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Solution Phase Combinatorial Synthesis of Arylpiperazines

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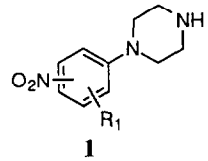
Abstract: A solution phase combinatorial synthesis of aryl piperazines **1** and **2** is described based on the S_NAr reaction and Schotten-Baumann acylation. The use of excess reagent is allowed and pure arylpiperazines **1** and **2** were obtained by simple acid/base washing. © 1997 Published by Elsevier Science Ltd.

Combinatorial synthesis of small organic molecules has been extensively investigated over the last several years and has emerged as a powerful technology for chemists to synthesize large number of compounds for biological evaluation.[1] In combination with high throughput screening techniques, it could enormously accelerate lead structure discovery as well as lead optimization process. While most of the library constructions have been carried out on a solid support,[2] solution phase combinatorial syntheses have started to attract much attention and several ingenious studies have recently appeared in the literature.[3-13]

Arylpiperazines have been frequently found as an important structural element in compounds possessing interesting biological activity.[14] Classic syntheses of arylpiperazines involve the cyclization of a substituted aniline with bis (2-chloroethyl) amine.[15] Several new solid phase syntheses of arylpiperazines and related arylamines have appeared in the recent literature[16-19] and a solid phase combinatorial synthesis of arylpiperazines has also been reported from Dankwardt's group[20] on the basis of nucleophilic aromatic substitution (S_NAr).[21] Based on this same reaction, we describe herein a *solution phase* combinatorial synthesis of arylpiperazines (compounds **1**) and subsequently *N*-Aryl-*N'*-acylpiperazines (compounds **2**). Central to our synthetic strategy was the observation of the *peculiar physical property of compound* **5** *(displaying a low* pK_a*)*[22] and the acid/base washing techniques recently developed by Boger et al.[9]



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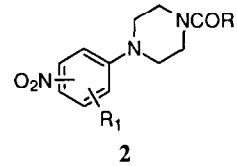

2

Figure 1

The basic synthetic strategy is outlined in Scheme 1. We hypothesized that the tertiaryl amine of arylpiperazine **5** should be of low basicity due to the presence of a strong electron withdrawing nitro function located at the *ortho* or *para* position. This property should in principal allow us to partition it between organic solvents and acidic aqueous solutions permitting thus 1) the use of *N*-Boc piperazine **4** in large excess in order to drive the reaction to completion and 2) the ability to remove the excess of **4** by simple acid washing. Furthermore unreacted, if there is any, nitro-fluoro substituted aromatic compound **3** (neutral, extracted together

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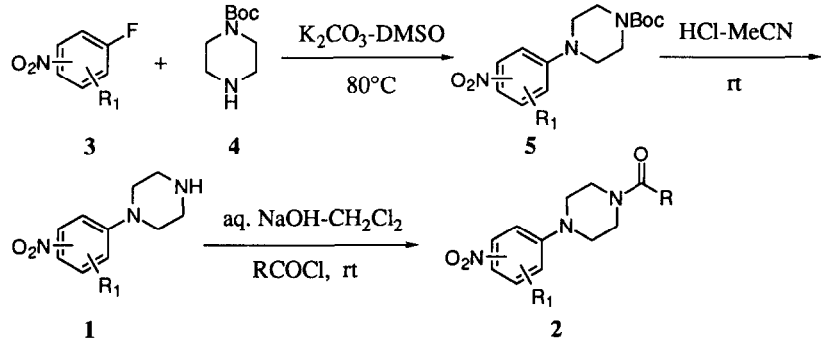
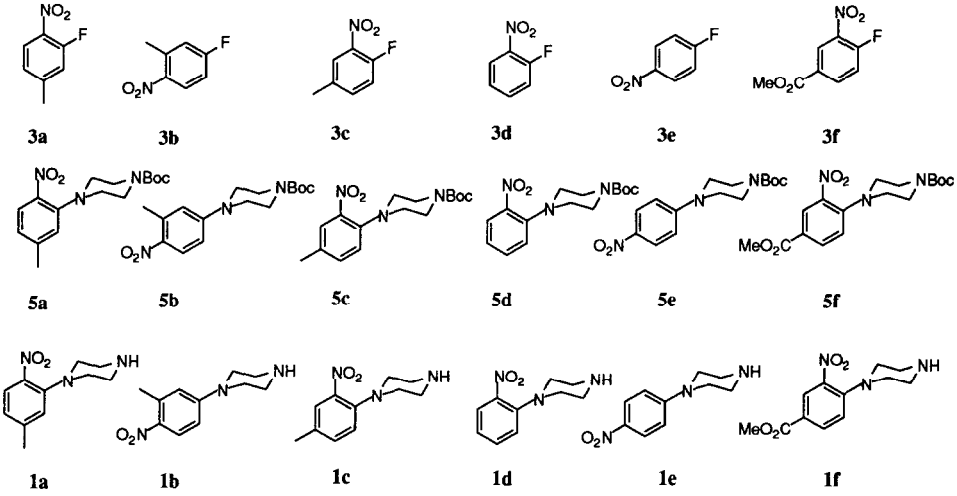
with **5**) can in turn be removed by acid-base washing once the *N*-Boc function has been removed from **5** since compound **1** is now soluble in acidic aqueous solution. This two step sequence should thus provide compound **1** in pure form. Acylation under Schotten-Baumann conditions will give amide **2** which could once again be separated from compound **1** (base) and acid (hydrolysis product of acyl chloride) by simple acid/base washing.



