A Simple, Efficient Synthesis of Dibenzyl and Di-*p*-nitrobenzyl 1-Hydroxyalkanephosphonates

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Dibenzyl and di-*p*-nitrobenzyl 1-hydroxyalkanephosphonates **3a–i** are prepared by alkylation of 1-hydroxyalkanephosphonic acids **1** with *O*-benzyl and *O*-(*p*-nitrobenzyl)-*N,N'*-dicyclohexylisoureas **2**.

In connection with our studies on the synthesis of *P*-protected phosphonodidepsipeptides, we became interested in developing a method for the synthesis of dibenzyl and di-*p*-nitrobenzyl 1-hydroxylalkanephosphonates. We hoped these esters would be crystalline and easily removable by catalytic hydrogenation. Dialkyl 1-hydroxyalkanephosphonates are accessible by condensation of aldehydes or ketones with dialkyl hydrogen phosphites,[1-4] but only a few examples of synthesis of dibenzyl 1-hydroxyalkanephosphonates derived from ketones had been described[4] and their yields were rather low. Also, preliminary experiments carried out in our laboratory using the reported methods to obtain dibenzyl 1-hydroxylalkanephosphonates derived from aldehydes gave poor yields. This may be the result of reported[5] unstability of dibenzyl phosphite. Furthermore, the reported methods are not suitable for the synthesis of optically active esters.

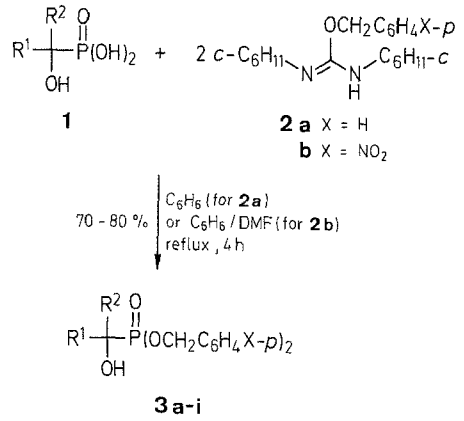
Dialkyl 1-hydroxylalkanephosphonates can also be obtained by alkylation of acids with diazoalkanes.[6,7] The drawback of the method is the instability and explosion hazard associated with diazoalkanes. Taking this into account, we have now developed a new synthesis of dibenzyl and di-*p*-nitrobenzyl 1-hydroxyalkanephosphonates, which involves the reaction of 1-hydroxyalkanephosphonic acid with *O*-benzyl and *O*-(*p*-nitrobenzyl)-*N,N'*-dicyclohexylisoureas. *O*-Benzyl-*N,N'*-dicyclohexylisourea has been used as the alkylating agent for active hydrogen compounds[8] such as carboxylic acids,[9,10] thiocarboxylic acids,[11] thiols,[12] and phosphorothioic acids.[11]

In this paper we report that *O*-benzyl and *O*-(*p*-nitrobenzyl)-*N,N'*-dicyclohexylisoureas are effective as alkylating agents for the synthesis of dibenzyl and di-*p*-nitrobenzyl 1-hydroxyalkanephosphonates (Scheme).

