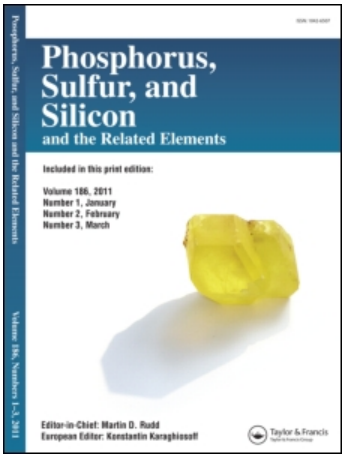

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE MANNICH REACTION OF DIETHYLPHOSPHONOACETIC ACID PART II.[1] A NEW ROUTE TO 1-(N-ALKYLAMINO)METHYLVINYLPHOSPHONATES

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To cite this Article Krawczyk, Henryk(1995) 'THE MANNICH REACTION OF DIETHYLPHOSPHONOACETIC ACID PART II.[1] A NEW ROUTE TO 1-(N-ALKYLAMINO)METHYLVINYLPHOSPHONATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 101: 1, 221 — 224
To link to this Article: DOI: 10.1080/10426509508042520
URL: http://dx.doi.org/10.1080/10426509508042520

Phosphorus, Sulfur, and Silicon, 1995, Vol. 101, pp. 221–224
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THE MANNICH REACTION OF DIETHYLPHOSPHONOACETIC ACID. PART II.[1] A NEW ROUTE TO 1-(N-ALKYLAMINO)METHYLVINYLPHOSPHONATES

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(Received October 25, 1994, in final form November 15, 1994)

The Mannich reaction of diethylphosphonoacetic acid (**1**) with paraformaldehyde and primary aliphatic amines provides a short and efficient approach to vinylphosphonates **5**.

Key words: Mannich reaction, diethylphosphonoacetic acid, vinylphosphonates.

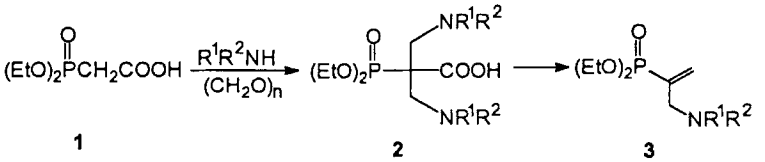
Diethylphosphonoacetic acid (**1**) and its esters have found widespread application in organic synthesis.[2–4]

We recently reported the preparation of novel 1-(N,N-dialkylamino)-methylvinylphosphonates **3** based on the Mannich reaction between the acid **1**, formaldehyde and secondary aliphatic amines[1] (Scheme I).

The hitherto unknown unsubstituted phosphonate **3**($R^1 = R^2 = H$) can be considered as a phosphorus analogue of the naturally occurring α-methylene-β-alanine.[5–7] The increasing interest in the synthesis of 2-aminophosphonates[8–14] stems from their potential pharmaceutical application. A number of 2-amino-phosphonic acids have been found in nature.[15–17] Naturally occurring 2-amino-phosphonic acids and certain synthetic congeners display interesting biological properties.[18–21] Due to the tetrahedral structure of the phosphonic acid moiety they can mimic the transition state of the hydrolysis reaction of esters and amides and thus serve as components of enzyme inhibitors.[22–25]

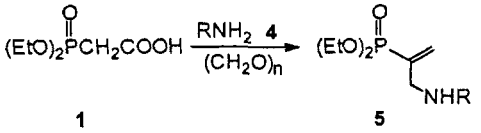
On the other hand, allylic amines are particularly attractive products because of their importance as synthetic intermediates and as crucial elements of many natural and bioactive products.[26–31]

In continuation of our study on the Mannich reaction[1] we wish to report that a range of 1-(N-alkylamino)methylvinylphosphonates **5** can be conveniently prepared



