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Ac_2O/K_2CO_3/DMSO: an efficient and practical reagent system for the synthesis of nitriles from aldoximes

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ABSTRACT

The transformation of aldoximes to nitriles using acetic anhydride as dehydration agent under mild reaction conditions is reported. The reaction, which proceeds under weak alkaline condition, allows for the conversion of a range of aldoximes including aromatic aldoximes, alphatic aldoximes, and heterocyclic aldoximes in good to excellent yields. This method has also been successfully applied to the synthesis of calcium channel blocker nilvadipine in pilot scale.

Nitrile is an important synthetic intermediate for pharmaceuticals, pesticides, dyes, and material sciences.[1] The strong electron withdrawing effects and excellent hydrogen bond acceptor properties of nitrile make it widely used in the design of drug molecules. There are over 30 nitrile-containing drugs in the pharmaceutical market with 20 additional nitrile-containing leads in clinical development.[2] Numerous methods to synthesize nitriles have been documented in the literature, such as the Sandmeyer reaction,[3] metal-catalyzed cyanation of aryl halides, the nucleophilic substitution of alkyl halides with cyanides, oxidation of amines,[4] and dehydration of amides and aldoximes.[5] Among these, the dehydration of oximes into nitriles is one of the most suitable and attractive strategies for the synthesis of nitriles as the availability of starting material and the avoidance of very toxic cyanide ion. In recent years a number of efficient reagents and conditions have been reported for the dehydration of aldoximes to nitriles,[6–40] and the search for better reagents continues.

Acetic anhydride as a common and cheap dehydrating agent has been reported in the conversion of aldoximes to nitrile but with unsatisfactory results.[41] It always proceeds under acidic conditions[41a,b] or in aqueous alkaline solution[41c] or used both as solvent and reactant,[41d–f] the acid-sensitive functional group such as ester was partly cleaved. The hydration of nitriles to the corresponding primary amides was also observed.[42] In some cases, the primary amide formed in the reaction could hardly be removed from nitriles by a conventional crystallization purification. To solve these problems, we tried to convert aldoximes to nitriles using acetic anhydride under weak alkaline conditions. After several attempts, we found treatment of *m*-nitrobenzaldehyde oxime with Ac_2O/K_2CO_3 in DMSO at room temperature afforded *m*-nitrobenzonitrile in 50% yield (Table 1, entry 1). The reaction rate increases with temperature up to 50 °C, above which there is no change in rate for the conversion of aldoxime (Table 1, entries 2–7). At 50 °C, reaction can be completed in 10 h with excellent yield (94%). The reaction was monitored by HPLC and no byproduct 3-nitrobenzamide was detected. Then several solvents, such as dimethylsulfoxide, THF, DMF, 1,4-dioxane, acetone, and MeCN were screened (Table 1, entries 8–12), and the results showed that dimethylsulfoxide was the best choice (see Scheme 1). The effect of various organic and inorganic bases on the model reaction was investigated (Table 1, entries 13–16). It is clear that K_2CO_3 gave the best result. Very low yield was obtained using organic base Et_3N and pyridine. In the absence of base, very little conversion was observed even though the reaction time was prolonged to 48 h (Table 1, entry 17).

This method[43] was applied for conversion of a range of aromatic aldoximes to corresponding nitriles in high yields (Table 2). Electronic variation on the aromatic substituents had little effect on the yield of the reaction (Table 2, entries 1–8). It was interesting that the dehydration of benzaldehyde oxime proceeded slowly

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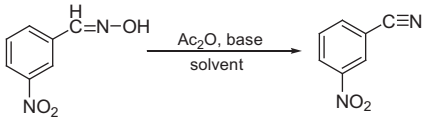
Table 1
Screen of reaction conditions[a]

Entry	Base	Temp. (°C)	Sol.	Time (h)	Yield[b] (%)
1	K_2CO_3	25	DMSO	24	50
2	K_2CO_3	40	DMSO	24	75
3	K_2CO_3	50	DMSO	10	94
4	K_2CO_3	60	DMSO	5	92
5	K_2CO_3	70	DMSO	3	90
6	K_2CO_3	80	DMSO	2	94
7	K_2CO_3	90	DMSO	1	93
8	K_2CO_3	50	DMF	10	50
9	K_2CO_3	50	1,4-Dioxane	10	<5
10	K_2CO_3	50	Acetone	10	<5
11	K_2CO_3	50	MeCN	10	<5
12	K_2CO_3	50	THF	10	<5
13	$NaHCO_3$	50	DMSO	10	30
14	Et_3N	50	DMSO	10	11
15	Pyridine	50	DMSO	10	10
16	Na_2CO_3	50	DMSO	10	45
17	—	50	DMSO	48	<5

[a] Reaction conditions: aldoximes[44] (1.5 mmol), Ac_2O (3 mmol), weak base (3 mmol), solvent (6 mL).
[b] Isolated yields.



Scheme 1.

