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Cyclometallated compounds

VI *. Cyclopalladation of 2-phenylpyrimidines with pendant pyrazole donors

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Abstract

The use of pendant pyrazole groups to induce double cyclopalladation of 2-phenylpyrimidines has been investigated. 4,6-Bis(pyrazol-1-yl)-2-phenylpyrimidine undergoes monocyclopalladation only, whilst 4-methyl-2-phenyl-6-(pyrazol-1-ylmethyl)pyrimidine reacts preferentially to give the cyclopalladated regioisomer in which the ligand exhibits tridentate coordination. 4,6-Bis(pyrazol-1-ylmethyl)-2-phenylpyrimidine gives a mixture of singly and doubly cyclopalladated products.

Introduction

We have previously described the preparation of complexes containing ligands which have undergone double cyclopalladation with internal coordination to nitrogen [1,2]. For example, 2,3-diphenylpyrazine was doubly cyclopalladated to give a complex of type **1** [2], which represents a cyclometallated analogue of complexes of type **2** formed from the well studied [3] binucleating ligand 2,3-bis(2′-pyridyl)pyrazine. Similarly, 4,6-diphenylpyrimidine was doubly cyclopalladated and converted into complex **3**, the X-ray structure of which was determined [1]. 4,6-Dimethyl-2-phenylpyrimidine (**4**), however, underwent mono-cyclopalladation to give **5** (M = Pd), and there was no evidence for the formation of a doubly metallated complex of type **6**. A complex of type **6** would represent a carbon analogue of complexes of type **7**, formed from the well-known [4] binucleating ligand 2,2′-bipyrimidine and would also be isomeric to complexes of type **8** (M = Pt) formed [5] from roll-over metallation of diaryl(2,2′-bipyridine)platinum(II) complexes. The resistance of **4** undergoing double cyclometallation might suggest that the double metallation of a

* For part V see ref. 2.

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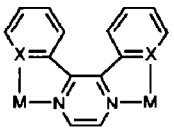
single phenyl ring, as in **6**, is an unfavourable process. However, successful double palladation on a single benzene ring has been previously reported [6].

We felt that it might be possible to induce double cyclopalladation of a 2-phenylpyrimidine by appending additional nitrogen donors at the 4- and 6-positions of the pyrimidine ring. This would allow initial bidentate coordination of the nitrogens to form a binuclear bis-chelate complex **9** ideally disposed to undergo bis-dehydrochlorination to the doubly cyclometallated complex **10**. Support for this approach is based on previously reported facilie cyclometallations of related bidentate ligands to produce *N,N,C*-tridentate complexes [7]. We report here the results of this approach to the double cyclopalladation of a phenyl ring.



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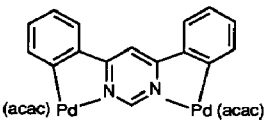
(2) X=N



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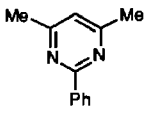

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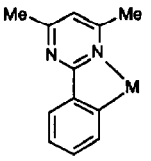

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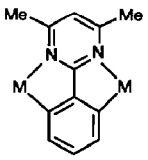

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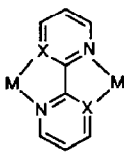
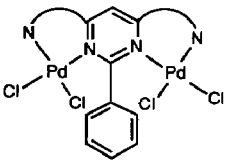


(7) X=N
(8) X=C



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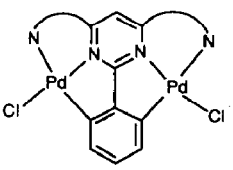
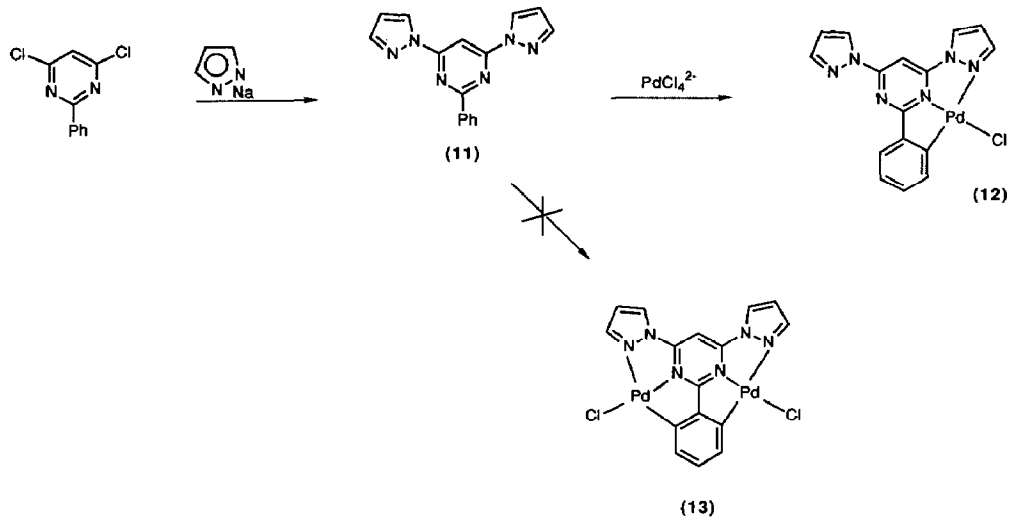


