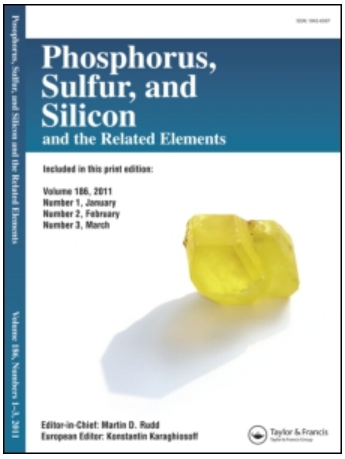

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SELECTIVE CLEAVAGE OF ONE ESTER GROUP IN DIBENZYL DI-P-NITROBENZYL AND DIMETHYL N-PROTECTED AMINOALKYLPHOSPHONATES

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Benzyl, p-nitrobenzyl and methyl hydrogen N-protected aminoalkylphosphonates were efficiently prepared by selective cleavage of one ester group in the corresponding diesters using DABCO (1,4-diazabicyclo(2.2.2]octane).

Keywords: Benzyl hydrogen N-protected aminoalkylphosphonates; p-nitrobenzyl hydrogen N-protected aminoalkylphosphonates; methyl. hydrogen N-protected aminoalkylphosphonate; DABCO (1,4-diazabicyclo(2.2.2]octane)

INTRODUCTION

Phosphonic acid monoesters can be prepared via direct monoesterification of phosphonic acid with alcohols in the presence of condensing reagents such as DCC,[1] DCC/base,[2] CCl_3CN,[3] $SOCl_2$/DMF,[4] BroP[5] or TPyClU.[5] Karanewsky[6] described an alternative procedure in which phosphonic acid monoesters are prepared in a two step procedure proceeding by DCC/DMAP mediated estirification of phosphonous acids and oxidation of the resulting phosphonous ester. Another strategy is based upon hydrolytic (LiOH,NaOH)[7] or non hydrolytic (NaI, TMsBr, PhSH)[8] selective ester cleavage of symmetrical or unsymmetrical phosphonate diesters. This synthesis requires however preparation of corresponding phosphonate diesters. Mixed diesters have been obtained in good yields from monomethyl [9,10] or monobenzyl esters [10]of N-protected α-amino phosphonic

acids using BoP or PyBoP as condensing agents or the Mitsunobu reaction.

Our previous papers described the synthesis of dibenzyl [8a] and dimethyl[11] esters of N-protected α-aminophosphonic acids. Recently a procedure for selective deprotection of organophosphorus benzyl and methyl esters using various nucleophilic amines (i.e. t-butylamine,[12] quinuclidine, 1,4-diazabicyclo[2.2.2]octane[13]) has been described. In this paper we wish to report that DABCO cleaves efficiently and selectively one benzyl, p-nitrobenzyl and methyl group in dibenzyl, di-p-nitrobenzyl and dimethyl N-protected aminoalkylphosphonates.

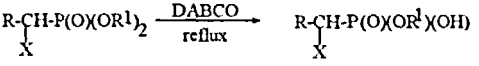
RESULTS AND DISCUSSION

Monoesters of N-protected aminoalkylphosphonic acids were synthesized according to Scheme 1.

Dibenzyl, di-p-nitrobenzyl and dimethyl N-benzyloxycarbonyl and N-phthalyl aminoalkylphosphonates **2a-o**, obtained according to the erlier described procedures [8a,11] reacted with an excess of DABCO in the boiling mixture of acetone and toluene to afford the corresponding monoesters **3a-o** in good yields. Reactions were monitored by thin layer chromatography. Physical and analytical properties of the newly prepared compounds are summarised in Tables I and II.

Using as a substrate optically pure dimethyl N-benzyloxycarbonyl aminobenzylphosphonate **2j**, optically active monoester **3j** was obtained with the specific rotation consistent with that reported in literature.[14] This fact indicates that the reported procedure is racemization free and can be employed to the synthesis of monoesters derived from optically active diesters. Moreover in the case of di-p-nitrobenzyl 3-(benzyloxycarbonylamino)-3-(p-nitrobenzyloxycarbonyl)propylphosphonate **4a** and dimethyl 3-(benzyloxycarbonylamino)-3-(p-methoxycarbonyl)propylphosphonate **4b**, the carboxylic ester remained intact upon treatment with DABCO.(Scheme 2).

