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Fluorous electrophilic scavengers for solution-phase parallel synthesis

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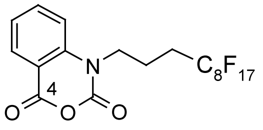
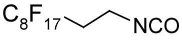
Abstract—A fluorous isatoic anhydride and isocyanate are synthesized and used as scavengers for amines in solution-phase parallel synthesis of urea, thiourea, and β-hydroxyamine analogs. The resulting fluorous derivatives are readily separated from the reaction mixture by solid-phase extractions (SPE) over Fluoro*Flash*™ cartridges to give products with good purity. The SPE cartridges can be reused. © 2003 Elsevier Science Ltd. All rights reserved.

Functionalized polymers can be used as scavengers to react with unwanted components. The scavenged species can be separated from the reaction mixture by a simple filtration. In many cases, the separation target is an excess reagent used to drive the reaction to completion. The capability of yield improvement combined with the straightforward separation makes scavenging a useful technique in the polymer-assisted solution-phase synthesis.[1] However, because of the nature of solid-phase and related loading issue, the polymer-supported scavenging is relatively slow, usually requires significant amount of excess scavengers with large volume of solvent.

Recent development of fluorous technologies successfully employed the fluorous tag strategy for easy separation.[2,3] This 'beadless' approach overcomes some drawbacks of heterogeneous reactions related to the use of polymer supports. In principle, any polymer-bound synthesis can have a fluorous counterpart. We recently reported the use of a fluorous thiol ($C_6F_{13}CH_2CH_2SH$) as nucleophilic scavenger and removal of the resulting fluorous derivatives over Fluoro*Flash*™ cartridges.[4–6] We found that the fluorous quenching was 5–10 times faster than use of the polymer analog and less fluorous scavenger was required. Further development of fluorous quenching technique is currently limited by the lack of commercially available fluorous scavenging reagents. Introduced in this paper are two new fluorous electrophilic scavengers, isatoic anhydride **1** and isocyanate **2**, that can be used to remove primary and secondary amines from the reaction mixtures.[7,8]

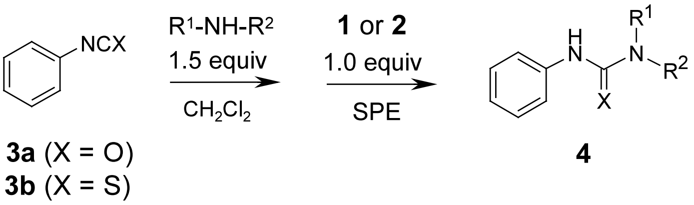


1



2

Compound **1** was readily prepared by *N*-alkylation of isatoic anhydride with $C_8F_{17}CH_2CH_2CH_2I$ using sodium hydride as a deprotonation agent. The C-4 carbonyl is an active site for nucleophilic attack. Fluorous isocyanate **2** was synthesized following a literature procedure.[9] To demonstrate the utility of these two compounds as scavengers for amines, two substrates, phenyl isocyanate and phenyl isothiocyanate were reacted with various primary and secondary amines to produce corresponding ureas and thioureas (Scheme 1). In each case, 1.5 equiv. of amine was used to ensure the consumption of the substrate. Upon completion of the reaction (as monitored by TLC or HPLC), 1.0 equiv. of fluorous scavenger was added to react with the excess



Scheme 1.

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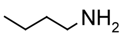
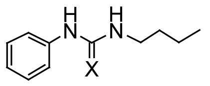
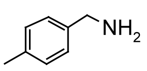
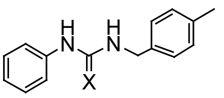
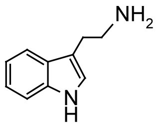
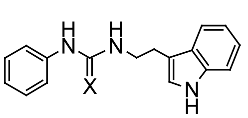
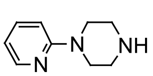
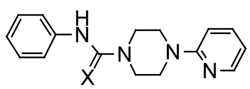
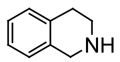
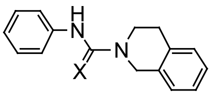
amine. The reaction mixture was then loaded onto a Fluoro*Flash*™ cartridge charged with fluorous silica. The cartridge was eluted with MeOH–H_2O (80:20) to collect the product fraction and then with 100% MeOH to wash off the scavenged product and the unreacted scavenger. Results listed in Table 1 demonstrate that the product purity is greater than 95% after the scavenging.[10,11] Use of fluorous isatoic anhydride **1** as scavenger usually give better yields (75–100%) than that of isocyanate **2** (34–100%).

