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Liquid-Phase Parallel Synthesis of Ureas

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Abstract—An efficient and general liquid-phase method has been developed for the synthesis of a piperazine containing urea library. Reactions of the polymer bound carbamoyl chloride with primary or secondary amines afford ureas at ambient temperature. Desired compounds are liberated from the polymer support under mild conditions in high yields and high purity by simple precipitation and washings.

The growing application of combinatorial organic synthesis on solid support has already been reflected in the rapidly increasing reaction types and synthetic strategies.[1,2] It has been regarded as an important tool for the synthesis of a large number of pharmaceutically interesting compounds. Coupled with high throughput screening systems, this technology may revolutionize the drug discovery process. The solid-phase approach of heterocyclic libraries usually needs additional research and development time because heterogeneous reaction conditions are applied. It is difficult to transfer traditional solution-phase chemistry directly to the solid-phase synthesis. We have focused on our research efforts on the liquid-phase combinatorial synthesis (LPCS) by the use of soluble polymer support to generate libraries.[3–6] Liquid-phase combinatorial synthesis is a unique approach since homogeneous reaction conditions can be applied, but product purification, just like that of the solid-phase method, can be carried out by simple filtration and washings.

The urea functionality is a key structural element, which plays as a nonhydrolysable surrogate of amide bonds in many pharmaceutically active molecules.[7,8] Urea-containing compounds are frequently found possessing broad biological activities, including potent HIV protease inhibitors,[9] CCK-B receptor antagonists[10] and endothelin antagonists.[11] Therefore, practical methods of the rapid synthesis urea containing molecules are of great interest in drug discovery and lead optimization. A previous report of Chapman described combinatorial synthesis of ureas via solid-supported *p*-nitrophenylcarbamate intermediate.[12] Burgess et al. also reported solid-phase synthesis of ureas, which proceeded through polymer-bound isocyanate.[13] In addition, solution-phase synthesis of ureas using nitrophenylcarbamates has been studied.[14–16] Here, we wish to report a promising liquid-phase approach for the synthesis of substituted urea libraries.

The basic synthetic route is outlined in Figure 1. PEG immobilized piperazine **2** and **3** are prepared according to our previous literature procedure.[17] The resulting diamine templates are first reacted with commercially available *N*,*N*′-carbonyldiimidazole (CDI), which has been used to prepare *N*,*N*′-disubstituted carbomyl imidazoles.[18] Polymer bound carbamoyl imidazoles are found to be inert toward primary and secondary amines even under more forcing conditions for prolonged periods (e.g., in refluxing toluene). It is necessary to activate the leaving imidazole group to form the desired ureas.[19] Recently, we have demonstrated the utility of triphosgene (bis(trichloromethyl)carbonate) as an *N*,*N*′-disubstituted carbamoyl cation equivalent to form benzimidazolones.[20] We reason that PEG bound diamines **2** and **3** would be similarly activated by initial conversion to the trichloromethyl carbamate intermediates **4**. Subsequent addition of an amine to **4** would then furnish the tetrasubstituted ureas **5** after cleavage.

PEG bound diamine templates **2** and **3** are chosen as representative starting material for the synthesis of the ureas. Isolated, stable trichloromethyl carbamates **4** are obtained in high yield from those amines using triphosgene in the presence of triethylamine. The reactive intermediates **4** require no additional purification for

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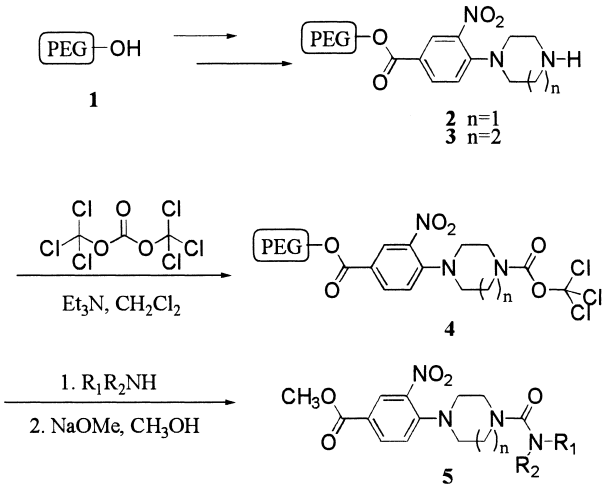
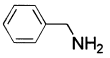
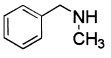
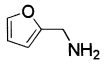


Figure 1. Liquid-phase synthesis of ureas.

use in the following steps to the ureas. Subsequent addition of primary or secondary amines to a solution of **4** in methylene chloride at room temperature cleanly forms the corresponding substituted ureas. Following solvents washes after precipitation, immobilized ureas are subjected to an efficient cleavage from the support with NaOMe in methanol to provide the desired compounds.[21] Complete cleavage of the PEG is verified by the observation of the downfield shift of α-methylene protons at the polymer attached site from δ 4.4 ppm to δ 3.6 ppm in the regular proton NMR. If the peak of α-methylene protons is still present after NMR checking, the recovered PEG bound products could be resubmitted to the same reaction conditions until complete scission is reached. In most cases, reactions are done overnight. Purity assessment of each library member by the HPLC is usually good, ranging from 76 to 94% (Table 1). Figure 2 shows a typical HPLC spectrum of the crude product **5d**.

