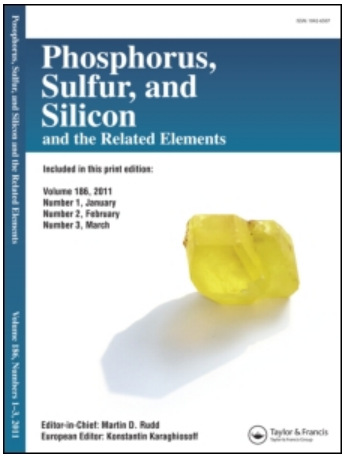

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NEW APPROACH TO DIETHYL 2-AMINOALKYLPHOSPHONATES

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NEW APPROACH TO DIETHYL 2-AMINOALKYLPHOSPHONATES

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Diethyl 2-aminoalkylphosphonates **5** have been obtained in good yields in a one-step procedure employing the Mitsunobu reaction of diethyl 2-hydroxyalkylphosphonates **2** with hydrazoic acid, and subsequent treatment of the intermediate azides **3** with triphenylphosphine, followed by hydrolysis of the iminophosphoranes **4** with water.

Key words: Diethyl 2-aminoalkylphosphonates, diethyl 2-hydroxyalkylphosphonates, Mitsunobu reaction, Staudinger reaction, azidation of alcohols.

INTRODUCTION

Over the last thirty five years the aminophosphonic acids have attracted considerable attention as biologically active surrogates for the natural amino acids in various peptides and peptide-based enzyme inhibitors.[1,2] Although several general procedures for the preparation of 1-aminoalkylphosphonic acids have been published,[2–6] relatively few reports have presented possible synthetic approaches to 2-aminoalkylphosphonic acids and their dialkyl esters.[7–10] Among the spectrum of these methods the reductive amination of 2-oxoalkylphosphonates by means of ammonium acetate/sodium cyanoborohydride[8] seems to be the most reliable procedure of choice. In addition to the methods leading to racemic products two multistep procedures starting from optically active amino acids and giving enantiomerically pure 2-aminoalkylphosphonic acids have been also published.[1,11]

RESULTS AND DISCUSSION

Reductive amination of dialkyl 2-oxoalkylphosphonates as a route to the corresponding 2-aminoalkylphosphonates albeit straightforward to follow suffers, however, from limited availability of the starting materials and the necessity of using expensive sodium cyanoborohydride.

It was found recently that azidation of diethyl 1-hydroxyalkylphosphonates under the Mitsunobu conditions followed by Staudinger reaction of the resulting crude azides and hydrolysis of the intermediate iminophosphoranes offers a convenient one-pot approach to diethyl 1-aminoalkylphosphonates[12] and O-ethyl-1-aminoalkylphosphinates.[13] Analogous approach has been also recently proposed for the preparation of both enantiomers of 2-amino-1-hydroxyethylphosphonic acid.[14] Diethyl 2-hydroxyalkylphosphonates, potential starting materials for the synthesis of

diethyl 2-aminoalkylphosphonates, became recently readily accessible by regioselective epoxide ring opening in diethyl 2,3-epoxypropylphosphonate[15] with Grignard reagents in the presence of catalytic amounts of CuI.[16,17]

In connection with our studies on converting a hydroxy function into the amino group we report herein a general protocol for a one-pot transformation of diethyl 2-hydroxyalkylphosphonates **2** into diethyl 2-aminoalkylphosphonates **5**. The starting materials, diethyl 2-hydroxyalkylphosphonates **2**, are conveniently prepared by the action of alkyl(aryl)magnesium bromides on diethyl 2,3-epoxypropylphosphonate **1** in the presence of 10 mol-% CuI.