(10)

Results and discussion

The first substrate synthesised in this study was the dipyrazolylpyrimidine **11** which was obtained in 86% yield (Scheme 1) from the reaction of 4,6-dichloro-2-phenylpyrimidine with two equivalents of sodium pyrazolate. Since 2-(pyrazol-1-yl)pyridines are excellent bidentate ligands for transition metal ions [8] and 4,6-bis(pyrazolyl)pyrimidines have previously been shown to act as binucleating ligands [9], the ligand **11** might be expected to form the binuclear cyclopalladated complex **13** on reaction with lithium tetrachloropalladate. In the event, however, reaction of **11** gave only the mono-cyclopalladated complex **12** (92% yield), which was readily identified by NMR spectroscopy from the unsymmetrical nature of the product and the characteristic pattern for four protons in an *ortho* disubstituted benzene ring. A notable feature of the NMR spectra of **12**, and other complexes described below, is that the substituent shifts induced by the PdCl substituent are significantly different from the characteristic shifts induced by a Pd(acac) substituent [10]. This supports previous conclusions [10,11] that the auxiliary coordinated anions make an important contribution to the magnitude of cyclometallation-induced NMR shifts.

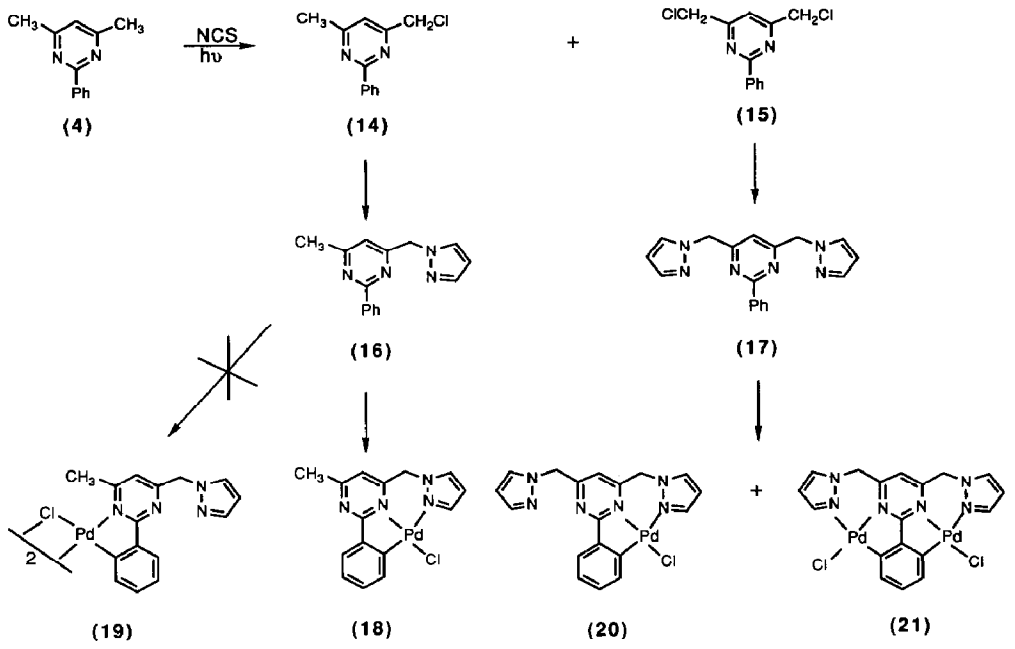


Scheme 1

No evidence was found for the formation of the doubly cyclopalladated product **13** from the reaction of **11**. In retrospect, this is perhaps not surprising, since molecular models indicate that a structure such as **13** would involve considerable internal strain. Although aromatic tridentate ligands, such as 2,2′,6,2″-terpyridine [12], readily form complexes incorporating two fused five-membered chelate rings, molecular models suggest that the simultaneous fusion of four five-membered chelate rings around a common six membered ring, as required in **13**, is highly unlikely. However, models also indicate that the introduction of an extra atom into the *N,N* chelate rings might allow formation of a complex containing cumulated 6,5,5,6-chelate ring fusion around the pyrimidine ring.

