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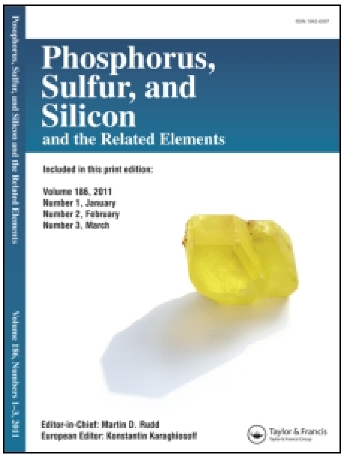

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The Synthesis and Chemistry of Formylphosphonate

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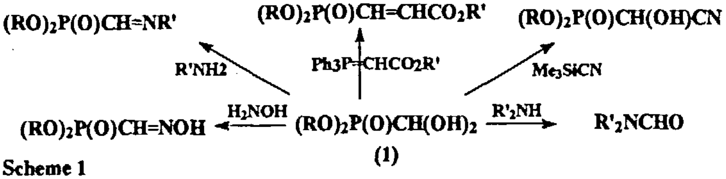
New methods of synthesis and reactions of formylphosphonate have been investigated. Attempts to deprotect the corresponding diethyl acetal with Ti^{IV} halides led instead to the formation of halo(ethoxy)methylphosphonates which undergo substitution reactions with a wide range of nucleophiles.The products of reactions of formylphosphonate with bifunctional nucleophiles are determined in most cases by Baldwin's Rules, while the imines derived from formylphosphonate undergo Diels-Alder reactions only in those cases which carry a strongly electron-withdrawing N-substituent.

Keywords: formylphosphonate; hetero Diels-Alder

INTRODUCTION

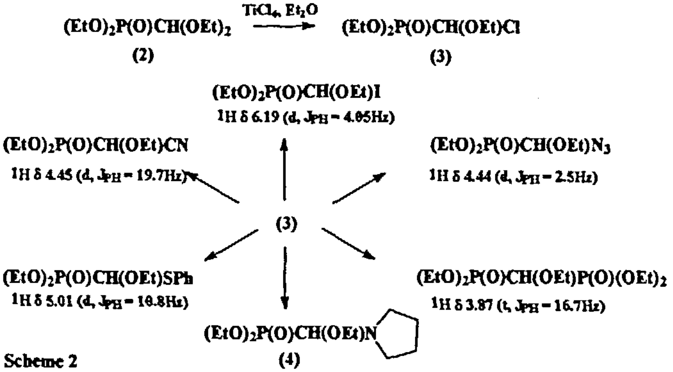
Formylphosphonate esters are of substantial interest as synthetic intermediates both in general organic chemistry and for the preparation of other organophosphorus compounds. In spite of this the first confirmed synthesis as the hydrate (1), by dimethyldioxirane (DMD) oxidation of dialkyl diazomethylphosphonates, has only recently been reported.[1] A summary of reactions of the hydrate, which acts as a synthetic equivalent of the aldehyde, is shown in scheme 1. Although the oxidation of diazomethylphosphonates to (1) is quantitative, the diazo compound is not readily available. In view of this we have investigated new approaches to the synthesis of (1) and extended its known chemistry.



Scheme 1

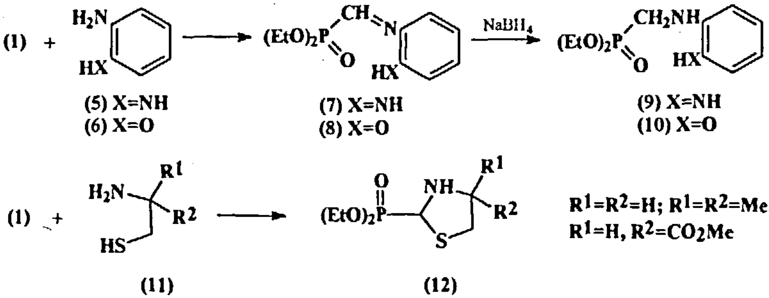
RESULTS AND DISCUSSION

The readily available[2] acetals (2) offer an attractive starting material for a synthesis of (1). However, attempts to deprotect (2) using acid hydrolysis lead to C-P bond cleavage and the formation of dialkyl hydrogenphosphonate and alkyl formate.[1] We have shown that such P-C cleavage is a common alternative pathway in many attempted syntheses of (1) from a variety of starting materials and reactions of (2) with a wide range of reagents known to deprotect acetals led to such cleavage or recovery of starting materials. In one case, treatment with $TiCl_4$ in ether, (2) was converted cleanly to the chloro(ethoxy)methylphosphonate (3), which was identified on the basis of its ^1H (δ 5.68 (1H, d, J_{PH} = 4.4Hz, PCH) and ^{31}P (δ 11.59) NMR spectra and mass spectrum. The corresponding bromo(ethoxy)phosphonate (^1H δ 5.94 (J_{PH} = 4.4Hz), ^{31}P δ 10.61) was prepared in a similar way by reaction with $TiBr_4$. In spite of its chloroether structure compound (3) is stable to cold water and sodium bicarbonate solution. However, it reacts readily with a wide variety of nucleophiles to give good to excellent yields of α-functionalised phosphonates (Scheme 2) which were identified on the basis of their ^1H and ^{31}P NMR spectra. The pyrrolidine analogue (4) is particularly unstable and evidence for its formation is the ^1H NMR spectrum of the reaction mixture.



