Pergamon

Tetrahedron Letters 43 (2002) 6319–6323

TETRAHEDRON LETTERS

Fluorous-tethered amine bases for organic and parallel synthesis: scope and limitations

Craig W. Lindsley,* Zhijian Zhao, William H. Leister and Kimberly A. Strauss

Department of Medicinal Chemistry, Technology Enabled Synthesis Group, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA

Received 1 June 2002; revised 8 July 2002; accepted 10 July 2002

Abstract—The synthesis of fluorous-tethered amine bases is described. These novel fluorous-tethered reagents promote reactions, remove acidic by-products, and scavenge electrophiles. They are readily separated from the reaction mixture by solid phase extraction on a novel mixed sorbent SPE (SCX/fluorous silica gel) delivering products in high yields and purities.

In recent Letters,[1] our laboratory, inspired by the work of Curran,[2] reported on the application of fluorous-tethered compounds as scavengers and reagents for both organic and parallel synthesis. The fluorous-tethered compounds were rapidly separated from the desired products by solid phase extraction (SPE) on fluorous silica gel cartridges referred to as Fluoro*Flash*™ SPE columns.[3] At the time of these first disclosures, we were employing resin-bound amine bases in our reaction schemes as we did not have fluorous-tethered equivalents. We now report the synthesis and applications of a diverse set of fluorous-tethered amine bases for organic and parallel synthesis that avoid the diminished kinetics of biphasic, resin-mediated reactions.

Since resin-bound amine bases are typically attached to the resin by a methylene spacer to the cross-linked polystyrene core (Fig. 1), we first directed our synthetic efforts at a fluorous-tethered benzylic amine equivalent. Reductive amination of commercial aldehyde **1**[4] with morpholine (Scheme 1) in the presence of MP-$CNBH_3$, followed by simple filtration afforded the desired fluorous-tethered NMM analog **2** in excellent yield and purity.[5]

Several other fluorous-tethered benzylic amines were prepared including piperidine and triethylamine analogs, all of which were white crystalline solids. This route provided access to several valuable reagents, but we envisioned the need for other amine bases whose synthesis could not be achieved via this route.

Based on the commercial availability of a large number of functionalized diamines and an F_{15} fluorous-tethered acid chloride,[6] we assembled a 'toolkit' of fluorous-tethered amine bases by simple acylation chemistry as shown in Table 1. By this method, we were able to access fluorous-tethered triethyl amine, TEA, (entry 1), diisopropylethyl amine, DIEA, (entry 2), imidazole, Imid, (entry 3), pyridine, Pyr, (entry 4), *N*-methyl morpholine, NMM, (entry 5) and a trisamine congener, Tris, (entry 6) in excellent isolated yields as white crystalline solids.[7] Table 1 also lists the shorthand abbreviation for each reagent that will be used throughout the remainder of this report.

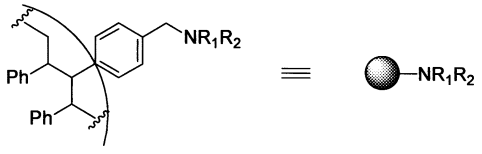
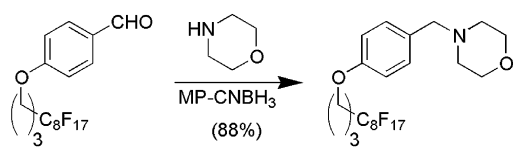


Figure 1. Generic resin-bound amine base.



1 2

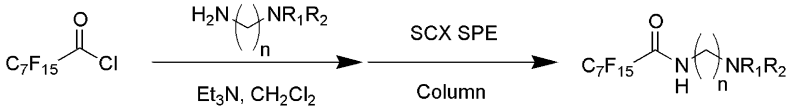
Scheme 1.

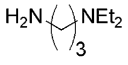
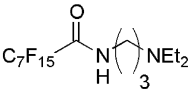
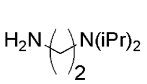
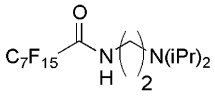
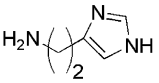
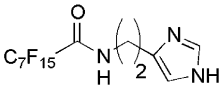
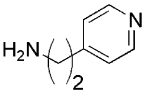
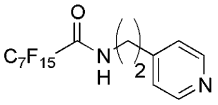
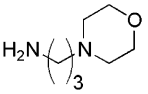
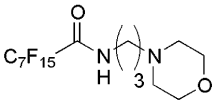
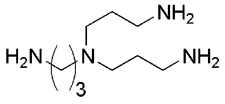
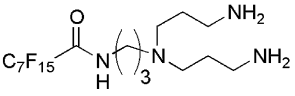
Keywords: fluorous; amines; combinatorial chemistry.

