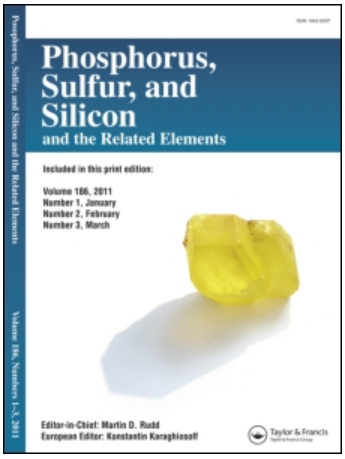


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE FACILE SYNTHESIS OF 1-AMINOPHOSPHONATES FROM 1-NITROPHOSPHONATE PRECURSORS

Donovan Green[a]; Said Elgendy[a]; Geeta Patel[a]; Jehan A. Baban[a]; Emmanuel Skordalakes[a]; Wahid Husman[a]; Vijay V. Kakkar[a]; John Deadman[a]
[a] Thrombosis Research Institute, London, United Kingdom

To cite this Article Green, Donovan , Elgendy, Said , Patel, Geeta , Baban, Jehan A. , Skordalakes, Emmanuel , Husman, Wahid , Kakkar, Vijay V. and Deadman, John(1996) 'THE FACILE SYNTHESIS OF 1-AMINOPHOSPHONATES FROM 1-NITROPHOSPHONATE PRECURSORS', Phosphorus, Sulfur, and Silicon and the Related Elements, 113: 1, 303 — 306
To link to this Article: DOI: 10.1080/10426509608046403
URL: http://dx.doi.org/10.1080/10426509608046403

Phosphorus, Sulfur, and Silicon, 1996, Vol. 113, pp. 303–306
Reprints available directly from the publisher
Photocopying permitted by license only

Communication

THE FACILE SYNTHESIS OF 1-AMINOPHOSPHONATES FROM 1-NITROPHOSPHONATE PRECURSORS

DONOVAN GREEN,* SAID ELGENDY, GEETA PATEL, JEHAN A. BABAN, EMMANUEL SKORDALAKES, WAHID HUSMAN, VIJAY V. KAKKAR, and JOHN DEADMAN

Thrombosis Research Institute, Emmanuel Kaye Building, Manresa Road, Chelsea, London SW3 6LR, United Kingdom

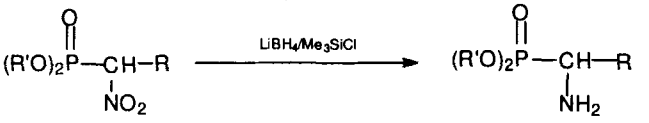
(Received October 23, 1995; in final form January 14, 1996)

1-Aminophosphonates may be generated in high yield and spectroscopic purity by the treatment of 1-nitrophosphonates with $LiBH_4/Me_3SiCl$ in THF at room temperature.

Key words: 1-nitrophosphonates, 1-aminophosphonates, thrombin, thrombin inhibition.

INTRODUCTION

We have reported earlier that O,O-dialkyl 1-hydroxyiminoalkanephosphonates may be conveniently converted to their corresponding 1-amino derivatives by treatment of the precursor with $LiBH_4/Me_3SiCl$ in THF at room temperature.[1] Biologically active, O,O-dialkyl 1-nitroalkanephosphonates **1**, prepared by the method of Zon,[2] may be similarly treated with nascent borane at ambient temperature to afford 1-amino analogues **2**, in comparable yields. In this current study when the nitro derivatives (entries 3, 5, 6 and 10 of Table I) were subjected to facile reduction, the yields of the amino products (Table II) were quantitative. As was the case in our earlier study, no further purification of the products were necessary, and led us to believe that the nitrophosphonates were also a useful alternative substrate for production of α-aminophosphonates, in good yield and on a large scale.



