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One pot synthesis of dihydroisoxazoles *via* 1,3-dipolar cycloaddition of nitrile oxides to allyl chloride

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Nitrile oxides derived from oxidative dehydrogenation of aldoximes by chloramine-T react with allyl chloride to afford 5-(chloromethyl)-3-aryl-4,5-dihydroisoxazoles in good yields. All compounds were characterized by IR, ^{1}H-NMR, and MS studies.

Key words: chloramine-T, nitrile oxide, dipolar cycloaddition, dihydroisoxazoles.

INTRODUCTION

Isoxazoles, isoxazolines, isoxazolidines and their derivatives have been isolated from natural sources or synthesized and individual compounds or closely related group of compounds have been reported to be active as herbicides, anti-protozoan drugs, hypoglycemic agents, anti-inflammatory agents or antipyretic agents. The 4,5-dihydroisoxazoles are versatile sources of the functional groups present in the natural products and there is renewed interest in the synthesis of these compounds *via* 1,3-dipolar cycloaddition of nitrile oxides to olefins. The 1,3-dipolar cycloaddition reactions are a useful tool for constructing biologically potent five-membered heterocyclic compounds [1]. Cycloaddition of nitrile oxide to olefinic or acetylenic compounds is of synthetic interest, since the obtained products are the versatile intermediates for the synthesis of bifunctional compounds [2]. Apart from the various dipolarophiles known, nitrile oxides have been extensively used.

The synthesis of nitrile oxides usually involves the oxidative dehydrogenation of aldoximes using oxidants such as lead tetraacetate [3], alkalihypohalite [4], *N*-bromosuccinimide in DMF followed by treatment with a base [5], chloramine-T [6], mercuric acetate [7] or 1-chlorobenzotriazole [8] as well as the reactions of nitro-compounds with aryl isocyanate [9] and di-*tert*-butyl-dicarbonate in the presence of *N,N*-dimethylaminopyridine [10].

In continuation of our earlier work on 1,3-dipolar cycloaddition reactions, an attempt was made by using allyl chloride as dienophile for the cycloaddition of preformed nitrile oxides to obtain dihydroisoxazoles. The reactions were successfully carried out at 40°C for 2 h in ethanol and the dihydroisoxazoles were obtained in 50–65% yield.

RESULTS AND DISCUSSION

Various reactions have been reported with isolated nitrile oxides and without isolation of nitrile oxide, in this paper we report intramolecular cycloaddition of *in situ* generated nitrile oxide with ally chloride afforded dihydroisoxazoles. In a typical reaction, aldoxime, excess of allyl chloride, ethanol, and chloramine-T were mixed together (Scheme 1). Exothermic reaction was observed with the formation of a product, though no effort was made to control this exothermic reaction. The reaction mixture was then allowed to cool down to room temperature, which after the usual processing gave the product in 65% yield. The cycloaddition reactions afforded 4,5-dihydroisoxazoles in good yields (Table 1).

The reaction was investigated using alkene/nitrile oxide ratios of 1:1, 2:1, 3:1 respectively, whereupon the reactions at lower ratios gave poor yields and polymerization of the nitrile oxide [11]. The fast reaction of aldoximes with chloramine-T explains why the reaction proceeds in the presence of olefinic double bonds. The role of chloramine-T in these transformations may be chlorination of aldoxime to a hydroxamic acid chloride, followed by base catalyzed HCl elimination. Although no blue colour was detected in the reactions of aldoximes with chloramine-T, we found that the treatment of cyclohexanone oxime with this reagent produced a blue colour suggesting of formation of 1-chloro-1-nitrosocyclohexane [12].