* Corresponding author. Tel.: 215-652-2265; fax: 215-652-6345; e-mail: craig_lindsley@merck.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01399-0

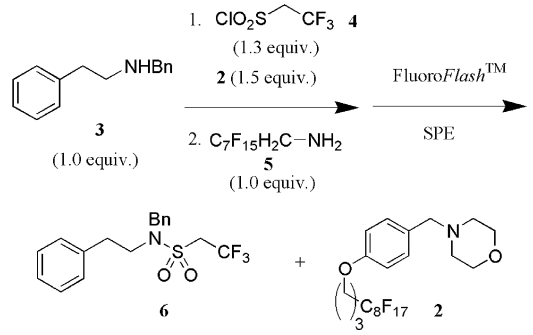
Table 1. Synthesis of fluorous-tethered amine bases



Entry	H_2N(n)NR_1R_2	% Yield[a]	Product	Abbreviation
1		92%		F—TEA
2		90%		F—DIEA
3		86%		F—Imid
4		85%		F—Pyr
5		92%		F—NMM
6		75%		F—Tris

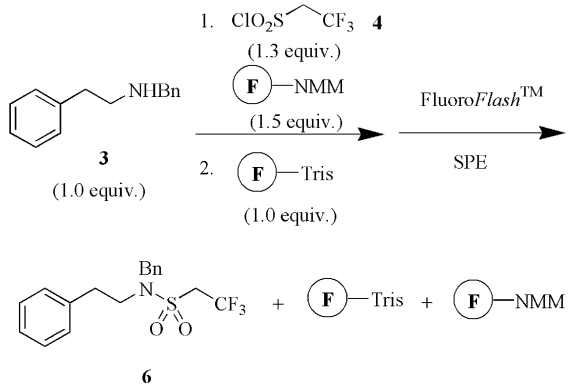
a: All compounds fully characterized by LCMS, NMR and HRMS. Yields refer to analytically pure materials.

With two distinct classes of fluorous-tethered amine bases in hand, we next focused our attention on exploring their utility for organic and parallel synthesis. As anticipated, the benzylic fluorous-tethered amines from Scheme 1 sequestered HCl generated from acylation and sulfonylation reactions and promoted urea formation. For example, amine **3** was exposed to excess sulfonyl chloride **4** and **2** for 2 hours (Scheme 2). Excess electrophile was quenched by the addition of fluorous-tethered amine **5** for 1 hour.[1a] It was anticipated that both fluorous-tethered reagents could be removed via Fluoro*Flash*™ SPE to provide the sulfonamide **6** in high yield and purity; however, ~15% of **2** co-eluted with **6** while **5** was retained. Puzzled by this result, we moved on to evaluate our non-benzylic congeners (Table 1). Application of these new reagents in the reaction sequence to deliver sulfonamide **6** proved problematic, as found with **2** (Scheme 3). Upon standard Fluoro*Flash*™ SPE purification, with the silica gel transfer column in place, we were surprised to find that both F-NMM and F-Tris were not completely retained on the Fluoro*Flash*™ SPE cartridge under typical 20% aqueous methanol elution.[8] In this instance, ~60% of F-Tris and ~25% of F-NMM passed through the SPE column with the first 5 mL collected; however, the majority of fluorous material was retained. This contamination proved to be problematic with all of the fluorous-tethered amine bases depicted in Table 1. Our experience and that of others in the field suggested that the ability of fluorous SPE to retain fluorous-tethered molecules was general, i.e. independent of the functionality attached to the fluorous chains.[9] In light of these results, we now know that appended basic and polar groups can override the fluorophilic interactions between fluorous-tethered materials and fluorous silica gel, even when eluted with fluorophobic solvent systems.



Scheme 2.

