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Parallel synthesis of *N*-arylpiperazines using polymer-assisted reactions

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Abstract—A series of *N*-arylpiperazines were prepared in a parallel fashion using palladium-catalyzed cross-coupling, or nucleophilic aromatic displacement chemistries, and polymer-assisted sequestration and purification techniques as key steps.

1. Introduction

Arylpiperazines are important structural elements in many molecules possessing biological activity.[1] Examples of such compounds include the 5-HT_{2C} receptor agonists, *N*-(*meta*-chlorophenyl)piperazine (*m*CPP) **1** and MK-212 **2**.[2,3] More complex molecules, such as the selective D_3 receptor agonist piribedil **3**, and the α_1-adrenoreceptor agonist prazosin **4** also contain an *N*-arylpiperazine moiety.[4,5] The presence of this structural motif in many substances of biological significance has led to a number of approaches being developed to access this chemotype, many of which have been employed in the preparation of pharmaceutical agents.[6] A high-throughput synthesis of this structural class would therefore be of benefit in the lead discovery and lead optimization stages of drug discovery. In this letter, we disclose a synthesis of *N*-arylpiperazines which utilize polymer-supported reagents and sequestration strategies to facilitate production of compounds in a parallel manner (Fig. 1).[7]

Our synthesis of *N*-arylpiperazines from 'non-activated' aryl halide precursors employed a palladium-catalyzed cross-coupling between an aryl bromide and *N*-*tert*-butoxycarbonylpiperazine (*N*-Boc piperazine—Scheme 1).[6,8] Excess *N*-Boc piperazine was removed by sequestration with polymer-supported isocyanate, a simple filtration of the reaction mixture providing the protected *N*-arylpiperazine **6**, which was smoothly deprotected by the use of Amberlyst® 15 ion-exchange resin in a 'catch-and-release' manner in a separate reaction step.[9]

As shown in Table 1, this method was used to prepare a range of monocyclic, bicyclic and heterocyclic *N*-arylpiperazines in good yields and purities. For example, *m*CPP **1** was prepared in an overall yield of 74% and with a purity of >95%, as judged by nuclear magnetic resonance (NMR) and high-performance liquid chromatography (HPLC) analysis.[10] Other monocyclic bromides furnished *N*-arylpiperazines in similar yields and purities using this two-step method (compounds **8**–**11**). The use of bicyclic, or heterocyclic bromides was also successful (compounds **12**–**14**), although the purities of final products were slightly diminished, as compared to their monocyclic counterparts.

In order to access *N*-arylpiperazines from 'activated aryl halide' precursors, a nucleophilic aromatic displacement reaction (S_NAr) was employed under two sets of reaction conditions (method A or B—Scheme 2). In method A, the halide **15** was displaced with *N*-Boc piperazine under thermal conditions and the excess piperazine reagent was removed with polymer-supported isocyanate. Deprotection of the Boc group was achieved using literature 'catch-and-release' conditions[9] to give the desired

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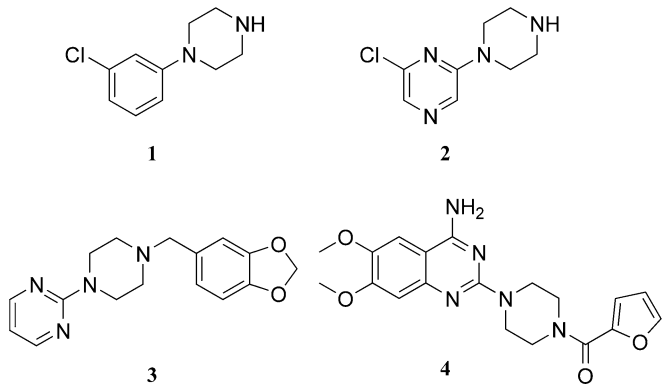
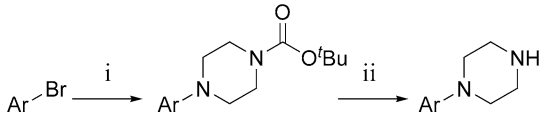
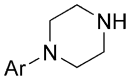


Figure 1.



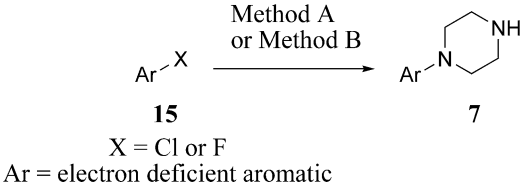
Scheme 1. Reagents and conditions: (i) *N*-Boc piperazine, $Pd(OAc)_2$, $^tBu_3P$, ^{t}BuONa, xylenes, 50 °C then MP-NCO, 50 °C; (ii) Amberlyst® 15, CH_2Cl_2, rt then 2 M NH_3/MeOH, rt. (Note: MP = macroporous.)

