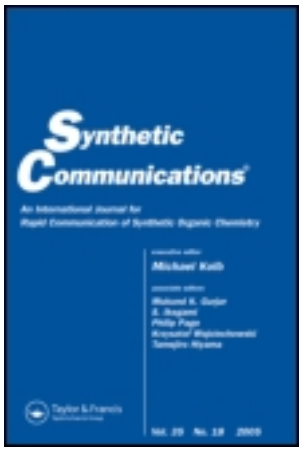

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A SIMPLE AND EFFICIENT METHOD FOR THE SYNTHESIS OF NITRILE OXIDE FROM ALDOXIME USING TRICHLOROISOCYANURIC ACID

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A SIMPLE AND EFFICIENT METHOD FOR THE SYNTHESIS OF NITRILE OXIDE FROM ALDOXIME USING TRICHLOROISOCYANURIC ACID

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ABSTRACT

Treatment of the aldoxime derived from vanilin with trichloroisocyanuric acid in the presence of olefins as dipolarophiles caused the formation of nitrile oxides and subsequent 1,3-dipolar cycloaddition forming the corresponding isoxazoline derivatives in good yields.

INTRODUCTION

1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of five membered heterocycles.[1] Cycloaddition of nitrile oxides to alkenes is a synthetically important tool since the product isoxazolines (4,5-dihydroisoxazoles) are useful intermediates for the preparation of

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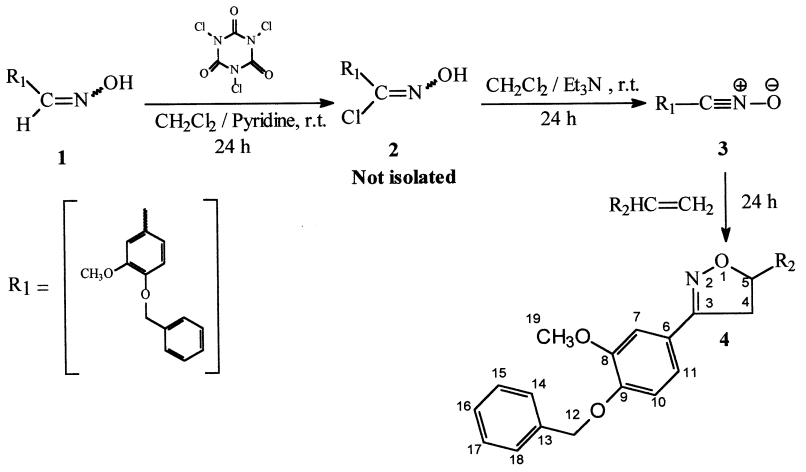
bifunctional compounds,[2] for example, β-hydroxy ketones, β-hydroxy nitriles and γ-amino alcohols. The usual synthetic methods for nitrile oxide preparation are the oxidative dehydrogenation of aldoximes,[3] the reaction using primary nitro compounds,[4] the dehydrohalogenation of hydroximoyl halides,[5] and the ring-fragmentation of furoxans.[6] We wish to report herein a new simple and efficient method for the direct conversion of aldoximes into their nitrile oxides using trichloroisocianuric acid as oxidation agent (*in situ*). Although different methods are known to form nitrile oxides, the methodology in the present communication, using trichloroisocyanuric acid, has not been reported in the literature.

RESULTS AND DISCUSSION

At first, vanilin was treated with benzyl bromide giving the etherified product (mp 64–65°C)[7] in 85% yield,[8] which was then treated with $NH_2OH.HCl$ affording **1** in 93% yield.[9] The hydroximoyl chloride **2** was obtained from the reaction of the respective aldoxime with an equimolar amount of trichloroisocyanuric acid in dichloromethane at room temperature. Finally, the alkene was added to this mixture, which was then stirred for 24 h at room temperature (Scheme 1). The cycloaddition reactions afforded four new 4,5-dihydroisoxazoles regioselectively[10] in good yields (Table).



Scheme 1.