We were at a loss to explain why reagents such as **5** are retained on Fluoro*Flash*™ SPE while reagents such as **2** and those in Table 1 are not. Fortunately, LCMS analysis of representative fluorous-tethered reagents



Scheme 3.

shed light on the issue.[10] As seen in Fig. 2, the retention time dramatically decreases as the polarity of pendant groups and the distance from the fluorous-chain increases. Of interest, the majority of fluorous-tethered reagents reported to date are non-polar entities such as triarylphosphines, trialkylstannanes and bis-fluorous-tethered DEAD. These materials have retention times of >4.1 minutes on our instrument and afford excellent separation by Fluoro*Flash*™ SPE.[9] The fluorous-tethered scavengers that were recently reported[1] have LCMS retention times >3.5 minutes, despite the presence of basic and polar functionalities (Fig. 3). Note, these groups are appended either directly to the fluorous chain or with a 1 or 2 carbon atom spacer. Similarly, these materials are readily separated by application of Fluoro*Flash*™ SPE. Our new fluorous-tethered amine bases elute between 3.4 and 2.2 minutes and are not completely retained under standard Fluoro*Flash*™ SPE.[8] Moreover, the basic moieties in these reagents are several atoms removed from the fluorous tether and, as in the case of the reagents in Table 1, contain an additional polar amide linkage.

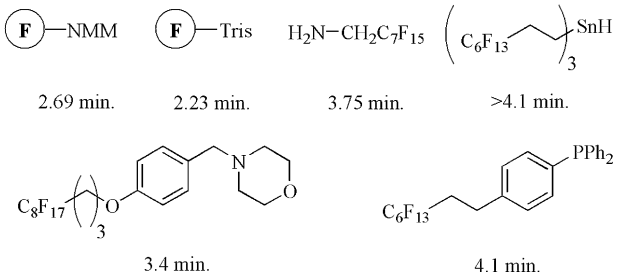


Figure 2. Retention times of fluorous-tethered reagents.

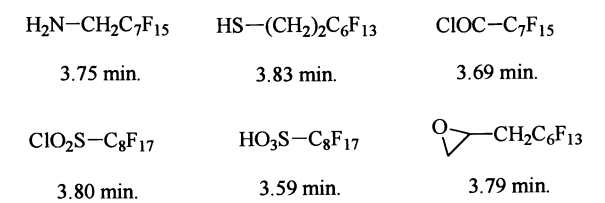


Figure 3.

After a thorough study of the matter, we have developed a general guide for the purification of fluorous-tethered reagents based on LCMS retention time (Table 2). Key to the development of this guide was the generation of a 'mixed sorbent' SPE cartridge wherein the silica gel transfer column is replaced with an ion exchange column resulting in a mixed ion exchange-fluorous SPE column.[11]

In accord with our guidelines, fluorous-tethered reagents that possess retention times >3.5 minutes can be separated from non-fluorous materials by standard Fluoro*Flash*™ SPE under the pull of a −5 psi vacuum as detailed previously.[1–3] In borderline cases (retention times between 2.9 and 3.4 minutes), clean products are obtained with Fluoro*Flash*™ SPE except gravity filtration is used in lieu of the normal −5 psi vacuum.[8] Indeed, allowing gravity filtration for the reaction in Scheme 2 afforded **6** in 88% yield and >95% purity.[12]