Table. Dibenzyl and Di-*p*-nitrobenzyl 1-Hydroxyalkanephosphonates **3**

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr)[c] ν(OH) (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
3a	77	103–104 (ether)	$C_{21}H_{21}PO_4$ (368.4)	3260	4.42 (s, 1H, OH); 4.79, 4.86 (td, 4H, J = 8, $2OCH_2$); 5.03 (d, 1H, J = 12, C_6H_5CH); 7.27 (m, $15H_{arom}$)
3b	76	63–64 (ether/hexane)	$C_{18}H_{23}PO_4$ (334.3)	3320	1.00 [d, 6H, J = 6, $(CH_3)_2CH$]; 1.95 [m, 1H, $(CH_3)_2CH$]; 2.70 (s, 1H, OH); 3.70 (dd, 1H, J = 10, 6, CHP); 5.05 (d, 4H, J = 8, $2OCH_2$); 7.30 (m, $10H_{arom}$)
3c	76	71.5–72 (ether/hexane)	$C_{19}H_{25}PO_4$ (348.4)	3300	0.70, 0.86 [td, 6H, J = 6, $(CH_3)_2CH$]; 1.55 (m, 3H, CH, CH_2); 3.55 (s, 1H, OH); 3.98 (m, 1H, CHP); 5.15 (d, 4H, J = 8, $2OCH_2$); 7.40 (m, $10H_{arom}$)
3d	75	81–82 (ether/hexane)	81[4]	3380	1.33 [d, 6H, J = 16, $(CH_3)_2C$]; 3.75 (s, 1H, OH); 5.00 (d, 4H, J = 8, $2OCH_2$); 7.21 (m, $10H_{arom}$)
3e	75	112–113 (ether)	$C_{20}H_{25}PO_4$ (360.4)	3350	1.60 (m, 10H, C_6H_{10}); 3.10 (s, 1H, OH); 5.00 (d, 4H, J = 8, $2OCH_2$); 7.26 (m, $10H_{arom}$)
3f	70	132–134 (benzene)	$C_{15}H_{15}N_2O_8P$ (382.3)	3300	2.70 (s, 1H, OH); 4.00 (d, 2H, J = 6, CH_2P); 5.19 (d, 4H, J = 8, $2OCH_2$); 7.80 (m, $8H_{arom}$)
3g	75	140–141 (benzene)	$C_{16}H_{17}N_2O_8P$ (396.3)	3280	1.42 (dd, 3H, J = 16, 6, CH_3); 4.00 (m, 2H, CHP, OH); 5.16 (d, 4H, J = 8, $2OCH_2$); 7.78 (m, $8H_{arom}$)
3h	80	143–145 (benzene)	$C_{19}H_{23}N_2O_8P$ (438.4)	3280	0.80, 0.90 [td, 6H, J = 6, $(CH_3)_2CH$]; 1.65 (m, 3H, CH_2CH); 3.50 (m, 1H, OH); 4.00 (m, 1H, CHP); 5.20 (d, 4H, J = 8, $2OCH_2$); 7.80 (m, $8H_{arom}$)
3i	80	146–147 (benzene)	$C_{20}H_{23}N_2O_8P$ (450.4)	3350	1.75 (m, 10H, C_6H_{10}); 3.50 (s, 1H, OH); 5.23 (d, 4H, J = 8, $2OCH_2$); 7.85 (m, $8H_{arom}$)

[a] Melting points are uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.18, N ±0.11.
[c] Recorded on a Jena-Zeiss UR-10 spectrometer.
[d] Recorded on a Varian EM-360A spectrometer.



3	R^1	R^2	X	3	R^1	R^2	X
a	C_6H_5	H	H	**f**	H	H	NO_2
b	*i*-C_3H_7	H	H	**g**	CH_3	H	NO_2
c	i-C_4H_9	H	H	**h**	i-C_4H_9	H	NO_2
d	CH_3	CH_3	H	**i**	$-(CH_2)_6-$		NO_2
e	$-(CH_2)_6-$						

In a typical procedure 1-hydroxyalkanephosphonic acid **1** reacted with *O*-benzyl or *O*-(*p*-nitrobenzyl)-*N,N'*-dicyclohexylisourea (**2a** or **2b**) in refluxing benzene (mole ratio, 1:2). The reaction appeared to be complete within 4 hours (TLC). In all cases the desired dibenzyl or di-*p*-nitrobenzyl 1-hydroxyalkanephosphonates **3** were obtained in good yields.

The above procedure was also carried out using optically active (+)-hydroxy(phenyl)methanephosphonic acid. The dibenzyl ester thus obtained was subjected to hydrogenolysis. The specific rotation of the product was identical with that of the starting (+)-hydroxy(phenyl)methanephosphonic acid. This result indicates that the described method is racemization free and can be employed for the synthesis of optically active 1-hydroxyalkanephosphonates.

O-Benzyl-*N,N'*-dicyclohexylisourea (**2a**) is prepared from *N,N'*-dicyclohexylcarbodiimide and benzyl alcohol according to a known procedure[13,14] and is used without further purification.

