CHEMO- AND REGIOSELECTIVE SYNTHESIS OF NEW PHOSPHORATED 4,5-DIHYDROISOXAZOLES FROM DIFFERENT MONOTERPENES

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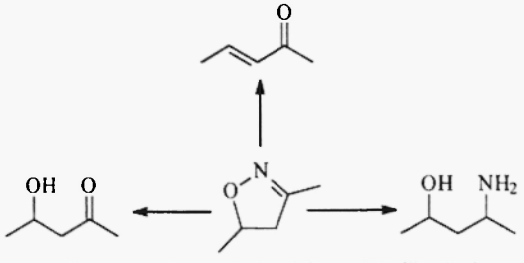
Abstract: We report a quimio and regioselective synthesis of three new phosphorated 4,5-dihydroisoxazoles using nitrile oxide cycloaddition to limonene 1, carvone 2 and perilaldehyde 3. Nitrile oxide was formed *in situ* by dehydrohalogenation of phosphorated imidoyl chloride with Et_3N. The products were isolated with yields of 38-50% and characterized by FTIR, MS, ^{13}C and ^{1}H NMR.

Introduction

Cycloaddition of nitrile oxide to alkenes is of great importance in organic synthesis as the 4,5-dihydroisoxazoles are flexible building blocks due to their ability to function as masked forms of β-hydroxy ketones, α,β-unsaturated ketones and γ-amino alcohols (1) (Scheme 1). Although the synthetic use of nitrile oxide cycloaddition has grown as shown by its wide application to differents synthetic routes, the number of papers that associate this reaction with phosphorus-functionalized nitrile oxide has been limited (2).

Phosphonates are substances that present many different applications: synthetic intermediates (3), fire inhibitors (4), additives for lubricants (5) and metal extractive agents (6). Due to their potential in commercial applications, several synthetic methods for functionalizing phosphonates have been developed (7). However, some of these methods use elaborate reagents and the routes lack versatility (8).



Scheme 1: Some products obained from 4,5-dihydroisoxazole

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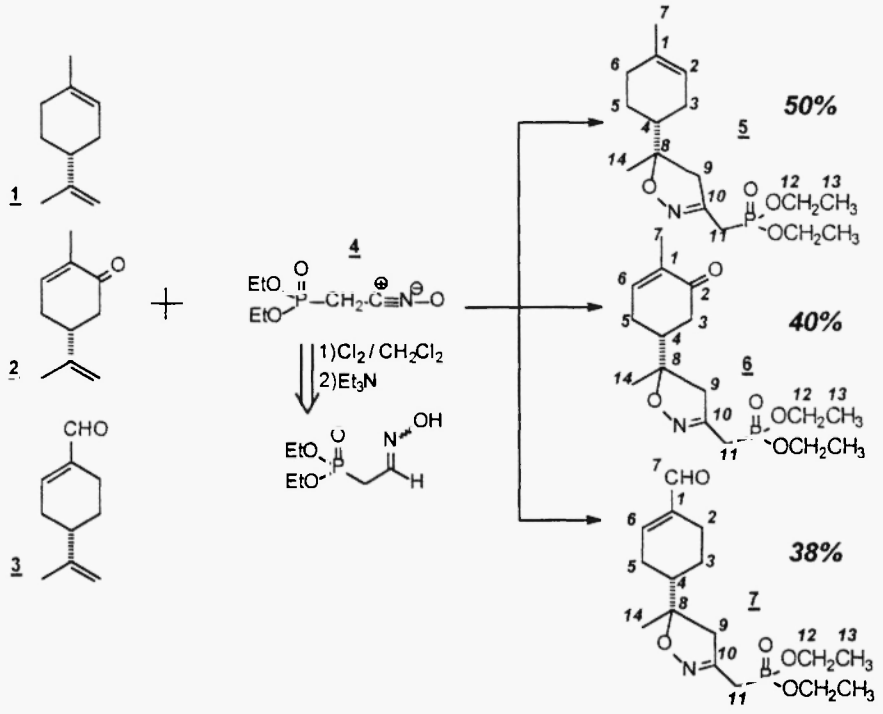
Experimental

Infrared spectra were recorded with a Perkin Elmer 1710 spectrometer. Mass spectra (MS) were performed with a HP 5987A (GC/MS) spectrometer by electron impact (EI) with a beam energy of 70 eV. ^{1}H and ^{13}CNMR spectra were recorded in $CDCl_3$ on a Varian VXR-300 spectrometer, using TMS as na internal standard. Gas chromatography (GC) was performed with HP 5890 Series II. Column chromatography was performed on Merck silica gel 60 (230-240 mesh) using a hexane/ethyl acetate (1/4).

