Convenient Conversion of Aldoximes into Nitriles with *N*-Chlorosuccinimide and Pyridine

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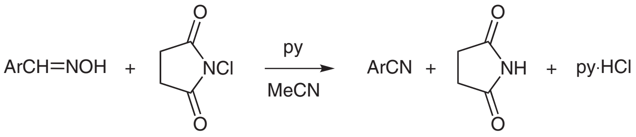
Abstract: Benzaldehyde oximes substituted with electron-donating groups are dehydrated to the corresponding benzonitriles by *N*-chlorosuccinimide/pyridine in acetonitrile. Benzaldehyde oxime itself and alkanal oximes afford the corresponding aldehydes.

Key words: aldoxime, aryl nitrile, *N*-chlorosuccinimide, pyridine, dehydration

In continuation of our interest in the application of *N*-chlorosuccinimide in organic synthesis we have examined the reaction of benzaldehyde oximes with *N*-chlorosuccinimide.[1] This reagent was recently used in combination with triphenylphosphine to accomplish dehydration of aldoximes and primary amides to nitriles.[2]

Nitriles are useful intermediates in the synthesis of amines, carboxylic acids, esters, and ketones. General methods of nitrile synthesis comprise direct cyanation of aromatic rings with trichloroacetonitrile, [3] reaction of aryl halides with copper(I) cyanide[4] or alkali cyanides in *N*,*N*-dimethylformamide in the presence of palladium(II) salts,[5] replacement of the diazonium group by the cyano group (Sandmeyer reaction);[6] these methods are not free from health hazards. There are many methods for conversion of aldehydes into nitriles via aldoximes. The most common reagent for aldoxime dehydration is acetic anhydride[7] and other similar compounds such as phthalic[8] and triflic anhydride.[9] Other methods involve treatment with lower organic acids such as formic,[10] or oxalic acid,[11] use of strong mineral acids (H_2SO_4, $ClSO_3H$),[12] the combination of acyl,[13] thionyl, silyl, or sulfonyl chloride and a base,[14] trivalent organophosphorus compounds, e. g. diethyl chlorophosphite[15] or triphenylphosphine iodine[16] (the driving force is the formation of a strong P=O bond), polychloroheteroaromatic compounds such as tetrachloropyridine[17] or trichlorotriazine,[18] quaternary ammonium,[19] or imidazolium salts,[20] Lewis acids,[21,22] ion exchangers,[23] modified[24] or unmodified montmorillonite clays,[25] enzymatic systems,[26] or heating without[27] or with a catalyst.[28] Some of these methods have only limited value due to low yields, expensive or not readily available reagents, use of strong acids or bases, drastic reaction conditions, or tedious workup. The use of clays generally requires long reaction times, reactive chemicals such as triflic anhydride involve inconveniently low temperatures (–78 °C); on the other hand some reactions suffer from high temperatures. The drawback of recently published method of primary amides and aldoximes dehydration with a mixture of triphenylphosphine and *N*-chlorosuccinimide is the requirement for chromatographic separation of the products from triphenylphosphine oxide.[2] Therefore, there is still a need to develop a new, mild, and efficient method for this conversion. Herein we present a new application of *N*-chlorosuccinimide in nitrile synthesis by dehydration of various aldoximes.

Following our studies on the 1,3-dipolar cycloaddition reaction of nitrile oxides to α,β-unsaturated compounds,[29] we examined the reaction of aldoximes **1a**–**h** with *N*-chlorosuccinimide. The reaction of aldoximes **1a**–**h** with *N*-chlorosuccinimide leads to the nitriles **2a**–**h** (Scheme 1 and Table 1). *N*-Chlorosuccinimide is the most popular reagent for the conversion of aldoximes into hydroximoyl chlorides,[30] which by treatment with base in situ generate nitrile oxides.[31] The original procedure for the synthesis of hydroximoyl chlorides with *N*-chlorosuccinimide using *N*,*N*-dimethylformamide as a solvent has limitations for strongly activated aldoximes, because it affords mixtures of ring chlorinated oximes and hydroximoyl chlorides. As a solution to this problem French chemists proposed the use of pyridine in chloroform as a solvent to quench the unwanted electrophilic nuclear chlorination favored by acidic catalyst (formed, e.g., by hydrolysis of NCS).[32] However, in our case, this approach resulted in the formation of a mixture of several products as well. We then tested different solvents and bases and were surprised to find that in several solvents (CH_2Cl_2, THF, and MeCN) the main products were, unexpectedly, nitriles. The best results were obtained with acetonitrile as a solvent and pyridine as a base (half molar equivalent). Promotion of aldoxime dehydration by acetonitrile has been previously reported.[33] The reaction was successfully carried out for benzaldehyde oximes substituted with electron-donating groups, such as methoxy, dialkylamino, or alkyl. Usually a small excess of *N*-chlorosuccinimide was required to carry the reaction to completion, which took 1–2 hours.



