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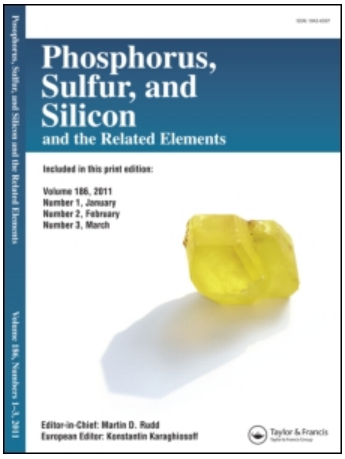

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α-AMINOPHOSPHONATE MONOESTERS IN ONE STEP

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N-Substituted α-amino-arylmethyl-phosphonate monoesters have been prepared in moderate to good yields and in a high state of purity by a convenient one-step synthesis. New compounds incorporating the pyridin-2-yl group are prepared and fully characterised. The method described here has also been employed to synthesize two known compounds for comparison.

Keywords: Phosphonates; monoesters; pyridyl

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INTRODUCTION

α-Aminophosphonic acid derivatives continue to elicit study due to interest in their biological properties, most notably those species having a direct P-N bond are investigated as transition-state analogues of the tetrahedral transition-state involved in peptide hydrolysis.[1] The key intermediate to obtain a P-N linkage are monoesters of N-protected α-aminoalkylphosphonic acids.[2] Examination of the literature shows that a number of routes to N-substituted α-aminophosphonate monoesters are available; directly from carbonyl, amino and phosphorus components;[3] partial hydrolytic,[4] or non-hydrolytic cleavage of diester precursors;[5] partial esterification of phosphonic diacids,[6] and oxidation of α-aminophosphinic acid precursors.[7]

*Corresponding author.

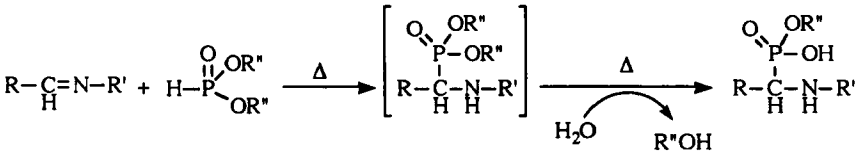
Our recent interest in lanthanide and transition metal complexes of phosphonate derivatives containing imino[8,9] and amino functional groups,[10] has led us to investigate methods of preparing novel heterocyclic α-aminophosphonate derivatives as potential complexing agents. In particular we have been looking at methods of limiting the oligomerization commonly observed in transition metal complexes of α-aminophosphonic acids. One such route involves preparing the complexes using the corresponding phosphonate monoesters.[10] During the course of our ligand synthesis we have observed that extension of a literature route,[11,12] readily leads to the isolation of a number of aromatic and heterocyclic phosphonate monoesters in moderate yields. Compounds **1–3** are novel compounds by this route, while **4** and **5** are fully characterized for the first time.

RESULTS AND DISCUSSION

The route to N-substituted α-aminomethylphosphonate monoesters involves prolonged heating of the preformed Schiff base with dimethyl or diethyl phosphite in an open air atmosphere and with the absence of solvent (Scheme 1).

Using this methodology (Scheme 1) a range of simple N-substituted methyl and ethyl hydrogen α-amino(pyridyl, benzyl, salicyl)methylphosphonates were prepared (Table I) and fully characterized. The yields are good apart from **1** and **2**, and the products are in a high state of purity. Previously aminobenzylphosphonate monoesters have been prepared by this route in only 3–6% yields.[13]

The IR spectra for these monoesters are very characteristic, with extensive ν(P═O...HO) and ν(P-O$^-$...NH$_2^+$) bands *ca.* 2250 to 2800 cm^{-1}. This suggests a zwitterionic nature for the monoesters. The parent ion or parent ion multiple ([M + H]$^+$, [n(M + H), n = 1,2..]$^+$ is the most abundant peak in the liquid secondary ion (LSI) mass spectrum. The ^{1}H NMR spectra of the phosphonate monoesters are also distinctive; in particular the α-methine proton resonates at δ_H *ca.* 3.5–5.0 ppm with a $^2J_{HCP}$ coupling constant of 15–18 Hz, considerably less than the 20–22 Hz observed in related phosphonate diesters.[12] The ^{31}P-{^{1}H} NMR spectra generally show single peaks some 10 ppm upfield from the diesters at δ_P *ca.* 10–15 ppm.



