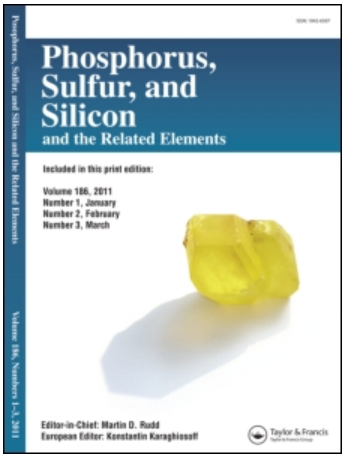

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SOLID-PHASE SYNTHESIS OF SOME ALKYL HYDROGEN METHYLPHOSPHONATES

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Eleven alkyl hydrogen methylphosphonates of structure RO(HO)P(O)Me were made by phosphoramidite chemistry on hydroxymethyl polystyrene resin; R = Me, Et, n-*Pr,* i-*Pr,* n-*Bu,* n-*hexyl,* n-*octyl, cyclohexyl, cycloheptyl, cyclooctyl, and 3,3-dimethylbutan-2-yl ie. pinacolyl or* Me_3C—*CH(Me)*—.

Keywords: Alkyl hydrogen methylphosphonates; alkyl methylphosphonic acids; chemical warfare agent; solid-phase chemistry; trivalent phosphorus

Verification of compliance is an important component of the Chemical Weapons Convention.[1] Alkyl hydrogen methylphosphonates of structure RO(HO)P(O)Me are the primary hydrolysis products of G and V-type nerve agents.[2] They do not occur naturally in the environment or in biological systems and are therefore important indicators of production or use of nerve agents. For example, isopropyl hydrogen methylphosphonate was identified in biomedical samples from casualties following the release of sarin, *i*-PrO(Me)P(O)F, by terrorists in the Tokyo subway[3] and in bomb craters found near a Kurdish community in Iraq.[4] Laboratories engaged in verification analysis require a range of alkyl hydrogen methylphosphonates, covering the nerve agents of possible concern. Recently we prepared a homologous series of these compounds in three-steps using solution chemistry.[5] We now describe their synthesis on a polymer support. The range of solid-phase reactions that can be performed has expanded considerably.[6] However, phosphorus

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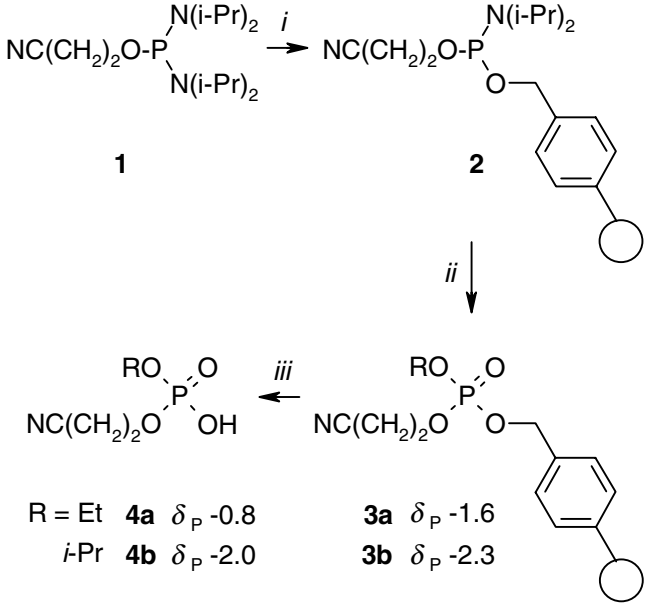
chemistry has not been featured to any great extent except in the long established use of versatile phosphoramidite reagents in the automated synthesis of oligonucleotides. Outside the oligonucleotide field, multistep transformations of small phosphorus species on solid-support are little known.[7] The chemistry described represents the first steps toward the goal of establishing a combinatorial library of alkyl hydrogen alkylphosphonates.