3 **4** **5** **1** **2**

Scheme 1



3a **3b** **3c** **3d** **3e** **3f**

5a **5b** **5c** **5d** **5e** **5f**

1a **1b** **1c** **1d** **1e** **1f**

Figure 2

At first, we investigated the feasibility of this strategy by synthesizing individual compounds. After several experimental trials, K_2CO_3-DMSO-80°C was found to be the best conditions in our hands for performing the desired S_NAr reaction. Two equivalents of *N*-Boc-piperazine **4** were generally employed and, under these conditions, all nitro-fluoro substituted aromatic compounds **3** were consumed after a period of 12 hours. Once the reaction was completed, the reaction mixture was diluted with diethyl ether, and acidified with 1N HCl. Extraction of the aqueous solution then gave the pure compound **5**. Removal of the *N*-Boc function was best achieved with concentrated HCl in MeCN (10% v/v). Acid-base extraction afforded the compound **1** in analytically pure form by NMR. The yield of this two step sequence was higher than 95% regardless of the electrophiles **3**. The ^1H NMR spectra of compounds **1a-1f** are shown in Figure 3.

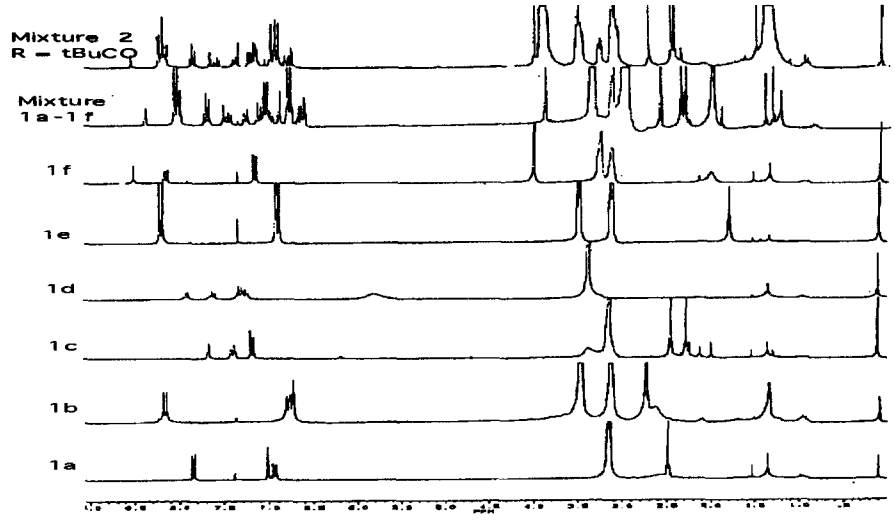
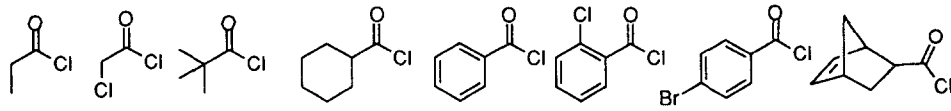


Figure 3

The split/combine technique[23] was then used for the construction of an indexed library.[4, 5] An equimolar mixture of compounds **3a** to **3f** was allowed to react with an excess of *N*-Boc-piperazine (2 equiv.) under the above established conditions. Work up followed by removal of *N*-Boc group under acidic conditions as described for an individual synthesis gave a mixture of compounds **1a-1f** in 88% yield. As observed from the ^{1}H NMR spectrum (figure 3), a clean reaction occurred to give a mixture of the six desired compounds in high purity. Each individual component was readily discernible from the ^{1}H NMR spectrum of the reaction mixture.



6a **6b** **6c** **6d** **6e** **6f** **6g** **6h**

Figure 4

To continue the library synthesis, this product mixture was divided evenly into 8 parts which were allowed to react individually with a single acyl chloride (Figure 4) under Schotten-Baumann conditions. The reaction course was monitored by TLC. When all the starting arylpiperazines were consumed (typically 3 h), CH_2Cl_2 was evaporated and residue acidified with 2N HCl and extracted with diethyl ether. The organic extracts were washed with 2N aqueous NaOH, water, brine, dried over Na_2SO_4 and evaporated to give the pure acylated compounds in overall yields higher than 95%. The reaction between a mixture of acyl chlorides and an individual aryl piperazine (slight excess) was equally efficient to give, after acid/base washing, the coupled products in near quantitative yields.

In summary, we have developed a complementary solution phase combinatorial synthesis of arylpiperazines. All three reactions involved (S_NAr reaction, deprotection and acylation) are highly efficient to give the desired compounds in high yield and high purity by simple acid/base washing. This synthesis retains

two important advantages of solid phase techniques, ie. use of excess reagent and simple product purification. While the nitro group (or other activating groups[24]) was required for S_NAr reaction, its presence in the final compounds can be beneficial for two reasons: 1) It is present in some bioactive molecule[25] ; 2) it provides a handle for further functionalization. Studies towards the synthesis of other types of piperazine containing libraries are in progress and will be reported in due course.

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