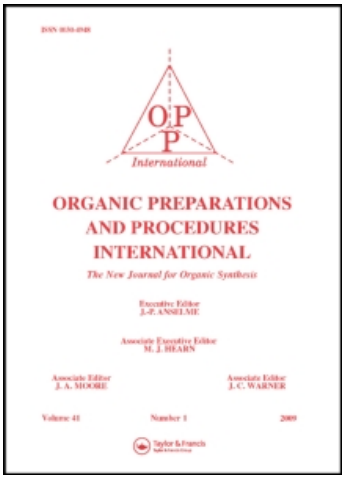

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A RAPID SYNTHESIS OF DIISOPROPYL 4-(CHLOROMETHYLBENZYL) AND 4-(BROMOMETHYLBENZYL) PHOSPHONATES

Bernard Moreau[a]; Paul-Alain Jaffrès[a]; Didier Villemin[a]
[a] Ecole Nationale Supérieure d'Ingénieur de Caen, Université de Caen, ISMRA, équipe arsociée au CNRS UMR 6507, Caen, France

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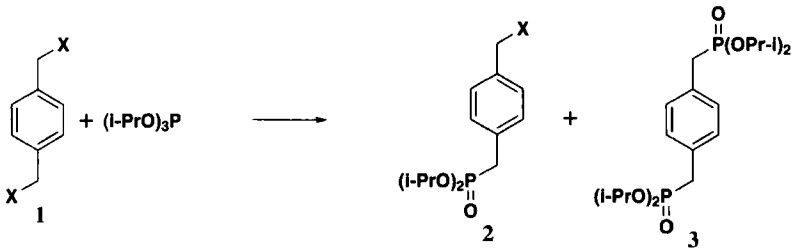
A RAPID SYNTHESIS OF DIISOPROPYL 4-(CHLOROMETHYLBENZYL) AND 4-(BROMOMETHYLBENZYL) PHOSPHONATES

Submitted by (12/06/01)

Bernard Moreau, Paul-Alain Jaffrès and Didier Villemin*

Ecole Nationale Supérieure d'Ingénieur de Caen,
Université de Caen, ISMRA, équipe associée au CNRS
UMR 6507, 6 Bd du Maréchal Juin, F-14050 Caen, FRANCE

Our interest in the synthesis of 4-(chloromethylbenzyl) and 4-(bromomethylbenzyl) phosphonic acids esters **2** stems from their possible use for the preparation of mixed metal-phosphonate materials[1] which generally possess a layered structure.[2] The use of these esters in the synthesis of such materials could offer hybrid organic-inorganic materials possessing a halomethyl group in the interlayer space as found in Merrifield resins.[3] Such materials should have better thermal stability and larger porosity than the classical Merrifield resin. The diethyl ester of 4-(chloromethylbenzyl) phosphonic acid had been obtained by Bigge *et al.*[4] in poor yield (20-25%) by the Michaelis reaction of sodium diethyl phosphite with α,α'-dichloro-*p*-xylene. The dimethyl ester of 4-(bromomethylbenzyl) phosphonic acid was prepared by Baczco *et al.*[5] from *p*-methylbenzyl bromide as the substrate *via* an Arbuzov reaction, followed by radical bromination; although the overall yield is good (52%), the presence of polybromination side-products makes purification of the product difficult.



a) X = Cl b) X = Br

In order to prepare **2a** or **2b** on a large scale using a simple work-up, we decided to use the Arbuzov reaction of α,α'-dihalo-*p*-xylene with triisopropyl phosphite. The formation of **2a** and **2b** is favored by the use of an excess of α,α'-dihalo-*p*-xylene and these esters were obtained in 91% and 86% yields respectively, by using a three-fold-excess of the dihalo-*p*-xylene. The reaction was carried out under a nitrogen atmosphere in dry toluene in order to avoid side-reactions, such as oxidation of triisopropyl phosphite or formation of diisopropyl phosphite.[6]. The separation of **2a** or **2b** from **3**, the major side-product of this synthesis, was readily achieved by distillation under vacuum. The most interesting feature of this direct route to these compounds is that the excess of α,α'-dihalo-*p*-xylene was easily recovered near quantitatively. Indeed, phosphonates **2a** and **2b** are soluble in methanol, whereas α,α'-dihalo-*p*-xylenes are poorly soluble. Although the diethyl esters could be obtained under similar conditions with triethyl phosphite, it might not be possible to separate the products easily.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded at 250 MHz and 62.9 MHz respectively, with TMS as an internal standard; ^{31}P NMR spectra at 101.25 MHz, and H_3PO_4 as an extern standard, in $CDCl_3$. Melting points were determined on a Kofler apparatus and are uncorrected. Tri-isopropyl phosphite, α,α'-dichloro-*p*-xylene and α,α'-dibromo-*p*-xylene were purchased from Acros.

