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An efficient one-pot, two-step synthesis of 4-substituted 1-heteroarylpiperazines under microwave irradiation conditions

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Abstract—A highly efficient one-pot, two-step microwave procedure has been developed for the synthesis of 4-substituted 1-heteroarylpiperazines. Microwave heating of heteroaryl chlorides with 1,4-diazabicyclo[2.2.2]octane (DABCO) at 160 °C for 15 min yielded 1-heteroaryl-4-(2-chloroethyl)piperazines, which could be further reacted with various nucleophiles, again under microwave irradiation conditions, to give an array of 4-substituted 1-heteroarylpiperazines in good to excellent yields.

4-Substituted 1-heteroarylpiperazines have demonstrated a wide range of activities including kinase inhibitors,[1a] 5-HT_{1A} receptor ligands,[1b,c] immunosuppressants,[1d] α 1A/B adrenoceptor antagonists,[1e] 5-HT_4 receptor ligands,[1f] dopamine D_4 ligands,[1g] and antagonists of NPY receptor subtype Y_5.[1h] Representative compounds in the family include two 5-HT_{1A} agonists approved for the treatment of anxiety, Buspirone and Tandospirone, depicted in Figure 1. Synthesis of these compounds typically involves arylation of the mono-protected piperazines followed by deprotection and alkylation.

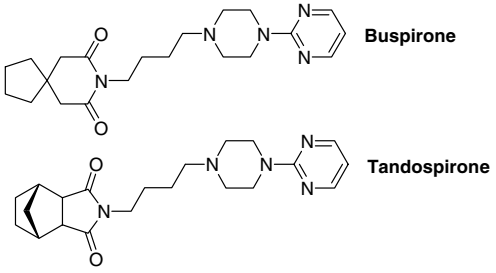

Figure 1.

As part of an ongoing research program we required a facile route into heteroaryl substituted piperazines with a 2-carbon tether attached to the piperazine 4-position. In particular, we required a very facile route, amenable to high throughput synthesis and library formation. We became interested in the possibility of utilizing DABCO in a tandem arylation/ring fragmentation procedure and saw this as a very rapid method for the construction of the appropriately substituted piperazine moiety.

A survey of the literature revealed that the quaternary ammonium salt N-dealkylation reaction has received very limited attention,[2] presumably because the tertiary amine products can be more conveniently synthesized by reaction of an electrophile with the corresponding secondary amines. However, when bicyclic tertiary amine DABCO is used in conjunction with a heteroaryl chloride, the N-dealkylation/ring fragmentation reaction leads to 1-heteroaryl-4-(2-chloroethyl)piperazines, which are extremely useful synthetic building blocks.[3] In particular, these compounds can be reacted with a wide variety of nucleophiles, allowing for the systematic introduction of two potential chemical diversity points. Herein, we would like to report our studies into the DABCO arylation/ring fragmentation procedure to construct a variety of disubstituted piperazines, and in particular the application of microwave irradiation to facilitate this transformation (see Fig. 2).

Microwave-assisted organic synthesis (MAOS) has attracted increasing attention due to its potential to speed

Keywords: Dealkylation; Heteroaryl; DABCO; Piperazine; Microwave irradiation.
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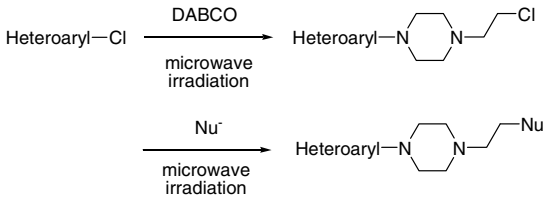
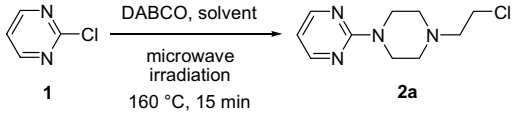


Figure 2.

up drug discovery research.[4] Many organic transformations have been accelerated by the use of microwave irradiation. The reaction times are often dramatically reduced from hours to minutes or even seconds. Moreover, there have been reports of microwave-assisted synthesis of combinatorial libraries.[5] As a test

Table 1. Solvent effects in the microwave-mediated arylation/ring fragmentation of DABCO

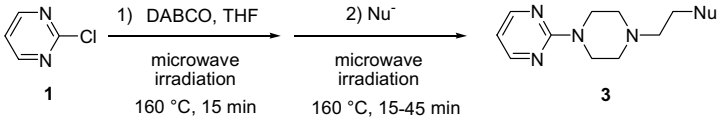


1 2a

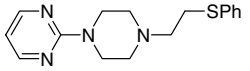
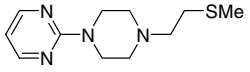
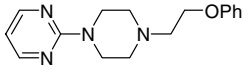
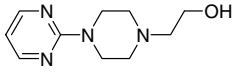
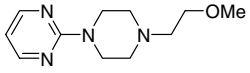
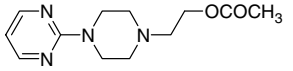
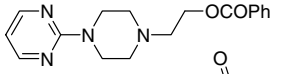
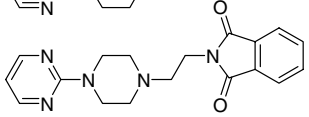
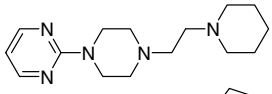
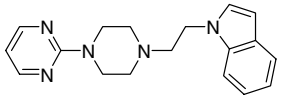
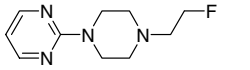
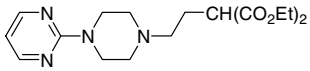
Entry	Solvent	Yield (%)[a]
1	THF	>98
2	1,4-Dioxane	>98
3	DME	>98
4	NMP	92
5	DMF	93
6	MeOH	43
7	CH_3CN	52

