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# Synthesis of Arylpiperazines via Palladium-Catalyzed Aromatic Amination Reaction with Unprotected Piperazines

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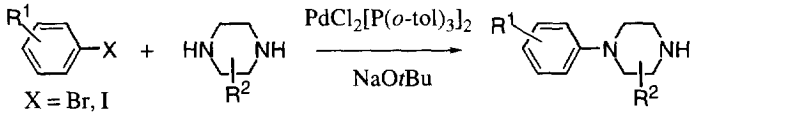
***Abstract***: A series of arylpiperazines were synthesized in moderate to good yields by palladium-catalyzed coupling reaction of aryl halides with unprotected piperazines. Very high regioselectivities were observed when using 2-methyl or 2,6-dimethylpiperazine.


Arylpiperazines are an important class of compounds in the field of medicinal chemistry. Many ligands for serotonin receptors have a piperazine moiety.[1] MCPP (**1**, 1-(*m*-chlorophenyl)piperazine), for instance, is a classical agonist for the $5HT_{2B}$ and $5HT_{2C}$ receptors. The classical synthesis of arylpiperazines usually involves a cyclization reaction of a substituted aniline with bis(2-chloroethyl)amine or diethanolamine.[2] A modified procedure using alumina support has also been reported.[3] The scope of the cyclization reaction for the synthesis of arylpiperazines bearing substituents on the carbon atoms of the piperazine ring (**2**) is limited due to poor availability of the corresponding substituted bis(2-chloroethyl)amines. Here, we report a convenient procedure for synthesizing arylpiperazines with or without substitution on the piperazine ring via palladium-catalyzed coupling reactions (Scheme 1).

**Scheme 1**

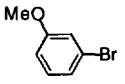
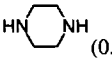
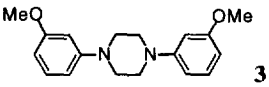
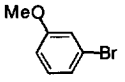
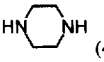
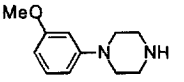
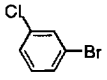
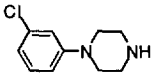
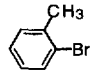
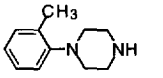
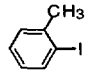
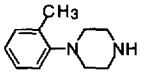
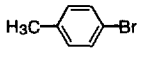
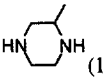
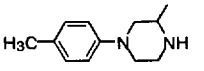
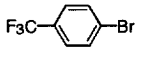
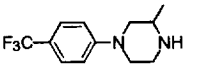
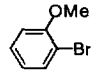
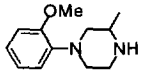
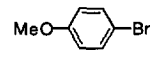
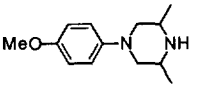
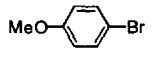
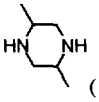
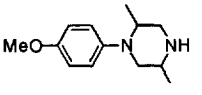



**1** (MCPP): $R^1$ = *m*-Cl; $R^2$ = H
**2** : $R^2 \neq H$

Palladium-catalyzed amination reactions of aryl halides were recently reported by Buchwald[4] and Hartwig.[5] This important discovery opens a new avenue for synthesizing many biologically important molecules that are otherwise difficult to prepare. The reaction gave good yields when using substrates with a single reactive amino group.[4a, 5b] We investigated the use of unprotected piperazines in this coupling reaction, primarily for the synthesis of N-monoarylpiperazines. Under standard reaction conditions reported in the literature,[4a] the amination of 3-bromoanisole in toluene using 1.2 equivalents of piperazine in the presence of 3 mol% of $[PdCl_2(P(o\text{-tolyl})_3)_2]$ and 1.4 equivalents of sodium *tert*-butoxide gave a mixture of N-mono and N,N'-bis-substituted piperazines (**4** and **3**, Table 1) in 3.3 : 1 ratio according to $^1H$ NMR analysis. An authentic sample of **3** was obtained in 46% isolated yield by reaction of 3-bromoanisole with half an equivalent of piperazine under the same reaction conditions (entry 1). Increasing the initial amount of piperazine to 2 and 4 equivalents led to improved product ratios (**4** :**3** ) of 7.3:1 and 19:1, respectively.[6] The isolated yield of **4** was 50% with 4 equivalents of piperazine (entry 2). Since piperazine is readily available