In conclusion, the described method provides a convenient and facile route for effective cleavage of one ester group in N-protected aminophosphonate due to its ease of use, selectivity, and good yields.



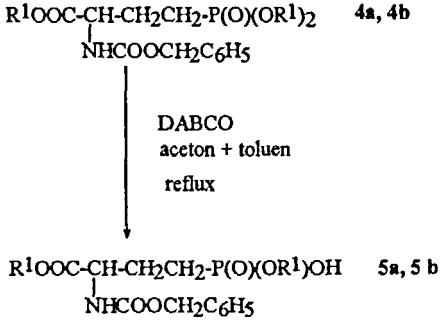
2 3

2, 3	R	R^1	X	2, 3	R	R^1	X
a	H	Nb	NHZ	h	i-C_4H_9	CH_3	NPht
b	CH_3	Nb	NHZ	i	i-C_4H_9	Bz	NHZ
c	CH_3	Nb	NPht	j	C_6H_5	CH_3	NHZ
d	CH_3	CH_3	NPht	k	C_6H_5	CH_3	NPht
e	i-C_3H_7	CH_3	NHZ	l	C_6H_5	Bz	NHZ
f	i-C_3H_7	CH_3	NPht	m	C_6H_5	Bz	NPht
g	i-C_3H_7	Bz	NPht	n	Bz	CH_3	NPht
				o	Bz	Bz	NHZ

Bz = $C_6H_5CH_2$ Pht = $C_6H_4(CO)_2$

Nb = $CH_2C_6H_4$-NO_2-p Z = $O(CO)CH_2C_6H_5$

SCHEME 1



4a, 5a R^1= p-O_2N-C_6H_4-CH_2

4b, 5b R^1= CH_3

SCHEME 2

TABLE I Yields and properties of benzyl, p-nitrobenzyl and methyl hydrogen N-protected 1-aminoalkylphosphonates **3a-o**

Compound No.	*Yield %*	*M.P.°C Recryst. Solvent*	*Molecular Formula or Lit. m.p.*	*% Analysis Calcd. /Found*		
				C	*H*	*N*
3a	80	119–121	$C_{16}H_{17}N_2O_7P$	50.52	4.50	7.37
		benzene	380.3	50.36	4.50	7.12
3b	80	151–153 benzene/hexane	151–153[8a]			
3c	80	149–150 benzene/hexane	149–150[8a]			
3d	66	155–157	$C_{11}H_{12}NO_5P$	49.07	4.49	5.20
		ethyl acetate/hexane	269.2	48.81	4.52	5.09
3e	80	105–106[4] ethyl acetate/hexane	105–106[4]			
3f	79	182–184	$C_{13}H_{16}NO_5P$	52.52	5.42	4.71
		ethyl acetate/hexane	297.2	52.53	5.46	4.55
3g	75	132–133	$C_{19}H_{20}NO_5P$	61.12	5.40	3.75
		ethyl acetate/hexane	373.3	61.13	5.44	3.73
3h	82	122–124	$C_{14}H_{18}NO_5P$	54.01	5.62	4.50
		benzene/hexane	311.3	54.16	5.60	4.43

Compound No.	*Yield %*	*M.P.°C Recryst. Solvent*	*Molecular Formula or Lit. m.p.*	*% Analysis Calcd. /Found*		
				C	*H*	*N*
3i	89	125–126	$C_{20}H_{26}NO_5P$	61.37	6.69	3.57
		ethyl acetate/hexane	391.4	61.65	6.42	3.47
3j*	80	157–159	155–156 [14]			
3k	70	185–187 ethyl acetate/hexane	183–184 [15]			
3l	85	156–157	152–154 [4]			
3m	95	164–166	$C_{22}H_{18}NO_5P$	64.86	4.45	3.43
		benzene/hexane	407.3	64.86	4.52	3.43
3n	81	162–164	$C_{17}H_{16}NO_5P$	59.14	4.67	4.05
		benzene/hexane	345.3	59.04	4.69	3.84
3o	83	130–131 ethyl acetate/hexane	130–131 [16]			

* Optically active.

