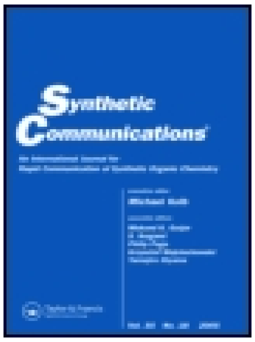

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Dehydration of aldoximes to nitriles using trichloroacetonitrile without catalyst

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ABSTRACT
Trichloroacetonitrile has been found to be an efficient dehydrating agent for a range of aldoximes including aromatic and heterocyclic aldoxime yielding the corresponding nitriles in moderate to good yields. The dehydration reactions can take place in non-acetonitrile media without the aid of a metal catalyst. In addition, it has been confirmed that trichloroacetonitrile was converted into trichloroacetamide in the reaction.

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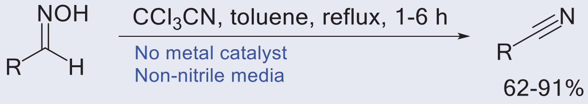
KEYWORDS
Nitrile; aldoxime; trichloroacetonitrile; toluene; trichloroacetamide

GRAPHICAL ABSTRACT



Introduction

Dehydration of aldoximes is a common method for the preparation of nitriles. There are many reports on the dehydration of aldoximes to nitriles, numerous reagents and various conditions have been developed. Among these, the metal-catalysed conversion of aldoximes to nitriles in acetonitrile or propionitrile has attracted the attention of many researchers over the last twenty years. To our knowledge, more than thirteen kinds of catalysts such as copper salts,[1] $SnCl_2$,[2] $GaCl_3$,[2] osmium-guanidinate complexes,[3] PhSeOH,[4] $Pd(OAc)_2$,[5] Palladium(II) complexes,[6] nickel catalysts,[7] $Ga(OTf)_3$,[8] $[RuCl_2(pcymene)]$,[9] $InCl_3$,[10] AlI_3,[11] and $[(CH_3CH_2CN)_2PtCl_4]$[12] have been reported for dehydration of aldoximes. Interestingly, these catalytic reactions should perform in a solvent containing the nitrile group such as CH_3CN, and the use of a catalyst is necessary.

Recently we reported the preparation of aromatic and heterocyclic nitriles by treating aldoximes with malononitrile and $Cu(OAc)_2$ in water, theses dehydration reactions can take place in non-acetonitrile media with loading stoichiometric malononitrile.[13] We now report an improved method in which the aldoximes react with trichloroacetonitrile in toluene to provide the corresponding nitriles, and no catalyst is required.

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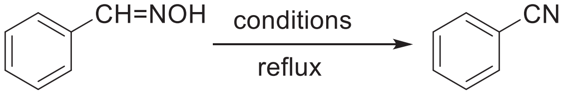
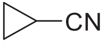
Table 1. Optimization of the reaction conditions (solvent, dehydration reagent) for the dehydration of benzaldoxime to benzonitrile.[a]



Entry	Reagent(equiv.)	Solvent	Time (h)	yield[b]/%
1	CCl_3CN (1.0)	toluene	6	81(80)[c]
2	CCl_3CN (1.0)	acetone	6	–
3	CCl_3CN (1.0)	acetonitrile	6	10
4	–	toluene	6	–
5	CCl_3CN (1.5)	toluene	4	88
6	CH_3CN (1.5)	toluene	4	–
7	$CH_3(CH_2)_3CN$	toluene	4	–
8		toluene	4	–
9	$ClCH_2CH_2CN$	toluene	4	trace
10	CH_2ClCN (1.5)	toluene	4	16
11	$CHCl_2CN$ (1.5)	toluene	4	67

[a] Reaction conditions: a stirred mixture of benzaldoxime (2 mmol) and a dehydration reagent in different solvent (6 mL) was reacted for various times.

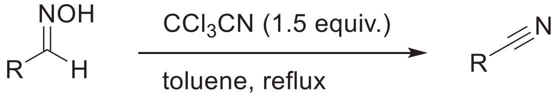
[b] Isolated yield.

[c] 0.1 mmol $Cu(OAc)_2$ was added, the mixture was stirred for 24 h at room temperature.

