A Highly Efficient Synthesis of 1-Amino-2-chloroethanephosphonates

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Although numerous synthetic methods have been reported for 1-aminoethanephosphonic acids and esters[1], the 1-amino-2-chloroethanephosphonic acids and esters are not known, except for the 1-amino-2-chloroethanephosphonic acid prepared by acid hydrolysis of diethyl 2-aziridinyl-phosphonate[2]. As part of our program directed to the design of new antimetabolites, we needed 1-amino-2-chloroethanephosphonic acid esters. We found that the precursor 2,2,2-trichloro compounds are easily available and that the reduction of alkyl halides by tri-*n*-butyltin hydride is

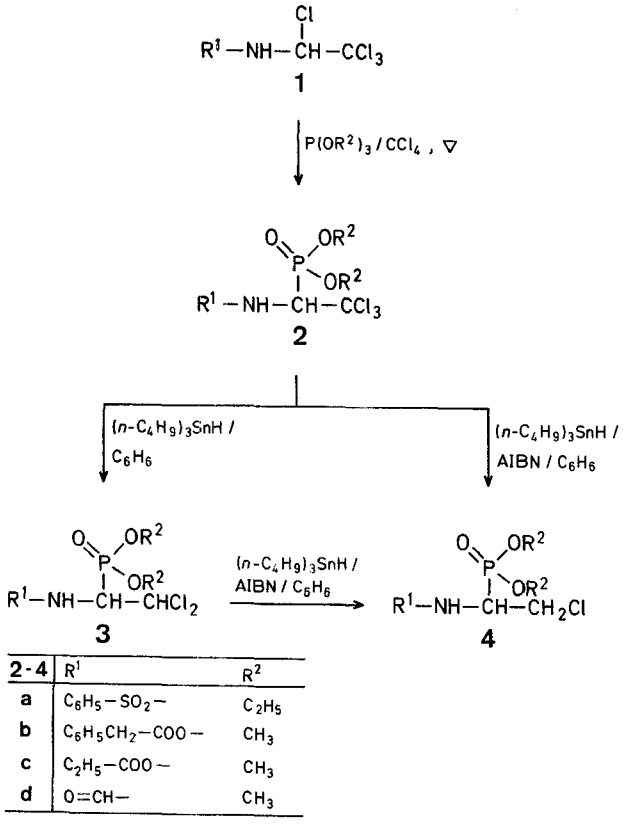
Table 1. Alkyl 1-Acylamino-2,2,2-trichloroethanephosphonates **2** prepared

Product No.	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ[ppm]
2a	70	112°	$C_{12}H_{17}Cl_3NO_5PS$ (424.7)	1.28 (dt, 3H, J_{H-H} = 7.0 Hz, J_{H-P} = 0.6 Hz); 1.33 (dt, 3H, J_{H-H} = 7 Hz, J_{H-P} = 0.6 Hz); 3.90–4.35 (m, 4H); 4.71 (dd, 1H, J_{H-NH} = 9.8 Hz, J_{H-P} = 19.6 Hz); 6.65 (dd, 1H, J_{H-NH} = 9.8 Hz, J_{H-P} = 6.2 Hz); 7.35–7.65 (m, 3H); 7.85–8.15 (m, 2H)
2b	70	96°	$C_{12}H_{15}Cl_3NO_5P$ (390.6)	3.73 (d, 6H, J_{H-P} = 10.8 Hz); 4.94 (dd, 1H, J_{H-NH} = 10.5 Hz, J_{H-P} = 20.0 Hz); 5.16 (s, 2H); 7.39 (s, 5H); 8.86 (dd, 1H, J_{H-NH} = 10.5 Hz, J_{H-P} = 2.1 Hz)[d]
2c	78	91°	88–89°[6]	1.30 (t, 3H, J_{H-H} = 7 Hz); 3.85 (d, 3H, J_{H-P} = 10.9 Hz); 3.87 (d, 3H, J_{H-P} = 11.1 Hz); 4.22 (q, 2H, J_{HH} = 7 Hz); 5.00 (dd, 1H, J_{H-NH} = 10.7 Hz, J_{H-P} = 19.3 Hz); 5.85 (dd, 1H, J_{H-NH} = 10.7 Hz, J_{H-P} = 3 Hz)
2d	62	159°	$C_5H_9Cl_3NO_4P$ (284.5)	3.82 (d, 3H, J_{H-P} = 11 Hz); 3.88 (d, 3H, J_{H-P} = 11.1 Hz); 5.43 (ddd, 1H, J_{H-CHO} = 0.4 Hz, J_{H-NH} = 10.5 Hz, J_{H-P} = 18.6 Hz); 7.08 (dd, 1H, J_{H-NH} = 10.5 Hz, J_{H-CHO} = 1 Hz); 8.38 (d, 1H, J_{NH-CHO} = 1 Hz)

