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Amide Bond Formation with a New Fluorous Carbodiimide: Separation by Reverse Fluorous Solid-Phase Extraction

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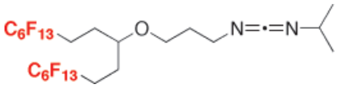
ABSTRACT



Fluorous carbodiimide for amide bond formation with separation by reverse fluorous solid phase extraction

A new fluorous carbodiimide is introduced along with a convenient procedure for amide coupling reactions. Reactions of acids and amines under standard conditions for carbodiimide couplings, followed by simple reverse fluorous solid-phase extraction (FSPE) over standard silica gel, provide the target amide products in good yields and purities. The use of HFE-7100 as a fluorous solvent is crucial for the success of the reverse FSPE.

Fluorous solid-phase extraction (FSPE) is an increasingly popular technique for the separation of reaction mixtures containing organic components and fluorous components.[1,2] In the standard method, a mixture is charged to fluorous silica gel, and the column is eluted with a fluorophobic solvent in a first pass to give an organic fraction, followed by a fluorophilic solvent in a second pass to give a fluorous fraction. Fluorophobic solvents are polar ones, such as methanol, acetonitrile, DMF, DMSO, and especially water.

Recognizing that the key to separation in standard fluorous solid-phase extraction is the combination of a fluorous solid phase with a polar liquid phase, we reversed the process (Figure 1); the technique of reverse fluorous solid-phase extraction combines a polar solid phase with a fluorous liquid phase.[3] The technique is attractive because the polar solid phase is simply standard silica gel. However, the application of reverse FSPE is currently limited because perfluorocarbons such as FC-72 (perfluorohexanes) are used as the key fluorous liquid component.[4]

Though not toxic compared to organic solvents, perfluorocarbons are expensive and environmentally persistent. Their extraordinary nonpolarity also poses problems in the common occurrence where the fluorous reaction components

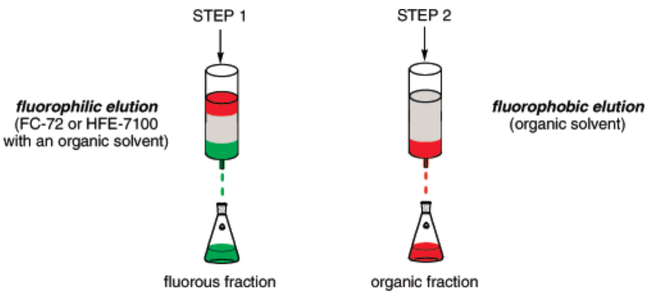


Figure 1. Reverse fluorous solid-phase extraction over standard silica gel (SiO_2).

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(1) Introduction: Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714−6715.

(2) Reviews: (a) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837−11865. (b) Curran, D. P. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 101−127. (c) Curran, D. P. *Synlett* **2001**, 1488−1496.

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are somewhat polar. This limitation can be overcome in principle by blending FC-72 with organic solvents. But FC-72 is not miscible with most organic solvents, so the range of solvent blends that can be used for reverse FSPE is limited.

We sought to expand the reverse FSPE technique by replacing the nonpolar perfluorocarbons with more polar hydrofluoroethers (HFEs, RfOR).[5,6] Solvents such as HFE-7100 (perfluorobutyl methyl ether, $C_4F_9OCH_3$)[7] are less expensive than perfluorocarbons and are much less persistent. Compared to organic solvents, they are still relatively safe.[8] Most importantly, from the performance standpoint they are more polar and are more readily blended with organic solvents. Accordingly, they have the potential to significantly increase the range of applications of reverse FSPE.

To probe the usefulness of HFE-7100 in reverse FSPE, we synthesized new fluorous carbodiimides (FCDIs) and investigated their use in amide coupling reactions. Among the many reagents for amide coupling, carbodiimides have shown enduring popularity because of their broad scope and ease of use.[9] Separation of the derived urea byproducts is often problematic, and many solutions have been offered.[10] Ureas are polar and often streak on silica. Accordingly, the separation of an inherently polar fluorous urea from an amide reaction product is a challenging process because the purpose of the fluorous tag is to move the urea more rapidly off the column in a reverse FSPE.

