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Synthesis of Arylpiperazines *via* Palladium-Catalysed Aromatic Amination Reactions of Bromoarenes with *N-tert*-Butoxycarbonylpiperazine

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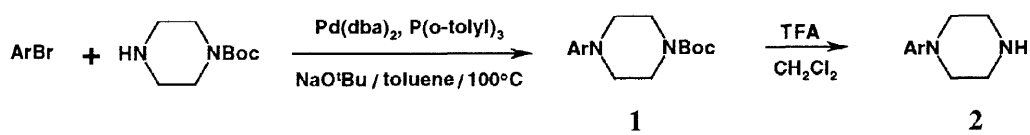
Absract: Reaction of a series of bicyclic bromoarenes with *N-tert*-butoxycarbonylpiperazine (*N*-Boc-piperazine) under palladium-catalysed coupling conditions followed by routine removal of the Boc group with trifluoroacetic acid in dichloromethane gave the corresponding arylpiperazines in moderate to good yield. © 1998 Elsevier Science Ltd. All rights reserved.

Arylpiperazines **2** form key pharmacophoric elements in a wide range of drugs which act within the mammalian central nervous system. In particular, many *N*-substituted arylpiperazines are ligands for the various classes of serotonin (5-HT) receptors.[1] Synthesis of arylpiperazines has classically involved the reaction of an aniline with either *bis*-(2-chloroethyl)amine[2] or diethanolamine.[3] However, the scope of these reactions is often limited by poor yields, harsh conditions and relatively long reaction times. Recent improvements to this classical methodology are *bis*-alkylation of simple substituted anilines under microwave irradiation in the absence of solvent[4] and alumina-supported synthesis.[5] In a different approach, Zhao *et. al.*[6] have synthesised arylpiperazines **2** *via* palladium-catalysed aromatic amination reactions between piperazine and a range of monocyclic bromoarenes, using the methodology developed by Buchwald[7] and Hartwig.[8] An alternative procedure, involving the synthesis of protected or unprotected arylpiperazines from (η^6–fluoroarene)tricarbonylchromium complexes, has also been reported.[9] For our work on 5-HT_{1A} ligands, we required a variety of bicyclic arylpiperazines (Table 1). In this communication we wish to report a convenient procedure for the synthesis of bicyclic arylpiperazines **2** which involves the reaction of *N-tert*-butoxycarbonylpiperazine (*N*-Boc-piperazine) with bicyclic bromoarenes under conditions developed by Buchwald,[7] followed by standard deprotection of the Boc-protected arylpiperazines **1** with trifluoroacetic acid (Scheme 1).

Scheme 1



1 **2**

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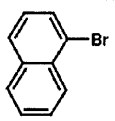
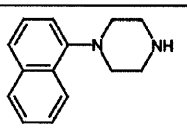
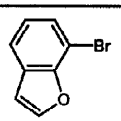
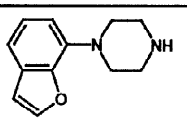
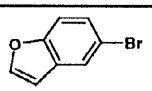
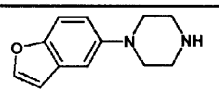
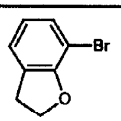
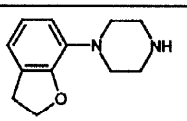
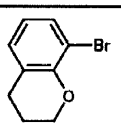
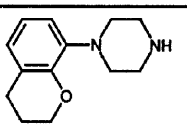
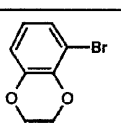
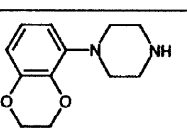
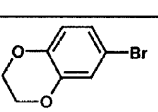
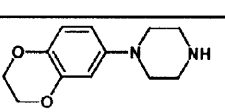
The use of a protected piperazine was investigated in order to circumvent the potential problem of *bis*-arylation in this coupling reaction, as seen by Zhao *et. al.*[6] Thus, the bromoarene, *N*-Boc-piperazine (1.2 equivalents) and the sterically hindered base, sodium *tert*-butoxide (1.4 equivalents), were heated in toluene at 100°C under nitrogen for 19 hours in the presence of 2 mol% of *bis*(dibenzylideneacetone)palladium(0) and 4 mol% of tri(*o*-tolyl)phosphine to give the Boc-protected arylpiperazines **1**. The Boc protection was then removed quantitatively using trifluoroacetic acid in dichloromethane to afford the desired bicyclic arylpiperazines **2** (Table1).

Table 1. Palladium-catalysed formation of arylpiperazines from bicyclic bromoarenes.

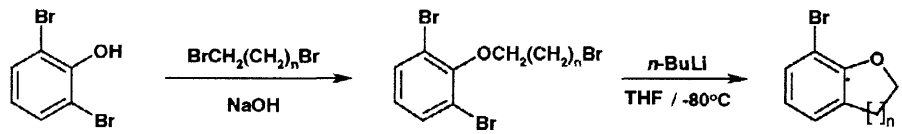
Entry	ArBr	Arylpiperazine	Overall Yield, %[10]
a			60
b			20
c			65
d			31
e			36
f			34
g			60

The relative success of the aryl amination reaction was dependent upon the nature of the bromoarene. 1-Bromonaphthalene underwent the reaction in 60% yield overall (Entry a).[11] This was a significant improvement upon the reaction of 1-bromonaphthalene with piperazine at 165° C under pressure for 5 days, which afforded 1-(1-naphthyl)piperazine in only 9% yield in the absence of any palladium species.

