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Synthesis of Heterocyclic Aza-Phosphinate Ligands Based on the Benzimidazole skeleton.

Chris D. Edlin and David Parker*

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

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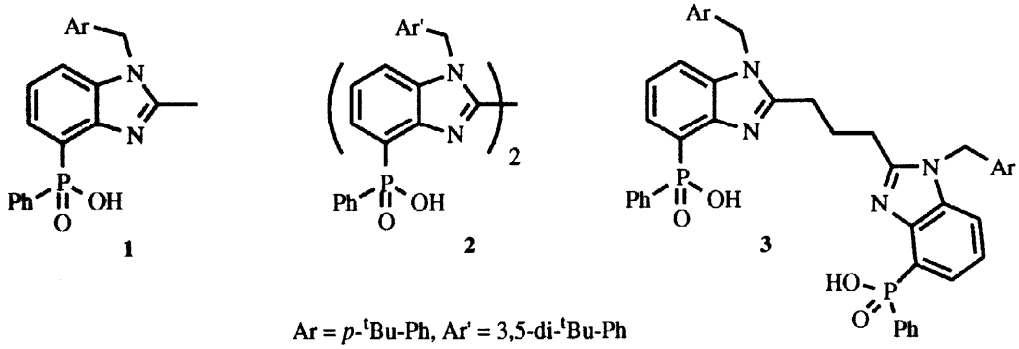
Abstract Three new heterocyclic ligand systems based on the benzimidazole ring system have been designed and synthesised. These ligands have been prepared with a view to the selective coordination of zinc ions in a tetrahedral environment.

Zinc is an important metal ion in biological chemistry, where zinc-protease enzymes are widespread and synthetic analogues are sought for use both as model systems for such enzymes and as sensors for Zn(II) *in vivo*.[1] Another important area is the solvent extraction of metals where lipophilic ligands that bind zinc selectively over other members of the transition metal series are desirable for the hydrometallurgic recovery of the metal.[2] With regard to the latter case, achieving selectivity for zinc presents a significant challenge if the interferent ions are near neighbours in the transition series. The correct choice of donor atom in the ligand can increase the affinity for zinc and upset the usual sequence of complex stability, Ni < Cu > Zn (Irving-Williams series).[3] The ligand architecture can be designed to present a tetrahedral array of donor atoms in ML_2, ML or M_2L_2 complexes, which when coupled with sterically encumbered ligands, should inhibit the formation of undesired octahedral and trigonal bipyramidal coordination geometries.



With these criteria in mind, we have designed a set of ligands based on the benzimidazole moiety (**1** to **3**) which are expected to form ML_2, M_2L_2 and ML complexes respectively with divalent zinc. In all three cases the lipophilicity can be modified by variation of the N-alkyl substituent or by manipulation of the substituents at pentavalent phosphorus.[4] The choice of the phosphinic acid ligating group should

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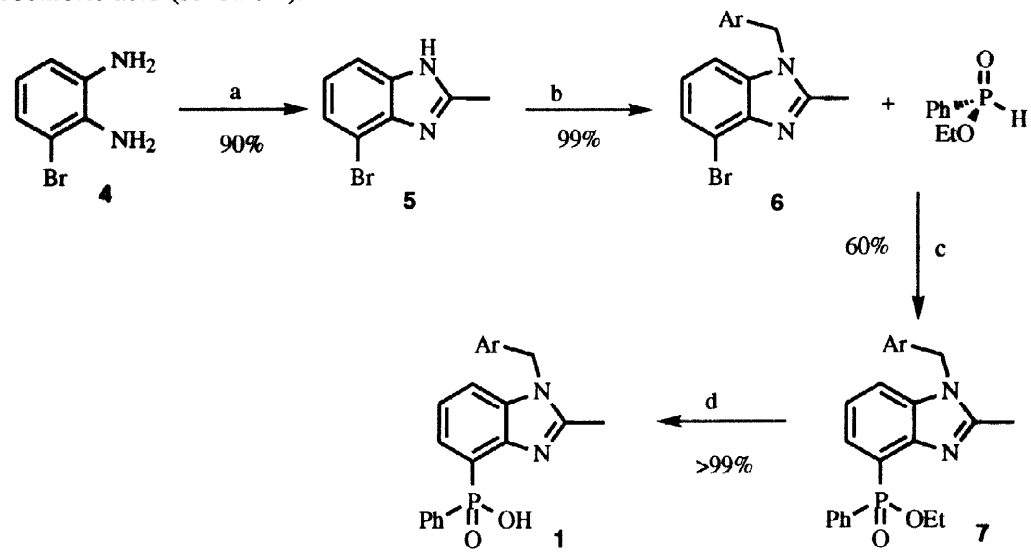
enhance the kinetic stability of the complexes, in acidic media compared to the corresponding carboxylates (c.f. $Et_2P(O)OH$ pKa = 3.29 *vs.* EtC(O)OH pKa = 4.87).[5]