SCHEME 1 'One-pot' route to α-aminomethylphosphonate monoesters.

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TABLE I Yields, Melting Point and ^{31}P NMR Data of α-Aminomethylphosphonate Monoesters

	R	*R'*	*R''*	*Yield (%)*	*M.p (°C)*	*^{31}P-{^{1}H} (δ_p, D_2O)*
1	Py	Me	Me	31	240–242	11.00
2	Py	^{i}Pr	Me	15	228–230	11.13
3	Sal	Py	Me	70	215	18.03 (DMSO-d_6)
4	Ph	Me	Me	73	220	12.08
5	Sal	Me	Et	52	218 (lit.[11] 230)	11.08

The nature of both the starting imine and dialkyl phosphites determine the ease with which the product monoester is formed. In general salicyl imines lead to phosphonate monoesters with both dimethyl and diethyl phosphites, whereas imines derived from benzaldehyde and pyridinecarboxaldehyde form the monoester in one step only with dimethyl phosphite. While the full mechanism is as yet to be fully elucidated, the diester is initially formed (observed by monitoring the reaction using ^{31}P-{^{1}H} NMR spectroscopy), with elevated temperatures leading to loss of an alkyl group.

In this work we have demonstrated that the preparation of α-aminophosphonate monoesters of this class of compounds can be achieved by this 'one-step' route while the diesters can be isolated by carrying out the reaction under a nitrogen atmosphere.

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Experimental

Microanalyses were determined using a Carlo-Erba 1106 microanalyser. IR spectra were recorded on a Digilab FTS-40 spectrophotometer as KBr microdisks. ^{1}H NMR spectra were obtained using a Bruker-Spectro-spin AM 250 FT spectrometer while the reactions were monitored by ^{31}P-{^{1}H} NMR spectroscopy on a Bruker WP80 FT instrument. LSI mass spectra were obtained using a Vacuum Generator Kratos 'Profile' Double Focusing instrument, equipped with a Cs fast ion gun operating at 10 kV. Samples were inserted immediately after mixing with the matrix; glycerol or 3-nitrobenzylalcohol. Reagents for synthesis were used as received from Aldrich Chemical Company. Melting points are uncorrected.

Preparation of Schiff Bases

The amine (0.1 mol) was added to the aldehyde (0.1 mol) at r.t. or below in an exothermic reaction. The solution was stirred at r.t. for 20 min and subsequently dichloromethane (30 ml) added. The lower organic layer was separated and

dried over anhydrous potassium carbonate (5 g) for 5 min. After removing the drying agent by filtration, the solvent was removed in vacuo leaving an oily residue or solid. After checking for purity (IR, ^{1}H NMR), these residues were used immediately.

'One-pot' Synthesis of α-Aminomethylphosphonate Monoesters

A mixture of the dialkyl phosphite and the preformed imine were heated together on a boiling water-bath during which time the solution became very viscous (deep red in the case of the pyridyl imines). Addition of acetone resulted in the formation of a white solid which was isolated by filtration, washed with acetone, diethyl ether and finally air-dried. In some cases the formation of a crystalline solid from the viscous oil occurred more slowly.

