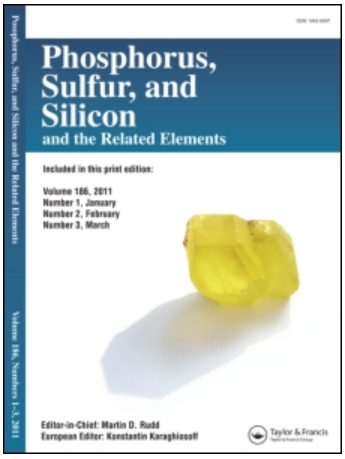

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Na 2 SO 3 /SOCl 2 , an Efficient Reagent for the Dehydration of Aldoximes to Nitriles

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$Na_2SO_3/SOCl_2$, AN EFFICIENT REAGENT FOR THE DEHYDRATION OF ALDOXIMES TO NITRILES

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Aldoximes undergo rapid dehydration with sodium sulfite, thionyl chloride, under mild reaction condition to afford nitriles in excellent isolated yields. Dehydration reactions were performed in solvent and under solvent free conditions.

Keywords: Aldoxime; nitrile; solid state; thionyl chloride

Nitriles are of particular interest in preparative organic chemistry due to their rich chemistry.[1] They serve as useful precursors for the synthesis of amines, carboxylic acids, amides, ketones, and hetrocyclic compounds such as tetrazoles, thiazoles, oxazoles, 2-oxazolines, and 1,3-diarylimidazoles.[1–3] It also has been well documented that the cyano group itself is present in HIV protease inhibitors, 5-lipoxygenase inhibitors, and many other bioactive significant molecules.[3] They usually are prepared by nucleophilic substitution with the cyanide anion or by regenerating the cyano group via oxidation, rearrangement, or elimination.[2] The most efficient route reported so far is based on the dehydration of aldoximes into the corresponding nitriles. A great variety of reagents have emerged as a result of sustained efforts by chemists to discover new and mild methods to effect this conversion.[2–13] However, many of these methods met with some limitations, including low yields, laborious procedures, expensive or not readily accessible reagents, harsh reaction conditions, use of aqueous medium, necessary presence of a PTC, need for the addition of an acid or a base, tedious work-up, or, perhaps, most importantly, a lack of generality for both the

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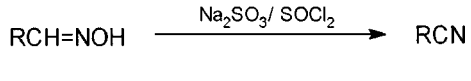
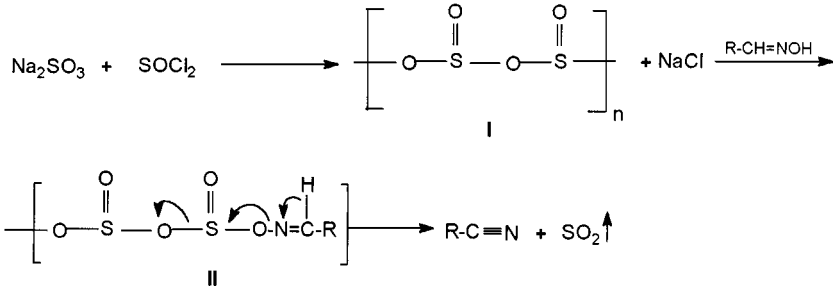
aliphatic and aromatic aldoximes. Reagents like triethylamine-sulfur dioxide and sulfuryl chloride fluoride allow the rapid and mild dehydration of aldoximes. However, the preparation of the reagents is inconvenient (−70°C).[5] Effective conversion of aldoximes to nitriles with zeolites (CsX)[8] requires high temperature (350°C) whereas montmorillonite KSF and Envirocat EPZG[9] require very long reaction time (12–24 h). The reagent like phosgene,[4] diphosgene,[7] and triphosgene[10] are hazardous to use. Consequently, it seems that there is a still great demand for a new and efficient method. In our development of new methods for functional group transformation,[14] we especially are interested in developing the application of a modified form of thionyl chloride in organic synthesis.[14h,i] Now we report on conditions whereby various types of nitriles can be conveniently synthesized from the corresponding aldoximes under mild nonaqueous reaction conditions by sodium sulfite/thionyl chloride in solvent and under solvent free conditions in high isolated yields.