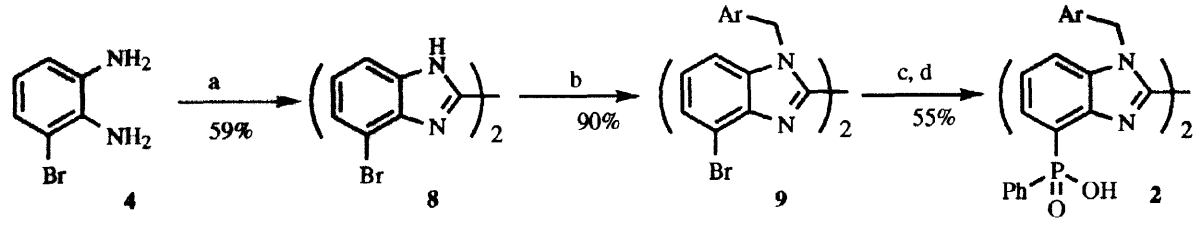
Efficacious routes to ligands **1** to **3** have been devised, with all three systems being derived from 1,2-diamino-3-bromobenzene[6] **4** utilising a versatile palladium catalysed coupling reaction[7] to introduce the phosphinate functionality. Condensation of the diamine **4** with acetic anhydride followed by acid hydrolysis and treatment with activated carbon, gave 2-methyl-4-bromobenzimidazole **5** in 90% yield. N-Alkylation was then affected using 4-*tert*-butylbenzyl bromide in DMF using caesium carbonate as the base to give the alkylated derivative **6** in near quantitative yield. The regiospecifity of this reaction is explained by the bulky bromo substituent at C-4, which directs alkylation to the least sterically hindered nitrogen. Cross-coupling of the N-alkyl-bromo benzimidazole with ethylphenyl phosphonite in toluene with tetrakis(triphenylphosphine)palladium(0) and triethylamine at 130°C[7, 8] gave the 4-ethyl-phenylphosphonate ester **7** in 60% yield following chromatographic separation on neutral alumina. The desired ligand **1** was produced in 53% overall yield based on the diamine following acid hydrolysis in 6M hydrochloric acid (scheme 1).



Scheme 1. a) Ac_2O, 110°C; H_3O^+, 3h, 100°C b) 4-^{t}Bu-benzyl bromide, DMF, Cs_2CO_3,18h, 25°C c) $Pd[PPh_3]_4$ (5 mol%), PhMe, 20h, NEt_3, 130°C d) 6M HCl, 16h, 110°C.