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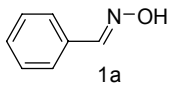
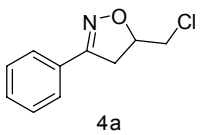
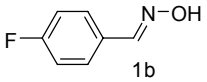
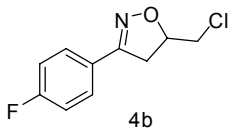
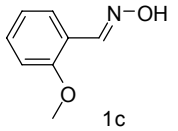
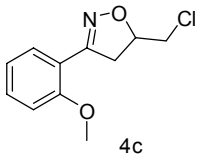
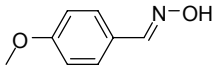
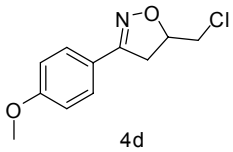
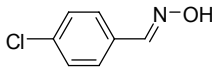
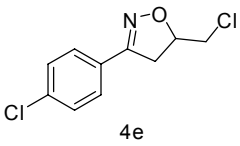
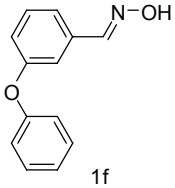
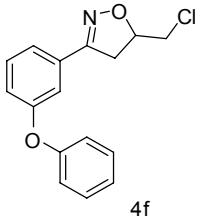
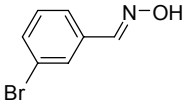
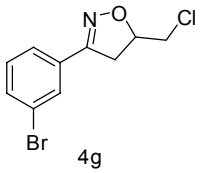
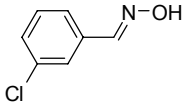
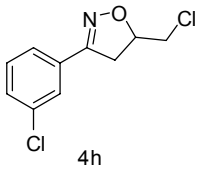
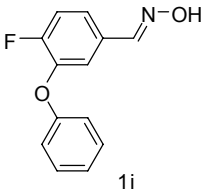
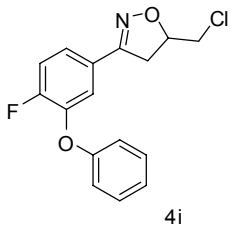
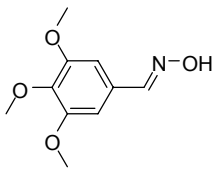
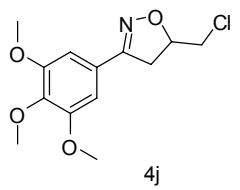
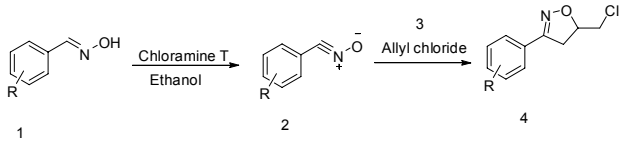
Table 1. 5-(chloromethyl)-3-aryl-4,5-dihydroisoxazoles.

Entry	Oxime	Structure	Yield, %
1	 1a	 4a	65
2	 1b	 4b	55
3	 1c	 4c	50
4	 1d	 4d	60
5	 1e	 4e	65
6	 1f	 4f	55
7	 1g	 4g	60
8	 1h	 4h	56
9	 1i	 4i	55
10	 1j	 4j	50



R = H; 4-F; 2-OMe; 4-OMe; 4-Cl; 3-OPh; 3-Br; 3-Cl; 4-F; 3-Oph; 3,4,5 $(OMe)_3$.

Scheme 1.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded on 400 MHz Bruker AVANCE 400 spectrometer and ^{13}C-NMR spectra were recorded on 100 MHz Bruker AVANCE 400 spectrometer, respectively, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 100 spectrometer. Mass spectra were recorded on ESI MS mass spectrometer. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on F_{254}, 0.25 mm silica gel coated plates (Merck). The plates were eluated with appropriate solvent systems prepared in the laboratory. The developed plates were analysed under UV light 254 nm. Column chromatography was performed using silica gel with particle size 100–200 mesh.

General procedures for the synthesis

3-aryl-5-(chloromethyl)-4,5-dihydroisoxazole. A mixture of aldoxime (10 mmol), ethanol (20 mL), chloramine-T (12 mmol) and allyl chloride (10 mL) was stirred at ambient temperature. An exothermic reaction occurred and the temperature rises to 45°C. After 30 min, the temperature was maintained at 40°C by heating in an oil bath for 2 h or till the disappearance of oxime. After the completion of the reaction, the solvent was evaporated in vacuum, and the residual mass was extracted with ether (25 mL), washed with water, 1 N NaOH solution (10 mL), brine solution (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure afforded a white mass, which was purified by column chromatography over silica gel using chloroform as eluent.

5-(chloromethyl)-3-phenyl-4,5-dihydroisoxazole (**4a**). White solid; m.p. 53–55°C; IRS (KBr): 3060, 2956, 1697, 1598, 1447 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.32–3.38 (dd, *J* = 6.4 and 16.8 Hz, 1H), 3.47–3.54 (dd, *J* = 10.4 and 16.8 Hz, 1H), 3.55–3.60 (dd, *J* = 7.6 and 11.2 Hz, 1H), 3.70–3.74 (dd, *J* = 4.4 and 11.2 Hz), 4.95–5.02 (m, 1H), 7.41–7.42 (m, 3H), 7.67–7.69 (m, 2 H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 128.2, 128.8, 131, 136, 156.2; ESI-MS *m/z*: 196 $[M+1]^+$.