[a] Based on ^{1}H NMR analysis.

Table 2. One-pot, two-step reactions with various nucleophiles



1 3

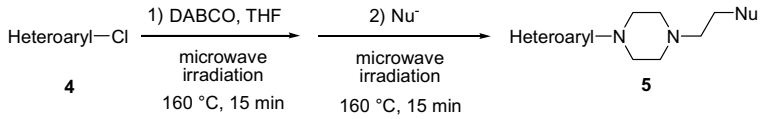
Entry	Microwave condition (2nd step)	Product **3**[a]	Isolated yield (%)
a	PhSNa (2 equiv), THF, CH_3CN, 160 °C, 15 min		95
b	NaSMe (3 equiv), THF, 160 °C, 15 min		87
c	PhOH (1.5 equiv), K_2CO_3 (3 equiv), THF, CH_3CN, 160 °C, 15 min		86
d	NaOH (6 equiv), THF, H_2O, 160 °C, 45 min		61
e	NaOMe (3 equiv), THF, MeOH, 160 °C, 45 min		58[b]
f	CH_3CO_2Na (3 equiv), THF, CH_3CN, 160 °C, 15 min		90
g	$PhCO_2H$ (2 equiv), K_2CO_3 (4 equiv), THF, CH_3CN, 160 °C, 30 min		91
h	Potassium phthalimide (1.5 equiv), THF, CH_3CN, 160 °C, 45 min		93
i	Piperidine (3 equiv), K_2CO_3 (3 equiv), THF, CH_3CN, 160 °C, 45 min		84
j	Indole (1.5 equiv), TBAB (0.2 equiv), K_2CO_3 (3 equiv), THF, CH_3CN, 160 °C, 15 min		36
k	KF (20 equiv), THF, EtOH, 160 °C, 15 min		58
l	$NaCH(CO_2Et)_2$ (1.5 equiv), THF, 160 °C, 15 min		39

[a] Final compounds were characterized by MS and ^{1}H NMR analyses.
[b] The hydrolyzed species **3d** was isolated as a side product (19%).

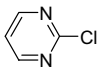
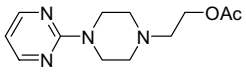
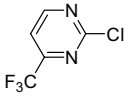
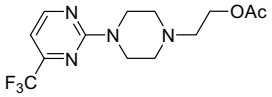
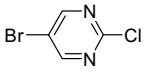
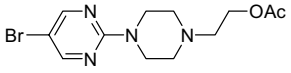
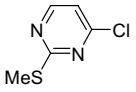
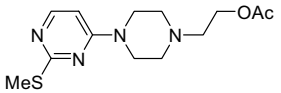
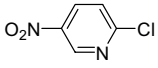
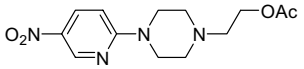
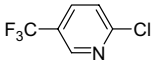
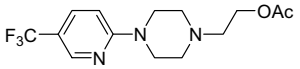
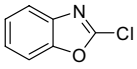
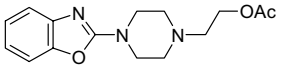
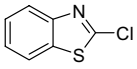
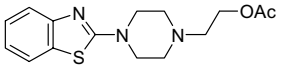
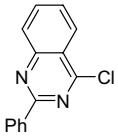
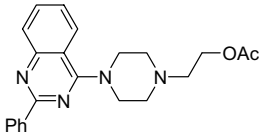
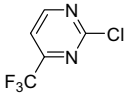
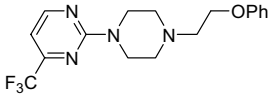
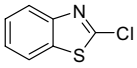
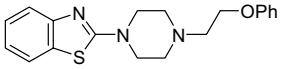
case, the arylation/ring fragmentation of DABCO with 2-chloropyrimidine was first explored under microwave irradiation (0.7 M, 160 °C, 15 min) in a variety of solvents. The reactions proceeded well in THF, 1,4-dioxane, and DME, affording the product quantitatively (Table 1, entries 1–3). While in NMP and DMF, minor uncharacterized impurities were observed by ^{1}H NMR (entries 4–5). It was found that acetonitrile and methanol were poor solvents for this reaction, and the yields were less than 60% based on ^{1}H NMR analysis (entries 6–7). The arylation/ring fragmentation of DABCO with 2-chloropyrimidine in THF was also examined under conventional heating condition (0.7 M, 60 °C, 19 h). ^{1}H NMR analysis revealed that only 8% of the piperazine was present and the major component of the reaction mixture was the quaternary ammonium salt.

