the elimination of the TfO^- anion by forming a three-membered ring (Intermediate **C**). The formation of the cation **C** explains why an electron-donating group is favourable for the conversion into isonitriles. The ring opening affords vinyl cation **D**, in which the proton is acidic enough to be eliminated by K_2HPO_4.



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Scheme 4 The proposed mechanism

Conclusions

In summary, we have described the use of NTSI as a dehydroxylation reagent for the conversion of aldoximes into nitriles and isonitriles. It is interesting that slight modifications of the reaction conditions could result in significantly different reaction paths. We have also shown that a dehydroxylation reagent and a base are important for the challenging transformation of aldoximes into isonitriles. NTSI may become an attractive dehydroxylation reagent because of its easy availability and high reactivity.

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Conflicts of interest

There are no conflicts to declare.

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