1 **2** **3**

SCHEME I



1 5

SCHEME II

TABLE I

Preparation of vinylphosphonates 5

Amine	Reaction time (h)	Product[a]	Yield[b] %
$(CH_3)_2CHCH_2NH_2$ (4a)	2	5a	57
c-$C_6H_{11}NH_2$ (4b)	2	5b	59
$(CH_3)_2CHNH_2$ (4c)	2	5c	58
$HOCH_2CH_2NH_2$ (4d)	6	5d	29
$CH_3(OH)CHCH_2NH_2$ (4e)	6	5e	72
$(CH_3)_3CNH_2$ (4f)	2	5f	65
$C_6H_5(CH_3)CHNH_2$ (4g)	2	5g	55
1-aminoadamantane (4h)	2	5h	85

[a] All products gave correct elemental analysis.

[b] Isolated yield after distillation.

by the condensation of the acid **1** with paraformaldehyde and primary aliphatic amines **4** (Scheme II).

The synthesis of this new class of compounds was accomplished by reacting equimolar amounts of the acid **1** and the amine **4** with a two-fold molar excess of paraformaldehyde in refluxing benzene. The method tolerates a wide variety of amines as shown in Table I including those bearing sterically demanding substituents as well as oxygen functionalities. Generally, the final products were obtained in good yield. Their structures were assigned using ^{1}H NMR, ^{31}P NMR and IR.

In conclusion, the reaction described here provides a convenient and efficient route to prepare 1-(N-alkylamino)methylvinylphosphonates.

EXPERIMENTAL

IR spectra were measured using a Specord M 80 (C. Zeiss) instrument. ^{1}H NMR spectra were recorded on a Tesla BS 547A instrument (80 MHz) using TMS as internal standard. ^{31}P NMR spectra were taken on a Bruker HFX-72 with H_3PO_4 as external standard. Amines **4a–h** were purchased from commercial suppliers. Compound **1** was prepared as described in the literature.[32]

General procedure for the preparation of vinylphosphonates **5a-h**:
To a solution of acid **1** (3.92 g, 20 mmol) in benzene (70 ml) amine **4** (20 mmol) and paraformaldehyde 1.2 g (40 mmol) were added. The mixture was heated at reflux under a Dean-Stark water separator for a period of time as shown in Table I. The solvent was removed under vacuum, the residue was

taken up in chloroform (80 ml), washed with water (2 × 10 ml) and dried ($MgSO_4$). Evaporation of the solvent followed by distillation afforded **5** as a colourless liquid.

Diethyl 1-(N-isobutylamino)methylvinylphosphonate (**5a**). B.p. 100°–102°C/0.2 Torr; ^{1}H NMR ($CDCl_3$) δ 0.91 (6H, t, J = 6.3, $2CH_3$), 1.33 (6H, t, J = 7.0, $2CH_3$) 1.70 (1H, m, CH), 2.1 (1H, s, NH), 2.38 (2H, d, J = 6.7, CH_2), 3.42 (2H, dt, $^3J_{HP}$ = 11.8, $^4J_{HH}$ = 1.5, CH_2), 4.10 (m, 4H, $2CH_2$), 5.94 (1H, ddt, $^3J_{HP}$ = 47.7, $^2J_{HH}$ = $^4J_{HH}$ = 1.5, P—C=CH_{trans}), 6.10 (1H, ddt, $^3J_{HH}$ = 22.6, $^2J_{HH}$ = $^4J_{HH}$ = 1.5, P—C=CH_{cis}); ^{31}P NMR (neat) δ 18.39; IR (film) 2956, 1254, 1028, 962, 792 cm^{-1}. Anal. Calcd for $C_{11}H_{24}NO_3P$: C, 52.99; H, 9.70; N, 5.61; P, 12.42. Found: C, 53.12; H, 9.61; N, 5.84; P, 12.25.

