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Use of fluorous silica gel to separate fluorous thiol quenching derivatives in solution-phase parallel synthesis

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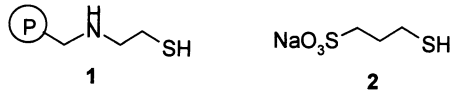
Abstract—A general fluorous thiol quenching method is introduced. Excess α-bromoketones or benzyl bromides in parallel *N*-alkylation reactions are quenched with a fluorous thiol ($C_6F_{13}CH_2CH_2SH$). The resulting fluorous derivatives can be separated from the reaction mixture by a solid phase extraction on fluorous silica gel. © 2002 Elsevier Science Ltd. All rights reserved.

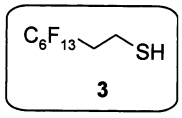
1. Introduction

The attachment of 'tags' to organic reaction components has become a general practice in combinatorial and parallel syntheses to facilitate the separation process. The most commonly used tags are solid-phase polymers. In both solid phase organic synthesis[1] (tagged substrates) and polymer-assisted solution-phase organic synthesis[2] (tagged reagents), polymers are involved in reactions such that the reaction medium becomes heterogeneous. The use of polymer-bound scavengers,[3] however, allows the reaction to proceed in homogeneous fashion because the scavengers are added only after the reaction is complete.

Fluorous synthesis[4] performed in homogeneous media overcomes some drawbacks of heterogeneous reactions associated with solid-phase synthesis. In principle, any polymer-bound synthetic technology has a counterpart in fluorous synthesis. Early fluorous synthesis technologies relied on heavy fluorous tags and liquid–liquid extraction to separate tagged-fluorous molecules from untagged organics.[5] In the recently introduced light fluorous synthesis method, fewer fluorines are used in the tag and the liquid–liquid extraction is replaced by a solid–liquid extraction over fluorous silica gel.[6] Fluorous solid phase extraction (FSPE) was developed based on the observation that the fluorine–fluorine interaction is strong and selective, such that the mobility of the fluorous molecules on fluorous reverse phase silica gel is dictated by the fluorous group. We describe here a new application of FSPE in the separation of fluorous species generated by fluorous scavengers.

Thiols are good nucleophiles and have been used as covalent scavengers. For example, addition of aminothiol resin **1** to an *N*-alkylation reaction mixture scavenges excess α-haloketones.[7,8] The resulting polymer-bound thioethers can be easily separated from the product mixture by filtration. Another report describes the use of 3-mercapto-1-propanesulfonic acid sodium salt **2** as a scavenger.[9] Purification can be carried out by water–organic biphasic workup if the thioethers are hydrophilic or by anion-exchange resin chromatography if the thioethers are hydrophobic. Development of the fluorous scavenger **3** will provide a new thiol quenching agent that relies on solid phase extraction for separation.





Although fluorous quenching was introduced about five years ago,[5] only three fluorous quenching applications have been reported so far. Fluorous trialkyltin hydride **4**[10] and fluorous amine **5**[11] have been used to scavenge excess alkenes and isocyanates, respectively, while fluorous vinyl ether **6**[12] has been used as a catch-and-release agent to separate alcohol products from a reaction mixture. These quenching agents have two or more fluorous chains and depend on liquid–liquid extraction for purification. The thiol scavenger **3** described in this paper has a single fluorous chain, yet its quenched derivatives can be easily separated by solid phase extraction. In addition to the scavenging uses introduced herein, fluorous thiols have been used recently as precursors of fluorous sulfides,

