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Reverse Fluorous Solid-Phase Extraction: A New Technique for Rapid Separation of Fluorous Compounds

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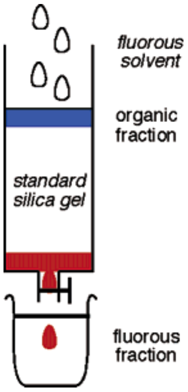
ABSTRACT



Fluorous-tagged compounds can rapidly be separated from organic (non-tagged) compounds by the new separation technique of reverse fluorous solid-phase extraction (r-fspe). In a reversal of the roles of solid and liquid phases in standard fluorous spe, a mixture is charged to a polar solid phase (standard silica gel) and then eluted with a fluorous solvent or solvent mixture. The organic components of the mixture are retained, while the fluorous components pass.

The separation of fluorous-tagged compounds from organic compounds has become increasingly popular,[1] and early methods based on liquid−liquid separations[2] have been augmented by solid−liquid separations such as fluorous solid-phase extraction (fspe) and fluorous chromatography.[3] Most of these types of separations rely on a fluorous silica solid-phase (silica gel with a fluorocarbon bonded phase) coupled with an organic solvent. We describe herein a new, complementary separation technique called reverse fluorous solid-phase extraction. As the name implies, the usual roles of the liquid and solid phases are reversed in this technique.

Since their introduction in 1997,[4] standard fluorous solid-phase extractions have proven to be broadly useful for separating light fluorous molecules[5] from organic molecules. As illustrated in Figure 1 (left), a mixture of organic and fluorous-tagged compounds is loaded onto fluorous silica gel followed by first-pass elution with a “fluorophobic” solvent. Polar organic solvents (for example, 80−100% aqueous methanol or acetonitrile) are the most common

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[1] (a) Zhang, W. *Tetrahedron* **2003**, *59*, 4475−4489. (b) Curran, D. P. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddardt, J. F., Shibasaki, M., Eds.; Wiley-VCH: New York, 2000.

[2] (a) Dobbs, A. P.; Kimberley, M. R. *J. Fluorine Chem.* **2002**, *118*, 3−17. (b) Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, *192*, 587−605.

[3] (a) Curran, D. P. *Synlett* **2001**, 1488−1496. (b) Curran, D. P. Separations with Fluorous Silica Gel and Related Materials. In *The Handbook of Fluorous Chemistry*; Gladysz, J., Horváth, I., Curran, D. P.; Wiley-VCH: Weinheim, 2004; pp 101−127.

[4] Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714−6715.

[5] (a) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866−8873. (b) Curran, D. P. A User’s Guide to Light Fluorous Chemistry. In *The Handbook of Fluorous Chemistry*; Gladysz, J., Horváth, I., Curran, D. P.; Wiley-VCH Weinheim, 2004; pp 128−155.

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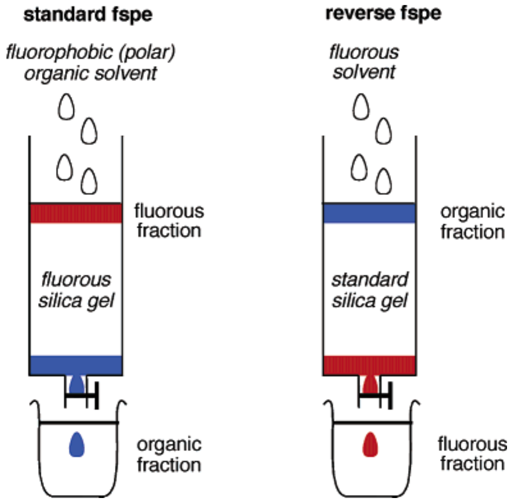

Figure 1. Fluorous solid-phase extractions. Left: a standard fluorous solid-phase extraction; Right: a new reverse fluorous solid-phase extraction.

fluorophobic solvents. During this first elution, the non-tagged organic compound is rapidly washed from the column, while the fluorous-tagged compound is retained. A second-pass elution (not shown) with a “fluorophilic” solvent (often Et_2O or THF) then washes the fluorous fraction from the column.

We hypothesized that the whole process could be “reversed” by exchanging the characteristics of the fluorophilic solid phase with the fluorophobic liquid phase. As shown in Figure 1 (right), reverse fluorous solid-phase extraction involves charging of a mixture of organic and fluorous-tagged compounds to a polar solid phase. First-pass elution with a fluorous liquid phase should elute the fluorous-tagged fraction from the column while leaving the organic fraction behind. If desired, second-phase elution with a suitable organic solvent should elute the organic fraction.

