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Methyl 2-Nitrosobenzoate: A Simple Dehydrating Agent for the Synthesis of Nitriles from Aldoximes

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A simple and convenient synthesis of nitriles from the corresponding aldoximes using methyl 2-nitrosobenzoate under milder condition has been developed. The reaction proceeds under weak alkaline conditions and, allows for the conversion of a wide variety of aldoximes including aromatic aldoximes, and heterocyclic aldoximes in good to excellent yields in short time. Notably, α, β-unsaturated aldoximes were also compatible with the reaction conditions without any *cis*/*trans* isomerization of the double bonds. An unprotected hydroxyl and amine group has no effect on the reaction outcome.

Introduction

Nitriles are highly important synthons in many natural products, dyes, herbicides, agrochemicals, functional materials and various fine chemicals.[1] They also play a major role in drug design because of its unique electron withdrawing and hydrogen bond acceptor properties,[2] There are nearly 30 nitrile-containing drugs in the market for a variety of diseases and many nitrile-containing leads in clinical development (Figure 1).[3] In addition, nitriles are extensively used for conversion into useful functionalities such as amides, amines, esters, carboxylic acids, tetrazoles and other heterocycles.[4]

Recently, nitrile functionality has been exploited as a promising directing group for metal-catalyzed C–H activation reactions.[5] One of the well-known methods for the synthesis of nitriles involves the nucleophilic substitution reaction of alkyl halides with cyanide source, however, the hazardousness associated with metal cyanides limit the practical utility of this approach.[6] Thus, other methods such as the dehydration of aldoximes remain a promising method.[7] Some of the recently reported methods for aldoxime dehydration involve classical dehydrating agents includes organoselenium,[8] BOP/DBU,[9] triethylamine sulfurdioxide,[10] Montmorillonite KSF,[11] $NaICl_2$/aq NH_3,[12] NCS/pyridine,[13] $Pd(en)_2(NO_3)_2$,[14] W–Sn mixed hydroxide,[15] ethyldichlorophosphate/DBU,[16] ZnO/AcCl,[17] Ga(III)OAc/MeCN,[18] dimethylacetylene dicarboxylate/Et_3N,[19] by Preyssler's Anion and $[NaP_5W_{30}O_{110}]^{14-}$.[20] Direct conversion of aldehydes to nitriles is also reported.[21] However, many of these methods suffer from certain limitations such as the use of expensive reagents, high toxicity, harsh reaction conditions, substandard yields, tedious work up procedures and use of excess reagents. Unfortunately, the common dehydrating agents are insufficient for this purpose and more active reagents are required. Hence, the development of new synthetic routes using mild and non-toxic reagents have gained much interest from last decade from an environmental point of view. Therefore, the design of environmentally benign reactions is a crucial goal for a chemist. In this context, aryl nitroso compounds are found to be a chemoselective ligating agents for sulfonic acids, where nitroso group act as an electrophilic center.[22]

