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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

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

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Published online: 16 Aug 2006.

To cite this article: Rogério da Conceição Rodrigues & Alcino Palermo de Aguiar (2001): A SIMPLE AND EFFICIENT METHOD FOR THE SYNTHESIS OF NITRILE OXIDE FROM ALDOXIME USING TRICHLOROISOCYANURIC ACID, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:20, 3075-3080

To link to this article: <u>http://dx.doi.org/10.1081/SCC-100105879</u>

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SYNTHETIC COMMUNICATIONS, 31(20), 3075-3080 (2001)

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 NH₂OH.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 affored four new 4,5-dihydroisoxazoles regioselectively¹⁰ in good yields (Table).



Scheme 1.

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NITRILE OXIDE

Table 1. Cycloaddition of Nitrile Oxides to Terminal Alkenes

Entry	Dipolarophyles	Compounds	Yield
1	CN		31
2	Br	R ₁ Br	51
3	<i>∕</i> _0	R_1	52
4	OCH3	N-O-OCH3 R1-OCH3	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 chromatography¹² using ethyl acetate–hexane (1:2) as eluent, affording the respective 4,5-dihydro-isoxazoles in 30–60% yield. All products were characterized by FTIR, MS, ¹³C and ¹H NMR techniques.

The regiochemistry for all the formed products can be predicted by frontier molecular orbital theory¹³ 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 ¹³C NMR spectra were recorded in $CDCl_3$ on a Varian Unity-300 (300 MHz ¹H and 75 MHz for ¹³C) and Bruker DPX 200 (200 MHz ¹H and 50 MHz for ¹³C) 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 CH₂Cl₂ are added the aldoxime (1) (mp 130–131°C) in 5 mL of CH₂Cl₂. 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 CH₂Cl₂ and washed with aqueous saturated NaHCO₃ solution (2 × 70 mL), dried over MgSO₄ 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), ¹³C NMR (75 MHz, CDCl₃, 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). ¹H NMR (300 MHz, CDCl₃) δ 3.68 (m, H-4), 3.91 (s, H-19), 5.20 (s, H-12), 5.31 (dd, ³J_{H5-4A} = 9.9 Hz, ³J_{H5-4B} = 6.8 Hz, H-5), 6.88 (d, ³J_{H-H} = 8.3 Hz, H-10), 6.97 (dd, ³J_{H-H} = 8.3 Hz, ⁴J_{H-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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂Br); ¹H NMR (300 MHz, CDCl₃) δ 3.42 (m, H_{4A,4B} and CH₂Br), 3.92 (s, H-19), 4.97 (m, H-5), 5.20 (s, H-12), 6.86 (d, ³J_{H-H} = 8.1 Hz, H-10), 6.97 (dd, ³J_{H-H} = 8.1 Hz, ⁴J_{H-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); ¹³C NMR (50 MHz, CDCl₃ PENDANT) δ 156.9 (C-3), 150.2 (C-9), 149.8 Copyright @ Marcel Dekker, Inc. All rights reserved

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NITRILE OXIDE

(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 (OCH₂C), 56.1 (C-19), 41.8 (C-4), 15.2 (OCCH₃); ¹H NMR (200 MHz, CDCl₃) δ 1.22 (t, ³J_{H-H} = 7.1 Hz, OCCH₃), 3.16 (dd, ²J_{4A-4B} = 17.2 Hz, ³J_{4A-H5} = 1.4 Hz, H-4), 3.36 (dd, ²J_{4B-4A} = 17.2 Hz, ³J_{4B-H5} = 6.4 Hz, H-4), 3.59 (m, OCH₂C, 1H), 3.90 (m, OCH₂C, 1H), 3.91 (s, H-19), 5.18 (s, H-12), 5.65 (dd, ³J_{H5-4B} = 6.4 Hz, ³J_{H5-4A} = 1.4 Hz, H-5), 6.85 (d, ³J_{H-H} = 8.3 Hz, H-10), 6.98 (dd, ³J_{H-H} = 8.3 Hz, ⁴J_{H-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); ¹³C NMR (75 MHz, CDCl₃) δ 170.8 (CO₂), 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 (CO₂CH₃), 38.9 (C-4); ¹H NMR (300 MHz, CDCl₃) δ 3.58 (m, H-4), 3.79 (s, CO₂CH₃), 3.90 (s, H-19), 5.13 (m, H-5), 5.18 (s, H-12), 6.85 (d, ³J_{H-H} = 8.3 Hz, H-10), 6.97 (dd, ³J_{H-H} = 8.3 Hz, ⁴J_{H-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 bioactive¹⁴ comportment of our products are in progress as well synthesis of new 4,5-dihydroisoxazoles.

ACKNOWLEDGMENT

We thanks CAPES and FAPERJ for the financial support of this work, and Dr. Edson Ferreira da Silva, Mônica Zucolotto, Dr. Elisabete Cruz and Lab. NMR of IQ/UFRJ for spectral analysis.

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Received in the USA December 4, 2000

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