SYNTHESIS OF NEW 4,5-DIHYDROISOXAZOLES WITH POTENTIAL ANTI-INFLAMMATORY ACTIVITY

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Abstract: This paper reports the synthesis of different 4,5-dihydroisoxazoles which may present anti-inflammatory activity. The methodology employed was based on the 1,3-dipolar cycloaddition of nitrile oxide derived from vanillin to unsaturated compounds. It was used trichloroisocyanuric acid as a suitable reagent to convert the aldoximes to imidoyl chlorides. The products were obtained with yields between 40 and 90% and were fully characterized using FTIR, GC/MS, ^{1}H and ^{13}C NMR.

Introduction

Compounds derived from substituted 4,5-dihydroisoxazoles (1) are important mainly because these compounds present a heterocyclic ring which confers them a variety of biological activities (2). These compounds can be produced using different methodologies of synthesis (3, 4), which has been reported recently (5). This reaction can produce 3,5 or 3,4-disubstituted dihydroisoxazoles as principal products and furoxan as byproduct (6).

Our group has conducted this reaction to produce new 4,5-dihydroisoxazoles (1, 7) derived from vanillin, employed trichloroisocyanuric acid as oxidation agent, focusing our work in the developing of products with potential anti-inflammatory activity (8). Results from the literature have pointed out a dependence of this activity upon the kind of substituent at C-5 of the heterocyclic (9). The main aim of this work was to synthesize new 4,5-dihydroisoxazoles with different functional groups at C-5 of the heterocyclic ring using 1,3-dipolar cycloaddition reactions (Scheme I).

Results and Discussion

The methodology used to synthesize three different 4,5-dihydroisoxazoles 4, 5, 6 (Scheme I), was based on the dipolar cycloaddition of nitrile oxide 3 to unsaturated compounds (Table I). It is well known that the alkyl-substituted olefins react smoothly with nitrile oxides and that the rate of this reaction is influenced by either electron-donating or electron-withdrawing groups (10). The regioselectivety of the reaction to produce the 3,5-disubstituted product was also investigated.

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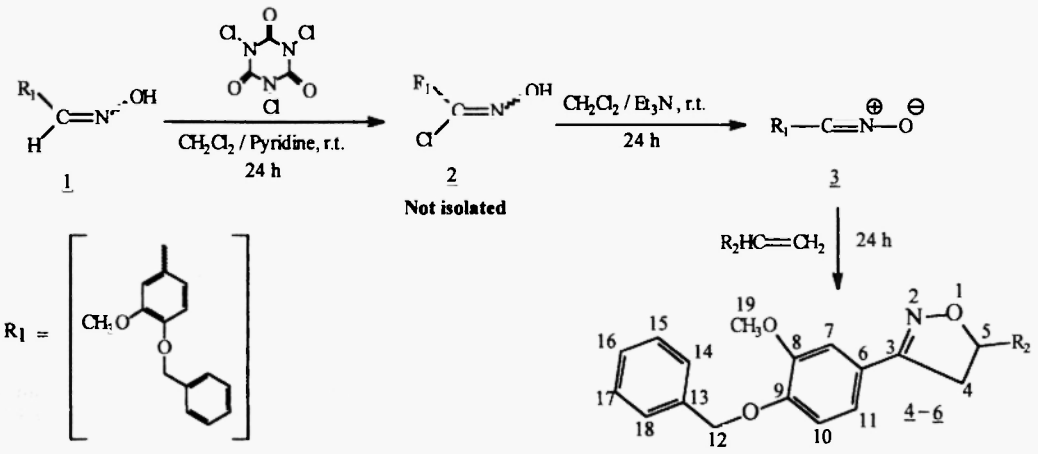
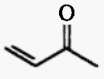
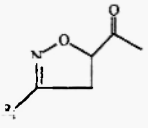
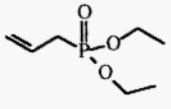
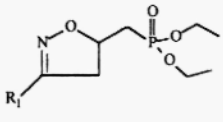
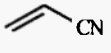
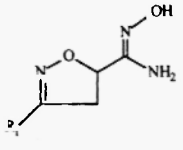
Initially, the simple alkylation of vanillin with benzylbromide was conduced in the presence of sodium carbonate, producing the alkylated aldehyde with 90% yield. This aldehyde was treated with $NH_2OH.HCl$ in ethanol solution to afford the aldoxime 1 in 85% yield, which was characterized by the disappearance of the 1715 cm^{-1} carbonyl band in the IR spectrum and a melting point of 124°–126°C (7).



