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SOLUTION-PHASE COMBINATORIAL SYNTHESIS OF UREAS USING NITROPHENYLCARBAMATES

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Abstract: Nitrophenycarbamates were reacted with various amines to yield ureas. A high throughput purification of these crude products was achieved by using polymer bound scavengers.

Combinatorial chemistry,[1] a rapidly evolving technology, is now a key component of the drug discovery process. Since the initial use of polymers by Merrifield in 1963 in the development of solid-phase technique[2] for the synthesis of peptides, there has been tremendous growth in the use of functionalized polymers[3] in organic synthesis. The use of polymer bound reagents, catalysts, or protecting groups in organic reactions as well as polymer bound scavengers to trap excess starting materials and byproducts all constitute attractive uses of solid phase-chemistry. The use of polymer bound scavengers as a two-phase system can lead to the isolation of pure products from the solution phase, obviating the need for extensive purification.[3,4]

The urea functionality, a common structural motif in biologically active molecules,[5] is a nonhydrolysable surrogate of an amide bond.[5i] In a continuation of our ongoing efforts to develop focused libraries of small molecules,[6] there arose a need for the synthesis of trisubstituted ureas. Although there are numerous classical methods known for the synthesis of symmetrical and unsymmetrical ureas,[7] the reaction of primary or secondary amines with carbamates or isocyanates seem to be the methods of choice for high-throughput synthesis. In fact, polymer bound nitrophenylcarbamates have been reported for the synthesis of urea libraries.[8] A high-throughput, solution-phase synthesis of ureas was also reported using isocyanates and polymer bound scavengers.[3f] The lack of commercial availability of diverse isocyanates demands their synthesis using phosgene or triphosgene and further purification of the resulting isocyanates is usually necessary. The ease of preparation of nitrophenylcarbamates, by reacting commercially available nitrophenyl chloroformate with an amine,[5b] and the further reaction of the resulting nitrophenylcarbamate with a second amine to provide ureas is an elegant approach, provided that the ureas can be purified in a high-throughput fashion.

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Scheme 1

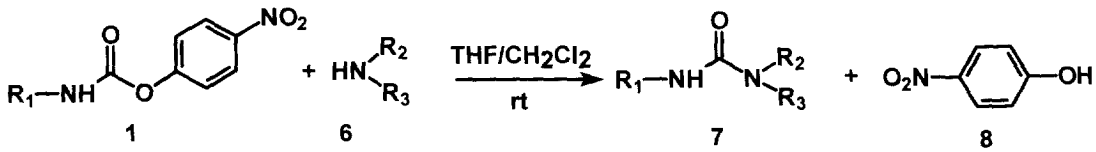
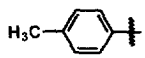
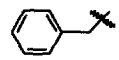
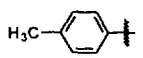
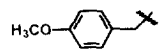
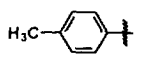
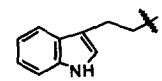
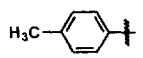
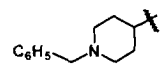
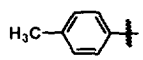
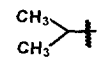
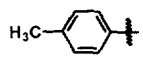
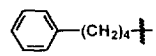
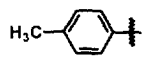
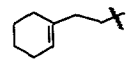
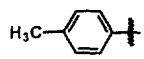
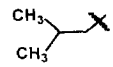
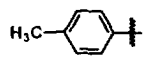
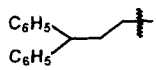
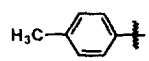
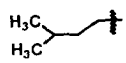
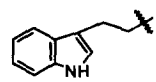
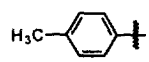
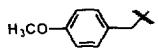
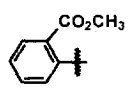
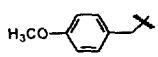
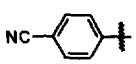
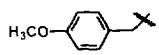


Table I

Entry	R_1	R_2	R_3	% Yield	% Purity[a,9]	Method[b,10]
a		CH_3-		89	94	A
b		H		84	93	A
c		H		46	94	A
d		H		74	100	B
e				100	80	A
f		H		100	98	A
g		H		100	98	A
h		H		99	99	A
i		H		98	99	A
j				100	96	B
k				95	100	B
l		H		64	85	A
m		H		93	97	A
n		H		89	96	A

[a]Analytical HPLC of the products using a C18 reverse-phase column (250 mm X 4.6 mm) eluting with a water/acetonitrile mixture containing 0.1 % TFA from 5% to 95% acetonitrile (linear gradient) over 30 min. [b]Efficient stirring was necessary for complete removal of nitrophenol.

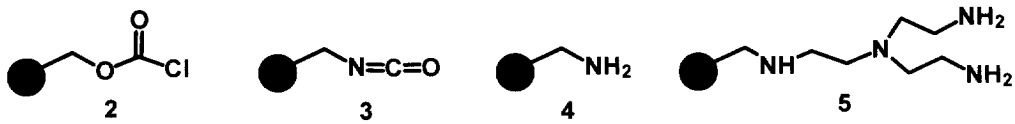


Figure 1. Functionalized polymers

Reaction of N-methylbenzylamine with nitrophenylcarbamate **1a** (Entry **a**, Table 1) gave the desired urea and nitrophenol as a byproduct (Scheme 1). The use of one of the two reactants in excess resulted in complete consumption of the other starting material. However, in the worst case scenario of incomplete reaction, the reaction mixture contained the desired urea, the byproduct nitrophenol and the starting materials. Treatment of the above reaction mixture with polymeric reagents such as chloroformate **2** or isocyanate **3** in combination with a basic polymer such as **4** or **5** (Figure 1) gave pure urea; nitrophenol and amine were completely scavenged as evidenced by NMR of the treated product (Figure 2). The resin bound amines[3i] **4** or **5** reacted with the nitrophenylcarbamate to give a polymer bound urea, while the resin bound isocyanate[3i] or chloroformate[6a] scavenged excess amine and the byproduct nitrophenol to form a polymer bound carbamate and carbonate, respectively. The yield and purity of the product obtained by using either the resin bound chloroformate or isocyanate along with resin **4** or **5** was identical. Encouraged by these observations, a series of amines were reacted with nitrophenylcarbamates to give ureas with excellent purity and yield (Table 1).