Keywords: fluorous; scavengers; thiol quenching; solid phase extraction; parallel synthesis.
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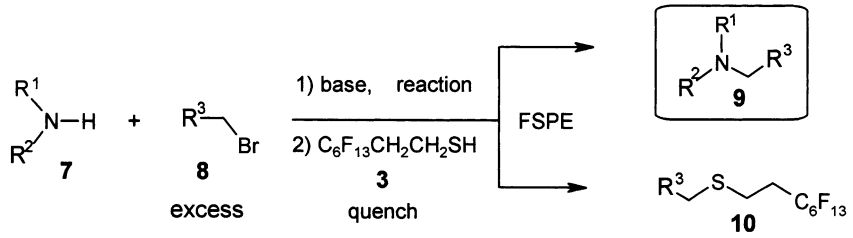
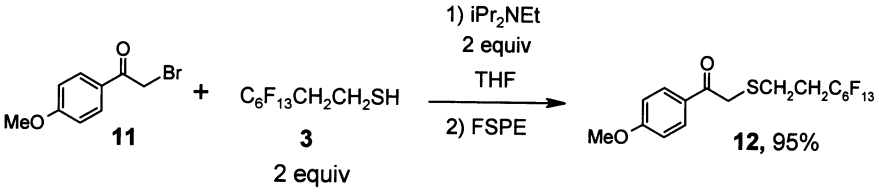


Scheme 1.



Scheme 2.

which in turn have their own uses as reagents and ligands. An accompanying paper by Rocaboy and Gladysz[13] in this issue introduces fluorous sulfide metal complexes and provides a nice summary of prior work with highly fluorinated organic sulfur compounds.

$(C_6F_{13}CH_2CH_2)_3SnH$ **4**

$(C_6F_{13}CH_2CH_2CH_2)_2NH$ **5**

$(C_8F_{17}CH_2CH_2)_2CH\text{-}O\text{-}CH{=}CH_2$ **6**

2. Results and discussion

Existing thiol quenching reagents **1** and **2** are mainly used in *N*-alkylation reactions, so we designed a similar reaction to evaluate the fluorous thiol scavengers. Commercially available 1*H*,1*H*,2*H*,2*H*-perfluorooctanethiol ($C_6F_{13}CH_2CH_2SH$, **3**) was identified as a potential fluorous quenching agent.[14] The ethylene spacer between the C_6F_{13} tag and SH group is expected to minimize the strong electron-withdrawing effect from the perfluoroalkyl group and maintain the nucleophilicity of the thiol. Cyclic amines were selected as substrates and α-bromoketones/benzyl bromides were selected as electrophiles for the *N*-alkylation reactions.

The general reaction and separation processes pursued in this work are outlined in Scheme 1. In the alkylation and thiol quenching steps, excess electrophile (bromide **8**) and excess quenching agent (thiol **3**) are used to drive the respective reaction to completion. In the presence of a base, a secondary amine **7** can be alkylated by the appropriate bromide **8** to give the corresponding tertiary amine **9**.

We expect that the unreacted electrophile **8** will be converted to the fluorous thioether **10** by reaction with the fluorous thiol scavenger **3**. The mixture that contains the desired product **9**, the thioether **10** and excess thiol **3** is loaded onto a cartridge charged with Fluoro*Flash*™ fluorous silica gel.[14] A fluorophobic solvent ($MeOH/H_2O$) is used to elute product **9** while **3** and **10** are retained. The fluorous compounds can be eluted out and the cartridge can be reconditioned by washing with a more fluorophilic solvent such as methanol or THF.

An initial experiment was carried out to test the quenching efficiency of $C_6F_{13}CH_2CH_2SH$ and to establish conditions for the solid phase extraction (Scheme 2). In the presence of 2.0 equiv. of diisopropylethylamine as a base, the quenching reaction of 2-bromo-4′-methoxyacetophenone **11** (23 mg, 0.1 mmol) with 2 equiv. of thiol **3** (76 mg, 0.2 mmol) was finished in less than 30 min. TLC analysis was used to monitor the disappearance of bromide **11**. The reaction mixture was then loaded directly onto a 5 g Fluoro*Flash*™ cartridge. This was eluted with CH_3OH/H_2O (80/20) to collect the first fraction and then with CH_3OH to collect the second fraction. Both fractions were concentrated and submitted to HPLC and ^1H NMR analyses. Neither bromide **11** nor thiol **3** but only diisopropylethylamine and its derived salt were detected from the first fraction. The quenched bromides (as thioether **12**) together with excess thiol **3** were found in the second fraction. Further purification by flash column chromatography afforded thioether **12** (50 mg) in 95% yield.[15] The quenching and the solid phase extraction processes are thus validated.