5-(chloromethyl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (**4b**). White solid; m.p. 65–67°C; IRS

(KBr): 3074, 2928, 1694, 1602, 1446 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.32–3.38 (dd, *J* = 6.4 and 16.8 Hz, 1H), 3.47–3.54 (dd, *J* = 10.4 and 16.8 Hz, 1H), 3.55–3.60 (dd, *J* = 7.6 and 11.2 Hz, 1H), 3.70–3.74 (dd, *J* = 4.4 and 11.2 Hz), 4.95–5.02 (m, 1H), 7.29–7.36 (m, 2H), 7.62–7.81 (m, 2H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 115.6, 126, 129.5, 156.2, 165.2; ESI-MS *m/z*: 214 $[M+1]^+$.

5-(chloromethyl)-3-(2-methoxyphenyl)-4,5-dihydroisoxazole (**4c**). White solid; m.p. 80–85°C; IRS (KBr): 3067, 2933, 1689, 1604, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.32–3.38 (dd, *J* = 6.4 and 16.8 Hz, 1H), 3.47–3.54 (dd, *J* = 10.4 and 16.8 Hz, 1H), 3.55–3.60 (dd, *J* = 7.6 and 11.2 Hz, 1H), 3.70–3.74 (dd, *J* = 4.4 and 11.2 Hz), 3.83 (s, 3H), 4.95–5.02 (m, 1H), 6.95–7.01 (m, 1H), 7.22–7.26 (m, 1H), 7.39–7.50 (m, 2H); ^{13}C-NMR ($CDCl_3$) 38.4, 51.6, 55.8, 69.6, 111.2, 117.2, 121.1, 131.7, 132, 156.2; ESI-MS *m/z*: 226 $[M+1]^+$.

5-(chloromethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**4d**). White solid; m.p. 75–76°C; IRS (KBr): 3068, 2932, 1690, 1607, 1445 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.32–3.38 (dd, *J* = 6.4 and 16.8 Hz, 1H), 3.47–3.54 (dd, *J* = 10.4 and 16.8 Hz, 1H), 3.55–3.60 (dd, *J* = 7.6 and 11.2 Hz, 1H), 3.70–3.74 (dd, *J* = 4.4 and 11.2 Hz), 3.83 (s, 3H), 4.95–5.02 (m, 1H), 7.03–7.08 (m, 2H), 7.89–7.93 (m, 2H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 55.8, 69.6, 114.4, 122.7, 128.7, 156.2, 162.9; ESI-MS *m/z*: 226 $[M+1]^+$.

5-(chloromethyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole (**4e**). White solid; m.p. 95–97°C; IRS (KBr): 3072, 2937, 1695, 1609, 1447 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.32–3.38 (dd, *J* = 6.4 and 16.8 Hz, 1H), 3.47–3.54 (dd, *J* = 10.4 and 16.8 Hz, 1H), 3.55–3.60 (dd, *J* = 7.6 and 11.2 Hz, 1H), 3.70–3.74 (dd, *J* = 4.4 and 11.2 Hz), 4.95–5.02 (m, 1H), 7.50–7.56 (m, 2H), 7.95–7.99 (m, 2H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 128.2, 128.5, 136.6, 156.2; ESI-MS *m/z*: 230 $[M+1]^+$.

5-(chloromethyl)-3-(3-phenoxyphenyl)-4,5-dihydroisoxazole (**4f**). White solid; m.p. 85–86°C; IRS (KBr): 3077, 2942, 1698, 1606, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.26–3.32 (dd, *J* = 6.4 and 17.2 Hz, 1H), 3.42–3.49 (dd, *J* = 10.4 and 17.2 Hz, 1H), 3.53–3.58 (dd, *J* = 7.2 and 11.2 Hz, 1H), 3.67–3.71 (dd, *J* = 4.4 and 12 Hz, 1H), 4.93–5.0 (m, 1H), 6.99–7.06 (m, 3H), 7.1–7.14 (m, 1H), 7.32–7.39 (m, 5H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 116.5, 118.9, 121.2, 121.3, 128.4, 128.5, 133.7, 156.2, 157, 157.1; ESI-MS *m/z*: 288 $[M+1]^+$.

