Synthesis of Novel Functionalized *gem*-Bisphosphonates

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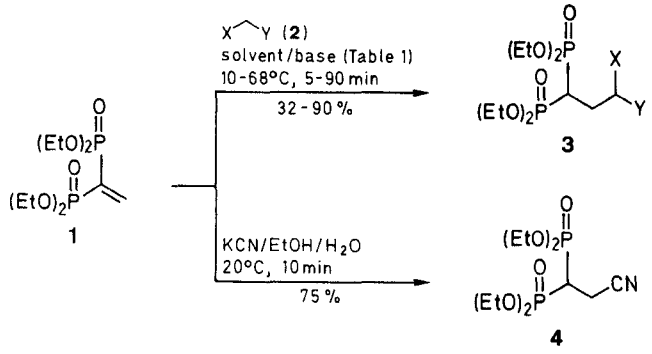
Michael-type addition of carbanions to tetraethyl ethylidenebisphosphonate affords functionalized gem-bisphosphonates, which are potentially useful in the therapy of bone tissues.

The relatively recent therapeutical potential shown by some compounds possessing *gem*-bisphosphonic moiety in the pathology of bone tissues[1] has led us to study new procedures for the synthesis of such molecules. The access to such compounds utilizing the nucleophilic character of the tetraethyl methylenebisphosphonate carbanion is limited to only certain alkylation reagents.[2,3] The possibility of phosponylation of a carbanion at the α carbon atom of a monophosphonate is also quite restrictive.[4,5]

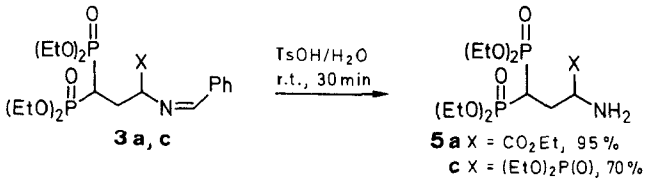
We envisaged that Michael condensation[6] of masked polyfunctional nucleophiles **2** with tetraethyl ethylidenebisphosphonate **(1)**[7,9,10] should afford the bisphosphonates of type **3** structures, and this therefore seemed a plausible method, to include different chemical functions X and Y in **3**. Addition of amines, phosphites and thiols to **1** is documented in the literature,[11] however, the addition of carbanions to **1** failed.

We report here that, after modification of the reaction conditions, it is possible to improve the addition of ethyl *N*-benzylideneglycinate **(2a)**,[12] which was initially studied in our laboratory,[7-9] and to extend it to include other nucleophiles.

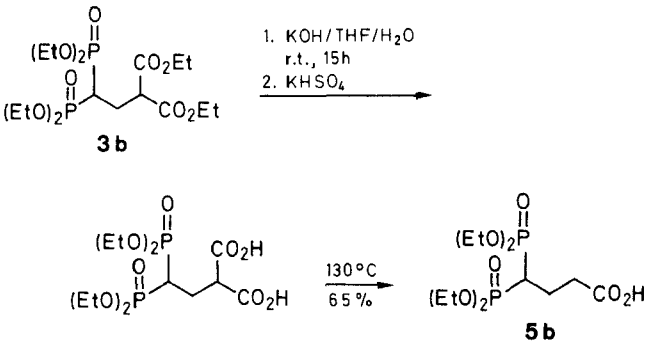
The addition of ethyl *N*-benzylideneglycinate **(2a)** to **1** is carried out in an ethanolate/ethanol medium and lasts only a few minutes. The reaction is followed by ^{31}P-NMR spectroscopy (Table 1). The addition of cyanide ion to **1** could also effectively be done in aqueous ethanol to give **4**.



The addition compounds **3a–g** are then treated with various reagents in order to deprotect the initially protected functions. Thus, treatment of **3a** and **3c** with an aqueous solution of *p*-toluenesulfonic acid deprotects the amine function,[13] without hydrolysing the phosphonate ester functions, and leads to **5a** and **5c**.



