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A Photoactivated Precipiton for Reagent Sequestration in Solution-Phase Synthesis

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High-throughput testing methods have created a demand for rapid chemical synthesis techniques. To meet this need, solid-phase organic synthesis (SPOS) has emerged as a means to create molecules in parallel or in a single flask.[1] In SPOS, products can be separated by filtration from excess reagent and from byproducts if they are not covalently attached to the resin. Solid−solid separations or bead sorting[2,3] allow large numbers of test substances to be generated in a small number of reaction vessels.

There has been concomitant growth in the use of parallel *solution-phase* methods for the synthesis of pure molecule libraries. In solution-phase syntheses, reactions are carried out in homogeneous solutions from which products may be isolated by selective capture. Techniques for selective product capture use phase tags[4] and include fluorocarbon-mediated phase transfers and fluorous chromatography,[5] precipitation or size-based sorting of soluble polymer-supported or dendrimer-tagged products,[6,7] Brønsted or Lewis acid/base enabled isolations,[8,9] and precipiton-based methods.[10]

Scavenging reagents for solution-phase syntheses contain a functional group attached to a soluble or insoluble phase tag, and the functional group is chosen to react with one or more of the components of a reaction mixture.[11] Kaldor et al. first demonstrated this approach with a polystyrene isocyanate resin.[12] These resin-bound reagents are now commercially available and may also be used to capture a desired product.[13]

Precipitons are low molecular weight nonpolymeric phase tags.[10] The phase transfer event (precipitation) is caused by structural isomerization of the phase tag. The first precipitons could not be used for reagent scavenging because they were chemically activated and the requisite precipiton-activating reagents remained in solution after the precipitation of product was complete. Here we describe the first photoactivated precipiton and demonstrate its use as a selective and fast scavenger for primary and secondary amines.

The synthesis of amine-scavenging precipiton **4** employs a palladium-catalyzed cross-coupling[14] reaction between arylbromide **1** (prepared via a Wittig reaction) and *p*-hydroxymethylphenylboronic acid to afford alcohol **2** in 93% yield (Scheme 1). Alcohol **2** was treated with phthalimide under Mitsunobu conditions and hydrazinolysis of the resulting imide afforded amine **3** in 91% yield. Amine **3** with 20% phosgene in toluene afforded isocyanate **4** in 96% yield.[15]

The ***Z*** isomer of this bis-biphenyl precipiton is soluble in THF, Et_2O:THF (5:1), CH_2Cl_2, $CHCl_3$, and EtOAc while the ***E*** isomer is very insoluble (<0.001 M) in most organic solvents. To evaluate photoisomerization conditions, a 0.016 M solution of urea **5Z** (Figure 1) in THF-d_8 containing isomenthol (an internal standard) was prepared. As the solution was irradiated at 350 nm a precipitate formed. After 15 min, ^{1}H NMR spectroscopy of the suspension showed <2% of unisomerized cis urea **5*Z*** and no trace of the insoluble trans urea, **5*E***.

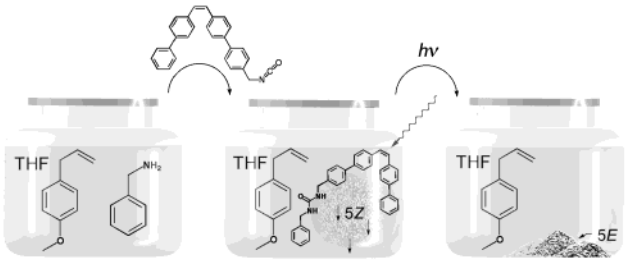
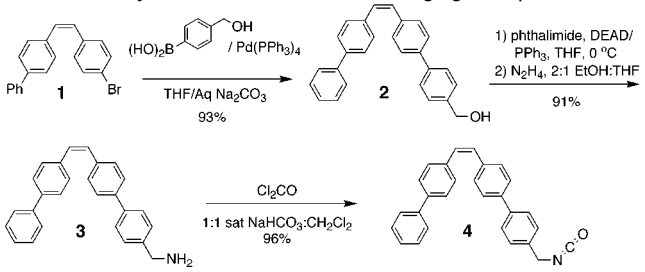


Figure 1. Benzylamine is removed from 4-allylanisole by reaction of the amine with precipiton **4** and subsequent photoinduced precipitation.

