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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Simple and Highly Efficient Procedure for Conversion of Aldoximes to Nitriles Using N-(p-Toluenesulfonyl) Imidazole

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Published online: 26 Jul 2010.

To cite this article: Mohammad Navid Soltani Rad , Ali Khalafi-Nezhad , Somayeh Behrouz , Zohreh Amini & Marzieh Behrouz (2010) Simple and Highly Efficient Procedure for Conversion of Aldoximes to Nitriles Using N-(p-Toluenesulfonyl) Imidazole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:16, 2429-2440, DOI: 10.1080/00397910903261395

To link to this article: http://dx.doi.org/10.1080/00397910903261395

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Synthetic Communications®, 40: 2429–2440, 2010
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903261395

SIMPLE AND HIGHLY EFFICIENT PROCEDURE FOR CONVERSION OF ALDOXIMES TO NITRILES USING *N*-(*p*-TOLUENESULFONYL) IMIDAZOLE

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A facile and efficient method for dehydration of aldoximes into nitriles using **N-(**p**-*toluenesulfonyl) imidazole (TsIm) is described. In this method, aldoximes were refluxed with TsIm in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dimethylformamide (DMF) to afford the corresponding nitriles in good yields. This methodology is highly efficient for various structurally diverse aldoximes including aromatic, heteroaromatic, and aliphatic oximes. A plausible mechanism for the conversion of aldoxime into nitriles using TsIm/DBU is explained.***

Keywords: Aldoximes; DBU; dehydration; DMF; nitriles; TsIm

INTRODUCTION

Nitriles[1] are valuable intermediates in organic synthesis because they are appropriate precursors for the introduction of various functional groups as well as the synthesis of *N*-heterocycles.[2] Numerous general methods have been established for the introduction of nitrile groups to various organic functional groups.[1] The most common routes to access aliphatic and aromatic nitriles involve nucleophilic substitution of alkyl halides with inorganic cyanides,[3] dehydration of amides,[1b,c] one pot-conversion of aldehydes to nitriles with various reagents,[4] oxidative conversion of primary alcohols and amines,[5] and Rosenmund[6] and Sandmeyer reactions.[7] The conversion of oximes[1] and *O*-substituted aldoximes[8] into nitriles is a well-known procedure for preparation of both aliphatic and aromatic nitriles. Numerous reagents and various conditions have been developed for the preparation of nitriles by dehydration of aldoximes. For example, $[RuCl_2(p\text{-cymene})]_2$/molecular sieves,[9] SeO_2,[10] triethyl-amine/SO_2,[11] PPh_3/CCl_4,[12] 1,1′-dicarbonyl-imidazole,[13] acetic

Received July 18, 2009.

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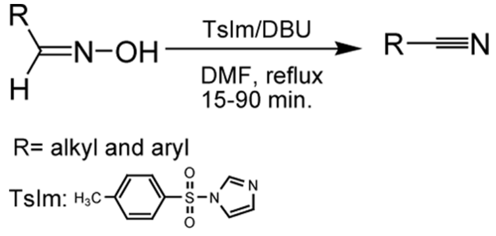


Scheme 1. Conversion of aldoximes to nitriles using TsIm.

anhydride,[14] Vilsmeier reagent,[15] Burgess reagent,[16] cyanuric chloride,[17] ZnO/CH_3COCl,[18] cytochrome P-450,[19] di-2-pyridylsulfite,[20] 2-chloro-1-methyl pyridinium iodide,[21] AlI_3,[22] $TiCl_3(OTf)$,[23] 1-chlorosulfinyl-4-dimethylaminopyridinium chloride,[24] chloro-sulfonyl isocyanate,[25] $AlCl_3 \cdot 6H_2O/KI$,[26] chlorosulfonic acid,[27] and S,S-dimethyl dithiocarbonate[28] have been employed for this transformation. Arenesulfonyl chlorides[29a] and methane sulfonyl chloride[29b] have also been used as dehydrating agents for this conversion. Although a large number of methods have been developed, they suffer from several disadvantages, such as poor yields, long reaction times, use of expensive or less readily available reagents, harsh reaction conditions, tedious workup, and limited substrate scope. Hence, there is still a need to develop practical and convenient methods for the conversion of aldoximes into nitriles.