TABLE II ^{1}H-NMR spectra of the newly prepared benzyl, p-nirtobenzyl and methyl hydrogen N-protected 1-aminoalkylphosphonates

Produkt	*^{1}H NMR (solvent) δ [ppm]*
3a	(DMSO-d_6) 3.46 (dd, 2H, J = 10.7 Hz, J = 6 Hz, CH_2P); 5.01 (s, 2H, $CH_2C_6H_5$); 5.07 (d, 2H, J = 7.4 Hz, $POCH_2$); 7.31 (s, 5H, C_6H_5); 7.59–7.63 (m, 3H, C_6H_4 NH); 8.19 (d, 2H, C_6H_4).
3d	($CDCl_3$) 1.70 (dd, 3H, J = 7.8 Hz, J = 16.4 Hz, CH_3); 3.79 (d, 3H, J = 11.2 Hz, $POCH_3$); 4.73 (dq, 1H, J = 7.4 Hz, J = 20 Hz, CH-P); 5.64 (s, 1H, OH); 7.65–7.90 (m, 4H, C_6H_4).
3f	($CDCl_3$) 0.72 (d, 3H, J = 6.3 Hz, CH_3C); 1.07 (d, 3H, J = 6.6 Hz, CH_3C); 2.55–2.80 (m, 1H, CH); 3.62 (d, 3H, J = 11 Hz, $POCH_3$); 4.04 (dd, 1H, J = 19 Hz, J = 11 Hz, CH-N); 7.57–7.75 (m, 4H, C_6H_4); 8.47 (s, 1H, OH).
3g	($CDCl_3$+DMSO) 0.72 (d, 3H, J = 6.8 Hz, CH_3C); 1.07 (d, 3H, J = 6.6 Hz, CH_3C); 4.10 (dd, 1H, J = 18.6 Hz, J = 11 Hz, CH-P); 4.99 (d, 2H, J = 7.4 Hz, $POCH_2$); 7.00–7.80 (m, 9H, C_6H_5, C_6H_4); 8.10 (br s, OH).
3h	($CDCl_3$) 0.90, 0.91 (two d, 6H, J = 6.4 Hz, $(CH_3)_2C$; 1.35–1.60 (m, 1H, CH); 1.60–1.80 (m, 1H, CH); 2.35–2.60 (m, 1H, CH); 3.78 (d, 3H, J = 11 Hz, $POCH_3$); 4.70 (ddd, 1H, J= 20.2 Hz, J = 11.8 Hz, J = 4 Hz, CH-P); 6.59 (s, 1H, OH); 7.65–7.85 (m, 4H, C_6H_4).
3i	($CDCl_3$) 0.70–1.00 (m, 6H, $(CH_3)_2C$); 1.30–1.80 (m, 3H, CH_2CH); 4.10–4.40 (m, 1H, CH-P); 5.00–5.30 (m, 5H, $POCH_2$, OCH_2, NH), 6.15 (br s, OH); 7.20–7.45 (m, 10H, 2 C_6H_5).
3k	($CDCl_3$ + DMSO) 3.58 (d, 3H, J = 11 Hz, $POCH_3$); 5.60 (d, 1H, J = 24.4 Hz, CH-P); 7.16–7.80 (m, 10H, C_6H_5, C_6H_4+OH).
3m	($CDCl_3$+ DMSO) 4.94 (d, 2H, J=7,6 Hz, $POCH_2$); 5.63 (d, 1H, J = 24.6 Hz, CH-P); 7.00–7.80 (m, 15H, 2 C_6H_5, C_6H_4, OH).
3n	($CDCl_3$) 3.25 –3.45 (m, 1H, CH); 3.60–3.76 (m, 1H, CH); 3.81 (d, 3H, J = 11 Hz, $POCH_3$); 4.93 (ddd, 1H, J = 19.4 Hz, J = 12.4 Hz, J = 4.4 Hz, CH); 5,72 (s, 1H, OH); 7.15 (s, 5H, C_6H_5); 7.60–7.80 (m, 4H, C_6H_4).

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on Varian 200 MHz spectrometer. DABCO (1,4-diazabicyclo[2.2.2.]octane) was purchased from Aldrich. Thin layer chromatography (TLC) was performed on silca gel 60 plates using solvent systems: iPrOH:NH_4OH:H_2O = 8:1:1 and $CHCl_3$:MeOH = 9:1.