However, bromoarenes containing an *ortho*-oxygen substituent (Entries b,d,e and f) gave the desired arylpiperazines in only moderate yields. This may be due to steric hindrance in the formation of the intermediate palladium species caused by the bulky phosphine ligands, or possibly the interaction of the oxygen lone pair at the metal centre. The major by-product observed was the debrominated arene, probably arising *via* base-induced β-hydride elimination of the intermediate Pd(II)-amido complex and subsequent reduction as proposed previously.[7a] This effect appears specific to *ortho*-oxygen, since 5-bromobenzo[*b*]furan (Entry c) and 6-bromo-1,4-benzodioxane (Entry g) underwent the reaction in yields comparable with that of 1-bromonaphthalene (Entry a).

The bromoarenes 7-bromo-2,3-dihydrobenzo[*b*]furan **5** and 8-bromo-3,4-dihydro-2*H*-benzopyran **6**, were prepared in excellent yield by Parham cyclialkylation[12] of the 2,6-dibromophenoxyalkyl bromides **3** and **4** using *n*-butyllithium in a mixture of tetrahydrofuran and hexane at -80° C. The aryloxyalkyl bromides **3** and **4** were conveniently prepared in good yield by alkylation of 2,6-dibromophenol with the appropriate dibromoalkane in aqueous sodium hydroxide solution (Scheme 2).[13]

Scheme 2



3 (n=1) **5** (n=1)

4 (n=2) **6** (n=2)

In conclusion, we have shown that a series of bicyclic arylpiperazines can be made efficiently by reaction of bicyclic bromoarenes with *N*-Boc-piperazine under palladium-catalysed aromatic amination conditions followed by routine deprotection under acidic conditions.

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References and Notes

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8. (a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708.

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10. Satisfactory spectral and analytical data were obtained for all new compounds.

11. Representative procedure : Tri(*o*-tolyl)phosphine (0.3 g, 1.0 mmol) was added at ambient temperature under nitrogen to a suspension of *bis*(dibenzylideneacetone)palladium(0) (0.3 g, 1.0 mmol) in toluene (150 ml). Sodium *tert*-butoxide (3.3 g, 33.9 mmol) was added followed by *N*-Boc-piperazine (5.2 g, 28.2 mmol) and 1-bromonaphthalene (5.0 g, 24.2 mmol). The mixture was stirred at 100° C for 19 h, then cooled. The organic solution was decanted from the palladium residues, washed with brine (2 x 250 ml) and dried over magnesium sulphate. The organic solution was concentrated *in vacuo* and the residue was purified by flash chromatography over silica using diethyl ether/petroleum ether (bp 60-80° C) (1:9) as the eluent to give *tert*-butyl 4-(1-naphthyl)piperazine-1-carboxylate (4.9 g, 65%) as a pale yellow solid, mp 56-58° C. Trifluoroacetic acid (10 ml) was added slowly at 0-5° C under nitrogen to a solution of *tert*-butyl 4-(1-naphthyl)piperazine-1-carboxylate (3.0 g, 9.6 mmol) in dichloromethane (10 ml). The mixture was stirred at ambient temperature for 1 h then poured on to cold water (50 ml). The aqueous solution was made basic by the addition of aqueous ammonia solution, then the product was extracted into dichloromethane (2 x 100 ml). The combined extracts were washed with brine (200 ml), dried over sodium sulphate, then concentrated *in vacuo*. The residue was purified by flash column chromatography over silica using methanol/dichloromethane (1:9) as the eluent to give 1-(1-naphthyl)piperazine (1.9 g, 91%) as a pale yellow oil. A saturated solution of HCl gas in diethyl ether was added to 1.55 g of the piperazine in ethyl acetate to yield 1.3 g of the hydrochloride salt. mp 311-313° C, [lit.[14] 313-315° C].

12. Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384-1388.

13. Representative procedure : 1,2-Dibromoethane (5.0 ml, 57.6 mmol) was added to a stirred solution of sodium hydroxide (2.5 g) and 2,6-dibromophenol (14.5 g, 57.6 mmol) in water (45 ml). The stirred mixture was heated under reflux for 17 h, cooled and the product extracted into diethyl ether (2 x 100ml). The combined extracts were washed with 1M aqueous sodium hydroxide solution (100 ml) and brine (100 ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash chromatography over silica using diethyl ether/petroleum ether (bp 60-80° C) (1:9) as the eluent to give 2-(2,6-dibromophenoxy)ethyl bromide (12.3 g, 61%) as a colourless oil.
n-Butyllithium (13.7 ml, 2.5M in hexanes, 34.2 mmol) was added at -80°C under nitrogen to a solution of 2-(2,6-dibromophenoxy)ethyl bromide (12.0 g, 33.5 mmol) in tetrahydrofuran (120 ml) and hexane (30 ml). The mixture was stirred at this temperature for 30 min, allowed to warm to 0° C, and poured into water (100 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 100 ml). The combined extracts were dried over sodium sulphate and concentrated *in vacuo*, to give a residue which was purified by flash chromatography over silica using diethyl ether/petroleum ether (bp 60-80° C) (1:24) as the eluent to give 7-bromo-2,3-dihydrobenzo[*b*]furan (5.8 g, 86%) as a colourless solid, mp 32-34° C.

14. Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Titeler, M.; McKenney, J. D. *J. Med. Chem.* **1986**, *29*, 2377.