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Solid Phase Synthesis of Urea Libraries Using a Diversifiable Thiophenoxy Carbonyl Linker

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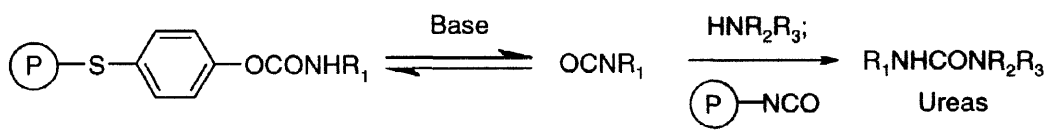
Abstract: A method for the solid phase synthesis of urea libraries from primary and secondary amines is described which utilizes a thiophenoxy carbonyl linker. Sequential release of different urea products from a common batch of resin using a "milking" procedure has also been accomplished.

Use of solid supports to facilitate parallel synthesis has become a popular way of producing libraries of small organic compounds for broad biological screening and directed structure activity studies using existing leads.[1] Ureas are a common functionality found in many compounds with biologic activity.[2] Our group has already published on methods for the parallel synthesis of urea libraries under solution phase conditions which utilize solid phase scavenging resins.[3] Scialdone has also recently published on a method for the solid phase synthesis (SPS) of bisurea libraries which utilizes a *p*-nitrophenyl ketoxime linker.[4] The scope and structural diversity of both of these methods is limited by the number of commercially available isocyanates (<320).[5] Our previous SPS work on the use of carbamate linkers to synthesize hydantoin libraries[6] has led us to develop a novel thiophenoxy carbamate linker which can be effectively used as a phosgene equivalent to generate ureas from readily available primary and secondary amines (Scheme 1). We wish to describe in this manuscript the scope of this methodology and its use in conjunction with scavenging resins to generate libraries of disubstituted and trisubstituted ureas.

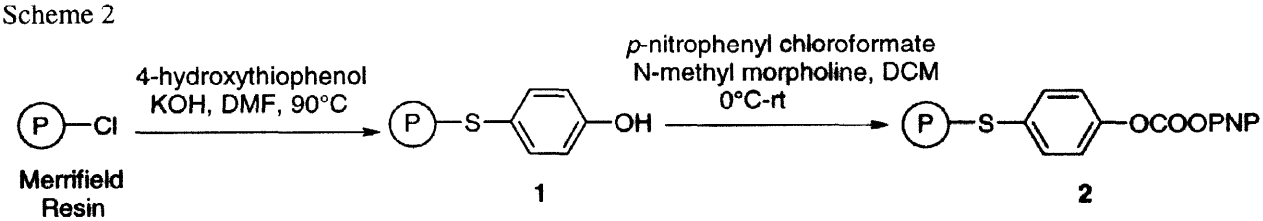
Scheme 1



Use of a 4-methylthiophenoxycarbonyl (Mtpc) group as an amine protecting/activating group has been reported by Lorenz.[7] The Mtpc protecting group is reported to be stable to both acidic and basic conditions and easily removed under mild basic conditions after oxidation of the sulfur atom. We speculated that a solid phase variant of this protecting group would provide a useful "diversifiable" linker for use in solid phase synthesis.[8,1]

Using a modification of the procedure of Flanigan,[8a] Merrifield resin could be readily converted to resin **1** using 4-hydroxythiophenol and KOH with heating in DMF (Scheme 2). Resin **1** was then converted to the *p*-nitrophenyl carbonate resin **2** using *p*-nitrophenyl chloroformate and N-methylmorpholine.[9] Resin **2** is a stable intermediate which maintains its activity for several months when stored at ambient temperature in a dessicator.[10]

Scheme 2



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Resin **2** was converted to resin bound carbamate **3** by treatment with 2 equivalents of a primary or secondary amine in DCM or DMF at ambient temperature (Table 1). A second treatment of resin **3** with amine was generally performed to ensure complete conversion to resin **3**. In our initial experiments we thought it necessary to oxidize the thioether linker in order to activate it sufficiently for cleavage with a second amine. This was accomplished by treatment of resin **3** with 3 equivalents of *m*-CPBA to presumably give the resin bound sulfone **4**. Overnight treatment of resin **4** with a second amine (1.3 eq.) and triethyl amine (1.3 eq.) at 60°C in THF followed by treatment with an isocyanate scavenging resin (2-3 eq.; 0.67 mmol / g)[3a,11] to remove excess amine provided the expected urea product in both good yield and purity (Table 1; entry 1).