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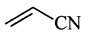
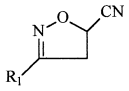
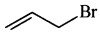
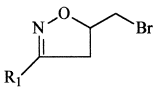
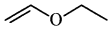
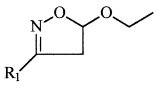
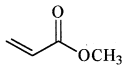
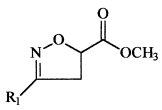
Table 1. Cycloaddition of Nitrile Oxides to Terminal Alkenes

Entry	Dipolarophyles	Compounds	Yield
1			31
2			51
3			52
4			60

This reaction was investigated using alkene/nitrile oxide ratios 1 : 1, 2 : 1 and 3 : 1, with the reactions using lower ratios giving poorer yields and evidence of polymerization of the nitrile oxide.[11] The reactions were accompanied by thin layer cromatography until disappearance of the aldoxime, then the reaction products were isolated by flash chromatography[12] using ethyl acetate–hexane (1 : 2) as eluent, affording the respective 4,5-dihydroisoxazoles in 30–60% yield. All products were characterized by FTIR, MS, ^{13}C and ^{1}H NMR techniques.

The regiochemistry for all the formed products can be predicted by frontier molecular orbital theory[13] which demonstrated that, in some cases, the most substituted carbon will bind to the oxygen of the nitrile oxide as a consequence of the interation HOMO-LUMO of the reagents.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity-300 (300 MHz ^{1}H and 75 MHz for ^{13}C) and Bruker DPX 200 (200 MHz ^{1}H and 50 MHz for ^{13}C) espectrometers, using TMS as an internal standard. HRMS were recorded at 70 eV on Kratos MS50. Infrared spectra were

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recorded with a Nicolet Magna IR 750. All melting points are uncorrected and measured in a Fisher-Johns apparatus. TLC was carried out on precoated Merck silica gel aluminum plates 60 F_{254}. Column chromatography was performed using silica gel 60 (230–240 mesh).

General Procedure

To a solution of trichloroisocyanuric acid (0.198 g–0.85 mmol), 0.15 mL of pyridine, and 15 mL de CH_2Cl_2 are added the aldoxime (1) (mp 130–131°C) in 5 mL of CH_2Cl_2. The mixture was stirred for about 24 h as RT and the alkenes in the ratios 1:1, 2:1 or 3:1 were added followed by triethylamine (0.40 mL–2.80 mmol). An exoterm reaction ensued and the mixture became dark yellow. After stirring for further 24 h at RT, the mixture was diluted to 50 mL with CH_2Cl_2 and washed with aqueous saturated $NaHCO_3$ solution (2 × 70 mL), dried over $MgSO_4$ and concentrated to dryness under vacuum. Purification by flash chromatography (20 g of silica gel) using ethyl acetate–hexane (1 : 2) gave the respectives 4,5-dihydroisoxazoles in 30–60%.

3-(3-methoxy-4-(phenylmethoxy)-5-cyano-4,5-dihydroisoxazole (5): (mp 104–105°C) **HRMS** (*m*/*z*-%) ($M^+ = 308.1171$-100%); **IR** (neat, cm^{-1}) 1681 (C=N), 1600 (C=C), 1270 (C-O-C), ^{13}**C NMR** (75 MHz, $CDCl_3$, APT) δ 155.9 (C-3), 150.5 (C-9), 149.6 (C-8), 136.1 (C-13), 128.5 (C-14/18), 127.9 (C-16), 127.1 (C-15/17), 120.6 (C-11), 120.1 (C-6), 117.1 (CN), 112.6 (C-10), 109.1 (C-7), 70.5 (C-12), 66.3 (C-5), 55.8 (C-19), 40.9 (C-4). ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 3.68 (m, H-4), 3.91 (s, H-19), 5.20 (s, H-12), 5.31 (dd, $^3J_{H5\text{-}4A} = 9.9$ Hz, $^3J_{H5\text{-}4B} = 6.8$ Hz, H-5), 6.88 (d, $^3J_{H\text{-}H} = 8.3$ Hz, H-10), 6.97 (dd, $^3J_{H\text{-}H} = 8.3$ Hz, $^4J_{H\text{-}H} = 2.0$ Hz, H-11), 7.40 (m, H-7, 14, 15, 16, 17, 18).

