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REACTIONS OF DIAZOMETHYLPHOSPHONATE: THE FIRST SYNTHESIS OF A FORMYLPHOSPHONATE HYDRATE

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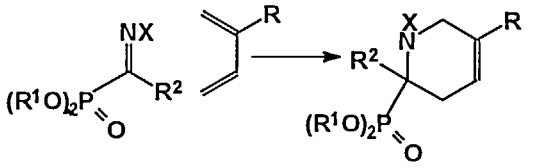
Abstract: Formylphosphonate hydrate has been synthesised by the oxidation of diazomethylphosphonate with dimethyldioxirane (DMD) and its reactions, including the formation of imines, oximes, and Wittig olefination products, have been investigated. Formylphosphonate also acts as an efficient, selective formylating agent of secondary amines. β-Ketophosphonic acids derived from a range of amino acids have been prepared by the tin (II) chloride-catalysed reaction of diazomethylphosphonate with amino aldehydes and in certain cases shown to be potent inhibitors of leucine aminopeptidase.

Key Words: Diazomethylphosphonate, formylphosphonate, amino acid-derived β-ketophosphonic acids, leucine aminopeptidase inhibitors.

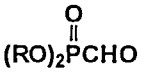
The range of biological activity observed for functionalised phosphonate derivatives, especially analogues of amino acids, has highlighted the need for new, flexible routes to such compounds.[1] Due to their predictable stereochemistry and wide range of established chemistry, cycloaddition reactions, e.g. the Diels-Alder reaction, offer many attractions. For example, such reactions of 1-iminoalkylphosphonates (**1**) should provide the basis for potentially enantioselective routes to a wide range of phosphonic amino acid derivatives. However, our attempts to carry out Diels-Alder reactions with the readily available imines (**1**, R^2=alkyl or aryl) derived from acylphosphonates were unsuccessful in spite of the fact that M.O. calculations indicated favourable LUMO/HOMO energy differences in many of the examples attempted. This suggested that steric effects are of overriding importance. In view of this we turned our attention to the synthesis of formylphosphonate esters (**2**) as a source of the corresponding aldimines (**1**, R^2=H).

The only reported[2] method of the synthesis of these compounds involves the formylation of dialkyl phosphites with formic acetic anhydride. Our attempts to obtain (**2**) by this procedure have been unsuccessful (dialkyl methylphosphonates being the only

identified products) and the n.m.r. data given in the original publication[2b] do not support the proposed structure (2).



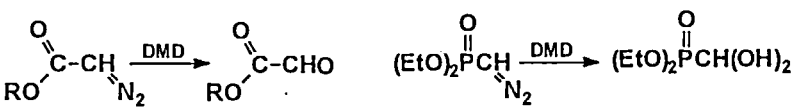
(1)



(2)

In view of this we investigated a range of alternative approaches to (2), including the hydrolysis under a variety of conditions of the available[3] diethyl acetal derivative of (2), reduction of alkoxycarbonylphosphonates, oxidation of hydroxymethylphosphonates, ozonolysis of vinylphosphonates under reducing conditions, and a variety of alternative formylation procedures, without success.

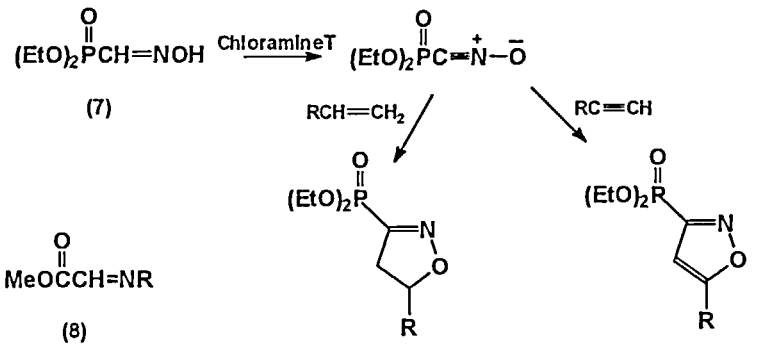
Glyoxals (4) have been conveniently prepared by the oxidation of α-diazoacetates (3) with dimethyldioxirane (DMD) in acetone solution.[4] Similar treatment of diethyl diazomethylphosphonate (5) gave diethyl formylphosphonate hydrate (6) as a yellow oil in quantitative yield as identified by its ^{13}C [δ_C ($CDCl_3$) 88.17 (d, $^1J_{PC}$=210Hz)] and ^1H [δ_H($CDCl_3$) 5.13 (1H, d, $^2J_{PH}$=9.1Hz)] n.m.r. and mass [M^+ =166.0392] spectra.[5] Further confirmation of the structure of (6), and the fact that it is synthetically equivalent to the corresponding aldehyde, is available from its Wittig reaction with *t*-butoxycarbonylmethylenephosphonium ylide to give the corresponding vinylphosphonate as an isomer mixture and the formation of a cyanohydrin derivative on reaction with trimethylsilyl cyanide.