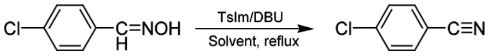
Recently, we reported that *N*-(*p*-toluenesulfonyl) imidazole (TsIm) is a highly efficient, cheap, neutral, and stable reagent for various organic transformations including one-pot conversion of alcohols to alkyl azides,[30a] alcohols to nitriles,[30b] esterification of alcohols,[30c] and *N*-alkylation of nucleobases.[30d] In continuation of our interest in the application of TsIm in organic synthesis, we hereby report that aromatic and aliphatic aldoximes can be efficiently converted into their corresponding nitriles using TsIm in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing dimethylformamide (DMF; Scheme 1).

RESULTS AND DISCUSSION

The first step of this synthetic approach was optimization of the reaction conditions. Initially, the effect of various solvents on the conversion of 4-chlorobenzaldehyde oxime into 4-chlorobenzonitrile in the presence of freshly prepared TsIm[30a] (1.2 equiv) was studied as a model reaction. The results are depicted in Table 1. As the data in Table 1 indicate, DMF (entry 2) was the most efficient solvent; hence, it was our solvent of choice. Anhydrous DMF, dimethylsulfoxide (DMSO), and hexamethylphosphoramide (HMPA) (Table 1, entries 1, 3, and 6) also afforded good yields of the corresponding nitrile but took longer for completion.

The choice of the base for activation of the aldoximes to react with TsIm and subsequent conversion into nitriles had great significance. In this case, we evaluated the potency of several organic and inorganic bases on the model reaction (Table 2). In the absence of a base, no reaction was achieved even after 72 h. DBU (Table 2, entry 4) proved to be the most efficient base for conversion of 4-chlorobenzaldehyde

Table 1. Effect of various solvents on the conversion of 4-chloro benzaldehyde oxime into 4-chlorobenzonitrile



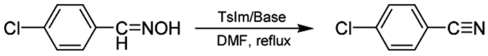
Entry	Solvent	Time (h)	Yield[b] (%)
1	DMF[a]	1	88
2	DMF	0.25	96
3	DMSO	0.5	91
4	THF	12	20
5	MeCN	6	65
6	HMPA	1.5	89
7	H_2O	30	NR[c]
8	Acetone/H_2O[d]	24	15
9	Toluene	30	Trace

[a] Anhydrous DMF.
[b] Isolated yield.
[c] No reaction.
[d] 1:1 ratio.

oxime into the corresponding nitrile. Other bases such as Cs_2CO_3, K_2CO_3, and NaH (Table 2, entries 6, 7, and 9) afforded lesser yields of nitrile.

The optimized amount of TsIm was 1.2–1.5 equiv. per equivalent of oxime. We also investigated the other TsIm analogs (Table 3). As the data in Table 3 indicate, a short reaction time and good yield of nitrile were obtained with TsIm (Table 3, entry 3) in comparison with other sulfonyl analogs. Replacing the tolyl in TsIm with methyl, trifluoromethyl, and phenyl (Table 3, entries 1, 2, and 4) caused no improvement in the reaction efficiency. Furthermore, other azole analogs of TsIm were not as efficient as imidazole (Table 3, entries 5 and 6). *N*-Tosyl phthalimide (Table 3, entry 7) was inactive for the conversion of 4-chlorobenzaldehyde oxime into its nitrile even after refluxing for 48 h.

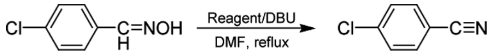
Table 2. Effect of various bases on the conversion of 4-chloro benzaldehyde oxime into 4-chlorobenzonitrile

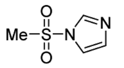
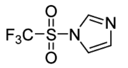
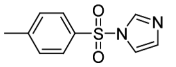
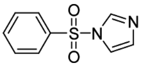
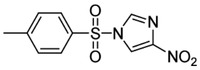
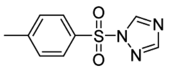
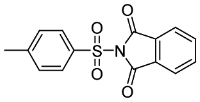


Entry	Base	Time (h)	Yield[a] (%)
1	None	72	0
2	DABCO	5	45
3	DMAP	21	18
4	DBU	0.25	96
5	MgO	24	15
6	Cs_2CO_3	0.5	91
7	K_2CO_3	2	90
8	TEA	5	20
9	NaH	0.5	92

[a] Isolated yield.

Table 3. Comparison of TsIm reactivity with analogs on the conversion of 4-chlorobenzaldehyde oxime into 4-chlorobenzonitrile



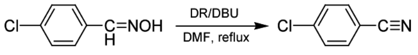
Entry	Reagent	Time (h)	Yield[a] (%)
1		1	90
2		1	91
3		0.25	96
4		1	82
5		12	68
6		12	63
7		48	NR[b]

[a] Isolated yield.
[b] No reaction.