Since fluorous solvents have only rarely been used in chromatographic processes,[6] we began with simple TLC experiments with fluorous esters **1a**−**c** and control **1d** to identify useful solvent and solid-phase pairings. By testing assorted combinations of TLC plates[7] (regular silica gel, base-coated silica gel, C18-silica gel, aluminum oxide, α-cellulose) and various fluorous solvents[8] (FC-72, c-$C_6F_{11}CF_3$, C_4F_9-OMe, BTF, hexafluoro-2-propanol), we discovered that a combination of a regular silica gel with mixtures of FC-72/Et_2O or FC-72/hexafluoro-2-propanol provided both good separations and convenient R_f[9] values. Figure 2 shows the R_f values of benzoate esters (**1a**−**d**) on a regular silica gel TLC plate eluted with 2/1 FC-72/Et_2O.

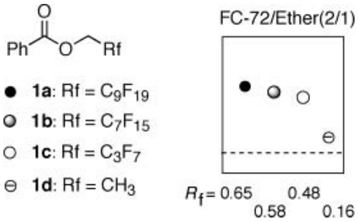

Figure 2. TLC of **1a**−**d** using reverse fluorous spe conditions.

As expected, the R_f values of the esters increased with their fluorine content. This is the reverse of their behavior on fluorous silica gel eluting with polar organic solvents. The fluorous esters **1a**−**c** had significantly higher R_f values than the ethyl ester **1d**.

Control TLC experiments with standard organic solvents revealed the unique features of using the fluorous solvent mixture with standard silica gel (Figure 3). For example, elution of a mixture of fluorous ester **1a** and triphenylphosphine on standard silica gel with 100% hexane showed that triphenylphosphine was the less polar of the two compounds (R_f values: PPh_3, 0.30; **1a**, 0.24).[10] When the same mixture was eluted with 2/1 FC-72/Et_2O on a silica TLC plate, the R_f of **1a** increased to 0.68, while the R_f of PPh_3 decreased dramatically to 0.03. This decrease reflects the “fluorophobicity” of triphenylphosphine, which has little or no solubility in FC-72. We conclude that the excellent separation provided by the fluorous solvents is unique and cannot be reproduced with the common organic solvents used in silica TLC and chromatography experiments.

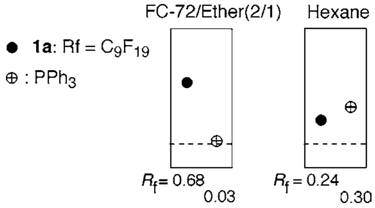

Figure 3. Comparison of TLC between reverse fluorous spe conditions and normal conditions.

Armed with these results, we next studied preparative separations of mixtures of fluorous and organic compounds by reverse fluorous spe. Ryu and co-workers described allylation of perfluoroalkyl iodides (RfI) with allyl stannanes to provide allyl perfluoroalkanes.[11] In this work, the target

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[6] (a) Attaway, J. A.; Barabas, J.; Wolford, R. W. *Anal. Chem.* 1965, *37*, 1289−1295. (b) Attaway, J. A. *J. Chromatog.* **1967**, *31*, 231−233. (c) Blackwell, J. A.; Schallinger, L. A. *J. Microcolumn Sep.* **1994**, *6*, 551−556. (d) Kagan, M. Z. *J. Chromatogr. A* **2001**, *918*, 293−302. (e) Matsuzawa, H.; Mikami, K. *Synlett* **2002**, 1607−1612.

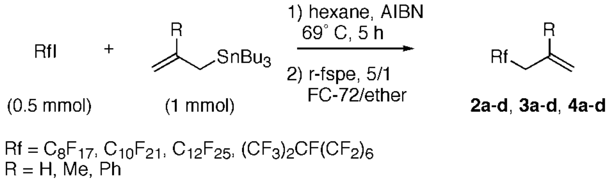
[7] TLC plates used in this study were as follows: regular silica gel, Silica Gel 60 F_{254} (MERCK); base-coated silica gel, NH-DM1020 (Fuji Silysia Chemical Co., Ltd.); C18-silica gel, C18-Silica Gel 60 F_{254} (MERCK); aluminum oxide, Aluminum oxide 150 F_{254} (MERCK); and α-cellulose, AVICEL F Microcrystalline Cellulose (ANALTECH).

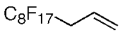
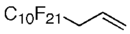
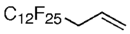
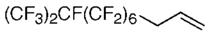
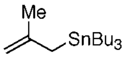
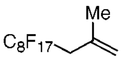
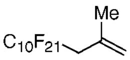
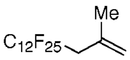
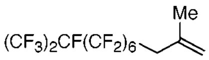
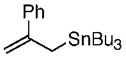
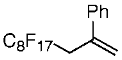
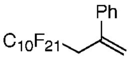
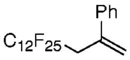
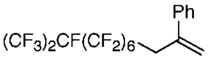
[8] FC-72 is a mixture of perfluorohexanes. BTF is benzotrifluoride: $C_6H_5CF_3$.