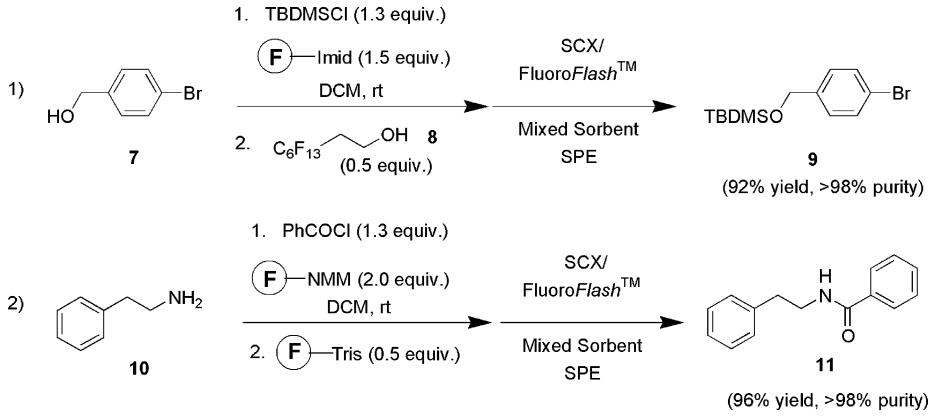
As indicated in Table 2, by application of the 'mixed sorbent' SPE protocol,[11] the sequence depicted in Scheme 3 now delivers sulfonamide **6** in 89% yield and >95% purity.[12] The mixed sorbent protocol retains all of the fluorous materials while allowing the organics to elute cleanly even under the pull of a −5 psi vacuum. This new protocol is scaleable and has applications for both parallel and organic synthesis. For instance, larger Fluoro*Flash*™ SPE (5–10 g) and ion-exchange columns (1–5 g) can be used to deliver products in the 0.1–1 mmol range with excellent purities. Additional examples of this protocol for synthesis are illustrated in Scheme 4. In the event, *p*-bromobenzyl alcohol **7** was treated with TBDMSCl in the presence of F-Imid for 1 hour. After this time, fluorous-tethered alcohol **8** was added to scavenge the excess TBDMSCl. After 45 minutes, the crude reaction was applied to a mixed sorbent (SCX/Fluoro*Flash*™) SPE column and eluted with 15% aqueous methanol to provide the protected derivative **9** in 92% yield and >98% purity.[13] In a similar fashion, amine **10** was treated with benzoyl chloride and F-NMM for 1 hour. Then, F-Tris was added as a 2.0 M THF solution. Following 30 minutes of reaction time, the crude reaction was applied to a mixed sorbent (SCX/Fluoro*Flash*™) SPE column and eluted with 15% aqueous methanol to provide amide **11** in 96% yield and >98% purity.[14]

Table 2. LCMS retention time guide for SPE

LCMS retention time[a]	Purification method
>3.5 min	Silica transfer column/Fluoro*Flash*™ SPE −5 psi vacuum
2.9–3.4 min	Silica transfer column/Fluoro*Flash*™ SPE gravity filtration
<2.8 min	Mixed sorbent SPE[b], ion exchange SPE/Fluoro*Flash*™ SPE

[a] 3.0×50 mm C18 J-Sphere80, 4 micron column; 5–95% MeCN:H_2O, 4 min run time.

[b] Ion exchange SPE columns: SCX or SAX (1 g cartridge).



Scheme 4.

In summary, the synthesis and application of novel fluorous-tethered amine bases is described. These reagents have the utility of their resin-bound congeners yet provide homogeneous reactions with solution phase kinetics. Fluoro*Flash*™ SPE alone is not sufficient as a *general* method for the separation of fluorous-tagged and non-fluorous-tagged materials when polar, basic functionalities are appended several atoms away from the fluorous chain. A set of guidelines for fluorous SPE purification based on LCMS retention time of the fluorous-tethered reagents was developed along with a 'mixed sorbent' SPE strategy for rapid parallel purification of reaction systems that employ fluorous-tethered amine bases. Additional investigations into the scope and limitations of fluorous technology for synthesis are in progress.

