Transesterification of Diphenyl Phosphonates using the Potassium Fluoride/Crown Ether/Alcohol System; Part 1. Transesterification of Diphenyl 1-(Benzyloxycarbonylamino)-alkanephosphonates

Jerzy SZEWCZYK

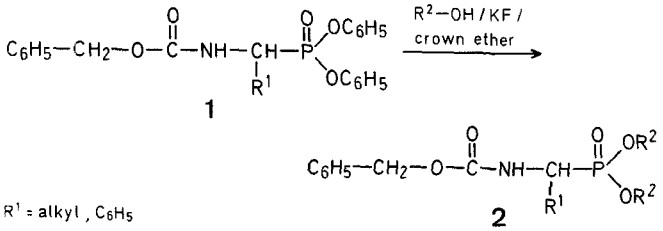
Department of Organic Chemistry, Technical University of Gdańsk, ul. Majakowskiego 11/12, 80-952 Gdańsk, Poland

Barbara LEJCZAK, Paweł KAFARSKI

Institute of Organic and Physical Chemistry, Technical University of Wrocław, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

The transesterification of phenyl phosphates and phosphonates appears to be an important step in some methods of nucleotide synthesis[1,2,3]. The most effective method for the conversion of triphenyl phosphates into the trialkyl esters described so far[1,2] is the use of excess caesium fluoride or tetrabutylammonium fluoride and the respective alcohol.

We report here an improved transesterification procedure using the potassium fluoride/crown ether system instead of caesium or tetrabutylammonium fluorides. Being significantly cheaper our method gives the same yields of the desired products. Since diphenyl 1-aminoalkanephosphonates seem to be potentially useful substrates for phosphonopeptide synthesis we chose diphenyl 1-(benzyloxycarbonylamino)-alkanephosphonates[4] **(1)** as model compounds for these studies. We found that treatment of the diphenyl phosphonates **1** with 10 mol equivalents of potassium fluoride in the respective alcohol in the presence of catalytic amounts of 18-crown-6 affords the desired dialkyl phosphonates **(2)** in yields of 36–91% of isolated product.



As can be seen from T.L.C. and ^{1}H-N.M.R. analysis of the reaction mixtures, the actual yields of esters **2** formed in the transesterification reaction are nearly quantitative; however, the yields of isolated esters **2** are distinctly lower due to partial ester hydrolysis which occurs to a minor extent when the phenol formed in the reaction is extracted from the product solution with aqueous sodium hydroxide and which produces the monoalkyl phosphonates **3**.

0039-7881/82/0532-0409 $ 03.00

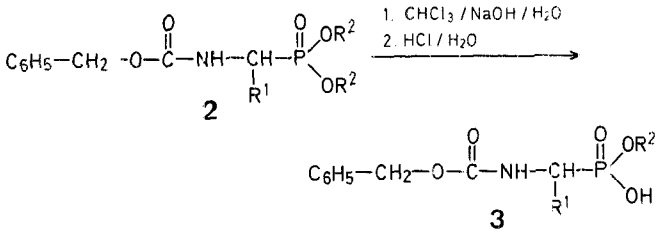
Table 1. [ ]alkyl 1-(Benzyloxycarbonylamino)-alkanephosphonates (**2**)

