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Designer Ligands. Part 3.[1] Synthesis of Pgm-Specific Bidentate and Tridentate Ligands

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Abstract. Bidentate and tridentate, sulfur-containing, mono-amide ligands, designed to exhibit specificity for platinum group metals (pgm), have been prepared. Preliminary extraction studies indicate that the tridentate ligands exhibit selectivity for palladium(II) in the presence of base metals.

The commercial separation of platinum group metals (pgm) from base metals, such as iron, copper, nickel and cobalt,[2] by precipitation and filtration[3] has largely been replaced by solvent extraction processes, which require metal-specific ligands. Platinum-specific ligands also find use in chelation therapy, minimising the toxic effects of platinum-based anti-cancer drugs.[4,5] Our research has focussed on the development of novel, pgm-specific ligands whose design features (illustrated in Figure 1) may be summarised as follows:-

I: an aromatic ring to enhance lipophilicity for solvent extraction applications, or for linkage to an inert polymeric matrix;

II: an amide function for pgm-specificity;

III: side-chains to accommodate additional sulfur donors;

IV: *ortho*-N,S-disubstitution to permit the formation of 5-membered chelates; and

V: a *para*-substituent to "fine-tune" electron density at the amide nitrogen.

In this communication, we discuss the synthesis of bidentate and tridentate ligands which incorporate such design features.

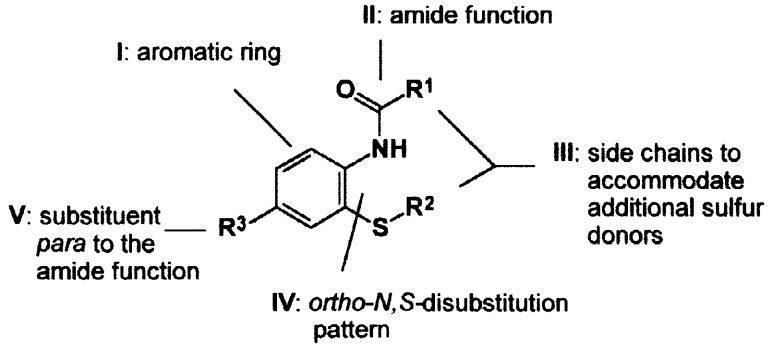

Figure 1. Design features of novel pgm-specific ligands.