Table 1. Synthesis of *N*-arylpiperazines using palladium(0)-chemistry



Compound number	Ar[a]	Yield % (purity %)[b]
1	3-Cl–C_6H_4	74 (>95)
8	3-(CF_3)–C_6H_4	68 (>95)
9	3-CN–C_6H_4	58 (90)
10	4-NO_2–C_6H_4	94 (89)
11	3,5-F_2–C_6H_3	80 (92)
12	β-Naphthyl	65 (88)
13	Pyrimidin-5-yl	62 (84)
14	Thiophen-3-yl	70 (90)

[a] All products were derived from the corresponding aryl bromide starting material.
[b] Purity established by NMR spectroscopy and HPLC analysis.

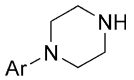


Scheme 2. Reagents and conditions: Method A: (i) *N*-Boc piperazine, MP-CO_3, DMSO, 100 °C; (ii) MP-NCO, CH_2Cl_2, 60 °C; (iii) MP-SO_3H, CH_2Cl_2, rt, filter then wash with MeOH and release with 2 M NH_3, MeOH. Method B: (i) *N*-Boc piperazine, MP-CO_3, CH_3CN, 140 °C, μ-wave; (ii) MP-NCO, CH_3CN, 140 °C, μ-wave; (iii) MP-SO_3H, CH_2Cl_2, 140 °C, μ-wave.

product. Method B employed microwave heating to accelerate the displacement, sequestration and deprotection steps (a CEM Explorer & Discover® microwave was used in these studies). Thus, the activated aryl halide **15** was allowed to react with *N*-Boc piperazine in the presence of polymer-supported carbonate at 140 °C in acetonitrile for 30 min. Excess piperazine reagent was sequestered by adding polymer-supported isocyanate and heating for a further 5 min at 140 °C. Significantly, it was also found that the Boc deprotection step could also be facilitated by the use of heating under microwave irradiation.

As shown in Table 2, a number of monocyclic and bicyclic *N*-arylpiperazines could be obtained by either of the above methods. Yields and purities were similar between the thermal and microwave heating protocols. For example, MK-212 **2** could be obtained in 80% yield and >95% purity using the thermal conditions (method A), or in 80% yield and 92% purity using the microwave-assisted approach (method B). However, microwave heating was found to significantly reduce reaction times. For example, nucleophilic aromatic displacement under thermal conditions was carried out at 100 °C, whereas under microwave heating, the reaction was performed at 140 °C for 30 min. Sequestration of excess *N*-Boc piperazine was also accelerated under

Table 2. Synthesis of *N*-arylpiperazines using S_NAr chemistry



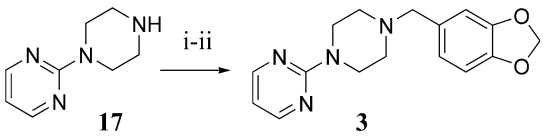
Compound number	Ar[a]	Yield % (purity %)[b,c]	Yield % (purity %)[b,d]
2	2-Cl–Pyrazin-5-yl	80 (>95)	80 (92)
16	Pyrazin-2-yl	20 (90)	0 (0)
17	Pyrimidin-2-yl	82 (>95)	46 (>95)
18	Quinoxalin-2-yl	85 (>95)	84 (90)
19	Benzothiazol-2-yl	78 (92)	68 (>95)
20	5-(CF_3)–Pyridin-2-yl	53 (91)	86 (>95)
21[e]	4-NO_2–C_6H_4	82 (>95)	83 (85)
22[e]	5-Me–2-NO_2–C_6H_3	91 (>95)	65 (>95)

[a] Products were obtained from the aryl chloride starting material except where noted separately.
[b] Purity determined by NMR spectroscopy and HPLC analysis.
[c] Results using method A.
[d] Results using method B.
[e] Aryl fluoride starting material employed.