Palomo and colleagues described several fluorous carbodiimides and introduced a protocol for separation based on liquid−liquid extraction with FC-72.[11] Strong fluorous acids were used to help draw the otherwise poorly soluble fluorous ureas into FC-72. In preliminary experiments with several fluorous carbodiimides and ureas, we encountered problems of solubility and gelling. To investigate these problems, we prepared the four new fluorous carbodiimides shown in Figure 2 and briefly investigated their properties. Carbodiimides **1a** and **1b** were soluble in dichloromethane (a common solvent for carbodiimide reactions), but their derived ureas gelled the reaction mixtures. These gelating properties might be interesting in other settings, but they are not very attractive for SPE because concentrated reaction mixtures cannot be pipetted or even poured; they can only be diluted. The urea derived from **1c** did not gel dichloromethane, but **1c** itself was unattractive because it was not very soluble in dichloromethane.

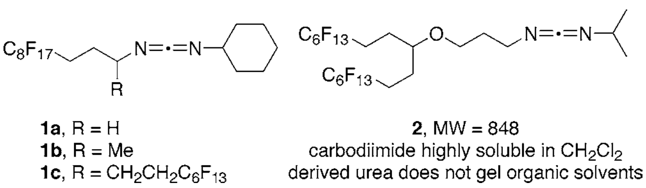
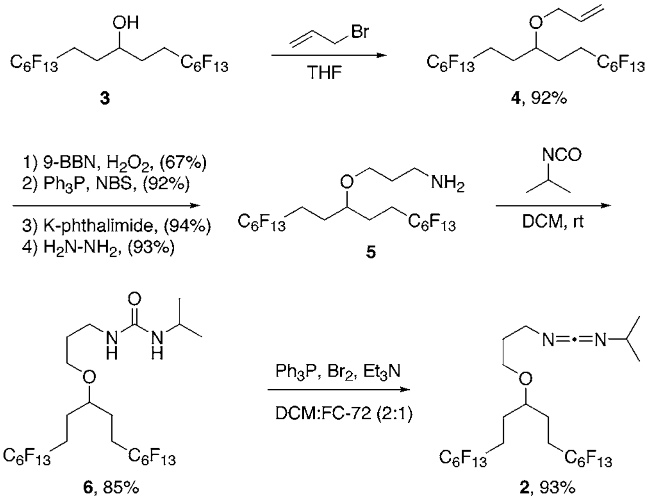


Figure 2. Fluorous carbodiimides prepared for preliminary solubility studies.

In contrast, carbodiimide **2** was soluble in dichloromethane and other common solvents, and its derived urea **6** did not gel (or even precipitate from) dichloromethane. Carbodiimide **2** is made starting from readily available alcohol **3** by the straightforward sequences of steps shown in Scheme 1 (see Supporting Information for details). *O*-Allylation provides **4**, which is converted to **5** by a sequence of hydroboration and oxidation to give an alcohol, bromination, and then

Scheme 1. Synthesis of Urea **6** and Carbodiimide **2**



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(3) Matsugi, M.; Curran, D. P. *Org. Lett.* **2004**, *6*, 2717−2720.

(4) (a) Gladysz, J. A.; Emnet, C. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 11−23. (b) Ryu, I.; Matsubara, H.; Emnet, C.; Gladysz, J. A.; Takeuchi, S.; Nakamura, Y.; Curran, D. P. In *Green Reaction Media in Organic Synthesis*; Blackwell: Ames, IO, 2005; pp 59−124.

(5) Examples of applications of HFEs as reaction solvents: (a) Mizuno, M.; Goto, K.; Miura, T.; Matsuura, T.; Inazu, T. *Tetrahedron Lett.* **2004**, *45*, 3425−3428. (b) Fukuyama, T.; Arai, M.; Matsubara, H.; Ryu, I. *J. Org. Chem.* **2004**, *69*, 8105−8107.