Fluorous isatoic anhydride **1** was further evaluated in the reaction of epoxide **5** with amines (Scheme 2). In a high loading experiment using 2.0 equiv. of amine and 3.0 equiv. of scavenger **1**, products **6a** (42%) and **6b** (67%) generated from primary amines had better yields than products **6d** (15%) and **6e** (29%) generated from secondary amines. We hypothesized that the low yield might have been caused by the interaction of excess scavenger with the β-hydroxyamine product. To test this hypothesis, reactions with lower input of the secondary amine (1.5 equiv.) and scavenger (0.7 equiv.) were performed. Significant yield improvement was observed for **6d** (62%) and **6e** (58%) (Table 2). However, under both reaction conditions, no clean desired product **6c** was isolated. It was contaminated with the di-*N*-alkylation product. The product yields of all other cases listed in Table 2 may vary in a broad range under different reaction conditions, the purities were consistently between 90 and 95% (Fig. 1).

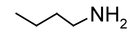
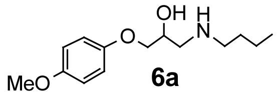
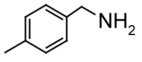
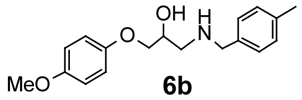
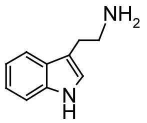
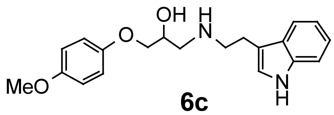
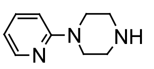
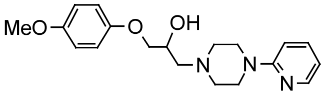
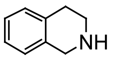
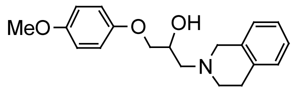
Table 1. Structures, yields, and purities of ureas and thioureas[a]

substrate	amine	scavenger	product	X	yield	purity[b]
3a		**1**		O	100%	>95%
3b		**1**		S	75%	95%
3a		**2**		O	52%	95%
3b		**2**		S	98%	95%
3a		**1**		O	100%	>95%
3b		**1**		S	72%	>95%
3a		**2**		O	100%	>95%
3b		**2**		S	80%	>95%
3a		**1**		O	100%	>95%
3b		**1**		S	95%	>95%
3a		**2**		O	100%	95%
3b		**2**		S	34%	95%
3a		**1**		O	100%	>95%
3b		**1**		S	100%	95%
3a		**2**		O	100%	95%
3b		**2**		S	68%	>95%
3a		**1**		O	100%	>95%
3b		**1**		S	100%	95%
3a		**2**		O	100%	95%
3b		**2**		S	96%	95%

[a] condition:1.0 equiv of substrate and 1.5 equiv of amine, CH_2Cl_2 , 60°C, 6-12 h in a capped vial, then quenched with 1.0 equiv of a scavenger, 60°C, 2.5 h. [b] purity was assessed by ^1H NMR.

Scheme 2.

Table 2. Structures, yields, and purities of β-hydroxyamines[a]

amine	(equiv)	scavenger **1** (equiv)	product	yield	purity[b]
	2.0	3.0	 **6a**	42%	95%
	2.0	3.0	 **6b**	67%	95%
	2.0 1.5	3.0 0.7	 **6c**	-- [c] -- [c]	-- --
	2.0 1.5	3.0 0.7	 **6d**	15% 62%	>95% >95%
	2.0 1.5	3.0 0.7	 **6e**	29% 58%	90% 90%

[a] condition: **5** and amine in CH_2Cl_2, 60°C, 6-12 h in a capped vial, then quenched with **1,** 60°C, 2.5 h. [b] purity was assessed by ^1H NMR. [c] product was comtaminated with significant amount of di-*N*-alkylation by product.

