A Facile Synthesis of Triphosphine Macrocycles, [12]aneP$_3$R$_3$(R=H, CH$_3$) by Template Reaction

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Received October 27, 1993

Macrocyclic compounds have been intensively studied and played an important role in the field of coordination chemistry, electrochemistry, biochemistry or catalysis. Considerable advances have been made in the preparation of oxygen, nitrogen and sulfur containing compounds but less progress has been made in the preparation of phosphorus containing ligands. For many syntheses involve multistep reactions accompanying low yields that are common in phosphorus chemistry.[1-4]

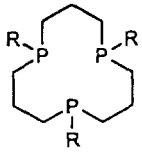
Numerous examples of acyclic polyphosphine ligands have been reported for last two decades.[5-7] In contrast a few examples of cyclic polyphosphine macrocycles have been reported.[8-10] In this communication, we report a facile synthesis of triphosphine macrocycles *via* metal template reaction (Scheme 1).

fac-{[12]aneP$_3$H$_3$}Mo(CO)$_3$, ([12]aneP$_3$H$_3$=12-cyclophosphinoalkane(II) was anaerobically[11] prepared by modifided Norman's procedure[12] in which (cht)Mo(CO)$_3$, (cht=cycloheptatriene)[13] was reacted with allylphosphine. In this study, however, allylphosphine has been prepared in the yield of up to 90% by reduction of allylphosphonate with AlHCl$_2$.[14] *fac*-[12]aneP$_3$(CH$_3$)$_3$Mo(CO)$_3$(III) was obtained by alkylation of *fac*-[12]aneP$_3$H$_3$Mo(CO)$_3$ with *n*-BuLi and methyl iodide in THF.

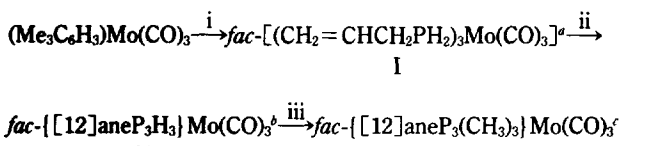
The ^{31}P-NMR spectrum of *fac*-[12]aneP$_3$(CH$_3$)$_3$Mo(CO)$_3$ consists of a single resonance with a chemical shift characteristic of coordinated tertiary phosphines. The occurrence of a singlet resonance is consistent with the formation of a facial complex. Furthermore, the presence of such a singlet indicates that the action of *n*-BuLi results in the deprotonation of all three secondary phosphine substituents leading to a tritertiary phosphine complex rather than to the products that would be expected to have arisen from deprotonation of just one (or possibly two) of the phosphines.

The ^{1}H-NMR spectrum of *fac*-[12]P$_3$(CH$_3$)$_3$Mo(CO)$_3$ shows three distinct resonances owing to the methyl group and two sets of different 1,3-propandiyl (backbone) protons. The IR spectra of *fac*-[12]aneP$_3$(CH$_3$)$_3$Mo(CO)$_3$ shows characteristic absorbances of *fac*-tris(phosphine)molybdenum tricarbonyl complexes.

Reaction of NaOH with *fac*-[12]aneP$_3$R$_3$Mo(CO)$_3$ followed by treatment of the systems with LiAlH$_4$ to reduce P(V) species back to phosphines produced triphosphine macrocycles [12]aneP$_3$R$_3$ in low yields. *fac*-[12]aneP$_3$R$_3$Mo(CO)$_3$ (R=H (II), CH$_3$(III)) was refluxed (17 hours) in sodium hydroxide solution (30%, 20 mL) and the resulting solution was transferred to a cold (0℃) solution of LiAlH$_4$ (3.01 g, 0.08 mole) in THF (45 mL). The reaction mixture was refluxed for 14 hours. The excess reducing agent was hydrolysed by the dropwise addition of water, 10% sodium hydroxide solution and water. The organic component was extracted with petroleum ether (3×15 mL) and diethyl ether. The solution was dried over potassium hydroxide pellets, filtered and the filterate was evaporated (0.1 mmHg) to leave yellow, viscous, and air-sensitive liquid product [12]aneP$_3$R$_3$ (R=H, IV; CH$_3$, V).