(6) Examples of applications of HFEs as liquid−liquid extraction solvents: Yu, M. S.; Curran, D. P.; Nagashima, T. *Org. Lett.* **2005**, *7*, 3677−3680. (b) Curran, D. P.; Bajpai, R.; Sanger, E. *Adv. Synth. Catal.* **2006**, *348*, 1621−1624. (c) Chu, Q.; Yu, M.; Curran, D. P. *Tetrahedron* **2007**, in press.

(7) (a) HFE solvents are produced by 3M under the tradename Novec: http://www.3m.com/Product/information/Novec-Engineered-Fluid.html. Most solvents are mixtures of isomers. For example, HFE-7100 is a mixture of perfluorobutyl methyl ether and perfluoroisobutyl methyl ether (*n*- and isobutyl groups). HFE-7100 is also available from Sigma-Aldrich. (b) DPC owns an equity interest in Fluorous Technologies, Inc.

(8) (a) Wallington, T. J.; Nielsen, O. J. In *Handbook of Environmental Chemistry: Organofluorines*; Neilson, A. H., Ed.; Springer-Verlag: Berlin, 2002; Vol. 3, pp 85−102. (b) Most HFEs are not classified as a volatile organic compound (VOC) and are approved for use under the US EPA Significant New Alternatives Program (SNAP): http://www.epa.gov/ozone/snap/regulations.html.

(9) (a) Podlech, J. In *Houben-Weyl Methods of Organic Chemistry. Synthesis of Peptides and Peptidomimetics*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme-Verlag: Stuttgart, 2001; Vol. E22a, pp 517−533. (b) *Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: New York, 2005.

(10) For examples, see: (a) Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721−4724. (b) Lannuzel, M.; Lamothe, M.; Perez, M. *Tetrahedron Lett.* **2001**, *42*, 6703−6705. (c) Jamieson, C.; Congreve, M. S.; Emiabata-Smith, D.; Ley, S. V. *Synlett* **2000**, 1603−1607.

(11) (a) Palomo, C.; Aizpurua, J. M.; Loinaz, I.; Fernandez-Berridi, M. J.; Irusta, L. *Org. Lett.* **2001**, *3*, 2361−2364. (b) Aizpurua, J. M.; Palomo, C.; Loinaz, I. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 459−461.

Gabriel synthesis. Reaction of amine **5** with isopropylisocyanate provides urea **6**.

Fluorous urea **6** was conveniently transformed to FCDI **2** in a biphasic reaction by taking advantage of the insolubility of F-26 urea **6** in FC-72. The urea was first dissolved in CH_2Cl_2, and FC-72 was added, resulting in two phases. Triphenylphosphine (3 equiv), bromine (3 equiv), and triethylamine (5 equiv) were added, and the reaction mixture was stirred vigorously until it was dark red. FCDI **2** was the only reaction component soluble in FC-72, so the FC-72 layer was separated and concentrated. The residue was filtered through celite to afford the pure carbodiimide **2** as a faint yellow oil in 93% yield.

Potential solvent systems for the reverse FSPE procedure were evaluated in a series of TLC experiments on standard silica TLC plates by using fluorous urea **6** and amide **7** as a model reaction mixture. These experiments are described in the thesis of A. Keller,[12] and two of the more informative ones are illustrated in Figure 3.

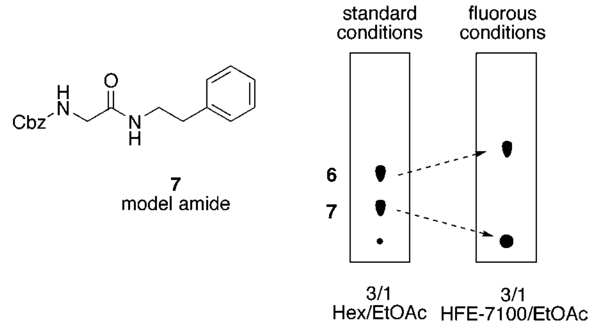

Figure 3. Standard silica gel TLC experiments with fluorous urea **6** and model amide **7**.

