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Synthesis of New Aza-thiophosphinate Ligands

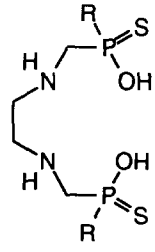
Morag A.M. Easson and David Parker*

Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK.

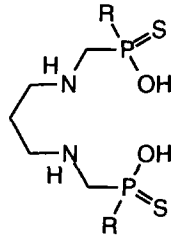
Abstract : A series of new tetradentate, acyclic ligands incorporating thiophosphinate functionalities has been synthesised with regard to the potential application of their complexes with metal radionuclides for diagnostic imaging. © 1997 Elsevier Science Ltd.

An important aspect of clinical imaging techniques involves the use of complexed gamma or positron-emitting radionuclides. e.g. ^{99m}Tc (γ, $t_{1/2}$ = 6.02 h, 141 keV) for Single Photon Emission Tomography (SPET) and ^{62}Cu (β^+,$t_{1/2}$ = 9.74 min, 1.315 MeV) for Positron Emission Tomography (PET).[1] Ligand systems with nitrogen and sulfur donor atoms are particularly suitable for these diagnostic applications.[2] Low molecular weight metal complexes may be tailored so that they are charge neutral and sufficiently lipophilic to allow them to penetrate the blood-brain barrier and be screened for use for brain imaging.[3]

A new class of ligands has been synthesised, **1a - d**, featuring an N_2S_2 donor system. This array of donor atoms is particularly attractive because of its 'soft' metal preference, favouring the complexation of radionuclides such as ^{64}Cu (β^+, $t_{1/2}$ = 12.8h, 278 keV) and ^{99m}Tc in diagnostic imaging of disease states, and $^{186/188}Re$ (β^-, $t_{1/2}$ = 90h) in targeted radiotherapy.



1a) R=Ph
1b) R=Me

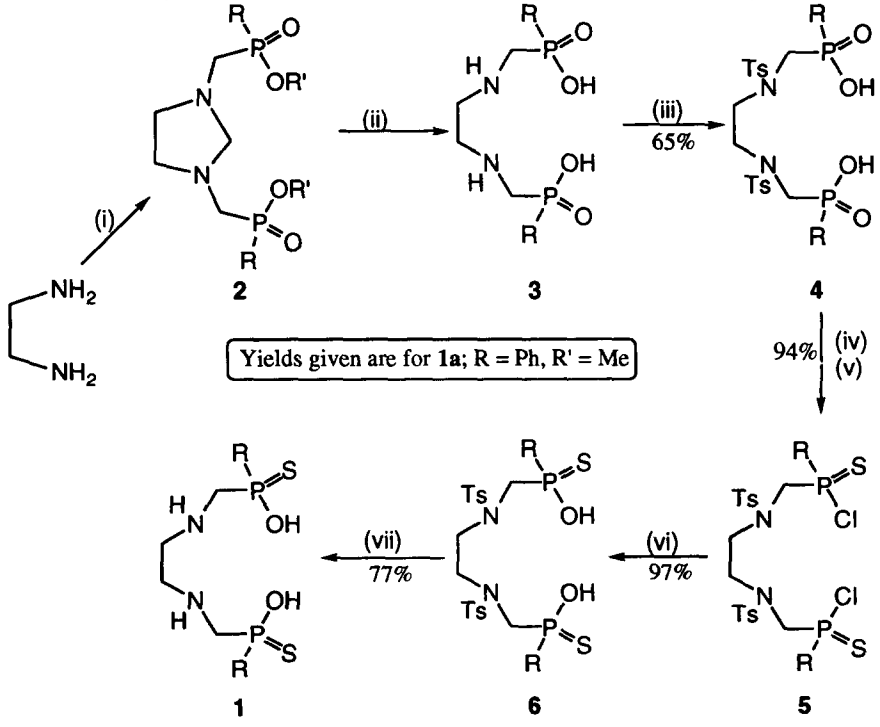


1c) R=Ph
1d) R=Me

In the above ligand series it is possible to vary the lipophilicity of the complex without compromising the metal binding properties. The pentavalency at phosphorus allows control over complex lipophilicity and may afford a means of conjugation to a suitable targeting vector through variation of the phosphorus alkyl or aryl substituents.[4] Thiophosphinic acids are more acidic than their corresponding phosphinic and carboxylic acid analogues (e.g. $Et_2P(O)OH$ pKa = 3.29, $Et_2P(S)OH$ pKa = 2.54,