Scheme 1. Synthesis of the Amine Scavenging Precipiton **4**



A model study to test amine scavenging was carried out (Figure 1). A THF solution containing 0.018 M benzylamine and 0.055 M 4-allyl anisole was prepared. We found that only 1.1 equiv of isocyanate **4** was required to consume primary, secondary, and aromatic amines within 10 min at room temperature. Irradiation at 350 nm (for **2**, $\lambda_{max} = 314$ nm, $\epsilon_{314} = 1.0 \times 10^5$ M^{-1} cm^{-1}, $\epsilon_{350} = 4.4 \times 10^4$ M^{-1} cm^{-1}) for 30 min and filtration provided solutions of clean allyl anisole containing no amine or residual precipiton scavenger. Benzylamine was equally well removed in the presence of excess benzoic acid. We have used precipitons at up to 0.1 M initial concentrations. During irradiation at these and higher concentrations, the solid that forms causes a progressive decrease in rate of isomerization. After removal of solid by filtration or centrifugation, the initial isomerization rate is reestablished.

We synthesized ureas, thioureas, amides, and imines by carrying out reactions between an excess of nonvolatile amine (1.1 to 1.2 equiv) and the corresponding isocyanate, isothiocyanate, acid chloride, or aldehyde (Table 1). Removal of the excess amine was accomplished by adding the precipiton isocyanate scavenger **4** (1.1 equiv relative to excess amine) to covalently trap the amine, irradiating the mixture at 350 nm, and filtering the resulting suspension. Products were isolated in excellent yields and purities (>95% by ^{1}H NMR spectroscopy). Process steps were mechanically

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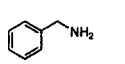
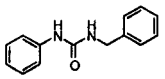
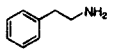
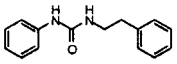
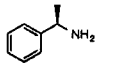
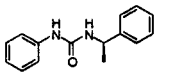
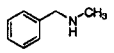
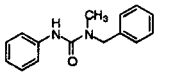
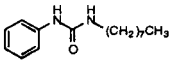
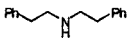
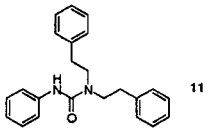
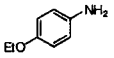
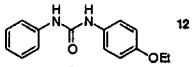
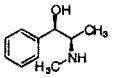
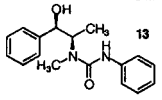
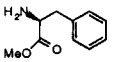
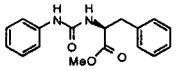
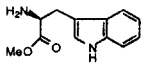
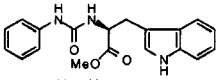
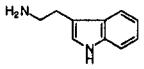
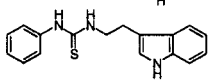
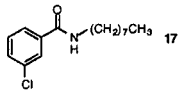
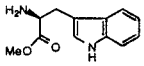
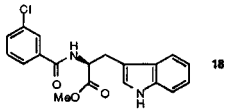
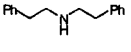
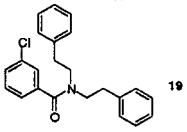
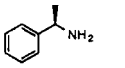
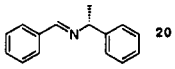
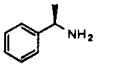
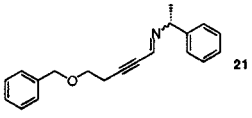
Table 1. Outcome of Precipiton-Based Solution-Phase Syntheses[a]