[a] Yield of recrystallized products.
[b] Satisfactory microanalyses obtained: C ±0.35, H ±0.17, Cl ±0.26, N ±0.23, P ±0.28, S ±0.01.
[c] ^{1}H-N.M.R. spectra were recorded on a Varian XL-100 spectrometer.
[d] Measured in DMSO-d_6.

also well documented[3]. As a consequence, the selective hydrogenolysis of one or two carbon-chlorine bonds in the trichloromethyl group would lead respectively to the 1-amino-2,2-dichloro- and -2-chloroethanephosphonic acid esters. This sequential hydrogenolysis is of particular interest, but only a limited amount of work has been reported[4].

The present paper describes a simple and practical method for preparing alkyl 1-amino-2-chloro- and 2,2-dichloroethanephosphonates **3** and **4** in high yield using this selective tri-*n*-butyltin hydride reduction on alkyl 1-acylamino-2,2,2-trichloroethanephosphonates **2**.



2-4	R^1	R^2
a	$C_6H_5-SO_2-$	C_2H_5
b	$C_6H_5CH_2-COO-$	CH_3
c	C_2H_5-COO-	CH_3
d	O=CH–	CH_3

Alkyl 1-acylamino-2,2,2-trichlorocthanephosphonates **2** are easily prepared by the Arbusov-Michaelis reaction of 1,2,2,2-tetrachloro-*N*-acylethylamines **1**[5,6,7] and trialkyl phosphites (Table 1). Heating the trichloroethyl compounds **2** with one equivalent of tri-*n*-butyltin hydride in benzene or toluene affords alkyl 1-acylamino-2,2-dichloroethanephosphonates **3** in almost quantitative yields (Table 2). The alkyl 1-acylamino-2-chloroethanephosphonates **4** are also conveniently synthesized in excellent yield from the trichloroethyl compounds **2** when two equivalents of tri-*n*-butyltin hydride and a catalyst, azobisisobutyronitrile (AIBN), are used in this reaction (Table 3).

Though synthetically less valuable, the reductive dechlorination of the dichloro derivatives **3** is also found to be possible. Thus methyl 1-ethoxycarbonylamino-2,2-dichloroethanephosphonate **(3c)** gives methyl 1-ethoxycarbonylamino-2-chloroethanephosphonate **(4c)** in practically quantitative yield, after a reflux of 9 h with tri-*n*-butyltin hydride (one equivalent) and a catalytic amount of AIBN. It is interesting to note that **4c** submitted to the same reductive conditions is only partially reduced to methyl 1-ethoxycarbonylaminoethanephosphonate (after 24 h 70% of **4c** remains unchanged).

Diethyl or Dimethyl 1-Acylamino-2,2,2-trichloroethanephosphonates 2; General Procedure:

To a stirred solution of the appropriate 1,2,2,2-tetrachloro-*N*-acylethylamine **1** (0.01 mol) in anhydrous carbon tetrachloride (100 ml), triethyl or trimethyl phosphite (0.1 mol) is added dropwise at 40–50 °C. The mixture is then refluxed for 1 or 2 h. Evaporation of the solvent and trituration with hexane or petroleum ether affords crude **2**, which is recrystallized from benzene/hexane (Table 1).

Diethyl or Dimethyl 1-Acylamino-2,2-dichloroethanephosphonates 3, General Procedure:

A mixture of **2** (0.01 mol), tri-*n*-butyltin hydride (2.9 g, 0.01 mol) and benzene or toluene (20 ml) is heated under reflux for 6–8 h. the solvent is removed under vacuum and the residue is dissolved in acetonitrile (20 ml). This solution is washed with dry hexane (5 × 20 ml) in order to eliminate tin-residues[8] and evaporated in vauco. According to spectroscopic data, the crude product obtained is practically pure (contamination by tin-residues less than 5%). Recryfrom-benzene/hexane yields pure **3a, 3c**, and from chloroform/hexane affords pure **3d** (Table 2).