The comparative dehydrating reagents under the same conditions were tested for conversion of 4-chlorobenzaldehyde oxime into 4-chlorobenzonitrile. The attained results are depicted in Table 4.

As data in Table 4 indicate, TsIm (Table 4, entry 5) and Ac_2O (Table 4, entry 3) demonstrated the best results; however, the reaction with TsIm was conducted in less

Table 4. Comparison of various dehydrating reagents with TsIm on the conversion of 4-chloro benzaldehyde oxime into 4-chlorobenzonitrile



DR:Dehydrating Reagent

Entry	Dehydrating reagent	Time (h)	Yield[a] (%)
1	TsCl	6	68
2	MsCl	6	55
3	Ac_2O	1	94
4	AcBr	1	78
5	TsIm	0.25	96

[a] Isolated yield.

reaction time. It is assumed that the greater efficiency of TsIm and Ac_2O than the other dehydrating reagents in Table 4 is attributable to the potential role of their corresponding counterion, because their separated counterions (OAc^- and imidazolide) have an apparent basic property that facilitates the 1,2-elimination. TsIm has several advantages with respect to all dehydrating agents used in Table 4, as these reagents are hygroscopic, corrosive, fuming, and toxic and/or create difficulty in handling; however, TsIm is nonhygroscopic, cheap, less toxic, and stable and can be easily prepared via a simple reaction.[30a] Thus, the TsIm is efficient enough to be considered as a suitable alternative for the other dehydrating agents.

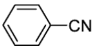
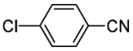
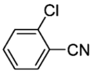
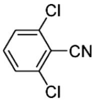
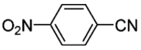
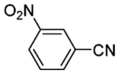
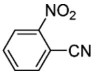
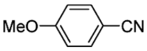
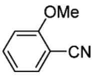
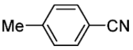
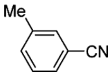
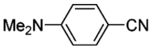
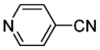
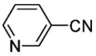
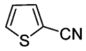
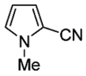
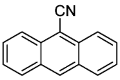
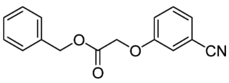
The generality and versatility of this method was examined by application to a set of structurally diverse aldoximes (Table 5). As the results in Table 4 indicate, this method is suitable for all oximes.

Both aromatic and aliphatic aldoximes were successfully converted into the corresponding nitriles in good yields. The capability of the method was confirmed with respect to aromatic (Table 5, entries 1–12, 17–19), heteroaromatic (Table 5, entries 13–16), aliphatic (Table 5, entries 24, 25), vinylic (Table 5, entry 23), and other aldoximes containing *N*-heterocycles (Table 5, entries 20, 21). Using this method, excellent results were obtained for aryl aldoximes with different substituted groups. Moreover, this methodology is highly chemoselective in the presence of various functional groups. Thiophene and pyrrole are also stable under the reaction conditions. By this procedure, both (*E*)- and (*Z*)-isomers of oximes can be converted into nitriles, and in most cases, the oximes used in this research were mixtures of (*Z*)- and (*E*)-isomers.

The TsIm/DBU-mediated conversion of aldoximes to nitriles is supposed to proceed by the reaction pathway shown in Scheme 2. We suggest that the preliminary acid–base reaction of DBU with oxime (**1**) affords DBU–oxime adduct **2**. The adduct **2** reacts with TsIm to provide *O*-tosyl-aldoxime **3** as the main intermediate. The generation of intermediate **3** was evidently endorsed through the course of the reaction by thin-layer chromatography (TLC) of in situ–generated **3** with authentic samples. Moreover, intermediate **3** was easily separated at an early stage of the reaction using column chromatography. The separated intermediate **3** was characterized by ^{1}H NMR,^{13}C NMR, and infrared (IR) spectroscopy methods. Two pathways (A and B) were postulated for conversion of **3** to nitrile **4**. In pathway A, the conversion proceeds by 1,2-elimination of **3**, whereas in pathway B, the conversion is achieved by 1,4-elimination in a concerted process. The reasons for suggesting a plausible mechanism comes from the facts that (i) in the absence of base, no nitrile is produced in a trace amount (Table 2) and (ii) 1 equiv. of DBU is enough for the reaction to proceed. Using extra amounts of DBU has negligible effects on the completion of the reaction. It is also assumed that released imidazole residue can regenerate DBU from protonated DBU. Finally, (iii) the thermal condition also facilitates the concerted-type process.