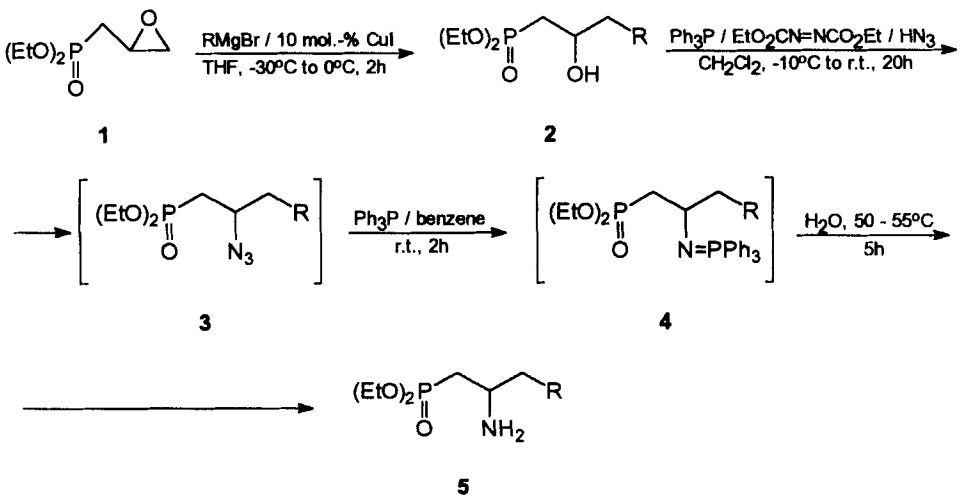
The previously described procedure[17] erroneously suggests the use of equimolar amount of CuI, which was now found to be inappropriate. All diethyl 2-hydroxyalkylphosphonates **2** thus formed (except diethyl 2-hydroxy-3-phenylpropylphosphonate **2g**) were in crude state notoriously contaminated with 5–15% of diethyl

TABLE I

Diethyl 2-Hydroxyalkylphosphonates **2a–g**

Compound No.	R	Yield[a] (%)	^{31}P-NMR δ(ppm)	Molecular formula[b]
2a	Me	55[c]	30.03	$C_8H_{19}O_4P$ (210.2)
2b	Et	70	30.16	$C_8H_{21}O_4P$ (224.2)
2c	i-Pr	56	29.85	$C_{10}H_{23}O_4P$ (238.3)
2d	Bu	50[d]	30.10	$C_{11}H_{25}O_4P$ (252.3)
2e	i-Bu	40	30.04	$C_{11}H_{25}O_4P$ (252.3)
2f	c-C_6H_{11}	36	30.16	$C_{13}H_{27}O_4P$ (278.3)
2g	Ph	86[e]	30.04	$C_{13}H_{21}O_4P$ (272.3)

[a] Yield of isolated, pure product. [b] Satisfactory analytical data obtained: C ± 0.25, H ± 0.12, P ± 0.35. [c] Prepared from the respective organocuprate according to the previously described procedure. [d] Crude product, containing ~15% of diethyl 2-hydroxy-3-bromopropylphosphonate (^{31}P-NMR), which could not be purified by distillation. Used in crude from for transformation into 5d. [e] Prepared by the action of 3 moles of phenylmagnesium bromide and 0.3 mole of CuI on 1 mole of 1; 2h at 0° and 2h at refuxing THF. Separated from biphenyl by bulb-to-bulb distillation.



1 2 3 4 5

1-5	a	b	c	d	e	f	g
R	Me	Et	i-Pr	Bu	i-Bu	c-C_6H_{11}	Ph

SCHEME I

TABLE II

Diethyl 2-Aminoalkylphosphonates **5a–g**

Compound No.	R	Yield[a] (%)	n_D^{20}	MS (m/z)	Hemioxalate[b] m.p.(°C)
5a	Me	72	1.4438	210(M+1)	95-96.5
5b	Et	81	1.4434	224(M+1)	107-109
5c	i-Pr	77	1.4436	238(M+1)	70-72.5
5d	Bu	64	1.4470	252(M+1)	96-97.5
5e	i-Bu	36	1.4483	252(M+1)	97-99
5f	c-C_6H_{11}	22[c]	1.4672	278(M+1)	130-132
5g	Ph	66	1.5054	272(M+1)	107-109

[a] Yield (2→5) of isolated, pure compound. [b] All hemioxalates were satisfactorily analysed: C ± 0.4, H ± 0.2, N ± 0.25, P ± 0.32. [c] Yield can be increased to 43% by careful reextraction with water the acidic dichloromethane extracts and subsequent standard work-up with solid K_2CO_3.

2-hydroxy-3-bromopropylphosphonate (^{31}P-NMR) resulting from the reaction of **1** with magnesium bromide present in equilibrium with the Grignard reagent.[18] This impurity could be, however, easily removed by bulb-to-bulb distillation. Yields of pure **2** and their ^{31}P-NMR spectra are listed in Table I.