Diethyl or Dimethyl 1-Acylamino-2-chloroethanephosphonates 4; General Procedure

A mixture of **2** (0.01 mol), tri-*n*-butyltin hydride (5.8 g, 0.02 mol), azobisisobutyronitrile (10–20 mg) and benzene or toluene (20 ml) is

Table 2. Alkyl 1-Acylamino-2,2-dichloroethanephosphonates **3** from **2**

Product No.	Yield[a] [%]	m.p. [°C]	Molecular formula	^{1}H-N.M.R. ($CDCl_3$/TMS)[b] δ [ppm]
3a	81	106°	$C_{12}H_{18}Cl_2NO_5PS$[c] (390.2)	1.28 (dt, 3H, J_{H-H} = 7.1 Hz, J_{H-P} = 0.5 Hz); 1.31 (dt, 3H, J_{H-H} = 7.1 Hz, J_{H-P} = 0.5 Hz); 4.12 (m, 4H); 4.37 (ddd, 1H, J_{H-H} = 2.3 Hz, J_{H-NH} = 9.6 Hz, J_{H-P} = 21.3 Hz); 5.99 (m, 1H, J_{H-NH} = 9.6 Hz); 6.13 (dd, 1H, J_{H-H} = 2.3 Hz, J_{H-P} = 6.9 Hz); 7.45–7.75 (m, 3H); 7.9–8.1 (m, 2H)
3b	95	oil	$C_{12}H_{16}Cl_2NO_5P$[g] (356.2)	3.76 (d, 3H, J_{H-P} = 10.9 Hz); 3.78 (d, 3H, J_{H-P} = 11 Hz); 4.80 (ddd, 1H, J_{H-H} = 2.5 Hz, J_{H-NH} = 10.5 Hz, J_{H-P} = 20.6 Hz); 5.18 (s, 2H); 5.84 (dd, 1H, J_{H-NH} = 10.5 Hz, J_{H-P} = 2 Hz); 6.24 (dd, 1H, J_{H-H} = 2.5 Hz, J_{H-P} = 3.6 Hz); 7.36 (s, 5H)
3c	98	oil	$C_7H_{14}Cl_2NO_5P$[d] (294.1)	1.29 (t, 3H, J_{H-H} = 7.1 Hz); 3.82 (d, 6H, J_{H-P} = 11 Hz); 4.21 (q, 2H, J_{H-H} = 7.1 Hz); 4.78 (ddd, 1H, J_{H-H} = 2.5 Hz, J_{H-NH} = 10.4 Hz, J_{H-P} = 20.3 Hz); 5.68 (br. d, 1H, J_{H-NH} = 10.4 Hz); 6.25 (dd, 1H, J_{H-H} = 2.5 Hz, J_{H-P} = 3.8 Hz)
3d	75	94–95°	$C_5H_{10}Cl_2NO_4P$[e] (250.0)	3.76 (d, 6H, J_{H-P} = 11 Hz); 5.13 (ddd, 1H, J_{H-H} = 2.7 Hz, J_{H-NH} = 10.5 Hz, J_{H-P} = 20.5 Hz); 6.60 (dd, 1H, J_{H-H} = 2.7 Hz, J_{H-P} = 2.7 Hz); 8.31 (s, 1H); 9.00 (br. d, 1H, J_{H-NH} = 10 Hz)[f]

[a] Yield of recrystallized product except **3b** and **3c**.
[b] Recorded on a Varian XL-100 spectrometer.
[c] calc. C 36.94 H 4.65 Cl 18.17 N 3.59 P 7.93 S 8.22
found 37.47 4.59 17.47 3.43 7.97 7.94.
[d] Not analytically pure.
[e] calc. C 24.02 H 4.03 Cl 28.36 N 5.60 P 12.39
found 24.09 4.03 28.19 5.48 12.38.
[f] Recorded on a Cameca-250 spectrometer in DMSO-d_6.
[g] calc. C 40.47 H 4.53 N 3.93 P 8.70
found 40.44 4.65 3.86 8.42.