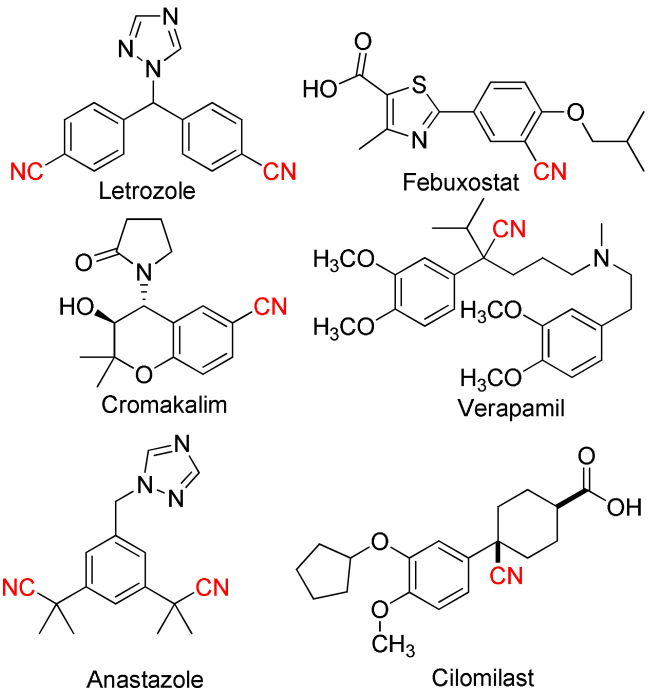

Figure 1. Examples of pharmaceutically important nitrile containing molecules.

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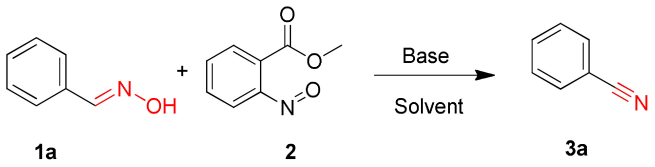
Results and discussion

We have utilized the electrophilic nature of nitroso group to act as dehydrating agent for converting aldoxime to corresponding nitriles. Herein, we report the methyl 2-nitrosobenzoate, a novel mild dehydrating agent for the synthesis of nitriles from aldoximes (Scheme 1).

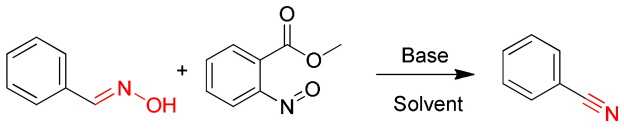


Scheme 1. Dehydration of benzaldoxime using methyl 2-nitrosobenzoate.

In order to investigate the dehydrating property of methyl 2-nitrosobenzoate **2**, we have selected benzaldoxime **1a** as a model substrate for the optimization of reaction condition. Initially, we have prepared the aldoximes from corresponding aldehydes and hydroxylamine hydrochloride by using reported procedure.[23]

Benzaldoxime **1a** (1.0 mmol) was treated with methyl 2-nitrosobenzoate **2** (1.0 mmol) using different solvents (2 mL) at different temperatures to optimize the reaction conditions to access desired nitrile **3a**. The results were shown in Table 1.

Table 1. Screening of reaction condition for dehydration of benzaldoxime by methyl 2-nitrosobenzoate.[a]



Entry	Base, Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	CH_3CN[c]	r.t	24	NA [e]
2	CH_3CN[c]	70	24	NA
3	Et_3N, CH_3CN[d]	r.t	24	NA
4	Et_3N, CH_3CN[d]	70	24	NA
5	Et_3N, CH_3CN	70	6	55
6	Piperidine, CH_3CN	70	4	60
7	DBU, CH_3CN	70	4	55
8	DABCO, CH_3CN	70	4	65
9	KO^tBu, CH_3CN	70	4	50
10	aq. NaOH, CH_3CN	70	4	40
11	K_2CO_3, CH_3CN	70	2	60
12	Cs_2CO_3, CH_3CN	70	2	80
13	Cs_2CO_3, CH_3CN	80	3	80
14	Cs_2CO_3, THF	70	3	70
15	Cs_2CO_3, 1,4-dioxane	70	8	50
16	Cs_2CO_3, Toluene	70	6	64

[a] Reactions were carried out by using **1a** (1.0 mmol), **2** (1.0 mmol) and base (1.0 mmol) in solvent (2.0 mL), unless otherwise mentioned. [b] Yield where reported is of isolated and purified product. [c] Reaction was conducted in absence of methyl 2-nitrosobenzoate **2** and base. [d] Reaction was conducted in absence of methyl 2-nitrosobenzoate **2**. [e] No product formation was observed.