RESULTS AND DISCUSSION

The reagent was easily prepared by the reaction of thionyl chloride with stiochiometric amount of sodium sulfite at room temperature. At first, (I) is probably formed, this kind of mechanism has been proposed in the reaction of thionyl chloride and polyvinylpyrrolidone,[14h] 1,4-diazabicyclo[2.2.2]octane,[14i] N-methylpyrolidone,[15] or N, N-dimethylformamide.[16] Representative aldoximes were treated with (I) in CH_2Cl_2 at room temperature or reflux conditions. The reaction proceeded, probably via O-substituted aldoxime (II), which then underwent fragmentation to afford the corresponding nitriles in high yield (Scheme 1).

The effects of other solvents such as CCl_4, n-hexane, ether, and THF also were studied, but in comparison with CH_2Cl_2 the reaction times were longer and the yields were considerably lower. The procedure turned out to be general for a range of structurally diverse aldoximes. Aliphatic and aromatic aldoximes with electron-withdrawing or electron-donating groups, were cleanly, easily, and efficiently dehydrated and afforded the corresponding nitriles as the



SCHEME 1

exclusive products in short reaction time periods and in excellent yields. The scope and generality of this process is illustrated with several examples and the results are summarized in Table I. The structure of all the products were settled from their analytical and spectral (IR, ^{1}H NMR) data and by direct comparison with authentic samples.[7,17–18]

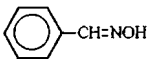
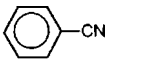
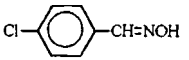
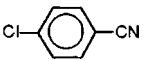
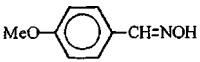
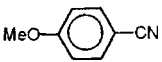
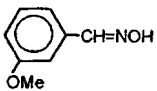
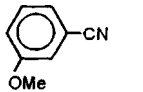
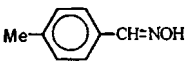
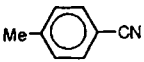
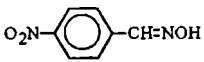
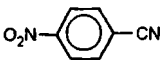
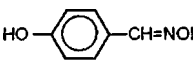
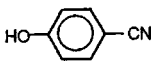
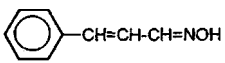
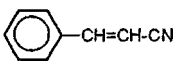
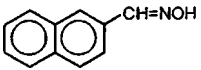
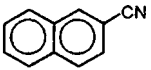
Recently, while exploring the scope and utility of solid-phase conditions in organic synthesis, we observed that the no solvent conditions are also effective for the dehydration of aldoxime. The required time for complete conversion of aldoximes to the corresponding nitriles by this simplified procedure were lower than in the solvent mediated procedure. For example, when 4-nitro benzaldoxime was reacted with sodium sulfite/thionyl chloride, monitoring of the reaction by TLC showed that in the absence of solvent the reaction was finished after 10 min at 0°C but in refluxing CH_2Cl_2 the reaction was not completed after 90 min (Table I, entry 6).

This procedure was compatible with substitutes such as hydroxyl and ether. The reaction of 4-hydroxy benzaldoxime, for example, clearly furnished the product 4-cyano phenol in 98% isolated yield (Table I, entry 7).

The advantage of using $Na_2SO_3/SOCl_2$ as reagent for the dehydration of aldoximes is shown by comparing our results with those previously reported in the literature (Table II).

Compared to some previously reported reagents with major or minor drawbacks, several noteworthy features of this system are apparent: the easy work-up procedure, availability of the reagent, operational simplicities, and use of inexpensive reagent. It also is not worthy that attempts to perform the dehydration with thionyl chloride alone were not successful due to its very high reactivity and mixture of unidentified products were obtained.

TABLE I Dehydration of Aldoximes to their Corresponding Nitriles Using Na_2SO_3/Thionyl Chloride

Entry	Substrate	Product	In CH_2Cl_2[a] Time (min)	Under Solvent[b,c] Free conditions Time (min)	Yield (%)[d,e,f]
1			7	5	98
2			10	5	98
3			20	10	94
4			30	10	90
5			7	2	93
6			—[g]	10	88
7			10	1	98
8			5	3	91
9			15	30	92
10	$CH_3(CH_2)_3CH(C_2H_5)CH{=}NOH$	$CH_3(CH_2)_3CH(C_2H_5)CN$	20	20	87

[a]Molar ratio of substrate to reagent was 1:1.5 and performed at r.t. except entries 9,10 where molar ratio was 1:2 and performed under reflux conditions.

