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A novel one-pot synthesis of hydroximoyl chlorides and 2-isoxazolines using *N*-*tert*-butyl-*N*-chlorocyanamide

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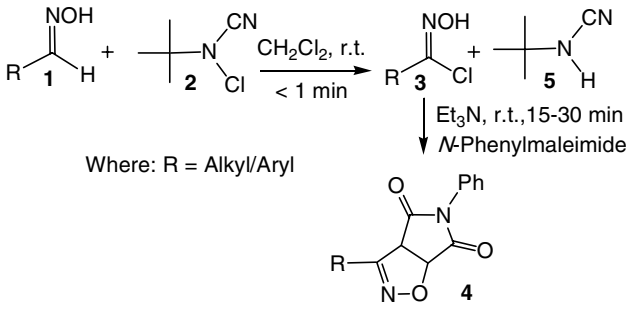
Abstract—Treatment of aldoximes with *N*-*tert*-butyl-*N*-chlorocyanamide gave hydroximoyl chlorides in quantitative yields in less than a minute, which on dehydrohalogenation in the presence of triethylamine gave the corresponding nitrile oxides. The nitrile oxides underwent 1,3-dipolar addition to dipolarophiles and gave 2-isoxazolines in excellent yields under mild conditions.

Nitrile oxides are versatile intermediates in heterocyclic chemistry, taking part in a variety of 1,3-dipolar cycloaddition reactions to give various five-membered heterocycles.[1] Huisgen's base-induced[2] dehydrohalogenation of hydroximoyl chlorides is the most common method for the generation of nitrile oxides. Although, the utility of nitrile oxides in organic synthesis has been investigated extensively, the synthesis of hydroximoyl chlorides has received less attention. Reagents such as Cl_2,[3] NBS,[4] NCS,[5] NaOCl,[6] alkyl hypochlorites,[7] chloramine-T,[8] and 1-chlorobenzotriazole[9] and others[10] have been utilized for chlorination of aldoximes to give hydroximoyl chlorides. All these methods have their limitations such as producing over-chlorinated products, needing long reaction times and multi-steps, variable yields,[6] sensitivity to other functional groups and requiring stringent reaction conditions (low/high temperatures).[4,5,7] Recently, benzyltrimethylammonium tetrachloroiodate ($BTMAICl_4$)[11] has also been reported to bring about the same transformation, efficiently under mild conditions but requiring long reaction times.

In continuation of our studies exploring the synthetic utility of *N*-*tert*-butyl-*N*-chlorocyanamide,[12,13] we have examined this reagent for the synthesis of hydroximoyl chlorides and 2-isoxazolines from aldoximes. Isoxazolines are pharmocophores of note in several pharmaceutically important compounds.[14] They are also useful intermediates for the synthesis of a variety of bioactive natural products[14] and synthetically useful functionalities.[15] Our work shows that *N*-*tert*-butyl-*N*-chlorocyanamide[16] is an efficient chlorinating agent for the preparation of hydroximoyl chlorides from aldoximes. A one-pot procedure using *N*-phenylmaleimide (Scheme 1) and other dipolarophiles (Table 2) as cycloadducts and triethylamine as a base leads to the direct formation of 2-isoxazolines.

Treatment of aldoximes with *N*-*tert*-butyl-*N*-chlorocyanamide in an equimolar ratio in DCM at room temperature gave the corresponding hydroximoyl chlorides (Scheme 1). The reactions took place immediately after mixing the substrates as indicated by the appearance of yellow colour in the reaction mixture. Completion of the reactions was finally assessed by TLC (except



Scheme 1. Synthesis of hydroximoyl chlorides and 2-isoxazolines from aldoximes.

Keywords: *N*-*tert*-Butyl-*N*-chlorocyanamide; Aldoximes; Hydroximoyl chlorides; *N*-Phenylmaleimide; Dipolarophiles; 2-Isoxazolines.
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Table 1. One-pot synthesis of the hydroximoyl[17] chlorides and 2-isoxazolines[18] using **2**