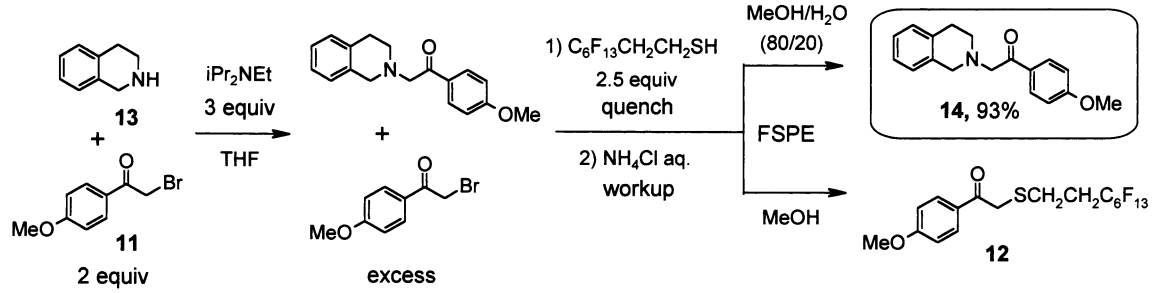
We also compared the reactivity of fluorous thiol **3** with the

11 + thiol (**1** or **3**) —base, THF→ thioether

				time*
a)	1 equiv	**1**, 2 equiv	iPr_2NEt, 2 equiv	50 min
b)	1 equiv	**1**, 4 equiv	iPr_2NEt, 4 equiv	25 min
c)	1 equiv	**3**, 2 equiv	iPr_2NEt, 2 equiv	5 min

* reaction time required for >95% (HPLC) conversion of **11**

Scheme 3.

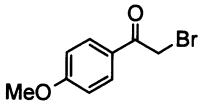
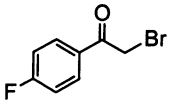
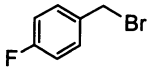
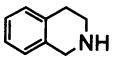
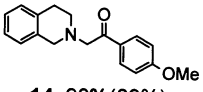
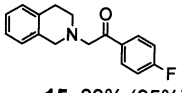
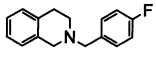
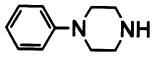
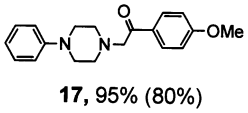
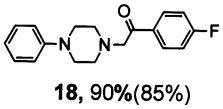
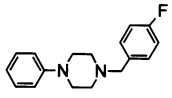
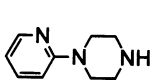
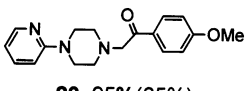
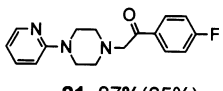
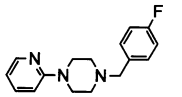
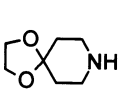
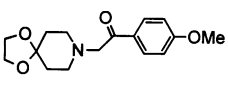
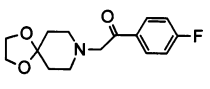
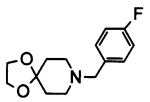


Scheme 4.

polymer-supported thiol **1** under identical conditions in quenching of α-bromoketone **11**. The preliminary results listed in Scheme 3 indicate that the reaction of fluorous thiol is significantly fast. It took only 5 min for fluorous thiol **3** to achieve >95% quenching of bromide **11**, while 50 min was required for polymer-supported thiol **1**. Doubling the amount of thiol **1** from 2 to 4 equiv. cut the reaction to 25 min, but that still does not match the speed of thiol **3**. The fast fluorous quenching is probably due to the fact that it occurring in solution. The benefits of solution phase quenching must be substantial since the strong electron-withdrawing perfluoroalkyl group should make fluorous thiol **3** inherently less reactive than **1**.

