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The orthopalladation of aniline via its 2-nitrophenylsulfenyl derivative

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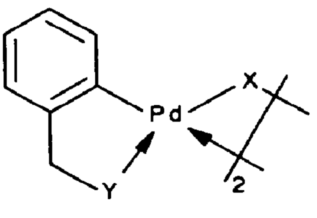
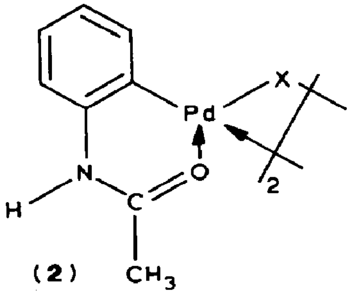
Abstract

2-Nitrophenylsulfenylanilide can be orthopalladated to give μ,μ-dichlorodipalladium-bis(2-nitrophenylsulfenylanilide), which on carbomethoxylation gives 2-nitrophenylsulfenylanthranilate.

The orthopalladation of aromatic compounds introduces a palladium atom regiospecifically into the ring and so provides a foundation for many organic synthesis [1]. In most cases [2] a five-membered ring is formed in which the palladium is σ-bonded to the *ortho*-carbon atom and is co-ordinated to a hetero-atom Y in the side chain as in **1**.



(**1**)



(**2**)

The orthopalladation of aniline presents a problem because a ring size of five cannot readily be achieved. However, it has been shown by Cameron and Kilner [3], and Horino and Inoue [4] that orthopalladation of acetanilide occurs with the formation of a six-membered ring, **2**. Attempts to carry out the analogous reaction with thioacetanilide led to desulfurisation [5], although orthometallation leading to five-membered rings with a sulfur donor atom has been reported by several authors [6]. The implied requirements for the orthopalladation of aniline are met by the 2-nitrophenylsulfenyl derivative (**3**), which can form a five-membered ring through orthopalladation and donation of the sulfur to palladium. 2-Nitrophenylsulfenyl amides are useful in peptide synthesis [7], and in this application have the merit that the phenyl ring attached to sulfur is deactivated towards electrophilic substitution by the electron-withdrawing nitro group.

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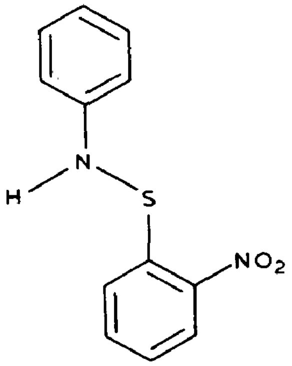
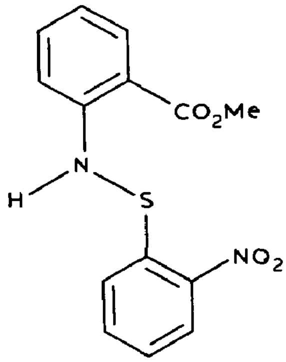
Results and discussion

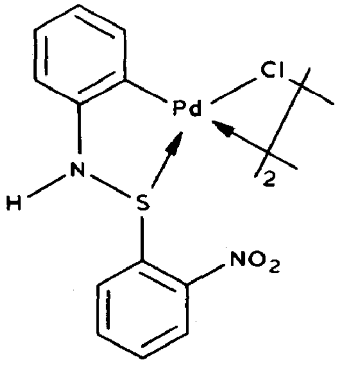
We tried several systems for the orthopalladation of **3**. The first successful system was based on work by Trofimenko [8] and involved reaction of Na_2PdCl_4 with **3** in the presence of diisopropylethylamine (Hünig's base) in aqueous acetone or tetrahydrofuran (thf). However, more recent work by McCrindle [9] and co-workers has shown that under some conditions Hünig's base can itself form complexes with palladium. The preferred method for the orthometallation follows the work of Gaunt and Shaw [10], and uses sodium acetate as the base in aqueous tetrahydrofuran. The yield of ca. 30% is lower than most orthopalladation reactions. The structure of the orthopalladation product was elucidated by carbomethoxylation. The ligand **3** contains 2 aromatic rings and so substitution could, in principle, give either **4a** or **4b**. However as mentioned above the ligand was selected partly because electrophilic substitution in the ring carrying the nitro group was unlikely, and **4a** was the expected product. The carbomethoxylation was carried out under one atmosphere pressure of carbon monoxide in refluxing methanol containing sodium



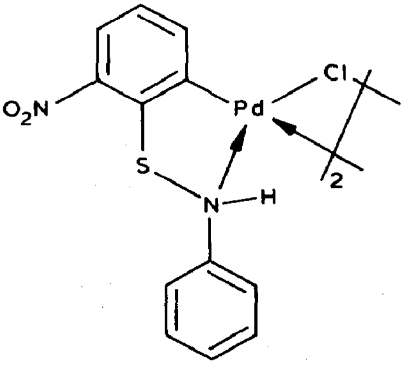
(3)



(5)



(4a)

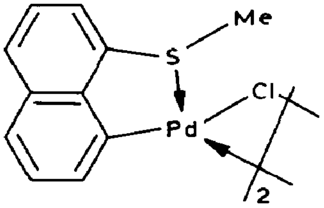


(4b)

acetate. The product was the known [11] 2-nitrophenylsulfenyl derivative of anthranilic acid (**5**) and was obtained in 79% yield, and this establishes the structure of the orthopalladation product as **4a**.