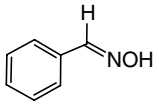
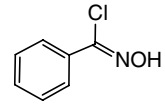
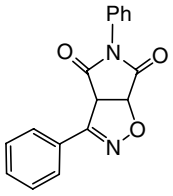
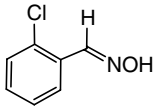
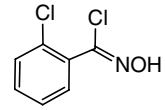
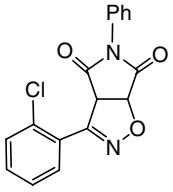
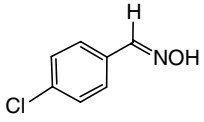
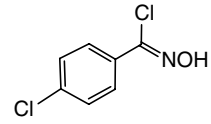
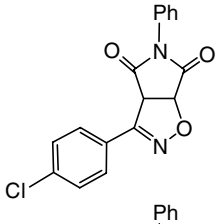
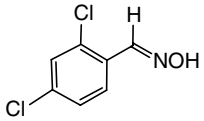
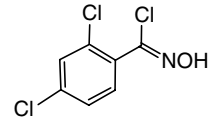
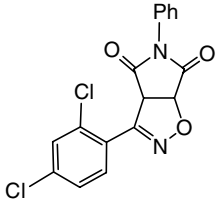
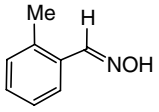
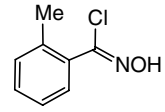
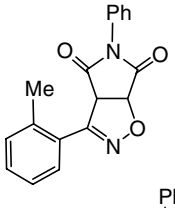
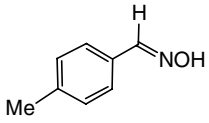
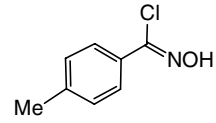
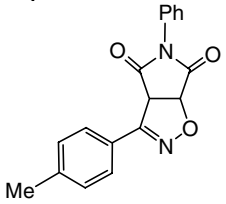
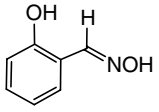
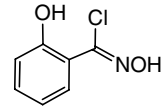
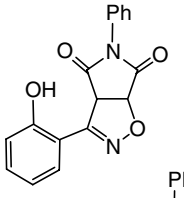
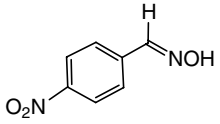
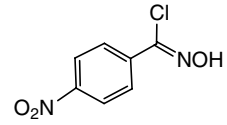
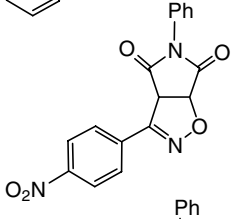
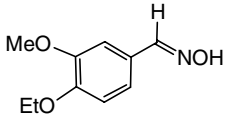
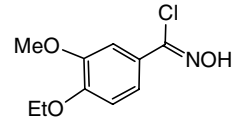
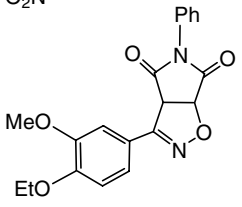
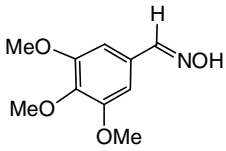
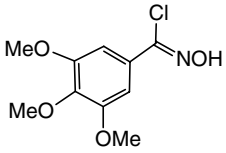
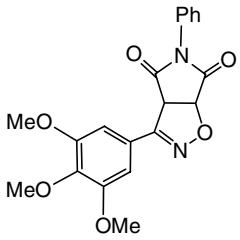
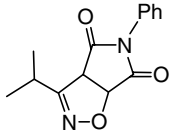
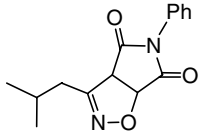
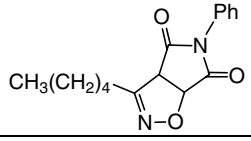
Entry	Substrate	Product **3**	Yield[a]	Product **4**	Yield[b]
1			95		90
2			92		88
3			93		90
4			92		89
5			90		88
6			94		90
7			95		92
8			93		89
9			92		87

Table 1 (*continued*)

Entry	Substrate	Product **3**	Yield[a]	Product **4**	Yield[b]
10			90		86
11[c]	$(CH_3)_2CHCH{=}NOH$	$(CH_3)_2CHC(Cl){=}NOH$	—		93
12[c]	$(CH_3)_2CHCH_2CH{=}NOH$	$(CH_3)_2CHCH_2C(Cl){=}NOH$	—		91
13[c]	$CH_3(CH_2)_4CH{=}NOH$	$CH_3(CH_2)_4C(Cl){=}NOH$	—		93

The structure of the products were established by spectral (^{1}H NMR and MS) data and compared with authentic samples prepared by known methods.[5]

[a] Isolated yields of hydroximoyl chlorides.

[b] Isolated yields of 2-isoxazolines.

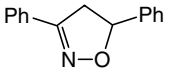
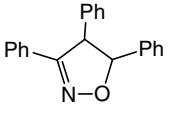
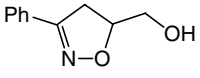
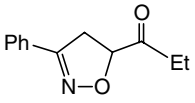
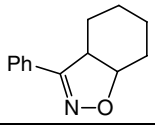
[c] Hydroximoyl chloride derivatives were not isolated.

for aliphatic hydroximoyl chlorides, which were unstable). The generality of this reaction was demonstrated by the synthesis of hydroximoyl chlorides with different functionalities (Table 1).

