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Liquid Phase Parallel Synthesis of Guanidines

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Abstract

Combinatorial synthesis of *N,N'*-di(Boc)-Protected guanidines containing piperazine and pyrrolidine scaffolds has been developed. We initiate a preliminary study on the reactivity of several guanylating reagents with soluble polymer-bound diamines in liquid phase. Guanidines are liberated from the polymer support under mild conditions in high yields and high purity by simple precipitation and washings. This combinatorial liquid-phase methodology proves to be a useful tool for constructing guanidine libraries containing diamine scaffolds.

The growing application of combinatorial organic synthesis [1-3] on solid support has already been reflected in the rapidly increasing reaction types and synthetic strategies. It has been regarded as an important tool for the synthesis of a large number of pharmaceutically interesting compounds. In couple with high throughput screening systems, this technology may revolutionize the drug discovery process. However, solid-phase approach usually needs additional research and development time. We are focusing our research efforts on the liquid-phase combinatorial synthesis (LPCS) by the use of soluble polymer support to generate libraries [4-6]. This macromolecular carrier, in contrast to an insoluble matrix, is soluble in most organic solvents and has a strong tendency for precipitation in particular solvents. In order to meet all requirements of a stepwise synthesis without intermediate purification, the homopolymer should be stable during all stages of synthesis. After reaction is complete, the product remains covalently bound to the support, and purification can be accomplished after precipitation simply by filtering and washing away the unwanted material.

The guanidine functional group is a crucial component in many medicinally interesting molecules [7-8]. Guanidine-containing compounds are frequently found possessing broad biological activities, ranging from antimicrobial, antiviral and antifungal to neurotoxic [9-10]. Therefore, practical methods of the rapidly synthesizing guanidine containing molecules are of great interests in the drug discovery and lead optimization. Typically, preparation of guanidines usually involves reaction of an amine with an electrophilic amidine species. The most commonly used guanylating reagents are *N,N'*-bis-Boc-1-guanylpyrazole **1** [11], *N,N'*-bis-Boc-thiourea **2** [12] and *N,N'*-di-(*tert*-butoxycarbonyl)-S-alkylisothioureas **3** [13]. Solid-phase synthesis of small-molecule alkylguanidines has recently appeared [14], and solution-phase synthesis of polyazapyridinocyclophanes containing guanidine functionality has been reported [15]. Here, we wish to report a novel route to the substituted guanidine libraries by the liquid-phase combinatorial approach using soluble polymer support (Table 1). The basic synthetic route is outlined in Scheme 1.

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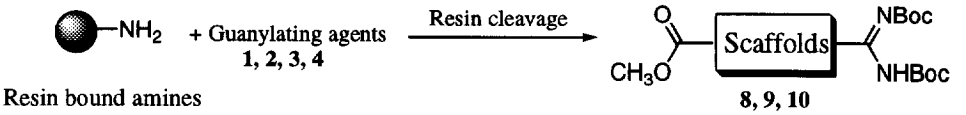
Scheme 1. Liquid Phase Syntheis of *N,N'*-bis-Boc-Guanidine



Guanylating agents

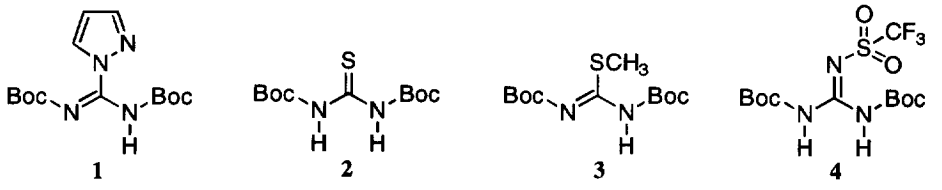
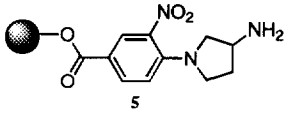
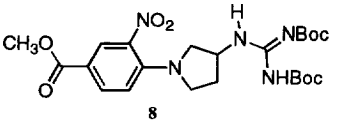
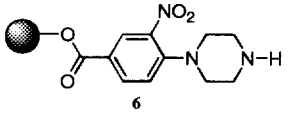
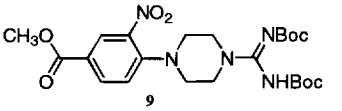
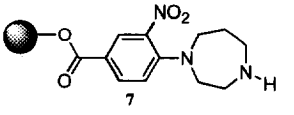
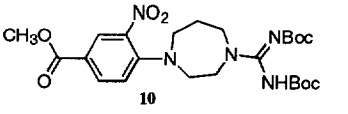
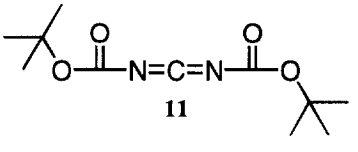


Table 1. Guanidinylation of resin bound amines with diprotected Boc-guanidines

Entry	Resin Bound Amine	Conditions	Product	Yield[a]	Purity[b]
1		A		75	90
2		B		83	78
3		C		84	88
4		D		80	82
5		A		72	98
6		B		85	96
7		C		84	89
8		D		85	96
9		A		76	88
10		B		83	92
11		C		72	90
12		D		83	76

a. Yields are based on weight of crude sample and are relative to the initial loading.
b. Purity determined by HPLC analysis of crude products. Products show satisfactory ^{1}H NMR and MS data, which are consistent with the proposed structure.
A: 1.2 eq. of **1** in CH_2Cl_2 (r.t.; 8 h)
B: 1.2 eq. of **2** and 1.2 eq. DICDI in CH_2Cl_2 (r.t.; 18 h)
C: 1.2 eq. of **3**, 2 eq of $HgCl_2$ and 3 eq. of Et_3N in CH_2Cl_2 (r.t.; 40 h)
D: 1.2 eq. of **4**, and 3 eq. of Et_3N in CH_2Cl_2 (r.t.; 10 h)