Entry	Amine	Product	Yield(%)
1		 6	95
2		 7	88
3		 8	92
4		 9	97
5		 10	97
6		 11	100
7		 12	100
8		 13	91
9		 14	97
10		 15	92
11		 16	95
12		 17	89
13		 18	86
14		 19	83
15		 20	83
16		 21	83

[a] All reactions were carried out with 1.1 equiv of scavenger **4** relative to excess amine. Purities of isolated products were >95% by ^{1}H NMR. Reactions were carried out in THF (entries 1, 2, 7, 11−16) or Et_2O/THF mixtures (entries 3−6, 8−10). For entries 12−16, reaction mixtures were diluted with Et_2O prior to addition of the scavenger.

simple. Except for the final filtration, no manipulations of the reaction solutions (transfers, extractions, liquid−liquid partitions) were required, and the syntheses involved only consecutive additions of solvents and reagents to a single vessel.

The solvents chosen for the urea syntheses fulfill two requirements: (1)[11a] that products would not precipitate from the reaction mixture prematurely and thereby diminish yields and (2) that the precipiton-bound urea formed from the excess amine and isocyanate **4** would be so insoluble that the amount remaining after filtration would be negligible. Typical times for going from starting amine to isolated urea were less than 1 h: 5−10 min for the reaction to take place between the amine and isocyanate/isothiocyanate, 5−10 min for the scavenger to react with the excess amine, and 30−40 min for the isomerization, filtration, and evaporation to give pure urea.

Amides and imines were synthesized by reactions of acid chlorides and aldehydes, respectively, with excess amine (1.2 equiv) in the presence of K_2CO_3 or $MgSO_4$ in THF. The overall times required for imine synthesis were about 4.5 h: 3.5 h for imine formation, 10 min for reaction with the scavenging precipiton, and 1 h for the isomerization and filtration. These isomerization times could be shortened by removing solid K_2CO_3 or $MgSO_4$ from the mixture before the irradiation.

We hope that this method will be useful to those engaged in parallel solution-phase library synthesis. Because all trapping reactions are performed in solution, experiment times are much shorter compared to scavenging conducted with solid supported scavengers and fewer equivalents of isocyanate are required.

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Supporting Information Available: Experimental details, copies of ^{1}H and ^{13}C NMR spectra, and complete characterization data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1385. (c) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215. (d) Lazo, J. S.; Wipf, P. *J. Pharm. Exp. Ther.* **2000**, *293*, 705.

(2) (a) Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487. (b) Lam, K. S.; Lebl, M.; Krchnák, V. *Chem. Rev.* **1997**, *97*, 411.

(3) Vaino, A. R.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7692.

(4) (a) Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174. (b) Link, A. *Angew Chem., Int. Ed.* **2000**, *39*, 4039.

(5) (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. (b) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2000**, *291*, 1766.

(6) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.

(7) (a) Kim, R. M.; Manna, M.; Hutchins, S. M.; Griffin, P. R.; Yates, N. A.; Bernick, A. M.; Chapman, K. T. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10012. (b) Malenfant, P. R. L.; Jayaraman, M.; Fréchet, J. M. *J. Chem. Mater.* **1999**, *11*, 3420.

(8) (a) Perrier, H.; Labelle, M. *J. Org. Chem.* **1999**, *64*, 2110. (b) Yoshida, J.; Itami, K.; Mitsudo, K.; Suga, S. *Tetrahedron Lett.* **1999**, *40*, 3403.

(9) Ley, S. V.; Massi, A.; Rodríguez, F.; Harwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1053.

(10) (a) Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1875. (b) Bosanac, T.; Wilcox, C. S. *Tetrahedron Lett.* **2001**, *42*, 4309. (c) Bosanac, T.; Wilcox, C. S. *Chem. Commun.* **2001**, 1618.

(11) (a) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. (b) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18. (c) Thompson, L. A. *Curr. Opin. Chem. Biol* **2000**, *4*, 324. (d) Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213.

(12) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193.

(13) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650.

(14) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(15) (a) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929. (b) McMinn, D. L.; Greenberg, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 3289.

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