Fluorous Synthesis with Fewer Fluorines (Light Fluorous Synthesis): Separation of Tagged from Untagged Products by Solid-Phase Extraction with Fluorous Reverse-Phase Silica Gel

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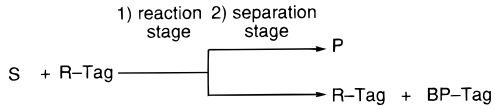
Abstract: Fluorous synthesis involves tagging an organic substrate with a fluorinated tag for the purposes of separation. To date, techniques of fluorous synthesis have relied on liquid−liquid extractions. This paper applies a simple solid−liquid extraction procedure over fluorous reverse-phase silica gel (silica with a fluorocarbon bonded phase) for use in fluorous synthesis. Four amino acids were tagged on nitrogen with the $C_9F_{19}CO-$ group, and the resulting acids were coupled in a parallel experiment with an excess of four amines. The resulting 16 crude fluorous amide products were separated from all the coupling reagents and excess amine by two-stage filtration through fluorous silica. In 15 of the 16 cases, the products were isolated in good to excellent yield and purity. All of the products are soluble in organic solvents and none is expected to have any significant solubility in fluorous solvents, so the experiment dramatically illustrates the advantages of the solid−liquid extraction over the liquid−liquid extraction. Future prospects for application of fluorous silica are briefly discussed.

Introduction

The attachment of "tags" to organic reaction components to influence phase behavior in the separation stage of a synthetic step has become increasingly popular, especially in combinatorial and parallel synthesis.[1] Effective phase tagging methods allow simple, binary separations of reaction mixtures into tagged and untagged fractions and thereby integrate synthesis with separation. A number of types of phase tags have been introduced; however, most of these have been restricted to tagging of small molecule components of a reaction mixture. This strategy is shown in eq 1.[2] Reaction substrates are left

Tagging Reagents/Reactants

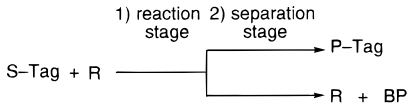


(1)

S = substrate (starting material)
R = reagent or reactant
P = (desired) product
BP = reagent/reactant byproduct

untagged, and added reagents or reactants are tagged for the purposes of separation of excess reagents/reactants and their byproducts. This powerful strategy is limited by the availability of tagged reagents/reactants, and is inefficient for multistep synthesis since new tags are needed for every step. The tagging of inherently larger substrates and desired products for use with untagged reagents and reactants (eq 2) is especially useful for

Tagging Substrates/Products



(2)

multistep parallel and combinatorial synthesis, but to date only polymeric tags (solid-phase synthesis) have been widely adopted as providing reliable, general separations of larger molecules.[3]

Following the introduction of "fluorous biphasic catalysis" by Horváth and Rábai,[4] we have expanded and generalized fluorous concepts and techniques.[1] In 1997, we introduced "fluorous synthesis",[5] which entails the tagging of a substrate (or a library of substrates) with a highly fluorinated tag. Tagged products were then separated from nontagged ones by partitioning between an organic liquid and a fluorous liquid in a liquid−liquid extraction. However, a large number of fluorines (as many as 60−120) can be required to induce tagged molecules to partition into a fluorous solvent (especially if the molecules have polar functional groups). Such highly fluorinated molecules can have little or no solubility in organic solvents, so finding suitable conditions for synthetic reactions is not trivial. This type of "heavy" fluorous synthesis then resembles solid-phase synthe-

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(5) (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. (b) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681. (c) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917. (d) Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937.

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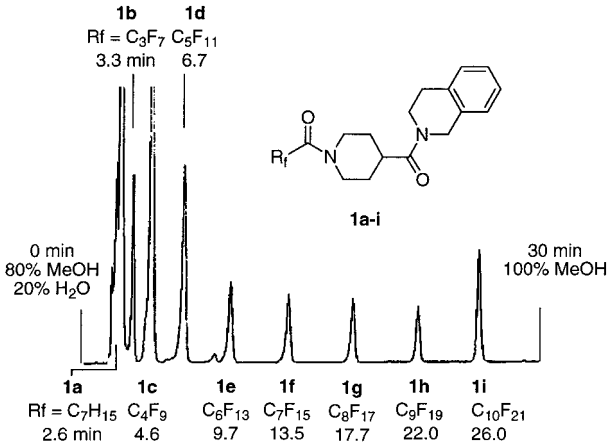


Figure 1. Separation of a mixture of amides **1a**−**i** on a Fluofix 120E column.

sis: it is very convenient for the separation stage of a synthetic step but has liabilities in the reaction stage.