Since 2-(pyrazol-1-ylmethyl)pyridines have also been shown [13] to be good chelating ligands for palladium and are readily available from chloromethyl-pyridines [13,14], a synthesis of the bis(pyrazolylmethyl)pyrimidine **17** was undertaken (Scheme 2). Chlorination [15] of 4,6-dimethyl-2-phenylpyrimidine (**4**) by *N*-chlorosuccinamide (2 equivalents) gave a mixture of products from which the monochloro product **14** was separated by radial chromatography. Phase-transfer catalysed [16] alkylation of pyrazole by **14** gave the mono-pyrazolylmethyl derivative **16** in almost quantitative yield. Reaction of **16** with lithium tetrachloropalladate at room temperature gave in 10 min a 90% yield of the cyclopalladated product **18**, which possesses 6,5-fused *N,N,C*-chelate rings. The structure of **18** was deduced from its ^{1}H and ^{13}C NMR spectra, which were fully assigned by a combination of one- and two-dimensional NMR techniques (see Experimental Section) according to well-established procedures [10]. Significant differences exist in the ^{1}H NMR chemical shifts of **18** in $CDCl_3$ and DMSO-d_6. The enhanced rate of formation of **18** and its selective formation in preference to the bidentate regioisomer **19**, which was not detected, clearly indicate the involvement of the pendant pyrazole donor in effecting cyclopalladation.

Encouraged by this result we then prepared the bis(pyrazolylmethyl) derivative **17** by phase-transfer catalysed alkylation of the symmetrical dichloro precursor **15**.



Scheme 2

The sample of **17** was contaminated (15%) with a tripyrazole derivative formed from a trichloro precursor. Treatment of this mixture with lithium tetrachloropalladate gave an immediate precipitate of a mixture of products. To date all attempts to separate this mixture into its components have been unsuccessful or resulted in decomposition of the products. However an FAB mass spectrum of the mixture included ions of mass 420 and 560 which correspond to loss of HCl from the singly and doubly cyclopalladated products **20** and **21** respectively. Thus although we have not been able to fully characterise the product, the mass spectrum provides clear evidence for the formation of **21** which containes a single doubly cyclopalladated benzene ring. Further studies of the double cyclometallation of other substrates are in progress.

Experimental

For general procedures and instrumentation see ref. 1.

Preparation of ***11***

Sodium pyrazolate was prepared from a solution of pyrazole (0.50 g) in dry tetrahydrofuran (20 ml) to which was added a suspension (0.35 g) of sodium hydride in oil and the mixture stirred for 1 h at room temperature. 4,6-Dichloro-2-phenylpyrimidine [17] (0.80 g) in dry THF (10 ml) was then added and the mixture refluxed for 5 h. After cautious addition of water (20 ml) the mixture was twice extracted with ether and the combined ether extracts dried ($MgSO_4$) and concentrated to give 4,6-bis(pyrazol-1-yl)-2-phenylpyrimidine (**11**) (0.88 g, 86%), which was recrystallised from ether : petroleum ether to give white needles, m.p. 198 °C. ^1H

NMR, $CDCl_3$ [DMSO-d_6], δ 6.54 [6.85], t, H4′; 7.54 [7.72], m, H-*meta* and H-*para*; 7.83 [8.14] (dd, H(3′)); 8.39 [8.27] (s, H(5)); 8.54 [8.77] (m, H-*ortho*); 8.76 [9.12] (dd, H(5′)). ^{13}C NMR, $CDCl_3$ [DMSO-d_6], δ 93.6 [92.5] (C(5)); 108.7 [109.6] (C(4′)); 127.8 [128.5] (C(5′)); 128.4 [128.6] (C-*ortho*); 128.5 [128.8] (C-*meta*); 131.4 [131.9] (C-*para*); 136.4 [135.6] (C-*ipso*); 143.7 [144.5] (C(3′)); 159.2 [158.8] (C(4) and C(6)); 164.1 [163.7] (C(2)). Found: M^+, 288.1115; C, 66.58; H, 4.28. $C_{16}H_{12}N_6$ calc: M^+, 288.1124; C, 66.66; H, 4.20%.