There are several changes in the IR spectrum on orthopalladation. The N–H vibration which is very strong and sharp (η(N–H) 3360 cm^{-1}) in **3** becomes weaker and broad in **4a** (ν(N–H) ~ 3300 cm^{-1}). Another significant change is that a medium intensity band at 900 cm^{-1} in **3** is replaced by a weak band at 880 cm^{-1} in **4a**. The very strong sharp band at 690 cm^{-1} in **3** is very weak in **4a**. The latter change is expected [12] when both rings are ortho-substituted.

We have attempted to synthesise heterocyclic compounds by reacting **4a** with a variety of alkenes and alkynes, but so far without success. We were initially surprised that the addition of two-carbon units was so much more difficult than the carbomethoxylation. However, comparable results were obtained by Pfeffer and co-workers [13], who recently reported that there is a marked difference in the reactivity of the naphthalene derivative **6** towards alkynes and carbon monoxide. In our case the reaction is further complicated by the activity of the S–N bond toward alkynes [14].



(**6**)

Experimental

The reactions were carried out in air with no special precautions. IR spectra were recorded as Nujol mulls on a Perkin–Elmer Model 983G spectrophotometer.

2-Nitrophenylsulfenylanilide (3)

A solution of 2-nitrophenylsulfenylchloride (10 g, 53 mmol) in diethyl ether (250 cm^3) was treated with a solution of aniline (9.5 cm^3, 104 mmol) in the same solvent (100 cm^3), and the mixture was stirred at room temperature for 1 h. The precipitated aniline hydrochloride was filtered off and the filtrate concentrated to give a red oil (ca. 12 g), which was dissolved in hot methanol (100 cm^3). The solution was treated with water (10 cm^3), heated with charcoal, filtered, and cooled, to give the product as orange crystals (8.4 g, 66%). The melting point varied slightly from sample to sample. The highest melting point we observed was 92.5–94 ° C, which agrees well with that reported by Zincke and Farr [15] but less well with that given by Billman and O'Mahoney [16] (88.5–89 ° C). Found: C, 58.51; H, 3.99; N, 11.12. $C_{12}H_{10}N_2O_2S$ calc.: C, 58.52; H, 4.09; N, 11.37%.

μ,μ-Dichloro dipalladium bis(2-nitrophenylsulfenylanilide) (4a)

A solution of sodium chloropalladate(II) was prepared by warming palladium(II) chloride (1 g, 5.6 mmol) with sodium chloride (0.66 g, 11.3 mmol) in water (50 cm^3).

Sodium acetate trihydrate (4 g, 20.2 mmol) was added, followed by a solution of the ligand **3** (1.4 g, 5.7 mmol) in thf (50 cm^3). The mixture was stirred at room temperature overnight and became very dark, but no precipitate was formed. The mixture was poured into chloroform (200 cm^3), and extracted with water (100 cm^3). The aqueous layer was shaken with chloroform (2 × 100 cm^3), and the combined chloroform solutions washed with water, dried over magnesium sulphate, filtered, and evaporated to give a dark oil. The oil was taken up in thf (5 cm^3) and 40–60 petroleum ether (250 cm^3) was added. The resulting brown solid was filtered off and dried in vacuo. Yield 0.70 g, 32%. The product, which is still slightly contaminated with the ligand, may be purified by dissolution in thf and reprecipitation with petroleum ether, or by chromatography on silica with dichloromethane/thf as eluant. Found: C, 37.86; H, 2.40; Cl; 9.07; N, 7.08. $C_{24}H_{18}Cl_2N_2O_4$ Pd_2S_2 calc.: C, 37.23; H, 2.34; Cl, 9.16, N, 7.24%.

*Carbomethoxylation of **4a***

A solution of the orthopalladated complex **4a** (0.2 g) and sodium acetate trihydrate (1.0 g) in methanol (50 cm^3) was heated under reflux for 2 h as carbon monoxide was bubbled through. The mixture was cooled, set aside overnight, and then filtered into diethyl ether. The ethereal layer was washed repeatedly with water the dried and evaporated, to give the product (125 mg, 79%) as an orange oil. Recrystallisation from methanol (charcoal) and then 60–80 petroleum ether gave yellow crystals m.p. 155–156 °C (lit. [11] 157 °C), and which were shown by IR comparison with an authentic sample to be 2-nitrophenylsulfenyl derivative of methyl anthranilate (ν(C=O) 1690 cm^{-1}). Found: C, 55.43; H, 3.96; N, 9.01. $C_{14}H_{12}N_2O_4S$ calc.: C, 55.25; H, 3.97; N, 9.21%.

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