All the aldoximes gave hydroximoyl chlorides, very rapidly and in virtually quantitative yields; no over-chlorination or interference of other substituents (Table 1, entries 5, 6, 9 and 10) was observed. The presence of an electron-donating groups (Table 1, entries 5–7, 9 and 10) or electron-withdrawing groups (Table 1, entries 2, 3, 4 and 8) on the aromatic ring did not affect the yields/efficiency or rate of reaction. Initially, treatment of aldoximes with **2** in DCM at room temperature and subsequent addition of triethylamine facilitated the in situ formation of nitrile oxides and then immediate addition of *N*-phenylmaleimide as the dipolarophile to the reaction mixture resulted in the formation of 2-isoxazolines. The complete procedure takes place in a single flask (Scheme 1). This reaction mixture was stirred at room temperature for 15–30 min and resulted in excellent yield of various 2-isoxazolines (Table 1). The generality of this reaction was demonstrated employing dipolarophiles having diverse structures (Table 2).

Aliphatic hydroximoyl chlorides, being unstable were directly converted to their respective 2-isoxazolines to avoid decomposition during isolation and/or purification. The present one-pot protocol for the synthesis of 2-isoxazolines uses mild reaction conditions, short reaction times, gives high yields and employs the inexpensive reagent **2** which can easily be prepared in the laboratory from commonly available chemicals.[16]

Table 2. One-pot synthesis of 2-isoxazolines[18] using reagent **2**

Entry	Dipolarophile	2-Isoxazolines	Yield[a]
1	Styrene		91
2[b]	*cis*-Stilbene		88
3	Allyl alcohol		90
4	Ethyl vinyl ketone		92
5	Cyclohexene		89

[a] Isolated yields.

[b] Reaction of benzalhydroximoyl chloride with *cis*-stilbene takes 1 h for completion. The structures of the products were established by spectral (^{1}H NMR and MS) data.

In summary, we have developed an efficient one-pot synthetic procedure for the preparation of hydroximoyl chlorides from aldoximes and *N*-*tert*-butyl-*N*-chlorocyanamide which can be converted into 2-isoxazolines in one-pot. The reactions have some merits such as one-pot reaction, very short reaction time, high yields, mild reaction conditions and the ease of separation. Moreover, under the reaction conditions, a variety of sensitive groups remain unaffected.

Acknowledgement

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16. *Preparation of N-tert-butyl-N-chlorocyanamide*:[19] A solution containing 0.28 mol of cyanogen bromide in 350 mL of anhydrous ether was cooled to 0 °C and *tert*-butylamine (1.0 equiv) was added slowly. The reaction mixture was stirred for another 15 min at the same temperature and the precipitate of amine hydrobromide formed was removed by filtration. This filtrate was washed with water (2×100 mL) dried over anhydrous Na_2SO_4 and the filtrate was evaporated to half its volume. The resulting solution was diluted with 75 mL of carbon tetrachloride, cooled to 0 °C, then treated with the theoretical amount of *tert*-butyl hypochlorite (1.0 equiv) in 30 mL of carbon tetrachloride and the mixture allowed to warm to room temperature. The yellow solution formed was evaporated and the residue was distilled to afford the desired product, bp 53.5 °C (8 mm Hg), IR (KBr): 2216 cm^{-1} (NCN) and weak band at 2082 cm^{-1}. The positive chlorine of *N*-*tert*-butyl-*N*-chlorocyanamide was determined by standard iodometric titration and found to be 26.54% (theoretical value 26.76%).
17. *General procedure for the synthesis of hydroximoyl chlorides*. To a stirred solution of aldoxime (5 mmol) in dry dichloromethane (10 mL) at room temperature was added slowly *N*-*tert*-butyl-*N*-chlorocyanamide (1.0 equiv) in dry dichloromethane (5 mL). The reaction took place immediately on mixing with the appearance of a yellow colour indicating the formation of the hydroximoyl chloride. Reaction completion was assessed by TLC (in the case of aromatic aldoximes). *tert*-Butylcyanamide **5** was formed as a side product due to dechlorination of reagent **2**. The reaction mixture was washed with water (2×20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a mixture of hydroximoyl chloride and *tert*-butylcyanamide. The pure hydroximoyl chloride was obtained either by recrystallization in DCM/petroleum ether (40–60 °C) in a 3:7 ratio (in the case of solid products) or distillation under vacuum (in the case of liquid products).
18. *General procedure for the synthesis of 2-isoxazolines*. *N*-*tert*-Butyl-*N*-chlorocyanamide (5 mmol) was added to a stirred solution of aldoxime (1.0 equiv) and *N*-phenylmaleimide (1.0 equiv) in dry DCM (10 mL) at room temperature with subsequent addition of triethylamine (1.5 equiv). The mixture was stirred for 15–30 min at the same temperature. After completion of the reaction, the mixture was washed thoroughly with water (3×20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave crude 2-isoxazolines, which were purified either by crystallization in DCM/petroleum ether (40–60 °C) in a 3:7 ratio (in the case of solid products) or distillation under vacuum (in the case of liquid products).
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