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Preparation of 6-chloro-5-fluoroindole via the use of palladium and copper-mediated heterocyclisations

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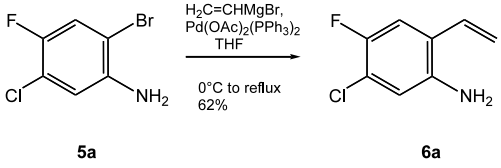
Abstract—The title indole, the heterocyclic core of the 5-HT_{2C} receptor agonist Ro 60-0175, was prepared by a modification to the Stille indole synthesis, or by the method of Gonzalez and co-workers.

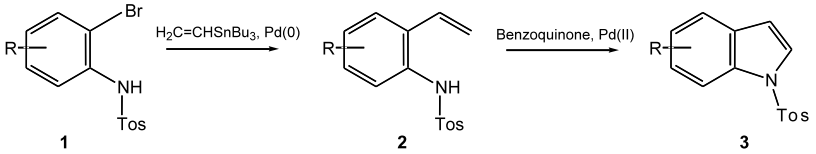
The palladium-mediated synthesis of heterocycles is an active area of research and is being increasingly employed for the formation of molecules of biological importance.[1] Of special note has been the use of these palladium-mediated methods to prepare substituted indole derivatives in a regioselective manner.[2] One such approach, described by Stille and co-workers, combines the use of a palladium(0)-catalysed coupling reaction between (vinyl)tributyltin and an *N*-protected 2-bromoaniline, followed by a palladium(II)-mediated intramolecular aminopalladation/dehydropalladation protocol, to afford *N*-protected indole derivatives (Scheme 1).[3] In this letter, we disclose a modification to the Stille method for preparing substituted indole derivatives, which alleviates the need for *N*-protection, or the use of (vinyl)tributyltin, a highly toxic organotin reagent. The usefulness of this modification was illustrated by preparing 6-chloro-5-fluoroindole **4a**, the heterocyclic core of the 5-HT_{2C} receptor agonist, Ro 60-0175,[4] from the known bromoaniline **5a**.[5] A complementary approach to the indole **4a** from the bromoaniline **5a** using palladium and copper chemistry is also disclosed. Both methods afford the desired indole **4a** in two steps from **5a** and in an overall yield of ca. 30%. A previous preparation of 6-chloro-5-fluoroindole required a sequence of four steps from the bromoaniline **5a** and required the use of methyllithium and *tert*-butyllithium.[4]



5a **6a**

Scheme 2.

The synthesis of the indole **4a** commenced with a palladium(0)-catalysed coupling reaction between the bromoaniline **5a** and 3 equiv. of vinylmagnesium bromide in refluxing THF to give the vinylaniline **6a** in good yield after column chromatography (Scheme 2). This palladium(0)-catalysed coupling of vinylmagnesium bromide was also extended to other bromoanilines (Table 1) and constitutes a useful synthesis of 2-alkenylanilines.[6,7]



1 **2** **3**

Scheme 1.

Keywords: indoles; palladium and compounds; catalysis; coupling reactions.

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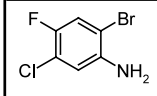
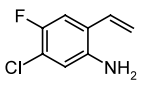
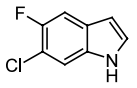
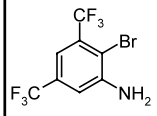
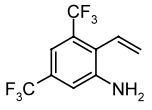
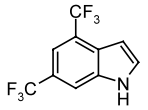
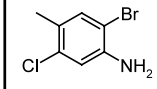
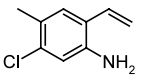
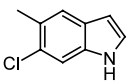
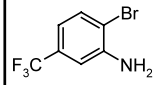
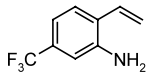
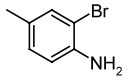
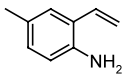
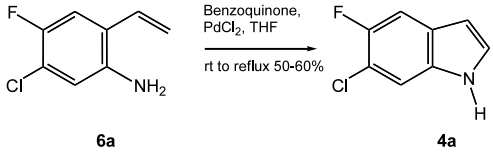
Table 1. Palladium catalysed alkenylaniline and indole formation

Starting material	Alkenyl aniline (% yield)	Indole (% yield)
 **5a**	 **6a** (62)	 **4a** (50)
 **5b**	 **6b** (51)	 **4b** (<10)
 **5c**	 **6c** (69)	 **4c** (0)
 **5d**	 **6d** (39)	Reaction not performed
 **5e**	 **6e** (29)	Reaction not performed



6a **4a**

Scheme 3.

