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The synthesis of benzhydroximoyl chloride and nitrile oxides under solvent free conditions

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Benzhydroximoyl chlorides were prepared as nitrile oxide precursors with acidic (HCl) silica gel/Oxone in solvent less media in excellent yields with the selective chlorination of aldoximes *vs.* aromatic substitution. Nitrile oxides were generated by Huisgen's method in solvent free conditions and were trapped via reactions with styrene yielding isoxazolines. The one pot preparation of isoxazolines from substituted benzaldehyde oximes was successfully investigated.

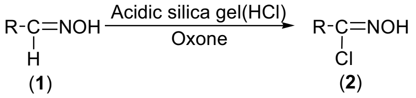
Keywords: benzhydroximoyl chloride, nitrile oxide, isoxazoline, solvent-free condition

Nitrile oxides are important intermediates in organic synthesis. They are known to be one of the most reactive 1,3-dipoles reacting with alkenes and alkynes as dipolarophiles; giving rise to substituted 2-isoxazolines and isoxazoles.[1–3]

Nitrile oxides are unstable and are dimerised readily; hence they are usually generated *in situ*. Among several methods developed for the *in situ* generation of nitrile oxides are the hydration of primary nitro compounds (Mukaiyama procedure for aliphatic nitrile oxides)[4] and the base-induced dehydrohalogenation of hydroximoyl chlorides (Huisgen's methodology for aromatic nitrile oxides).[5]

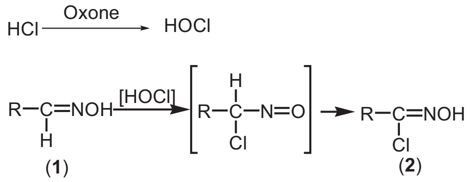
Previously reported preparations of benzhydroximoyl chloride via chlorination of the corresponding aldoximes have required either the use of chlorine,[6a] nitrosyl chloride,[6b] *tert*-butyl hypochlorite[6c] or a complex experimental procedure utilising N-chlorosuccinimide (NCS) in *N,N*-dimethylformamide(DMF).[6d] The NCS/DMF method provides satisfactory yields of products for several types of aromatic aldoximes. Ring chlorination, however, could not be satisfactorily controlled with activated aromatic aldoximes. An alternative method for the chlorination of benzaldoximes having electron-donating substituents using tert-butyl hypochlorite in carbon tetrachloride suffered from low yields. Chlorination of oximes using chlorine gas is not only hazardous but it also suffers from ring chlorination in the case of benzaldehyde oximes with electron-donating substituents. Thus, a more convenient method for the synthesis of substituted benzhydroximoyl chlorides (aromatic nitrile oxide precursors) was required.

Ryu reported the preparation of hydroximoyl chlorides by HCl/Oxone in DMF[7] This method, however, had the disadvantage of using dried DMF and dried gaseous HCl. In addition, the workup procedure was lengthy and cumbersome. We wish to report a new method for the preparation of hydroximoyl chlorides and nitrile oxides. The solvent less silica gel (acidified with HCl)/Oxone system is shown to be a selective and more convenient method for preparing hydroximoyl chlorides (eqn (1)).



$$\underset{(\mathbf{1})}{\mathrm{R{-}CH{=}NOH}} \xrightarrow[\text{Oxone}]{\text{Acidic silica gel(HCl)}} \underset{(\mathbf{2})}{\mathrm{R{-}C(Cl){=}NOH}} \qquad (1)$$

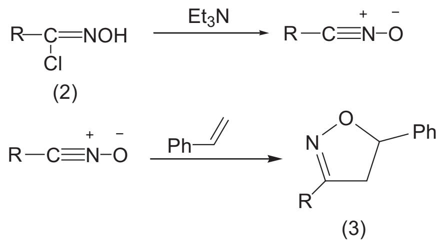
This method can be used for highly reactive aromatic rings without the usual competitive reaction of ring chlorination. The solvent less acidic silica gel/Oxone system provides a reliable method for the preparation of benzhydroximoyl chlorides since the reagents are easily available and inexpensive, and the amounts of HCl or Oxone can be easily controlled. The work up procedures are convenient, giving regioselectively chlorinated pure hydroximoyl chlorides in high yields. The reactions are environmental friendly and the reaction times are short.