2	R^1	R^2	Yield [%]			m.p. [°C]	Molecular formula[b]
			Method A[a]	Method B[a]	using CsF		
a	CH	CH_3	81 (64)[c]	89		oil	$C_{12}H_{18}NO_5P$ (287.2)
b	CH	C_2H_5	45	86		oil	$C_{14}H_{22}NO_5P$ (315.3)
c	CH	n-C_3H_7	60			oil	$C_{16}H_{26}NO_5P$ (353.4)
d	CH	$-CH_2-CH=CH_2$	48			oil	$C_{16}H_{22}NO_5P$ (349.3)
e	CH	n-C_4H_9	60			oil	$C_{18}H_{30}NO_5P$ (371.9)
f	$-CH(CH_3)_2$	CH_3	87	91	95	oil	$C_{14}H_{22}NO_5P$ (315.3)
g	$-CH(CH_3)_2$	C_2H_5	57	84	30	85–86°	$C_{16}H_{26}NO_5P$ (353.4)
h	$-CH(CH_3)_2$	n-C_4H_9	90			oil	$C_{20}H_{34}NO_5P$ (399.5)
i	$-CH_2-CH(CH_3)_2$	CH_3	85 (74)[c]			34–35°	$C_{15}H_{24}NO_5P$ (329.3)
j	$-CH_2-CH(CH_3)_2$	C_2H_5	66		67	41–43°	$C_{17}H_{28}NO_5P$ (357.4)
k	$-CH_2-CH(CH_3)_2$	n-C_3H_7	79			61–62°	$C_{19}H_{32}NO_5P$ (385.4)
l	$-CH_2-CH(CH_3)_2$	n-C_4H_9	73			36–37°	$C_{21}H_{36}NO_5P$ (413.5)
m	$-CH_2-CH(CH_3)_2$	$-CH_2-CH=CH_2$	56			35–36°	$C_{19}H_{28}NO_5P$ (381.4)
n	C_6H	CH_3		96		117–118.5°	$C_{17}H_{20}NO_5P$ (349.3)
o	C_6H	C_2H_5		86		113–114°	$C_{19}H_{24}NO_5P$ (377.4)

[a] Isolation method, see procedure.

[b] The microanalyses showed the following maximum deviations from the calculated values: N, ±0.34; P, ±0.38. Exceptions: **2b**, P, −0.44; **2**, N, +0.40.

[c] Using the anhydrous KF/crown ether system.



The high yield of esters **2** formed in the transesterification was additionally confirmed by using column chromatography on silica gel to remove phenol. In this case, the esters **2** were obtained in 85–95% yield of isolated product.

In order to compare our procedure with the literature procedure[1,2] we performed the same reaction in the presence of caesium fluoride and we found that the yields of analytically pure esters **2** are nearly the same in both cases indicating that our procedure compares favourably with the procedure of Ref.[1,2].

Additional studies on the influence of the presence of water in the reaction mixture on the yields of esters **2** showed that the use of anhydrous potassium fluoride does not affect the reaction yield. We further found that treatment of the diphenyl phosphonates **1** with potassium fluoride/water/crown ether in acetone or 1,4-dioxan does not lead to hydrolysis.

On searching for a convenient method for the ester cleavage of diphenyl phosphonates **1**, we applied the potassium fluoride/crown ether system to the hydrolysis of esters **1** with aqueous potassium hydroxide. However, the reaction with excess sodium hydroxide led only to the formation of the monoester **4**.

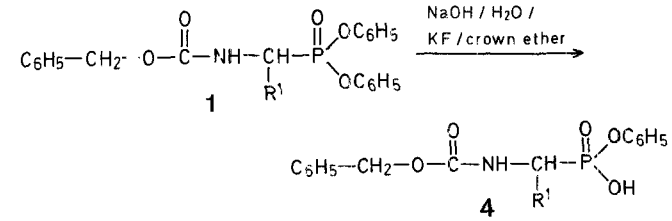


Table 2. Phenyl Hydrogen 1-(Benzyloxycarbonylamino)-alkanephosphonates (**4**)

4	R^1	Yield[a] [%]	m.p. [°C]	Molecular formula[b]
a	CH_3	80	125–126°	$C_{16}H_{18}NO_5P$ (335.4)
b	$-CH(CH_3)_2$	75	133–134°	$C_{18}H_{22}NO_5P$ (363.4)
c	$-CH_2-CH(CH_3)_2$	77	132–133°	$C_{19}H_{24}NO_5P$ (377.4)
d	C_6H_5	91 (79[c], 96[d])	161–162°	$C_{21}H_{20}NO_5P$ (397.4)

[a] Hydrolysis carried out in the presence of KF and crown ether.