Scheme I: General Methodology of Synthesis of the 4,5-dihydroisoxazoles

Table I : Cycloaddition of nitrile oxide to terminal alkenes

Compounds	Dipolarophyles	4,5-Dihydroisoxazoles	Yield (%)
4			50
5			40
6			90

The treatment of the aldoxime with trichloroisocyanuric acid during 35 min. under constant stirring at room temperature smoothly lead to the imidoyl chloride 2. The reaction mixture was filtered off to separate the isocyanuric acid formed during the oxidation reaction and the solution containing the imidoyl chloride was treated with triethylamine and the desired alkene with constant stirring at room temperature for 24 h. The reaction was monitored by TLC until the desapearance of the imidoyl chloride.

In fact, it was noted that the regiochemistry (multiplicity for the C-5 of the heterocyclic ring -^{13}C NMR) for all the products could be explained by frontier molecular orbital (11). The nitrile oxide involves a relatively high-lying highest occupied molecular orbital (HOMO) and low-lying unoccupied molecular orbital (LUMO), thus leading the negative charge at the oxygen atom of the nitrile oxide 3 to bond to the most substituted carbon at the dipolarophile.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in a Varian Unity-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and a Bruker DPX 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) spectrometers, using TMS as an internal standard. Infrared spectra were recorded with a Nicolet Protége 460 E.S.P. All melting points are uncorrected and measured in a Fisher-Johns apparatus. TLC analyses were carried out using precoated silica gel aluminium plates 60 F_{254} (Merck). Column chromatography was performed using Merck silica gel 60 (230-400 mesh).

General Procedure - To a solution of aldoxime 1 (0.6g, 2.3mmol) in methylene chloride (30 mL), trichloroisocyanuric acid (0.2g, 0.9 mmol) in pyridine (0.2 mL, 2.5 mmol) was slowly added. After 35 minutes of vigorous stirring at room temperature, the solid isocyanuric acid formed was filtered off. The dipolarophile (4.6 mmol) and triethylamine (0.3 mL, 2.3 mmol) were added to the filtrate. After stirring for 24 h at room temperature, the mixture was diluted to 50 mL with CH_2Cl_2, was washed with water (2x50mL), dried (Na_2SO_4) and concentrated in a rotatory evaporator. The products were purified by flash chromatography (20g of silica gel) using ethyl-acetate/hexane (1/4) as eluent, affording the respective 4,5-dihydroisoxazoles in 40–90% yield.

Compound 4 - It was obtained from methylvinyl ketone (0.4 mL, 4.6 mmol) as a solid (mp 108-110 °C) in 50% yield - **FTIR** (neat, cm^{-1}) 1716 (C=O), 1598 (C=N), 1516 (C=C); **GC/MS** (M^+ = 325-1%), (239-10%), (91-100%), (65-16%); **^{13}C NMR** (75 MHz, CDC^{13}, Pendant) δ 26.4 (C-21), 37.4 (C-4), 56.0 (C-19), 70.7 (C-12), 84.3 (C-5), 109.2 (C-7), 112.9 (C-10), 120.5 (C-11), 121.6 (C-6), 127.2 (C-15, C-17), 128.0 (C-16), 128.6 (C-14, C-18), 136.5 (C-13), 149.7 (C-8), 150.3 (C-9), 156.3 (C-3), 207.9 (C-20); **^{1}H NMR** (300 MHz $CDCl_3$) δ 2.35 (s, H-21), 3.47 (dd, $^2J_{H4A-4B}$ = 17.1 Hz, $^3J_{H4A-H5}$ = 11.7 Hz, H-4a), 3.56 (dd, ^{2}J $_{4A-4B}$ = 17.1 Hz, ^{3}J H_{4B-H5} = 6.3 Hz, H-4b), 3.91 (s, H-19), 4.99 (dd, $^3J_{4A-H5}$ = 11.7 Hz, $^3J_{H4B-H5}$ = 6.3 Hz H-5), 5.19 (s, H-12), 6.85 (d, ^{3}J = 8.4 Hz, H-10), 6.98 (dd, $^3J_{H-H}$ = 8.4 Hz e $^4J_{H-H}$ = 2.1 Hz H-11),7.40 (m, 6H 7,14,15,16,17,18).