No attempts are made to optimize reaction conditions and all reagents are used directly without any purification. Products from validation libraries are characterized by mass spectrometry and ^{1}H NMR. Expected molecular ions (M^+, or M + H) are observed for all the products, in most case as the base peak.

Table 1. Ureas synthesized from polymer bound carbamoyl chloride

Entry	R_1R_2NH	*n*	Observed MS[a]	Crude yield[b] (%)	Crude purity[c] (%)
5a		1	365 (M + 1)	98	84
5b		2	378	98	86
5c		1	376	97	84
5d		2	391 (M + 1)	96	85
5e		1	398	90	85
5f		2	412	91	81
5g		1	413 (M + 1)	90	89
5h		2	426	85	89
5i		1	389 (M + 1)	92	82
5j		2	403 (M + 1)	93	76
5k		1	377 (M + 1)	98	89
5l		2	390	96	84

[a]M + 1 peak (FAB).
[b]Based on loading of original resin.
[c]Purity determined by HPLC analysis (UV detection at λ = 254 nm) of crude products. Products show satisfactory ^{1}H NMR and MS data.

After each reaction step, polymer bound product is purified by precipitation and washings with diethyl ether. Further recrystallization can be done from ethanol, but a small loss of material is observed. A TLC analysis also confirms the removal of the excess reagent and soluble byproducts. The liquid-phase synthesis performed in homogeneous solution usually required less excess reagents than solid-phase synthesis. Moreover, the reaction progress is easily monitored by non-destructive spectral analysis. In general, all mono-functional, primary aliphatic or aromatic amines give substituted ureas in excellent yields and more than 76% crude purity (entries **5a**–**5f**, **5i**–**5j**) including relatively hindered amines (entries **5c**–**5d**). With unhindered secondary nucleophiles, amine acylations give the same good results compared to that of regular primary amines (entries **5g**–**5h**, **5k**–**5l**).

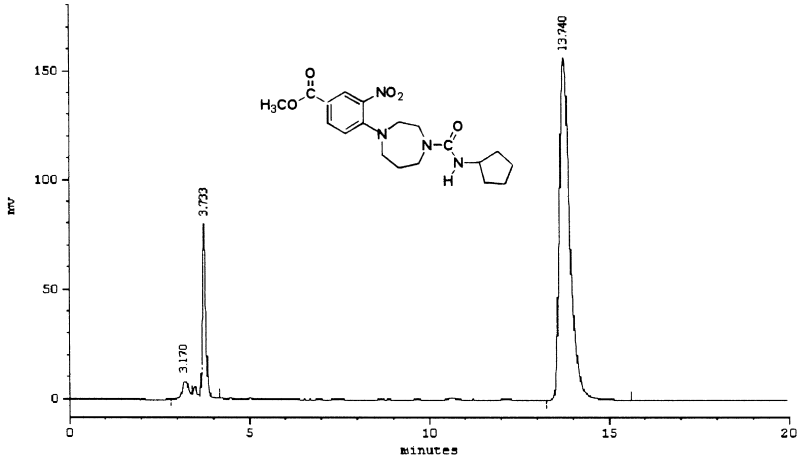


Figure 2. HPLC analysis of crude product **5d**, with UV detection at λ = 254 nm. Column: Sphereclone 5μ Si (250×4.6 mm); gradient: 100% ethyl acetate; flow rate: 1 mL/min.

In conclusion, we have established an efficient new protocol for the formation of unsymmetrical, substituted ureas (Table 1). Although the aromatic fragment contains a methyl ester and nitro substituent, they could be further elaborated to other functional groups. This methodology should decrease the difficulties of adapting established solution-phase precedents to polymer-supported reactions because reactions can be carried out in homogeneous solution. Using this method, many ureas can be readily accessed and should be useful in future synthesis of related structurally diverse libraries.

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21. All the compounds listed in the Table 1 give satisfactory ^{1}H NMR, ^{13}C NMR and mass data. The data for **5l** are as follow: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, $J=2.1$ Hz, 1H), 7.98 (dd, $J=9.0$, 2.1Hz, 1H), 7.03 (d, $J=9.0$ Hz, 1H), 3.88 (s, 3H), 3.38–3.54 (m, 10H), 3.02–3.16 (m, 4H), 2.05 (m, 2H), 1.46–1.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.9, 148.0, 138.7, 134.1, 129.3, 119.6, 118.3, 53.1, 52.6, 52.0, 49.2, 48.6, 48.4, 28.3, 26.0, 25.0; IR (neat) 1718, 1613, 1526 ($\nu_{as}NO_2$), 1435 ($\nu_{s}NO_2$); mass spectrum (EI) m/z 390 (M^+). Exact mass calcd for $C_{19}H_{26}N_4O_5$: m/z 390.1903. Found 390.1903.