References

1. (a) Lindsley, C. W.; Zhao, Z.; Leister, W. H. *Tetrahedron Lett*. **2002**, *43*, 4225; (b) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Strauss, K. A. *Tetrahedron Lett*. **2002**, *43*, 4467; (c) For related fluorous-tethered scavenger work see: Zhang, W.; Curran, D. P.; Chen, C. H.-T. *Tetrahedron* **2002**, *58*, 3871.
2. (a) Ref. 1c; (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.
3. Fluoro*Flash*™ columns are available from FTI, Fluorous Technologies Incorporated; www.fluorous.com and Refs. 1 and 2.
4. Compound **1** is commercially available from FTI, cat. no. F017022-0010, $40/g.
5. Experimental for **2**: To an 8 mL vial was placed **1** (116 mg, 0.20 mmol), MP-$CNBH_3$ (178 mg, 0.40 mmol, 2.52 mmol/g) and 5 mL of a 5% AcOH/THF solution. Then, morpholine (22 μL, 0.22 mmol) was added and the vial rotated overnight at room temperature. After this time, the contents of the vial were filtered, washed with THF (2×2 mL) and concentrated in a Genevac HTII-12 to afford 115 mg (88%) of **2** as a white crystalline solid. LCMS indicates a single peak at 3.41 min, ($MeCN/H_2O$/0.05%TFA), 4 min gradient, >99% pure; ^1H NMR (300 MHz, DMSO-d_6): δ 7.39 (d, $J=8$ Hz, 2H), 7.01 (d, $J=8$ Hz, 2H), 4.25 (m, 2H), 4.09 (t, $J=11$ Hz, 2H), 3.9 (m, 2H), 3.6 (m, 2H), 3.2 (m, 2H), 3.1 (m, 2H), 2.4 (m, 2H), 1.98 (m, 2H); HRMS calcd for $C_{22}H_{20}F_{17}NO_2$ (M+H), 654.1295; found 654.1294.
6. $F_{15}C_7COCl$ is available from Aldrich Chemical, cat. no. 29,090-4, $2.88/g. The diamines were purchased from Aldrich, Lancaster and TCI.
7. Entries 1–5 were prepared by reacting 1.3 equiv. of $F_{15}C_7COCl$ with 1 equiv. of diamine in DCM on a 1 mmol scale and were purified by standard SCX chromatography on a 5 g SPE column (vide infra). Entry 6 was prepared by reacting 1 equiv. of $F_{15}C_7COCl$ with 5 equiv. of the trisamine. The resulting material was purified by Mass Guided HPLC and free-based on a 5 g SCX column. Experimental for entry **3** (Table 1): To an oven-dried 25 mL round-bottom flask, colled and pourged under Ar (g) was added diamine (111 μL, 1.0 mmol), triethylamine (208 μL, 1.5 mmol) and dry DCM (10 mL, 0.1 M). Then, $F_{15}C_7COCl$ (563 μL, 1.3 mmol) was added via syringe at room temperature. After 30 min, the reaction was concentrated, diluted with MeOH and applied to a 5 g SCX column. The 5 g SCX column was first conditioned by treatment with 5% aqueous MeOH (10 mL). The crude reaction was then applied to the SCX column and allowed to absorb by gravity filtration. Once absorbed, the column was eluted with MeOH (10 mL) to remove all non-basic entities. The F-Imid was collected by eluting the column with 2.0 M NH_3/MeOH (5 mL). Concentration of the NH_3/MeOH elutant afforded 436 mg (86%) of an off-white crystalline solid. LCMS indicates a single peak at 2.70 min, ($MeCN/H_2O$/0.05%TFA), 4 min gradient, >99% pure; ^1H NMR (300 MHz, DMSO-d_6): δ 13.9 (bs, 1H), 9.62 (t, $J=5.4$ Hz, 1H), 8.5 (s, 1H), 7.2 (s, 1H), 3.48 (q, $J=6$ Hz, 2H), 2.8 (t, $J=6$ Hz, 2H); HRMS calcd for $C_{13}H_8F_{15}N_3O$ (M+H), 508.0501; found 508.0495.
8. The crude reaction is applied to a 2 g silica transfer column (Part #: 622-0057S) atop a 5 g Fluoro*Flash*™ column (Part #: 801-0058S), pre-washed with aqueous methanol and attached to a multi-port vacuum manifold. Air is drawn through for 2 min, and then 10 mL of a 20% aqueous methanol solution is added and slowly eluted under a −5 psi vacuum and the first 5 mL collected into a test tube.
9. (a) Refs. 2a,b; (b) Dandapani, S.; Curran, D. P.; Ley, S. V.; Massi, A.; Rodriguez, F.; Harwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M.; Zhang,

S.-Q.; Fukase, K.; Izumi, M.; Fukase, Y.; Kusumoto, S.; Bosanac, T.; Yang, J.; Wilcox, C. S. *Chemtracts* **2001**, *11*, 635–641.

10. Data collected on an Agilent 1100 Analytical LCMS: 3.0×50 mm C18 J-sphere80, 4 micron column, 4.1 min gradient (5%[0.05%TFA/MeCN]:95%[0.05%TFA:H_2O] to 100% (0.05%TFA/MeCN).
11. Replacement of the 2 g silica transfer column (Part #: 622-0057S) atop a 5 g Fluoro*Flash*™ column (Part #: 801-0058S) with a Varian Bond Elut 1 g SCX column (Part #: 12256011) generates the 'mixed sorbent' SPE column. Elution with aqueous methanol under a −5 psi vacuum.
12. All compounds fully characterized by LCMS, NMR and HRMS (accurate mass measurements provide by Chuck W. Ross III).
13. LCMS indicates a single peak for **9** at 3.32 min, (MeCN/H_2O/0.05%TFA), 4 min gradient, >98% pure.
14. For a detailed procedure, refer to Ref. 1a,b; LCMS indicates a single peak for **11** at 2.88 min, (MeCN/H_2O/0.05%TFA), 4 min gradient, >98% pure.