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# Soluble Polymer-Supported Synthesis of Arylpiperazines#

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**Abstract**

A method for soluble, inexpensive polymer-supported synthesis of piperazine and piperidine libraries on the basis of nucleophilic aryl substitution ($S_NAr$) and N-acylation is reported. Asymmetric N, N'-disubstituted piperazine and piperidine derivatives, that are potential drug candidates, can be synthesized in quantitative yields and excellent purity after several steps by simple precipitation and washing. This liquid phase method should prove to be a useful tool for constructing combinatorial libraries containing diamine moiety.

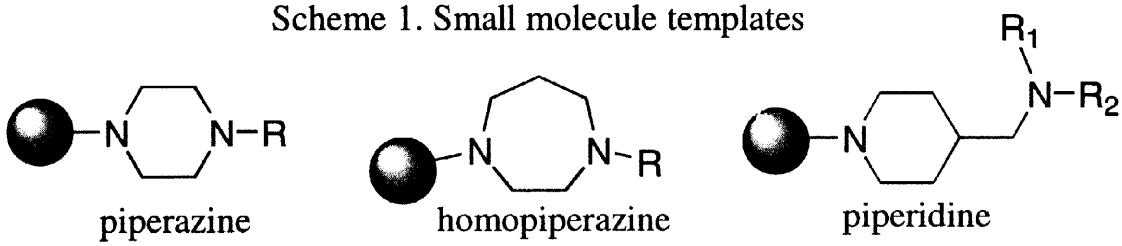


*Keywords: alkylation, acylation, piperazine, solid-phase synthesis*

Combinatorial organic synthesis [1-3] on solid support has already emerged as an important tool for chemists to synthesize a large number of pharmaceutically interesting compounds. In combination with high throughput screening, this technology may dramatically accelerate drug lead discovery. While most of the libraries have been synthesized on solid support, liquid-phase combinatorial synthesis (LPCS) provides an interesting approach, where molecules are prepared on a liquid, soluble polymer-poly(ethylene glycol) [4]. This polymer support is soluble in most organic solvents and has a strong tendency for crystallization. Inclusions due to gelatinous precipitation can be avoided. Upon reaction, the product remains covalently bound to the resin, and purification can be accomplished after precipitation simply by filtering and washing away the unreacted solution-phase reagents and side products.

It is known that those 1,4 disubstituted piperazines, homopiperazines and piperidines (Scheme 1) are highly potent ligands for various receptors that belong to the family of G protein-coupled receptors. They are frequently found as a key structural element in compounds possessing broad therapeutic effects for several diseases [5]. Therefore, a general method for the rapid multiple synthesis of these molecules would be of great value for drug discovery and lead optimization. Classical synthesis of arylpiperazines usually requires the cyclization of a substituted aniline with bis 2-chloroethylamine. Solid phase synthesis of arylpiperazines has been reported from Syntex's group [6], and solution phase synthesis of arylpiperazines has recently been studied [7,8]. Herein, we report a promising liquid-phase approach for the synthesis of substituted piperazine

Scheme 1. Small molecule templates

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and piperidine libraries on soluble polymer support in quantitative yield and excellent chemical purity (Table 1).