Scheme 1 Benzaldoximes chlorination mechanism.

A plausible mechanism for the chlorination of benzaldoximes is believed to be carried out by hypochlorous acid arising from the oxone oxidation of hydrochloric acid. The reaction of hypochlorous acid with the aldoximes **(1)** forms the nitroso intermediate,[7] and this intermediate isomerises to the hydroximoyl chlorides (**2**) as shown in Scheme 1.

Huisgen reported that dehydrochlorination of hydroximoyl chlorides with triethylamine generate nitrile oxides.[5] We prepared aromatic nitrile oxides in solvent less conditions by dehydrochlorination of benzhydroximoyl chloride derivatives in the presence of triethylamine and we trapped the nitrile oxides with styrene, as a dipolarophiles, which gave 2-oxazoline **(3)** (eqn (2)). This method is simple, efficient, reaction times are short and yields are high.



(2)

Results and discussion

A summary of the preparation of hydroximoyl chlorides is provided in Table 1.

The results show that the reactions were completed in short times (5–9 min) and the yields were excellent. It was found that the volume to weight (V/W) ratio of HCl/silica gel of 18 : 20 was the best ratio for the optimum conditions. Using this ratio, the shortest reaction times were found. Lesser ratios of HCl resulted in higher reaction times and lower yields. A series of reactions were carried out in order to find the best possible ratio of acidic silica gel to oxone to oxime which indicated ratios of 4 g: 3 g: 1 mmol of oxime as the optimum ratio. Aromatic oximes with either electron-donating or electron-withdrawing substituents gave high yields without

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Table 1 The preparation of benzhydroximoyl chlorides **(2)** at room temperature

Entry	R	Time/min	Product	Yield/%[a]	M.p./°C	Ref. m.p./°C[b]
1	4-ClC_6H_4	5	**2a**	96	87–89	87.5–89[6d]
2	3-ClC_6H_4	9	**2b**	95	64–67	65–67[6d]
3	2,6-ClC_6H_3	5	**2c**	96	93–95	92–94[7]
4	2-$CH_3OC_6H_4$	9	**2d**	95	112–114	112–112.5[6d]
5	4-$CH_3OC_6H_4$	9	**2e**	98	87.5–89	87–88[7]
6	3-$NO_2C_6H_4$	9	**2f**	95	93–95	94–96.5[6d]
7	4-$CH_3C_6H_4$	5	**2g**	98	66–67	66–67[13]
8	4-$NO_2C_6H_4$	9	**2h**	92	66–67	66–67[13]
9	2,4-$(CH_3O)_2C_6H_3$	9	**2i**	95	102–105	104–106[6c]
10	2-HOC_6H_4	9	**2j**	95	132–134	132–134[14]

[a] Isolated yields.

[b] Products were characterised by comparison of their melting point or spectroscopic data with those reported in the literature.

any sign of ring chlorination reactions.

Table 2 shows the generality of our method for the preparation of nitrile oxides and isoxazolines.

Table 2 indicates that in most cases the reactions proceeded readily to produce isoxazolines in high yields. Products of entries 1–8 were isolated by dry flash chromatography which gave NMR ready products. Entry 9 did not give the appropriate product. We believe this to be due to the presence of the hydroxyl group which is acidic enough to compete with hydrogen of the hydroximoyl chloride in dehydrogenation process.

Table 3 shows the result of the one-pot preparation of isoxazolines.

In these experiments, products of chlorination processes were not isolated or purified. Triethylamine and styrene were added to the crude product mixture in one-pot to give the adducts.