and inexpensive, the latter conditions (4 equiv. of piperazine) were employed for the synthesis of MCPP (**1**) from 3-bromochlorobenzene, which afforded **1** in 46% isolated yield (entry 3) and the corresponding bis coupling product in less than 5% yield.

**Table 1.** Palladium-Catalyzed Conversion of Aryl Bromides to Arylpiperazines[a,7]

| Entry | ArX | Piperazine (equiv.) | Arylpiperazine | | Yield(%)[c] |
|---|---|---|---|---|---|
| 1 |  |  (0.5) |  | **3** | 46 |
| 2 |  |  (4) |  | **4** | 50 |
| 3 |  | " |  | **1** | 46 |
| 4 |  | " |  | **5** | 10 |
| 5[b] |  | " |  | **6** | 30 |
| 6 |  |  (1.2) |  | **7** | 57 |
| 7 |  | " |  | **8** | 49 |
| 8 |  | " |  | **9** | 13 |
| 9 |  |  (1.2) |  | **10** | 63 |
| 10 |  |  (1.2, trans) |  | **11** (cis/trans 1:5) | 19 |

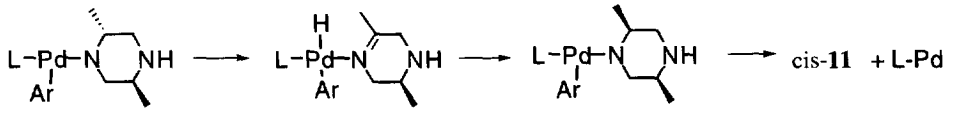
[a] With 2-3 mol% of $PdCl_2[P(o\text{-}tol)_3]_2$; toluene, at 100 °C for 2-5h except entry 5. [b] Dioxane as solvent at 60 °C. [c] Yields reported are based on analytically pure, isolated compounds after column chromatography.

The aromatic amination reaction was found to be very sensitive to the steric hindrance of the substrates. Ortho-substituted aryl bromides gave the desired arylpiperazines in low yields (entries 4 and 8);

debromination of the starting aryl bromides was the major competitive side reaction in these examples. Using 2-iodotoluene and dioxane as solvent[4c] at 60°C gave the coupling product in slightly better yield (entry 5) than using 2-bromotoluene in toluene (entry 4).

We also examined the amination of aryl bromides with piperazines bearing methyl substituents on the carbon atoms. Using 1.2 equivalents of the C-substituted piperazines and 1.4 equivalent of NaO*t*-Bu and 2-3% $PdCl_2[P(o\text{-}tol)_3]_2$ in toluene at 100 °C, satisfactory yields were usually obtained for the N-monoarylpiperazines (entries 6-10). In the cases of unsymmetrical piperazines (entries 6-9), the coupling reactions occurred with the less hindered nitrogen atom of the starting piperazine; thus, neither the other possible regioisomer nor the bis-coupling product was detected in the crude reaction mixtures. The high regioselectivity of the palladium-catalyzed amination reaction may be explained by the steric sensitivity of the reaction which is probably caused by the bulkiness of the palladium catalyst bearing large tri-*o*-tolylphosphine ligands. This steric sensitivity is further evidenced by the relatively low yield of the coupling reaction using *trans*-2,5-dimethylpiperazine in which both nitrogen atoms are hindered (Entry 10). Interestingly, a 5:1 mixture of *trans*- and *cis*-1-(4-methoxyphenyl)-2,5-dimethylpiperazine was obtained starting from *trans*-2,5-dimethylpiperazine.[8] The formation of the cis isomer may be explained by a sequence of β-hydride elimination and insertion reactions of reaction intermediates shown in Scheme 2. The β-hydride elimination pathway has been proposed for the formation of imines and debromination side products in related coupling reactions.[4a]

