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Report

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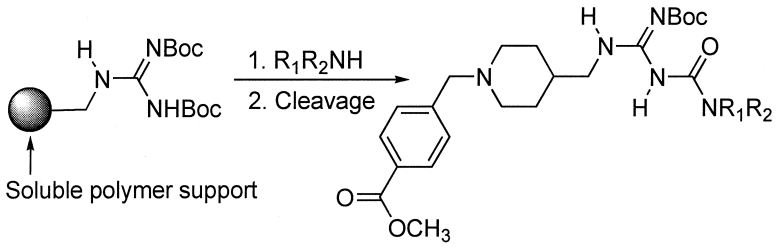

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Reports

High-Throughput Synthesis of Boc-Substituted Amidinoureas by Liquid-Phase Approach

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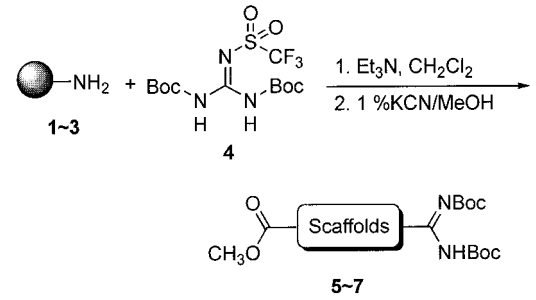
The growing application of combinatorial organic synthesis[1] on solid support has been reflected in the rapidly increasing reaction types and synthetic strategies. It has been regarded as an important tool for the synthesis of a large number of pharmaceutically interesting compounds. Coupled with high-capacity screening systems, this technology may revolutionize the drug discovery process. However, the solid-phase approach often requires additional research and development time. We are focusing our research efforts on liquid-phase combinatorial synthesis (LPCS) using soluble polymer support—poly(ethylene glycol) monomethyl ether—of MW 5000 to generate libraries.[2] This macromolecular carrier, in contrast to an insoluble matrix, is soluble in most organic solvents and has a strong tendency for precipitation in certain solvents. After complete reaction, the product remains covalently bound to the support, and purification can be accomplished after precipitation simply by filtering and washing away the unwanted material.

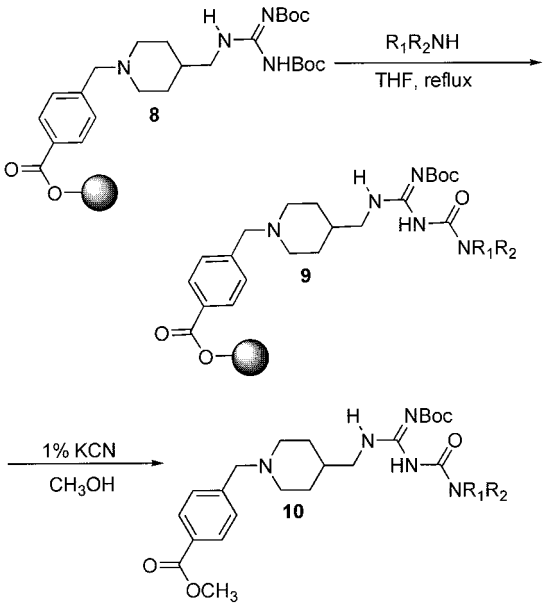
The guanidine and urea functional groups are crucial components in many medicinally interesting molecules.[3] Therefore, practical methods of rapidly synthesizing guanidine- or urea-containing molecules are of great interest in drug discovery and lead optimization. To study the soluble polymer-supported synthesis of piperidine- and piperazine-containing guanidines,[4] we investigated the reactions of three separate PEG-bound amines[2f] (**1**−**3**) with the newly developed guanylating reagent[5] *N*,*N*′-di-Boc-*N*′′-triflylguanidine **4** under basic conditions in CH_2Cl_2 (Scheme 1).

Results are summarized in Table 1. It can be seen that aminoguanylation proceeds smoothly at room temperature to give the corresponding *N*,*N*′-di(Boc)-protected guanidines. Progress of reaction is easily followed by TLC analysis (observation of disappearing **4**) and is conveniently estimated by ^{1}H NMR without any polymer cleavage. Guanidines are liberated from the polymer support by 1% KCN/MeOH in high yield (80−95%) and high purity (82−86%).[6] Although the exact intermediates for the guanidine formation are unknown, the possible in situ generated highly electrophilic bis(Boc)carbodiimide may be the reactive species.[7]

Scheme 1



Scheme 2



To increase the chemical diversity of the library, polymer-bound guanidine **8** is reacted with various amines. It is expected that the desired product could be cleaved by the transamination from the polymer support. However, we find that no products are liberated from the PEG-supported guanidines in refluxing THF. Instead of the desired aminolysis product, one compound has been isolated and identified as the amidinourea **10** after cleavage (Scheme 2).[8]

Although aminolysis of many carbamates is well understood,[9a] the Boc-protecting group is known to be particularly stable under basic conditions and is also strongly resistant toward various nucleophilic reagents.[9b] Therefore, a brief investigation of the range of applicability in this discovery was carried out. Results are reported in Table 2. Treatment of polymer-bound guanidine **8** with several different primary amines (entries 1−7) results in the complete conversion of *N*,*N*′-bis(*tert*-butoxycarbonyl)guanidines to the *N*-(*N*′-*tert*-butoxycarbonylamidino)ureas on the support. The coupling reaction proceeds well by treatment with 3 equiv of an amine

