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A Versatile and Practical Microwave-Assisted Synthesis of Sterically Hindered *N*-Arylpiperazines

Rong Gao and Daniel J. Canney*

Temple University School of Pharmacy, Department of Pharmaceutical Sciences, 3307 North Broad Street, Philadelphia, Pennsylvania 19140

canney@temple.edu

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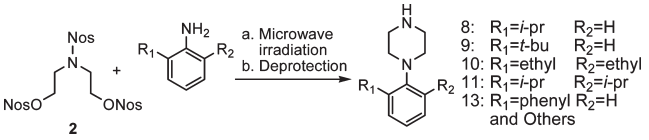

A wide-ranging and practical synthesis of structurally diverse, sterically hindered *N*-arylpiperazines from 2,2′-(4-nitrophenylsulfonylazanediyl) bis(ethane-2,1-diyl) bis(4-nitrobenzenesulfonate) and substituted anilines has been achieved using microwave irradiation in acetonitrile followed by deprotection with PhSH.

N-Arylpiperazines are a class of heterocyclic compounds that are important intermediates in organic synthesis and are commonly found as fragments in natural products, receptor ligands, and in many pharmacologically active molecules.[1] There are several well-established syntheses of *N*-arylpiperazines that include the reaction of anilines with *N*,*N*-bis-(2-chloroethyl)amine reported by Prelog.[2] Modifications of this method provided some improvements to the reaction but were largely restricted to unhindered substituents.[3] Aromatic substitution of electron-poor aryl halides by unsubstituted piperazines represents an alternative approach,[4] and catalysts have been developed to facilitate this type of coupling reaction.[5] Limitations to the currently available methods include low to moderate yields and restrictions on the type of aromatic substituents that are tolerated. Efficient routes for the synthesis of *N*-arylpiperazines with bulky aromatic substituents are extremely scarce. For example, the reaction of isopropylaniline and *N*,*N*-bis(2-chloroethyl)amine provides 1-(2-isopropylphenyl)piperazine in 21% yield.[6] This compound can also be prepared from a 3-substituted 2-oxazolidinone precursor in 36% yield.[7] Alternatively, the synthesis of the same compound has been reported using a Pd catalyst, but no yield is included. Under the same reaction conditions, the less hindered *N*-(2-ethylphenyl)piperazine was prepared in 56% yield.[8] To date, an efficient and practical method for preparing structurally diverse, sterically demanding *N*-arylpiperazines (e.g., 1-(2-*tert*-butylphenyl)piperazine, 1-(2-iodophenyl)-piperazine, and 1-(2,6-diisopropyl phenyl)piperazine) is lacking.

Our interest in developing novel ligands for G-protein coupled receptors (GPCRs) required the incorporation of substituted *N*-arylpiperazines such as 1-(2-isopropylphenyl)-piperazine and 1-(2-*tert*-butylphenyl)piperazine as key fragments in the target molecules. Thus, the goal of the present work was to design an efficient synthetic route which provided ready access to a series of substituted *N*-arylpiperazines with a wide range of steric hindrance. A review of the literature revealed a general paucity of systematic studies involving the preparation of these important intermediates. Thus, we set out to systematically investigate leaving/protecting groups, reaction temperature (microwave assisted), bases, solvents, and deprotecting conditions. The protection of the amine during the reaction was hypothesized to lead to improved yields by limiting possible side reactions.

Several approaches were considered as potential means of improving the scope and yields of previously reported routes to the target compounds. Microwave irradiation has been reported in aniline alkylation reactions involving *N*,*N*-bis(2-bromoethyl)amines under aqueous conditions.[9] A small series of unhindered *N*-arylpiperazines were synthesized in low to moderate yields using a modified domestic microwave oven.[10] Hence, microwave irradiation was investigated here for the preparation of sterically demanding arylpiperazines. Replacing the halides of starting materials with better leaving groups and protecting the amine with same group has been considered as an approach to improve reaction yields. Employment of the tosyl and mesyl groups has been reported to give 37% and 50% (prior to deprotection) yields, respectively, suggesting that these groups are not sufficient given the poor nucleophilicity of the aniline nitrogen.[11] Moreover, these leaving/protecting groups are not ideal due to the harsh

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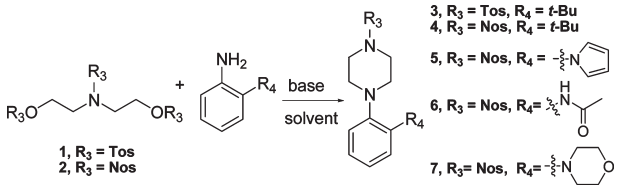
TABLE 1. Optimization of the Coupling Reaction To Give 3−7