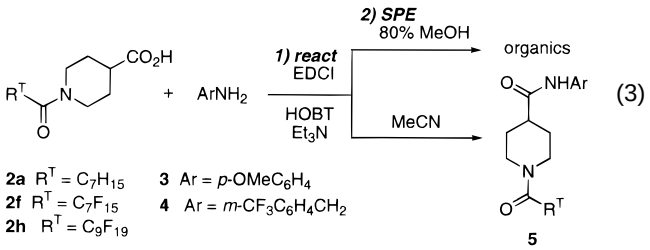
The liquid−liquid extractions can be replaced by solid−liquid extractions over fluorous reverse-phase silica gel. In the few examples published to date,[6] the solid-phase extraction method has been employed largely for reasons of convenience: partition coefficient measurements showed that liquid−liquid separations were possible, but that multiple extractions would be needed to fully separate the fluorous-tagged reagents (or reagent byproducts) from the nontagged organic products. We now show that the solid-phase extraction method can be used to reduce the number of fluorines required for fluorous synthesis—tagged product molecules that are essentially insoluble in fluorocarbon solvents and fully soluble in organic solvents can still be separated from nontagged molecules with ease.[7] This advance dramatically expands the usefulness of fluorous synthesis.

Results and Discussion

Silica gel with a fluorocarbon bonded phase (silica-$OSi(Me)_2$-$(CH_2)_nR_f$, hereafter called fluorous silica gel) has been known for about two decades,[8] and it is occasionally used in a chromatographic mode for polar/nonpolar separations; it works in a "reverse-phase" mode so polar compounds elute first. However, its utility here is limited by its very low retention capability for organic compounds. We find fluorous reverse-phase silica gel much more useful for separating molecules based on their fluorine content—the more fluorines a molecule possesses the slower it moves.

The dramatic effect of fluorine content on retention time is illustrated by the analytical separation shown in Figure 1. Nine amides **1a**−**i** were prepared by standard acylation reactions and then mixed together and injected on a commercial Fluofix 120E analytical column.[9] The gradient elution began with 80% MeOH/H_2O and the MeOH content was increased to 100% over 30 min. Despite its relatively low polarity, the control amide **1a** bearing the C_7H_{15} (hydrocarbon) tag emerged with the solvent front, as indeed do most other organic compounds randomly selected from our collection for injection under these conditions.[10] The amides bearing fluorocarbon chains then eluted smoothly in order of their fluorine content from C_3F_7 (3.3 min) through $C_{10}F_{21}$ (26 min). Under isocratic conditions (80% MeOH), the separations are even more dramatic; amide **1f** has a retention time of 17 min, amide **1h** emerges in a very broad peak between 51 and 56 min. To assess the possibility of using these perfluoroalkyl amide tags in the liquid−liquid extraction method, we attempted to measure partition coefficients of amides **1f,h** between FC-72 and dichloromethane. Both of these amides were soluble in CH_2Cl_2, and no trace could be detected in the FC-72 phase after thorough mixing and phase separation. In other words, the tags attached to amides **1f,h** do not contain anywhere near enough fluorines to be useful for separation by standard liquid−liquid extraction.

These results suggest that tagged molecules with modest numbers of fluorines can readily be separated from untagged molecules by a simple solid-phase extraction. To test this, we conducted the six parallel amide couplings shown in eq 3.



