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A General Method for the Solid Phase Synthesis of Ureas

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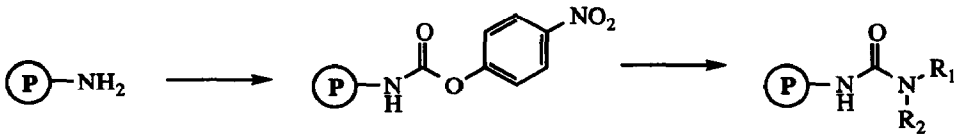
Abstract: A general method for the solid-phase synthesis of ureas has been developed. The key intermediate being a *p*-nitrophenylcarbamate which is transformed into the urea by reaction with primary or secondary amines. The products obtained are of high chemical purity.

The generation of molecular diversity has become a topic of much discussion.[1] Peptide libraries have been generated that contain millions of peptides *via* the use of combinatorial and other solid phase techniques.[2] Due to their limited oral absorption and poor metabolic stability, however, peptides are rarely useful drug candidates. In the past two years there have been reports of successful solid-phase preparations of non-peptide compounds such as: peptoids,[3] oligosaccharides,[4] benzodiazepines,[5,6] and hydantoins.[6] We have developed a general method for the preparation of ureas on a solid support. The urea linkage is more metabolically stable than the amide linkage and compounds which contain a urea are more desirable as potential drug candidates. We have therefore developed versatile chemistry (general scheme shown below) for the solid-phase synthesis of these moieties.

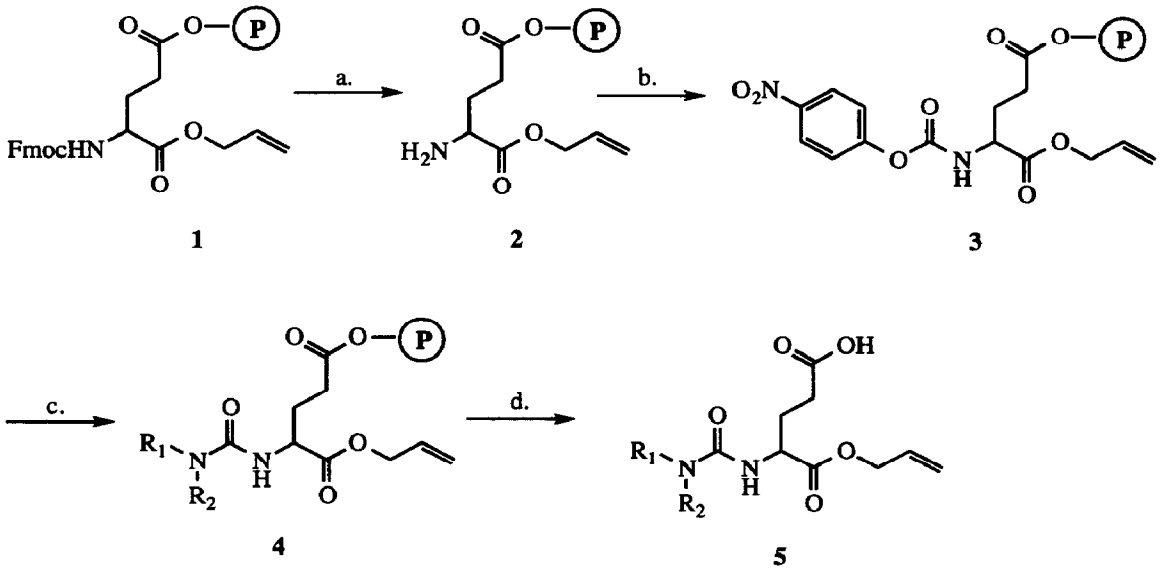


The solution-phase synthesis of symmetrical and unsymmetrical di- and tri-substituted ureas *via* the *p*-nitrophenylcarbamate intermediate has been reported.[7,8,9] Formation of the carbamate proceeds *via* reaction of either bis(4-nitrophenyl) carbonate [7,8] or *p*-nitrophenylchloroformate [9] with an amine and yields range from 44 - 78%. Reaction of the carbamate intermediate with either primary or secondary amines produces the desired ureas with yields of 50 - 96%. However, the total reaction time for these procedures is 6 - 10 hours, a rate too slow to be convenient for solid-phase synthesis. The solid-phase synthesis of disubstituted ureas has been reported.[6] Formation of the urea proceeds by the reaction of an isocyanate with a resin bound amine in dimethylformamide for 6 hours. We now report the solid-phase synthesis of di- and tri-substituted ureas from amines using the *p*-nitrophenylcarbamate intermediate with a total reaction time of 45 minutes for both steps and affording high final product purities.