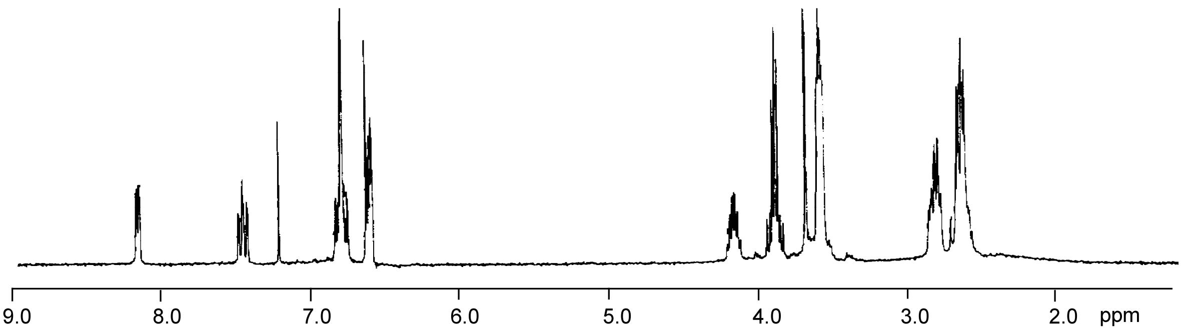


Figure 1. ^1H NMR of β-hydroxyamine **6d** after scavenging and SPE.

In summary, we have prepared two fluorous electrophilic scavengers isatoic anhydride **1** and isocyanate **2** and demonstrated their utility in the parallel synthesis of urea, thiourea, and β-hydroxyamine analogs. The scope of fluorous technologies in solution-phase synthesis has been expanded.

Acknowledgements

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8. Polymer-supported isocyanate: (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dessman, B. A.; Hahn, P. *Tetrahedron Lett*. **1996**, *37*, 7193; (b) Booth, J. R.; Hodges, J. C. *J*. *Am*. *Chem*. *Soc*. **1997**, *119*, 4882.
9. Ouari, O.; Polidori, A.; Pucci, B.; Tordo, P.; Chalier, F. *J*. *Org*. *Chem*. **1999**, *64*, 3554.
10. Typical procedure for the reaction of **3a** with amines: To a solution of phenyl isocyanate (0.2 mmol) in CH_2Cl_2 (0.5–1.0 mL) was added an excess amount of amine (1.5 equiv., 0.3 mmol). The resulting solution was stirred at 60°C for 6–12 h in a capped vial. Upon completion of the reaction, fluorous isatoic anhydride **1** was added (1.0 equiv., 0.2 mmol) and the reaction mixture was stirred for 2.5 h at 60°C. The reaction mixture was concentrated to 0.2–0.5 mL and loaded onto a 5 g Fluoro*Flash*™ SPE cartridge[12] pre-conditioned with MeOH–H_2O (80:20) on an SPE manifold. The cartridge was eluted with 10 mL of MeOH–H_2O (80:20), then with 100% MeOH to wash off fluorous compounds from the cartridge. The MeOH–H_2O fraction containing the desired product was evaporated in a Speedvac to give the corresponding urea in quantitative yield. The SPE cartridge can be reconditioned by washing with fluorophilic solvents such as THF or acetone and equilibrated with MeOH–H_2O (80:20) for the next round of SPE. The cartridge can be reused up to 10 times.
11. Representative analytical data, **3b**, ^{1}H NMR ($CDCl_3$) δ 3.09 (t, $J=5.5$ Hz, 2H), 3.98 (t, $J=5.5$ Hz, 2H), 6.10 (br s, 1H), 6.80–6.95 (3H), 7.15 (t, $J=5.4$ Hz, 1H), 7.18–7.26 (4 H), 7.35 (d, $J=5.4$ Hz, 1H), 7.52 (br s, 1H), 7.60 (d, $J=5.4$ Hz, 1H), 8.00 (br s, 1H); MS (EI) m/z (rel. intensity) 295 (M^+, 80), 261 (35), 143 (100), 130 (80). **6d**, ^{1}H NMR ($CDCl_3$) δ 2.73 (m, 4H), 2.92 (m, 2H), 3.70 (m, 4H), 3.78 (s, 3H), 3.98 (m, 2H), 4.25 (m, 1H), 6.65–6.75 (2H), 6.80–6.70 (4H), 7.51 (t, $J=8.2$ Hz, 1H), 8.25 (d, $J=4.9$ Hz, 1H); MS (CI) m/z (rel. intensity) 344 (M^++H, 100).
12. Fluorous isatoic anhydride **1**, isocyanate **2**, and Fluoro*Flash*™ SPE cartridges are available from Fluorous Technologies, Inc. http://www.fluorous.com