According to Scheme I diethyl 2-aminoalkylphosphonates **5** are obtained by reacting diethyl 2-hydroxyalkylphosphonates **2** with the preformed betaine-type adduct to triphenylphosphine-diethyl azodicarboxylate—hydrazoic acid under the

TABLE III

Spectroscopic data of diethyl 2-aminoalkylphosphonates **5a–g**

Compound No.	^{1}H-NMR ($CDCl_3$/TMS) δ(ppm), J(Hz)	^{31}P-NMR δ(ppm)	IR (film) ν (cm^{-1})
5a	0.92(t,3H,J=7.4),1.31(t,6H,J=7.1), 1.35-1.53(m,2H),1.59-2.05(m,4H), 3.00-3.20(m,1H),4.00-4.20(m,4H),	30.64 (CH_2Cl_2)	3368w,2980s,2932s,2888s, 1240s,1164s,1098s,1028s, 962s,828s
5b	0.82(bt,3H,J=7.0),1.23(t,6H,J=7.0), 1.25-1.35(m,4H),1.50-1.91(m,4H), 3.04-3.13(m,1H),3.92-4.09(m,4H)	30.52 (neat)	3372w,2960s,2944s,2884s, 1238s,1164s,1050s,1028s, 962s
5c	0.88(d,6H,J=6.6),1.19-1.30 (m,1H), 1.31(t,6H,J=7.0),1.56-1.98(m,6H), 3.10-3.32(m,1H),4.00-4.18(m,4H)	30.58 (CH_2Cl_2)	3364w,2956s,2884s,1238s, 1164s,1098s,1030s,962s
5d	0.85(dist.t,3H),1.20-1.44(m,14H), 1.56-1.99(m,4H),3.04-3.23(m,1H), 3.99-4.17(m,4H)	30.71 (CH_2Cl_2)	3368w,2924s,2860s,1240s, 1164s,1098s,1048s,956s, 828s
5e	0.87(d,6H,J=6.5),1.11-1.26(m,2H), 1.41-1.59(m,3H),1.63-2.05 (m,2H), 2.38(bs,2H),3.03-3.28(m,1H), 4.00-4.21(m,4H)	30.40 (neat)	3372w,2956s,2868s,1242s, 1058s,1028s,960s
5f	0.81-1.0(m,2H),1.12-1.33(m,11H), 1.56-1.95(m,10H),3.15-3.34(m,1H), 3.98-4.15(m,4H)	30.58 (neat)	3368w,2924s,1238s,1164s, 1056s,1028s,962s
5g	1.29-1.30(2t,6H,J=7.1), 1.65-2.06(m,4H),2.57-2.84(m,2H), 3.35-3.55(m,1H),3.98-4.16(m,4H), 7.15-7.30(m,5H)	30.34 (CH_2Cl_2)	3372w,2984m,2908m, 1238s,1164s,1028s,962s, 786s,704s

Mitsunobu conditions. The azides **3** thus formed are converted "in situ" by the Staudinger reaction into the iminophosphoranes **4** giving the corresponding diethyl 2-aminoalkylphosphonates **5** in good yield (36–81%) directly on hydrolysis with water. The results are summarized in Table II. The structure of diethyl 2-aminoalkylphosphonates **5** was unequivocally confirmed by IR, ^{1}H-NMR and ^{31}P-NMR spectroscopy (Table III) and additionally ascertained by molecular weight determination and derivatisation with oxalic acid (Table II).

In conclusion, the procedure described here offers a general, convenient, and economic route to diethyl 2-aminoalkylphosphonates **5** with a relatively wide range of substituents at C-3 carbon. Owing to the use of easily accessible substrates and mild conditions of transforming the hydroxy group into the amino functionality the method can be considered as a useful alternative to the existing procedures.

EXPERIMENTAL

^{31}P-NMR spectra were recorded on a Bruker HFX-90 spectrometer operating at 36.43 MHz. Positive chemical shifts are downfield from ext. H_3PO_4. ^{1}H-NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz ($CDCl_3$ solns/TMS int.) FAB/MS were measured on a APO Electron (Ukraine) Modell MI 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). Melting points are determined in open capillaries and are uncorrected.

Diethyl 2,3-epoxypropylphosphonate was prepared as described previously[15,17] but only in about 50% yield. ^{31}P-NMR (neat):δ = 26.32 ppm.

Diethyl 2-hydroxyalkylphosphonates **2b–f** were obtained following essentially the procedure published earlier[17] but using 10 mol-% of CuI instead of erroneously recommended equimolar amount of this catalyst.

Diethyl 2-hydroxybutylphosphonate **2a** was obtained from the respective organocuprate.[17]

Preparation of *diethyl 2-hydroxy-3-phenylpropylphosphonate* **2g** was substantially modified (see footnote e, Table II).

