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Liquid Phase Combinatorial Synthesis of Benzylpiperazines[#]

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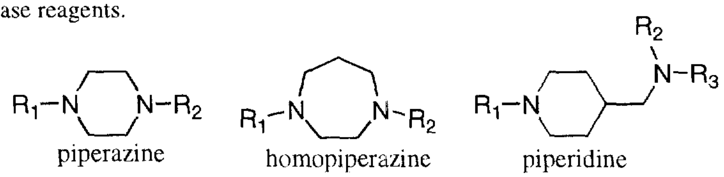
Abstract

A novel method for soluble, inexpensive polymer-supported synthesis of piperazine and piperidine libraries on the basis of nucleophilic benzylic substitution and N-acylation is reported. Disubstituted piperazine and piperidine derivatives, that are potential drug candidates, can be isolated in high yields and excellent purity by simple precipitation and washing. This liquid phase method proves to be a useful tool for constructing combinatorial libraries containing diamine moieties.

Keywords: solid-phase synthesis, polymers, receptors, NMR

Combinatorial organic synthesis [1-3] on solid support has emerged as an important technology 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 in solid or solution phase, liquid-phase combinatorial synthesis (LPCS) provides an interesting approach, where molecules are prepared on a liquid, soluble polymer-poly(ethylene glycol) [4-5]. This polymer support, in contrast to an insoluble matrix, is soluble in many organic solvents and has a strong tendency for precipitation in particular solvent. Upon reaction, the desired product remains covalently bound to the resin and purification can be accomplished simply by filtering and washing away the unreacted solution-phase reagents.



It is known that those 1,4 disubstituted piperazines, homopiperazines and piperidines 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 [6]. Therefore, a general method for the rapid multiple synthesis of these molecules would be of great value for drug discovery and lead optimization. Solid phase synthesis of arylpiperazines has been reported from the Syntex group [7], and solution phase synthesis of arylpiperazines has recently been studied [8]. Herein, we report a promising approach for the synthesis of substituted piperazine and piperidine libraries on soluble polymer support in high yield and excellent chemical purity (Table 1).

PII: S0960-894X(99)00026-8

Scheme 1

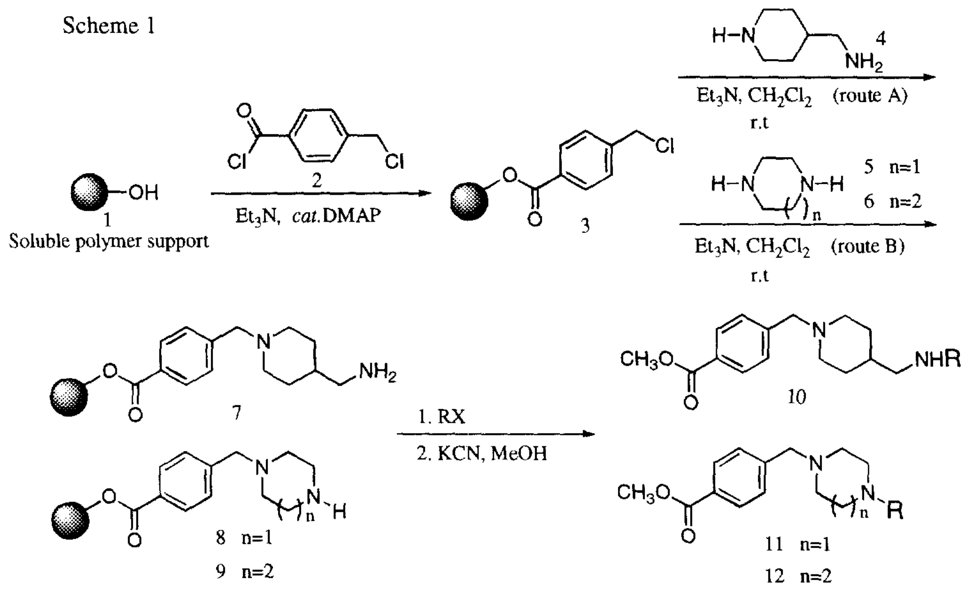
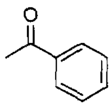
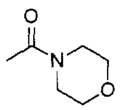
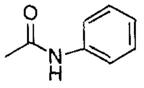
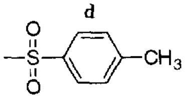
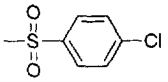


Table 1

Entry	R	Route	n	Observed MS[a]	Crude yield[b] (%)	Crude purity[c] (%)
1	**a** 	A	1	367	98	91
2		B	1	339	90	98
3		B	2	353	87	97
4	**b** 	A	1	376	95	81
5		B	1	348	93	89
6		B	2	362	90	81
7	**c** 	A	1	382	81	85
8		B	1	354	91	96
9		B	2	368	94	97
10	**d** 	A	1	417	84	93
11		B	1	389	90	96
12		B	2	403	92	95
13	**e** 	A	1	436	83	92
14		B	1	409	94	92
15		B	2	423	84	93

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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.