N-Fmoc-L-glutamic acid-α-allyl ester was tethered to a polystyrene resin [10] *via* its gamma carboxylic acid utilizing a 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB) handle (**1**). The Fmoc

protecting group was removed using 20% piperidine in dimethylformamide (see Scheme) to yield the free amine (**2**). The amine was reacted with *p*-nitrophenylchloroformate using diisopropylethylamine as a base to afford the *p*-nitrophenylcarbamate (**3**). A 1:1 tetrahydrofuran - methylene chloride solvent system was employed to allow for the solubilization of the diisopropylethylamine hydrochloride generated. Carbamate **3** was then reacted with a variety of amines in dimethylformamide at ambient temperature to yield the desired urea derivatives (**4**). This reaction also proceeds in tetrahydrofuran but is considerably slower. With the desired urea prepared, the resin is treated with 2% trifluoroacetic acid in methylene chloride for cleavage from the resin yielding compounds of structure **5**.

Scheme:



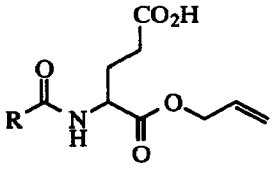
1 **2** **3** **4** **5**

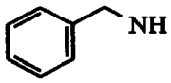
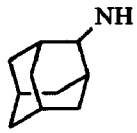
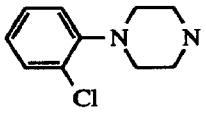
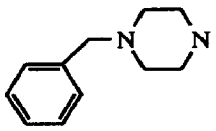
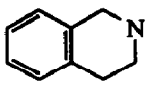
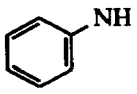
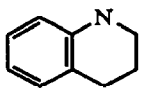
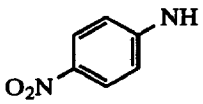
(P) = polystyrene resin with an HMPB handle

a. 20% piperidine in DMF, 20 minutes b. *p*-nitrophenylchloroformate, DIEA, THF/CH_2Cl_2, 30 minutes
c. R_1R_2NH, DMF, 15 minutes d. 2% TFA in CH_2Cl_2, 10 minutes

The table below illustrates a variety of compounds prepared by this method along with characterization data. As can be seen from the table, primary alkyl amines whether hindered (**5b**) or unhindered (**5a**) and secondary alkyl amines (**5c**, **5d** & **5e**) react with the carbamate very cleanly to form the desired urea. Primary aromatic amines such as aniline produces its desired urea (**5f**) with a high degree of purity. A secondary aromatic amine (1,2,3,4-tetrahydroquinoline) is reactive enough to form the appropriate urea (**5g**) in reasonable purity. However, when the aniline is substituted with the highly electron withdrawing 4-nitro group, the desired urea (**5h**) is not formed.

Table:



Entry	R Group	HPLC Retention Time (min) [11]	HPLC Purity [11]	Mass Spec[12] (M+1 peak)
5a		6.98	96%	321
5b		7.94	92%	365
5c		7.98	95%	410
5d		4.57	96%	390
5e		7.38	98%	347
5f		7.32	96%	307
5g		7.57	90%	347
5h		-	No Reaction	-

In summary, a method for the solid-phase synthesis of ureas from amines has been developed that produces compounds that can be cleaved from the solid support with high degrees of purity. The ready availability of amines from commercial sources together with this procedure allows the preparation of large nonpeptide libraries.

General Procedure: To 50 mg of resin is added 1 mL of 20% piperidine in dimethylformamide. After mixing for 20 minutes, the resin is washed with dimethylformamide (2x1mL), tetrahydrofuran (2x1mL) and 1:1 tetrahydrofuran - methylene chloride (2x1mL). Next, 1 mL of a mixture of *p*-nitrophenylchloroformate (0.5 M) and diisopropylethylamine (0.5 M) in 1:1 tetrahydrofuran - methylene chloride is added and the reaction mixed for 30 minutes. The resin is then washed with 1:1 tetrahydrofuran - methylene chloride (2x1mL) and 1 mL of the desired amine (0.5 M) and diisopropylethylamine or triethylamine[13] (0.5 M for free amines or 1.0 M for amine salts) in dimethylformamide is added. After mixing for 15 minutes the resin is washed with dimethylformamide (2x1mL), tetrahydrofuran (2x1mL) and methylene chloride (2x1mL). The resin is treated with 2% trifluoroacetic acid in methylene chloride for 10 minutes and the solution is then removed and concentrated to yield the desired urea.

References and Notes:

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10. The resin used was purchased from Rapp Polymere (Polyethyleneglycol spacer on a polystyrene bead (130 micron, 0.27 mmol/g) - TentaGel S-NH_2 - cat. # S30132)
11. HPLC Conditions: 10 - 100% CH_3CN in H_2O + 0.1% TFA, linear gradient over 10 minutes, flow rate 1.5 mL/min, Astec Polymer C4 column (150x4.6 mm), 214 nm
12. All samples were run on a Finnigan Mat TSQ700 using electrospray ionization.
13. Triethylamine was used instead of diisopropylethylamine for the formation of ureas from unreactive amines (aromatic and substituted aromatic) since diisopropylurea (presumably from the reaction of the carbamate and residual diisopropylamine found in diisopropylethylamine) was isolated as a byproduct in these reactions.

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