Diethyl 2-aminoalkylphosphonates **5a–g**; *General procedure.* A solution of diethyl azodicarboxylate (DEAD) (2.09 g, 0.012 mol) in CH_2Cl_2 (5 mL) is added dropwise with stirring and external cooling (dry ice-acetone bath) to a solution of Ph_3P (3.14 g, 0.012 mol) in CH_2Cl_2 (20 mL) at −5°C. The mixture is cooled to −10°C, and 1.85 molar solution of HN_3 in benzene[19] (0.0125 mol) is slowly added. Stirring is continued for 5 min at 0°C, and appropriate 2-hydroxyalkylphosphonate **2** (0.01 mol) is then added. The mixture is kept for 30 min at 0°C, and stirring is then continued for 20 h at r.t. The precipitate of ethyl 3-(ethoxycarbonyl)carbazate is filtered off, the filtrate is evaporated under reduced pressure, and the semisolid residue is extracted with hexane (3 × 50 mL). The combined extracts are evaporated in vacuo. The oily residue is dissolved in benzene (10 mL), and Ph_3P (2.75 g, 0.0105 mol) is added in one portion to the solution. Stirring is continued for 2 h at r.t. Water (1.8 mL, 0.1 mol) is then added and the mixture is heated for 5 h at 50–55°C. The mixture is cooled to r.t., and the product is extracted with 5% aq. HCl (3 × 5 mL). The combined acid extracts, are then reextracted with CH_2Cl_2 (3 × 15 mL). The acid phase is then cooled to 0°C, and the solution is made alkaline by the addition of an excess of solid K_2CO_3. The product is extracted with CH_2Cl_2 (5 × 30 mL) and is then dried over Na_2SO_4. Solvent is evaporated under reduced pressure and the rest of the volatile material is removed at 40°C/0.02 Torr, to give pure 2-aminoalkylphosphonate **5** (Tables II and III).

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REFERENCES

1. M. E. Duggan and D. S. Karanewsky, *Tetrahedron Lett.*, **24,** 2935 (1983) and references cited therein.

2. S. Hanessian, Y. L. Bennani and Y. Hervé, *Synlett*, 35 (1993) and references cited therein.
3. K. Prager and J. Rachoń, *Z. Chem.*, **15,** 209 (1975).
4. D. Redmore, in "Topics in Phosphorus Chemistry," ed. E. J. Griffith and M. Grayson, John Wiley and Sons, New York, Vol. 8, 1976.
5. P. Mastalerz and P. Kafarski, "Beitrage zur Wirkstofforschung," Institute für Wirkstofforschung, Berlin, 1984, Vol. 21.
6. V. P. Kukhar and V. A. Solodenko, *Usp. Khim.*, **56,** 1504 (1987); *Russ. Chem. Rev.*, **56,** 859 (1987).
7. J. Blanchard, N. Collignon, P. Savignac and H. Normant, *Tetrahedron*, **32,** 455 (1976) and references cited therein.
8. J-M. Varlet, N. Collignon and P. Savignac, *Synth. Commun.*, **8,** 335 (1978).
9. D. Brigot, N. Collingnon and P. Savignac, *Tetrahedron*, **35,** 1345 (1979).
10. J-M. Varlet, N. Collignon and P. Savignac, *Tetrahedron*, **37,** 3713 (1981).
11. T. Oshikawa and M. Yamashita, *Bull. Chem. Soc. Jpn.*, **63,** 2728 (1990).
12. T. Gajda and M. Matusiak, *Synth. Commun.*, **22,** 2193 (1992).
13. T. Gajda, *Phosphorus, Sulfur, and Silicon*, **85,** 59 (1993).
14. F. Hammerschmidt and H. Völlenkle, *Liebigs Ann. Chem.*, 577 (1989).
15. C. E. Griffin and S. K. Kundu, *J. Org. Chem.*, **34,** 1532 (1969).
16. T. Nagase, T. Kawashima and N. Inamoto, *Chem. Lett.*, 1977 (1984).
17. A. M. M. M. Phillips, M. J. Mphahlele, A. M. Modro, T. A. Modro and A. Zwierzak, *Phosphorus, Sulfur, and Silicon*, **71,** 165 (1992).
18. R. E. Parker and N. S. Issacs, *Chem. Rev.*, **59,** 737 (1959).
19. H. Wolf, in "Organic Reactions," ed. R. Adams, John Wiley and Sons, New York, Vol. 3, 327, 1947.