[b] The microanalyses showed the following maximum deviations from the calculated values: N, ±0.29; P, ±0.25.

[c] Hydrolysis carried out in the presence of crown ether.

[d] Hydrolysis carried out in the presence of KF.

The same reaction carried out without crown ether and potassium fluoride gave a mixture of compounds **1** and **4** while hydrolysis in the presence of crown ether or potassium fluoride alone gave the monoester **4** with the same yield.

The melting points were determined on Koefller apparatus and are uncorrected. The I.R. spectra were taken on a Perkin Elmer 621 instrument. The ^{1}H-N.M.R. spectra were recorded on a Tesla BS 467 instrument at 60 MHz.

Transesterification of Diphenyl 1-(Benzyloxycarbonylamino)-alkanephosphonates (1) with Alcohols; General Procedure:

The diphenyl 1-(benzyloxycarbonylamino)-alkanephosphonate **1** (5 mmol) and potassium fluoride dihydrate (4.7 g, 50 mmol) are dissolved in the respective alcohol (30–40 ml) and a catalytic amount (~50 mg) of 18-crown-6 is added. The mixture is then heated to boiling for 10 min and left at room temperature overnight.

Isolation Method A, Extraction: The solvent is removed under reduced pressure and the oily residue is mixed with water (50 ml). The transesterification product **2** is then extracted into ethyl acetate or chloroform (3 × 20 ml). The organic extract is washed with 1 normal sodium hydroxide solution (3 × 20 ml), water (20 ml), and saturated sodium chloride solution (20 ml), dried with magnesium sulfate, and evaporated in vacuo to give the pure esters **2** (Table 1).

Isolation Method B, Column Chromatography: The solution is evaporated to dryness in vacuo. The residue is finely divided and digested with benzene (50 ml). Potassium fluoride is filtered off, the solution concentrated, and placed on a column (40 cm × 2 cm^2) of silica gel (Macherey & Nagel minus 200 mesh gel). The ester **2** is eluted with benzene/acetone (20/1). The products thus obtained are analytically pure (Table 1).