The conversion of the vinylaniline **6a** into the requisite indole **4a** was accomplished by using a catalytic amount of palladium(II) chloride (10 mol%) in the presence of *p*-benzoquinone as a stoichiometric co-oxidant (Scheme 3).[3] This method gave a good yield (50–60%) of the desired heterocycle **4a** when the reaction was carried out on a small scale (up to 5 mmol of **6a**). However, when greater quantities of the precursor **6a** were employed, it was found that the yield of the desired indole **4a** decreased substantially. The conversion of other 2-vinylanilines into indoles by the use of this aminopalladation/dehydropalladation procedure proved to be substrate dependent (Table 1). For example, **6b** gave the desired indole **4b** in low yield under the standard conditions of palladium(II) chloride/*p*-benzoquinone, whereas the reaction of **6c**, using an identical method, gave no indole product at all.

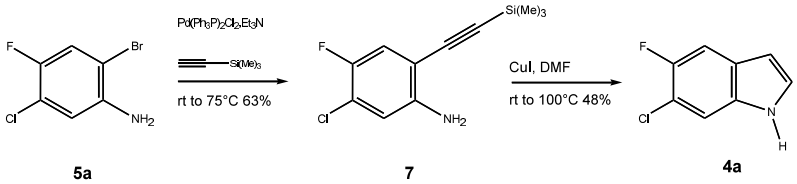
The capricious nature of the palladium(II)-catalysed aromatisation step prompted us to explore a more robust synthesis of indoles and in particular 6-chloro-5-fluoroindole. Towards this end we decided to employ the method of Gonzalez et al.[8] Thus, the bromoaniline **5a** was coupled with (trimethylsilyl)acetylene under palladium(0)-catalysis to afford the 2-alkynylaniline **7**, which was cyclised to the target indole **4a**, by the use of copper(I) iodide in DMF at 100°C (Scheme 4). The overall yield for this two step process (ca. 30%) was comparable to the overall yield obtained using our modified Stille indole synthesis (30–35%). However, unlike our previous synthesis, we found that the formation of **4a** from **7** could be performed on a reasonably large scale (up to 25 mmol of **7**).

In conclusion, we have developed a modification to the Stille synthesis of indoles and used this modified procedure to prepare 6-chloro-5-fluoroindole. In addition, we have shown that 6-chloro-5-fluoroindole may be synthesised on a larger scale using the protocol described by Gonzalez and co-workers.[9]

Experimental section

Preparation of 2-bromo-5-chloro-4-fluoroaniline 5a: Bromine (27.4 g, 170 mmol) in dichloromethane (100 mL) was added dropwise over 4 h to a stirred solution of 3-chloro-4-fluoroaniline (25 g, 170 mmol) and pyridine (20.1 g, 250 mmol) in dichloromethane (300 mL) at 0°C. After complete addition of the bromine, the mixture was stirred for 1 h at 0°C then washed with H_2O (3×100 mL) and brine (1×100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil. The oil was purified by column chromatography on silica gel using heptane/ethyl acetate (24:1) as eluent to give the title compound (15.3 g, 41%) as a white solid. δ_H (400 MHz; $CDCl_3$) 3.98 (2H, br. s), 6.76 (1H, d, $J=6.6$ Hz), 7.21 (1H, d, $J=8.2$ Hz).