$Et_2P(S)SH$ pKa = 1.71).[5] This may enhance the stability of the metal complexes with respect to dissociation in acidic media. The set of compounds described herein allows evaluation of the coordination preferences of the ligands. For example, the use of a diaminoethane or diaminopropane moiety allows the effect of a five-membered chelate ring versus a six-membered chelate ring to be assessed with either a P-phenyl or a P-methyl substituent.

Efficacious synthetic routes to such ligands have now been devised. Initial attempts to synthesise **1** involved the treatment of the sulfur-containing P(III) species, PhP(SMe)OMe with the diamine and paraformaldehyde. Such reactions failed to give the desired condensation products. The analogous procedure with substituted dialkoxyphosphines is well known to be an efficient method of synthesising the corresponding phosphinates.[6] The successful method of synthesis of **1** therefore relied upon preparation of the analogous phosphinate and subsequent transfer of sulfur to phosphorus, as exemplified by the preparation of **1a** (Scheme 1). The phosphinate ester **2a** was prepared by reaction of diaminoethane with freshly sublimed paraformaldehyde and $PhP(OMe)_2$ in dry tetrahydrofuran.[6] Acid hydrolysis yielded the precursor amino-acid **3a**. Protection of the amine functionalities was effected by tosylation in aqueous sodium hydroxide solution, maintaining the pH around 10, to give **4a**. The toluenesulphonyl groups prevented the nitrogen lone pair from interfering in the subsequent reactions at phosphorus. The phosphinic chloride was formed as a 1:1 mixture of RR/SS and RS diastereoisomers by treatment with oxalyl chloride in dichloromethane. Subsequent exchange of oxygen for sulfur was



Scheme 1 (i) $(CHO)_n$, $RP(OR')_2$, THF (ii) 6M HCl, 100°C (iii) TsCl, $NaOH_{(aq)}$ pH10, 40°C, (iv) $(COCl)_2$, CH_2Cl_2 (v) $PSCl_3$, cat. DMF 110°C (vi) $KOH_{(aq)}$ 100°C (vii) HBr/CH_3CO_2H, phenol, 40°C

achieved by heating in $PSCl_3$ with a catalytic amount of dimethylformamide[7] using a procedure originally reported by Coogan and Harger.[8] The P-Cl bond of **5a** (and **5b** - **d**) showed unexpected stability with respect to hydrolysis and required heating with potassium hydroxide for 16h in order to achieve complete hydrolysis to the thiophosphinic acid **6a**. Detosylation of the ligand to give **1a** required gentle heating at 40°C in HBr/acetic acid in the presence of a ten-fold excess of phenol.[9] Higher temperatures led to C-P bond cleavage while neither treatment with $Na/NH_3/THF/EtOH$ nor the use of samarium (II) iodide[10] led to satisfactory detosylation.

Preparation of the related thiophosphinates **1b**, **c** and **d** was achieved via analogous syntheses employing 1,3-diaminopropane or the dialkylphosphine, $RP(OR')_2$ [R=Ph, R'=Me; R=Me, R'=Et] precursors. The amino-acids **1a** and **1b** precipitated from the HBr/acetic acid reaction mixture as the ligand-dihydrobromide salts, whereas **1c** and **1d** were isolated by precipitation with diethyl ether prior to isolation following centrifugation. The ligands and intermediates gave ^1H, ^{13}C and ^{31}P NMR (Table 1) spectra, mass spectra and elemental analyses consistent with the structures shown.