Table 3. Alkyl 1-Acylamino-2-chloroethanephosphonates **4** from **2** or **3**

Product No.[a]	Yield [%]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
4a	72	$C_{12}H_{19}ClNO_5PS$ (355.8)	1.27 (t, 3H, J_{H-H} = 7 Hz); 1.28 (t, 3H, J_{H-H} = 7 Hz); 3.67 (m, 1H, J_{H-H} = 4.6 and 14 Hz); 3.69 (m, 1H, J_{H-H} = 5.6 and 14 Hz); 3.99–4.22 (m, 5H, J_{H-P} = 20 Hz); 6.72 (br. d, J_{N-NH} = 9.1 Hz); 7.46–7.60 (m, 3H); 7.89–7.99 (m, 2H)
4b	89	$C_{12}H_{17}ClNO_5P$ (321.7)	3.73 (d, 3H, J_{H-P} = 10.8 Hz); 3.75 (d, 3H, J_{H-P} = 10.8 Hz); 3.75 (m, 1H, J_{H-H} = 7.3 and 11.8 Hz); 3.81 (m, 1H, J_{H-H} = 4.5 and 11.8 Hz); 4.44 (m, 1H, J_{H-H} = 4.5 and 7.3 Hz, J_{H-NH} = 9.7 Hz, J_{H-P} = 18.8 Hz); 5.14 (s, 2H); 5.92 (br. d, J_{H-NH} = 9.7 Hz); 7.35 (s, 5H)[d]
4c	97	$C_7H_{15}ClNO_5P$ (259.6)	1.27 (t, 3H, J_{H-H} = 7.1 Hz); 3.82 (d, 6H, J_{H-P} = 10.8 Hz); 3.89 (m, 1H, J_{H-H} = 3.8 and 13.7 Hz); 3.91 (m, 1H, J_{H-H} = 4.1 and 13.7 Hz); 4.18 (q, 2H, J_{H-H} = 7.1 Hz); 4.47 (m, 1H, J_{H-P} = 19 Hz); 5.96 (br. d, J_{H-NH} = 9.3 Hz)
4d	89	$C_5H_{11}ClNO_4P$ (215.6)	3.78 (d, 6H, J_{H-P} = 11 Hz); 3.94 (m, 1H, J_{H-H} = 3.3 and 10.6 Hz); 3.96 (m, 1H, J_{H-H} = 3.0 and 10.6 Hz); 4.74 (m, 1H, J_{H-H} = 3.0 and 3.3 Hz, J_{H-NH} = 9.6 Hz, J_{H-P} = 18.4 Hz); 8.22 (s, 1H); 8.59 (br. d, J_{H-NH} = 9.6 Hz)[e]

[a] All products are oily in appearance.
[b] Satisfactory micro analyses oblained (C ± 0.36, H ± 0.26, Cl ± 0.23, N ± 0.19, P ± 0.19), except for **4d** which could not be obtained in analytically pure form.
[c] Recorded on a Brucker WM-500 spectrometer.
[d] Recorded on a Varian XL-100 spectrometer.
[e] Measured in DMSO-d_6.

heated under reflux for 8–10 h. After the evaporation of the solvent, the residue is dissolved in acetonitrile (20 ml) and washed with dry hexane (5 × 20 ml)[8]. The solvent is then removed in vacuo. The oily products **4** are pure (according to spectroscopic data, contamination by tin-residues less then 5%) (Table 3).

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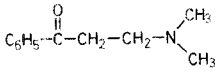
[1] D. Redmore, in: *Topics in Phosphorus Chemistry*, E.J. Griffith, M. Grayson, Eds., Vol. 8, John Wiley & Sons, New York 1976.
P.G. Baraldi, M. Guarneri, F. Moroder, G.P. Pollini, D. Simoni, *Synthesis* **1982**, 653.
[2] J. Zygmunt, P. Mastalerz, *Pol. J. Chem.* **52**, 2271 (1978).
[3] H.G. Kuivila, *Synthesis* **1970**, 499.
[4] E.C. Chukovskaya, R.Kh. Freidlina, N.A. Kuz'mina, *Synthesis* **1983**, 773.
H.G. Kuivila, L.W. Menapace, C.R. Warner, *J. Am. Chem. Soc.* **84**, 3584 (1962).
[5] F. Feist, *Ber. Dtsch. Chem. Ges.* **47**, 1173 (1914).
[6] H. Ulrich, B. Tucker, A.A.R. Sayigh, *J. Org. Chem.* **33**, 2887 (1968).
[7] F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Maierhofer, W. Oettmeier, Chem. Ber. **99**, 1944 (1966).
[8] J.M. Berge, S.M. Roberts, *Synthesis* **1979**, 471.

Errata and Addenda 1985

K. Matsumoto, A. Sera, T. Uchida, *Synthesis* **1985** (1), 1–26:
The structure of the second product in Table 16 (p. 18) should be:

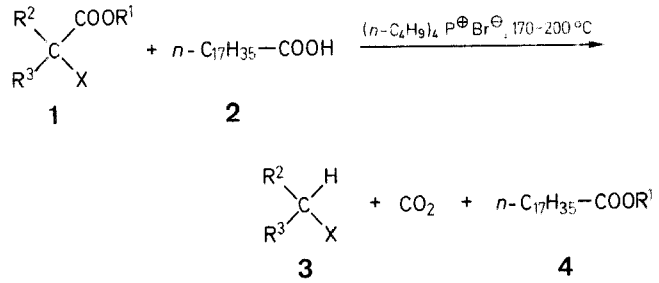


Y. Vo Quang, D. Carniato, L. Vo Quang, F. Le Goffic, *Synthesis* **1985** (1), 62–64:
The substituents R^1 for the compounds **2–4b** and **c** (p. 63) should be $C_6H_5—CH_2—O—CO—$ and $C_2H_5—O—CO—$, respectively.