1 2

RESULTS AND DISCUSSION

The nitrophosphonates **1** shown in Table I display distinct spectroscopic differences to their amino analogues **2** (Table II), in the α-CH region of the molecule. The

TABLE I

1-Nitrophosphonate Precursors **1**, of 1-aminophosphonates **2**
$(R'O)_2P(O)CH(NO_2)R$

Entry	R'	R	δαCH ^{13}C($CDCl_3$) ($^1J_{PC}$)	δ^{31}P ($CDCl_3$)
1	CH_3CH_2	CH_3	79.45(144.23)	14.15
2	$(CH_3)_2CH$	$(CH_2)_2CH_3$	85.87(143.36)	11.63
3	$ClCH_2CH_2$	$(CH_2)_4CH_3$	85.46(146.15)	14.42
4	CH_3CH_2	C_6H_5	88.04(148.95)	11.02
5	$ClCH_2CH_2$	$(CH_2)_3CH_3$	85.09(146.50)	14.36
6	$ClCH_2CH_2$	C_6H_5	87.53(153.20)	11.82
7	CH_3CH_2	$(CH_2)_3CH_3$	85.24(142.44)	13.53
8	$(CH_3)_2CH$	$(CH_2)_3CH_3$	85.84(143.44)	11.59
9	CH_3	$(CH_2)_2CH_3$	84.43(143.44)	16.04
10	$ClCH_2CH_2$	$CH(CH_3)_2$	91.65(147.13)	14.29

TABLE II

1-Aminophosphonates **2**, from 1-nitrophosphonates **1** $(R'O)_2P(O)CH(NH_2)R$

Entry	R'	R	δαCH ^{13}C($CDCl_3$) ($^1J_{PC}$)	δ^{31}P ($CDCl_3$)	Yield(%)
1	CH_3CH_2	CH_3	44.02(150.14)	29.30	95
2	$(CH_3)_2CH$	$(CH_2)_2CH_3$	48.97(148.85)	28.22	97
3	$ClCH_2CH_2$	$(CH_2)_4CH_3$	47.90(148.63)	30.70	96
4	CH_3CH_2	C_6H_5	53.96(149.49)	25.54	98
5[6]	$ClCH_2CH_2$	$(CH_2)_3CH_3$	48.83(148.63)	30.73	97
6	$ClCH_2CH_2$	C_6H_5	54.22(151.06)	26.40	98
7	CH_3CH_2	$(CH_2)_3CH_3$	48.66(148.71)	29.80	98
8	$(CH_3)_2CH$	$(CH_2)_3CH_3$	49.19(148.88)	28.10	96
9	CH_3	$(CH_2)_2CH_3$	47.99(149.34)	32.21	93
10	$ClCH_2CH_2$	$CH(CH_3)_2$	54.86(146.36)	30.25	97

substrate is characterised by a very sharp and clearly resolved ABX type multiplet (overlapping ddd) with a chemical shift of around 5.00 ppm for the α-methine proton (except for entries 4 and 6, where the α-CH is a doublet). This area becomes a less well resolved multiplet (also overlapping ddd), moving upfield upon its conversion to the amino analogue to resonate at 2.50–3.00 ppm. This has proved to be a very useful preliminary marker for determining conversion. Such monitoring is useful, while difficult for routes via hydroxyimino substrates, due to exchange broadening of the low field hydroxyl.

Concomitant changes are also observed in the ^{13}C N.M.R. spectra of the α-C region

of the molecules' where the intense doublet in the nitro compound **1** (δ 80–90), moves appreciably upfield in the amino product **2** (δ 45–55). $^{1}J_{PC}$ is of the same order in both compounds. The ^{31}P N.M.R. chemical shifts move 14–15 ppm downfield in going from the nitro substrate (Table I) to the amino analogue (Table II); the products being formed in quantitative yield as further evidenced by the observance of only one ^{31}P N.M.R. signal.