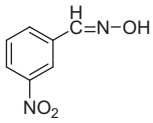
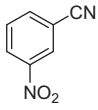
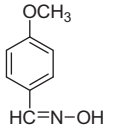
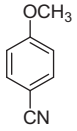
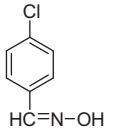
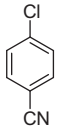
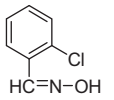
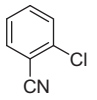
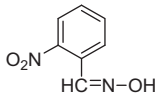
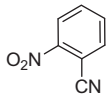
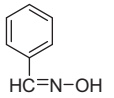
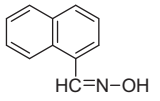
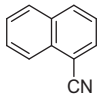
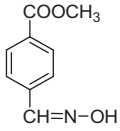
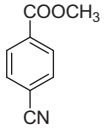
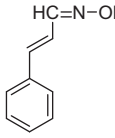
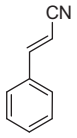
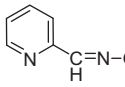
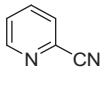
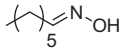
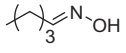
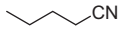
under these conditions, we can improve the reaction temperature to complete it. Benzonitrile could be isolated in 96% yield after 24 h (90 °C) (entry 6). It is worth noting that the ester group would not be hydrolyzed under these conditions (entry 8). Furthermore, *trans*-cinnamoxime was also compatible with the employed reaction conditions with no isomerization of the double bonds (entry 9). In addition, as a typical heteroaromatic aldoxime, 2-pyridinealdoxime was smoothly converted into 2-pyridylnitrile in good yield (entry 10). Aliphatic aldoximes could also be employed as good substrates to afford the corresponding aliphatic nitriles, but the conversion rate was much slower than aromatic aldoximes (entries 11 and 12). For example, valeraldoxime was dehydrated to give valeronitrile in only 55% yield, and the improvement of temperature had little effect on the reaction conversion. All the structures of products were characterized by ^1H NMR and MS and the data were identical with literature records.

The possible reaction mechanism for conversion of aldoxime to nitrile using acetic anhydride in the presence of base is shown in Scheme 2. It includes reaction of the aldoxime with acetic anhydride to form *O*-acetyl-oxime, which was subsequently attacked by base to form the nitrile compound and acetate anion.

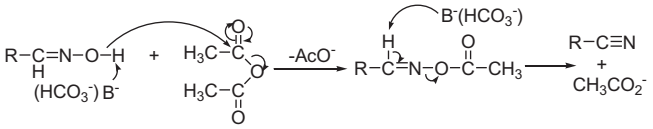
We next applied this method to the synthesis of nilvadipine, which is an effective antihypertensive drug (Scheme 3). According to the reported procedure, two byproducts (III and IV) would appear, and they should be removed by column chromatography using the mixture of benzene and ethyl acetate as eluent.[45] We also found that these two byproducts cannot be eliminated after two recrystallization in our lab. According to our developed method no formation of these two byproducts was observed in the dehydration step, we can get the final product with 99.9% purity and 85.1% yield (dehydration step after one recrystallization) at pilot scale.

In conclusion, a practical and efficient method has been established for the conversion of aldoximes to the corresponding nitriles using acetic anhydride as dehydration agent in the presence K_2CO_3 and DMSO. The availability of dehydration agent, mild reaction conditions, simple experimental procedure, high efficiency, and selectivity are advantages of the current method.

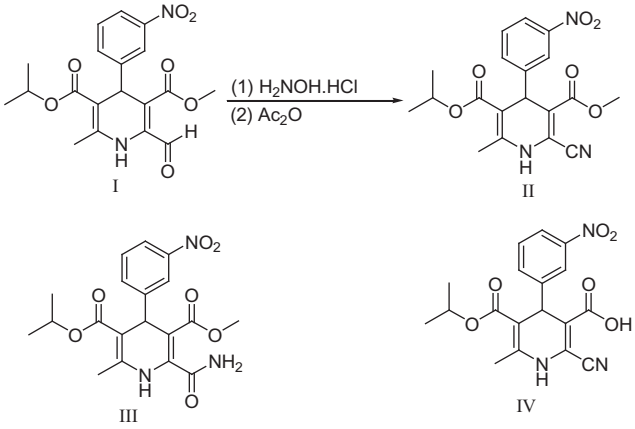
Table 2
Dehydration of various aldoximes using K_2CO_3 and Ac_2O[a]

Entry	Substrate	Product	Reaction time (h)	Yield[b] (%)
1			10	91
2			16	92
3			30	95
4			12	89
5			3.5	95
6			24	96[c]
7			11	87
8			21	95
9			24	90
10			24	88
11			40	75
12			48	55

[a] Reaction conditions: aldoximes (1.5 mmol), K_2CO_3(3 mmol), Ac_2O (3 mmol), DMSO (6 mL), 50 °C.
[b] Isolated yield.
[c] Yields were obtained from reactions running at 90 °C.



Scheme 2.



Scheme 3.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.079.

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43. A general procedure for the preparation of nitrile from aldoxime using acetic anhydride as the dehydration agent: K_2CO_3 (3 mmol) was added to a stirred mixture of aldoxime (1.5 mmol) and 6 mL DMSO, followed by Ac_2O (3 mmol). The resulting mixture was stirred at 50 °C for a specified period (Table 2). After the reaction was completed, 30 mL water was added then extracted with CH_2Cl_2 (10 × 3 mL). The organic phase was washed with water (10 × 3 mL) then dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the nitrile products.
44. All of the aldoxime used in this method were synthesized in excellent yields by a mixture of 1.0 equiv of the aldehydes, 1.4 equiv of NH_2OH·HCl, and 2.0 equiv of NaOAc in aqueous MeOH. The crude aldoxime after general post-treatment was directly used for the dehydration reaction without further purification.
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