Table 3. Spectral Data of Compounds **2** and **4**

Compound	I.R. (KBr or film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/$HMDSO_{int}$) δ [ppm]
2a	3270 (NH); 1730 (CO); 1555 (NH); 1270, 1250 (PO); 1060 (P—O—C)	1.71 (dd, 3H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 16.5 Hz, N—CH—CH$_3$); 4.04 (d, 3H, $^3J_{PH}$ = 10.5 Hz, P—O—CH$_3$); 4.06 (d, 3H, $^3J_{PH}$ = 10.5 Hz, P—O—CH$_3$); 4.0–4.9 (m, 1H, N—CH); 5.45 (s, 2H, CH$_2$—O); 6.32 (br d, 1H, $^3J_{HH}$ = 10.0 Hz, NH); 7.69 (s, 5H$_{arom}$)
2b	3240 (NH); 1715 (CO); 1545 (NH); 1255, 1220 (PO); 1045, 1025 (P—O—C)	1.08 (t, 3H, $^3J_{HH}$ = 7.5 Hz, P—O—CH$_2$—CH$_3$); 1.14 (t, 3H, $^3J_{HH}$ = 7.5 Hz, P—O—CH$_2$—CH$_3$); 1.25 (dd, 3H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 17.5 Hz, P—CH—CH$_3$); 4.1–4.75 (m, 5H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 7.5 Hz, N—CH, 2P—O—CH$_2$); 5.41 (s, 2H, CH$_2$—O—CO); 6.44 (br d, 1H, $^3J_{HH}$ = 10.0 Hz, NH); 7.52 (s, 5H$_{arom}$)
2c	3160 (NH); 1705 (CO); 1530 (NH); 1245, 1210 (PO); 1045 (P—O—C)	0.75 (t, 3H, $^3J_{HH}$ = 6.5 Hz, P—O—CH$_2$—CH$_2$—CH$_3$); 0.78 (t, 3H, $^3J_{HH}$ = 6.5 Hz, P—O—CH$_2$—CH$_2$—CH$_3$); 1.22 (dd, 3H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 16.5 Hz, P—CH—CH$_3$); 0.97–1.7 [m, 4H, P(O—CH$_2$—CH$_2$—CH$_3$); 3.5–4.2 [m, 5H, $^3J_{HH}$ = 7.0 Hz, CH—P, P(O—CH$_2$—CH$_2$—CH$_3$)$_2$]; 4.98 (s, 2H, CH$_2$—O—CO); 7.26 (s, 5H$_{arom}$)
2d	3250 (NH); 1725 (CO); 1550 (NH); 1255, 1235 (PO); 1045 (P—O—C)	1.65 (dd, 3H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 17.0 Hz, P—CH—CH$_3$); 4.1–4.6 (m, 1H, N—CH); 4.78 (br d, 4H, $^3J_{HH}$ = 7.0 Hz, $^3J_{PH}$ = 7.0 Hz, 2 O—CH$_2$—CH=CH$_2$); 5.37 (s, 2H, CH$_2$—O—CO); 5.25–5.75 (m, 4H, 2 O—CH$_2$—CH=CH$_2$); 5.75–6.35 (m, 2H, 2 O—CH$_2$—CH=CH$_2$); 6.59 (br d, 1H, $^3J_{HH}$ = 10.0 Hz, NH); 7.59 (s, 5H$_{arom}$)
2e	3280 (NH); 1725 (CO); 1540 (NH); 1225 (PO); 1020 (P—O—C)	1.25 (br t, 6H, $^3J_{HH}$ = 5.5 Hz, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 1.25–2.15 (m, 11H, P—CH—CH$_3$, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 4.0–4.75 (m, 5H, N—CH, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 5.36 (s, 2H, CH$_2$—O—CO); 6.02 (br d, 1H, $^3J_{HH}$ = 9.5 Hz, NH); 7.61 (s, 5H$_{arom}$)
2f	3300 (NH); 1700 (CO); 1530 (NH); 1250 (PO); 1025 (P—O—C)	0.92 [br d, 6H, $^3J_{HH}$ = 7.0 Hz, CH(CH$_3$)$_2$]; 1.8–2.4 [m, 1H, CH(CH$_3$)$_2$]; 3.5–4.3 (m, 1H, CH); 3.57 (d, 3H, $^3J_{PH}$ = 10.5 Hz, P—O—CH$_3$); 3.62 (d, 3H, $^3J_{PH}$ = 10.5 Hz, P—O—CH$_3$); 5.08 (s, 2H, CH$_2$—O—CO); 5.97 (br d, 1H, $^3J_{HH}$ = 10.0 Hz, NH); 7.32 (s, 5H$_{arom}$)
2g	3290 (NH); 1715 (CO); 1535 (NH); 1240, 1215 (PO); 1035 (P—O—C)	0.91 [d, 6H, $^3J_{HH}$ = 7.0 Hz, CH(CH$_3$)$_2$]; 1.02 (t, 3H, $^3J_{HH}$ = 6.0 Hz, P—O—CH$_2$—CH$_3$); 1.08 (t, 3H, $^3J_{HH}$ = 6.0 Hz, P—O—CH$_2$—CH$_3$); 1.98 (br oct, 1H, $^3J_{HH}$ = 7.0 Hz, CH—CH—P); 3.5–4.3 (m, 5H, N—CH, 2 O—CH$_2$—CH$_3$); 5.83 (br d, 1H, $^3J_{HH}$ = 10.0 Hz, NH); 7.18 (s, 5H$_{arom}$)
2h	3305 (NH); 1700 (CO); 1530 (NH); 1245 (PO); 1045 (P—O—C)	0.88 (t, 6H, $^3J_{HH}$ = 7.0 Hz, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 0.89 [d, 6H, $^3J_{HH}$ = 7.0 Hz, CH(CH$_3$)$_2$]; 1.0–1.7 (m, 8H, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 1.7–2.6 [m, 1H, CH(CH$_3$)$_2$]; 3.4–4.2 (m, 5H, N—CH, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 5.06 (s, 2H, CH$_2$—O—CO); 5.45 (br d, 1H, $^3J_{HH}$ = 11.5 Hz, NH); 7.27 (s, 5H$_{arom}$)
2i	3190 (NH); 1700 (CO); 1525 (NH); 1250 (PO); 1045, 1020 (P—O—C)	0.93 [d, 6H, $^3J_{HH}$ = 6.0 Hz, CH(CH$_3$)$_2$]; 1.15–1.7 [m, 3H, CH$_2$—CH(CH$_3$)$_2$]; 3.50 (d, 3H, $^3J_{PH}$ = 10.5 Hz, P—O—CH$_3$); 3.53 (d, 3H, $^3J_{PH}$ = 10.5 Hz, P—O—CH$_3$); 3.5–4.4 (m, 1H, CH—P); 4.83 (s, 2H, CH$_2$—O—CO); 6.35 (br d, 1H, $^3J_{HH}$ = 9.5 Hz, NH); 7.20 (s, 5H$_{arom}$)
2j	3180 (NH); 1700 (CO); 1525 (NH); 1240, 1205 (PO); 1005 (P—O—C)	0.83 [d, 6H, $^3J_{HH}$ = 5.5 Hz, CH(CH$_3$)$_2$]; 1.11 (t, 3H, $^3J_{HH}$ = 7.0 Hz, O—CH$_2$—CH$_3$); 1.18 (t, 3H, $^3J_{HH}$ = 7.0 Hz, O—CH$_2$—CH$_3$); 1.1–1.9 [m, 3H, CH$_2$—CH(CH$_3$)$_2$]; 3.35–4.3 (m, 5H, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 7.0 Hz, N—CH, 2 O—CH$_2$—CH$_3$); 5.07 (br s, 2H, CH$_2$—O—CO); 5.93 (br d, 1H, $^3J_{HH}$ = 10.0 Hz, NH); 7.28 (s, 5H$_{arom}$)
2k	3180 (NH); 1690 (CO); 1505 (NH); 1235 (PO); 1020 (P—O—C)	0.73 (t, 6H, $^3J_{HH}$ = 7.5 Hz, 2 O—CH$_2$—CH$_2$—CH$_3$); 0.75 [d, 6H, $^3J_{HH}$ = 7.0 Hz, CH(CH$_3$)$_2$]; 1.0–1.8 [m, 7H, CH$_2$—CH(CH$_3$)$_2$, 2 O—CH$_2$—CH$_2$—CH$_3$]; 3.5–4.2 (m, 5H, N—CH, 2 O—CH$_2$—CH$_2$—CH$_3$); 4.97 (s, 2H, CH$_2$—O—CO); 5.32 (br d, $^3J_{HH}$ = 10.5 Hz, NH); 7.20 (s, 5H$_{arom}$)
2l	3200 (NH); 1700 (CO); 1525 (NH); 1240, 1205 (PO); 1005 (P—O—C)	0.5–0.95 (m, 6H, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 1.0–2.0 [m, 11H, CH$_2$—CH(CH$_3$)$_2$, 2 O—CH$_2$—CH$_2$—CH$_2$—CH$_3$); 3.7–4.4 (m, 5H, $^3J_{HH}$ = 7.0 Hz, $^3J_{PH}$ = 7.0 Hz, 2 P—O—CH$_2$, CH—P); 5.01 (s, 2H, CH$_2$—O—CO); 6.32 (br d, 1H, $^3J_{HH}$ = 9.5 Hz, NH); 7.25 (s, 5H$_{arom}$)
2m	3200 (NH); 1695 (CO); 1525 (NH); 1235, 1205 (PO); 1000 (P—O—C)	0.80 [d, 6H, $^3J_{HH}$ = 5.5 Hz, CH(CH$_3$)$_2$]; 1.2–2.0 [m, 3H, CH$_2$—CH(CH$_3$)$_2$]; 4.2–4.7 (m, 5H, CH—P, 2 O—CH$_2$—CH=CH$_2$); 5.01 (s, 2H, CH$_2$—O—CO); 4.9–6.1 (m, 6H, 2 O—CH$_2$—CH=CH$_2$); 6.43 (d, 1H, $^3J_{HH}$ = 10.5 Hz, NH); 7.24 (s, 5H$_{arom}$)
2n	3245 (NH); 1710 (CO); 1545 (NH); 1250 (PO); 1030 (P—O—C)	3.93 (d, 6H, $^3J_{PH}$ = 8.0 Hz, 2 OCH$_3$); 5.00 (s, 2H, CH$_2$O—CO); 5.01 (dd, 1H, $^3J_{HH}$ = 10.5 Hz, $^2J_{PH}$ = 21.5 Hz, CH—P); 6.4–6.8 (m, 11H, NH, 10H$_{arom}$)
2o	3230 (NH); 1715 (CO); 1550 (NH); 1255 (PO); 1035, 1025 (P—O—C)	1.00 (t, 3H, $^3J_{HH}$ = 7.5 Hz, P—O—CH$_2$—CH$_3$); 1.18 (t, 3H, $^3J_{HH}$ = 7.5 Hz, P—O—CH$_2$—CH$_3$); 3.65 (qq, 2H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 7.5 Hz, O—CH$_2$—CH$_3$); 4.01 (qq, 2H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 7.5 Hz, O—CH$_2$—CH$_3$); 5.00 (s, 2H, CH$_2$—O—CO); 5.01 (dd, 1H, $^3J_{HH}$ = 9.5 Hz, $^2J_{PH}$ = 22.0 Hz, CH—P); 6.33 (br d, 1H, $^3J_{HH}$ = 9.5 Hz, NH); 7.0–7.5 (m, 10H$_{arom}$)
4a	3300 (NH); 1690 (CO); 1545 (NH); 1225 (PO); 1160 (PO$^{\ominus}$)	1.24 (dd, 3H, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 17.5 Hz, CH$_3$); 3.7–4.7 (m, 1H, CH—P); 4.97 (s, 2H, CH$_2$—O—CO); 5.60 (br d, 1H, $^3J_{HH}$ = 8.0 Hz, NH); 7.06 (s, 5H, OC$_6$H$_5$); 7.22 (s, 5H, C—C$_6$H$_5$); 10.53 (s, 1H, OH)
4b	3400–2100, 3310 (NH); 1700 (CO); 1510 (NH); 1225 (PO); 1175, 1000 (PO$^{\ominus}$)	0.86 (d, 3H, $^3J_{HH}$ = 6.5 Hz, CH$_3$); 0.89 (d, 3H, $^3J_{HH}$ = 6.5 Hz, CH$_3$); 1.8–2.7 [m, 1H, CH(CH$_3$)$_2$]; 4.08 (qq, 1H, $^3J_{HH}$ = 4.5 Hz, 12.0 Hz, $^2J_{PH}$ = 20.5 Hz, CH—P); 5.00 (s, 2H, CH$_2$—O—CO); 5.23 (br d, 1H, $^3J_{HH}$ = 12.0 Hz, NH); 7.07 (s, 5H, OC$_6$H$_5$); 7.25 (s, 5H, C—C$_6$H$_5$); 11.06 (s, OH)
4c	3500–2000, 3300 (NH); 1700 (CO); 1510 (NH); 1245 (PO); 1200	[a] 0.75 [br d, 6H, $^3J_{HH}$ = 5.5 Hz, CH(CH$_3$); 1.1–2.0 [m, 3H, CH$_2$—CH(CH$_3$)$_2$]; 3.5–4.3 (m, 1H, CH—P); 6.99 (s, 1H, OH); 7.07, 7.10 (2s, 5H, OC$_6$H$_5$); 7.23 (s, 5H, C—C$_6$H$_5$); 7.46 (d, 1H, $^3J_{HH}$ = 10.5 Hz, NH)
4d	3600–2000, 3305 (NH); 1695 (CO); 1510 (NH); 1230, 1205 (PO); 1055 (PO$^{\ominus}$)	4.93 (s, 2H, CH$_2$—O—CO); 5.08 (dd, 1H, $^3J_{HH}$ = 10.5 Hz, $^2J_{PH}$ = 22.5 Hz, CH—P); 6.52 (s, 1H, OH); 6.8–7.5 (m, 10H, C—C$_6$H$_5$, O—C$_6$H$_5$); 7.23 (s, 5H, C—C$_6$H$_5$); 8.30 (br d, 1H, $^3J_{HH}$ = 10.5 Hz, NH)

[a] In DMSO-d_6/$HMDSO_{int}$.

Hydrolysis of Dibutyl 1-(Benzyloxycarbonylamino)-ethanephosphonate (2e) during Extraction; Typical Example:

Diphenyl 1-(benzyloxycarbonylamino)-ethanephosphonate (2.0 g, 5.0 mmol) is tr nsesterified with butanol as described above. The sodium hydroxide solutions obtained during extraction of phenol are collected and acidified to pH ~1 with concentrated hydrochloric acid. The crude monoester **3e** precipitates. It is purified by dissolving in aqueous 0.5 normal sodium hydroxide followed by precipitation with hydrochlor c acid; yield of *butyl hydrogen 1-(benzyloxycarbonylamino)-ethanephos honate* **(3e):** 0.4 g (25%); m.p. 94–96 °C; yield of *dibutyl ester* **(2e):** 1. g (60%).

3e:	$C_{14}H_{22}NO_5P$	calc.	N 4.44	P 9.84
	(315.3)	found	4.55	9.73

I.R. (KBr): ν = 3305 (NH); 3600–2000, 1685 (C=O); 1540 (NH); 1215 (PO); 1155 1060 ($PO^{\ominus}$) cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6/HMDSO$_{int}$): δ = 0.7–1.5 (m, 10H, $2CH_3$, O—CH_2—CH_2—CH_2); 3.4–4.1 (m, 3H, $^3J_{PH}$ = 7.0 Hz, $^3J_{HH}$ = 7.0 Hz, P—O—CH_2, P—CH); 5.05 (s, 2H, CH_2—O—CO); 5.63 (s, 2H, P—OH, N); 7.40 ppm (s, $5H_{arom}$).

Phenyl Hyd ogen 1-(Benzyloxycarbonylamino)-alkanephosphonates (4); General Pr cedure:

Aqueous 1 normal sodium hydroxide (20 ml) is added to a stirred solution of th e diphenyl 1-(benzyloxycarbonylamino)-alkanephosphonate **1** (5 mm ol) in 1,4-dioxan (20 ml). Then, water (~20 ml) is added to homogeniz the mixture and stirring is continued overnight. The solvents are re noved under reduced pressure. The residue is dissolved in water (~30 ml) and this solution is acidified to pH ~1 with concentrated hydr chloric acid to precipitate the monoester **4**. Product **4** is isolated by uction and purified by dissolving in aqueous 0.05 normal sodium hy roxide and precipitation with concentrated hydrochloric acid (Table 2).

This work w as supported by grant R.I.9.

Received: November 13, 1981

[1] K. K. Ol gvie, S. L. Beaucage, *J. Chem. Soc. Chem. Commun.* **1976**, 443.

[2] K. K. Ol gvie, S. L. Beaucage, *Nucleic Acid Res.* **7**, 805 (1979).

[3] G. H. Jo es, J. G. Moffatt, *U. S. Patent* 3583974 (1971), Syntex Corp.; C *A.* **75**, 130091 (1971).

[4] J. Oleksy zyn, L. Subotkowska, P. Mastalerz, *Synthesis* **1979**, 985.

0039-7881 82/0532-0412 $ 03.00