Preparation of 3-chloro-4-fluoro-6-vinylaniline 6a: Triphenylphosphine (1.1 g, 4.0 mmol) was added in one portion to a stirred solution of palladium(II) acetate (0.23 g, 1.0 mmol) in THF (50 mL) under argon at room temperature. The mixture was stirred for 15 min then 2-bromo-5-chloro-4-fluoroaniline **5a** (11 g, 50 mmol) was added in one portion. The mixture was stirred for 5 min, cooled to 0°C and a solution of



5a **7** **4a**

Scheme 4.

vinylmagnesium bromide in THF (1 M; 150 mL, 150 mmol) was added dropwise over 40 min. The mixture was then stirred at reflux for 1 h. After allowing to cool to room temperature, the mixture was quenched by pouring into saturated aqueous ammonium chloride (500 mL) and ether (100 mL). The aqueous and organic layers were partitioned and the aqueous layer was extracted with ether (2×100 mL). The combined organic phases were washed with brine (1×100 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo to leave a crude oil. The oil was purified by column chromatography on silica gel using heptane/ethyl acetate (20:1) as eluent to give the title compound (5.3 g, 62%) as a colourless solid. δ_H (400 MHz; $CDCl_3$) 3.70 (2H, br. s), 5.38 (1H, d, $J=9.5$ Hz), 5.62 (1H, d, $J=17.5$ Hz), 6.65 (1H, m), 6.70 (1H, d, $J=6.5$ Hz and 7.06 (1H, d, $J=10$ Hz).

Preparation of 6-chloro-5-fluoroindole 4a from 6a: A mixture of 3-chloro-4-fluoro-6-vinylaniline **6a** (0.34 g, 2 mmol) and THF (20 mL) was stirred at room temperature under an argon atmosphere. Lithium chloride (0.42 g, 10 mmol), palladium(II) chloride (0.035 g, 0.2 mmol) and *p*-benzoquinone (0.34 g, 3.2 mmol) were added and the mixture was stirred at reflux for 16 h. After allowing to cool to room temperature, the mixture was concentrated in vacuo to leave a crude solid. The solid was purified by column chromatography on silica gel using heptane/dichloromethane (3:1) as eluent to give the title compound (0.18 g, 53%) as a pale brown solid. Mp 105–107°C; δ_H (400 MHz; $CDCl_3$) 6.50–6.51 (1H, m), 7.25 (1H, t, $J=2.8$ Hz), 7.35 (1H, d, $J=9.4$ Hz), 7.40 (1H, d, $J=9.4$ Hz) and 8.01 (1H, br. s).

Preparation of 5-chloro-4-fluoro-2-(trimethylsilylethynyl) aniline 7: A mixture of 2-bromo-5-chloro-4-fluoroaniline **5a** (6.6 g, 30 mmol) and triethylamine (60 mL) was stirred at room temperature under an argon atmosphere. Bis(triphenylphosphine) palladium(II) chloride (0.4 g, 0.6 mmol) and trimethylacetylene (7.8 mL, 54 mmol) were added and the mixture was stirred at 60°C for 16 h. After allowing to cool to room temperature, ether (100 mL) was added and the mixture was filtered through a bed of Celite®. The filter cake was washed with ether (2×100 mL) and the filtrate was dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil. The oil was purified by column chromatography on silica gel using heptane/ethyl acetate (30:1) as eluent to give the title compound (4.5 g, 63%) as a pale brown oil. δ_H (400 MHz; $CDCl_3$) 0.26 (9H, s), 4.13 (2H, br. s), 6.70 (1H, d, $J=6.5$ Hz) and 7.05 (1H, d, $J=9$ Hz).

Preparation of 6-chloro-5-fluoroindole 4a from 7: Copper(I) iodide (7.1 g, 38 mmol) was added in one portion to a stirred solution of 5-chloro-4-fluoro-2-(trimethylsilylethynyl)aniline **7** (4.5 g, 19 mmol) in DMF (80 mL) under an argon atmosphere. The suspension was stirred at room temperature for 10 min then at 100°C for 2 h. After allowing to cool to room temperature, ether (100 mL) was added and the mixture was filtered through a bed of Celite®. The filter cake was washed with ether (2×100 mL) and the filtrate was dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil. The oil was purified by column chromatography on silica gel using heptane/ethyl acetate (5:1) as eluent to give the title compound (1.5 g, 48%) as a pale brown solid. The data was identical to previously synthesised material.

Acknowledgements

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9. A large scale preparation of 6-chloro-5-fluoroindole using a modified Leimgruber–Batcho route will be detailed elsewhere.