When the reaction was performed at room temperature in acetonitrile in the absence of both the methyl 2-nitrosobenzoate **2** and base, product **3a** was not formed, the aldoxime was not consumed even after 24 h at 70 °C and prolonged time resulted in the hydrolysis of aldoxime (entries 1 and 2). Addition of the base to the reaction mixture did not give nitrile **3a** (entries 3 and 4). However, the starting material was consumed in presence of methyl2-nitrosobenzoate **2** and triethylamine at 70 °C and gave desired product in 55% (entry 5). Other organic bases such as piperidine, DBU and DABCO gave poor yields (entries 6-8).

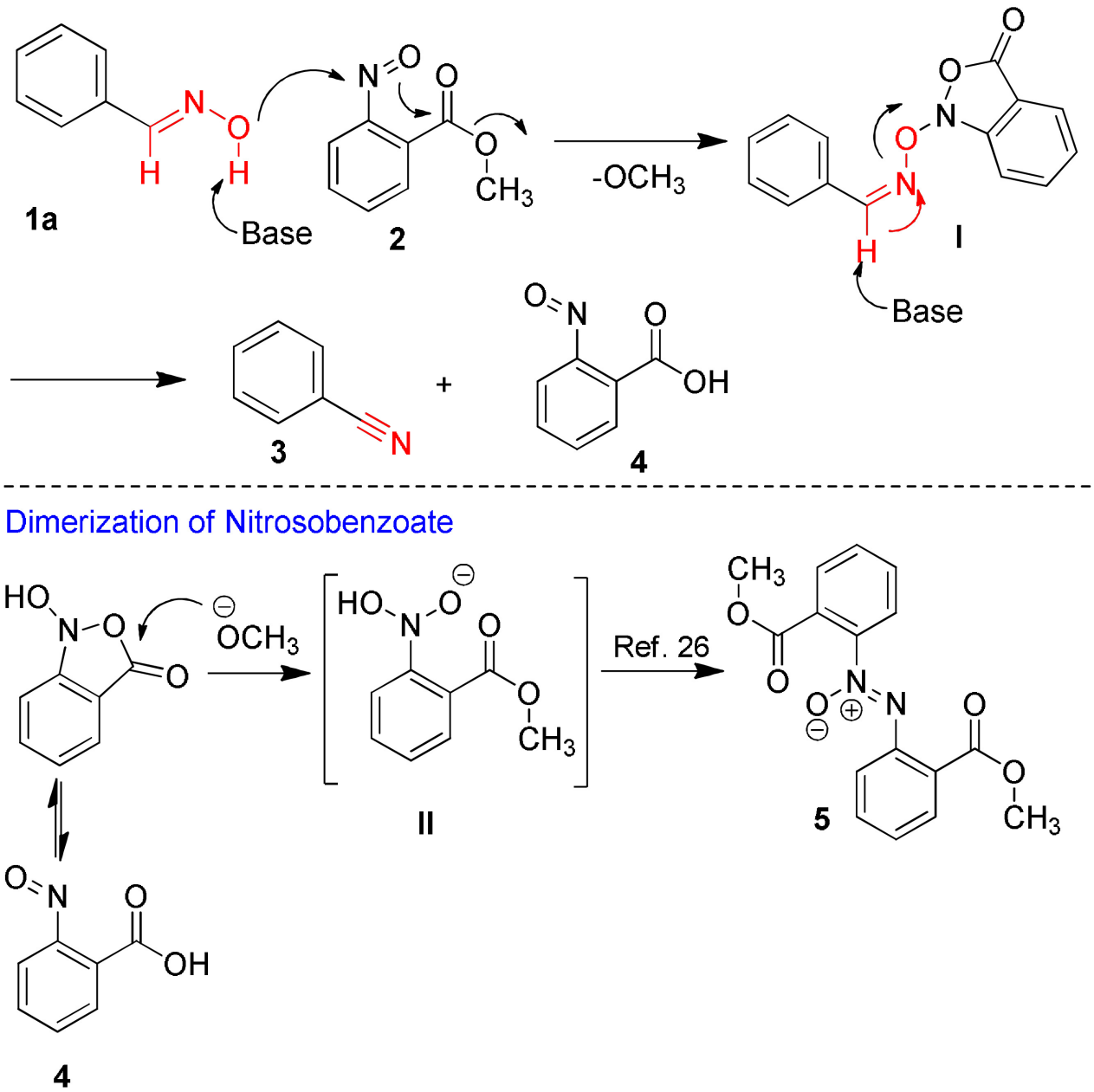
It was reported in the literature that use of strong base accelerates the hydration of nitriles to the corresponding primary amides and lower the yields and weak bases give better yields.[24] Our results support the same, use of Cs_2CO_3 in acetonitrile at 70 °C furnished **3a** in 80% yield (Table 1 entry 12) and increasing the reaction temperature did not improve the yield of the product (Table 1, entry 13). Then several solvents, such as THF, 1,4-dioxane and toluene were screened (Table 1, entries 14-16), and the results showed that acetonitrile was found to be the best choice. The effect of various inorganic bases on the model reaction was also investigated (Table 1, entries 9-12). It is clear that the Cs_2CO_3 gave the best result (Table 1, entry 12). With the optimized reaction conditions in hand, we explored the optimized reaction condition for conversion of a wide variety of aromatic aldoximes to corresponding nitriles in high yields (Table 2).

