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A general and convenient synthesis of *N*-aryl piperazines

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Abstract—A general and convenient synthesis of *N*-aryl piperazines from bis(2-chloroethyl)amine hydrochloride and a broad range of anilines in diethylene glycol monomethyl ether is described.

N-Aryl piperazines are key structural elements of a variety of biologically active compounds. In the neuroscience field in particular, they are often found in ligands for serotonin (5-hydroxytryptamine, 5-HT) and dopamine receptors and monoamine transporters.[1,2] The established syntheses of *N*-aryl piperazines include formation of the piperazine ring by reaction between an aniline and *N*,*N*-bis(2-haloethyl)amine first reported by Prelog.[3,4] Aromatic substitution of an aryl halide by an unsubstituted piperazine facilitated by an electron-withdrawing group on the aromatic ring or by a palladium catalyst[5,6] based on Buchwald[7] and Hartwig[8] amination chemistry are other common approaches to this key moiety. Noteworthy also is an interesting synthesis using 3-substituted 2-oxazolidinone derivatives, which serve as piperazine ring precursors.[9]

Recently, as part of our efforts in developing therapeutic agents for CNS diseases, we desired a number of *N*-aryl piperazines as key component of ligands for the SAR. Our initial approach was from their corresponding aniline intermediates and therefore we investigated Prelog's original synthesis and its variants. In this approach, the reaction was carried out in low boiling alcohols such as methanol or butanol using excess anilines or Na_2CO_3 as acid scavengers, which resulted in poor to moderate yields of *N*-aryl piperazines. Subsequent modification with higher boiling point solvents including 2-butoxyethanol,[10] chlorobenzene,[11] DMF,[12] and diglyme[13] at elevated temperatures in the presence of K_2CO_3, which have been shown to give higher yields for a limited number of *N*-aryl piperazines, gave equally poor results. Furthermore, it has been shown that a nonpolar solvent, such as chlorobenzene, in the absence of base provides improved yields where traditional conditions have failed.[14] However, due to the poor solubility of certain key aniline substrates in this nonpolar solvent, this approach was not optimal. There are several other notable approaches to these key moieties, however, for our purposes they were not utilized due to more severe reaction conditions or poor reported yields.[15–17]

As discussed earlier, much of the previously reported syntheses of *N*-aryl piperazines involving *N*,*N*-bis(2-haloethyl)amine are carried out in the presence of a base in a way similar to standard amine alkylation. This is presumably done in order to facilitate the alkylation by scavenging the halogen chloride generated in the reaction. It seemed to us that these basic conditions may have been partially responsible for the general low yields of the products, possibly due to the competitive side reaction between the resultant *N*-aryl piperazine and the *N*,*N*-bis(2-haloethyl)amine. Hence, we investigated the formation of *N*-aryl piperazines using *N*,*N*-bis(2-haloethyl)amine HCl salt and anilines in the absence of base. It was our hope that the electrophilicity of the carbon proximal to the halogen of the *N*,*N*-bis(2-haloethyl)amine would be increased upon protonation on the nitrogen. Toward that end, a number of solvents particularly those with relatively high boiling points, for example, toluene, chlorobenzene, DMF, DMA, 2-butoxyethanol, diglyme, ethylene glycol, and diethylene glycol monomethyl ether were screened. While a number of the solvents utilized provided good yields in selected examples, diethylene glycol monomethyl ether was shown to be a general solvent that gave consistently good to excellent results.

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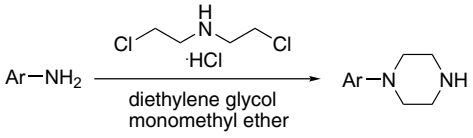
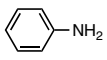
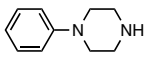
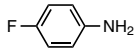
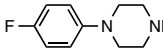
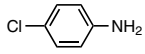
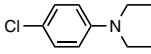
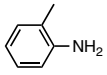
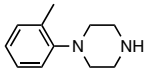
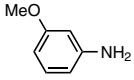
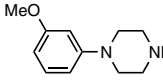
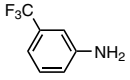
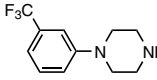
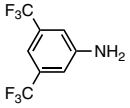
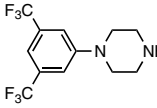
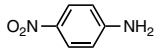
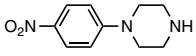
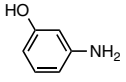
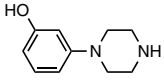
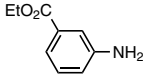
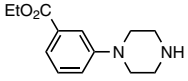
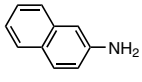
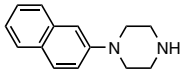
To demonstrate the generality of this approach, a broad range of anilines were chosen to explore the scope of this reaction. The results are summarized in Table 1. In general, good to excellent yields were obtained for all aniline substrates, including those containing electron-donating (entry 5), electron-withdrawing (entries 6–8), and sterically hindered moieties (entry 4). *N*-Aryl piperazines with functional groups such as phenols and esters that posed problems in the previously reported syntheses have also been successfully assembled (entries 9 and 10).

General procedure: In an atmosphere of dry N_2, a mixture of aniline (3.0 mmol), bis(2-chloroethyl)amine hydrochloride (3.0 mmol), and diethylene glycol monomethyl ether (0.75 mL) was heated at 150 °C for 6–12 h.[18] After being cooled to room temperature, the mixture was dissolved in MeOH (~4 mL) followed by addition of Et_2O (~150 mL). The precipitate was filtered off and washed with Et_2O to provide HCl salt. The HCl salt was further converted to free amine by treatment with Na_2CO_3 solution and extracted with EtOAc (2×). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to provide the pure free amine product in most cases. If needed the product was further purified by column chromatography.

In summary, we have developed a general and convenient procedure for the synthesis of *N*-aryl piperazines from anilines using bis(2-chloroethyl)amine hydrochloride in diethylene glycol monomethyl ether in the absence of base and high reaction temperatures.

Table 1. Synthesis of *N*-aryl piperazines from anilines



Entry	Ar–NH_2	Product	Yield (%)[a]
1			79
2			87
3			87
4			66
5			95
6			67
7			65
8			90
9			87[b]
10			90
11			60

[a] Isolated yields based on free amine.
[b] Yield based on HCl salt.

Acknowledgments

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References and notes

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18. The reaction time can be significantly shortened under microwave conditions. For example, in the case of aniline (Table 1, entry 1) the reaction was complete within 10 min under microwave irradiation at 180 °C (unoptimized).