RESULTS AND DISCUSSION

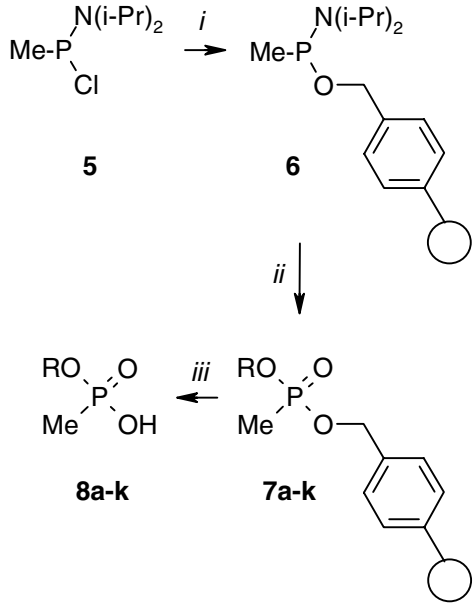
We focused initially on the synthesis of model dialkyl hydrogen phosphates from 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite **1** using a coupling strategy similar to one developed for constructing internucleotide linkages.[8] Reagent **1** was attached to hydroxymethylpolystyrene resin using tetrazole as an activator (Scheme 1). Displacement of the diisopropylamino group by ethanol or isopropanol in the presence of tetrazole took place rapidly and, after oxidation with *t*-butyl hydroperoxide in toluene, gave phosphates **3a–b**. Selective



SCHEME 1 Reagents and conditions: i, hydroxymethyl polystyrene, tetrazole, CH_2Cl_2; ii, ROH, tetrazole, MeCN, 25°C, 5 min, then 1M *t*-BuOOH, toluene, 25°C, 5 min; iii, CF_3CO_2H, 25°C, 60 min.

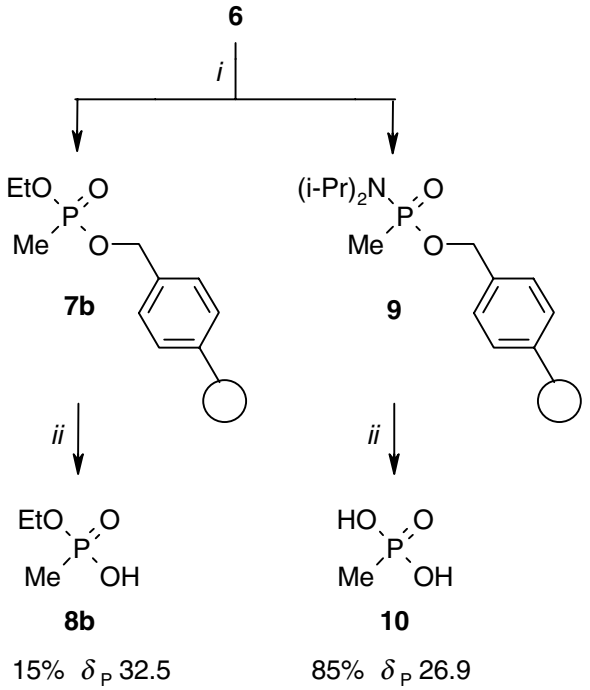
cleavage from the resin was effected by trifluoroacetic acid and gave target compounds **4a–b** in 90+% purity by multinuclear NMR analysis (Table I).

Alkyl hydrogen methylphosphonates derived from the G nerve agents were prepared next (Scheme 2). Hydroxymethyl polystyrene was derived with chloro(*N*,*N*-diisopropylamino)methylphosphine **5**[9] using a molar equivalent of triethylamine in dichloromethane. Treatment of the product **6** with a range of alcohols, followed by oxidation, gave the polymer-bound alkyl methylphosphonates **7a–k** which, on acidic cleavage from the resin, yielded the desired methylphosphonates **8a–k**. Their phosphorus NMR shifts agreed with literature values and structures were confirmed by LC-MS analyses (Table II). Overall yields were no greater than 30% but purities were high. The low yields reflected



R = Me **a**, Et **b**, *n*-Pr **c**, *i*-Pr **d**, *n*-Bu **e**,
n-hexyl **f**, *n*-octyl **g**, cyclohexyl **h**,
cycloheptyl **i**, cyclooctyl **j**, pinacolyl **k**

SCHEME 2 Reagents and conditions: i, hydroxymethyl polystyrene, Et_3N, CH_2Cl_2; ii, ROH, tetrazole, MeCN, 25°C, 15 min, then 1M *t*-BuOOH, toluene, 25°C, 5 min; iii, CF_3CO_2H, 25°C, 60 min.



SCHEME 3 Reagents and conditions: i, EtOH, tetrazole, MeCN, 25°C, 5 min then 1M *t*-BuOOH, toluene, 25°C, 5 min; ii, CF_3CO_2H, CH_2Cl_2, 25°C, 60 min.

difficulty in release of product, a fact established by NMR analysis of the resin.

The same transformations were achieved using Wang resin (4-benzyloxybenzyl alcohol) instead of hydroxymethyl polystyrene. Regardless of the support, success of the route depended on the time allowed for alcoholysis of phosphoramidite **6**. The optimal time was 15 min. Lesser times resulted in incomplete reaction and complicated the outcome: when ethanolysis was stopped after 5 min, and the synthetic sequence continued, two phosphorus acids formed (Scheme 3).

