Pergamon

Tetrahedron Letters 43 (2002) 4225–4228

TETRAHEDRON LETTERS

Fluorous-tethered quenching reagents for solution phase parallel synthesis

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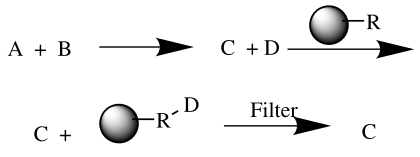
Received 27 March 2002; revised 9 April 2002; accepted 16 April 2002

Abstract—Commercially available fluorous-tethered reagents are employed to quench excess reactants and remove known impurities from crude reaction mixtures generated via solution phase parallel synthesis. Fluorous quenching reagents are expediently removed via Fluoro*Flash*™ SPE columns to afford products in high yields and purities.

The need for expedient chemical lead identification in early stage medicinal chemistry programs is crucial for the development of these programs and the rapid delivery of safety assessment candidates for clinical evaluation. In recent years, the pharmaceutical industry has addressed this issue by establishing groups whose mission is to synthesize analog arrays based on high throughput screening hits while employing solution phase parallel synthesis.[1] The key to the success of this approach was the application of resin-bound reagents and scavengers to drive reactions to completion and quench excess reagents in the solution phase (Scheme 1).[2] Simple filtration with or without solid phase extraction (SPE) protocols (SCX, SAX) can afford pure, single compounds in sufficient quantities (50 mg) for screening, full characterization and archiving.[3] However, resin-bound reagents and scavengers do have limitations. First, hindered access to functional groups within the resin core, especially in higher loading resins, and the biphasic nature of the reaction systems that contain polymer-bound entities result in slower overall kinetics.[4] Second, solvent selection for both the synthetic and scavenging steps is dictated by the swelling requirements of the resin matrix as well as the large solvent volumes.[5] Third, resin-mediated reactions are not readily scaleable (increasing from 0.1 to 10 mmol) for the resynthesis of active compounds.[6] These limitations impact the widespread use of resin-based scavengers across medicinal chemistry departments. With the goal of addressing these issues, our group began to examine new technologies for solution phase parallel synthesis.



Scheme 1.

Evaluation of emerging fluorous technologies pioneered by Curran, indicated to us the efficiency of employing fluorous protecting groups in combination with Fluoro*Flash*™ SPE columns as exemplified in Scheme 2.[7] Moreover, high chemical yields and purities were obtained both in the literature and in our hands. Based on our heavy reliance on scavenger resins for parallel purification, we hoped to contribute to this new field by developing a 'toolkit' of fluorous-tethered quenching reagents (scavengers) that could be employed as traditional solution phase reagents. We envisioned that these fluorous-tethered reagents would provide rapid quenching due to homogeneous solution phase kinetics, could be easily removed in parallel by Fluoro*Flash*™ SPE and might reduce the barrier for the general practice of solution phase parallel synthesis. This new application of fluorous technology (Scheme 3) would compliment the existing scavenger resin paradigm depicted in Scheme 1.

We initially examined a set of six inexpensive, functionalized fluorous-tethered reagents (Fig. 1) that we felt

Keywords: combinatorial chemistry; fluorine and compounds.

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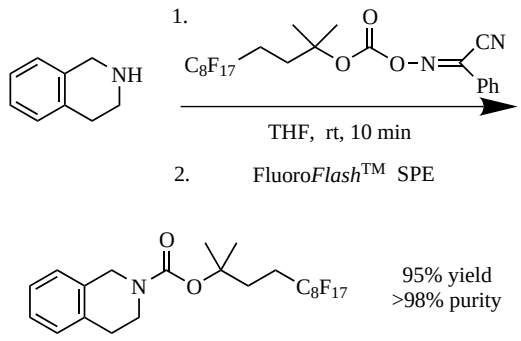
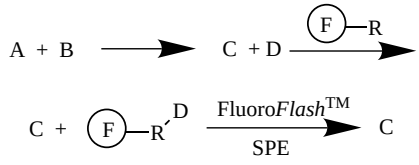


Scheme 2.



Scheme 3.