Diethyl 1-(N-cyclohexylamino)methylvinylphosphonate (**5b**). B.p. 110°–112°C/0.2 Torr; ^{1}H NMR ($CDCl_3$) δ 1.05–2.0 (10H, m, $5CH_2$), 1.33 (6H, t, J = 7.1, $2CH_3$), 2.10 (1H, s, NH), 2.45 (1H, m, CH), 3.46 (2H, dt, $^3J_{HP}$ = 11.4, $^4J_{HH}$ = 1.3, CH_2), 4.10 (4H, dq, $^3J_{HH}$ = $^3J_{HP}$ = 7.1, $2CH_2$), 5.93 (1H, ddt, $^3J_{HP}$ = 47.5, $^2J_{HH}$ = $^4J_{HH}$ = 1.3, P—C=CH_{trans}), 6.09 (1H, ddt, $^3J_{HP}$ = 23.1, $^2J_{HH}$ = $^4J_{HH}$ = 1.3, P—C=CH_{cis}); ^{31}P NMR (neat) δ 18.45; IR (film) 2928, 1250, 1028, 962, 792 cm^{-1}.

Diethyl 1-(N-isopropylamino)methylvinylphosphonate (**5c**). B.p. 82°–83°C/0.6 Torr; ^{1}H NMR ($CDCl_3$) δ 1.06 (6H, d, J = 6.2, $2CH_3$), 1.33 (6H, t, J = 7.2, $2CH_3$), 2.1 (1H, s, NH), 2.81 (1H, sep, J = 6.2, CH), 3.43 (2H, dt, $^3J_{HP}$ = 11.8, $^4J_{HH}$ = 1.8, CH_2), 4.10 (4H, dq, $^3J_{HH}$ = $^3J_{HP}$ = 7.2, $2CH_2$), 5.94 (1H, ddt, $^3J_{HP}$ = 47.4, $^2J_{HH}$ = $^4J_{HH}$ = 1.8, P—C=CH_{trans}), 6.11 (1H, ddt, $^3J_{HP}$ = 21.0, $^2J_{HH}$ = $^4J_{HH}$ = 1.8, P—C=CH_{cis}); ^{31}P NMR (neat) δ 18.34; IR (film) 2968, 1250, 1028, 964, 792 cm^{-1}.

Diethyl 1-[N-(2-hydroxyethyl)amino]methylvinylphosphonate (**5d**). B.p. 112°C/0.5 Torr; ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, t, J = 7.0, $2CH_3$), 2.97 (2H, t, J = 6.8, CH_2N), 3.36 (2H, dt, $^3J_{HP}$ = 9.8, $^4J_{HH}$ = 1.7, CH_2), 3.77 (2H, t, J = 6.8, CH_2OH), 4.10 (4H, dq, $^3J_{HH}$ = $^3J_{HP}$ = 7.0, $2CH_2$), 4.29 (2H, s, O, NH), 6.09 (1H, ddt, $^3J_{HP}$ = 47.2, $^2J_{HH}$ = $^4J_{HH}$ = 1.7, P—C=CH_{trans}), 6.14 (1H, ddt, $^3J_{HP}$ = 22.1, $^2J_{HH}$ = $^4J_{HH}$ = 1.7, P—C=CH_{cis}); ^{31}P NMR (neat) δ 17.54; IR (film) 3404, 2980, 1256, 1028, 968, 792 cm^{-1}. Anal. Calcd for $C_6H_{20}NO_4P$: C, 45.56; H, 8.50; N, 5.90; P, 13.05. Found: C, 45.70; H, 8.38; N, 6.12; P, 13.28.

Diethyl 1-[N-(2-hydroxypropyl)amino]methylvinylphosphonate (**5e**). B.p. 115°C/0.1 Torr; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 6.2, CH_3), 1.33 (6H, t, J = 7.0, $2CH_3$), 2.46 (1H, dd, J_{AB} = 10.8, J_{AX} = 7.5, N—CH_A), 3.10 (1H, dd, J_{AB} = 10.8, J_{BX} = 6.8, N—CH_B), 3.39 (2H, dt, $^3J_{HP}$ = 9.6, $^4J_{HH}$ = 1.8, CH_2), 3.9–4.3 (5H, m, $2CH_2$, CH_X—O), 4.32 (2H, s, OH, NH). 6.06 (1H, ddt, $^3J_{HP}$ = 47.2, $^2J_{HH}$ = $^4J_{HH}$ = 1.8, P—C=CH_{trans}), 6.12 (ddt, 1H, $^3J_{HP}$ = 21.2, $^2J_{HH}$ = $^4J_{HH}$ = 1.8, P—C=CH_{cis}); ^{31}P NMR (neat) δ 17.42; IR (film) 3404, 2984, 1254, 1032, 966, 792 cm^{-1}.