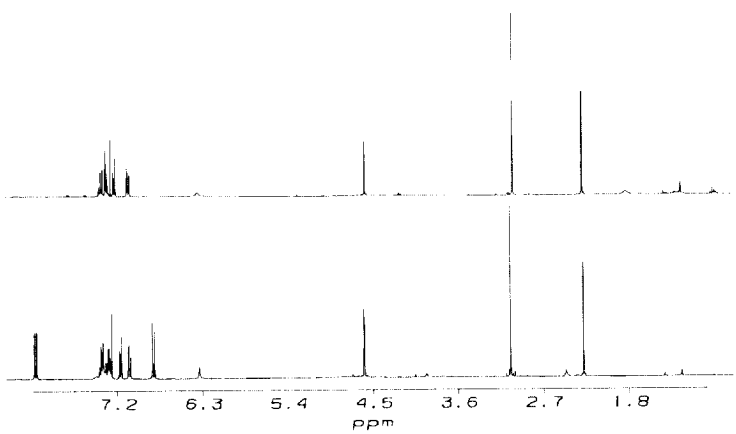


Figure 2. NMR of product treated with resin **2** and **4** (top), NMR of crude reaction mixture (bottom) [Table 1, Entry **a**]

The presence of basic functionality, as exemplified in entry **6d** (Table 1), did not give any product using the resin bound chloroformate as a scavenger, probably due to formation of a quaternary salt, but gave the desired product by using resin bound isocyanate as a scavenger. To further extend the scope of this methodology and generate a combinatorial mixture of ureas, an equimolar mixture of five amines was treated with the nitrophenylcarbamate **1m** to get an approximately equimolar mixture of five ureas as determined by HPLC (Figure 3).

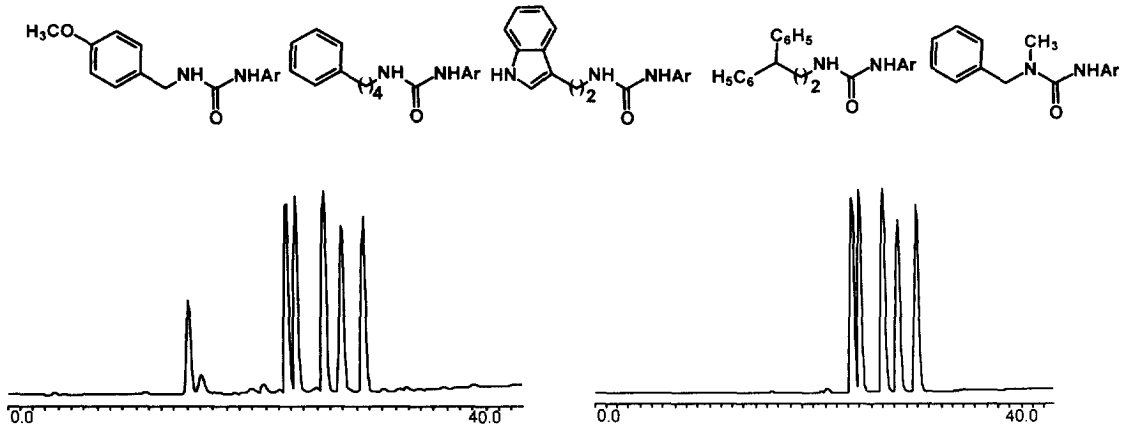


Figure 3. HPLC of crude reaction mixture of five ureas shown above (left), HPLC of product treated with resin **2** and **4** (right).

The availability of structurally diversified primary or secondary amines, from both commercial sources as well as based on recent synthetic methodologies developed to generate amines in a combinatorial fashion,[11] permitted the generation of diversified urea libraries using the above methodology. Although a series of trisubstituted ureas can be generated using this methodology, formation of terasubstituted ureas is prevented due to the lack of reactivity of nitrophenylcarbamates derived from secondary amines with either a primary or secondary amine.

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9. All the final products gave satisfactory high resolution ^{1}H NMR spectra. Correct Fab mass spectral data were obtained on subset of samples which were investigated.
10. Method A: To a stirred solution of a nitrophenylcarbamate (0.05 mmol) in dry THF (0.6 mL) was added an amine (0.05 to 0.07 mmol) and stirred at room temperature for 30 min (reaction was monitored by TLC). The reaction mixture was diluted with dry methylene chloride and polymer bound chloroformate (200 mg, prepared from hydroxymethyl resin,[6a] 0.7 meq of OH/g of resin) and aminomethyl polystyrene (100 mg, 1.37 meq of N/g of resin) were added. Stirring was continued for 14 h at rt. The resin was filtered, washed with methylene chloride, and the combined filtrate was concentrated to obtain the product; (b) Method B: As Method A except that polymer bound isocyanate (200 mg, prepared from aminomethyl polystyrene,1.2 meq of N/g of resin) and basic polymer **5** were used.
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