Dibenzyl and di-p-nitrobenzyl N-protected aminophosphonates 2a-c, 2g, 2i, 2l, 2m, 2o,5a

Were obtained from N-protected aminophosphonic acids and O-benzyl and O-p-nitrobenzyl-N,N′-dicyclohexylisourea according to the procedure described in lit.[8a]/

Compound **2i**: Yield 80%; m.p.95–96°C; ^{1}H-NMR ($CDCl_3$) δ:0.89 (d, 6H, J = 6 Hz, $(CH_3)_2CH$); 1.40–1.80 (m, 3H, CH_2CH); 4.15–4.40 (m, 1H, CHP); 4.80 (d, 1H, J = 8 Hz, NH); 4.90–5.10 (m, 6H, $P(OCH_2)_2$, OCH_2); 7.25–7.40 (m, 15 H, 3 C_6H_5);

Compound **2l**.: Yield 77%; m.p.136–138°C. ^{1}H-NMR ($CDCl_3$) δ:4.62 (dd, 1H, J = 11.6 Hz, J = 8.4 Hz, 0.5 $POCH_2$); 4.85 (dd, 1H, J = 11.6 Hz, J = 7.2 Hz, 0.5 $POCH_2$); 4.98 (d, 2H, J = 8.4 Hz, $POCH_2$); 5.03–5.14 (m, 1H, OCH_2); 5.26 (dd, 1H, J = 21.6 Hz, J = 9.9 Hz, CHP); 5.80–5.90 (m, 1H, NH); 7.00–7.50 (m, 20 H, $4C_6H_5$).

Compound **2m**: Yield 78%; m.p.76–77°C; ^{1}H-NMR ($CDCl_3$) δ: 4.88 (dd, 1H, J = 11.8 Hz, J = 8.3 Hz, 0.5 $POCH_2$); 4.99 (dd, 1H, J = 11.8 Hz, J = 8.8 Hz, 0.5 $POCH_2$); 5.16 (d, 2H, J = 8.4 Hz, $POCH_2$); 5.80 (d, 1H, J = 24.9 Hz, CHP); 7.20–7.90 (m, 19 H, 3 C_6H_5, C_6H_4).

Compound **4a**: Yield 82%; m.p. 131–132°C; ^{1}H-NMR ($CDCl_3$) δ: 1.80–2.20 (m, 4H, CH_2CH_2); 4.20–4.35 (m, 1H, CHN); 4.97–5.10 (m, 2H, $OCH_2C_6H_5$); 5.18 (d, 4H, J = 8.3 Hz, $POCH_2$); 5.27 (s, 2H, $COOCH_2$); 7.20–7.40 (m, 5H, C_6H_5); 7.50–7.70 (m, 6H, C_6H_4), 7.96 (d, 1H, J = 8 Hz, NH); 8.10–8.25 (m, 6H, C_6H_4).

Dimethyl N-protected aminoalkylphosphonates 2d-f, 2h, 2j, 2k, 2n

Were obtained from N-protected aminoalkylphosphonic acids and diazomethane according to lit.[11].

Compound **2h**: Yield 100%. ^{1}H-NMR ($CDCl_3$) δ: 0.84, 0.86 (two d, 6H, J = 4Hz, $(CH_3)_2C$); 1.35–1.59 (m, 1H, CH); 1.60–1.80 (m, 1H, 0.5 CH_2); 2.40–2.60 (m, 1H, 0.5 CH_2); 3.81, 3.83 (two d, 6H, J = 11 Hz, $P(OCH_3)_2$); 4.70 (ddd, 1H, J = 19.7 Hz, J = 12.3 Hz, J = 3.9 Hz, CHP); 7.70–7.95 (m, 4H, C_6H_4).

Compound **2n**: Yield 90%; m.p. 104–105°C; ^{1}H-NMR ($CDCl_3$) δ: 3.30–3.44 (m, 1H, 0.5 CH_2); 3.62–3.78 (m, 1H, 0.5 CH_2); 3.85, 3.88 (two d, 6H, J = 11 Hz, $P(OCH)_3)_2$); 4.93 (ddd, 1H, J = 19.2 Hz, J = 12.4 Hz, J = 4 Hz, CHP); 7.10–7.15 (m, 5H, C_6H_5); 7.60–7.85 (m, 4H, C_6H_4).

Benzyl, p-Nitrobenzyl and Methyl Hydrogen N-protected 1-Aminoalkylphosphonates 3a, 3b, 3c, 3e, 3g, 3i, 3l, 3m, 3o

A solution of dibenzyl, di-p-nitrobenzyl and dimethyl N-protected 1-aminoalkylphosphonate (1 mmol) in the (1:1) mixture of acetone and toluene (10 ml) containing DABCO (168 mg, 1.5 mmol) was refluxed for 5h before the solvents were removed in vacuo and the residue was dissolved in 5% aqueous HCl. The aqueous layer was extracted with ethyl acetate (10 ml) and the organic layer washed with water, dried over magnesium sulfate, filtered and evaporated. The residue was recrystallized. Yields and properties of the compounds obtained are listed in Table I.