It was thought possible that the appropriately tethered $ClCH_2CH_2$ moiety (as in entries 3, 5, 6 and 10 of Tables I and II) could interact with the catalytic triad of thrombin in a similar fashion to that of substrate derived chloromethylketones such as PPACK (D-phenylalanyl-prolyl-arginylchloromethane), which is a very potent inhibitor of the enzyme (PPACK, a monovalent inhibitor, alkylates the reactive centre histidine of the catalytic triad of thrombin to inactivate it.)[3] Earlier results had shown that $ClCH_2CH_2$ derived hydroxyiminophosphonates gave moderate yields when converted to their amino analogues with nascent borane (55%–60%). Indeed the 'substrate-like' phosphonotripeptide Z-D-Dpa-Pro-NHPgl^{P}$(OCH_2CH_2Cl)_2$ derived from the mixed anhydride coupling of Z-D-Dpa-Pro-OH and O,O,-(2,chloroethyl) α-aminohexanephosphonate (isolated in 96% yield from the corresponding nitro substrate) displayed competitive inhibition of thrombin, with an initial K_i in the micromolar range.[4] This was in contrast to the two stage slow-tight binding inhibition of thrombin exhibited by a series of O,O-diphenylpeptidylaminophosphonates that had been prepared earlier in our laboratory.[5]

Although it is well known that very electronegative (leaving) groups on the phosphorus will amplify its reactivity toward serine proteases,[7] so that the catalytic site serine is more rapidly phosphorylated, this is paralleled by an increased rate of hydrolysis. Also dialkoxy groups whilst considerably improving the chemical stability of the inhibitor, can attenuate its effect upon this class of enzymes, and can make them less viable as clinically applicable reagents. The $ClCH_2CH_2$ moiety may represent a useful compromise between the lability of, for example, phenyl protected phosphorus, and the stability of an alkoxy protected phosphorus nucleus, in its reactivity towards the active site of thrombin.

ACKNOWLEDGEMENTS

We would like to take this opportunity to thank the Bruker AMX 400 University of London Intercollegiate Research Service for N.M.R. at King's College, for ^{1}H, ^{13}C and ^{31}P N.M.R. Spectra. We also thank the Department of Pharmaceutical Chemistry, School of Pharmacy, University of London, for FAB mass spectral analyses. We wish to thank Mr. S. Boyer for elemental analyses and Prof. H. R. Hudson for helpful discussions at the School of Chemistry, University of North London. This work is sponsored by the Thrombosis Research Trust.

REFERENCES AND NOTES

1. D. Green, G. Patel, S. Elgendy, J. A. Baban, G. Claeson, V. V. Kakkar and J. Deadman, *Tetrahedron Lett.*, **34**, 6917 (1993).
2. J. Zon, *Synthesis*, 661 (1984). (*General procedure for preparation of nitrophosphonates.* O,O-Dialkyl 1-hydroxyiminophosphonate (1 mol equivalent) was dissolved in CH_2Cl_2 and treated with *m*-chloroperoxybenzoic acid (57–86%, 1 mol equivalent) before being vigorously stirred for 48 h, at ambient temperature. The suspension was carefully washed with 10% aq Na_2SO_3/10% aq $NaHCO_3$, H_2O and brine, before being dried over anhydrous Na_2SO_4. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure to afford a pleasant smelling, clear oily product. Analysis by ^{1}H,

^{13}C and ^{31}P N.M.R. spectroscopy; FABMS and C,H,N, showed that the nitrophosphonate had been isolated as a pure compound).