Attempts to use resin bound carbamates of secondary amines under the cleavage conditions failed to produce the expected urea product, presumably due to its inability to form an isocyanate intermediate (Table 1; entry 2). To confirm that urea formation does proceed through an isocyanate intermediate the resin bound benzylamine **5** was heated in THF in the presence of triethylamine (2.0 eq.) overnight. Resin **5** was then removed from the reaction mixture by filtration and the resulting filtrate was treated with cyclohexylamine (1.3 eq.) to give the urea product in 20% yield after purification by treatment with isocyanate scavenging resin.[12]

After further exploration of the scope of amines which could be used in our method as resin bound intermediate **4** we encountered several unacceptable limitations as a result of the oxidative activation step: indole ring systems which were highly desired in our libraries were completely destroyed under the oxidation conditions; basic nitrogens were quantitatively converted to there N-oxides. As a result of these limitations, we examined cleavage conditions which could be used on the unoxidized resin intermediate **3**.

Application of our initial cleavage protocol to the unactivated resin bound intermediate **6** provided the expected urea product in low yield (Table 1; entry 3). A moderate yield (57%) of urea product could be obtained from **6** by extending the reaction time (72 h) and increasing the concentration of triethylamine to 10 equivalents (Table 1; entry 4). Interestingly, attempts to carry out the final cleavage of resin **6** using neat triethyl amine as the solvent provided no detectable product. During the course of our investigation, Freer published a report on the benefits of using acetonitrile as solvent when converting unsymmetrical diaryl carbonates to ureas.[13] Changing the solvent in the cleavage step to acetonitrile and increasing the amount of triethyl amine in the cleavage step to 4 equivalents provided both high yields and purities (>95% by ^{1}H NMR) of urea products using a variety of resin bound carbamate scaffolds (Table 1; entries 5-9).

Next we turned our attention to investigating the feasibility of treating a single batch of the activated resin **4** sequentially with different amines, in effect, "milking" the resin of its products.[1] To accomplish this goal we chose not to use any triethylamine in cleavage conditions to control the amount of isocyanate formed during the reaction. In our pilot experiments, resin **5** (10 eq.) was treated with an amine (1 eq.) in acetonitrile for 24 h (Scheme 3). The filtrate was collected and the resin was washed extensively with acetonitrile and DCM.[14] Acetonitrile and a second amine (1.0 eq.) were then added to the resin and an the procedure was repeated. Using this sequence five unique urea products were obtained in both good chemical yield and purity (>95% by ^{1}H NMR)[15] from a single batch of resin **5**. Attempts to carry out this procedure on an unoxidized resin intermediate **3** were unsuccessful due to incomplete consumption of amine.