[b]Molar ratio of substrate to reagent was 1:1.5 except entry 6 with molar ratio 1:3 and entries 9, 10 with molar ratio 1:2.

[c]Reactions were performed at 0°C.

[d]Yields refer to pure isolated products.

[e]Similar yields were obtained with or without solvent.

[f]Products were characterized by comparsion of their physical data, IR, NMR spectra with known samples.[7,17,18]

[g]The reaction with molar ratio 1:3 was not completed after 2 h and about 50% of the starting material was recovered.

TABLE II Comparison of Some Results Obtained from the Reaction of Aldoximes with $Na_2SO_3/SOCl_2$ with Those Reported from Other Methods

	Benzaldoxime			*p*-Methoxy benzaldoxime			Cinemaldoxime		
Method	Time (h)	Temp. (°C)	Yield (%)	Time (h)	Temp. (°C)	Yield (%)	Time (h)	Temp. (°C)	Yield (%)
A[a]	0.08	0	98	0.17	0	94	0.05	0	91
B[b]	0.66	r.t.	92	0.83	r.t.	85	0.66	r.t.	88
C[c]	24	100	81	24	100	60	24	100	50
D[d]	16	120	81	15	120	70	—	—	—
E[e]	48	−70	60	78	−70	90	—	—	—

[a]The present method (solvent free procedure).
[b]Dobco/$SOCl_2$ was used.
[c]t-BuMe_2SiCl/imidazole was used.[13]
[d]Montmorillonite KSF was used.[9]
[e]Ortho ester $CH_3C(OEt)_3$, H^+ was used.[12]

CONCLUSION

We believe that the present procedure for dehydration of aldoximes provides an easy, mild, efficient, versatile and general methodology for the preparation of nitriles from different classes of aldoximes, and we feel that it may be a suitable addition to methodologies already present in the literature.

EXPERIMENTAL

General

IR spectra were recorded on a Shimadzo 450 spectrophotometer; and ^{1}HNMR spectra in $CDCl_3$ on a Bruker Avance DPX instrument (250 MHz). Sodium sulfite and thionyl chloride were purchased from Fluka Company. Aldoximes were purchased from Fluka and Merck or were prepared in our laboratory from the corresponding aldehydes according to known procedures.[19] Products were characterized by comparison of their physical data, IR, and ^{1}H NMR spectra with authentic samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

General Procedure for the Conversion of Aldoximes to Nitriles with $Na_2SO_3/SOCl_2$ in CH_2Cl_2

To a suspension solution of sodium sulfite (1.5 mmol, 0.189 g) in anhydrous CH_2Cl_2 (3 ml), was added a solution of freshly distilled thionyl

chloride (1.5 mmol, 0.179 g) in CH_2Cl_2 (2 ml). The heterogeneous mixture was stirred for about 3 min at ambient temperature. To the reaction mixture, aldoxime (1 mmol) was slowly added and stirred at room temperature or under reflux conditions for 7–40 min. The progress of the reaction was followed by TLC until no starting material could be detected. After cooling to ambient temperature, the product was then filtered and the residue washed thoroughly with CH_2Cl_2 (5 ml). Evaporation of solvent under reduced pressure furnished the desired nitrile in 87–98% isolated yields.

General Procedure for the Conversion of Aldoximes to Nitriles with $Na_2SO_3/SOCl_2$ under Solvent Free Conditions

Fine powdered sodium sulfite (1.5 mmol, 0.189 g) was mixed with the freshly distilled thionyl chloride (1.5 mmol, 0.179 g) in a 25 ml round-bottomed flask. To the resulting powder, aldoxime (1 mmol) was slowly added and stirred at 0°C for 1–30 min. The progress of the reaction was followed by TLC until no starting material could be detected. The mixture was shaken with CH_2Cl_2 (5 ml), and filtered. The residue was washed with CH_2Cl_2 and the solvent evaporated under reduced pressure to afford the TLC and ^{1}HNMR pure products in 87–98% isolated yields.

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