Compound **3b** is first saponified with potassium hydroxide in aqueous tetrahydrofuran solution. After acidification, it undergoes decarboxylation on heating at 130 °C[14] and gives directly the expected compound **3b**. The spectral data of the compounds **3** and **5** are given in Table 2.



^{13}C-NMR spectra were recorded on a Bruker AC 300 spectrometer. ^{31}P-NMR spectra were recorded on a Jeol FX100 FT spectrometer.

Commercial reagents used were purchased from Aldrich or Janssen. Tetraethyl ethylidenebisphosphonate **(1)**[7,9,10] and ethyl *N*-benzylideneglycinate **(2a)**[12] were prepared by literature procedures. *N*-Benzylideneaminomethylphosphonate **(2c)** was synthesized from diethyl phthalimidophosphonate[15] followed by treatment with ammonia.[16]

Ethyl 4,4-Bis(diethoxyphosphoryl)-2-ethoxycarbonyl Butyrate (3b); Typical Procedure:

Diethyl malonate (3.2 g, 20 mmol) is added to a solution of NaOEt (0.14 g, 2 mmol) in EtOH (30 mL). Compound **1** (6 g, 20 mmol) is then added at r.t. and the mixture stirred for 15 min. The mixture is neutralized with sat. NH_4Cl solution (10 mL), the EtOH evaporated on a rotary evaporator, and the residue is extracted with EtOAc (3 × 20 mL). The combined organic phases are dried ($MgSO_4$) and evaporated at reduced pressure; yield: 8.2 g (90%) (Table 1).

Remarks: After the reaction, compounds **3a,c,d,f** and **g** are extracted with $CHCl_3$, while Et_2O is used to extract **3e**. Compounds **3c, 3e** and **3f** are purified by chromatography on silica gel (Merck, 70–230 mesh, 10 g for 0.1 mol) using $CHCl_3$ **(3c)**, EtOAc/EtOH (1:1) **(3e)** and EtOAc/EtOH (5:1) **(3f)**, respectively.

3,3-Bis(diethoxyphosphoryl)propionitrile (4):

This compound is prepared in a similar to the typical procedure for **3b** using KCN (0.1 equiv) as the base in EtOH/H_2O (1:1) at 20 °C for 10 min. The product is extracted with $CHCl_3$ and the solvent removed; yield: 75%; bp 134 °C/0.1 Torr.

$C_{11}H_{23}NO_6P_2$	calc.	C 40.37	H 7.08	N 4.28
(327.3)	found	40.54	7.24	4.31

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.4, 15.7, 33.2 ($J_{C,P}$ = 135.4 Hz), 62.9, 116.6.

^{31}P-NMR [$CDCl_3$/H_3PO_4 (85%)$_{ext}$]: δ = 18.9.

Table 1. *gem*-Bisphonates **3a–g** Prepared

Reactant **2**		Reaction Conditions				Product	Yield (%)	bp (°C)/ Torr	Molecular Formula[a]
X	Y	Solvent	Base (equiv)	Temp. (°C)	Time (min)				
a CO_2Et	N=CHPh	EtOH	NaOEt (0.1)	< 10	15	**3a**	85	oil[b]	$C_{21}H_{35}NO_8P_2$ (491.5)
b CO_2Et	CO_2Et	EtOH	NaOEt (0.1)	20	15	**3b**	90	oil[b]	$C_{17}H_{34}O_{10}P_2$ (460.4)
c $(EtO)_2P(O)$	N=CHPh	THF	NaH (1)	20	10	**3c**	65	oil[b]	$C_{22}H_{40}NO_9P_3$ (555.5)
d $(EtO)_2P(O)$	$(EtO)_2P(O)$	THF	NaH (1)	20	10	**3d**	77	120/0.025	$C_{19}H_{44}O_{12}P_4$ (588.4)
e PhCO	H	THF	KOH (0.1)	20	60	**3e**	32	oil[b]	$C_{18}H_{30}O_7P_2$ (420.4)
f $-(CH_2CO)_2$	CH_3	THF	*i*-Pr_2NH (1)	68	90	**3f**	55	oil[b]	$C_{16}H_{30}O_8P_2$ (412.4)
g NO_2	H	THF	*i*-Pr_2NH (1.1)	20	5	**3g**	90	148/0.025	$C_{11}H_{25}NO_8P_2$ (361.3)

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.20.
[b] These compounds are sensitive towards heat and decomposition often occurred before their boiling point.