Scheme 2

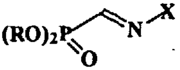
Compound (4) was decomposed by water to give diethyl hydrogenphosphonate and N-formyl pyrrolidine, one interpretation of which would involve intermediate formation of the hydrate (1), since this compound is known to efficiently formylate secondary amines.[1] In the light of this we have investigated the reaction of formylphosphonate (1) with bifunctional nucleophiles (Scheme 3) with a view to synthesising cyclic mixed hetero acetals via initial imine formation followed by intramolecular nucleophilic addition. However, reactions (CH_2Cl_2, $MgSO_4$, 20°C) of (1) with phenylene diamine (5) and 2-hydroxyaniline (6) gave the imines (7) and (8), respectively. Confirmation of the structure of (7) and (8) was obtained from their ^1H NMR spectra and reduction by $NaBH_4$ to give the corresponding aminomethylphosphonates (9) and (10). Similar reactions of (1) with 1,2-amino thiols (11), and 2-aminothiophenol, gave the corresponding thiazolines (12).



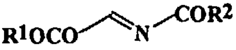
Scheme 3

These results can be explained on the basis of Baldwin's rules[3] since the 5-endo-trig cyclisation required for (7) and (8) is disfavoured. However, the larger, more polarisable sulfur atom does not have the same rigid stereochemical requirements in such reactions and thus the disfavoured cyclisation to (12) occurs. Similar reactions with 2-hydroxy- and 2-amino-benzylamine, which should involve the favoured 6-endo-trig cyclisation, gave diethyl hydrogenphosphonate as the only identified product. Attempts to hydrolyse (12) under a variety of conditions gave either no reaction or formation of diethyl hydrogenphosphonate.

In an attempt to develop the synthetic potential of (1) we have investigated hetero Diels-Alder reactions of the derived imines. These, and the corresponding ene reactions, are attractive since they may provide synthetic, including enantioselective, approaches to a variety of α-aminoalkylphosphorus acid structures, compounds which display a wide range of biological activity. We have previously shown that N-alkyl- or N-arylimines derived from (1) do not undergo Diels-Alder reactions under a range of conditions, a failure which is supported by theoretical results.[4] However, Steglich has reported[5] that imines (13) carrying strongly electron-withdrawing N-substituents and generated *in situ* by base treatment of the 1-bromo-1-aminoalkylphosphonate, do undergo Diels-Alder

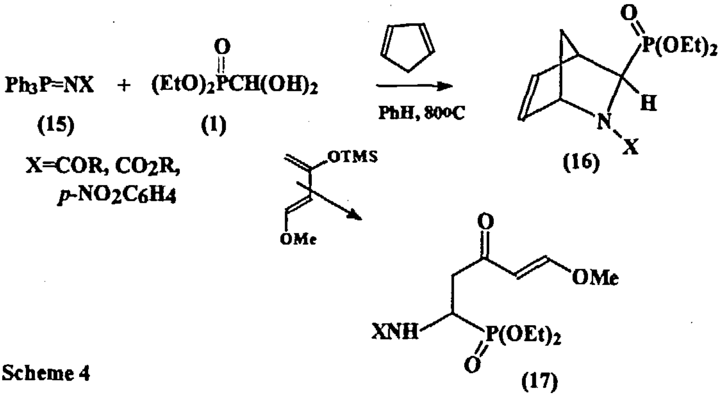


(13) $X = SO_2Ph$, COPh



(14) R^1=Et, Me; R^2=OR, Me

reactions and Jung[6] has succeeded with analogous reactions of the carboxylic analogues (14). In view of this we reacted formylphosphonate (1) with a variety of phosphine imines (15) in the presence of dienes (Scheme 4). The expected Diels-Alder products (16) were obtained as single isomers in moderate to poor yields from reactions with cyclopentadiene while similar reactions with Danishefsky's diene gave the open-chain product (17).[5] The *exo* stereochemistry of the phosphonate group in (16) is inferred by comparison of their ^1H NMR spectra with those of products obtained by Jung[6] from similar reactions of (14).



Scheme 4

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