4-(Chloromethylbenzyl)phosphonic Acid Diisopropyl Ester (2a).- Triisopropyl phosphite (3.5 ml, 13 mmol) was added slowly to α,α'-dichloro-*p*-xylene (7 g, 40 mmol) in dry toluene. The mixture was stirred for 42 h at reflux under nitrogen. Toluene was removed under vacuum and then methanol (40 mL) was added. The precipitate [the excess of α,α'-dichloro-*p*-xylene (5 g)] was collected and washed with methanol (10 mL). The filtrate was evaporated and the resulting oil (4.2g) was purified by distillation under vacuum. The product (**2a**) was obtained as a colorless liquid (3.15g, 91%), bp. 130° (4 mm Hg).

Anal. Calcd for $C_{14}H_{22}ClO_3P$: C, 55.18; H, 7.28. Found: C, 55.20; H, 7.31

^1H NMR: δ 1.17 and 1.28 (2d, 12H, $^3J_{HH}$ = 6.1 Hz, O-CH(C**H**$_3$)$_2$), 3.1 (d, 2H, $^2J_{HP}$ = 21.8 Hz, C**H**$_2$-

P(O)), 4.56 (s, 2H, C**H**$_2$-Cl), 4.59-4.67 (m , 2H, O-C**H**(Me)$_2$), 7.27-7.34 (m, 4H, Ar**H**). ^{13}C NMR: δ 24.18 and 24.42 (2d, $^3J_{CP}$ = 4 Hz, O-CH(**C**H$_3$)$_2$), 34.94 (d, $^1J_{CP}$ = 139.5 Hz, **C**H$_2$-P(O)), 46.34 (-**C**H$_2$-Cl), 71.0 (d, $^2J_{CP}$ = 7 Hz, O-**C**H), 129.0 (d, $^4J_{CP}$ = 3.2 Hz, **C**$_2$ and **C**$_6$), 130.58 (d, $^3J_{CP}$ = 6.4 Hz, **C**$_3$ and **C**$_5$), 132.8 (d, $^2J_{CP}$= 9 Hz, **C**$_4$), 136.35 (d; $^5J_{CP}$ = 3.6 Hz, **C**$_1$). ^{31}P NMR: δ 25.6. Mass m/z (%) : 305 (M$^+$+1, 11); 304 (M$^+$, 5); 269 (M$^+$- Cl, 27.5); 226 (269 - C_3H_7, 32); 186 (269 -(C_3H_7 +C_3H_6), 71); 185 (269 - 2 C_3H_6, 61); 167 (185 - H_2O, 26); 139 (43); 104 (185 - PO_3H_2, 100); 43 (C_3H_7, 28).

4-(Bromomethylbenzyl)phosphonic Acid Diisopropyl Ester (2b).- The product was prepared under similar conditions from triisopropyl phosphite (0.9 g, 3,89 mmol) and α,α'-dibromo-*p*-xylene (3.06 g, 11.6 mmol) under reflux for 15 h. The product **2b** was obtained as a colorless liquid (1.16g, 86%), bp. 205-206° (12 mmHg).

Anal. Calcd for $C_{14}H_{22}BrO_3P$: C, 48.15; H, 6.35. Found: C, 48.14; H, 6.28.

^{1}H NMR: δ 1.16 and 1.27 (2d, 12H, $^3J_{HH}$ = 6.2 Hz, O-CH(**C**H$_3$)$_2$), 3.09 (d, 2H, $^2J_{HP}$ = 21.8 Hz, **C**H$_2$-P(O)), 4.47 (s, 2H, **C**H$_2$-Br), 4.54-4.66 (m, 2H, O-C**H**(CH$_3$)$_2$), 7.25-7.35 (m, 4H, Ar**H**). ^{13}C NMR: δ 23.90 and 24.14 (2d, $^3J_{CP}$ ≈ 4.Hz, O-CH(**C**H$_3$)$_2$), 33.43 (**C**H$_2$-Br), 34.67 (d, $^1J_{CP}$ = 140.Hz, **C**H$_2$-P(O)), 70.72 (d, $^2J_{CP}$ = 7.1 Hz, O-**C**H(CH$_3$)$_2$), 129.19 (d, $^4J_{CP}$ = 2.7 Hz, **C**$_2$ and **C**$_6$), 130.37 (d, $^3J_{CP}$ = 2.7 Hz, **C**$_3$ and **C**$_5$), 132.56 (d, $^2J_{CP}$ = 9.0 Hz, **C**$_4$), 136.38 (d, $^5J_{CP}$ = 4.5 Hz, **C**$_1$). ^{31}P NMR: δ 24.2. Mass m/z (%) : 349 and 351(M$^+$+1, 0.8 and 0.7); 348 and 350 (M$^+$, 1.2 and 1.1); 291 and 293 (M$^+$- C_3H_5O, 3 and 2.2); 269 (M$^+$- Br, 100); 227 (269 - C_3H_6, 23.3); 185 (269 - 2 C_3H_6, 58.8); 167 (185 - H_2O, 11.6); 104 (185 - PO_3H_2, 16.1); 43 (C_3H_7, 26.7).