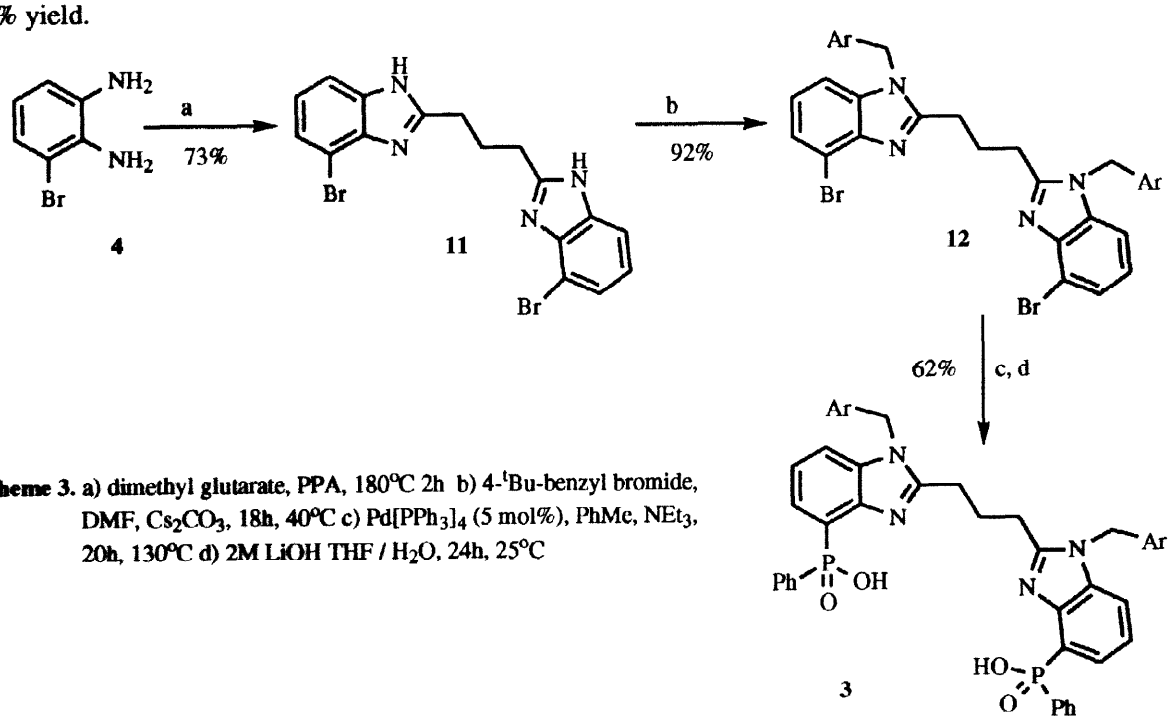
The synthesis of the 2, 2'-bisbenzimidazole bis-phosphinic acid **2** framework was accomplished utilising an existing procedure,[9] involving the coupling of the diamine **4** with a half molar equivalent of methyl trichloroacetimidate, $Cl_3CC(NH)OMe$, in methanol. The reaction was initiated by addition of HCl, however this hindered further reaction and potassium carbonate was subsequently added to complete the reaction yielding the bisbenzimidazole, as its free base **8**, in 59% yield. N-Alkylation was accomplished in a similar manner to the preparation of **6**. In this case a more lipophilic benzylic bromide was employed due to the poor solubility of **8**; reaction of **8** with 3, 5-di-*tert*-butyl benzyl bromide in DMF at 80°C in the presence of Cs_2CO_3 gave the bis-N-alkyl derivative **9** in 90% yield. Palladium [0] catalysed cross-coupling[7, 8] of the bis-bromo compound **9** with ethylphenyl phosphonite in toluene at 130°C gave the bis-phosphonate ester **10** in 55% yield following column chromotography on neutral

alumina. Hydrolysis of **10** with 2M LiOH in aqueous THF (1:10) at room temperature gave the bis-phosphinic acid **2** in 30% overall yield (scheme 2).



Scheme 2. a) $Cl_3CC(NH)OMe$, HCl 3h, then K_2CO_3, 25°C b) 3, 5-di-^{t}Bu-benzyl bromide, DMF, Cs_2CO_3, 18h, 80°C c) $Pd[PPh_3]_4$ (5 mol%), PhMe, NEt_3, 20h, 130°C d) 2M LiOH THF / H_2O, 36h, 25°C