Displacement of the diisopropylamino group and oxidation gave the required phosphonate **7b** that, after treatment with acid, gave ethyl hydrogen methylphosphonate **8b**. Unreacted starting material also underwent oxidation to give phosphoramidate **9**. Trifluoroacetic acid caused P—N and benzylic P—O bond cleavage, yielding unwanted methylphosphonic acid **10**.[11] This side process, detrimental to making alkyl hydrogen methylphosphonates, could be applied to the synthesis of other alkylphosphonic acids of structure $RP(O)(OH)_2$, where R is Et, *n*- or *i*-Pr.

TABLE I NMR Data for Alkyl 2-Cyanoethyl Hydrogen Phosphates **4a–b** of Structure $RO(CNCH_2CH_2O)_2P(O)OH$ Measured in $CDCl_3$

R		^{1}H NMR δ, J/Hz	^{13}C NMR δ, J/Hz
Et	**4a**	10.38 (1H, br s, OH), 4.3–4.06 (4H, m, OCH_2), 2.75 (2H, t, $J = 6.2$, CH_2CN), 1.36 (3H, t, $J = 6.2$, CH_3)	116.7 (CN), 64.6 (OCH_2), 61.8 (OCH_2), 19.7 (CH_2CN), 16.3 (CH_3)
i-Pr	**4b**	11.32 (1H, br s, OH), 4.62 (1H, sep, $J = 6.2$, OCH), 4.26–4.12 (2H, m, OCH_2), 2.75 (2H, t, $J = 6.2$ Hz, CH_2CN), 1.4–1.3 (6H, m, CH_3)	116.6 (CN), 73.1 (OCH), 61.2 (OCH_2), 23.4 (CH_3), 19.4 (CH_2CN)

These compounds also may be environmental indicators of nerve agent use and could be made similarly from phosphoramidites $RP[N(i\text{-}Pr)_2]_2$ with omission of the alcoholysis step.

For the chemistry to allow access to a diverse range of pentavalent phosphorus species, several cleavage reagents should ideally be available. Trifluoroacetic acid, poorly effective in dilute solution, worked efficiently and cleanly in the minimum volume of dichloromethane. Better results were obtained with hydroxymethyl polystyrene rather than Wang resin. However, trifluoroacetic acid cannot be used when the derived resin contains acid-sensitive groups required in the end product.

TABLE II Phosphorus NMR Data for Resin-Bound Intermediates **7a–k** and the Alkyl Hydrogen Methylphosphonates **8a–k** (Measured in $CDCl_3$) and LC-MS Data for the Latter

Compound	R	^{31}P (δ, ppm) **7**	^{31}P (δ, ppm) **8**	^{31}P lit. data for **8**	LC-MS data for **8** MH^+ (m/z)
a	Me	34.0	34.6	—	111
b	Et	32.4	32.5	34.1[b]	125
c	*n*-Pr	32.4	32.8	—	139
d	*i*-Pr	32.7	33.8	33.4[b], 31.4[c]	139
e	*n*-Bu	32.5	33.9	31.6 [c]	153
f	*n*-hexyl	32.8	36.9	—	181
g	*n*-octyl	32.3	33.2	—	209
h	cyclohexyl	32.4	34.9	33.2[b], 31[c]	179
i	cycloheptyl	32.4	35.2	—	193
j	cyclooctyl	32.6	37.2	—	207
k	pinacolyl[a]	32.5/35.8	34.2/37	33.4[b], 31.5[c]	181

[a]Pair of diastereoisomers.
[b]From Pienaar et al.[10]
[c]From Timperley et al.[5]

In this case, the design of milder reagents is essential for success and presents a significant challenge: Classical chemistry that works well in solution is not necessarily suited to the solid-phase. For example, treatment of phosphonate **7b** in dichloromethane with hydrogen in the presence of 5% palladium on charcoal or with 30% hydrobromic acid, gave no reaction after 24 h (both methods deprotect alkyl benzyl methylphosphonates in solution). Failure is due presumably to the heterogeneity of the first system and insufficient reactivity of the second. Clearly a better understanding of the steric and electronic effects of the resin is required before the solid-phase methodology can be extended to the synthesis of more complex organophosphorus compounds.

In conclusion, we have made two dialkyl hydrogen phosphates and eleven alkyl hydrogen methylphosphonates on solid support. Overall yields were not high and reflected difficulties in releasing the products from the hydroxymethyl polystyrene resin A phosphonamidate strategy using an aminated polystyrene, and acid release in the last step, may overcome this limitation. The methodology described here complements the solution phase route to alkyl hydrogen methylphosphonates that we developed earlier[5] but does not surpass it in terms of efficiency.