***O*-(*p*-Nitrobenzyl)-*N,N'*-dicyclohexylisourea (2b):**
p-Nitrobenzyl alcohol (1.53 g, 0.01 mol) is added to a mixture of copper(I) chloride (7 mg, 0.071 mmol) and *N,N'*-dicyclohexylcarbodiimide (2.06 g, 0.01 mol) in benzene (1 mL) at 40°C. The mixture is stirred at room temperature for 48 h. The volume is then doubled with hexane, and the solution applied to a filter pad of neutral alumina in order to remove copper salts. The product is eluted with a total volume of 50 mL of hexane. The solvent is evaporated under reduced pressure, and the residue is crystallized from *n*-pentane to give **2b**; yield: 3.4 g (94%); mp 65–66°C.

$C_{20}H_{29}N_3O_3$ (359.5) calc. C 66.82 H 8.06 N 11.69; found 66.84 8.20 11.64

IR (CCl_4): δ = 1670 (C=N) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.67–2.20 (m, 20H, 2 *c*-C_6H_{10}); 2.50–3.00 (m, 1H); 3.20–3.66 (m, 1H); 5.20 (s, 2H); 7.40–8.33 (m, $4H_{arom}$).

Dibenzyl and di-*p*-Nitrobenzyl 1-Hydroxyalkanephosphonates 3; General Procedure:
The appropriate 1-hydroxyalkanephosphonic acid[7] **1** (1 mmol) is added to a solution of *O*-benzyl-*N,N'*-dicyclohexylisourea (**2a**; 0.629 g, 2 mmol) in benzene (10 mL) or *O*-(*p*-nitrobenzyl)-*N,N'*-dicyclohexylisourea (**2b**; 0.719 g, 2 mmol) in a mixture of benzene (15 mL) and DMF (2 mL). The reaction mixture is then refluxed for 4 h, the reaction course being monitored by TLC (silica gel, i-PrOH/NH_3/H_2O, 8:1:1). The precipitated urea is filtered. The filtrate is evaporated under reduced pressure, and EtOAc (20 mL) is added to the residue. The solution is washed successively with a 3% aq. $NaHCO_3$ (2 × 15 mL) and water (15 mL), dried ($MgSO_4$), filtered and evaporated. The crude esters **3** are purified by recrystallization (see Table).

***(R)*-(+)-Hydroxy(phenyl)methanephosphonic acid:**
Resolution of racemic acid with (−)-ephedrine according to the literature[15] gives the (R)-acid. The *R*-configuration of this compound is established by comparing the specific rotation of its dimethyl ester (obtained by alkylation of the acid with diazomethane), $[\alpha]_D^{20}$ + 46 (*c* = 1, acetone), with that described in the literature as (*S*)-(−): Lit.[16] (*S*)-(−)-dimethyl 1-hydroxy-1-phenylmethanephosphonate, $[\alpha]_D^{20}$ − 46 (*c* = 1, acetone).

(*R*)-(+)-Dibenzyl Hydroxy(phenyl)methanephosphonate:
The title compound is obtained according to the above general procedure from (*R*)-(+)-hydroxy(phenyl)methanephosphonic acid [0.188 g, 1 mmol, $[\alpha]_D^{20} + 36$ ($c = 1$, H_2O)] and *O*-benzyl-*N*,*N*'-dicyclohexylisourea (0.629 g, 2 mmol); yield: 0.277 g (75%); mp 127–128 °C (benzene/hexane); $[\alpha]_D^{20} + 16$ ($c = 1$, CH_3OH).

$C_{21}H_{21}PO_4$	calc.	C 68.47	H 5.74
(368.3)	found	68.20	5.77

(*R*)-(+)-Hydroxy(phenyl)methanephosphonic acid:
(*R*)-(+)-Dibenzyl hydroxy(phenyl)methanephosphonate (0.368 g, 1 mmol) is dissolved in CH_3OH (15 mL). Then 10% Pd-C (0.05 g) is added and the mixture is hydrogenated at 20 °C for 2 h under 1 atm H_2. The catalyst is filtered, washed with CH_3OH and water, and the filtrate is evaporated to dryness under reduced pressure. The product crystallizes after addition of ether; yield: 170 mg (90%); mp 144–146 °C; $[\alpha]_D^{20} + 36$ ($c = 1$, CH_3OH).

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