Scheme 2. Synthetic route

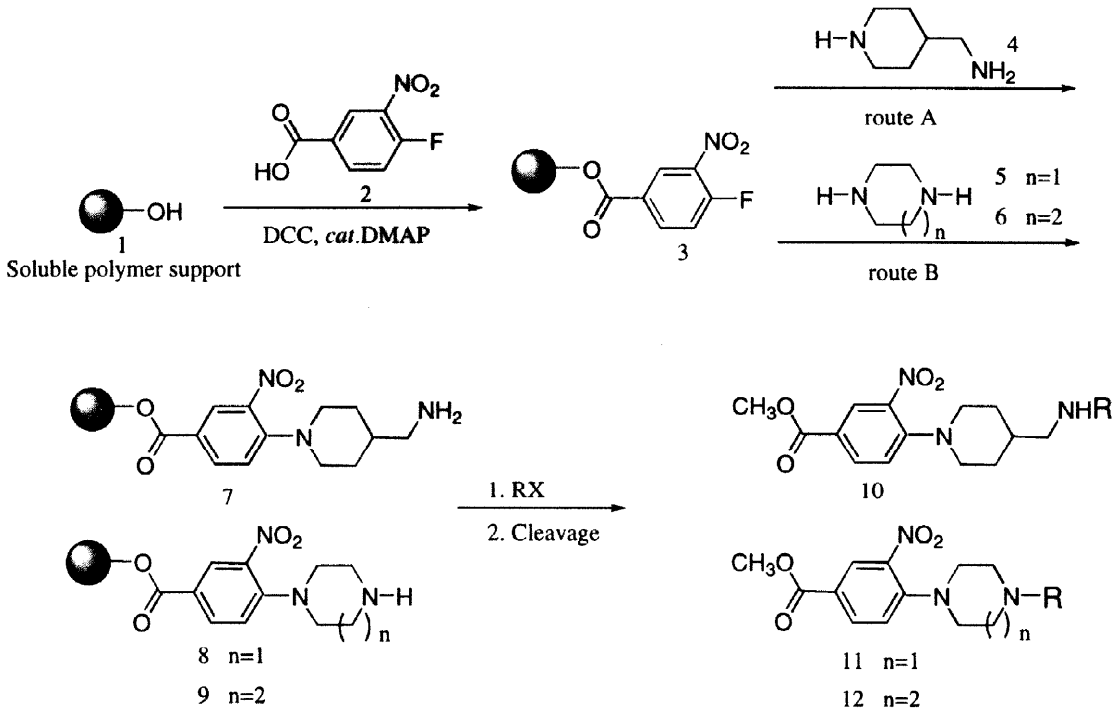
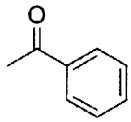
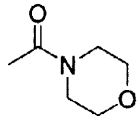
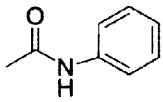
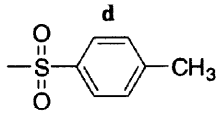



Table 1

| Entry | R | Route | n | Observed MS[a] | Crude yield[b] (%) | Crude purity[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | A | 1 | 397 | 99 | 86 |
| 2 |  | B | 1 | 370 | 99 | 91 |
| 3 | | B | 2 | 384 | 99 | 94 |
| 4 | **b** | A | 1 | 407 | 99 | 83 |
| 5 |  | B | 1 | 379 | 99 | 86 |
| 6 | | B | 2 | 393 | 99 | 83 |
| 7 | **c** | A | 1 | 414 | 99 | 85 |
| 8 |  | B | 1 | 385 | 99 | 94 |
| 9 | | B | 2 | 400 | 99 | 93 |
| 10 | **d** | A | 1 | 448 | 99 | 84 |
| 11 |  | B | 1 | 420 | 99 | 97 |
| 12 | | B | 2 | 434 | 99 | 93 |

a. Confirmed by electrospray mass spectra ($MH^+$).
b. Determined based on weight of crude sample.
c. Purity determined by HPLC analysis of crude products. Products show satisfactory $^1H$ NMR and MS data.

For application to the synthesis of various molecular scaffolds, this approach requires the polymer building blocks (Scheme 1) to be soluble under conditions of alkylation and to be insoluble during the workup of reaction mixtures while other impurities are soluble. The solubility of the reactants and polymer support allows reaction kinetics control similar to those observed in solution chemistry. Our liquid phase method then retains two crucial advantages of solid phase synthesis, *i.e.* addition of excess reagents and simple product purification.

The basic synthetic route is outlined in Scheme 2. The resin bound activated aryl fluoride **3** was prepared from MeO-PEG **1** (MW: 5000), 4-fluoro-3-nitrobenzoic acid **2** and N,N'-dicyclohexylcarbodiimide (DCC) *via* ester linkage. The conversion of linker attachment estimated by $^1$H NMR was more than 95%. The resulting polymer-supported aryl fluoride **3** reacted readily with a variety of amines at ambient temperature. Nucleophilic addition reactions were monitored using proton NMR for the change of signals of polymer-bound aryl protons. Diamine building blocks (piperidine **4**, piperazine **5** and homopiperazine **6**) were then successfully attached to a suitable linker, which was anchored with MeO-PEG resin **1**. After the reactions were completed, the PEG-bound products (**7~9**) were precipitated by the addition of an ice-cold *t*-butyl methyl ether and after drying the products were ready for the next synthetic step. This two step sequence should then furnish compounds (**7~9**) in analytically pure form. It should be mentioned that 4-(aminomethyl)piperidine **4**, a difunctional amine reacted with polymer-supported aryl fluoride **3** using secondary amine moiety only. Because of site isolation, our support strategy is able to achieve monoalkylation of symmetric diamines without time-consuming protection-alkylation-deprotection sequence [9]. But it is essential to use excess of a diamine component in this reaction in order to decrease the risk of polymer cross-linking. Resin bound, unfunctionalized templates (**7~9**) can be acylated with various electrophiles (benzoyl chloride **a**, morpholine carbonyl chloride **b**, phenyl isocyanate **c** and sulfonyl chlorides **d** ) individually at room temperature. No attempts were made to optimize the reaction conditions and all reagents were used directly without further purification. Table 1 shows a representative selection of compounds synthesized[1]. Treatment of acylated products with 1 % KCN in methanol resulted in a very