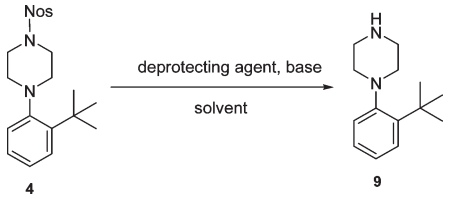
R_3	R_4	base	solvent	T (°C)	yield (%)
tos	*t*-Bu	Et_3N	CH_3CN	160	18 [b]
tos	*t*-Bu	Pyridine	CH_3CN	160	N.A. [a]
tos	*t*-Bu	DMAP	CH_3CN	160	N.A. [a]
tos	*t*-Bu	DIPEA	CH_3CN	160	40 [b]
nos	*t*-Bu	DIPEA	CH_3CN	160	91 [b]
nos	*t*-Bu	DIPEA	THF	160	52 [b]
nos	*t*-Bu	DIPEA	1,4-Dioxane	160	66 [b]
nos	*t*-Bu	DIPEA	CH_3CN	175	90 [b]
nos	*t*-Bu	DIPEA	CH_3CN	145	84 [b]
nos	*t*-Bu	DIPEA	CH_3CN	130	42 [b]
nos		DIPEA	CH_3CN	160	83 [b]
nos		DIPEA	CH_3CN	175	82 [b]
nos		DIPEA	CH_3CN	160	50 [b]
nos		DIPEA	CH_3CN	175	81 [b]
nos		DIPEA	CH_3CN	160	74 [b]
nos		DIPEA	CH_3CN	175	86 [b]

[a]No product is formed on the basis of LC−MS analysis. [b]Isolated yield.

conditions required for deprotection.[12] Thus, in our hands, the nosyl group was shown to be a superior leaving/protecting group and was employed in future reactions to improve the yield.

The starting materials utilized in our initial efforts to investigate the use of several bases were **1** and 2-*tert*-butyl aniline since both are commercially available and the tosyl group is both a reliable leaving group and a stable protecting group (Table 1). Several bases (Et_3N, pyridine, DMAP, *N*,*N*-diisopropylethylamine) were screened under the conditions outlined in Table 1 in a microwave reactor (1 h at 160 °C). The use of DIPEA (*N*,*N*-diisopropylethylamine) in CH_3CN (acetonitrile) under these conditions provided the highest yield (40%), and DIPEA was used in subsequent reactions. Changing the leaving/protecting group from tosyl to nosyl resulted in a dramatic improvement in yield (91%), and the nosyl group was used to explore the suitability of several solvents. Importantly, the nosylated starting material is easily synthesized in bulk quantities (40 g in our hands) and purified by recrystallization precluding the need for column chromatography.[13] Due to the susceptibility of some starting materials to hydrolysis, polar aprotic solvents were used here instead of water. Acetonitrile (CH_3CN), THF, and 1,4-dioxane were chosen because of their excellent solubilizing properties, the ability to reach high temperatures under pressure, and the relative ease of removal under reduced pressure. The preliminary results of these reactions indicate that CH_3CN gave superior yields. Finally, to explore the effect of temperature, the reaction was carried out under varying temperatures for 1 h (Table 1). When R_2 = *t*-Bu or acetamide, a temperature of 160 °C or above provided yields of 80% or higher. When R_2 = pyrrole and morpholine, higher temperatures (175 °C) were required to provide high yields. Thus, 175 °C was chosen for future reactions involving nosyl-protected diethanolamine and inexpensive, substituted anilines in CH_3CN to prepare nosyl-protected substituted *N*-arylpiperazines in moderate to high yields. Purification of the protected intermediates are straightforward and involves either recrystallization or passage through a pad of silica precluding the need for column chromatography.

TABLE 2. Optimization of the Deprotection Reaction To Give 9



deprotecting agent	base	solvent	*T* (°C)	yield (%)
$HSCH_2COOH$	K_2CO_3	DMF	24	N.A.[a]
$HSCH_2COOH$	DIPEA	DMF	24	N.A.[a]
$HSCH_2COOH$	LiOH	DMF	24	N.A.[a]
PhSH	K_2CO_3	DMF	24	45[b]
PhSH	K_2CO_3	DMF	60	32[b]
PhSH	K_2CO_3	CH_3CN, 2% DMSO	50	86[b]

[a]No product is formed on the basis of LC−MS analysis. [b]Isolated yield.

In an effort to optimize the recovery of the deprotected *N*-arylpiperazines, several deprotection conditions were tested.[14] The use of $HSCH_2COOH$ in the presence of base (K_2CO_3, DIPEA, LiOH) provided none of the deprotected amine. PhSH in the presence of K_2CO_3 afforded low yields of the amine when attempted in DMF presumably due to the formation of 4-phenyl thioether.[15] The use of PhSH with K_2CO_3 in CH_3CN and 2% DMSO gave the highest yield of the methods tested (Table 2). The unpleasant smell of PhSH can be easily removed by addition of concentrated NaOH solution followed by extraction with organic solvent. Thus, nosyl-protected piperazines are stable intermediates that are easily deprotected and may be used to prepare structurally diverse, synthetically important target molecules.