MeCN fraction contains

	2a	2f	2h
3	nothing	5	5
4	nothing	5	5

Tagged acids **2a,f,h** were coupled with amines **3** and **4** (3 equiv) under standard conditions with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.2 equiv), 1-hydroxybenzotriazole (HOBT, 1.2 equiv), and Et_3N (1.2 equiv). The crude reaction mixtures were then passed through homemade[6a,d] fluorous silica gel in a two-stage extraction eluting first with 80% MeOH/H_2O (to remove the nontagged products) and then with CH_3CN (to remove the tagged products). The CH_3CN fractions were evaporated on a vacuum centrifuge. In the case of the hydrocarbon-tagged (control) experiments with **2a**, the CH_3CN fraction contained nothing. To verify that the coupling had occurred, we evaporated the MeOH/H_2O phase, which indeed contained the expected amide product along with all the excess reactant, reagents, and reagent byproducts. In contrast, the CH_3CN phase from fluorous-tagged experiments with **2f** and **2h** provided pure coupled products **5**.

To provide quantitative information about the efficiency of the reaction and separation, we prepared a library of 16 amides

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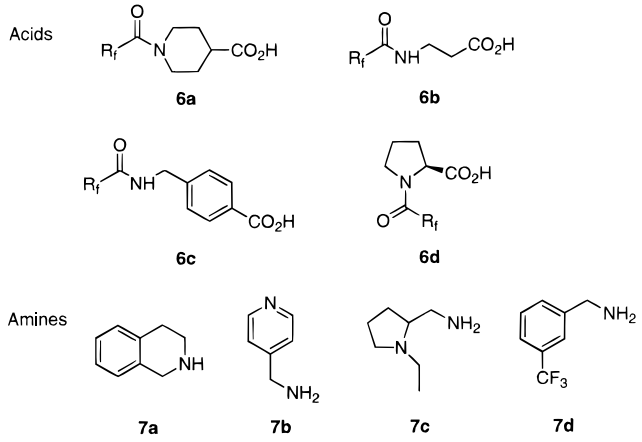
(9) Fluofix columns are manufactured by NEOS, Co., Japan, and can be purchased from Keystone Scientific. Related FluoroSep-RP columns are available from ES Industries.

(10) Amines can sometimes be retained by these columns, presumably due to interactions with the silica itself. See ref 8.



Amide Products %yield (%GC purity)

RfCON–acid(A)–CON–amine(B)

7 \ 6	a	b	c	d
a	85 (94)	92 (99)	60 (88)	89 (97)
b	100 (94)	60 (94)	21 (64)	91 (89)
c	90 (94)	78 (78)	45 (87)	61 (92)
d	80 (97)	71 (92)	67 (84)	88 (98)

Figure 2. 4×4 amide library ($R_f = C_9F_{19}$).

in parallel as summarized in Figure 2. We selected the C_9F_{19} tag and coupled this to make acid-amides **6a**−**d**. These were then coupled with amines **7a**−**d** under the conditions of the experiment in eq 3 and the crude reactions were again purified only by solid-phase extraction. The products where then assayed for yield and purity (by ^{1}H NMR and GCMS, and in several cases, by LCMS). The results are summarized in Figure 2, and all the raw data are contained in the Supporting Information. Couplings with acids **6a,b,d** all worked very well, while the couplings with benzoic acid **6c** (not completely soluble under the reaction conditions) gave lower but still satisfactory yields in three cases, and an unsatisfactory result in one case (**6c** and **7b**). These results clearly show the applicability of the solid-phase extraction method for separating reaction mixtures containing lightly fluorous-tagged molecules bearing polar functional groups.

To complete the cycle of tagging/reaction/detagging, we have also investigated a number of cleavage reactions. We first cleaved the whole library with K_2CO_3/MeOH; however, only the amides derived from acid **6a** reliably gave clean crude products. In probing other conditions, we cleaved crude products from **6b** with LiOH, followed by acylation and flash chromatography. Likewise, amides from **6d** were cleaved with $NaBH_4$, acylated, and chromographed to give the corresponding products. In both cases, the acetamide derived from the coupling product of **7e** was not produced cleanly. All the data for the cleavage reactions are contained in Figure 3.

RfCON–acid(A)–CON–amine(B) $\xrightarrow{\text{cleave}}$ HN–acid(A)–CON–amine(B)

	6a[a]	6b[b]	6d[c]
7a	77%	24%	49%
7b	80%	73%	50%
7c	85%	–[d]	–[d]
7d	74%	60%	59%

a) K_2CO_3, MeOH.
b) i) LiOH, ii) MeCOCl
c) I) $NaBH_4$, ii) MeCOCl
d) clean product was not isolated.