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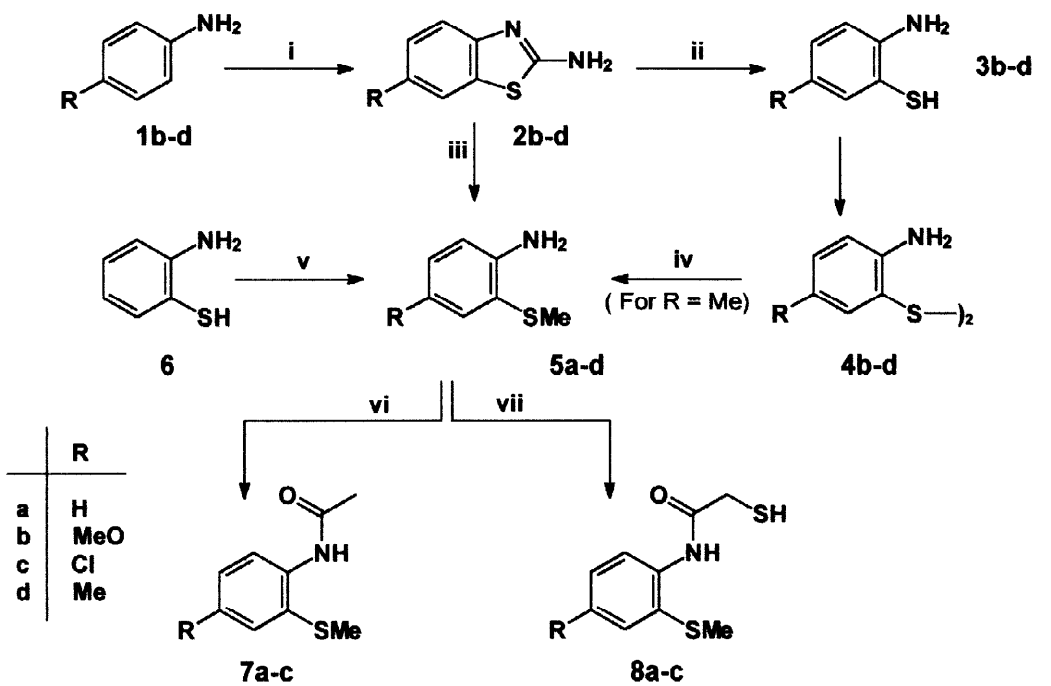
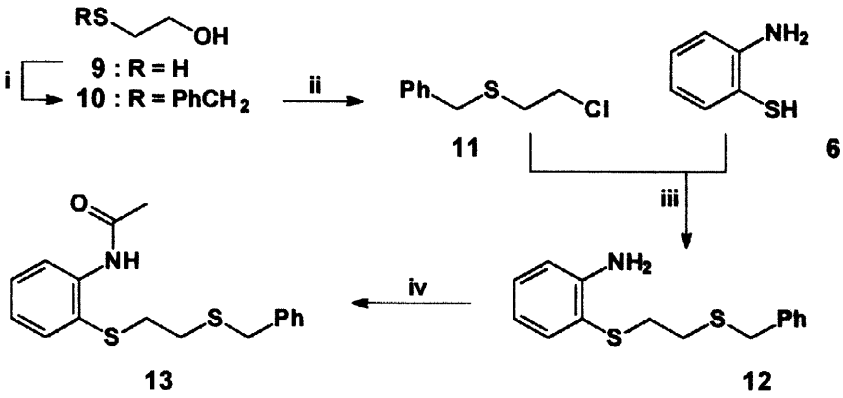
The strategy adopted was to commence with *para*-substituted anilines **1** [*i.e.* with the substituent R^3 (Fig.1) already in place], *ortho*-thiolation of which would provide the appropriately substituted intermediates **3** (Scheme 1). Reported methods of preparing 5-substituted-2-aminobenzenethiols include the reduction of substituted aryl disulfides,[6] the formation and base-catalysed cleavage of thiazathiolium chloride intermediates (Herz compounds),[7] and the cleavage of 2-aminobenzothiazoles.[8] The last-mentioned approach was followed, sequential treatment of *p*-chloroaniline **1c** and *p*-methylaniline **1d** with ammonium thiocyanate and bromine in acetic acid affording the 2-aminobenzothiazoles **2c** (35%) and **2d** (30%). Thiocyanogen,[9] the active reagent produced *in situ*, is particularly sensitive to hydrolysis; this can be inhibited at < *ca.* 10°C but, at this temperature, the solvent (CH_3CO_2H) freezes. It was found that addition of water or chloroform (5% $^v/_v$) lowered the freezing-point making the cold slurry easier to handle. The *p*-methoxy analogue **2b** was obtained in extremely poor yield and various methods were explored to increase the efficiency of the transformation. Reaction at lower temperature in methanol saturated with sodium bromide failed to improve the yield, while the use of copper(II) chloride as an oxidant in place of bromine[9a] gave a viscous black oil. A more acceptable yield (39%) of the *p*-methoxy analogue **2b** was finally obtained by generating the thiocyanogen separately, using bromine and excess sodium thiocyanate, thus preventing ring-bromination of the highly activated *p*-anisidine **1b**. Base-catalysed hydrolysis of the 2-aminobenzothiazoles **2** to the mercaptans **3** was complicated by their ready oxidation to the corresponding disulfides **4** and, consequently, the stable methyl sulfides **5a-d** were prepared directly (in 46-92% yield) by adding methyl iodide to the alkaline solution containing the potassuim mercaptide salt. The *p*-methyl derivative **5d** was also obtained *via* triphenylphosphine reduction of the disulfide **4d**. However, attempts to prepare the *p*-nitro analogue by thiocyanation of *p*-nitroaniline or hydrolysis of 2-methyl-6-nitrobenzothiazole



Scheme 1. *Reagents and conditions:* i, NaNCS or NH_4NCS, Br_2, AcOH ; ii, KOH, H_2O then AcOH; iii, KOH, heat, MeI; iv, Ph_3P, MeI ; v, KOH, MeI ; vi, Ac_2O ; vii, $HSCH_2CO_2H$, heat, N_2.

(prepared by nitration of 2-methylbenzothiazole) proved unsuccessful, the latter reaction affording a black, water-soluble residue.

