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Bisphosphonic Compounds VIII. A Facile and Selective One-Pot Synthesis of P,P-Dialkyl (Dichloromethylene)bisphosphonate Partial Esters

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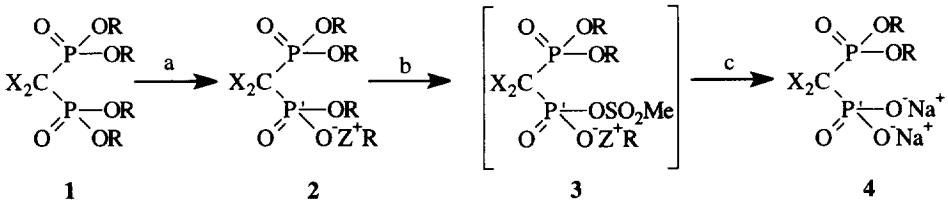
Abstract: The preparations of P,P-dialkyl partial esters of (dichloromethylene)bisphosphonic acid from readily available tetraesters with good selectivity and purity have been developed.

Methylenebisphosphonates (MBP), containing a stable P-C-P bridge, are widely used for the treatment of bone formation and resorption disorders.[1] Recently, these well tolerated MBP compounds have been accepted to use also as drugs to osteoporosis.[2] MBP tetraesters, acids and their salts have been widely studied in order to modify their biological properties by varying the substituents at the bridging carbon.[1] Clodronate, Cl_2MBP, which is one of the best documented and tolerated MBP derivative is, like the other tetraacidic MBP compounds too polar leading to a compact binding of drug to bone surface, and its therapeutic index is narrow and bioavailability is low as well.[3] One obvious solution to less acidic derivative is to modify the phosphorus ends by preparing partial ester (PE) derivatives of MBP. Several X_2MBP PEs[4,5] have been prepared and some biological activity information is already available for these PE compounds.[6]

In our previous studies we have developed selective synthetic procedures for preparing tri- and P,P'-dialkyl X_2MBP PEs from tetraesters using tertiary and secondary amines as dealkylating reagents with high yields.[4] Also a general procedure to synthesise all kind of PEs but methyl esters *via* silyl derivatives has been published. Unfortunately, this method requires the suitable mixed tetraesters as starting point being tediously prepared from monophosphorus species.[5] Now we report a new, selective and easy one-pot procedure to make P,P-dialkyl PEs from readily available Cl_2MBP tetraalkylesters.

All the tetraalkyl Cl_2MBP starting materials **1**[7] and the ammonium salts **2**[1] were prepared using the methods described earlier. Tetramethyl Cl_2MBP (**1a**) reacted with tributylamine in dry CH_3CN as cosolvent quantitively to mono N,N,N-tributyl-N-methyl ammonium salt without any impurities, but with the other tetraesters less bulkier tertiary amines were required until the amount of triester had reached a maximum. Tetraethyl ester **1d** reacted rapidly with pyridine to triethyl partial ester, but the more hindered isopropyl derivative **1c** required an excess of amine and had to be heated under reflux for 3.5 h. The only impurities with

the other tetraesters were the unreacted starting material and overreacted P,P'-diester, but these by-products were removed during crystallization.



Scheme 1. Synthesis of P,P-dialkyl (dihalomethylene)bisphosphonate partial ester from tetraesters. a) NBu_3 or pyridine (=Z); b) CH_3SO_2Cl; c) $NaHCO_3$ or NaOH.

Treating the arised triester **2** with a small excess of mesyl chloride in dry acetonitrile only a single product was obtained. The structure of the formed sulphonic mixed "anhydride" **3** was confirmed from ^{31}P NMR spectra by comparing the chemical shifts to the corresponding silyl derivatives[5] and from proton coupled ^{31}P spectra in which one phosphorus contains two alkoxy groups while the other remains a doublet. After solvent evaporation the unseparated **3** is treated with aqueous base in acetone and the crystalline precipitate **4** is obtained without any phosphorus containing impurities. Methyl derivative **3a** is treated with $NaHCO_3$ because one of the P-C bonds is cleaved easily under more basic conditions while bulkier PEs were resistant to higher pH. We also tried to prepare corresponding Br_2MBP analogues with poor success, since hydrolysis of mesyl group from **3b** was very slow due to less electronegative bromine in the middle carbon and a complicated mixture of different Br_2MBP compounds were obtained.

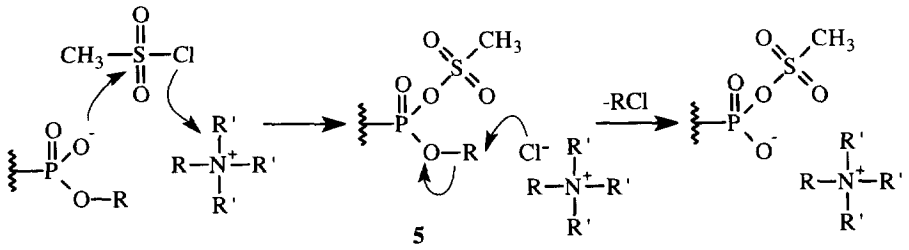
Table 1. Preparation of X_2MBP P,P-dialkyl Esters from X_2MBP Tetraesters.[8]

Starting				Reaction step			Yield	Purity
material	X	R	Z	a	b	c	a-c [%]	[mol-%]
1a	Cl	Me	Bu_3N	50°/30 min	Refl/20 min	r.t./48h	72	98
1b	Br	Me	Bu_3N	50°/30 min	Refl/20 min	r.t./48h	15	[a]
1c	Cl	Pr^i	Pyridine	refl./3.5h	Refl./30 min	r.t./30 min	60	100
1d	Cl	Et	Pyridine	120°/15 min	Refl./30 min	r.t./30 min	65	97
1e	Cl	Hex	Pyridine	120°/1 h	Refl./30 min	r.t./30 min	33	99

a) According to ^{31}P NMR spectrum a complicated mixture of Br_2MBP derivatives.