To investigate the relative efficiency of guanylating reagents in the soluble polymer-supported synthesis, we examined reactions of three separated resin-bound amines (**5~7**) with four different reagents (**1~4**) under several conditions (A~D). These resin-bound amines were reported from this lab. before [5]. Results from evaluation of these reagents are shown in Table 1. The aminoguanylation reactions were carried out smoothly at ambient temperature to give the corresponding products (**8~10**) after resin cleavage. Treatment of polymer bound primary amine **5** with *N,N'*-bis(Boc)-1-guanylpyrazole **1** resulted in the complete consumption of amine and formation of the desired *N,N'*-bis(*tert*-butoxycarbonyl) guanidines at room temperature in 8 h (procedure A- entries 1,5,9). It is clear that 1-pyrazolyl substituent represents a good leaving group. Progress of reaction was easily followed by TLC analysis (observation of disappearing **1**) and was conveniently estimated by ^{1}H NMR without any resin cleavage. A different protocol (procedure B- entries 2,6,10) was also adopted for guanidinylation using the combination of reagent **2** and diisopropylcarbodimide (DICDI). This process worked very well at room temperature to give final products in good yields and purity. According to solution phase precedents [15-16], our treatment of commercially available reagent **3** with polymer bound amine **5~7** failed to deliver any desired product even under harsh conditions (e.g. refluxing in toluene). However, we found that subsequent aminolysis of *N,N'*-di(Boc)-S-methylisothiourea **3** by the promotion of mercury (II) and triethylamine provided a very efficient route for the bis-protected guanidines formation (procedure C-entries 3,7,11). Without addition of triethylamine, the reaction was proceeded very sluggish. Formation of insoluble mercuric sulfide was easily removed by using fluted filter paper before precipitation and washing. It is apparent that this protocol is not amenable to solid-phase synthesis because of the existence of insoluble precipitate. A new class of guanidinylation reagent-*N,N'*-di-Boc-*N''*-triflylguanidine **4** [17] was also allowed the synthesis of protected guanidines with great ease and efficiency (procedure D -entries 4,8,12). Although the exact intermediates for the mercuric chloride-or DICDI-promoted guanidine formation are unknown, the possible *in-situ* generated a highly electrophilic bis(Boc)carbodiimide **11** may be the reactive species.



11

It is worthy to note that, in contrast to the various restrictions on the analysis of reaction development in solid-phase synthesis, liquid-phase synthesis allows routine analytical instruments (UV, IR, NMR, TLC) to monitor reaction progress without following *cleave-&-analyze* technique. This non-destructive approach to monitor reaction progress makes LPCS method even more valuable. Further, our liquid-phase strategy retains two attractive features of solid-phase synthesis, *i.e.* addition of excess reagents and simple product purification.

In summary, a facile and efficient liquid-phase method that employs soluble polymer support to synthesize guanidines containing diamine templates has been presented. 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, guanylation and resin cleavage) involved are highly efficient in giving the desired compounds in high yields and high purity just by simple precipitation and washing. This method of synthesis is versatile and produces compounds with known pharmacophoric scaffolds, and which are thus ideally suited for combinatorial library generation. Further applications of this technology are ongoing and will be reported in the near future.

In a typical procedure for the synthesis of **9** is as follow (entry 8): PEG supported piperazine **6**[5] (500mg, 9.6×10^{-2}mmol), *N,N'*-Di-Boc-*N''*-trifluoromethanesulfonyl guanidine (56mg, 1.4×10^{-1}mol) and triethylamine (88mg, 8.7×10^{-1} mmol) were stirred in 5 ml CH_2Cl_2 for overnight. After completion, the solution was concentrated by rotary evaporation and reaction mixture was precipitated by addition of ether with stirring. Polymer bound product was then filtered under aspirator pressure using a fritted funnel and washed several times with ethanol. Transesterification of guanylated product in KCN/methanol is representative for the cleavage procedure: 530mg of polymer-bound guanylated piperazine was dissolved in 5ml 1% KCN/CH_3OH and stirred at room temperature for 6 h. The solution was evaporated under vacuum to remove methanol and polymer bound product was precipitated in ethanol. The polymer was filtered and the combined filtrate was dried to give crude product **9** as a slight yellow solid (41mg, crude yield: 85%); The crude purity of this compound after four steps was determined to be 96 % by the HPLC analysis (250x4.6 mm Sphereclone 5μ Si, gradient elution 50 % ethyl acetate/hexane, 1 mL/min.); ^{1}H NMR(300MHz, $CDCl_3$) δ9.95(s, 1H), 8.38(d, *J*=2.1 Hz, 1H), 8.02(dd, *J*=9.0, 2.1 Hz, 1H), 7.04(d, *J*=9.0 Hz, 1H), 3.89(s, 3H), 3.84(m, 2H), 3.66(m, 2H), 3.50(m, 2H), 3.42(m, 2H), 1.54(s, 18H); ^{13}C NMR(75MHz, $CDCl_3$) δ 165.1, 155.0, 148.2, 140.4, 134.4, 128.4, 122.3, 119.4, 107.4, 81.3, 52.3, 50.2, 46.7, 28.1. IR (neat) 2924, 1717, 1612, 1527, 1436, 1295. MS (FAB$^+$) *m/z* 508 (M+1).

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