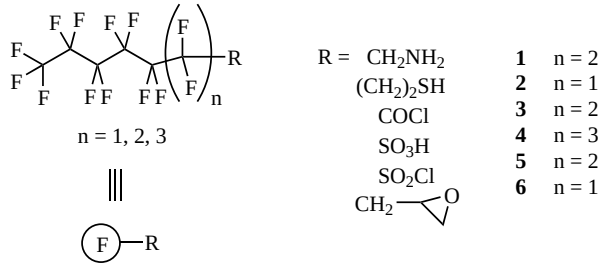


Figure 1. Fluorous-tethered quenching reagents.

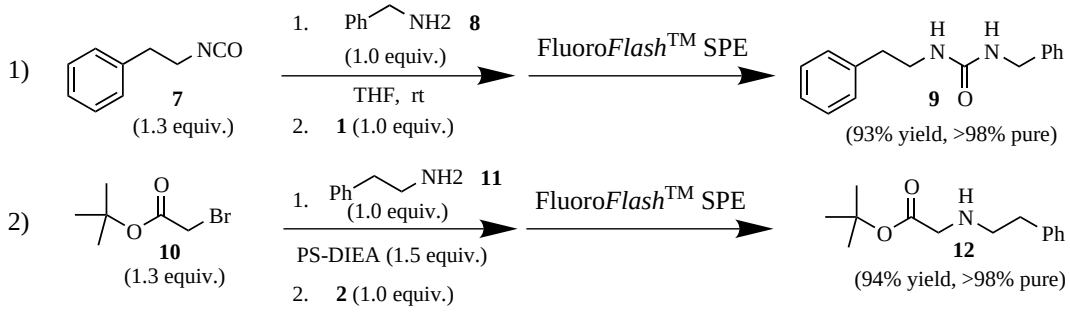
would allow for general scavenging of the most common chemical moieties we encounter in parallel synthesis libraries.[8] In general, the fluorous-tethered reagents contain between 13 and 17 fluorine atoms. We chose to generically represent the reagents by an open circle with an embedded 'F' to compliment the generic resin convention. All six reagents are liquids that can be used neat or stored and dispensed as 0.5 to 2.0 M THF stock solutions. The key to the success of this new approach is the removal of the fluorous scavengers in a rapid and general manner with Fluoro*Flash*™ SPE columns.[7,9]

Reagents **1** and **2** are utilized in the general scavenging of electrophiles when used in slight excess (typically, 1.0 equiv. of scavenger for every 0.3 equiv. of excess electrophile) in under 1 h at room temperature.[10] Representative examples are shown in Scheme 4.[11] In the event, treatment of isocyanate **7** with amine **8** for 2 h followed by addition of **1** to scavenge excess **7** provided, after Fluoro*Flash*™ SPE, urea **9** in excellent yield and >98% purity.[12] In a similar fashion, **2** removed excess **10** to afford the α-aminoester **12** in high yield and purity.

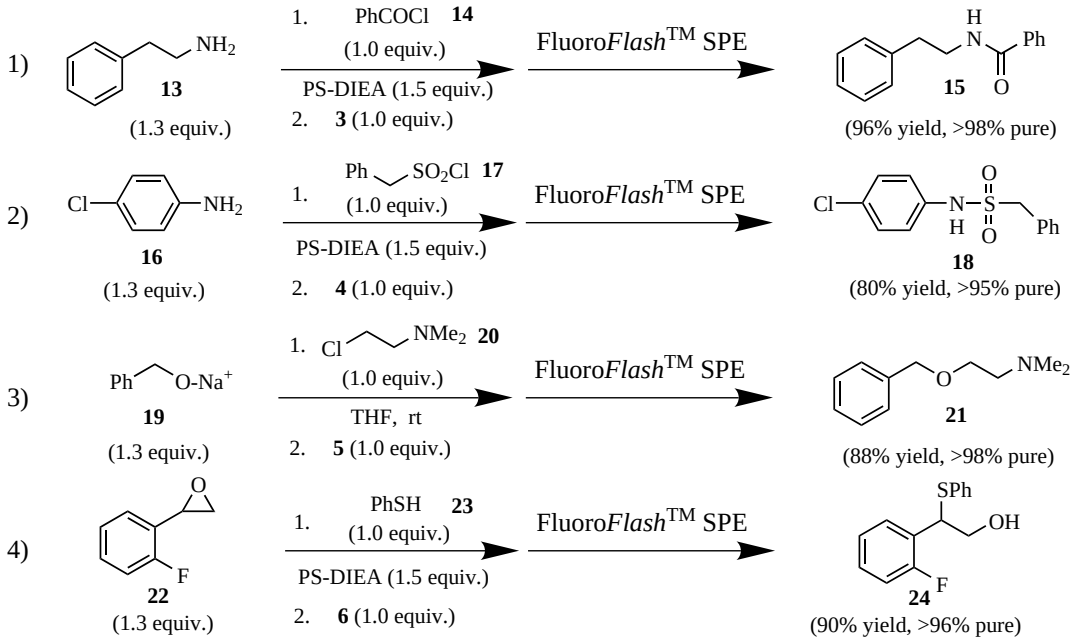
Reagents **3**, **4**, **5** and **6** are utilized in the general scavenging of nucleophiles when used in slight excess (typically, 1.0 equiv. of scavenger for every 0.3 equiv. of excess nucleophile) in under 1 h at room temperature.[10] Representative examples are shown in Scheme 5 and include amide and sulfonamide formation, alkoxide alkylation and epoxide openings wherein fluorous reagents scavenge amines, anilines, alkoxides and epoxides, respectively.[13] For the cases examined, good chemical yields (>80%) and excellent purities (>95%) were obtained.[12]