While acetylation of the substituted anilines **5a-c** gave the corresponding bidentate ligands **7a-c** in yields of 47-65%, the tridentate ligands **8a-c** were obtained in variable yield (15-43%) by heating the methyl sulfides **5a-c** with mercaptoacetic acid in a stream of dry nitrogen. Protection of the aromatic mercapto group as the methyl thioether (as in compounds 7 and **8**) is essential to prevent oxidation to disulfides or cyclisation to benzothiazoles - processes which occur readily at room temperature. Attention was then given to extending the side-arms R^1 and R^2 (Fig. 1) and, to this end, 2-mercaptoaniline **6** was reacted with benzyl 2-chloroethyl sulfide **11** (Scheme 2). The resulting aniline derivative **12** was readily acetylated to give the tridentate ligand **13** in good yield (73%).



Scheme 2. *Reagents and conditions:* i, $PhCH_2Cl$, KOH, MeOH ; ii, $SOCl_2$, pyridine ; iii, KOH, MeOH ; iv, Ac_2O, H_2SO_4.

Preliminary extraction studies[10] using **7a**, **8a** and **13** indicate that the *tridentate* ligands **8a** and **13** exhibit significant selectivity for palladium(II) over the base metals copper(II), nickel(II) and cobalt(II). The extraction efficiency of the *bidentate* ligand **7a**, however, appears to be very low - an observation attributed to the formation of coloured, water-soluble complexes. The extraction potential of the title ligands and the associated coordination chemistry will be addressed in ongoing investigations.

EXPERIMENTAL

NMR spectra were recorded for $CDCl_3$ solutions on a Bruker AMX 400 NMR spectrometer and referenced using the solvent signals (δ_H 7.25 and δ_C 77.0 ppm). Low-resolution mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer and high-resolution analyses on a Kratos MS 80RF mass spectrometer (Cape Technikon Mass Spectrometry Unit).

Compounds **2b-d**,[11,12] **3b-d**,[8] **5a**,[13] **5b**,[14] **7a**,[13] **7c**,[15] and **11**[16] have been reported previously; the disulfides **4b-d** resisted complete purification and were characterised by ^1H NMR spectroscopy.

4-Methoxy-2-(methylthio)acetanilide **7b**.- A solution of NaOAc (trihydrate; 15 g) in H_2O (75 mL) and then Ac_2O (17 mL) were added to a solution of 4-methoxy-2-(methylthio)aniline **5b** (1.50 g, 8.86 mmol) in 2M HCl (55 mL). The resulting mixture was stirred for 2.5 h affording the crude product as a precipitate. Purification by flash chromatography [elution with EtOAc - hexane (6:4)] followed by recrystallisation from EtOH - H_2O afforded, as colourless crystals, *4-methoxy-2-(methylthio)acetanilide* **7b** (1.06 g, 61%), mp 93.5-94.5°C(from EtOH - H_2O) (Found: C, 56.6; H, 6.4; N, 6.7; M^+, 211.0664. $C_{10}H_{13}NO_2S$ requires C, 56.85; H, 6.2; N, 6.6%; *M*, 211.0667); υ_{max}(KBr)/cm^{-1} 3250 (NH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.19 (3H, s, $CO.CH_3$), 2.39 (3H, s, SCH_3), 3.78 (3H, s, OCH_3), 6.80 (1H, dd, *J* 2.6 and 9.0 Hz, 5-H), 6.95 (1H, d, *J* 2.6 Hz, 3-H) 7.80 (1H, br s, NH) and 8.04 (1H, d, *J* 9.0 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 18.2 (SCH_3), 24.5 ($CO.CH_3$), 55.6 (OCH_3), 113.1, 116.9 and 122.9 (C-3, C-5 and C-6), 128.0, 130.9 and 156.3 (C-1, C-2 and C-4) and 168.2 (CO); *m/z* 211 (M^+, 73%) and 154 (100).