Preparation of ***12***

To a methanolic solution of lithium tetrachloropalladate, prepared from palladium chloride (0.10 g) and lithium chloride (0.060 g), was added a solution of **11** (0.16 g) in methanol, and the solution stirred for 5 d at room temperature. This resulted in precipitation of chloro[2-(4,6-bis(pyrazol-1-yl)pyrimidin-2-yl)phenyl-*C*,*N*,*N*]palladium(II) (**12**) (0.22 g, 92%) as a pale green solid. m.p. > 350 °C. ^{1}H NMR, DMSO-d_6, δ 6.90 (t, 6′-H(4)); 7.08 (t, 4′-H(4)); 7.29 (m, H(4) and H(5)); 7.67 (m, H(6)); 7.94 (m, H(3)); 8.16 (4′-H(3)); 8.21 (6′-H(3)); 8.47 (s, H(5′)); 9.05 (d, 6′-H(5)); 9.53 (d, 4′-H(5)). ^{13}C NMR, DMSO-d_6, δ 91.6 (C(5′)); 110.6 (6′-C(4)); 111.7 (4′-C(4)); 125.1 (C(4)); 127.3 (C(3)); 129.5 (6′-C(5)); 132.0 (C(5)); 132.7 (4′-C(5)); 135.5 (C(6)); 144.8 (6′-C(3)); 145.4 (4′-C(3)). Found: C, 42.84; H, 2.39; N, 18.48. $C_{16}H_{11}ClN_6Pd \cdot H_2O$ calc: C, 42.98; H, 2.93; N, 18.79%. Similar reaction of **11** with two equivalents of lithium tetrachloropalladate gave the hydrochloride salt of **12**. Found: C, 41.28; H, 2.36; N, 17.84. $C_{16}H_{11}ClN_6Pd \cdot HCl$ calc: C, 41.27; H, 2.60; N, 18.05%.

Preparations of ***16*** *and* ***17***

A solution of 4,6-dimethyl-2-phenylpyrimidine (**4**) [18] (1.22 g), *N*-chlorosuccinimide (1.77 g) and benzoyl peroxide (0.050 g) in carbon tetrachloride (50 ml) was refluxed for 20 h under nitrogen. The resulting mixture * was cooled, filtered, and concentrated to give an oil, which was absorbed on to a silica gel radial chromatography plate. Elution with ether : petroleum ether (1 : 15) gave 4-chloromethyl-6-methyl-2-phenylpyrimidine (**14**) (0.51 g, 35%) as an oil. ^{1}H NMR, $CDCl_3$, δ 2.59 (s, CH_3); 4.62 (s, CH_2Cl); 7.25 (s, H(5)); 7.46 (m, H-*meta* and H-*para*); 8.45 (m, H-*ortho*).

A mixture of **14** (0.20 g), pyrazole (0.070 g), benzene (25 ml), 40% aqueous sodium hydroxide (10 ml) and 40% aqueous tetrabutyl ammonium hydroxide (5 drops) was stirred and refluxed for 5 h. The benzene layer was separated and the aqueous phase extracted with ether. The combined organic phases were dried and concentrated under vacuum to give a residue which was then absorbed on to an alumina column (25 g). Elution with chloroform gave 4-methyl-2-phenyl-6-(pyrazol-1-ylmethyl)pyrimidine (**16**) (0.22 g, 97%) as white crystals. M.p. 90–91 °C. ^{1}H NMR, $CDCl_3$, δ 2.50 (s (CH_3); 5.46 (s, CH_2); 6.38 (t, H(4′)); 6.56 (s, H(5)); 7.48 (m, H-*meta* and H-*para*); 7.58 (dd, H(5′)); 7.63 (dd, H(3′)); 8.44 (m, H-*ortho*). ^{13}C

* This mixture was estimated by ^{1}H NMR (300 MHz) spectroscopy to contain the following substituted 2-phenylpyrimidines: 4,6-dimethyl (**4**) (10%) 2.54 ppm (CH_3); 4-chloromethyl-6-methyl (**14**) (37%) 2.59 (CH_3), 4.62 (CH_2); 4-dichloromethyl-6-methyl (10%) 2.64 (CH_3), 6.65 (CH); 4-methyl-6-trichloromethyl (16%) 2.70 (CH_3); 4,6-bis(chloromethyl) (**15**) (18%) 4.67 (CH_2); 4-chloromethyl-6-dichloromethyl (6%) 4.71 (CH_2), 6.69 (CH).