α,α'-*p*-Xylenediphosphonic Acid Tetraisopropyl Ester (3) obtained (0.43 g, 9%) as a second fraction, bp.153-155° (4 mm Hg). Upon standing, it solidified as a white solid, mp. 104°, lit[7]. 94 - 95°. ^{1}H NMR: δ 1.10 and 1.19 (2d, 24H, J_{HH} = 6.1 Hz, O-CH-(**C**H$_3$)$_2$), 3.0 (d, 4H, J_{HP} = 20.3 Hz, **C**H$_2$-P), 4.48-4.56 (m , 4H, O-C**H**), 7.16-7.2 (m, 4H, Ar**H**). ^{13}C NMR: δ 22.85 and 23.01 (2d, 3*J* CP = 2 Hz, CH(**C**H$_3$)$_2$), 33.38 (d, $^1J_{CP}$ = 140.6 Hz, **C**H$_2$-P), 69.47 (d, $^2J_{CP}$ = 3.3 Hz, O-**C**H), 128.87 (**C**$_{2,3,5,6}$), 129.47 (d, $^2J_{CP}$ = 2.3 Hz, **C**$_1$ and **C**$_4$). ^{31}P NMR: δ 26.0. Mass m/z (%) : 435 (M$^+$+1, 23.3); 434 (M$^+$, 91.8); 308 (M$^+$- 3 C_3H_6, 68.1); 293 (32.5); 270 (M$^+$- (iPrO)$_2$P(O) + H, 100); 266 (M$^+$- 4 C_3H_6, 44.5); 228 (270 - C_3H_7, 62.7); 213 (36.6); 186 (270 - 2 C_3H_6, 62.7); 104 (CH_2-C_6H_4-CH_2, 29.1); 43 (C_3H_7, 29.8). R.N. : [17919-43-6].

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SYNTHESIS OF CALIX[4]ARENE DIAZACROWN CONTAINING *m*-XYLYLENE PHENOL SUBUNIT

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Xiao-Bing Wan, Guo-Yuan Lu*, Zhu Bo, Chuan-Ming Jin, Fang Liu

Department of Chemistry, Nanjing University
Nanjing 210093, P. R. CHINA

Calixcrowns, the combination of calixarene and crown ether, are a novel class of host compounds which have attracted increasing attention because of their increased ability for selective complexation of cations and neutral molecules compared with crown ethers or calixarenes.[1-3] During the past decade various calixcrowns have been synthesized[4-9] and applied as ionophores in extractive processes[8-9] or as selective ligands in ion selective electrodes.[10-12] Apart from the cavity geometry, the nature of donor sites plays an important role in determining complexation selectivity, *i.e.* azacrown ether in which nitrogen atoms are incorporated, was found to be the best liganding agent for transition metal ions.[13] In particular, the complexes of azacrowns containing *m*-xylylene phenol subunits with transition metal ions were extensively investigated as enzyme models for metalloproteins like superoxide dismutase, oxidases, and peptidases.[14-15] However, the studies of calixarene azacrowns in which the azacrown ether moiety is incorporated into the calixarene framework are relatively rare. Only a few papers report the synthesis of calixarene azacrowns, in which calix[4]arene azacrowns containing diamides were prepared by the condensation of 25, 27- dihydroxy-26, 28-*bis*[(carboxy-methyl)oxy]calix[4]arene derivatives (diester or diacid chloride) with various diamines,[16-18] and in which calix[4]arene monoazacrowns were formed by intermolecular ring closure of 25,27-dihydroxy-26,28-*bis*[(chloroethoxy)ethoxy] calix[4]arene with the appropriate amine.[19-20] We now report a novel synthetic method for calix[4]arene diazacrowns in which calix[4]arene diazacrowns **5a-c** containing *m*-xylylene phenol subunits are prepared by $NaBH_4$ reduction of the Schiff bases **4a-c**, obtained from condensation of calix[4]arene diamine **3** with 2,6-diformyl-4-substituted phenols **6a-c** under high dilution in refluxing anhydrous ethanol (*Scheme 1*). The calix[4]arene diamine **3** was easily obtained *via* a two-step synthesis in which *p*-tetra-*tert*-butyl