2-Mercapto-N-*[2-(methylthio)phenyl]ethanamide* **8a**.- A melt of 2-(methylthio)aniline **5a** (2.00 g, 14.4 mmol) and 2-mercaptoacetic acid (1.30 g, 14.4 mmol) was heated for 2 h at 110-120°C, with stirring, in a stream of dry N_2. The melt was poured into cold water (50 mL), and the resulting mixture extracted with EtOAc (3 x 30 mL). The EtOAc extracts were washed (1M HCl) and dried (anhyd. $MgSO_4$), and the EtOAc evaporated *in vacuo*. The residue was purified by flash chromatography [elution with EtOAc - hexane (1:9)] followed by recrystallisation from EtOH - H_2O (7:3) to afford , as colourless crystals, *2-mercapto*-N-*[2-(methylthio)-phenyl]ethanamide* **8a** (0.44 g, 15%), mp 51.5-53°C (from EtOH - H_2O) (Found: C, 50.55; H, 5.2; N, 6.5; M^+, 213.0285. $C_9H_{11}NOS_2$ requires C, 50.7; H, 5.2; N, 6.6%; *M*, 213.0282); υ_{max}(KBr)/cm^{-1} 3240 (NH), 2250 (SH) and 1650 (CO); δ_H (400 MHz; $CDCl_3$) 2.05 (1H, t, *J* 9.2 Hz, SH), 2.40 (3H, s, SCH_3), 3.44 (2H, d, *J* 9.2 Hz, CH_2S), 7.08 and 7.29 (2H, 2 x t, 4-H and 5-H), 7.47 (1H, d, 3-H), 8.29 (1H, d, 6-H) and 9.52 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 18.7 (SCH_3), 29.6 (CH_2S), 120.4, 124.8, 128.7 and 132.7 (C-3, C-4, C-5 and C-6), 126.1 and 137.7 (C-1 and C-2) and 167.3 (CO); *m/z* 213 (M^+, 23%) and 139 (100).

2-Mercapto-N-*[4-methoxy-2-(methylthio)phenyl]ethanamide* **8b**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-[2-(methylthio)phenyl]ethanamide **8a** was followed, using 4-methoxy-2-(methylthio)aniline **5b** (2.14 g, 12.7 mmol) and 2-mercaptoacetic acid (1.17 g, 12.7 mmol). The melt solidified on cooling and was transferred to aqueous 1M HCl (100 mL), in which medium it was crushed into a powder. The powder was collected by filtration, washed with water and recrystallised twice from EtOH - H_2O to afford, as colourless crystals, *2-mercapto*-N-*[4-methoxy-2-(methylthio)phenyl]ethanamide* **8b** (1.23 g, 43%), mp 91.5-92.5°C (from EtOH - H_2O) (Found: C, 49.2; H, 5.5; N, 5.6; M^+, 243.0388. $C_{10}H_{13}NO_2S_2$ requires C, 49.4; H, 5.4; N, 5.8%; *M*, 243.0388); υ_{max}(KBr)/cm^{-1} 3240 (NH), 2250 (SH) and 1640 (CO); δ_H(400 MHz; $CDCl_3$) 2.03 (1H, t, *J* 9.2 Hz, SH), 2.41 (3H, s, SCH_3), 3.43 (2H, d, *J* 9.2 Hz, $CO.CH_2S$), 3.79 (3H, s, OCH_3), 6.81 (1H, dd, *J* 2.8 and 8.9 Hz, 5-H), 6.98 (1H, d, *J* 2.8 Hz, 3-H) 8.08 (1H, d, *J* 8.9 Hz, 6-H) and 9.16 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 18.1 (SCH_3), 29.4 (CH_2S), 55.6 (OCH_3), 113.1, 117.0 and 122.4 (C-3, C-5 and C-6), 128.7, 130.1 and 156.6 (C-1, C-2 and C-4) and 167.04 (CO); *m/z* 243 (M^+, 30%) and 55 (100).

2-Mercapto-N-*[4-chloro-2-(methylthio)phenyl]ethanamide* **8c**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-[2-(methylthio)phenyl]ethanamide **8a** was followed, using 4-chloro-2-(methylthio)aniline **5c** (3.30 g, 19.0 mmol) and 2-mercaptoacetic acid (1.75 g, 19.0 mmol). The melt solidified upon pouring into cold water. The precipitate was crushed, collected by filtration and washed sequentially with