**Scheme 2**. Postulated mechanism for the formation of *cis*-**11**




**12** **13** **14**

In summary, we have demonstrated that the palladium-catalyzed amination of aryl halides is a useful and convenient method for the synthesis of N-arylpiperazines. In the case of piperazine itself, the appropriate choice of reaction stoichiometry leads to either a symmetrical N,N'-bisarylpiperazine or N-monoarylpiperazine in a synthetically useful yield. Amination reactions with C-substituted unsymmetrical piperazines proceeded with high regioselectivity, allowing facile preparation of several novel arylpiperazines.

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**References and Notes**:

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(c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

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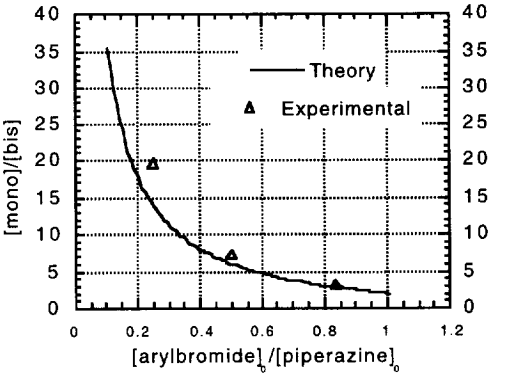
(b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
(c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708.

6. A good fit was found between the experimental results and the product ratio (mono/bis) calculated according to a simplified irreversible consecutive first order reaction model shown below. The model was obtained based on the assumptions that: (1) the concentration of ArPdBrL is in steady state;[5b] (2) the coupling reaction is first order in the concentration of piperazine or monoarylpiperazine and (3) the first nitrogen and the second nitrogen of piperazine behave identically in the coupling reactions ($k_1=2k_2$).




$$\text{Piperazine} \xrightarrow{k_1} \text{Monoarylpiperazine} \xrightarrow{k_2} \text{Bisarylpiperazine}$$

7. A representative experimental procedure is given below:
Synthesis of 1-(4-methylphenyl)-3-methylpiperazine **7**. A mixture of *p*-bromotoluene (340 mg, 2 mmol), 2-methylpiperazine (245 mg, 2.44 mmol, 1.2 equiv.), sodium tert-butoxide(278 mg, 2.9 mmol, 1.45 equiv.) and $PdCl_2[P(o\text{-}tol)_3]_2$ (44 mg, 3 mol%) in 17 mL of anhydrous toluene was heated at 100 °C under nitrogen for 3 h. TLC indicated complete disappearance of the starting p-bromotoluene. The dark colored reaction mixture was filtered through celite and the celite was washed with 2x50 mL of dichloromethane. The filtrate was concentrated and chromatographed on silica gel using $CH_2Cl_2$/MeOH/$NH_4OH$ (200 : 10 : 1) to give 213 mg of an oily product (56.5% yield). $^1$H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.12 (d, J = 6.3 Hz, 6H), 2.26 (s, 3H), 2.30 (m, 1H), 2.65 (td, J = 11.3 and 3.8 Hz, 1H), 2.9-3.2 (m, 3H), 3.45 (m, 2H), 6.8 (d, J = 8.6 Hz, 2H) 7.05 (d, J = 8.6 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 75MHz) δ (ppm) 19.9, 20.4, 46.1, 50.2, 50.6, 57.7, 116.5, 129.16, 129.6, 149.6. NOE experiments determined that the méthyl group was attached to the 3 position of the piperazine ring and not the 2 position.

8. *trans*-2,5-Dimethylpiperazine employed in the reaction was purchased from Aldrich Chemical Co. and was found to be free of the cis isomer by 300 MHz $^1$H NMR analysis.

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