Methyl Hydrogen N-phthalyl 1-Aminoalkylphosphonate 3d, 3f, 3h, 3k, 3n

A solution of dimethyl N-phthalyl 1-aminoalkylphosphonate (1 mmol) in the (1:1) mixture of acetone and toluene (10 ml) containing DABCO (168 mg, 1.5 mmol) was refluxed for 5h before the solvents were removed in vacuo. The residue was dissolved in methanol (10 ml) and this solution was passed through Amberlite IR 120 H^+ (20 ml). The filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized. Yields and properties of the compounds obtained are listed in Table I.

(S) Methyl Hydrogen 1-(Benzyloxycarbonylamino)-phenylmethylphosphonate 3j

This compound was obtained according to the above general procedure from (S) Dimethyl 1-(Benzyloxycarbonylamino)phenylmethylphosphonate $[\alpha]= -14$ (c2, MeOH), (175 mg, 0.5 mmol) and DABCO (84 mg, 0.75 mmol). Yield 144 mg (80%). M.p. 157–159°C ; $[\alpha]_D= -24$ (cl, 1N NaOH). Ref. m.p. 155–156°C; $[\alpha]_D= -19.3$ (cl, 1N NaOH).

Synthesis of p-Nitrobenzyl Hydrogen (RS) 3-(Benzyloxycarbonylamino)-3-(p-Nitrobenzyloxycarbonyl)-propylphosphonate 5a and Methyl Hydrogen (RS) 3-(Benzyloxycarbonylamino)-3-(Methoxycarbonyl)-propylphosphonate 5b

A solution of compound **4a** (361mg, 0,5 mmol) or **4b** (179 mg, 0,5 mmol) in the (1:1) mixture of acetone and toluene (10 ml) containing DABCO

(84 mg, 1.5 mmol) was refluxed for 5h before the solvents were removed in vacuo. In the case of compound **4a** aqueous 5% HCl was added to the residue and the reaction mixture was extracted with ethyl acetate (15 ml). The organic layer was washed with water, dried over magnesium sulfate and evaporated.The residue was crystallized, from ethyl acetate. Yield of **5a** 265 mg (90%), m.p. 128-130°C

$C_{26}H_{26}N_{30}O_{11}P$(587,46) calc. C 53.15 H 4.44 N 7.15
found C 53.21 H 4.47 N 7.03

^{1}H-NMR (DMSO-d_6) δ: 1.70–2.10 (m, 4H, CH_2CH_2); 4.20–4.35 (m, 1H, CH-N); 5.02–5.10 (m, 2H, $OCH_2C_6H_5$); 5.08 (d, 2H, J = 8.7 Hz, $POCH_2$); 5.29 (s, 2H, $OCH_2C_6H_4$); 7.20–7.40 (m, 5H, C_6H_5); 7.60–7.67 (m, 4H, C_6H_4); 7.95 (d, 1H, J = 7.5 Hz, NH); 8.15–8.25 (m, 4H, C_6H_4).

In the case of compound **4b** the residue was dissolved in methanol (10 ml) and the solution was filtered through Amberlite IR 120 H^+(30 ml). The filtrate was evaporated to dryness under reduced pressure. The oily product **5b** was dissolved in ethyl acetate 10 ml and extracted with saturated $NaHCO_3$ solution (5ml) and water (5ml). The combined $NaHCO_3$ and water layer were acidified with concentrated HCl and extracted twice with ethyl acetate (2 × 5ml). The organic layer was dried over magnesium sulfate and evaporated to afford the oily product **5b**. Yield 290 mg (80%).

^{1}H-NMR ($CDCl_3$) δ: 1.65–2.35 (m, 4H, CH_2CH_2); 3.70 (d, 3H, J = 11 Hz, $POCH_3$); 3.75 (s, 3H, $COOCH_3$); 4.35–4.50 (m, 1H, CH); 5.11 (s, 2H, $CH_2C_6H_5$); 5.40–5.70 (br, 1H, NH); 7.35 (s, 5H, C_6H_5).

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