EXPERIMENTAL

Materials

Reagents were commercial quality. Re-distilled triethylamine was stored over calcium hydride. 2-Cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite **1**, hydroxymethyl polystyrene (70–90 mesh), and 4-benzyloxybenzyl alcohol (70–90 mesh) were purchased from Aldrich, Ltd., UK. Anhydrous solvents and argon atmospheres were used in all experiments. NMR data were measured in $CDCl_3$ using previously described instrumentation.[5]

NMR Method

$^{31}P\{^1H\}$ NMR spectra of derived resins were obtained by placing the resin in a conventional 5 mm tube to a depth of ca. 0.5 cm and carefully adding $CDCl_3$ until one-half of the coil volume was occupied by the swollen resin and the other half by $CDCl_3$. The sample was shimmed and the spectra recorded in non-spinning mode (1000 pulses). The spectra were transformed using an exponential line broadening of 20 Hz.

LC-MS Method

Compounds were analyzed as 10 mg/mL solutions in water. LC-MS was performed using a published method.[12] Brief details are as follows: A Hewlett-Packard LC system consisting of a model 1050 pump plus solvent conditioner was used. The system was fitted with a 150 × 2 mm internal diameter Columbus C_{18} column (Phenomenex). The mobile phase comprised 0.02 M ammonium formate in H_2O (solvent A) and 0.02 M ammonium formate in MeOH (solvent B). The elution gradient was 5% B (0–5 min) to 90% B (15–20 min) at a flow rate of 0.2 mL/min. Injections (10 mL) were made using a Rheodyne 9125 injector fitted with a 20 mL PEEK loop. The effluent was introduced into a Finnigan TSQ700 mass spectrometer operated in atmospheric pressure chemical ionisation mode. Source conditions: corona current 2 mA, vaporiser temperature 400°C, capillary temperature 150°C, sheath gas (nitrogen) 60 psi and auxiliary gas (nitrogen) flow meter reading 20. The source octapole (Q_0) was operated at an offset of −5 V. Compounds gave a single major peak in the total ion chromatogram (Table II). All produced protonated molecular ions (MH^+) and the ammoniated ion ($M + NH_4^+$).

Resin-Bound (*N,N*-Diisopropylamino)methylphosphine 6

Hydroxymethyl polystyrene (2 g, 0.67 mmol/g substitution) was suspended in dichloromethane (20 cm^3) and stirred for 15 min at room temperature. Triethylamine (0.18 cm^3, 1.34 mmol) was added, followed by chloro(*N*,*N*-diisopropylamino)methylphosphine **5** (0.24 g, 1.34 mmol). The mixture was stirred at room temperature for 2 h, filtered, and the resin washed successively with dichloromethane (125 cm^3) and acetonitrile (125 cm^3). It was dried with a stream of argon (1.98 g, 99 %). δ_p 121.3 ppm (broad singlet).

General Procedure for Resin-Bound Alkyl Methylphosphonates 7a–k

Intermediate **6** (1.98 g, 0.67 mmol/g) in a reactor column connected to an Applied Biosystems 392 DNA/RNA synthesizer was subjected to this sequence: addition of acetonitrile to column (300 s), flush to waste (30 s), block flush (30 s), reverse flush (30 s), addition of 1-*H* tetrazole (0.5M in acetonitrile) and isopropanol (1.5 cm^3) in acetonitrile (6 cm^3) to column (30 s delivery then 15 min), flush to waste (30 s), block flush (30 s), reverse flush (30 s), addition of acetonitrile to column (300 s), flush to waste (30 s), block flush (30 s), reverse flush (30 s), addition of *t*-BuOOH (1M solution in toluene) to column (30 s delivery with 5 min

waiting time), flush to waste (30 s), block flush (30 s), reverse flush (30 s), addition of acetonitrile to column (300 s), flush to waste (30 s), block flush (30 s), reverse flush (900 s). The resin was dried under argon to give **7d** (1.98 g). δ_p 32.7 ppm (broad singlet). Other derivatives were prepared similarly from different alcohols.

Preparation of Isopropyl Methylphosphonic Acid 8d

Intermediate **7d** (1.98 g, 0.67 mmol/g) was suspended in dichloromethane (2 cm^3) in a Wheaton vial and stirred for 30 min at room temperature. Trifluoroacetic acid (0.2 cm^3) was added and stirring continued for a further 3 h. The mixture was filtered and the resin washed with dichloromethane (3×5 cm^3) and acetonitrile (3×5 cm^3). The filtrate was concentrated to yield **8d** as a colorless liquid (δ_p 33.8 ppm).

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