Dehydration of benzaldoxime proceeded fast under these conditions (Table 2, **3a**). It is worth noting that electronic effect of the substituents on aromatic aldoxime had little effect on the product yield (Table 2, entries **3b-3g**). It was observed that the halogen substituted aldoximes were reacted smoothly to give the corresponding nitriles in good yields (Table 2, **3h-l**).

Notably, *trans*-cinnamaldoximes were also compatible with the reaction conditions without any *cis*/*trans* isomerization of the double bonds (Table 2, **3r-s**). To our

delight, the unprotected hydroxyl and amine substituted aldoximes also reacted efficiently without causing any side reaction (Table 2, **3n**, **3t** and **3x**). Napthaldoximes and indole-3-oximes underwent dehydration in good yields (Table 2, **3t-3w**). In addition, as a typical heteroaromatic aldoxime, pyrazole-3-carbaldehyde oxime was smoothly converted into pyrazole-3-carbonitrile in good yield (Table 2, **3aa**, **3ab**). Unfortunately, aliphatic aldoximes do not undergo dehydration with our optimized reaction condition. All the structures of the products were characterized by ^{1}H NMR, ^{13}C NMR and the data were identical with literature records.[8a,21f,25]

A possible reaction mechanism was proposed in Scheme 2 for conversion of benzaldoxime to nitrile using methyl 2-nitrosobenzoate **2** based on literature reports.[22] Upon deprotonation of oxime **1a** by Cs_2CO_3 reaction could occur at the nitrogen atom of methyl 2-nitrosobenzoate **2** with the elimination of methoxide to form intermediate **I**, which was subsequently attacked by the base to form the corresponding nitrile compound and nitrosobenzoic acid **4** (Scheme 2). Although, nitrosobenzoic acid **4** was unable to isolate by column chromatography but was confirmed by mass spectrum



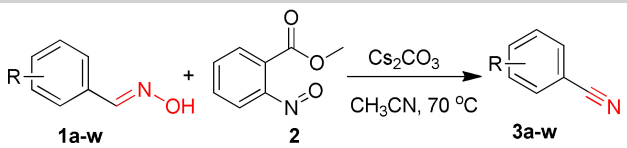
Scheme 2. Plausible reaction mechanism for the formation of nitriles by methyl 2-nitrosobenzoate and Cs_2CO_3.