Diethyl 1-(N-t-butylamino)methylvinylphosphonate (**5f**). B.p. 100°–102°C/0.7 Torr; ^{1}H NMR ($CDCl_3$) δ 1.12 (9H, s, $3CH_3$), 1.33 (6H, t, J = 7.0, $2CH_3$), 2.11 (1H, s, NH), 3.37 (2H, dt, $^3J_{HP}$ = 10.6, $^4J_{HH}$ = 1.7, CH_2), 4.10 (4H, dq, $^3J_{HH}$ = $^3J_{HP}$ = 7.0, $2CH_2$), 6.03 (1H, ddt, $^3J_{HP}$ = 47.8, $^2J_{HH}$ = $^4H_{HH}$ = 1.7, P—C=CH_{trans}), 6.08 (1H, ddt, $^3J_{HP}$ = 22.6, $^2J_{HH}$ = $^4J_{HH}$ = 1.7, P—C=CH_{cis}); ^{31}P NMR (neat) δ 18.58; IR (film) 2968, 1252, 1030, 966, 794 cm^{-1}.

Diethyl 1-[N-(1-phenyl)ethylamino]methylvinylphosphonate (**5g**). B.p. 133–135°C/0.2 Torr; ^{1}H NMR ($CDCl_3$) δ 1.29 (6H, t, J = 7.0, $2CH_3$), 1.34 (3H, d, J = 6.5, CH_3), 1.93 (1H, s, NH), 3.28 (2H, dm, $^3J_{HP}$ = 12.5, CH_2), 3.78 (1H, q, J = 6.5, CH), 4.07 (4H, dq, $^3J_{HH}$ = $^3J_{HP}$ = 7.0, $2CH_2$), 5.89 (1H, ddt, $^3J_{HP}$ = 48.3, $^2J_{HH}$ = $^4J_{HH}$ = 1.6, P—C=CH_{trans}), 6.07 (1H, dm, $^3J_{HP}$ = 21.5, P—C=CH_{cis}), 7.29 (5H, m, Ar); ^{31}P (neat) δ 18.27; IR (film) 2976, 1246, 1028, 962, 792 cm^{-1}. Anal. Calcd for $C_{15}H_{24}NO_3P$: C, 60.57; H, 8.16; N, 4.70; P, 10.41. Found: C, 60.42; H, 8.04; N, 4.53; P, 10.62.

Diethyl 1-[N-(1-adamantyl)amino]methylvinylphosphonate (**5h**). B.p. 106°C/0.4 Torr; ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, t, J = 7.0, $2CH_3$), 1.64–1.68 (12H, m, $6CH_2$), 2.07 (4H, m, 3CH, NH), 3.41 (2H, dt, $^3J_{HP}$ = 10.4, $^4J_{HH}$ = 1.5, CH_2), 4.10 (4H, dq, $^3J_{HH}$ = $^3J_{HP}$ = 7.0, $2CH_2$), 6.04 (1H, ddt, $^3J_{HP}$ = 47.8, $^2J_{HH}$ = $^4J_{HH}$ = 1.5, P—C=CH_{trans}), 6.08 (1H, ddt, $^3J_{HP}$ = 22.7, $^2J_{HH}$ = $^4J_{HH}$ = 1.5, P—C=CH_{cis}); ^{31}P NMR (neat) δ 19.13; IR (film) 2964, 2904, 1252, 1028, 962, 792 cm^{-1}.

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