[9] R_f is the chromatographic retention factor, and Rf is a perfluoroalkyl group.

[10] R_f values in 100% hexane were variable, possibly due to the water content of the silica gel. However, the relative polarities were not variable.

Table 1. Preparation of 3-(Perfluoroalkyl)prop-1-enes by Reverse Fluorous Solid Phase Extraction



RfI allyl stannane	$C_8F_{17}I$	$C_{10}F_{21}I$	$C_{12}F_{25}I$	$(CF_3)_2CF(CF_2)_6I$
 (1 mmol scale)	 **2a**, 82%	 **2b**, 97%	 **2c**, 89%	 **2d**, 86%
 (1 mmol scale)	 **3a**, 69%	 **3b**, 89%	 **3c**, 75%	 **3d**, 84%
 (0.4 mmol scale)	 **4a**, 93%	 **4b**, 90%	 **4c**, 90%	 **4d**, 86%

allylated products (fluorous) were separated from the tin residues (organic) by standard fluorous spe. We conducted a similar set of reactions with purification by reverse fluorous spe, and the results of 12 experiments are summarized in Table 1. A mixture of a perfluoroalkyl iodide (RfI, 0.5 mmol), excess allylstannane (1.0 mmol), and AIBN (10 mol %) in hexane was heated at reflux for 5 h.[12] The reaction mixture was cooled, concentrated, and charged to a column containing 6 g of standard silica gel. The column was eluted with 20 mL of 2/1 FC-72/ether, and the solvent was evaporated to provide the allylated products **2a**−**d**, **3a**−**d**, and **4a**−**d** in yields ranging from 69 to 97%. The NMR spectra of these products were clean, and GC or HPLC purities exceeded 90% in all cases.[13]

To show that reverse fspe can be used to clean up multistep sequences, we conducted the sequence of allylation and nitrile oxide cycloaddition shown in Figure 4. Five iodides were allylated as above, and the crude products were directly subjected to nitrile oxide cycloaddition under oxidative conditions[14] with excess benzaldehyde oxime. TLC of the crude products using standard organic solvents showed multiple spots and was suggestive of difficult chromatographic purifications. In contrast, TLC experiments with 2/1 FC-72/ether showed only a single spot ($R_f \sim 0.2$) above the origin. Reverse fluorous spe provided clean isoxazolines **5a**−**e** in 48−68% yield.

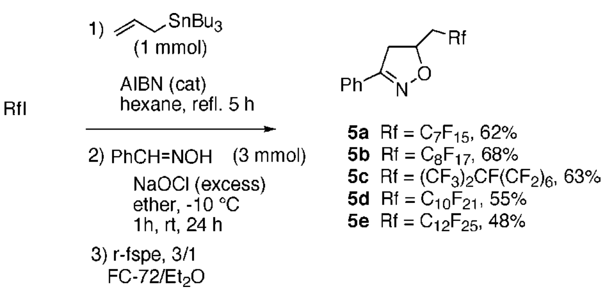


Figure 4. Two-step reaction with reverse fluorous spe purification.

The TLC experiments in Figure 3 suggest that reverse fluorous spe should be useful for removing triphenylphosphine and its derived oxide from fluorous compounds. To show this, we reacted limiting amounts of four fluorous alcohols **6a**−**d** (0. 5 mmol) with excess (0.75 mmol) butyric acid, triphenyl phosphine, and aldrichthiol-2 (2,2-dipyridyl disulfide).[15] Reaction for 24 h in refluxing benzene, followed by cooling and reverse fluorous spe, provided the products

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(11) Ryu, I.; Kreimerman, S.; Niguma, T.; Minakata, S.; Komatsu, M.; Luo, Z.; Curran, D. P. *Tetrahedron Lett.* **2001**, *42*, 947−950.

(12) **Typical Procedure for Reverse Fluorous Spe in Table 1.** Perfluorodecyl iodide (323 mg, 0.5 mmol), allyltributyltin (330 mg, 1 mmol), AIBN (9 mg, 0.05 mmol), and hexane (5 mL) were placed in a flask under an argon atmosphere, and the mixture was refluxed for 5 h. After removal of the volatile components by evaporation, the mixture was submitted to separation by reverse fluorous spe. A short column was packed with regular silica gel (6.0 g) using FC-72/Et_2O (2/1) as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 20 mL of FC-72/Et_2O (2/1) to give 3-(perfluorodecyl)prop-1-ene in 97% yield (271 mg).

(13) Purity of the products was determined by GC in the case of R = H or R = Me and HPLC (Nova Pak Silica, UV detection at 254 nm) in the case of R = Ph.