The product in the planned *N*-alkylation synthesis was expected to quickly elute from the cartridge. To avoid contamination of diisopropylethylamine and its salt, an aqueous workup was employed prior to the solid phase extraction to separate the base and derivatives from the reaction mixture. The reaction conditions were thus optimized and a general procedure was developed by the reaction of 1,2,3,4-tetrahydroisoquinoline **13** with 2-bromo-4′-methoxyacetophenone **11** (Scheme 4). The reaction was carried out by addition of 2.0 equiv. of bromide **11** (46 mg, 0.2 mmol) to a solution of cyclic amine **13** (14 mg, 0.1 mmol) in 0.3 mL of THF. Excess diisopropylethylamine (55 μL, 3 equiv.) was employed to promote both alkylation and thiol quenching reactions. After 30 min, TLC analysis showed two spots corresponding to the alkylated product **14** (lower R_f) and the unreacted bromide **11** (higher R_f). Thiol **3** (2.5 equiv.) was then added to scavenge the remaining bromide **11**. After an additional 30 min, TLC analysis again showed two spots: the alkylated product **11** remained unchanged, while the thioether **12** appeared at a slightly higher R_f than the corresponding bromide **11**. The excess thiol **3** lacks a chromophore and cannot be detected in this

Table 1. Structures, yields and purities of the tertiary amines

			
	 **14,** 93%(89%)	 **15,** 83% (95%)	 **16,** 90% (86%)
	 **17,** 95% (80%)	 **18,** 90%(85%)	 **19,** 93%(88%)
	 **20,** 95%(85%)	 **21,** 87%(85%)	 **22,** 92% (90%)
	 **23,** 89% (90%)	 **24,** 83% (84%)	 **25,** 75% (94%)

Number in the parenthesis shows the purity by HPLC; column: Novapak C_{18}, 4.6×150 mm^2, 5 μm; mobile phase: CH_3OH/H_2O (85/15) 1 mL/min; UV detection at 254 nm.

analysis. A quick aqueous workup was conducted by addition of aqueous NH_4Cl to the reaction mixture. The water layer was pipetted out to remove diisopropylethylamine and its salt. The organic phase was loaded onto a 5 g Fluoro*Flash*™ cartridge and eluted with MeOH/H_2O (80/20). The first fraction containing the desired product was collected and concentrated to afford *N*-alkylated amine **14** in 93% yield. The structure of **14** was characterized by ^{1}H NMR and MS analyses. The purity was checked by HPLC analysis.

Following the general procedure described above, four cyclic amines were each alkylated with two α-bromoketones and a benzyl bromide to generate a 12-compound library in parallel. The structures of the products are shown in Table 1, including tetrahydroisoquinoline, *N*-substituted piperazine and acetal piperidine derivatives. The structures of the final products were confirmed by ^{1}H NMR and MS analyses.[16] The product yields are in the range of 75–95% and the purities are between 85–95% as determined by HPLC analysis.

The heavier fluorous thiol $C_8F_{17}CH_2CH_2SH$ was also used for thiol quenching in the preparation of **15**, **16**, **20**, **21** and **24**, and results comparable to those shown in Table 1 were obtained. In these cases, a 2 g Fluoro*Flash*™ cartridge instead of a 5 g one is enough for an efficient separation of quenching derivatives by FSPE. The stronger retention of the heavier fluorous scavenger derivatives on a SPE cartridge suggests that $C_8F_{17}CH_2CH_2SH$ has potential utility in quenching of larger electrophilic molecules.

3. Conclusion

We have demonstrated that commercially available thiols $C_6F_{13}CH_2CH_2SH$ and $C_8F_{17}CH_2CH_2SH$ can be used to scavenge excess α-bromoketones/benzyl bromides from alkylation reactions. The quenching derivatives can be readily separated from the mixture by solid phase extraction on fluorous silica gel. In addition to quenching active bromides, fluorous thiols have the potential to scavenge other electrophiles and have broad utility in solution phase parallel synthesis.