Results and discussion

For our optimization studies, we selected benzaldoxime as a model substrate to investigate the influence of reaction solvent and dehydration reagents on the yields of the reaction. The results are listed in Table 1. As shown in the table, we found that benzaldoxime was easily converted to benzonitrile by the action of trichloroacetonitrile in refluxing toluene, benzonitrile was obtained in 81% yield without the aid of a catalyst (Table 1, entry 1). The combination use of trichloroacetonitrile and a metal catalyst, which is similar to our previous work,[13] can lower the required reaction temperature. Benzaldoxime was easily converted to benzonitrile in presence of trichloroacetonitrile and cupric acetate at room temperature, and benzonitrile was obtained in 80% yield (Table 1, entry 1). Although a catalyst can reduce the activation energy of the reaction, we did not intend to explore the combination use of trichloroacetonitrile and a metal catalyst in this reaction because a number of methods have been published for the aldoxime – nitrile transformation in the presence of transition metals and nitrile such as acetonitrile, propionitrile and malononitrile. Being a nitrile, trichloroacetonitrile should have the same role in these transformations. Thus, we only explored the dehydration of aldoximes under non-catalytic conditions in this paper. Use of acetone instead of toluene resulted in no product (Table 1, entry 2). When acetonitrile was used in place of toluene as solvent, the yield of benzonitrile was only 10% (Table 1, entry 3). On the basis of the results obtained, toluene is suitable solvent for the dehydration reaction without a catalyst. It is worth noting that a higher boiling point solvents such as paraxylene are also an effective solvent, they were not selected as reaction media in this paper because they are not easy to remove by distillation.

Table 2. Yields of a series of nitriles prepared by reaction of an aldoxime with trichloroacetonitrile in toluene[a].



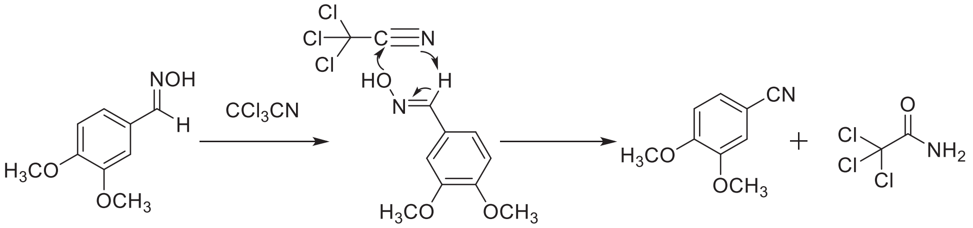
Entry	Substrate (R)	Time (h)	Yield (%)[b]
1	3-NO_2-C_6H_4	5	80
2	4- NO_2-C_6H_4	5	90[c]
3	2-Cl-C_6H_4	5	83
4	4- $N(CH_3)_2$-C_6H_4	1	87
5	4-OH-C_6H_4	2	84
6	4-CH_3O-C_6H_4	2	83
7	3-MeO-4-MeO-C_6H_3	2	86
8	4-CH_3-C_6H_5	6	62[c]
9	9-Anthryl	4	76
10	1-Naphthyl	4	85
11	(*E*)-C_6H_5-CH = CH	3	91
12	2-Thienyl	2	90

[a] Reaction conditions: aldoxime (2 mmol), trichloroacetonitrile (3 mmol), toluene (6 mL), reflux.
[b] Isolated yield.
[c] 2.0 equiv. trichloroacetonitrile was used.

Trichloroacetonitrile was necessary, no product formation was detected in the absence of trichloroacetonitrile (Table 1, entry 4). Increasing the amount of trichloroacetonitrile to 1.5 equiv. shortened the reaction time and raised the yield slightly, and benzaldoxime was dehydrated to the corresponding nitrile with complete conversion (Table 1, entry 5). In addition, we investigated the reactivities of acetonitrile, pentanenitrile, cyclopropanecarbonitrile, 3-chloropropanenitrile, chloroacetonitrile and dichloroacetonitrile. No product was detected when acetonitrile, pentanenitrile or cyclopropanecarbonitrile was used as a dehydrating agent (Table 1, entries 6–8). In the case of 3-chloropropanenitrile, a trace amount of benzonitrile was detected by TLC. However, the yield of benzonitrile was very low and it was difficult to separate by column chromatography (Table 1, entry 9). Chloroacetonitrile and dichloroacetonitrile exhibited relatively high reactivities, and the reaction of benzaldoxime with chloroacetonitrile and dichloroacetonitrile gave benzonitrile in 16% and 67% yields, respectively (Table 1, entries 10–11). In general, trichloroacetonitrile show the highest reactivity in the dehydration reaction. We thought that the strong negative inductive effect of the trichloromethyl group enhance electrophilicity of the nitrile carbon, which facilitating the nucleophilic addition of aldoxime.