NMR, $CDCl_3$, δ 24.5 (CH_3); 56.7 (CH_2); 106.5 (C(4′)); 115.3 (C(5)); 128.3 and 128.5 (C-*ortho* and C-*meta*); 130.3 (C(5′)); 130.6 (C-*para*); 137.5 (C-*ipso*); 140.3 (C(3′)); 164.2 (C(2)); 165.3 (C(6)); 168.5 (C(4)). Found: M^+, 250.1223; C, 71.85; H, 5.35; N, 22.35. $C_{15}H_{14}N_4$ calc: M^+, 250.1219; C, 71.98; H, 5.64; N, 22.38%.

The product mixture from a separate chlorination reaction was subjected to a phase-transfer catalysed reaction with pyrazole as described above. The crude product mixture from this reaction was absorbed on to a silica gel radial chromatography plate. Elution with methanol : ether (1 : 50) gave a fraction consisting mainly (85%) of 4,6-bis(pyrazol-1-ylmethyl)-2-phenylpyrimidine (**17**). ^{1}H NMR, $CDCl_3$, δ 5.41 (s, CH_2); 6.20 (s, H(5)); 6.32 (t, H(4′)); 7.47 (m, H-*meta* and H-*para*); 7.52 (dd, H(5′)); 7.55 (dd, H(3′)); 8.41 (m, H-*ortho*). ^{13}C NMR, $CDCl_3$, δ 56.6 (CH_2); 106.5 (C(4′)); 113.1 (C(5)); 128.4 and 128.4 (C-*ortho* and C-*meta*); 130.4 (C(5′)); 131.0 (C-*para*); 136.9 (C-*ipso*); 140.3 (C(3′)); 164.2 (C(2)); 166.7 (C(4) and C(6)). Found: M^+, 316.1428. $C_{18}H_{16}N_6$ calc: M^+, 316.1436. This sample of **17**, m.p. 138–142 °C, was contaminated by ca. 15% of a product thought to be 4-(dipyrazol-1-ylmethyl)-2-phenyl-6-(pyrazol-1-ylmethyl)pyrimidine formed from the corresponding trichloride. The above impure sample was used in the cyclopalladation reaction.

Preparation of ***18***

Reaction of **16** (0.14 g) with lithium tetrachloropalladate as described above gave immediate precipitation of chloro[2-(4-methyl-6-(pyrazol-1-ylmethyl)pyrimidin-2-yl)phenyl-*C*,*N*,*N*′]palladium(II) (**18**) (0.18 g, 90%). M.p. 219 °C (dec). ^{1}H NMR, $CDCl_3$ [DMSO-d_6], δ 2.62 [2.71] (s, CH_3); 5.30 [5.77] (s, CH_2); 6.42 [6.63] (t, 6′-H(4)); 6.98 [7.53] (s, H(5′)); 7.13 [7.22] (m, H(4)); 7.22 [7.26] (m, H(5)); 7.62 [8.26] (dd, 6′-H(3)); 7.81 [7.82] (m, H(3)); 8.01 [7.91] (m, H(6)); 8.29 [8.12] (dd, 6′-H(5)). ^{13}C NMR, $CDCl_3$ [DMSO-d_6], δ 24.9 [24.4] (CH_3); 54.5 [53.2] (CH_2); 107.1 [106.5] (6′-C(4)); 116.4 [118.1] (C(5′)); 125.0 [124.7] (C(4)); 127.7 [126.7] (C(3)); 131.9 [130.7] (C(5)); 132.9 [135.0] (6′-C(5)); 136.1 [135.8] (C(6)); 144.3 [142.5] (6′-C(3)). Found: C, 45.95; H, 3.31; N, 14.60. $C_{15}H_{13}ClN_4Pd$ calc: C, 46.06; H, 3.35; N, 14.32%.

Preparation of ***20*** *and* ***21***

Reaction of **17** (0.090 g) with lithium tetrachlorpalladate as described above gave immediate precipitation of a mixture of products (0.135 g). NMR and mass spectrometry showed evidence for the presence of both **20** and **21** in the product mixture. All attempts to separate this mixture were unsuccessful and/or resulted in decomposition.

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