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[1] In a typical procedure for the synthesis of **12b** (Entry 6) is as follow: PEG supported homopiperazine **9** (265 mg, $5.0\times10^{-2}$ mmol) and morpholine 4-carbonyl chloride **b** (9.2 mg, $6.0\times10^{-2}$ mmol) were stirred in 5 mL $CH_2Cl_2$ for 8 h. After completion, the solution was concentrated by rotary evaporation and reaction mixture was precipitated by slow addition of cold *t*-butyl methyl ether with stirring. Polymer bound product was then filtered under aspirator pressure using a fritted funnel and washed several times with cold ether. The crude PEG product was redissolved, precipitated twice and dried *in vacuo* for the next sequence. The transesterification of acylated product in KCN/methanol is representative for the cleavage procedure: 272 mg of polymer-bound acylated homopiperazine was dissolved in 5 mL 1% KCN/$CH_3OH$ and stirred at room temperature for overnight. The solution was evaporated under vacuum to remove methanol and PEG product was dissolved in 4 mL methylene chloride, precipitated into icy cold ether. The polymer was filtered and the combined filtrate was dried to give crude product **12b** as a bright yellow solid (19.3 mg, 99%) ; The crude purity of this compound was determined to be 83% by the HPLC analysis (250x4.6 mm Sphereclone 5μ Si, gradient elution 50% ethyl acetate/hexane, 1 mL/min.); $^1$H NMR (300 MHz, $CDCl_3$ ) $\delta$ 8.36 (d, $J$ = 2.1 Hz, 1 H ), 7.99 (dd, $J$ = 8.9, 2.1 Hz, 1 H), 7.04 (d, $J$ = 8.9 Hz, 1 H), 3.89 (s, 3 H), 3.65 (t, $J$ = 4.7 Hz, 4 H), 3.53-3.41 (m, 8 H), 3.14 (t, $J$ = 4.7 Hz, 4 H), 2.06 (m, 2 H); $^{13}$C NMR($CDCl_3$) $\delta$ 165.5, 164.2, 147.8, 138.7, 133.9, 129.0, 119.7, 118.2, 66.7, 52.8, 52.4, 51.9, 48.7, 48.0, 47.8, 28.0. IR (neat) 3108, 1677, 1613, 1516. MS: m/z 393 ($MH^+$). HRMS: calcd. for $C_{18}H_{24}N_4O_6$ 392.1697($M^+$), found 392.1682.

efficient cleavage from polymer support to provide the desired molecules (**10~12**) in quantitative yield. Each crude product was then analyzed by HPLC and gave excellent purity (83~97%). Most of the compounds were characterized by low-resolution mass spectrometry and $^1$H NMR confirming that in each reaction the major compound had a molecular ion corresponding to the appropriate product.

It is worthy of note that, in contrast to the various restrictions on the analysis of reaction development in solid-phase synthesis, liquid phase synthesis allows routine analytical methods (UV, IR, NMR, TLC) to monitor reaction progress without following cleave-&-analyze technique. This non-destructive method to monitor reaction progress makes LPCS method even more valuable.

In summary, a novel liquid phase combinatorial synthesis of piperazine and piperidine libraries has been developed. All four reactions involved (linker attachment, $S_NAr$ reaction, acylation and resin cleavage) are highly efficient to give the desired compounds in high yields and excellent purity by simple precipitation and washing. Although nitro-activating group was necessary for $S_NAr$ reaction, it can be further functionalized to benzopiperazinones [10] and this aromatic nitro group is also present in some bioactive molecule [11]. This method of synthesis is versatile and produces compounds based on known pharmacophoric scaffolds, and which are thus ideally suited for combinatorial library generation. Further applications of this technology to other transformations are ongoing and will be reported in later papers.

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