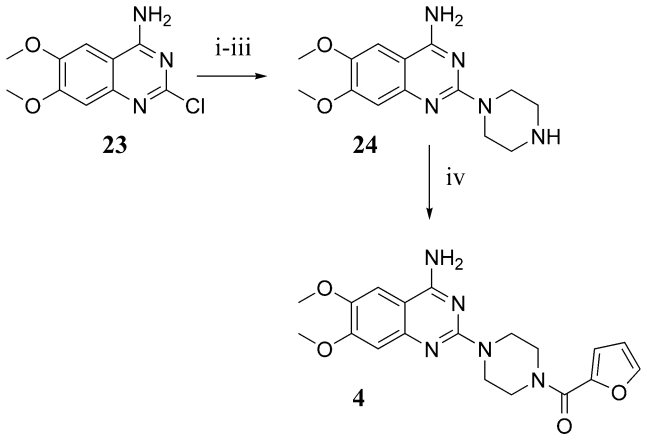
microwave heating. Thus, under thermal conditions excess *N*-Boc piperazine was sequestered over 24 h at 60 °C; under microwave heating the excess *N*-Boc piperazine was sequestered in 5 min at 140 °C. Deprotection of the Boc protecting group was also found to be accelerated under our microwave conditions. For example, *N*-Boc deprotection took 24 h at room temperature, compared to 30 min at 140 °C under microwave heating.

The products from the previous chemistries could be elaborated further to provide compounds with increased diversity. As an example, piribedil **3** was synthesized from **17** by reductive-alkylation with piperonal using polymer-supported cyanoborohydride as the reductant. Purification by ion-exchange chromatography in a 'catch-and-release' manner afforded **3** in an overall yield of 73% and in 93% purity (Scheme 3). Similarly, prazosin **4** was obtained in 89% yield and in 95% purity using only polymer-supported sequestration routines and 'catch-and-release' purification (Scheme 4).

In summary, we have developed a number of methods for the parallel synthesis of *N*-arylpiperazines using either nucleophilic aromatic substitution, or palladium-catalyzed cross-coupling, in conjunction with polymer-supported sequestration and 'catch-and-release' techniques. As an illustration of the versatility of our approach, the biologically active substances *m*CPP, MK-212, piribedil and prazosin were prepared using the above methodology as a key step. It is envisaged that the techniques illustrated in this letter will be of interest to medicinal chemists when looking to prepare a series of *N*-arylpiperazine derivatives in a parallel fashion.



Scheme 3. Reagents and conditions: (i) piperonal, CH_2Cl_2, AcOH, PS-$CNBH_3$; (ii) SCX-2, wash MeOH, release with 2 M NH_3/MeOH.



Scheme 4. Reagents and conditions: (i) *N*-Boc piperazine, MP-CO_3, DMSO, 100 °C; (ii) PS-SH, MP-NCO, 60 °C; (iii) MP-TsOH, CH_2Cl_2, rt, filter then wash with MeOH and release with 2 M NH_3/MeOH; (iv) 2-furoyl chloride, MP-CO_3, CH_2Cl_2, rt then PS-trisamine.

2. Experimental

Parallel synthesis of N-arylpiperazines from 'non-activated' aryl bromides (all reactions were performed in parallel using a Carousel from Radley's Ltd): Tri-*tert*-butylphosphine (4 mg, 0.02 mmol) was added in one portion to a stirred solution of palladium(II) acetate (1.2 mg, 0.005 mmol) in xylenes (mixture of isomers; 5 mL) at room temperature under argon. The mixture was stirred for 5 min, then a solution of the aryl bromide (1.0 mmol) in xylenes (5 mL) was added in one portion. After another 5 min, *N*-Boc piperazine (0.37 g, 2 mmol) and sodium *tert*-butoxide (0.14 g, 1.4 mmol) were added separately in one portion. The mixture was heated to 50 °C and stirred overnight. Polymer-supported isocyanate (loading: 1 mmol/g; 2.0 g, 2 mmol) was added in one portion and the mixture was stirred at 50 °C for 24 h, then filtered and the filter cake washed with xylenes and MeOH.

Concentration of the filtrate under vacuum left the *N*-Boc arylpiperazine (1.0 mmol; reaction assumed to be quantitative), which was used directly in the next step.

Amberlyst® 15 ion-exchange resin (4.5 g) was added in one portion to a stirred solution of the *N*-Boc *N*-arylpiperazine (assumed to be 1.0 mmol) in CH_2Cl_2 (8 mL) at room temperature under argon. The mixture was stirred overnight, then filtered and the filter cake washed with CH_2Cl_2, THF and MeOH. The filter cake was then transferred back to an individual carousel reaction vessel and 2 M NH_3/MeOH added. The mixture was stirred at room temperature for 90 min then filtered. Concentration of the filtrate under vacuum gave the desired *N*-arylpiperazine product (see Table 1 for yields and purities).

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References and notes

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10. HPLC was used for analysis of purities of final products and not for product purification.