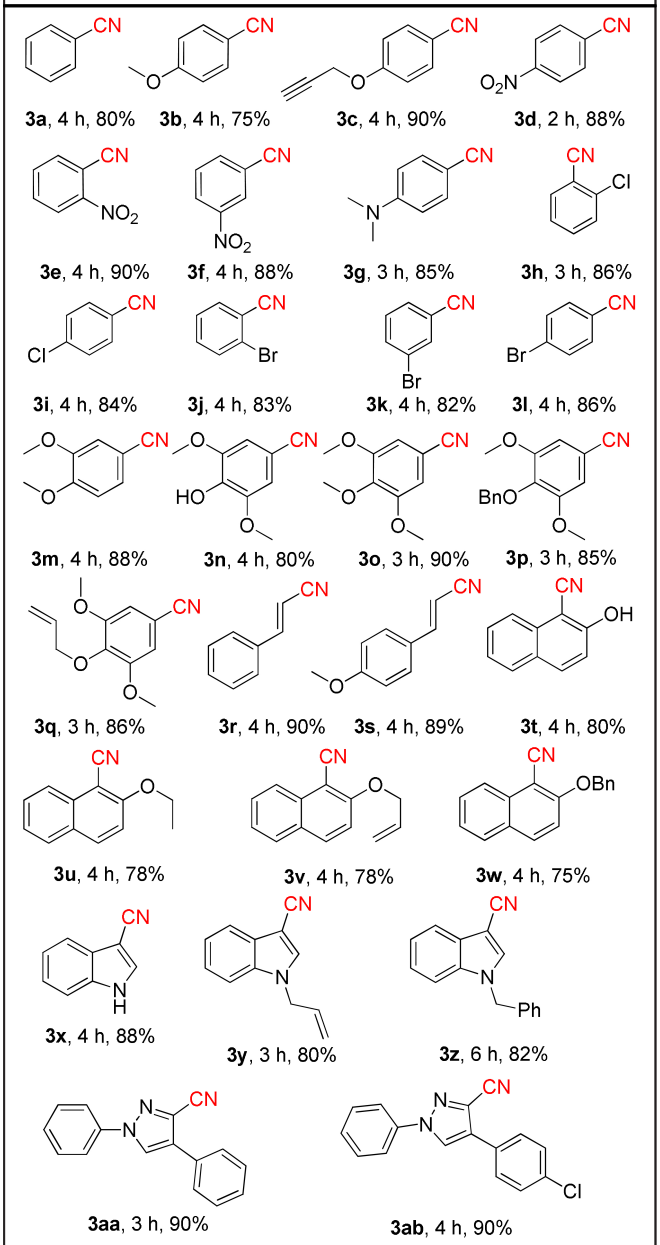
(*m/z* = 152.05). Nitrosobenzoic acid **4** again attacks by methoxide ion in basic condition to form intermediate **II**. There is mounting evidence that 2-substituted nitrosobenzoates undergo dimerization in basic condition to afford compound **5**.[26] The dimer **5** is characterized by ^{1}H NMR, ^{13}C NMR and mass spectral data.

Conclusion

A facile methodology for the conversion of aldehydes into nitriles is described. Using methyl 2-nitrosobenzoate, aldoximes were converted under mild reaction conditions into the desired nitriles in excellent yields and with less reaction time. Furthermore, the reaction is widely applicable for aromatic and heteroaromatic aldoximes; in fact, it works well with different aldoximes and occurs keeping unchanged the geometrical integrity of alkene substrates. The methyl 2-nitrosobenzoate assisted conversion of oximes to nitriles proceeded in shorter times and with good yields. This methodology can be readily applied to wide variety of aromatic and heteroaromatic aldoximes for the conversion into desired nitriles.

Table 2. Substrate scope of the dehydration methodology using methyl 2-nitrosobenzoate and Cs_2CO_3.[a,b]





[a] All the reactions were conducted on a 1 mmol scale. [b] Yield of isolated and column purified product.

Supporting Information Summary

Detailed experimental procedure, characterization data (^{1}H, ^{13}C NMR spectra) for all synthesized products **3a-3ab** and **5** are available in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aldoximes · Dehydration · Methyl 2-Nitrosobenzoate · Nitriles

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