Table 1 ^{31}P NMR Shifts of **1-6**

δ_P	a	b	c	d
1	62.7(D_2O)	67.5(D_2O)	58.0(D_2O)	63.1(D_2O)
2	40.8($CDCl_3$)	51.5($CDCl_3$)	41.6($CDCl_3$)	52.6($CDCl_3$)
3	27.7(D_2O, pD14)	20.36(D_2O/pD14)	39.5(D_2O/pD14)	40.3 (D_2O, pD14)
4	25.0(D_2O, pD14)	47.7($CDCl_3$)	25.3(D_2O/pD14)	34.7(D_2O, pD14)
5	79.8, 80.2($CDCl_3$)	87.0, 86.8($CDCl_3$)	77.9($CDCl_3$)	85.9($CDCl_3$)
6	58.1, 58.3(D_2O/pD14)	64.3(D_2O/pD14)	59.0(CD_3OD)	86.0, 86.5(D_2O)

In summary, an efficient route to this new class of aza-thiophosphinate ligands has been developed. Metal complexation and radiolabelling studies with radionuclides such as ^{99m}Tc and $^{62/64}Cu$ are now in progress.

REFERENCES AND NOTES

1. Parker, D., 'Imaging and Targeting', *Comprehensive Supramolecular Chemistry,* 'Supramolecular Technology' Vol 10, Ch. 5, Ed. D.N. Reinhoudt, Pergamon **1996**
2. Deutsch, E., Lisbon, K., Jurisson, S., 'Technetium Chemistry and Radiopharmaceuticals', *Progress in Inorganic Chemistry*, Ed. Lippard, J.S., **1983**, 30
3. Green, M.A., PET Imaging with Metal Radionuclides, *Advances in Metals in Chemistry*, **1993**, **1**, p75-114
4. Broan, C.J., Cole, E., Jankowski, KJ, Parker, D., Pulukkody, K., Boyce, B.A., Beeley, N.R.A., Millar, K., Millican, A.T., *Synthesis*, **1992**, 63-68
5. Corbridge, D.E.C., 'Phosphorus: An Outline of its Chemistry, Biochemistry and Technology', 4th Ed., Elsevier, **1990**, ch.4 & 7
6. Bates, G.B.; Cole, E.; Kataky, R.; Parker, D.; *J. Chem Soc. Dalton Trans.*, **1996**, 2693