On the basis of the above results, we can conclude that using trichloroacetonitrile in refluxing toluene is the optimal condition for the dehydration of aldoximes to nitriles.

This optimum method was then applied to other aldoximes and the yields of the corresponding nitriles are shown in Table 2. Compared with benzaldoxime, substrates bearing electron-withdrawing group showed relatively low reactivity and longer reaction time was needed (Table 2, entries 1–3). The yields of 4-nitrobenzonitrile, 3-nitrobenzonitrile and 2-chlorobenzonitrile are not less than 80%, in the case of 4-nitrobenzaldehyde oxime, 2 equiv. trichloroacetonitrile was used and the yield of 4-nitrobenzonitrile went up to 90% (Table 2, entry 2).



Scheme 1. Proposed mechanism for the preparation of nitriles from aldoximes

Aldoximes bearing strong electron-donating groups show relatively high reactivity and the reaction could be completed within 2 h, the corresponding nitriles were obtained in good yield (Table 2, entries 4–7). In the case of 4-methylbenzaldehyde oxime, although it has a weak electron-donating methyl group at the 4th position, the conversion rate was found to be relatively lower. Increasing the amount of trichloroacetonitrile and extending reaction time cannot effectively improve the conversion of 4-methylbenzaldehyde oxime to 4-methylbenzonitrile, the yield of the reaction was only 62% (Table 2, entries 8).

In the case of polycyclic aromatic aldoxime, cinnamaldehyde oxime and heterocyclic aldoxime the reaction process were similar to the aldoxime mentioned above, and they were smoothly converted to the corresponding nitriles in good yields under the employed reaction conditions (Table 2, 9–12). In addition, it should be noted that aliphatic aldoximes could not effectively be converted to the corresponding nitriles in this reaction system, various by-products were formed and separation was difficult.

A possible reaction mechanism is proposed in Scheme 1. We thought that the reaction mechanism is similar to that reported in the literatures.[1a,1b,3,5a,12], which explained metal-catalysed conversion of aldoximes to nitriles in acetonitrile or propionitrile solvent. As shown in Scheme 1, unlike the mechanism reported in the literatures, 3,4-dimethoxybenzaldehyde oxime react with trichloroacetonitrile to provide 3,4-dimethoxybenzonitrile without the aid of a catalyst, the strong negative inductive effect of the trichloromethyl group results in an enhanced electrophilicity of the nitrile carbon facilitating the nucleophilic addition of 3,4-dimethoxybenzaldehyde oxime, the resulting complex disproportionating to give 3,4-dimethoxybenzonitrile and trichloroacetamide.

Trichloroacetamide can be separated easily by a simple method: 3,4-dimethoxybenzaldehyde oxime react with trichloroacetonitrile in refluxing toluene for 2 h, then the resulted mixture was cooled to room temperature and kept for 2 h, the precipitated solid was filtered off and washed with carbon tetrachloride, petroleum ether/ethyl acetate (15:1) and water to give pure trichloroacetamide and it has been characterized by ^{1}H NMR and melting point determination.

Conclusions

In conclusion, we disclosed a method for the dehydration of aldoximes to nitriles using trichloroacetonitrile as a dehydrating agent in reflux toluene. Using this method aldoximes, including aromatic aldoximes and heterocyclic aldoxime, were converted into the corresponding nitriles in moderate to high yield. A possible reaction mechanism was proposed and it was confirmed that trichloroacetonitrile was transformed into trichloroacetamide in the dehydration reaction.

Experimental

Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. ^{1}HNMR spectra were obtained from a Bruker Avance NEO 600 spectrometer. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (300 mesh). Aldoximes were synthesized according to the method reported in the literature.[14] All the nitriles products and 2,2,2-trichloroacetamide are known compounds and they were characterized by ^{1}H NMR spectra.

General procedure for the synthesis of nitriles

To a 25 mL round-bottom flask equipped with magnetic stirrer were added aldoxime (2 mmol), trichloroacetonitrile (3 mmol) and toluene (6 mL). The mixture was heated to reflux for 1–6 h. After cooling to room temperature, the solution was directly evaporated to dryness and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to give the corresponding nitriles.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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