The reaction mechanism of the selective P,P-didealkylation of X_2MBP tetraester is somewhat surprising, but can tentatively be rationalized as depicted in Scheme 2. Ammonium cation R_4Z^+, obtained after the cleavage of the first alkyl group by tertiary amine, possess a very powerful electron withdrawing effect and the reaction of mesyl chloride is most likely started by attaction of chlorine to the ammonium group while the mesyl part converts regiospecifically the triester salt into tetrasubstituted intermediate **5** in which the oxygen-carbon bond of the second same side alkoxy group is additionally weakened due to the electron withdrawing $MeSO_2$-moiety.

The proximal quaternary ammonium group with chloride as the counter anion facilates the cleavage of PO-R-bond immediately after the formation **5** on the same phosphono-side leading to formation of alkyl chloride. According to NMR results alkyls in quaternary nitrogen remain untouched and alkyl chloride is formed from the alkoxy group bound to phosphorus. More over, if RZ^+ is replaced *e.g.* by proton, the trialkyl ester structure remains.



Scheme 2. Proposed mechanism for the formation of P,P-dialkyl X_2MBP PEs.

The progress of the reactions was followed using ^{31}P NMR spectroscopy and the purity of the products was also analysed from ^1H NMR spectra using H_3PO_4 or TMS as chemical shift standard. The multiplicity of the ^{31}P signals offered an unambiguous method to assign the numbers and the types of alkyls in each phosphorus atom. Also the $^1J_{CP}$ couplings were informative being approximately 150 Hz for $P(O)(OR)_2$ and 110 Hz for $P(O)(OZ)_2$ fragments.

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8. Preparation of the compounds and product analyses. NMR: Bruker AM 400 WB, ^{31}P, ^{13}C and ^1H at 161, 101 and 400 MHz. Elemental analyses: Univ. of Joensuu, Dept. Chem.

   4a: Tetraester **1a** (12.3 g, 41.1 mmol), acetonitrile (200 ml) and tributylamine (7.6 g, 41.1 mmol) were refluxed for 30 min. Mesyl chloride (6 g, 52.4 mmol) was added and the mixture was refluxed for 20 minutes followed by evaporation to constant weight. Saturated $NaHCO_3$ solution (200 ml) was added to

the residue and allowed to react 48 h at 20°C. Acetone (200 ml) was added and the mixture was cooled overnight at 0°C followed by filtration, washing the white resipitate with acetone and dried under vacuum. **3a**: NMR (dry $CDCl_3$): δ_P 13.12 d+sep ($^2J_{PP'}$=20.3 Hz, $^3J_{PH}$=10.7 Hz), -2.42 d. **4a**: NMR (D_2O): δ_P 19.32 ($^2J_{PP}$=14.3 Hz, $^3J_{PH}$=10.2 Hz), 6.86 d; δ_H 3.77 (6H, d); δ_C 78.48 d+d ($^1J_{CP}$=151.6 Hz, $^1J_{CP'}$=110.5 Hz), 58.94 q+d ($^1J_{CH}$=148.0 Hz, $^2J_{CP}$=7.4 Hz). Anal. Calcd for $C_3H_6Cl_2O_6P_2Na_2$: C, 11.37; H, 1.91. Found: C, 11.21; H, 1.93.

4b: Prepared as **4a** from $Br_2C[P(O)(OMe)_2]_2$. **3b**: NMR (dry $CDCl_3$): δ_P 12.99 d+sep ($^2J_{PP'}$=15.7 Hz, $^3J_{PH}$=10.6 Hz), -2.82 d. **4b**: See table 1.

4c: Tetraester **1c** (30.0 g, 72.6 mmol) and pydine (90 ml) were refluxed for 3.5 h and the excess of pyridine was evaporated. Dry acetonitrile (40 ml) and mesyl chloride (5.6 ml, 72.4 mmol) were added to the residue and refluxed 30 min. Solvent was evaporated and the remaining brown oil was dissolved into acetone (100 ml), cooled to +10°C and 2M NaOH solution (66 ml) was added at this temperature followed by evaporating the mixture to constant weight. The brown residue was suspended into acetone and filtrated several times untill white crystals were afforded (23.7 g, 87%). The crude product was recrystallised from water-ethanol (25/125 ml). **3c**: NMR (dry $CDCl_3$): δ_P 7.79 d+t ($^2J_{PP}$=23.3 Hz, $^3J_{PH}$=6.4 Hz), -1.45 d. **4c**: NMR information as in Kivikoski, J.; Garcia-Ruiz, J.M.; Vepsäläinen, J.; Higes, F.; Pohjala, E.; Välisaari, J. *J. Phys. D Appl. Phys.* **1993**, *26*, B172.

4d: Prepared from tetraester **1d** as **4c**. **3d**: NMR (dry $CDCl_3$): δ_P 9.71 d+qv ($^2J_{PP}$=23.4 Hz, $^3J_{PH}$=7.8 Hz), -1.52 d. **4d**: NMR information as in ref. 5.

4e: Prepared from tetraester **1e** as **4c**. **3e**: NMR (dry $CDCl_3$): δ_P 9.56 d+qv ($^2J_{PP'}$=22.3 Hz, $^3J_{PH}$=7.3 Hz), -1.97 d. **4e**: NMR information as in ref. 5.

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