Table 2. Spectral Data of Compounds **3a–g** and **5a–c**

Compound	^{13}C-NMR ($CDCl_3$/TMS) δ, J (Hz)	^{31}P-NMR ($CDCl_3$)[a], δ
3a	–	22.1, 22.3
3b	15.4, 15.6, 20.0, 31.2, 34.3 ($J_{C,P}$ = 134.1), 60.7, 62.1, 173.6	22.2
3c	–	22.3, 22.4, 25.6
3d	15.6, 21.0, 33.2 ($J_{C,P}$ = 131.8, 6.8), 61.7	22.7
3e	15.7, 27.2, 33.8 ($J_{C,P}$ = 133.5), 43.2, 62.3, 128.1, 128.5, 132.9, 136.0, 201.5	23.0
3f	16.1, 24.6, 30.1 ($J_{C,P}$ = 132.5), 34.1, 54.6, 62.4, 63.6, 214.5	22.7
3g	15.9, 29.8, 33.1 ($J_{C,P}$ = 133.7), 62.6, 84.6	21.2, 21.6
5a	13.4, 15.6, 29.8, 31.9 ($J_{C,P}$ = 135.0), 52.0, 60.2, 61.8, 174.8	23.2, 23.5
5b	15.7, 20.4, 31.9, 34.8 ($J_{C,P}$ = 133.7), 62.2, 172.0	23.1
5c	16.1, 27.0, 31.7 ($J_{C,P}$ = 134.0, 13.2), 46.3 ($J_{C,P}$ = 146.0, 9.8), 62.4	23.4, 23.6, 23.8, 28.1, 28.3

[a] H_3PO_4 (85%) is used as the external standard.

Deprotection of Amino Function: Ethyl 2-Amino-4,4-bis(diethoxyphosphoryl)butyrate (5a); Typical Procedure:
To a solution of **3a** (9.8 g, 20 mmol) in water (25 mL) is added TsOH (4.2 g, 22 mmol) and the mixture is stirred for 30 min at r.t. The mixture is extracted with Et_2O (2 × 15 mL), the aqueous phase is rendered alkaline with sat. $NaHCO_3$ solution (10 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases are dried ($MgSO_4$) and evaporated; yield: 7.6 g (95%); bp 184°C/ 0.025 Torr (Table 2).

$C_{14}H_{31}NO_8P_2$	calc.	C 41.68	H 7.75	N 3.47
(403.4)	found	41.53	7.87	3.38

5c; yield: 70%; mp oil°C (Table 2).

$C_{15}H_{36}NO_9P_3$	calc.	C 38.55	H 7.76	N 3.00
(467.4)	found	38.83	7.84	2.95

4,4-Bis(diethoxyphosphoryl)butanoic Acid (5b):
To a solution of **3b** (9.25 g, 20 mmol) in THF (20 mL) is added a solution of KOH (2.24 g, 40 mmol) in water (5 mL) at 15°C. The mixture is stirred for 15 h at r.t. and the THF is evaporated under reduced pressure. The residue is redissolved in a solution of sat. $KHSO_4$ (10 mL) and extracted with EtOAc (3 × 15 mL). The organic phase is dried ($MgSO_4$) and the solvent evaporated to give the diacid as an oil. This is heated at 130°C for 3 h to afford the desired product **5b**; yield: 5.3 g (65%); bp 208°C/0.025 Torr.

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