With the aim of developing an efficient parallel protocol for the synthesis of combinatorial libraries, we further examined the potential for a one-pot, two-step synthesis of 4-substituted-1-pyrimidinylpiperazines by reaction of intermediate **2a** with a range of nucleophiles under microwave conditions.[6] As shown in Table 2, excellent yields were observed for thioethers **3a**, **3b**, and ether **3c** (entries a–c) and treatment with sodium hydroxide led to **3d** (entry d). Reaction with sodium methoxide gave **3e** in a yield of 58%, and the hydrolyzed species **3d** was isolated as a side product (19%, entry e). Esters **3f** and **3g** were obtained by alkylation with the corresponding acid salts (entries f–g). Amine derivatives **3h–j** were synthesized by similar alkylation reactions (entries h–j). Reaction with potassium fluoride yielded **3k** (entry k), and reaction with the pre-

Table 3. One-pot, two-step reactions using various heteroaryl chlorides



4 **5**

Entry	Heteroaryl-Cl **4**	Condition (2nd step)[a]	Product **5**[b]	Isolated yield (%)
a		A		90
b		A		91
c		A		90
d		A		85
e		A		92
f		A		68
g		A		91
h		A		78
i		A		81
j		B		79
k		B		85

[a] Reagents and conditions: (A) CH_3CO_2Na (3 equiv), THF, CH_3CN, microwave irradiation, 160 °C, 15 min; (B) PhOH (1.5 equiv), K_2CO_3 (3 equiv), THF, CH_3CN, microwave irradiation, 160 °C, 15 min.

[b] Final compounds were characterized by MS and ^{1}H NMR analyses.

formed sodium malonate afforded the malonate derivative **3l** (entry l).

To further determine the scope of this reaction a range of heteroaryl chlorides were examined (Table 3). Excellent yields were obtained for chloropyrimidines bearing electron-donating and electron-withdrawing substituents (entries a–d). Two activated pyridine substrates, 2-chloro-5-nitropyridine and 2-chloro-5-trifluoromethylpyridine, also gave yields of 92% and 68%, respectively (entries e–f). However, when an unactivated pyridine substrate 2-chloro-4-methylpyridine was employed, the ring fragmentation product was not observed. Reactions of DABCO with other heteroaryl chlorides, such as 2-chlorobenzoxazole, 2-chlorobenzothiazole, and 4-chloro-2-phenylquinazoline, also led to good results (entries g–i). It is noteworthy that, in most cases, substantially pure products were obtained by simple filtration through a pad of silica gel or Celite.

In conclusion, we have developed a one-pot, two-step microwave procedure for the synthesis of 4-substituted 1-heteroarylpiperazines. Microwave irradiation of heteroaryl chlorides with DABCO at 160 °C for 15 min leads to 1-heteroaryl-4-(2-chloroethyl)piperazines, which further react with different nucleophiles under similar conditions to give diversified 4-substituted 1-heteroarylpiperazines in good to excellent yields. This efficient microwave-assisted transformation, together with a relatively straightforward purification process, makes this protocol ideal for the synthesis of parallel combinatorial libraries.

Acknowledgment

We thank Dr. Peter R. Guzzo for helpful discussions during the course of this study.

References and notes

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6. *Procedure for the microwave-mediated synthesis of 2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl acetate* **3f**: A 2–5 mL Smith Process vial containing a magnetic stir bar was charged with the 2-chloropyrimidine (228 mg, 2.0 mmol), DABCO (231 mg, 2.06 mmol) and tetrahydrofuran (3.0 mL). The vial was sealed and irradiated in the SmithCreator™ to reach 160 °C in 2–3 min, and held at 160 °C for 15 min. The reaction vial was then cooled and unsealed, and half of the reaction mixture was removed from the vial for characterization. To the remaining half of reaction mixture were added sodium acetate (246 mg, 3.0 mmol) and acetonitrile (1.5 mL). The reaction vial was again sealed and irradiated to reach 160 °C in 1–2 min, and held at 160 °C for another 15 min. After this time, the reaction mixture was diluted with methylene chloride (40 mL), and the resulting mixture was filtered through a pad of silica gel (5.0 mL) and Celite (5.0 mL). The pad was further eluted with ethyl acetate (100 mL) and the combined organic solutions were concentrated to give product **3f**, which was determined pure by ^{1}H NMR analysis. ^{1}H NMR (300 MHz, CD_3OD) δ 8.31 (d, $J = 4.7$ Hz, 2H), 6.59 (t, $J = 4.8$ Hz, 1H), 4.24 (t, $J = 5.7$ Hz, 2H), 3.81 (t, $J = 5.1$ Hz, 4H), 2.69 (t, $J = 5.7$ Hz, 2H), 2.58 (t, $J = 5.1$ Hz, 4H), 2.06 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 172.8, 162.9, 159.1, 111.3, 62.5, 57.8, 54.3, 44.6, 20.9 ppm; MS(APCI) m/z 251 $(M+1)^+$.