3. W. Bode, I. Mayr, U. Baumann, R. Huber, S. R. Stone and J. Hofsteenge, *EMBO J*, **8,** 3467 (1989); W. Bode, D. Turk and A. J. Karshikov, *Protein Science*, **1,** 426 (1992); "The Design of Synthetic Inhibitors of Thrombin," eds. G. Claeson, M. F. Scully, V. V. Kakkar and J. Deadman, Plenum Publishing Corporation, New York, 1993.
4. D. Green, S. Elgendy, G. Patel, J. A. Baban, E. Skordalakes, W. Husman, C. A. Goodwin, M. F. Scully, V. V. Kakkar and J. Deadman, Abstract, XIIIth ICPC, Jerusalem, Israel, July 16–21, 1995; *Phosphorus, Sulfur and Silicon*, in press.
5. L. Cheng, C. A. Goodwin, M. F. Scully, V. V. Kakkar and G. Claeson, *Tetrahedron Lett.*, **32,** 7333 (1991); J. Deadman, G. Claeson and M. F. Scully, *J. Enzyme Inhibition*, **9,** 29 (1995).
6. The 1-aminophosphonates **2** (and also the 1-nitrophosphonates **1**) were fully characterised by: ^{1}H, ^{13}C and ^{31}P N.M.R. ($CDCl_3$) spectroscopy; FAB mass spectrometry and C, H, N analyses; as shown by the example (entry 5 in Tables I and II). O,O-2-chloroethyl 1-nitropentanephosphonate C, H, N (Found C: 33.19, H: 5.22, N: 4.06. Calc. for $C_9H_{18}NO_5PCl_2$, C: 33.54, H: 5.59, N: 4.35%); ^{1}H ($CDCl_3$): δ 0.92 (t, 3H, terminal $C\underline{H}_3$, $^{3}J_{HCCH}$ 6.41), 1.25–1.75 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$), 2.02–2.54 (m, 2H, P—$CHC\underline{H}_2$), 3.75 (m, 4H, $ClC\underline{H}_2CH_2O \times 2$), 4.45 (m, 4H, $ClCH_2C\underline{H}_2O \times 2$), 5.03 (ddd, 1H, P—C$\underline{H}$); $^{13}C(CDCl_3)$: δ 13.60 (s, $CH_2\underline{C}H_3$), 21.79 (s, $\underline{C}H_2CH_3$), 28.31 (d, P—$CHCH_2\underline{C}H_2$, $^{3}J_{PCCC}$ 12.44), 29.04 (d, P—$CH\underline{C}H_2$, $^{2}J_{PCC}$ 2.92, 42.77 (dd, $Cl\underline{C}H_2O \times 2$, $^{3}J_{POCC}$ 6.43), 67.47 (dd, $ClCH_2\underline{C}H_2O \times 2$, $^{2}J_{POC}$ 6.32), 85.09 (d, P—$\underline{C}H$, $^{1}J_{PC}$ 146.50); $^{31}P(CDCl_3)$: δ 14.36 (s); FABMS(3-NOBA): m/z (%) 322 (M^+, 91). O,O-2-chloroethyl 1-aminopentanephosphonate C, H, N (Found C: 37.23, H: 6.91, N: 4.80. Calc. for $C_9H_{20}NO_3PCl_2$, C: 36.99, H: 6.85, N: 4.80%); $^{1}H(CDCl_3)$: δ 0.91 (t, 3H, terminal $C\underline{H}_3$, $^{3}J_{HCCH}$ 6.80), 1.15–1.61 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.44–1.85 (m, 2H, P—$CHC\underline{H}_2$), 3.03 (ddd, 1H, P—C$\underline{H}$), 3.70 (m, 4H, $ClC\underline{H}_2CH_2O \times 2$), 4.29 (m, 4H, $ClCH_2C\underline{H}_2O \times 2$); $^{13}C(CDCl_3)$: Δ 13.90 (s, $CH_2\underline{C}H_3$), 22.37 (s, $\underline{C}H_2CH_3$), 28.10 (d, P—$CHCH_2\underline{C}H_2$, $^{3}J_{PCCC}$) 12.91), 43.15 (d, $Cl\underline{C}H_2CH_2O \times 2$), $^{3}J_{POCC}$ 6.10), 48.83 (d, P—$\underline{C}H$, $^{1}J_{PC}$ 148.63), 65.88 (dd, $ClCH_2\underline{C}H_2O \times 2$, $^{2}J_{POC}$ 7.29); ^{31}P ($CDCl_3$): δ 30.73 (s); FABMS (3-NOBA): m/z (%) 292 (M^+, 64).
7. M. Hoffmann, *Synthesis*, 62 (1988): P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, **63,** 193 (1991); Q. Zhao, I. M. Kovach, A. Bencsura and A. Papathanassiu, *Biochemistry*, **33,** 8128 (1994); C. Bergin, R. Hamilton, E. O'Maitui, B. Walker and B. J. Walker, *Poster XIIth ICPC*, Jerusalem, Israel, July 16–21, 1995. (NB 3-NOBA is 3-Nitrobenzylalcohol).