3-(3-bromophenyl)-5-(chloromethyl)-4,5-dihydroisoxazole (**4g**). White solid; m.p. 80–83°C; IRS (KBr): 3075, 2941, 1695, 1606, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.26–3.32 (dd, *J* = 6.4 and 17.2 Hz, 1H), 3.42–3.49 (dd, *J* = 10.4 and 17.2 Hz, 1H), 3.53–3.58 (dd, *J* = 7.2 and 11.2 Hz, 1H), 3.67–3.71 (dd, *J* = 4.4 and 12 Hz, 1H), 4.93–5.0 (m, 1H), 7.39–7.42 (m, 1H), 7.54–7.59 (m, 1H), 7.97–7.98 (m, 2H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 123, 126.6, 127.2, 129.8, 133.9, 136.2, 156.2; ESI-MS *m/z*: 275 $[M+1]^+$.

5-(chloromethyl)-3-(3-chlorophenyl)-4,5-dihydroisoxazole (**4h**). White solid; m.p. 77–79°C; IRS (KBr): 3074, 2940, 1696, 1605, 1445 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.26–3.32 (dd, *J* = 6.4 and 17.2 Hz, 1H), 3.42–3.49 (dd, *J* = 10.4 and 17.2 Hz, 1H), 3.53–3.58 (dd, *J* = 7.2 and 11.2 Hz, 1H), 3.67–3.71 (dd, *J* = 4.4 and 12 Hz, 1H), 4.93–5.0 (m, 1H), 7.44–7.54 (m, 2H), 7.8–7.92 (m, 2H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 126.3, 129.2, 130.2, 131.1, 134.4, 135.4, 156.2; ESI-MS *m/z*: 231 $[M+1]^+$.

5-(chloromethyl)-3-(4-fluoro-3-phenoxyphenyl)-4,5-dihydroisoxazole (**4i**). White solid; m.p. 85–87°C; IRS (KBr): 3073, 2941, 1698, 1604, 1448 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.26–3.32 (dd, *J* = 6.4 and 17.2 Hz, 1H), 3.42–3.49 (dd, *J* = 10.4 and 17.2 Hz, 1H), 3.53–3.58 (dd, *J* = 7.2 and 11.2 Hz, 1H), 3.67–3.71 (dd, *J* = 4.4 and 12 Hz, 1H), 4.93–5.0 (m, 1H), 7.12–7.19 (m, 3H), 7.3–7.42 (m, 3H), 7.51–7.55 (m, 1H), 7.62–7.65 (m, 1H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 69.6, 115.3, 118.1, 118.9, 121.8, 122.6, 128.4, 129.3, 143.2, 156.2, 157, 157.6; ESI-MS *m/z*: 306 $[M+1]^+$.

5-(chloromethyl)-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole (**4j**). White solid; m.p. 96–99°C; IRS (KBr): 3078, 2945, 1699, 1610, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.26–3.32 (dd, *J* = 6.4 and 17.2 Hz, 1H), 3.42–3.49 (dd, *J* = 10.4 and 17.2 Hz, 1H), 3.53–3.58 (dd, *J* = 7.2 and 11.2 Hz, 1H), 3.67–3.71 (dd, *J* = 4.4 and 12 Hz, 1H), 3.83 (s, 9H), 4.93–5.0 (m, 1H), 6.95 (dd, 2H); ^{13}C-NMR ($CDCl_3$) 38.1, 51.6, 56.1, 60.8, 69.6, 106.6, 128.3, 141.5, 153.2, 156.2; ESI-MS *m/z*: 286 $[M+1]^+$.

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ЕДНОСТАДИЕН СИНТЕЗ НА ДИХИДРОИЗОКСАЗОЛИ ЧРЕЗ 1,3-ДИПОЛЯРНО ЦИКЛОПРИСЪЕДИНЯВАНЕ НА НИТРИЛОКСИДИ КЪМ АЛИЛХЛОРИД

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(Резюме)

При реакцията на нитрилоксиди, получени чрез окислително дехидрогениране на алдоксими с хлорамин-Т, с алилхлорид са получени 5-(хлорометил)-3-арил-4,5-дихидроизоксазоли с добър добив. Всички съединения са охарактеризирани чрез ИЧ, ^{1}Н ЯМР и масспектрални изследвания.