4. Experimental

4.1. General procedure for alkylation, thiol quenching and solid phase extraction; preparation of 14

To a 5 mL vial charged with a solution of 1,2,3,4-tetrahydroisoquinoline **13** (14 mg, 0.1 mmol) in 0.3 mL of THF was added 2-bromo-4′-methoxyacetophenone **11** (46 mg, 0.2 mmol) followed by diisopropylethylamine (55 μL, 0.3 mmol). After stirring at 25°C for 30 min, thiol **3** (95 mg, 0.25 mmol) was added and the mixture was stirred for an additional 30 min. Aqueous NH_4Cl (0.8 mL) was added, the aqueous layer was pipetted out and the organic phase was loaded onto a 5 g Fluoro*Flash*™ cartridge[14] that has been pre-conditioned with MeOH/H_2O (80/20). The cartridge was eluted with 5 mL of MeOH/H_2O (80/20) and was collected as the first fraction (desired product). Then an elution with MeOH was performed and a second fraction of 10 mL was collected (fluorous compounds). Concentration of the first fraction afforded *N*-alkylated amine **14** (26 mg) in 93% yield. ^{1}H NMR ($CDCl_3$) δ 3.07 (br s, 2H), 3.17 (br s, 2H), 3.85 (s, 3H), 4.07 (s, 2H), 4.18 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.00–7.25 (4H), 8.24 (d, J=8.8 Hz, 2H). MS *m/z* (rel. intensity) 281 (M^+, 6%), 267 (39%), 146 (45%), 135 (59%), 114 (84%). HRMS calculated for $C_{17}H_{17}NO_2$ (M^+-CH_2) 267.1259, found 267.1247. The purity of **14** is 89% as determined by HPLC analysis on a Novapak C_{18} column (4.6×150 mm^2, 5 μm) using CH_3OH/H_2O (85/15) as a mobile phase (1 mL/min) and UV detection at 254 nm.

15: ^{1}H NMR (CD_3OD) δ 2.75–3.15 (m, 6H), 3.90 (s, 2H), 6.85–7.10 (m, 4H), 7.16 (t, J=9.0 Hz, 2H), 8.03 (m, 2H). MS *m/z* (rel. intensity) 269 (M^+, 3%), 241 (4%), 190 (6%), 160 (35%), 123 (100%), 95, 44%).

16: ^{1}H NMR ($CDCl_3$) δ 2.87 (br, 2H), 2.97 (m, 2H), 3.73 (s, 2H), 3.76 (s, 2H), 6.90–7.25 (6H), 7.43 (m, 2H). MS *m/z* (rel. intensity) 241 (M^+, 40%), 240 (67%), 132 (16%), 109 (100%).

17: ^{1}H NMR ($CDCl_3$) δ 2.77 (br t, 4H), 3.27 (br t, 4H), 3.83 (s, 2H), 3.87 (s, 3H), 6.80–6.95 (5H), 7.26 (t, J=9.0 Hz, 2H), 8.03 (d, J=9.0 Hz, 2H). MS *m/z* (rel. intensity) 310 (M^+, 6%), 281 (12%), 253 (6%), 207 (80%), 191 (12%), 175 (100).

18: ^{1}H NMR ($CDCl_3$) δ 2.82 (br, 4H), 3.28 (br, 4H), 3.88 (s, 2H), 6.87 (t, J=6.0 Hz, 1H), 6.94 (d, J=9.0 Hz, 2H), 7.13 (t, J=9.0 Hz, 2H), 7.27 (t, J=6.0 Hz, 2H), 8.08 (br t, 2H). MS *m/z* (rel. intensity) 298 (M^+, 3%), 207 (7%), 175 (100%), 160 (9%), 132 (32%).