The final ligand system to be addressed was the C-3 spaced bisbenzimidazole **3** whose framework is derived from the diamine **4** and a suitably functionalised glutarate derivative. Various condensation conditions were attempted with the diamine **4** and glutaric acid, dimethyl glutarate and gluataryl chloride. Difficulties were experienced with condensation of diamines possessing electron withdrawing or donating substituents on the aryl ring. However, such reactions have been reported to proceed cleanly and quickly in polyphosphoric acid (PPA) at 180°C,[10] and condensation of the diamine **4** with dimethyl glutarate in PPA at 180°C for two hours gave the product **11** following addition of water and basification (pH 8), in 73% yield. Alkylation of both the N-1 nitrogens was effected in DMF as in the previous examples, using 4-^{t}Bu-benzyl bromide in the presence of Cs_2CO_3 to give the bis-alkylated product **12** in 92% yield.



Scheme 3. a) dimethyl glutarate, PPA, 180°C 2h b) 4-^{t}Bu-benzyl bromide, DMF, Cs_2CO_3, 18h, 40°C c) $Pd[PPh_3]_4$ (5 mol%), PhMe, NEt_3, 20h, 130°C d) 2M LiOH THF / H_2O, 24h, 25°C

Cross-coupling of **12** with two equivalents of ethylphenyl phosphonite and a catalytic amount of tetrakis (triphenylphosphine)palladium [0] gave the bis-phosphonate ester **13** in 62% yield following

chromotographic seperation on neutral alumina. Hydrolysis of **13** with 2M LiOH in aqueous THF gave the desired bis-phosphinic acid **3** in 42% overall yield (scheme 3).

All ligands and intermediates give ^{1}H, ^{13}C and ^{31}P NMR spectra, mass spectra and combustion analyses consistent with the structures shown.

In summary we have synthesised three new ligand classes which have been designed to engender tetrahedral coordination to zinc, through use of defined ligand architectures and careful choice of donor atoms. The lipophilicity can be readily varied by modification of the N1 substituent of manipulation at phosphorus. Investigation into the solution complexation and extraction potential of these new ligands is currently underway.

Acknowledgements.

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References and Notes.

1. Bertini, I.; Luchinat, C.; Movet, W.; Zeppezaur, M.; *Zinc Enzymes*, Birkhauser, Boston, **1986**.
2. *Hydrometallurgy-Fundamentals, Technology and Innovations.* Hiskey, J. B.; Warren, G. W. Eds.; Soc. Min. Metall Expl., Littleton, Colorado.
3. Irving, H. M. N. H.; Williams, R. J. P.; *J. Chem. Soc.*, **1953**, 3192.
4. Broan, C. J.; Cole, E.; Jankowski, K. J.; Parker, D.; Pulukkody, K.; Boyce, B. A.; Millar, A. T.; 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 and 7.
6. Neilson, T.; Wood, H. C. S.; Wylie, A. G.; *J. Chem. Soc.*, **1962**, 371.
7. Yuanyo, X.; Zhang, L.; Jiazhi, X.; Huiju, G.; Yaozeng, H.; *Synthesis*, **1983**, 377.
8. A typical procedure for the cross-coupling reaction is as follows:
   Ethyl-phenylphosphonite (0.14ml, 0.924mmol) and triethylamine (0.39ml, 2.77mmol) were added to a solution of the aryl bromide (300mg, 0.84mmol) in dry toluene(1ml), . The mixture was degassed twice using a freeze-thaw cycle.
   Tetrakis(triphenylphosphine)palladium(0)(46mg, 0.04mmol) was added and the mixture degassed twice more and heated at 130°C for 20 hours. Dichloromethane (20ml) was added and the solids removed by filtration. The solution was washed with 5% aqueous hydrochloric acid (2x20ml) and water (3x20ml), dried (K_2CO_3) and the solvent removed under reduced pressure. The crude product was purified by column chromatography on neutral almunia (gradient elution 100% Dichloromethane to 98% Dichloromethane/2% Methanol).
9. Bates, G. B.; Parker, D.; Tasker, P. A.; *J. Chem. Soc., Perkin Trans. 2*, **1996**, 117.
10. Koshits-Porai, B. A.; Ginsburg, O. F.; Efros, L. F.; *Zh. Obshch. Khim*,.19, **1949**, 1545.