K. N. Mehrotra, I. S. Singh, J. Roy, *Synthesis* **1985** (1), 81–83:
In the Table (p. 82), the I. R. assignment (C=O) should read (C=C) for all products.

J. M. Aizpurua, C. Palomo, *Synthesis* **1985** (2), 206–207:
The following paragraph should be added:
The procedure described is a specific adaption of Roesky's method [H. W. Roesky, H. H. Gieve, *Z. Naturforsch. [b]* **25**, 773 (1970)].
The authors regret the omission of this acknowledgement in the above communication.

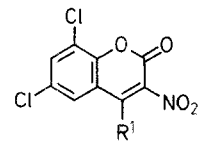
E. V. Dehmlow, E. Kunesch, *Synthesis* **1985** (3), 320–321:
The first formula scheme (p. 320) should be:



X = $COOC_2H_5$, $COOCH_3$, $CO—CH_3$, —CN

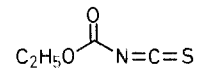
R. J. K. Taylor, *Synthesis* **1985** (4), 364–392:
The heading for the experimental procedure on p. 379 should be:
2-Benzyl-3-*n*-butylcyclopentanone (23)[90]:

A. Cașcaval, *Synthesis* **1985** (4), 428–429:
The structure of product **5** (p. 428) should be:



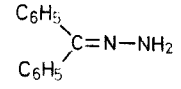
5

Y. Sanemitsu, *Synthesis* **1985** (4), 429–430:
The structure of compound **2** (p. 429) should be:



2

L. Lapatsanis, G. Milias, S. Paraskewas, *Synthesis* **1985** (5), 513–515:
The structure of compound **2** should be:

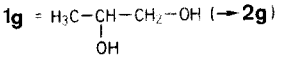


2

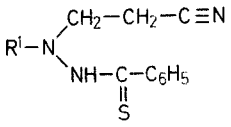
T. Eicher, R. Rohde, *Synthesis* **1985** (6/7), 619–625:
The heading for the last experimental procedure on p. 621 should be:
***endo*/*exo*-6a-Dimethylamino-6-oxo-4,5-diphenyl-2a,6,6a,7-tetrahydro-7*H*-cyclobuta[b]pyrrolizin (*endo*/*exo*-3d):**
The heading for the 3rd experimental procedure on p. 624 (left-hand column) should be:

11a-Dimethylamino-1,2-diphenyl-3-oxo-5,6,11,11a-tetrahydro-3*H*-pyrrolo[2,1-b][3]benzazepin (17):

Xue-Ping Gu, I. Ikeda, M. Okahara, *Synthesis* 1985 (6/7), 649–651:
The structure of product **1g** (p. 650) should be:



I. Yamamoto, K. Fukui, S. Yamamoto, K. Ohta, K. Matsuzaki, *Synthesis* **1985** (6/7), 686–688:
The structure of compounds **3e, f** should be:

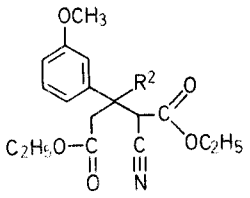


3e,f

I. Monkovic, H. Wong, C. Bachand, *Synthesis* **1985** (8), 770–773:
Reference 9 (p. 772) should be:
[9]Scherer, C. A., Dorschel, C. A., Cook, J. M., Le Quesne, P. W. *J. Org. Chem.* **1972**, *37*, 1083.

A. Cornelis, P. Laszlo, *Synthesis* **1985** (10), 909–918:
Footnotes a and b of Table 10 (p. 916) should be:
[a] 5-Methyl-2-nitro product.
[b] 3-Hydroxy-4-nitro product.

Abstract 7192, *Synthesis* **1985** (11), 1079:
The structure of product **3** should be:



3

D. Moderhack, *Synthesis* **1985** (12), 1083–1096:
The abbreviated name of compound **23** (p. 1087) should read 3-amino-4-imino-2-azetine.

S. M. Fahmy, R. M. Mohareb, *Synthesis* **1985** (12), 1135–1137:
The heading for the last experimental procedure on p. 1136 should be:
3-Amino-N^5-(2-aminophenyl)-2-cyano-2-pentenediamide (15):

F. Fülöp, G. Bernáth, *Synthesis* **1985** (12), 1148–1149:
The heading for the first experimental procedure on p. 1148 should be:
2-Substituted-1,2,3,4,5,6,7,8-octahydroquinazolines (3); General Procedure: