A Convenient Synthesis of Alkyl Hydrogen 1-(Benzyloxycarbonylamino)-alkanephosphonates

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Alkyl hydrogen 1-(benzyloxycarbonylamino)-alkanephosphonates are prepared by condensation of 1-(benzyloxycarbonylamino)-alkanephosphonic acids with primary and secondary alcohols in the presence of thionyl chloride in dimethylformamide.

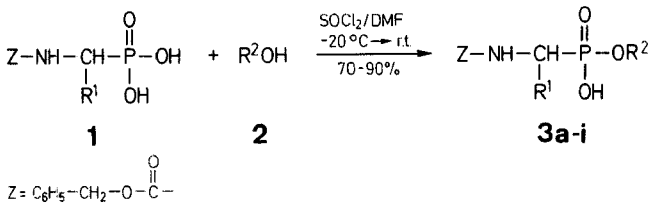
As part of our program directed to the synthesis of phosphonic analogs of peptides and depsipeptides we needed alkyl hydrogen 1-(benzyloxycarbonylamino)-alkanephosphonates.

Two general synthetic routes lead to these compounds. The first one involves partial hydrolytic[1,2] or non hydrolytic[3] cleavage of dialkyl 1-(benzyloxycarbonylamino)-alkanephosphonates and the other uses the reaction of 1-(benzyloxycarbonylamino)-alkanephosphonic acids with alcohols in the presence of such condensing agents as dicyclohexylcarbodiimide[4,5] (DCC) or trichloroacetonitrile[6].

One of the limitations of the first method is that corresponding dialkyl phosphonate has to be prepared in a separate step. The disadvantage of the DCC procedure is that a large excess of alcohol[5,7] or DCC[4] is required and the product formed is often contaminated with dicyclohexylurea. Moreover, both methods are not applicable for the preparation of optically active alkyl hydrogen 1-(benzyloxycarbonylamino)-alkanephosphonates because of the basic medium needed.

In this communication we present a convenient synthetic route leading to alkyl hydrogen 1-(benzyloxycarbonylamino)-alkanephosphonates **3** via reaction of 1-(benzyloxycarbonylamino)-alkanephosphonic

acids **1** with primary and secondary alcohols **2** in the presence of a small excess of thionyl chloride in dimethylformamide (Table).



1 **2** **3a-i**

3	R^1	R^2	3	R^1	R^2
a	C_6H_5	CH_3	**f**	C_2H_5	CH_3
b	C_6H_5	C_2H_5	**g**	C_2H_5	$i\text{-}C_3H_7$
c	C_6H_5	$i\text{-}C_3H_7$	**h**	$i\text{-}C_3H_7$	CH_3
d	C_6H_5	$CH_2C_6H_5$	**i**	$i\text{-}C_4H_9$	$i\text{-}C_3H_7$
e	C_6H_5	CH_2CCl_3			

The synthetic value of this activation of 1-(benzyloxycarbonylamino)-alkanephosphonic acid is connected with the mild conditions used and good yields of the products. Thus the treatment of **1** in dimethylformamide with a small excess of thionyl chloride at − 20 °C followed by an addition of primary or secondary alcohol **2** at − 5 °C at room temperature gave monoesters **3**. Several monoesters **3** including the optically active ethyl hydrogen 1-(benzyloxycarbonylamino)-phenylmethanephosphonate (**3j**) were prepared by this procedure.

Compound **3j** showed the specific rotation consistent with that reported in literature[8]. This fact indicates that the reported procedure is racemization-free and can be employed in the synthesis of monoesters derived from the optically active 1-(benzyloxycarbonylamino)-alkanephosphonic acids. Moreover it has been found out that neither the use of larger amounts of thionyl chloride and alcohol nor a prolonged reaction time afforded the corresponding diesters.

Table. Alkyl Hydrogen 1-(Benzyloxycarbonylamino)-alkanephosphonates **3** Prepared

Product No.	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a] Lit. m.p. [°C]	I.R. (KBr) ν [cm⁻¹]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$) δ [ppm]
3a	80	174–175° (chloroform/ hexane	173–175°[6]	330/0, 1550 (NH); 1720 (C=O); 1250 (P=O); 1050 (P—O—C)	3.50 (d, 3H, J = 11 Hz, $POCH_3$); 4.80–5.30 (m, 1H, CH—P); 5.00 (s, 2H, $CH_2C_6H_5$); 7.10–7.56 (m, 10H, $2C_6H_5$); 8.00–8.46 (m, 1H, NH)
3b	81	188–190° (chloroform/ hexane)	188–190°[5]	3300, 1560 (NH); 1720 (C=O); 1250 (P=O); 1060 (P—O—C)	1.00 (t, 3H, J = 6 Hz, CH_3CH_2); 3.70–4.20 (m, 2H, $POCH_2$); 4.90–5.40 (m, 1H, CH—P); 5.10 (s, 2H, $CH_2C_6H_5$); 7.10–70 (m, 10H, $2C_6H_5$); 7.90–8.40 (m, 1H, NH)
3c	90	198–199° (50% methanol)	193–194°[6]	3305, 1540 (NH); 1710 (C=O); 1250 (P=O); 1050 (P—O—C)	1.10 (dd, 6H, $J_{H,H}$ = 8 Hz, $J_{P,H}$ = 2 Hz, $POCH(CH_3)_2$); 4.20–4.60 (m, 1H, POCH); 4.65–5.30 (m, 1H, CH—P); 5.00 (s, 2H, $CH_2C_6H_5$); 7.10–7.60 (m, 10H, $2C_6H_5$); 7.80–8.30 (m, 1H, NH)
3d	85	152–154° (70% methanol)	152–154°[6]	3305, 1540 (NH); 1730 (C=O); 1250 (P=O); 1070 (P—O—C)	4.76–5.26 (m, 5H, CH—P, CH_2O, $CH_2C_6H_5$); 7.10–7.76 (m, 16H, $3C_6H_5$); 8.10–8.40 (m, 1H, NH)
3e	80	170–172° (ethyl acetate)	170–172°[9]	3320, 1530 (NH); 1725 (C=O); 1230 (P=O); 1050 (P—O—C)	4.42 (d, 2H, $J_{P,H}$ = 7 Hz, $POCH_2$); 4.90–5.50 (m, 1H, CH—P); 5.00 (s, 2H, $CH_2C_6H_5$); 7.16–7.80 (m, 10H, $2C_6H_5$); 8.10–8.50 (m, 1H, NH)
3f	75	118–119° (ethyl acetate hexane)	113–115°[6]	3300, 1550 (NH); 1690 (C=O); 1225 (P=O); 1070 (P—O—C)	0.56 (t, 3H, J = 6 Hz, CH_3CH_2); 1.00–1.80 (m, 2H, CH_2CH_3); 3.42 (d, 3H, J = 11 Hz, $POCH_3$); 3.50–4.10 (m, 1H, CH—P); 4.75 (s, 2H, $CH_2C_6H_5$); 5.70 (bm, 1H, NH); 6.86 (s, 5H, C_6H_5)[b]
3g	75	102–103° (CCl_4/hexane)	$C_{14}H_{22}NO_5P$ (315.3)	3290, 1540 (NH); 1680 (C=O); 1220 (P=O); 1020 (P—O—C)	0.90 (t, 3H, J = 6 Hz, CH_3CH_2); 1.23 (d, 6H, J = 6 Hz, $POCH(CH_3)_2$); 1.30–2.00 (m, 2H, CH_2CH_3); 3.26–4.20 (m, 1H, CH—P); 4.20–4.80 (m, 1H, POCH); 5.00 (s, 2H, $CH_2C_6H_5$); 5.70 (bm, 1H, NH); 7.20 (s, 5H, C_6H_5)[c]
3h	80	105–106° (ethyl acetate/ hexane)	93–96°	3310, 1510 (NH); 1710 (C=O); 1225 (P=O); 1050 (P—O—C)	1.02 [d, 6H, J = 6 Hz, $(CH_3)_2CH$]; 1.90–2.40 [m, 1H, $CH(CH_3)_2$]; 3.70 (d, 3H, J = 10 Hz, $POCH_3$); 3.75–4.20 (m, 1H, CH—P); 5.20 (s, 2H, $CH_2C_6H_5$); 7.30–7.60 (m, 6H, C_6H_5NH)
3i	70	136–137° (50% methanol)	$C_{16}H_{26}NO_5P$ (343.3)	3320, 1560 (NH); 1720 (C=O); 1250 (P=O); 1050 (P—O—C)	0.50–2.00 [m, 6H, $(CH_3)_2CH$]; 1.10 [d, 6H, J = 6 Hz, $POCH(CH_3)_2$]; 1.25–1.85 (m, 3H, CH_2—CH); 3.35–4.20 (m, 1H, CH—P); 4.20–4.70 (m, 1H, POCH); 5.00 (s, 2H, $CH_2C_6H_5$); 7.10–7.55 (m, 6H, C_6H_5, NH)

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.1, N ±0.1. [b] Solvent: TFA [c] Solvent: carbon tetrachloride.

All melting points are uncorrected. The I.R. and ^{1}H-N.M.R. spectra were recorded with Jena-Zeiss UR-10 and Varian EM-360A instruments respectively.

Alkyl Hydrogen 1-(Benzyloxycarbonylamino)-alkanephosphonates 3; General Procedure:

To a solution of 1-(benzyloxycarbonylamino)-alkanephosphonic acid **1** (1 mmol) in dry dimethylformamide (4 ml) cooled to $-20\,^\circ C$ is added thionyl chloride (0.075 ml, 1.2 mmol). The mixture is kept at $-5\,^\circ C$ for 20 min. Then the anhydrous alcohol **2** (2 mmol) is added. The reaction mixture is kept 4 h at room temperature and a solution of saturated sodium hydrogen carbonate (10 ml) is added. The aqueous solution is washed with ether (2 × 10 ml) and acidified with concentrated hydrochloric acid (Congo Red). Alkyl hydrogen 1-(benzyloxycarbonylamino)phenylmethanephosphonates crystallize readily after acidification. Other compounds separate as pale oil after acidification and have to be extracted with ethyl acetate to isolate the desired product. The crude esters are purified by recrystallization. The purity of compounds **3** thus prepared was checked by I.R. and ^{1}H-N.M.R. spectroscopy and by T.L.C. (silica gel; isopropanol-ammonia-water 8:1:1).

(*S*)-1-(Benzyloxycarbonylamino)-phenylmethanephosphonic Acid:[10]

This compound is prepared for the first time from (*S*)-1-aminophenylmethanephosphonic acid, $[\alpha]_D^{20}$: -19.4° (*c* 2, 1 normal NaOH), (374 mg, 2 mmol) using Gilmore procedure[10] for racemic compounds. Yield: 450 mg (70%); m.p. 142–143 °C; $[\alpha]_D^{20}$: -7.7° (*c* 2, 1 normal NaOH).

$C_{15}H_{16}NO_5P$	calc.	C 56.1	H 5.0	N 4.4
(321.3)	found	56.3	4.9	4.1

(*S*)-Ethyl Hydrogen 1-(Benzyloxycarbonylamino)-phenylmethanephosphonate (3j):

This compound is obtained according to the above general procedure from (*S*)-1-(benzyloxycarbonylamino)-phenylmethanephosphonic acid (321 mg, 1 mmol) and ethanol (0.12 ml, 2 mmol). Yield: 280 mg (80%); m.p. 172–173 °C; $[\alpha]_D^{20}$: -19.0° (*c* 2, 1 normal NaOH). (Ref.[8], m.p. 172 °C; $[\alpha]_D^{20}$: -18.8° (*c* 2, 1 normal NaOH) (Table).

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