(14) Naji, N.; Soufiaoui, M.; Moreau, P. *J. Fluorine Chem.* **1996**, *79*, 179−183.

(15) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, *22*, 1901−1904.

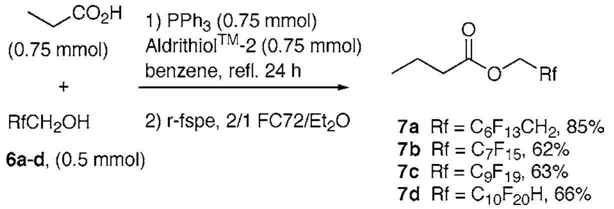

Figure 5. Separation of fluorous esters from triphenylphosphine, triphenylphosphine oxide, and other coupling products.

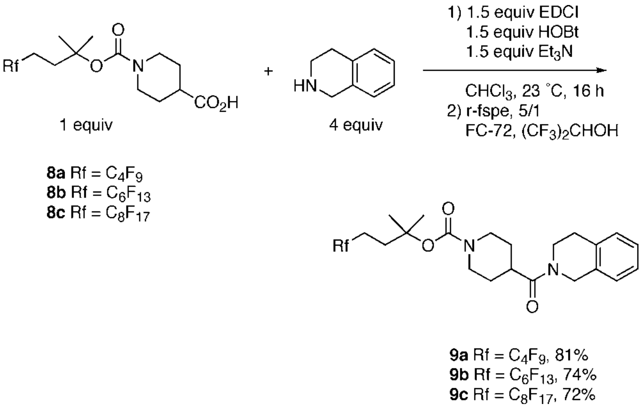

Figure 6. Isolation of F-Boc amides by using reverse fluorous spe.

7a−d in 62−85% yield, free from reagents and reagent-derived byproducts (Figure 5).

Finally, we applied the reverse fluorous spe procedure to a standard amide coupling reaction of isonipecotic acid protected on nitrogen with three different fluorous Boc groups.[16,17] Couplings of **8a−c** (0.06 mmol) with excess tetrahydroisoquinoline (0.24 mmol) were effected under standard conditions with EDCI, HOBt, and Et_3N in $CHCl_3$ (1 mL). The mixtures were partially concentrated and charged to 1 g of silica gel. Elution with 5 mL of FC-72/hexafluoro-2-propanol (5/1) provided products **9a−c** in 72−81% yield with HPLC purities of 93−96%.[18] Unreacted or spent reagent and reactant byproducts were not evident in the ^1H NMR spectra of any of these products. The satisfactory result with the substrate **8a** bearing the small C_4F_9 fluorous tag is especially noteworthy because these tags are normally considered to be too small for reliable separations by standard fluorous spe. The relative polarities of the reagents and reactants likely contribute to the success of this separation.

In summary, we have introduced the new technique of reverse fluorous solid-phase extraction for separating fluorous-tagged molecules from organic molecules. The technique uses inexpensive silica gel along with fluorous solvents that are routinely recovered and recycled.[19] Several useful solvent conditions have been identified, and these and others can readily be evaluated by simple TLC experiments. Because the fluorous products elute first, the method is especially useful when the fluorous products are the target of a given reaction. This is the case in fluorous tagging methods (such as in Figure 6) and in the synthesis of highly fluorinated molecules (such as in Table 1). The separation in the reverse fluorous solid-phase extraction can be augmented by choosing organic components that are polar, since these are naturally better retained on silica gel, and by choosing fluorous compounds that are nonpolar. Extensions to flash chromatographic and HPLC separations are readily envisioned.

Acknowledgment. The idea for reverse fluorous solid-phase extractions emerged from a conversation with Dr. Marvin Yu of Fluorous Technologies, Inc. We thank the National Institutes of Health for funding this work. We also thank Asahi Glass Co., Ltd. (hexafluoro-2-propanol), 3M (C_4F_9OEt), and Fuji Silisia Co. (base-coated TLC plates) for important samples.

Supporting Information Available: Procedures for reactions and spe purifications along with spectroscopic data for products and copies of NMR spectra of typical products after spe. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Luo, Z.; Williams, J.; Read, R. W.; Curran, D. P. *J. Org. Chem.* **2001**, *66*, 4261−4266.

[17] Tabuchi, S.; Itani, H.; Sakata, Y.; Oohashi, H.; Satoh, Y. *Biol. Med. Chem. Lett.* **2002**, *12*, 1171−1175.

[18] Purity of the products was determined by HPLC (Nova Pak Silica) with UV detection at 254 nm.

[19] Other readily available fluorous solvents can be used in place of FC-72; see ref 2c. FC-72 can be recovered from FC-72/ether mixtures by simple distillation; the fraction boiling at 54−57 °C was collected and reused.