Compound 5 - It was obtained from allyl phosphonate (0.8 mL, 4.6 mmol) as a yellow oil in 40% yield, after purification by column chromatography using ethyl-acetate/hexane (1/1) as eluent. - **FTIR** (neat, cm-1) - 2984 (C-H); 1515 (C=C); 1248 (P=O); 1028-968 (P-O-C); **GC/MS** (433-9%), (282-30%), (152-98%), (125-99%), (91-100%); **^{13}C NMR** (50 MHz, CDCl3, Pendant) δ 16.2 (d, $^2J_{CCOP}$ = 5.9 Hz, C-22, C- 24), 31.7 (d, J_{CP} = 136.7 Hz C-20), 40.6 (C-4), 55.8 (C-19), 61.8 (d, $^2J_{COP}$ =6.5 Hz, C-21, C-23), 70.6 (C-12), 75.8 (C-5), 108.9 (C-7), 112.8 (C-10), 120.1 (C-11), 122.2 (C-6), 127.0 (C-15, C-17), 127.8 (C-16), 128.4 (C-14, C-18), 136.4 (C-13), 149.5 (C-8), 149.8 (C-9), 156.5 (C-3); **^{1}H NMR** (200 MHz, CDCl3) δ 1.35 (m, H-22, 24, CH_3COP), 2.30 (m, H-20, CH_2P), 3.26 (dd, $^2J_{H4A-4B}$ = 16.8 Hz, $^3J_{H4A-H5X}$ = 7.6 Hz, H-4A), 3.48 (dd, $^2J_{H4A-4B}$ =16.8 Hz, $^3J_{H4B-H5X}$ = 10.0 Hz, H-4B), 3.91 (s, H-19), 4.10 (m, H-21, H-23, CH_2OP) 4.90 (m, H-5), 5.18 (s, H-12), 6.85 (d, $^3J_{H-H}$ = 8.2 Hz H-10), 6.99 (dd, $^3J_{H-H}$ = 8.2 Hz e $^4J_{H-H}$ = 2.0 Hz H-11), 7.35 (m, H-7,14,15,16,17,18).

Compound 6 - A solution of 5-cyane-3-[(4-phenylmethoxy-3-methoxy)-phenyl]-4,5-dihydroisoxazole (7) (0.2g, (0.64 mmol) in methanol (8 mL) was treated with a 1 mL of a previously prepared solution containing hydroxylamine hydrochloride (0.173g, 2.25 mmol) and sodium hydroxide (0.173g, 2.25mmol) . The reaction mixture was worked out after 2 h of reflux by the addition of water (10 mL). The solid (mp 152-154 °C) was filtered off and washed with water (50 mL) - **FTIR** (neat, cm^{-1}) - 3375-3205 (NH_2); 1635 (C=N); 1515 (C=C); 1268 (C-O-C); **GC/MS** (M^+ = 341- 3%), (281-3%); (239-6 %); (91-100%); (77- 3%); (65-10%); **^{13}C NMR** (50 MHz, CDCl3, Pendant) δ 37.5 (C-4), 56.0 (C-19), 70.2 (C-12), 79.2 (C-5), 109.7 (C-7), 113.5 (C-10), 120.7 (C-11), 122.5 (C-6), 128.3 (C-15, C-17), 128.4 (C-16), 128.9 (C-14, C-18), 137.2 (C-13), 149.5 (C-8), 149.9 (C-9), 151.0 (C-20), 157.1 (C-3); **^{1}H NMR** (200 MHz, CDCl3) δ 3.45 ($^2J_{H4A-4B}$ = 16.8 Hz, $^3J_{H4A-H5X}$ = 10.6 Hz), 3.60 ($^2J_{H4A-4B}$ = 16.8 Hz, $^3J_{H4B-H5X}$ = 8.7 Hz), 3.80 (s, H-19), 4.99 ($^3J_{H4A-H5X}$ = 10.6 Hz, $^3J_{H4B-H5X}$ = 8.7 Hz H-5), 5.14 (s, H-12), 5.55 (s, NH_2), δ 7.10 (d, $^3J_{H-H}$ = 8.3 Hz, H-10), 7.15 (dd, $^3J_{H-H}$ = 8.3 Hz e $^4J_{H-H}$ = 1.9 Hz, H-11), 9.41 (s, OH).

Conclusions

The methodology using trichloroisocianuric acid was efficient for the adopted synthesis procedure, leading to the desired 4,5-dihydroisoxazoles in good yields (40-90%). This work is being continued by the preparation of new heterocyclic 4,5-dihydroisoxazoles and the determination of the activities of all the obtained products.

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