R = H(IV), CH$_3$(V)



i=$C_3H_5PH_2$, toluene
ii=AIBN, 90℃, toluene
iii=3*n*-BuLi, $CH_3I/N_2(l)$ in ether
iv=NaOH/$LiAlH_4$

^{a}*fac*-{$(C_3H_5PH_2)_3$Mo(CO)$_3$(I). air-sensitive liquid, Yield: 95% (based on molybdenum), ^{31}P{^{1}H} NMR (CH_2Cl_2, internal D_2O lock) spectrum: δ −59.10 ppm, ^{1}H-NMR ($CDCl_3$): 5.98 (m, 1H), 5.14 (d, 1H), 5.02 (d, 1H), 4.58 (q, 1H), 3.71 (q, 1H), 2.58 (t, 2H). ^{b}*fac*-[12]aneP$_3$H$_3$MO(CO)$_3$(II), Yield: 96% (based on molybdenum), Elemental Analysis: C 35.46 (35.84), H 4.98 (5.27); ^{31}P-NMR spectrum ($CDCl_3$): δ-32.41 ppm, ^{1}H-NMR ($CDCl_3$): 4.24 (t, 1H), 1.84 (d, 4H), 1.51 (d, 2H). ^{c}*fac*-[12]aneP$_3$(CH$_3$)$_3$Mo(CO)$_3$(III). Yield: 46%, Elemental Analysis: C 40.11 (40.55), H 5.64 (6.14); ^{1}H-NMR ($CDCl_3$): 1.73 (d, 4H), 1.42 (s, 3H), 1.04 (d, 2H), ^{31}P{^{1}H} NMR (CH_2Cl_2, internal D_2O lock): −4.04 ppm, IR spectrum: 3012 (w), 2968 (w), 2958 (w), 1968 (s), 1872 (s), 1601 (w), 1473 (m), 1452 (w), 1383 (w), 1341 (m), 1173 (m), 1090 (s), 863 (m), 823 (w), 732 (w), 678 (m), 524 (m), 498 (w). ^{d}[12]aneP$_3$H$_3$(IV). Yield: 36%, ^{1}H-NMR spectrum ($CDCl_3$): 3.42 (q, 1H), 1.91 (d, 4H), 1.14 (d, 2H); ^{31}P{^{1}H} NMR ($CDCl_3$): −67.21 ppm ($^1J_{P-H}$=196 Hz). Mass spectrum: m/e=223 (M^+). IR spectrum (neat film): 2960 (m), 2940 (m), 2295 (m), 1720 (s), 1600 (m), 1490 (s), 1450 (s), 1400 (w), 1380 (w), 1300 (w, br), 1200 (m, br), 1050 (m, br), 890 (s), 860 (m), 800 (s), 760 (m), 500 (s), 430 (m, br). ^{e}[12]aneP$_3$(CH$_3$)$_3$(V). Yield: 46%, ^{1}H-NMR ($CDCl_3$): 1.97 (d, 4H), 1.74 (s, 3H), 1.21 (d, 2H); ^{31}P{^{1}H} NMR (C_6H_6): −47.48 ppm. Mass spectrum: m/e=264 (M^+). IR spectrum (neat film): 3010 (w), 2960 (w), 2940 (w), 1710 (m), 1586 (s), 1490 (m), 1450 (m), 1402 (w), 1380 (w), 1300 (w, br), 1216 (s), 890 (w), 850 (m, br), 798 (m), 761 (m), 502 (s), 430 (m).

Scheme 1.