7. Preparation of ***5a,*** *N,N' bis p-Toluenesulphonyl N,N' bis (methylene phenylthiophosphinic chloride)-1,2-diaminoethane:* The ditosylamide **4a** (2.13g, 3mmol) was dissolved in dry dichloromethane (50ml) and oxalyl chloride (2.5ml) was added. The solution was stirred at room temperature under an inert atmosphere for 20 mins giving the acid chloride (δ_P 46.8 and 47.0). The solvent was removed *in vacuo* and 2 further portions of dichloromethane (25ml) were added and evaporated. The crystalline solid was dried thoroughly *in vacuo*. Excess thiophosphorylchloride (40ml) was added to the solid with a drop of DMF and the reaction mixture was stirred at 110°C for 18 hours. The solvent was removed *in vacuo* and 3 portions of dichloromethane (5ml) were added and removed by evaporation under reduced pressure to give a yellow crystalline solid (2.2g, 94%), m.p. 42-44°C ; ^{31}P NMR (101.26 MHz, $CDCl_3$) (two diastereoisomers observed) δ_P 79.75, 80.16; ^1H NMR (399.96 MHz, $CDCl_3$) δ_H 2.33 (3H, s, Ts-$C\underline{H}_3$), 2.34 (3H, s, Ts-$C\underline{H}_3$), 3.49 (4H, m, $NC\underline{H}_2C\underline{H}_2N$), 4.09 (0.5H, dd, $^2J_{HaHb}$= 5.2 Hz, ^2J_P= 3.2 Hz, $PC\underline{H}_2N$), 4.16 (0.5H, dd, $^2J_{HaHb}$= 15.2 Hz, ^2J_P= 3.2 Hz, $PC\underline{H}_2N$), 4.37 (0.5H, d, $^2J_{HaHb}$= 15.2 Hz, $PC\underline{H}_2N$), 4.51 (0.5H, d, $^2J_{HaHb}$=15.2 Hz, $PC\underline{H}_2N$), 7.17 (4H, m, Ts), 7.44-7.48 (6H, m, $\underline{m}$-$\underline{p}$-Ph), 7.50-7.54 (4H, m, Ts), 7.92 (4H, m, $\underline{o}$-Ph); ^{13}C NMR (62.9 MHz,) δ_C 21.59 (s, Ts-$\underline{C}H_3$), 47.97 (s, $N\underline{C}H_2\underline{C}H_2N$), 57.17 (d, ^1J_P= 107 Hz, $N\underline{C}H_2P$), 58.36 (d, ^1J_P= 107 Hz, $N\underline{C}H_2P$), 127.76 (Ts), 128.65 (d, ^3J= 14 Hz, $\underline{m}$-Ph), 129.80 (Ts), 130.78 (Ts), 132.02 (d, ^1J_P = 24 Hz, Ph), 133.38 (s, $\underline{p}$-Ph), 134.57, (d, ^2J_P= 5 Hz, $\underline{o}$-Ph), 144.92 (Ts); m/z (ESIMS $^-$, MeCN) 744.6 (100%, M^-)

1a *Ethylenediiminodimethylenebis(phenylthiophosphinic acid)* was prepared by adding the ditosylamide **6a** (1.065, 1.5mmol) portionwise to a solution of phenol (1.4g, 15mmol) in 45% HBr in glacial acetic acid (30ml). The mixture was stirred at 40°C for 4 days and the resulting precipitate was separated from the liquor. The solid was washed with portions of ether (4 x 35ml) to remove the remaining phenol and dried to give a pale yellow solid (650mg, 77%); m.p. 183-185°C ; ^{31}P NMR (101.26 MHz, D_2O, pD14) δ_P 62.7; ^1H NMR (250.13 MHz, D_2O, pD14) δ_H 2.09 (4H, s, $NC\underline{H}_2C\underline{H}_2N$), 2.96 (4H, dd, $^2J_{HaHb}$= 12 Hz, ^2J_P= 5.9 Hz, $PC\underline{H}_2N$), 7.49 (6H, m, $\underline{m}$-$\underline{p}$-Ph$\underline{H}$), 7.74-7.82 (4H, m, $\underline{o}$-Ph$\underline{H}$); ^{13}C NMR (62.9 MHz, D_2O, pD14) δ_C 50.98 (d, ^3J_P= 9.7 Hz, $N\underline{C}H_2\underline{C}H_2N$), 57.52 (d, ^1J_P= 77 Hz, $N\underline{C}H_2P$), 131.17 (d, ^2J= 11 Hz, $\underline{o}$-Ph), 133.04 (d, ^3J= 9.1 Hz, $\underline{m}$-Ph), 133.87 (s, $\underline{p}$-Ph), 141.09 (d, ^1J_P= 96.1Hz, Ph), m/z (ESIMS $^-$) 421 (100%, M - $2H^+$ + Na^+); elemental analysis found C, 33.92; H, 4.24; N, 4.81; $C_{16}H_{22}N_2O_2P_2S_2$ .2HBr requires C, 34.18; H, 4.30; N, 4.98 %.

8. Coogan, M.P.; Harger, M.J.P.; *J. Chem. Soc. Perkin Trans. 2*, **1994**, 2101-2107
9. Roemmele, R.C.; Rapoport, H.; *J. Org Chem.*, **1988**, 53, 2367-2371
10. Vedejs, E.; Lin, S.; *J. Org. Chem.*, **1994**, 59, 1602-1603

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