dilute HCl and H_2O. Three recrystallisations from EtOH - H_2O afforded, as colourless crystals, *2-mercapto-N-[4-chloro-2-(methylthio)phenyl]ethanamide* **8c** (1.48 g, 31%), mp 86-87°C (from EtOH - H_2O) (Found: C, 43.45; H, 4.3; N, 5.7; M^+, 246.9883. $C_9H_{10}ClNOS_2$ requires C, 43.6; H, 4.1; N, 5.65%; *M*, 246.9892); υ_{max}(KBr)/cm^{-1} 3230 (NH), 2540 (SH) and 1660 (CO); δ_H (400 MHz; $CDCl_3$) 2.04 (1H, t, *J* 9.3 Hz, SH), 2.42 (3H, s, SCH_3), 3.44 (2H, d, *J* 9.2 Hz, CH_2S), 7.23 (1H, dd, *J* 2.3 and 8.8 Hz, 5-H), 7.41 (1H, d, *J* 2.3 Hz, 3-H), 8.22 (1H, d, *J* 8.8 Hz, 6-H) and 9.40 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 18.2 (SCH_3), 29.5 (CH_2S), 121.6, 128.2 and 131.1 (C-3, C-5 and C-6), 128.3, 129.6 and 135.8 (C-1, C-2 and C-4) and 167.3 (CO).

2-(5-Phenyl-1,4-dithiapentyl)aniline **12**.- A solution of KOH (3.73 g, 66.5 mmol) in H_2O (50 mL) and a solution of benzyl 2-chloroethyl sulfide **11** (12.43 g, 66.59 mmol) in MeOH (30 mL) were added, sequentially, to a stirred solution of 2-aminobenzenethiol **6** (8.34 g, 66.6 mmol) in MeOH (50 mL), under N_2. The resulting mixture was boiled gently under reflux for 1 h, during which time a black oil (18 g) separated out. A portion of this black oil (5.0 g) was purified by flash chromatography [elution with EtOAc - hexane (1:9)] to afford *2-(5-phenyl-1,4-dithiapentyl)aniline* **12** (4.0 g, 80%) [δ_H(400MHz; $CDCl_3$) 3.13 (2H, m, CH_2S), 3.42 (2H, m, $ArSCH_2$), 4.21 (2H, s, $ArCH_2S$), 4.76 (2H, br s, NH_2), 7.21-7.29 (2H, m, ArH) and 7.67-7.91 (7H, m, ArH); δ_C(100 MHz; $CDCl_3$) 30.9, 34.3 and 36.0 ($ArCH_2S$ and SCH_2CH_2S), 114.9, 116.6, 118.4, 126.9, 128.4, 128.7, 132.0, 136.3, 138.1 and 148.5 (ArC)] as a dark yellow oil, which was used without further purification.

2-(5-Phenyl-1,4-dithiapentyl)acetanilide **13**.- Conc. H_2SO_4 (5 drops) was added to a solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **12** (2.29 g, 8.31 mmol) in Ac_2O (46 mL). The mixture was stirred for 5 h at room temperature and then poured into warm water (200 mL). The aqueous mixture was extracted with EtOAc (3 x 40 mL) and the combined EtOAc extracts were dried (anhyd. $MgSO_4$). Removal of the EtOAc *in vacuo* afforded a brown oil (3.7 g) which was purified by flash chromatography [elution with EtOAc - hexane (2:8)] to afford, as a colourless solid, *2-(5-phenyl-1,4-dithiapentyl)acetanilide* **13** (1.94 g, 73%), mp 48-49 °C (from EtOAc - hexane) (Found: C, 64.1; H, 6.1; N, 4.2; M^+, 317.0910. $C_{17}H_{19}NOS_2$ requires C, 64.3; H, 6.0; N, 4.4%; *M*, 317.0908); υ_{max}(KBr)/cm^{-1} 3340 (NH) and 1690 (CO); δ_H(400MHz; $CDCl_3$) 2.11 (3H, s, $CO.CH_3$), 2.44 (2H, m, CH_2S), 2.75 (2H, m, $ArSCH_2$), 3.56 (2H, s, $ArCH_2S$), 6.90-7.38 (8H, m, ArH); 8.32 (1H, d, ArH) and 8.49 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.8 (CH_3), 30.7, 36.0 and 36.1 ($ArCH_2S$ and SCH_2CH_2S), 120.2, 121.2, 123.9, 127.1, 128.5, 128.6, 130.0, 135.5, 137.7 and 140.0 (ArC) and 168.3 (CO).

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