The compounds (**IV**) and (**V**) were isolated by reaction of their molybdenum complexes with sodium hydroxide and $LiAlH_4$ and characterized by ^1H and ^{31}P-NMR spectroscopies and mass spectrometry. The ^{31}P-NMR spectra of (**IV**) and (**V**) consist, in each case, of one resonance of virtually singlet peak indicating the magnetic equivalence of the phosphine groups. The ^1H and ^{13}C-NMR spectra of (**IV**) and (**V**) consist of distinctively characteristic resonances (all complex multiplets) whose assignments were made by considering chemical shift and to the ratio of the intensities. The ^1H-NMR spectrum of each compound shows resonances that are consistent with the magnetic equivalence of the backbone α-protons $PC\underline{H}_2CH_2C\underline{H}_2P$ which are mutually inequivalent to the β-protons ($PCH_2C\underline{H}_2CH_2P$). In addition, the remaining substituents of phosphines, P-R (R=H, Me), were all magnetically equivalent. The compounds (**IV**) and (**V**) were studied by mass spectrometry; in both cases, the molecular ions were observed.

Acknowledgement. The present study was supported by a grant from the Basic Science Research Institute Progarm, Ministry of Education, Korea, 1993.

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Synthesis of Symmetrically α-*N*-Functionalized Piperazine-2,5-diones

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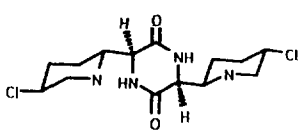
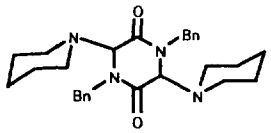
Received December 17, 1993

Piperazine-2,5-diones are one of the most important classes of peptides found in nature[1] and constitute a large class of organic substances that are formally derived by the removed of two molecules of water from two amino acid derivatives.[2] During the course of our synthetic model studies on the anti-tumour antibiotic agent DKP 593-A, **1**[3], we found that 1,4-dibenzyl-3,6-bis(piperidyl)-piperazine-2,5-dione, **2**, can be easily prepared from glycine anhydride. Surprisingly, this compound was stable as a number of its analogues.



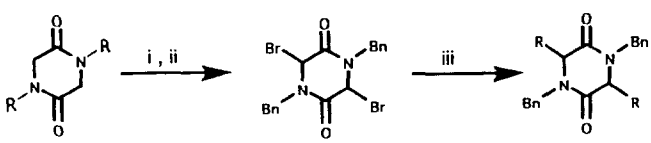
1



2

The compound **2** is of particular interest for QSAR (Quantitative Structure-Activity Relationship) study since its structure is quite similar to that of **1**. Synthetic approachs to monoaryl or alkylidene derivatives have been reported for α-carbon[4], α-oxygen[5] or α-sulfur[6] functionalized piperazine-2,5-dione derivatives. However synthetic studies of symmetrically *N*-functionalized piperazine-2,5-diones have received very little attention. In this paper, we wish to report a facile approach to α-*N*-functionalized piperazine-2,5-diones that features the nucleophilic reaction of a variety of amines with 1,4-dibenzyl-3,6-bis(bromo)-piperazine-2,5-dione in the presence of NaH.

As shown in Scheme 1, commercially available glycine anhydride, **3**, was treated with NaH/benzylbromide to afford *N,N'*-dibenzyl piperazine-2,5-dione, **4**. Bromination was accomplished by treating **4** with NBS/benzoyl peroxide.[7] Treatment of the secondary amines such as piperidine(a), pyrrolidine(b), *N*-methylpiperazine(c), imidazole(d), and morpholine (e) with 2,2 equiv. of sodium hydride at 0℃ generated sodium metallated nitrogen anions which were reacted with dibromide, **5**, to give the corresponding coupled products **6a-**



3 (R=H)
4 (R=Benzyl)

5

6

Scheme 1. Reagents and conditions; (i) NaH, DMF, BnBr, 0℃; (ii) NBS, CCl_4, $(PhCOO)_2$, 60℃ (iii) amines, NaH, THF.