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Methyl hydrogen α-(N-methylamino)pyridin-2-ylmethylphosphonate (1)

Dimethyl phosphite (7.3 g, 66.6 mmol) and the imine formed from pyridinecarbaldehyde and methylamine (4.0 g, 33.3 mmol) were mixed together at 70 °C, stirred for 30 min and left standing overnight. Addition of petroleum spirits (B.p. 40–65 °C) and cooling to −18 °C gave a yellow solid which was isolated by filtration, washed with acetone and air-dried. Found: C, 44.6; H, 6.08; N, 12.90. Required for $C_8H_{12}N_2O_3P$: C, 44.5; H, 6.06; N, 12.96 %. LSI ms: *m/z* 217 $[M + H]^+$ (100.0). ^{1}H (D_2O, TSP) δ_H: 2.76 (s, 3H, NCH_3), 3.53 (d, 3H, OCH_3, $^3J_{POCH}$ = 10.7 Hz), 4.65 (d, 1H, α-C*H*, $^2J_{PCH}$ = 16.0 Hz), 7.4–8.6 (m, 4H, aromatic). ^{13}C-{^{1}H} (D_2O) δ_C: 35.82 (d, NCH_3, $^2J_{PCNC}$ = 6.54 Hz), 55.35 (d, OCH_3, $^2J_{POC}$ = 6.54 Hz), 63.77 (d, α-*C*H, $^1J_{PC}$ = 133.34 Hz), 126–153 (m, aromatic carbons). IR (KBr disk): ν/cm^{-1} $\nu(OH_2)$ 3415 br, w, ν(POH) 2250–2800 br, ν(py) 1639, 1570 s, ν(P═O) 1211 vs, ν(P-O) 1100 s, 1053 s.

Methyl hydrogen α-(N-isopropylamino)pyridin-2-ylmethylphosphonate (2)

Dimethyl phosphite (5.0 g, 46.7 mmol) and the imine formed from pyridinecarbaldehyde and isopropylamine (10.3 g, 93.4 mmol) were heated together on a boiling water bath and the resulting blood-red solution deposited solid after 15 min of heating. The solid was isolated by filtration, washed with acetone, yielding a white solid which was air-dried. Found: C, 49.4; H, 6.83; N, 11.06. Required for $C_{10}H_{17}N_2O_3P$: C, 49.2; H, 7.02; N, 11.42 %. LSI ms: *m/z* 245 $[M + H]^+$ (100.0). ^{1}H (D_2O, TSP) δ_H: 1.35 (dd, 6H, $CHCH_3$), 3.47 (m, 1H, $CHCH_3$),

3.53 (d, 3H, OC*H*$_3$, $^3J_{POCH}$ = 10.7 Hz), 4.87 (d, 1H, α-C*H*, $^2J_{PCH}$ = 15.0 Hz), 7.4–8.63 (m, 4H, aromatic). ^{13}C-{^{1}H} (D_2O) δ_C: 20.4 and 21.6 (s, CH*C*H$_3$), 54.08 (d, O*C*H$_3$, $^2J_{POC}$ = 5.53 Hz), 54.46 (d, *C*HCH$_3$, $^2J_{PCNC}$ = 6.42 Hz), 59.70 (d, α-*C*H, $^1J_{PC}$ = 132.58 Hz), 127–153 (m, aromatic carbons). IR (KBr disk): ν/cm^{-1} ν(OH$_2$) 3426 w, ν(POH) 2450–2835 br, ν(py) 1619 s, ν(P═O) 1253 s, 1234 s, ν(P-O) 1088 s, 1055 vs.

Sodium methyl α-(N-pyridylamino)o-hydroxybenzylmethylphosphonate (3)

Dimethyl phosphite (5.6 g, 50.4 mmol) and the imine formed from salicylaldehyde and 2-pyridylamine (5.0 g, 25.2 mmol) with 2 ml of a saturated NaOMe/MeOH solution was heated on a boiling water-bath and the resulting orange solution deposited solid after 30 min of heating. The solid was isolated by filtration, washed with acetone, yielding a white solid which was subsequently air-dried. Found: C, 49.5; H, 5.18; N, 8.74. Required for $C_{13}H_{14}N_2O_3PNa$: C, 49.6; H, 5.18; N, 8.84. ^{1}H (DMSO-d_6, TMS) δ_H: 3.42 (d, 3H, OC*H*$_3$, $^3J_{POCH}$ = 10.3 Hz), 5.30 (dd, 1H, α-C*H*, $^2J_{PCH}$ = 19.55 Hz, J = 8.73 Hz), 6.8–8.7 (m, 9H, aromatic + NH). ^{13}C-{^{1}H} (D_2O) δ_C: 52.28 (d, O*C*H$_3$, $^2J_{POC}$ = 6.42 Hz), 53.32 (d, α-*C*H, $^1J_{PC}$ = *ca.* 170 Hz), 112–155 (m, aromatic carbons). IR (KBr disk): ν/cm^{-1} ν(OH$_2$) 3327 w, ν(POH) 2450–2875 br, ν(py) 1659, 1616 s, ν(P═O) 1245 m, 1183 s, ν(P-O) 1082 s, 1054 vs.