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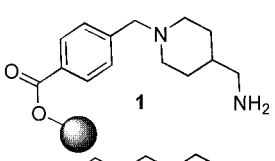
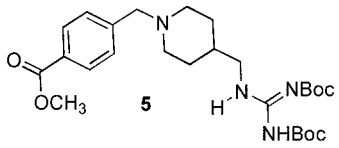
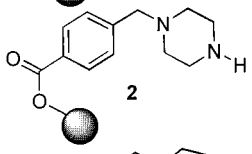
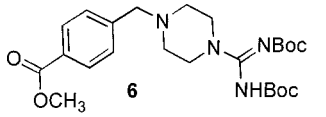
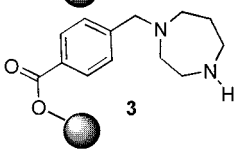
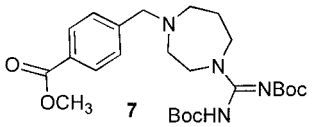
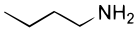
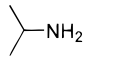
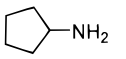
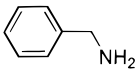
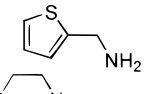
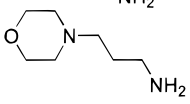
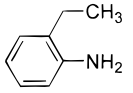
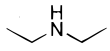
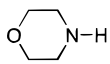
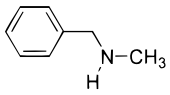
Table 1. Liquid-Phase Synthesis of *N,N′*-Bis-Boc-guanidines

Entry	Resin bound amines	Product	Yield[a](%)	Purity[b](%)
1			81	86
2			95	83
3			80	82

[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.

Table 2. Preparation of Amidinoureas **10** from *N,N′*-Di(Boc)guanidine on the Support

Entry	R_1R_2NH	Observed MS[a]	Yield[b](product)	Crude purity[c](%)
1		504	78(**10a**)	86
2		490	95(**10b**)	83
3		516	80(**10c**)	84
4		538	80(**10d**)	93
5		544	78(**10e**)	74
6		575	72(**10f**)	86
7		552	82(**10g**)	90
8		504	92(**10h**)	93
9		518	80(**10i**)	86
10		552	82(**10j**)	88

[a] Confirmed by mass spectra (FAB$^+$). [b] Yields are based on weight of crude sample and are relative to the initial loading. [c] Purity determined by HPLC analysis of crude products. Products show satisfactory ^{1}H NMR and MS data, which are consistent with the proposed structure.

in THF after heating for 8 h. Excess amines can be easily washed away after precipitation of PEG-bound products. It is worth mentioning that poorly nucleophilic, sterically hindered aniline also reacts well to form corresponding amidinourea (entry 7). Moreover, this method is also successfully applied to secondary amines and generated the *N,N,N′*-trisubstituted ureas in high yield and high purity (entries 8−10). The greater reactivity of the secondary amines can be realized by the fact that secondary amines need less time (around 5 h) to complete reactions, since they are more nucleophilic than primary amines. In contrast to the other approaches[10] using *n*-BuLi for carbamate deprotection, our method demonstrates the advantages of the one-pot procedure to prepare Boc-substituted amidinoureas. 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 the *cleave-and-analyze* technique. This nondestructive approach to monitor reaction progress makes the LPCS method even more valuable.

In conclusion, a facile and efficient liquid-phase method that employs a soluble polymer support to synthesize guanidines and amidinoureas has been presented. The scope of the coupling method is assessed using a variety of aromatic and aliphatic amines including aniline. All reactions 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, which are thus ideally suited for combinatorial library generation. Further work on the mechanism of aminolysis is actively in progress.

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Supporting Information Available. Complete experimental details for the preparation of all products and characterization data for compounds, including copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) A typical procedure for the synthesis of **5** (Table 1, entry 1) is as follows: PEG-supported piperidine **1** (500 mg, 0.096 mmol), triethylamine (39.8 μL, 0.29 mmol), and *N*,*N*′-di(Boc)-*N*′′-trifluoromethanesulfonyl guanidine **4** (56.1 mg, 0.143 mmol) were stirred in 5 mL of CH_2Cl_2 for 8 h. After completion, the solution was concentrated by rotary evaporation, and the reaction mixture was precipitated by slow addition of cold *tert*-butyl methyl ether. Polymer-bound product was then filtered under aspirator pressure using a fritted funnel and washed several times with cold ethanol. 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: polymer-bound guanidine was dissolved in 5 mL of 1% KCN/CH_3OH and stirred at room temperature overnight. The solution was precipitated into icy cold ether. The polymer was filtered, and the combined filtrate was dried to give crude product **5** as a bright yellow solid (40.0 mg, 81%). The crude purity of this compound was determined to be 86% by HPLC analysis (250 × 4.6 mm Sphereclone 5μ Si, gradient elution 100% ethyl acetate, 1 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.49 (s, 1H), 8.39 (t, J = 4.6 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 3.90 (s, 3H), 3.53 (s, 2H), 3.32 (m, 2H), 2.87 (m, 2H), 1.98 (m, 2H), 1.71 (m, 2H), 1.49 (s, 9H, H-Boc), 1.48 (s, 9H, H-Boc), 1.34 (m, 3H). MS (FAB$^+$): *m*/*z* 405 (M^+ − Boc) 305, 246, 149. Exact mass calcd for $C_{21}H_{32}N_4O_4$: *m*/*z* 405.2504. Found: 405.2523.

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