Spectral data of **Compound** 5: *IR*(neat, cm^{-1}) - 1255 (P=O), 1023, 965 (P-O-C); *MS* (e/m-%) - (M^+, 329-4), (234-100), (206-40), (178-80), (138-4), (81-15); *^{13}C NMR* (75 MHz, $CDCl_3$, PENDANT, δ) – 16.35 (d, J^3_{C-P} = 6.0 Hz, C_{13}), 22.95-23.82 (C_{14}), 23.29-23.68 ($2C_7$), 23.68 (C_5), 26.52 (d, J^1_{C-P} = 140 Hz, C_{11}), 26.50-26.86 ($2C_{3.}$), 30.35 (C_6), 42.08-42.20, ($2C_4$), 41.71-45.73 ($2C_{10.}$), 44.70-45.73 ($2C_9$) 62.31 (2d, J^2_{C-P} = 6.5 Hz, C_{12}), 89.30-89.66 ($2C_8$), 119.63-119.67 ($2C_2$), 133.68-133.80 ($2C_1$), 150.05-150.18 (2d, J^2_{C-P} = 13.0 Hz, C_{10}); *^{1}H NMR* (300 MHz, $CDCl_3$, TMS - δ,) – 1.305 (t, J^3_{H-H} = 7.0 Hz, 6H, H_{13}), 1.274 (s, 3H, H_{14}), 1.607 (s, 3H, H_7) 1.717-1.943 (m, 7H, $H_{3,4,5,6}$), 2.586-2.693 (m, 1H, H_{9A}), 2.894-3.001 (m, 1H, H_{9B}), 2.886 (d, J^2_{H11-P} = 22.0 Hz, 2H, H_{11}), 4.113 (m, 4H, H_{12}), 5.334 (sl, 1H, H_2). **Compound** 6: *IR*(neat, cm^{-1}) - 1673 ($C=O_{conj}$), 1250 (P=O), 1101, 1026, 971 (P-O-C); *MS* (e/m-%) - (M^+, 343-4), (259-22), (234-30), (178-70), (152-60), (109-80), (81-100); *^{13}C NMR* (75 MHz, $CDCl_3$, PENDANT, δ) – 15.56 (C_7), 16.38 (**d**, J^3_{C-P} = 6.0 Hz, C_{13}), 23.23 e 23.98 ($2C_{14}$), 26.39 (d, J^1_{C-P} = 140 Hz, C_{11}), 25.46 (C_5), 39.19 (C_3), 43.59 (C_4), 45.64 e 45.91 ($2C_{9.}$), 62.58 (2d, J^2_{C-P} = 6.0 Hz, C_{12}), 87.77 e 87.80 ($2C_8$), 35.35 e 135.42 ($2C_{1.}$), 144.30 (C_6), 150.58 ($2C_{10.}$) 198.82 (C_2); *^{1}H NMR* (300 MHz, $CDCl_3$, TMS - δ) – 1.274 (t, J^3_{H-H} = 7.0 Hz, 6H, H_{13}), 1.284 e 1.307 (2s, 3H, $H_{14diast.}$), 1.693 (**s**, 3H, H_7), 1.90-2.50 (m, 5H, H_3, H_4, H_5), 2.695 (2d, J_{HA-HB} = 17.5 Hz, J^4_{H-P} = 4.0 Hz, 1H, H_{9A}), 2.813-2.885 (2d, 2H, J^2_{H-P} = 21.6 Hz, $H_{11diast.}$), 2.945-3.033 (m, 1H, H_{9B}), 4.073 (m, 4H, H_{12}), 6.681 (sl, 1H, H_6). **Compound** 7: *IR* (neat, cm^{-1}) - 1678 ($C=O_{conj}$), 1635 (C=C), 1251 (P=O), 1024, 971 (P-O-C); *MS* (e/m-%) - (M^+, 343-3), (241-18), (234-20), (178-60), (152-65), (109-100), (81-62); *^{13}C NMR* (75 MHz, $CDCl_3$, PENDANT, δ) – 15.89 (d, J^3_{C-P} = 6.0 Hz, C_{13}), 21.30 (C_5), 22.15 (C_6), 22.39 e 22.80 ($2C_{14}$), 26.04 (d, J^1_{C-P} =140 Hz, C_{11}), 27.51-27.26 ($2C_{3.}$), 41.78-41.89 (C_4), 45.13-45.34 (C_9), 62.12 (d, J^2_{C-P} = 6.7 Hz, C_{12}), 88.32-88.62 (2C), 140.89-140.80 (2C), 149.57-149.64 ($2C_{2.}$), 150.28-150.15 ($2C_{11.}$), 193.27 (C_7); *^{1}H NMR* (300 MHz, $CDCl_3$, TMS - δ) - 1.298 (t, J^3_{H-H} = 7.0 Hz, 6H, H_{13}), 1.306-1.339 (2**s**, 3H, $H_{14diast}$), 1.817-2.530 (m, 7H, $H_{3,4,5,6}$), 2.682-2.740 (dt, J^2_{H-H} = 17.5 Hz, J^4_{H-P} = 4.0 Hz, J^4_{H9-H4} = 4.0 Hz, 1H, H_{9A}), 2.967-3.021 (dd, J^2_{H-H} = 1.5 Hz, J^4_{H-P} = 4.0 Hz, 1H, H_{9B}), 2.885-2.888 (2d, J^2_{H-P} = 21.7 Hz, 2H, $H_{11diast}$), 4.122 (m, 4H, H_{12}), 6.769 (sl, 1H, H_2), 9.388 (s, 1H, H_7).