(3) (4) (5) (6)

The condensation of (6) with primary amines ($PhNH_2$, *t*-$BuNH_2$, *c*-$HexNH_2$, and $PhCH(Me)NH_2$) leads to the formation of aldimines (1, R^2=H), as identified by their (for X=Ph) ^{13}C [δ_C ($CDCl_3$) 157.79 (d, $^1J_{PC}$=222.5Hz)] and ^1H [δ_H($CDCl_3$) 8.22 (1H, d, $^2J_{PH}$=61.2Hz)] n.m.r. and mass [M^+ =241.0856] spectra, generally in excellent yield. These $^1J_{PC}$ and $^2J_{PH}$ values are the largest so far reported and are diagnostic for the

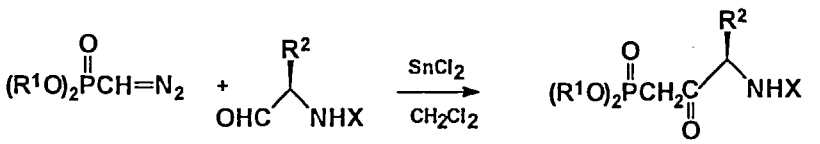
aldiminylphosphonate structure. Further confirmation of the structure of (**1**, R^2=H, X=Ph) is available from its synthesis by the Wadsworth-Emmons reaction of tetraethyl methylenediphosphonate with nitrosobenzene. The only previous report[6] of compounds (**1**, R^2=H) relies on their generation and trapping in situ and no spectroscopic or other data is available. The oxime (**7**) derived from (**6**) is readily formed in excellent yield [δ_C ($CDCl_3$) 142.19 (d, $^1J_{PC}$=236Hz), δ_H($CDCl_3$) 7.56 (1H, d, $^2J_{PH}$=37.9Hz); M^+ =241.0856] and, when treated with chloramine-T in the presence of alkene or alkyne, (**7**) provides a convenient route to the corresponding isoxazolines or isoxazoles, respectively (Scheme **1**). However, in no case did the oxime or the imines (**1**, R^2=H) prepared in this study undergo Diels-Alder reactions under the wide range of conditions tried, in spite of the fact that the direct ester analogues (e.g. **8**, X=Ph) readily undergo such reactions. In view of the in situ Diels-Alder trapping, albeit in low yield, of presumed aldimines (**1**, R=H) carrying an aryl sulfonyl or keto substituent on nitrogen[6] it seems likely that, unlike the corresponding ester analogues (**8**), an electron-withdrawing group attached to nitrogen is necessary for successful reaction. We are currently preparing such compounds.



Scheme 1

The hydrate (**6**) acts as a formylating agent towards secondary amines. Reaction with morpholine, piperidine, pyrrolidine, or dibenzylamine at room temperature leads to formation of diethyl phosphite and the corresponding *N*-formylamine in virtually quantitative yield, and a similar reaction of one mole equivalent of (**6**) with *N*-methylethylenediamine gave an excellent yield of *N*-formyl-*N*-methylethylene diamine with no evidence of competing imine formation.

In view of the postulated mechanism of action of leucine aminopeptidases and the successful design[7] of transition state inhibitors of such enzymes, it has been suggested[8] that β-ketophosphonic acids (**9**, R^1=H) derived from amino acids should also act as inhibitors. Diethyl diazomethylphosphonate reacts with N-protected amino aldehydes in the presence of tin dichloride to provide the corresponding β-ketophosphonates (**9**, R^1=Et, R^2=Me, ^{i}Pr, ^{i}Bu, Benzyl) in excellent yield. The structures of (**9**) were assigned on the basis of their n.m.r spectra, particularly the characteristic two doublets of doublets, due to the diastereotopic methylene protons adjacent to phosphorus, observed in the region δ_H 3 to 3.5 ppm. Although compounds (**9**) show substantial specific rotations, attempts to determine their optical purity using the chiral lanthanide shift reagent Eu(h.f.c.)$_3$ gave no peak separations. The compounds obtained were converted into the fully deprotected phosphonic acids (**9**, R^1 and X=H) and both these and the corresponding esters (**9**, R^1=Et) were tested against microsomal, cytosolic, and *E. Coli* leucine aminopeptidase. While the esters were inactive in all cases, the phosphonic acids acted as potent competitive reversible inhibitors.[8]



(**9**)

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