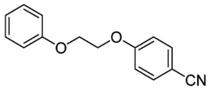
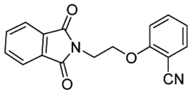
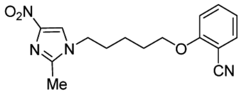
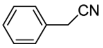
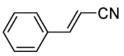
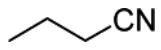
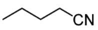
To understand whether a single mechanism (pathway A or B) or both are achieved in our reaction, we first synthesized and isolated 4-chlorobenzaldehyde *O*-tosyl oxime via reaction of 4-chlorobenzaldehyde oxime with TsCl in the presence of triethylamine (TEA) at room temperature in anhydrous DCM. Subsequently, the pure 4-chlorobenzaldehyde *O*-tosyl oxime was divided into equal amounts in two separate double-necked, round-bottom flasks, each equipped with a condenser.

Table 5. Dehydration of aldoximes into nitriles using TsIm/DBU in refluxing DMF

Entry	R-CN[a]	(ν cm^{-1})[b]	Time (min)	Yield[c] (%)	Ref.
1		2231	20	91	18, 22, 32, 34
2		2233	15	96	12, 18, 22, 32, 34
3		2220	15	93	12, 18, 34
4		2223	20	91	12, 18
5		2230	30	89	12, 18, 32, 33, 34
6		2228	30	87	12, 18, 33
7		2237	35	86	12
8		2224	20	95	18, 20, 32, 33, 34
9		2219	20	92	33
10		2232	25	94	18, 32, 34
11		2226	25	90	18
12		2214	20	93	34
13		2230	25	91	32
14		2233	25	89	18, 32, 34
15		2225	25	90	18, 32, 34
16		2202	25	87	–
17		2217	30	91	–
18		2221	50	81	–

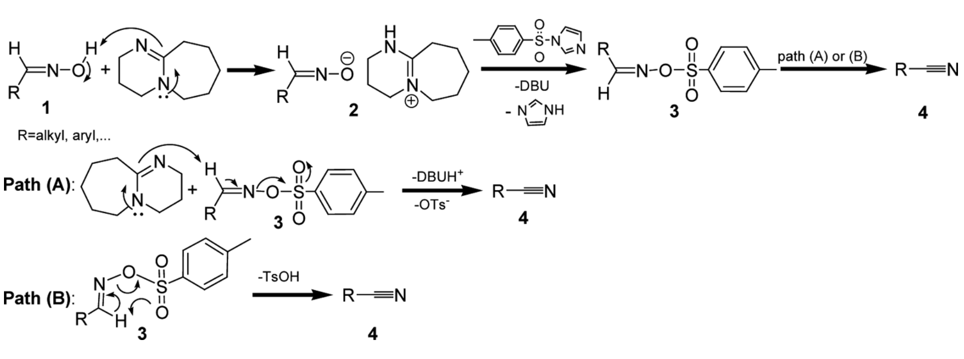
(*Continued*)

Table 5. Continued

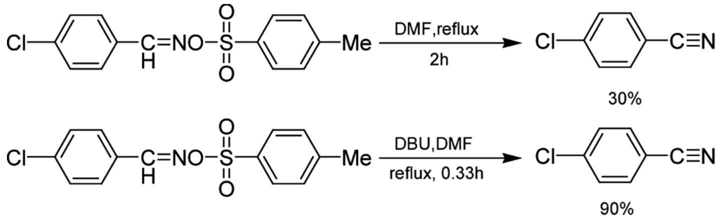
Entry	R-CN[a]	$(\nu\ \mathrm{cm}^{-1})$[b]	Time (min)	Yield[c] (%)	Ref.
19		2223	50	83	–
20		2215	90	84	–
21		2222	90	87	–
22		2205	40	85	22, 30b
23		2214	35	88	18, 20, 33, 34
24		2227	35	86	18
25		2232	35	86	18

[a] All products were characterized by ^{1}H and ^{13}C NMR, IR, CHN, and MS analysis.
[b] IR signal of nitrile in wavenumbers (cm^{-1}).
[c] Isolated yield.