In cases where a resin-bound base is also employed, the SPE column serves as a general filtration method for removal of both the resin-bound base and the fluorous-tethered scavenger as illustrated in several examples in Schemes 4 and 5. The entire compendium of resin-bound reagents is compatible under this protocol and multi-step reactions can be undertaken with various combinations of resin-bound reagents and fluorous-tethered scavengers (Scheme 6). In this instance, the reductive amination of **25** with **26** using MP-$CNBH_3$ proceeds smoothly, and excess **26** is removed by the addition of **1** providing **27** in 84% yield and >98% purity after Fluoro*Flash*™ SPE. Sulfonylation of **27** with **28** utilizing a resin-bound base, PS-NMM, results in sulfonamide **29** in 88% yield and >95% purity after Fluoro*Flash*™ SPE.[12]

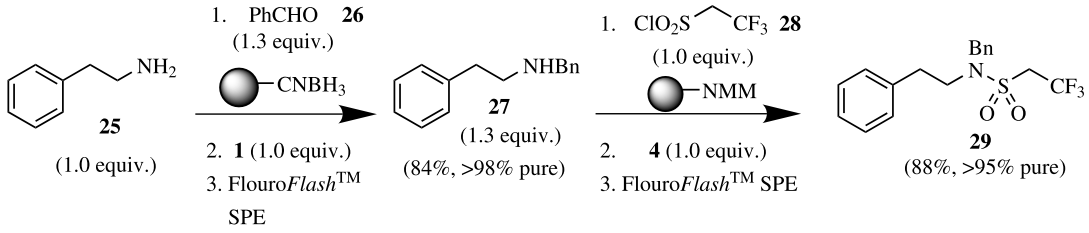
In summary, we have developed a novel protocol for the parallel purification of solution phase libraries using fluorous-tethered quenching reagents (scavengers) in conjunction with Fluoro*Flash*™ SPE. This new fluorous technology has several advantages over traditional resin-bound scavenger reagents: (1) fluorous reagents are inexpensive and available from several commercial sources; (2) Fluoro*Flash*™ SPE columns can be reused up to ten times; (3) homogeneous solu-



Scheme 4.



Scheme 5.



Scheme 6.

tion phase kinetics are observed, and (4) reactions are easily scaleable and free from solvent limitations. Current work is focused on the preparation of more specialized fluorous-tethered scavengers and reagents and will be reported in due course.

Note added in proof: In parallel, independent work, Curran and co-workers at FTI report the successful application of the fluorous thiol **2** as a fluorous quenching agent in combination with Fluoro*Flash*™ SPE columns. See, Zhang, W.; Curran, D. P.; Chen, C. H.-T. *Tetrahedron*, in press.

Acknowledgements

We would like to thank Professor Dennis Curran and Dr. Philip Yeske (FTI) for helpful conversations and Dr. Charles W. Ross, III for obtaining HRMS (accurate mass measurements).