The basic synthetic route is outlined in Scheme 1. For application to the synthesis of various molecular scaffolds, this approach requires the polymer building blocks to be soluble under conditions of acylation 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 retains two crucial advantages of solid phase synthesis, *i.e.* addition of excess reagents and simple product purification.

The liquid-phase synthesis was initiated by treating MeO-PEG **1** (MW: 5000) with 4-chloromethyl benzoyl chloride **2** (1.2 equiv., CH_2Cl_2, 24 h, R.T.) to give the resin bound benzyl chloride **3** *via* ester linkage. The conversion of linker attachment estimated by ^1H NMR was more than 95%. The resulting polymer-supported benzylic halide **3** reacted readily with a variety of amines in the presence of Et_3N at room temperature. These nucleophilic substitution reactions were monitored using proton NMR for the disappearance of polymer-bound benzylic protons (MeOPEGCOPh-$\underline{CH_2}$-Cl) at 4.58 ppm. Small molecule templates (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 benzylic chloride **3** using secondary amine moiety only. It is essential to use excess of a diamine component in this coupling reaction in order to decrease the risk of polymer cross-linking. Our support strategy is then able to achieve monoalkylation of symmetric diamines without time-consuming protection-alkylation-deprotection sequence [9]. Polymer 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**,**e**) 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. Treatment of acylated products with KCN in methanol resulted in a very efficient cleavage from polymer support to provide the desired molecules (**10**~**12**) in high yield (86~98%) and high purity (81~98%). Compounds were characterized by low-resolution mass spectrometry and ^1H NMR confirming that in each reaction the major compound had a molecular ion corresponding to the appropriate product [10].

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, and TLC) to monitor reaction progress without following cleave-&-analyze technique. This non-destructive approach to monitor reaction progress makes LPCS method even more valuable.

In summary, a novel liquid phase synthesis of piperazine and piperidine derivatives has been developed. This methodology should decrease the difficulties of adapting established solution-phase precedents to polymer supported reactions since reactions can be carried out in homogeneous solution. All four reactions (linker attachment, S_N2 reaction, acylation and resin cleavage) involved are highly efficient to give the desired compounds in high yields and excellent purity by simple precipitation and washing. 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 exploration of this technology to other transformations is ongoing and will be reported in later papers.

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[10] A typical procedure for the synthesis of **11c** (Entry 8) is as follow: polymer bound benzyl chloride **3** (505 mg, 9.8×10^{-2} mmol) and piperazine **5** (68 mg, 7.8×10^{-1} mmol) were stirred in 10 mL CH_2Cl_2 for overnight. After completion, the solution was concentrated by rotary evaporation and reaction mixture was precipitated by slow addition of cold diethyl 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 **8** was redissolved, precipitated twice and dried *in vacuo* for the next sequence. PEG supported piperazine **8** (510 mg, 9.8×10^{-2} mmol) and phenyl isocyanate **c** (35 mg, 2.94×10^{-1} mmol) were stirred in 5 mL CH_2Cl_2 for 48 h. After completion, the solution was concentrated by rotary evaporation and reaction mixture was crystallized in ethanol. Polymer bound product was then filtered using a fritted funnel and washed several times with ethanol. The transesterification of acylated product in KCN/methanol is representative for the cleavage procedure: 522 mg of polymer-bound acylated piperazine 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, crystallized into icy cold ether. The polymer was filtered and the combined filtrated was dried to give crude product **11c** as a light yellow solid (32 mg, 91%) ; The crude purity of this compound was determined to be 96% by the HPLC analysis (250x4.6 mm Sphereclone 5μ Si, gradient elution 50% ethyl acetate/hexane, 1 mL/min.); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2 H), 7.38 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.22 (m, 2 H), 6.99 (t, J = 7.2 Hz, 1 H), 6.45 (s, 1 H), 3.88 (s, 3 H), 3.55 (s, 2 H), 3.47 (t, J = 4.9 Hz, 4 H), 2.44 (t, J = 4.9 Hz, 4 H); ^{13}C NMR($CDCl_3$) δ 166.9, 155.0, 143.2, 139.0, 129.6, 129.1, 128.8, 128.7, 123.0, 120.0, 62.4, 52.7, 52.0, 44.0. IR (neat) 3328, 2920, 1720, 1642. HRMS: calcd. for $C_{20}H_{23}N_3O_3$ 353.1741, found 353.1737.