3-(3-methoxy-4-(phenylmethoxy)-5-bromomethane-4,5-dihydroisoxazole (6): (mp 93–94°C) **HRMS** (*m*/*z*-%) ($M^+ = 375.0484$ – 100%); **IR** (neat, cm^{-1}) 3070 (=C-H), 1599 (C=C), 1263 (C-O-C); ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 155.6 (C-3), 150.0 (C-9), 149.6 (C-8), 136.4 (C-13), 128.5 (C-14/18), 127.9 (C-16), 127.1 (C-15/17), 122.0 (C-11), 120.2 (C-6), 112.8 (C-10), 109.0 (C-7), 79.4 (C-5), 70.6 (C-12), 55.9 (C-19), 39.5 (C-4), 33.1 (CH_2Br); ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 3.42 (m, $H_{4A,4B}$ and CH_2Br), 3.92 (s, H-19), 4.97 (m, H-5), 5.20 (s, H-12), 6.86 (d, $^3J_{H\text{-}H} = 8.1$ Hz, H-10), 6.97 (dd, $^3J_{H\text{-}H} = 8.1$ Hz, $^4J_{H\text{-}H} = 2.1$ Hz, H-11), 7.37 (m, H-7, 14, 15, 16, 17, 18).

3-(3-methoxy-4-(phenylmethoxy)-5-ethoxy-4,5-dihydroisoxazole (7): (mp 80–81°C) **HRMS** (*m*/*z*-%) ($M^+ = 327.1435$-100%); **IR** (neat, cm^{-1}) 2974 (CH_{3as}), 2937 (CH_{2as}), 2871 (CH_{3s}), 1600 (C=C), 1265 (C-O-C); ^{13}**C NMR** (50 MHz, $CDCl_3$ PENDANT) δ 156.9 (C-3), 150.2 (C-9), 149.8

(C-8), 136.7 (C-13), 128.7 (C-14/18), 128.1 (C-16), 127.3 (C-15/17), 122.5 (C-6), 120.6 (C-11), 113.2 (C-10), 109.4 (C-7), 103.0 (C-5), 70.9 (C-12), 63.8 (OCH_2C), 56.1 (C-19), 41.8 (C-4), 15.2 ($OCCH_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.22 (t, $^3J_{H\text{-}H} = 7.1$ Hz, $OCCH_3$), 3.16 (dd, $^2J_{4A\text{-}4B} = 17.2$ Hz, $^3J_{4A\text{-}H5} = 1.4$ Hz, H-4), 3.36 (dd, $^2J_{4B\text{-}4A} = 17.2$ Hz, $^3J_{4B\text{-}H5} = 6.4$ Hz, H-4), 3.59 (m, OCH_2C, 1H), 3.90 (m, OCH_2C, 1H), 3.91 (s, H-19), 5.18 (s, H-12), 5.65 (dd, $^3J_{H5\text{-}4B} = 6.4$ Hz, $^3J_{H5\text{-}4A} = 1.4$ Hz, H-5), 6.85 (d, $^3J_{H\text{-}H} = 8.3$ Hz, H-10), 6.98 (dd, $^3J_{H\text{-}H} = 8.3$ Hz, $^4J_{H\text{-}H} = 1.6$ Hz, H-11), 7.35 (m, H-7, 14, 15, 16, 17, 18).

3-(3-methoxy-4-(phenylmethoxy)-5-methylcarboxylate-4,5-dihydroisoxazole (8): (mp 111–112°C) **HRMS** (*m*/*z*-%) ($M^+ = 341.1254$-100%); **IR** (neat, cm^{-1}) 1742 (C=O), 1601 (C=C), 1238 (C-O-C); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (CO_2), 155.7 (C-3), 150.1 (C-9), 149.6 (C-8), 136.3 (C-13), 128.5 (C-14/18), 127.9 (C-16), 127.1 (C-15/17), 121.4 (C-11), 120.4 (C-6), 112.7 (C-10), 109.2 (C-7), 77.7 (C-5), 70.6 (C-12), 55.9 (C-19), 52.7 (CO_2CH_3), 38.9 (C-4); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.58 (m, H-4), 3.79 (s, CO_2CH_3), 3.90 (s, H-19), 5.13 (m, H-5), 5.18 (s, H-12), 6.85 (d, $^3J_{H\text{-}H} = 8.3$ Hz, H-10), 6.97 (dd, $^3J_{H\text{-}H} = 8.3$ Hz, $^4J_{H\text{-}H} = 2.0$ Hz, H-11), 7.40 (m, H-7, 14, 15, 16, 17, 18).

CONCLUSION

We have developed a facile and effective procedure to convert hydroximoyl chloride into the corresponding nitrile oxide which gives 4,5-dihydroisoxazoles *via* 1,3-dipolar cycloaddition. Further studies involving bioactive[14] comportment of our products are in progress as well synthesis of new 4,5-dihydroisoxazoles.

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