19: ^{1}H NMR (CD_3OD) δ 2.92 (br s, 4H), 3.22 (br s, 4H), 3.89 (s, 2H), 6.78 (t, J=6.0 Hz, 1H), 6.90 (d, J=9.0 Hz, 2H), 7.07 (t, J=9.0 Hz, 2H), 7.16 (t, J=6.0 Hz, 2H), 7.43 (dd, J=9.0, 6.0 Hz, 2H). MS *m/z* (rel. intensity) 270 (M^+, 78%), 161 (45%), 137 (46%), 109 (100).

20: ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J=5.0 Hz, 4H), 3.68 (t, J=5.0 Hz, 4H), 3.88 (s, 2H), 3.88 (s, 3H), 6.60–6.70 (m, 2H), 6.95 (d, J=6.9 Hz, 2H), 7.51 (t, 1H), 8.02 (d, J=6.9 Hz, 2H), 8.20 (dd, 1H). MS *m/z* (rel. intensity) 311 (M^+, 12%), 176 (100%), 147 (40%), 121 (72%).

21: ^{1}H NMR (CD_3OD) δ 2.75 (br, 4H), 3.30–3.60 (6H), 6.61 (t, 1H), 6.77 (d, J=6.0 Hz, 1H), 7.16 (t, J=9.0 Hz), 7.49 (t, 1H), 7.90–8.20 (2H). MS *m/z* (rel. intensity) 299 (M^+, 4%), 285 (12%), 207 (8%), 176 (32%), 147 (17%), 133 (66%), 107 (100%), 95 (52%).

22: ^{1}H NMR (CD_3OD) δ 3.05 (br s, 4H), 3.67 (br s, 4H), 4.08 (s, 2H), 6.68 (t, 1H), 6.83 (d, J=9.0 Hz, 1H), 7.12 (t, J=9.0 Hz, 2H), 7.30–7.65 (4H), 8.05 (br, 1H). MS *m/z* (rel. intensity) 271 (M^+, 24%), 177 (25%), 164 (20%), 133 (16%), 120 (28%), 107 (100%), 95 (23%), 84 (45%).

23: ^{1}H NMR (CD_3OD) δ 1.81 (br s, 4H), 3.15 (br s, 4H), 3.69 (s, 3H), 3.80 (s, 4H), 4.52 (s, 1H), 4.66 (s, 1H), 6.87 (d, J=7.5 Hz, 2H), 7.81 (d, J=7.5 Hz, 2H). MS *m/z* (rel.

intensity) 291 (M^+, 5%), 276 (25%), 205 (45%), 177 (26%), 156 (66%), 135 (53%).

24: ^{1}H NMR (CD_3OD) δ 1.85 (br, 4H), 3.04 (br 4H), 3.89 (s, 4H), 7.18 (t, J=9.0 Hz, 2H), 8.02 (t, J=9.0 Hz, 2H). MS *m/z* (rel. intensity) 279 (M^+, <1%), 193 (3%), 156 (100%), 123 (10%), 99 (13%).

25: ^{1}H NMR ($CDCl_3$) δ 1.97 (br s, 4H), 2.85 (br s, 4H), 3.82 (s, 2H), 3.96 (s, 4H), 7.07 (t, J=8.7 Hz, 2H), 7.50 (br t, 2H). MS *m/z* (rel. intensity) 251 (M^+, 16%), 206 (12%), 164 (20%), 156 (11%), 109 (100%).

5. Note added in proof

In parallel, independent work, Lindsley and co-workers from Merck are reporting the successful use of a number of fluorous-tethered quenching reagents for parallel synthesis, including thiol **3**. See Lindsley, C.; Zhao, Z.; Leister, W., submitted for publication.

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15. ^{1}H NMR ($CDCl_3$) of **12**: δ 2.41 (m, 2H), 2.82 (br, 2H), 3.83 (s, 2H), 3.89 (s, 3H), 6.97 (d, J=8.8 Hz, 2H), 7.96 (d, J=8.8 Hz, 2H). MS *m/z* (rel. intensity) 528 (M^+, 15%), 509 (42%), 499 (32%), 486 (40%), 453 (19%), 435 (35%), 150 (37%), 135 (100%).
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