In the first flask, a solution of 4-chlorobenzaldehyde *O*-tosyl oxime in DMF was refluxed for 2 h. After this time, no progress in the reaction was observed, as indicated by TLC. After workup and separation via column chromatography, 4-chlorobenzonitrile was attained only in 30% yield. In the second flask, which contained the same equivalent of 4-chlorobenzaldehyde *O*-tosyl oxime in DMF in the presence of DBU, the reaction finished after 20 min, and 4-chlorobenzonitrile was attained in 90% yield (Scheme 3).



Scheme 2. A plausible mechanism for conversion of aldoximes into nitriles using TsIm. Path (A): 1,2-elimination; Path (B): 1,4-elimination.



Scheme 3. The study for indicating reaction pathways A and B in the absence or presence of DBU.

These experiments have revealed that both mechanisms happen simultaneously. However, the base has an undeniable role in progress and termination of the reaction, and thus we can conclude that the reaction is mostly achieved via 1,2-elemination.

In conclusion, we have described TsIm as an efficient, stable, neutral, and cheap reagent for high-yield conversions of aldoximes to nitriles. The significant features of this method include short reaction time, good yields of product, simple experimental procedure, generality, and versatility.

EXPERIMENTAL

General Information

All chemicals were prepared from Fluka or Merck chemical companies except TsIm, which was freshly prepared using the explained methods.[30a] Solvents were purified and dried by reported methods[35] and stored over 0.3-nm molecular sieves. The progress of the reaction was followed with TLC using silica-gel SILG/UV 254 plates. Silica gel 60, 0.063–0.200 mm (70–230 mesh ASTM), was used for column chromatography. IR spectra were run on a Shimadzu Fourier transform (FT)–IR 8300 spectrophotometer. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Brüker Avance DPX-250 FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are in hertz. Mass spectra (MS) were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points (mp) were recorded on a Büchi 510 apparatus in open capillary tubes and are uncorrected.

General Procedure for Dehydration of Aldoximes into Nitriles

A mixture of aldoxime (0.01 mol),[31] freshly prepared TsIm[30a] (0.012 mol), and DBU (0.01 mol) in DMF (15 mL) was added to a double-necked, round-bottom flask (100 mL) equipped with a condenser. The mixture was refluxed, and in most cases, darkening occurred. Reflux was continued until TLC monitoring indicated no further improvement in the conversion (Table 4). After that, the reaction mixture was dissolved in CH_2Cl_2 (150 mL) and subsequently washed with water (3 × 150 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel, eluting with a mixture of *n*-hexane and EtOAc.

All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, CHN, and MS analysis. Selected spectral data for entries 20 and 21 are given.

Selected Spectral Data

2-(2-(1,3-Dioxoisoindolin-2-yl)ethoxy)benzonitrile (Table 4, Entry 20). White solid; R_f (EtOAc/*n*-hexane) (1:1) 0.48; mp 148.1 °C; ^{1}H NMR (CDCl$_3$, 250 MHz) δ_{ppm}: 4.03 (t, $J = 5.9$ Hz, 2H), 4.22 (t, $J = 5.9$ Hz, 2H), 6.88–6.91 (m, 2H), 7.36–7.42 (m, 2H), 7.58–7.63(m, 2H), 7.68–7.73 (m, 2H); ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ_{ppm}: 36.52, 65.19, 102.29, 112.29, 115.88, 121.31, 123.34, 131.86, 133.59, 133.76, 134.11, 159.66, 167.89; IR (KBr) ((cm^{-1}): 2215 (CN); MS (EI) [*m*/*z* (%)]: 292.08 (52). Anal. calc. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58%. Found: C, 69.82; H, 4.17; N, 9.63%.

2-(5-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)pentyloxy)benzonitrile (Table 4, Entry 21). Bright yellow oil; R_f (EtOAc) 0.45; ^{1}H NMR (CDCl$_3$, 250 MHz) δ_{ppm}: 0.75 (m, 2H), 1.05 (m, 4H), 1.59 (s, 3H), 3.20 (complex, 4H), 6.16–6.19 (m, 2H), 6.67–6.68 (m, 2H), 7.13 (s, 1H); ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ_{ppm}: 12.42, 22.37, 27.68, 29.28, 46.51, 68.12, 100.81, 111.99, 116.02, 120.23, 132.97, 134.15, 144.42, 145.57, 159.94, 161.84; IR (liquid film) ν (cm^{-1}): 2222 (CN); MS (EI) [*m*/*z* (%)]: 314.1 (48). Anal. calc. for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82%. Found: C, 61.15; H, 5.81; N, 17.79%.

ACKNOWLEDGMENT

We thank the Shiraz University of Technology and Shiraz University Research Councils for partial support of this work.

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