Methyl hydrogen α-(N-methylamino)benzylmethylphosphonate (4)

Dimethyl phosphite (1.5 g, 13.9 mmol) and the imine formed from benzaldehyde and methylamine (1.1 g, 9.2 mmol) was heated on a boiling water-bath for 15 min during which time the original clear solution went opague and finally formed a viscous clear mass. Ethanol (10 ml) was added to solidify the gum and the resulting white solid was isolated by filtration, washed with ether and air-dried. Found: C, 50.3; H, 6.22; N, 6.37. Required for $C_9H_{13}NO_3P$: C, 50.5; H, 6.12; N, 6.54 %. LSI ms: *m/z* 217 [M + H]$^+$ (100.0). ^{1}H (D_2O, TSP) δ_H: 2.76 (s, 3H, NC*H*$_3$), 3.53 (dd, 3H, OC*H*$_3$, $^3J_{POCH}$ = 10.7 Hz), 4.65 (d, 1H, α-C*H*, $^2J_{PCH}$ = 16.0 Hz), 7.4–8.63 (m, 4H, aromatic). ^{13}C-{^{1}H} (D_2O) δ_C: 34.87 (s, N*C*H$_3$, $^2J_{PCNC}$ = 6.35 Hz), 55.02 (d, O*C*H$_3$, $^2J_{POC}$ = 6.60 Hz), 62.86 (d, α-*C*H, $^1J_{PC}$ = 139.19 Hz), 131–133 (m, aromatic carbons). IR (KBr disk): ν/cm^{-1} ν(OH$_2$) 3422 vw, w, ν(POH) 2250–2800 vbr, ν(NH) 1627 s, ν(P═O) 1258 s, 1223 s, ν(P-O) 1092 s, 1048 s.

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Ethyl hydrogen α-(N-methylamino)o-hydroxybenzylmethylphosphonate (5)

Diethyl phosphite (5.1 g, 37.0 mmol) and the imine formed from salicylaldehyde and methylamine (5.0 g, 37.1 mmol) was heated on a boiling water-bath for 2 h during which time the original clear solution went opague and finally formed a viscous yellow mass. After standing for three days the addition of ethanol/ether (1:1, 30 ml) solidified the sticky mixture and the resulting white solid was isolated by filtration, washed with ether and air-dried. Found: C, 49.3; H, 6.25; N, 5.57. Required for $C_{10}H_{15}NO_3P$: C, 49.0; H, 6.58; N, 5.71 %. ^1H (D_2O, TSP) δ_H: 1.20 (t, 3H, OCH_2CH_3, $^3J_{HCCH}$ = 7.2 Hz), 2.68 (s, 3H, NCH_3), 3.87 (m, 2H, OCH_2CH_3, $^3J_{HCCH}$ = 7.2 Hz), 4.63 (d, 1H, α-CH, $^2J_{PCH}$ = 16.4 Hz), 7.0–7.4 (m, 4H, aromatic). ^{13}C-{^1H} (D_2O) δ_C: 18.83 (d, OCH_2CH_3, $^3J_{POCC}$ = 5.66 Hz), 35.28 (d, NCH_3, $^2J_{PCNC}$ = 6.73 Hz), 59.91 (d, α-CH, $^1J_{PC}$ = 140.57 Hz), 65.19 (d, OCH_2CH3, $^2J_{POC}$ = 6.54 Hz), 119–158 (m, aromatic carbons). IR (KBr disk): ν/cm^{-1} ν(POH) 2520–2785 br, ν(P=O) 1206 vs, ν(P-O) 1078, 1048 vs.

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