To explore the efficiency and scope of the approach, a broad range of sterically hindered, electronically and lipophilically diverse anilines were reacted with **2**. The results of those efforts are summarized in Table 3 and illustrate the general applicability of the method and the moderate to high yields of the target *N*-arylpiperazines obtained. Furthermore, a diverse series of aniline substrates have been utlized including those containing substituents with considerable steric hindrance (e.g., **8**, **9**, **11**, **13**−**16**), ethers (**16**), halogens (**14**), esters (**19**), amides (**12**), and heterocycles (**15**, **18**).

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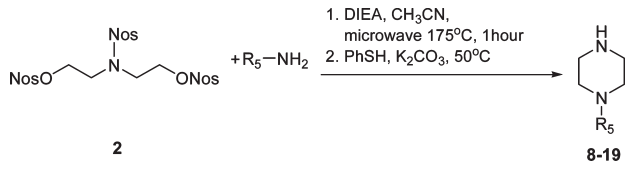
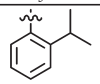
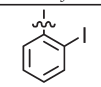
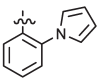
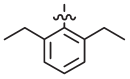
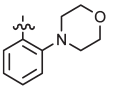
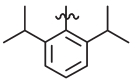
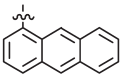
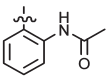
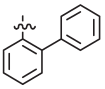
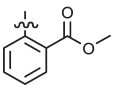
TABLE 3. Microwave-Assisted Synthesis of *N*-Arylpiperazines 8−19



2 **8-19**

#	R_5	yield (%) [a,b]	#	R_5	yield (%)[a,b]
8		80	**14**		65
9		71	**15**		71
10		72	**16**		81
11		61	**17**		71
12		68	**18**		60
13		86	**19**		66

[a]Isolated yield. [b]Yield calculated on the basis of compound **2**.

Importantly, the short duration of the reaction provides rapid access to a wide variety of interesting piperazines in 1 day, making it very practical for use in organic synthesis, parallel synthesis, and combinatory chemistry.

In summary, *N*-arylpiperazines are important intermediates in organic synthesis and are commonly used fragments in the drug discovery process. Currently available synthetic routes to these important heterocyclic compounds have limited scope, and yields are often highly dependent on substituents and substitution patterns. The method described herein provides an improved, general, and practical procedure for the synthesis of sterically hindered *N*-arylpiperazines from inexpensive, commercially available anilines and nosyl-protected diethanolamine in CH_3CN using microwave irradiation. The wide acceptance and improved access to microwave reactors in recent years will make this approach available to chemists in a variety of research settings. In our hands, these structurally diverse heterocycles are readily coupled with other fragments to afford novel piperazine-based ligands for GPCRs. Screening of those compounds is underway and the results of those efforts will be reported elsewhere.

Experimental Section

General Procedure for the Synthesis of Protected *N*-Arylpiperazines (3−7). The reactions were performed in a CEM microwave reaction system operated at 175 °C for 1 h. The nosyl-protected diethanolamine (660 mg, 0.99 mmol), the representative aniline (1.2 mmol), DIPEA (516 mg, 4.0 mmol), and CH_3CN (3 mL) were mixed in a microwave reaction vial (10 mL) fitted with a no-invasive vial cap. The reaction vials containing the mixture were reacted in the microwave for 1 h at 175 °C. The typical reaction temperature−time profile is shown in the Supporting Information. After 1 h, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (DCM) and washed with HCl (10%, 3 × 30 mL) and saturated $NaHCO_3$ (40 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford the crude product. This crude product was purified by passage through a pad of silica (hexanes/DCM = 1:4, silica pad thickness: 10 cm, diameter: 4 cm) and used in subsequent reactions.

General Procedure for the Synthesis of Unprotected *N*-Arylpiperazines 8−19. The general procedure described above for the synthesis of protected *N*-arylpiperazines was used to prepare the corresponding nosyl-protected precursors for **8−19**. The deprotection of the precursors to the target amines is described below.

Potassium carbonate (3.52 g, 25.47 mmol) was added to a mixture of acetonitrile and dimethyl sulfoxide (CH_3CN/DMSO = 49:1) and heated to 50 °C. Thiophenol (2.34 g, 21.23 mmol) was added dropwise via syringe to the mixture with stirring. After 30 min, a solution of the nosyl-protected *N*-arylpiperazine (2.12 mmol) in CH_3CN and DMSO (CH_3CN/DMSO = 49:1) was added dropwise. The reaction mixture was stirred for 3 h, quenched with excess NaOH solution (40%; also removed the unpleasant smell of PhSH), and concentrated under reduced pressure. The residue was extracted with DCM (5 × 30 mL), and the organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a crude oil. The oil was purified by reversed-phase chromatography (CH_3CN in H_2O, gradient from 1%∼100% with 0.1% formic acid) to afford the formic acid salt of the desired piperazine. The salt was dissolved in DCM and washed with saturated $NaHCO_3$ solution and the organic phase concentrated in vacuo to provide the target piperazines in moderate to high yields (see Table 3 and the Supporting Information).

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Supporting Information Available: General experimental methods, temperature−time profile, compound characterization data, and copies of spectra for the products **3−19**. This material is available free of charge via the Internet at http://pubs.acs.org.