Results and Discussion

The following methodology describes the synthesis of three different 4,5 dihydroisoxazoles (5, 6 and 7), which are potentially useful starting materials for sesquiterpenes as well as bifunctionalized phosphonates (2). It is well known that alkyl substituted olefins react smoothly with nitrile oxides, with the rate of the reaction being influenced by either electron-donating or electron-withdrawing groups. In the light of this, we have investigated the dipolar cycloaddition of the phosphonated nitrile oxide with three different monoterpenes (9) (1, 2 and 3) (Scheme 2).



Scheme 2: Cycloaddition reaction of the diethoxyphosphoryl acetonitrile oxide to limonene 1, carvone 2 and perialdehyde 3

At first, the phosphorated aldoxime was obtained by treatment of the corresponding phosphorated aldehyde with $NH_2OH.HCl$ to give a 60% yield (10). Chlorine was bubbled through a solution, at -78°C, containing the phosphorated aldoxime (11 mmol / 50 mL CH_2Cl_2), after reaching room temperature the solution was placed in vacuum to remove the chlorine excess. The chlorinated aldoxime was added to a mixture containing the respective monoterpene (60 mmol / 50 mL CH_2Cl_2) followed by catalytic quantities of Et_3N (5 drops) with the system temperature at 5°C. The solution was stirred at room temperature for 24 h and poured into water. The organic layer was removed and dried over Na_2SO_4. This reaction was investigated using an alkene/nitrile oxide ratios of 2:1, 4:1 and 6:1, with the reactions using lower ratios giving poorer yields and evidence of polymerization of the nitriie oxide.

The capillary gas chromatography analysis (11) of the reaction mixtures showed the presence of two products (expected diastereoisomers) when the mixture was isolated by flash chromatography (12) (hexane:ethyl acetate 1:4) in 38-50% yield. The diastereoisomers were characterized by FTIR, MS, ^{13}C and ^{1}H NMR techniques.

The similar regiochemistry obtained for all in this family of products can be predicts by frontier molecular orbital theory which demonstrated that, in some cases, the most substituted carbon will bind to the oxygen of the nitrile oxide (13) as a consequence of the interaction between HOMO-LUMO of the reagents. The chemoselectivity was attributed to steric fators (9).

Conclusion

The advantages of the present methodology are the use of chlorine as the halogenation agent of the aldoxime and the use of a solvent without special drying before formation of the nitrile oxide, instead of systems such as N-Chlorosuccinimide, N-Bromosuccinimide (14) or oxidation agents like $Pb(OAc)_4$ (15). Another interesting aspect of this methodology using terpenes as starting materials is the possibility of the products serving as intermediates in the preparation of the bisabolenic structure (16). This work is being continued using differents techniques to optimize the reaction yield, and to investigate the opening of the heterocyclic ring to form bifunctionalized phosphonates.

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(11) Column SE 54 (20m x 0,30μm x 0,3mm) - flow (CH_4) 2mL/min., T_i.= 60°C, T_f.= 220°C, rate= 8°C/min..

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