Figure 3. Summary of deprotection reactions.

Conclusions

The results outlined in this paper hold out the promise for a dramatically increased practicality for fluorous synthesis techniques that involve substrate tagging. The tags used here are considerably lighter yet they retain all the attractive features of their heavier predecessors. These include the following: stability under diverse reaction conditions, straightforward chromatographic and spectroscopic characterization, and ease of introduction via modifications of standard protecting groups. "Heavy" tags suitable for inducing large molecules to partion into a fluorous liquid phase require large numbers of fluorines (60−120).[5] The resulting molecules are >60% fluorine by molecular weight and have total molecular weights of 2000−3000 or more.

The lighter tags used in this work provide tagged substrates that are less than 50% fluorine by molecular weight. This is a very dramatic reduction in fluorine content considering that the maximum fluorine content in these molecules (that is, the content of the tag alone) is not 100% but less than 75%. The decrease is more readily seen in total molecular weights; all of the molecules in Figure 2 have molecular weights well under 1000. In addition, the lighter tags have dramatically increased solubility in organic solvents and this facilitates reactions. The ability to use commercial analytical columns in straightforward methods development experiments to find suitable conditions for the parallel solid-phase extractions and the unique ability to analyze and characterize the libraries by GCMS are added attractions. Furthermore, we have recently purchased our first preparative fluorous HPLC column from Keystone Scientific, and the coupling of this with a modern serial or parallel liquid chromatography apparatus should further facilitate experimental execution of the techniques reported in this paper. In short, the potential offered by fluorous synthesis techniques may now be realized much more readily.

The work in this paper has focused on developing lighter fluorous tags for substrates (eq 2), but the techniques will clearly be applicable to reagent and reactant tagging (eq 1) as well. On moving from liquid−liquid to solid−liquid extractions, it will be possible to dramatically decrease the number of fluorines in the tagged reagent or reactant. We have already demonstrated this to some extent with organotin reagents,[6] but the results herein suggest that even more lightly fluorinated versions are possible. In effect, the reduction of the fluorine content in a flourous reagent coupled with a replacement of liquid−liquid extraction by solid-phase extraction should provide a very general alternative to the technique of "fluorous biphase catalysis".[4]

While the goal of this work has been to develop separations based on solid-phase extraction rather than chromatography, it is already clear from results such as those in Figure 1 that fluorous reverse-phase silica gel will have interesting chromatographic applications as well. For example, our early results suggest that if reactions such as those in Figure 2 are incomplete based on the fluorous tagged component, then this unreacted tagged component may elute reliably after the coupled, tagged product. This is because the tag is attached to a larger "nonfluorous" piece in the product, so this is less well retained by the column. We also suggest that fluorous columns have untapped potential in chemical analysis.[8] For example, reaction of a mixture with a fluorous reagent would then tag a product

or subset of products for analysis. These products would be retained on a column under which nontagged compounds would not. The ability to separate molecules based largely on fluorine content should prove to be a nice complement to traditional polar/nonpolar separations in synthesis, chemical analysis, and other areas.

Finally, a frank assessment of the fluorous amide protecting groups introduced in this paper shows that they have limited potential utility. On the upside, the needed perfluorinated acids are already commercially available and are easily attached. However, more general cleavage conditions will be needed before these groups are considered as viable replacements of the standard trifluoroacetamide group.[11] In the longer run, we feel that these will not be optional nitrogen protecting groups for many synthetic needs since trifluoroacetamide itself is not among the most common nitrogen protecting groups. We already have fluorous variants of a number of more common nitrogen protecting groups and we will be reporting results with these new protecting groups in due course. Both Wipf and co-workers[12] and our group have also developed new oxygen protecting groups suited to solid−liquid extraction as well. As the number of these groups continues to expand, so will the usefulness of the techniques reported in this paper.

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Supporting Information Available: Complete experimental details and copies of all the spectra and chromatograms (^{1}H NMR, GCMS, LCMS) used to characterize the library (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991496R

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