Scheme 1

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Table 1 Reaction of Benzaldehyde Oximes Substituted with Electron-Donating Groups with *N*-Chlorosuccinimide/Pyridine in Acetonitrile

Substrates		Molar ratio oxime/NCS/pyridine	Product		Yield[a] (%)	Mp (°C)
1a	4-$Me_2NC_6H_4CH{=}NOH$	1: 0.9: 0.8	**2a**	4-$Me_2NC_6H_4CN$	87[b]	73–74 (74)[34]
1b	4-$Et_2NC_6H_4CH{=}NOH$	1:1.1:2.3	**2b**	4-$Et_2NC_6H_4CN$	71[b]	65–66 (66–67)[34]
1c	2,4-$(MeO)_2C_6H_3CH{=}NOH$	1:1:1	**2c**	2,4-$(MeO)_2C_6H_3CN$	50[c]	93–94 (93)[35]
1d	2,4,6-$(MeO)_3C_6H_2CH{=}NOH$	1: 2:0.7	**2d**	2,4,6-$(MeO)_3C_6H_2CN$	80	141–141 (142–143)[36]
1e	2,5-Me_2-4-$MeOC_6H_2CH{=}NOH$	1:1:0.7	**2e**	2,5-Me_2-4-$MeOC_6H_2CN$	90	70–72 (71–72)[37]
1f	2,4,6-$Me_3C_6H_2CH{=}NOH$	1:1:0.6	**2f**	2,4,6-$Me_3C_6H_2CN$	95	54 (55)[38]
1g	4-*i*-$PrC_6H_4CH{=}NOH$	1:1:1	**2g**	4-*i*-PrC_6H_4CN	70[c]	–
1h	4-$MeOC_6H_4CH{=}NOH$	1:1:0.7	**2h**	4-$MeOC_6H_4CN$	50[c]	61–62 (62)[39]

[a] Isolated yield.

[b] Reaction in CH_2Cl_2.

[c] The product was accompanied by the corresponding aldehyde.

Table 2 Spectral Data for Compounds **2a**–**h**

Compound	IR (neat) cm^{-1}	^1H NMR δ, *J* (Hz) (200 MHz, $CDCl_3$)
2a	2213	9.74 (s, 1 H), 7.74 (d, *J* = 9.2, 2 H), 6.71 (d, *J* = 9.2, 2 H), 3.08 (s, 6 H)
2b	2211	7.43 (d, *J* = 9.1, 2 H), 6.60 (d, *J* = 9.1, 2 H), 3.39 (q, *J* = 7.1, 4 H), 1.18 (t, *J* = 7.1, 6 H)
2c	2226	7.51 (s, 1 H), 6.48 (s, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H)
2d	2306	6.07 (s, 2 H), 3.85 (s, 6 H), 3.84 (s, 3 H)
2e	2292	7.14 (s, 1 H), 6.62 (s, 1 H), 3.81 (s, 3 H), 2.33 (s, 3 H), 2.13 (s, 3 H)
2f	2291	6.91 (s, 2 H, H3, H5), 2.41 (s, 6 H, 2 CH_3), 2.3 (s, 3 H
2g	2228	7.58 (dm, *J* = 8.3, 2 H), 7.32 (dm, *J* = 8.3, 2 H), 2.96 (septuplet, *J* = 6.8, 1 H), 1.26 (d, *J* = 6.8, 6 H)
2h	2225	7.66 (d, *J* = 8.9, 2 H), 7.08 (d, *J* = 8.9, 2 H), 3.90 (s, 3 H)

This is a new method for the mild dehydration of various electron-donating group substituted benzaldehyde oximes to the corresponding benzonitriles. Products **2a**–**h**, all of which are known compounds, were characterized by spectroscopic analysis (Table 2). Benzaldehyde oxime itself and oximes of aliphatic aldehydes reacted in a different way and gave the corresponding aldehydes due to simple deprotection at room temperature.

Benzaldehyde oximes substituted with electron-withdrawing groups, on the other hand, afforded hydroximoyl chlorides as the major product accompanied by a small amount of nitriles and benzaldehydes. These reactions are carried out more efficiently in *N*,*N*-dimethylformamide without base.

In conclusion, a new, mild method for conversion of electron-donating group substituted benzaldehyde oximes into the corresponding benzonitriles has been developed. Benzaldehyde oxime itself and oximes of aliphatic aldehydes are deprotected to the parent aldehydes.

Oximes were prepared from aldehydes by a standard method. The products, all of which are known compounds, were characterized by spectral analysis. Spectra were obtained as follows: IR spectra on a JASCO FTIR-420 spectrophotometer, ^1H NMR spectra on Varian 500 UNITY plus-500 and Varian 200 UNITY plus 200 spectrometers in $CDCl_3$ using TMS as internal standard, EI-MS on AMD M-40. Flash chromatography was carried out using silica gel S 230–400 mesh (Merck).

Electron-Donating Group Substituted Benzonitriles 2a–h; General Procedure

NCS (2 mmol) was added in small portions over 10 min to a stirred soln of oxime **1** (2 mmol) and anhyd pyridine (1 mmol) in anhyd MeCN (5 mL). The mixture was stirred for 1–2 h at r.t. (TLC control), diluted with CH_2Cl_2 (20 mL), washed with H_2O (5 × 20 mL), dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by dissolving in CH_2Cl_2 and impurities precipitated with hexanes followed by crystallization, if needed, and in a few cases by flash chromatography (silica gel, gradient hexanes–EtOAc).

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