Scheme 3

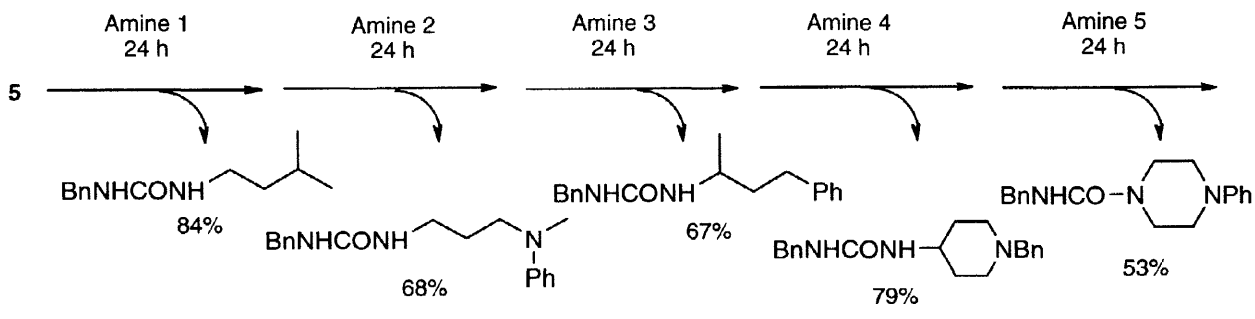
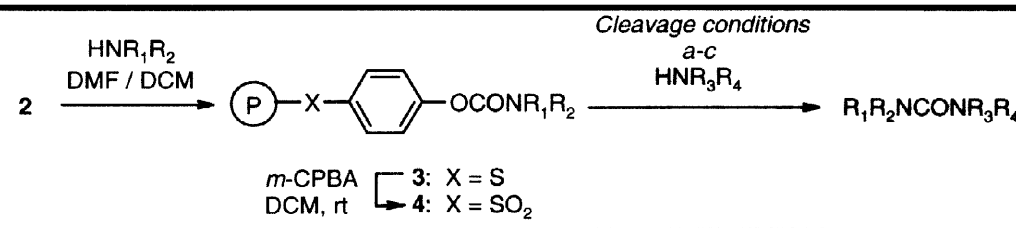
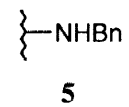
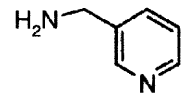
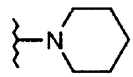
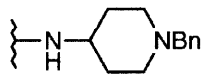
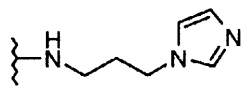
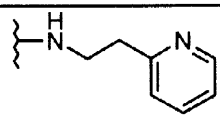
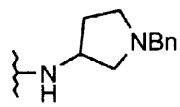
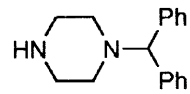
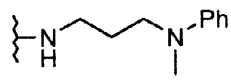
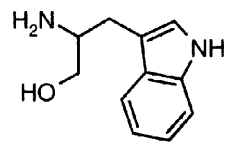


Table 1.



Entry	P–X–OCONR$_1$R$_2$	X	HNR$_3$R$_4$	Cleavage Conditions	Product Mass Recovery [¥]	Product HPLC Purity @ 220 nm [£]
1	 **5**	SO_2		a	88%	>98%
2		SO_2	$BnNH_2$	a	<1%	NA
3	 **6**	S	$BnNH_2$	a	4%	>98%
4	**6**	S	$BnNH_2$	b	57%	>90%
5	**6**	S	$BnNH_2$	c	89%[16]	>98%
6		S	$BnNH_2$	c	83%	>98%
7		S	$BnNH_2$	c	92%	>98%
8		S		c	98%	>95%
9		S		c	79%	>95%

Cleavage Conditions: a). amine (1.3 eq.), triethyl amine (1.3 eq.), THF, 60°C, 24 h; excess amine scavenging with polymer bound isocyanate , 2 h; filter. b). amine (1.3 eq.), triethyl amine (10 eq.), THF, 60°C, 72 h; excess amine scavenging with polymer bound isocyanate, 2 h; filter. c). amine (1.3 eq.), triethyl amine (4 eq.), CH_3CN, 60°C, 24 h; excess amine scavenging with polymer bound isocyanate, 2 h; filter. [¥]Mass recovery calculated from initial Merrifield resin loading. All structures were confirmed by ^{1}H NMR and electrospray MS. [£] HPLC conditions (4.6 mm X 50 mm YMC ODS-A with 5 µm particle size); gradient elution 0-100% acetonitrile (0.08% TFA)/water (0.1% TFA), 2.5 mL/min for 8 min then 100% acetonitrile (0.08% TFA), 2.5 mL/min for 1 min.

In conclusion, a highly general method for the synthesis of urea libraries from primary and secondary amines using a thiophenoxy carbonyl linker has been described. Use of this resin for both heterocycle synthesis and resin capture applications are currently under investigation and will be reported at a later date.