In conclusion, the present procedure shows significant improvements in the conditions for preparation of nitrile oxides and isoxazolines. It utilises acidic (HCl) silica gel/oxone as a new and efficient solid supported system for the preparation of benzhydroximoyl chlorides affording excellent yields, convenient workup procedure, regioselectivity, ecofriendliness and short reaction times.

Experimental

Melting points were determined on Electrothermal 9100 and uncorrected. IR spectra were obtained using a Perkin-Elmer 843 spectrometer with KBr plates. ^1H NMR spectra were recorded in $CDCl_3$ solutions on Brucker Avance 300 MHz spectrometer with TMS as an internal standard.

General procedure for the preparation using acidic (HCl)/silica gel

In a typical procedure, HCl 37%(18 ml) was added to silica gel 60 (mesh 15–40) (20 g) in acetone as a solvent. The acetone was evaporated on a rotary evaporator to give the acidic silica gel.

General procedure for the synthesis of hydroximoyl chloride

A mixture of benzaldoximes (1 mmol), oxone (3 g, 10 equiv of $KHSO_5$) and acidic silica gel (4 g) was ground together for 5–9 min. The reaction mixture was extracted with chloroform. The pure products were obtained by recrystallisation from the reported solvents.[6, 8–12]

General procedure for preparation of isoxazolines

To a mixture of compound 2 (1 mmol) and styrene (1 mmol) was added triethylamine (2 mmol). The mixture was ground together for 30 s. TLC monitoring of the reaction showed a spot to spot reaction. Column chromatography with: *n*-hexane-CH_3CN and then evaporation of solvent afforded pure isoxazolines.

General procedure for one pot synthesis of isoxazolines

A mixture of benzaldoximes (1 mmol), Oxone (3 g, 10 equiv of $KHSO_5$) and acidic silica gel (4 g) was ground together for 13 min. Styrene and triethylamine (1: 4 mmol) were added and grinded together for 2 min. TLC monitoring of the reaction showed a spot to spot reaction. The reaction mixture was eluted with *n*-hexane/ethyl acetate (using dry flash chromatography technique) followed by evaporation of the solvent to afford pure isoxazolines.

Table 2 Nitrile oxide generations and styrene cycloadditions at room temperature

Entry	R	Time/s	Product	Yield/%[a]	M.p./°C	Ref. m.p./°C[b]
1	4-ClC_6H_4	30	**3a**	96	124–127	124–126[15]
2	3-ClC_6H_4	30	**3b**	95	73–74	74–75[15]
3	2,6-ClC_6H_3	30	**3c**	96	68–70.5	67–691[5]
4	2-$CH_3OC_6H_4$	30	**3d**	95	113–114	112–114[16]
5	4-$CH_3OC_6H_4$	30	**3e**	96	103–106	104–105[13]
6	3-$NO_2C_6H_4$	30	**3f**	94	129–132	129–130[15]
7	4-$CH_3C_6H_4$	30	**3g**	96	99–101	100–101[13]
8	4-$NO_2C_6H_4$	30	**3h**	94	127–129	127–129[13]
9	2-HOC_6H_4	120	No reaction	0.0	_	_

[a] Isolated yields.

[b] Products were characterised by comparison of their melting point or spectroscopic data with those reported in the literature.

Table 3 One pot preparation of isoxazolines at of room temperature

Entry	R	Time/min	Product	Yield/%
1	4-ClC_6H_4	15	**3a**	90
2	3-ClC_6H_4	15	**3b**	92
3	2,6-ClC_6H_3	15	**3c**	90
4	2-$CH_3OC_6H_4$	15	**3d**	90
5	4-$CH_3OC_6H_4$	15	**3e**	90
6	3-$NO_2C_6H_4$	15	**3f**	90
7	4-$CH_3C_6H_4$	15	**3g**	90
8	4-$NO_2C_6H_4$	15	**3h**	92

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