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2. 1(b): Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. *Tetrahedron Lett*. **1996**, *37*, 7193–7196.
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4. Charette, A. B.; James, J. K.; Boezio, A. A. *J. Org. Chem*. **2001**, *66*, 2178–2180 and references cited therein.
5. (a) See Refs. 1 and 2 and references therein; (b) www.argotech.com.
6. The large amounts of solvent required (~1 L) to scale-up from 0.1 to 10 mmol employing resin-bound scavengers makes this unattractive versus 40 mL for fluorous reagents.
7. (a) Fluoro*Flash*™ columns are commercially available from FTI, Fluorous Technologies Incorporated; www.fluorous.com; (b) for excellent reviews of the area see: (1) Curran, D. P. *Synlett* **2001**, 1488–1496; (2) Curran, D. P. *Pure A Chem*. **2000**, *72*, 1649–1653; (c) Lou, Z. Y.; Williams, J.; Read, R. W.; Curran, D. P. *J. Org. Chem*. **2001**, *66*, 4261–4266; (d) in house data from an FTI evaluation kit (Part # 801-1000S) of the fluorous Boc reagent; (e) the exact ratio of water:methanol for the Fluoro*Flash*™ SPE column varies based on the polarity/hydrophobicity of both the fluorous scavenger and the substrate which is most readily determined by fluorous

TLC analysis of a representative library member and the scavenger.

8. (a) Fluorous reagents are available from FTI, Aldrich, Avocado and Lancaster and average $8/g; (b) the fluorous reagents **1**–**6** were originally prepared decades ago for use in the polymer and coatings industry and can be prepared according to the following patent literature: **1**: Ellzey, S. E.; Wittman, J. S.; Connick, W. J.; Guire, W. A. US 3338968, 1967; **2** and **4**: Haszeldine, R. N.; Tipping, A. E. DE 2238458, 1973; **3**: Platz, R.; Christof, P. DE 1285999, 1969; **5**: Millauer, H. DE 1964988, 1971; **6**: Anello, L. G.; Sweeney, R. F. US 3384627, 1968.
9. (a) Zhang, Q. S.; Luo, Z. Y.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866–8873; (b) By eluting the fluorous materials by exhaustive washing with THF and drying overnight in a vacuum oven at 40°, the columns can be reused up to 10 times with no loss of binding efficiency or contamination.
10. In a typical experiment, isocyanate **7** (60 μL, 0.39 mmol), benzyl amine **8** (35 μL, 0.3 mmol) and THF (2 mL, 0.35 M) are placed in a 4 mL vial. The vial is placed on a rotator for 3 h. After this time, **1** (300 μL, 0.3 mmol, 1.0 M THF) was added. After 50 min, the crude reaction was applied to a silica transfer column (Part #: 622-0057S) atop a 5 g Fluoro*Flash*™ column (Part #: 801-0058S), pre-washed with methanol and attached to a multi-port vacuum manifold. Air was drawn through for 2 min, and then 10 mL of a 15% aqueous methanol solution was added and slowly eluted under an ~−5 psi vacuum and collected into a test tube. The test tube was concentrated in a Genevac HT II-12 to afford 70.8 mg (93%) of urea **9** as a white solid. Analytical LCMS indicated a single peak (2.817 min, CH_3CN/H_2O/0.1% TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. (^{1}H NMR, 300 MHz, $CDCl_3$): δ 7.23 (m, 10H), 4.61 (s, 1H), 4.36 (s, 1H), 4.31 (d, J=6 Hz, 2H), 3.44 (q, J=6.6 Hz, 2H), 2.78 (t, J=6.6 Hz, 2H). HRMS: calcd for $C_{16}H_{18}N_2O$ (M+H), 255.1492; found 255.1492 (M+H).
11. Though not exemplified, **1** was also found to completely scavenge acid chlorides, sulfonyl chlorides and isocyanates. Similarly, **2** was found to completely scavenge epoxides, α-bromo carbonyl derivatives, Michael acceptors and activated halides.
12. All compounds fully characterized by HPLC (UV and ELSD), NMR and HRMS (Accurate Mass MS).
13. Though not exemplified, **3** was also found to completely scavenge amines (1° and 2°), anilines and alkoxides; **4** was found to completely scavenge amines (1° and 2°) and anilines; **5** scavenged amines (1° and 2°), alcohols and alkoxides; and **6** scavenged 1° amines, thiols, thiophenols and organometallic reagents (RLi, RMgX, etc…).