Acknowledgments: Structure searches were performed using ACD and MDDR software provided by MDL Information Systems, Inc., 14600 Catalina St., San Leandro, CA 94577, USA.

References and Notes

1. Ellman, J. A.; Thompson, L. A. *Chem. Rev.* **1996**, *96*, 555-600.
2. A search of the MDDR database using a urea scaffold produced 6700 hits.
3. a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196. b) Kaldor, S. W.; Fritz, J. E.; Tang, J. McKinney, E. R. *Bioorg. Med. Chem. Lett.* **1996**, 6, 3041-3044. c) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4886. d) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886. e) Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, *38*, 7959-7962.
4. Scialdone, M. A. *Tetrahedron Lett.* **1996**, *37*, 8141-8144. Additional references on the use of solid phase chemistries for the synthesis of urea libraries; Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055-4058. Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 2583-2586.
5. A search of the ACD database produced 318 hits most of which were aryl isocyanates.
6. Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937-940.
7. Lorenz, K.; Kunz, H. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 932-933.
8. a) Flanigan, E.; Marshall, G. R. *Tetrahedron Lett.* **1970**, *27*, 2403-2406. b) Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, 35, 867-868.
9. Preparation of resin **1**: A mixture of Merrifield resin (100 g, 1.0 mmol / g; Novabiochem; HL 100-200 mesh), 4-hydroxythiophenol (75 g, 595 mmol) and crushed KOH (22 g, 393 mmol) in DMF (1000 mL) was heated with mechanical stirring at 90° C for 16 h. After cooling, the resin was filtered and washed with DMF and water. The resin was stirred in 700 mL of water for 10 min., filtered and washed with DMF and water. The resin was taken up in 700 mL aqueous 1N HCl and stirred 10 min., filtered and washed sequentially with water, methanol, DCM and ether. After drying overnight in a heated vacuum oven (40° C), 103.6 g of resin **1** was obtained as a white solid. Elemental Analysis; C, 87.00; H, 7.46; S, 3.23. Preparation of resin **2**: To a mixture of resin **1** (103 g, Calc. Loading 0.93 mmol/ g) and N-methyl morpholine (19.4 g, 191.6 mmol) in anhydrous DCM (1500 mL) at 0° C was added *p*-nitrophenyl chloroformate (38.5 g, 191.6 mmol) in one portion. The reaction mixture was warmed to room temperature and stirred overnight using a mechanical stirrer. The resulting resin was filtered and washed with DCM (2 L). The resin was stirred twice with 1 L portions of DCM for 15 min. and finally washed with DCM and ether. After drying overnight in a vacuum oven, 121.9 g of resin **2** was obtained as a light yellow solid. IR (KBr) 1777.9 cm^{-1}.
10. A slight loss in activity (10-20%) of resin **2** was noted in resin batches which were stored in a dessicator at room temperature for >9 months.
11. Methylisocyanate polystyrene is currently available from Novabiochem.
12. Further mechanistic studies have demonstrated that isocyanate formation is a reversible process in the absence of a nucleophile accounting for the low yield of urea product.
13. Freer, R.; McKillop, A. *Synth. Commun.* **1996**, *26*(2), 331-349. More recently, Thavonekham has published similar results: Thavonekham, B. *Synthesis* **1997**, *10*, 1189-1194.
14. Insufficient washing of resin in between amine additions resulted in contamination of expected urea products with previously formed urea products.
15. All products gave the expected M+1 peak by electrospray MS.
16. ^{1}H NMR ($CDCl_3$) δ 1.30-1.50 (m, 2H), 1.85-1.95 (m, 2H), 2.05-2.20 (m, 2H), 2.70-2.85 (m, 2H), 3.52 (s, 2H), 3.53-3.70 (m, 1H), 4.33 (d, J = 5.73 Hz, 2H), 4.57 (br s, 1H), 4.93 (br s, 1H), 7.15-7.45 (m, 10H).