Elution of the model mixture with a standard 3:1 blend of hexane/ethyl acetate showed the urea spot at R_f 0.38 and the amide at 0.21. Replacing the hexane with HFE-7100 increased the R_f of the urea spot to 0.54 while at the same time planting the amide spot on the baseline. These contrasting effects can be attributed to the fluorous nature of HFE-7100, which promotes the mobility of **6** and retards that of **7**. The same effect cannot be generated by FC-72 because it cannot be mixed with ethyl acetate to provide a suitable solvent blend due to immiscibility.

Following some preliminary development experiments,[12] a small library of 15 amides was made by coupling acids **8** and amines **9** with FCDI **2** followed by reverse FSPE and direct analysis of the crude product for fluorous content by ^{19}F or ^{1}H NMR. The acids **8a**−**e** and amines **9a**−**e** used are shown in Figure 4, and the results of the couplings are summarized in Table 1.

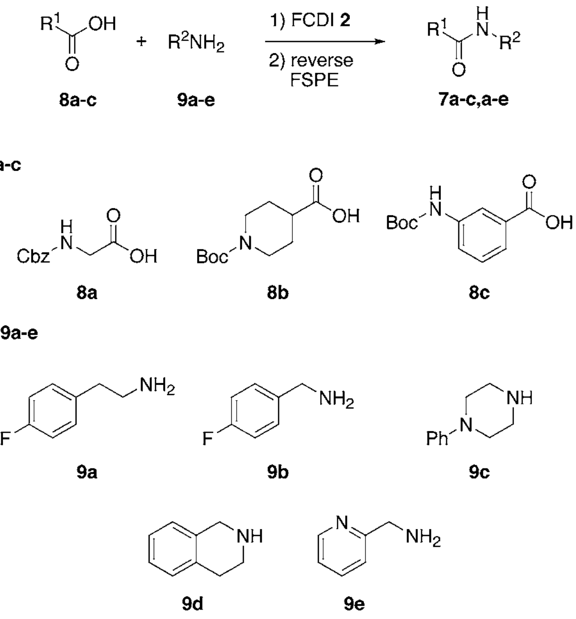

Figure 4. Acid **8** and amine **9** components in the amide coupling reactions.

In the standard procedure, the amine **9** (0.12 mmol) was added to FCDI **2** (0.14 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was cooled to 0 °C under argon. After 15 min, the carboxylic acid **8** (0.11 mmol) was added and the mixture was warmed to rt and, 3 h later, concentrated to dryness. The crude product was dissolved in a small amount of THF (0.4 mL) and loaded onto a 2 g SiO_2 cartridge. Initial washing with HFE-7100/EtOAc (3:1) provided a fluorous fraction,[13] and subsequent elution with EtOAc provided a product fraction, which was concentrated and analyzed.

With a few exceptions, the yields of products **7** were above 70% and the purities were 95% or better. Some of the trace

Table 1. Crude Yields and Purities of Amides from FCDI Coupling Followed by Reverse FSPE[a]

entry	acid **8**	amine **9**	amide **7**	yield (%)	purity (%)
1	**a**	**a**	**aa**	87	95^b
2	**a**	**b**	**ab**	71	99^b
3	**a**	**c**	**ac**	86	95^c
4	**a**	**d**	**ad**	58	95^c
5	**a**	**e**	**ae**	87	99^c
6	**b**	**a**	**ba**	86	98^b
7	**b**	**b**	**bb**	73	98^b
8	**b**	**c**	**bc**	73	95^c
9	**b**	**d**	**bd**	61	95^c
10	**b**	**e**	**be**	70	99^c
11	**c**	**a**	**ca**	68 (57)	85^b $(99)^{b,d}$
12	**c**	**b**	**cb**	62 (45)	80^b $(96)^{b,d}$
13	**c**	**c**	**cc**	75	97^c
14	**c**	**d**	**cd**	57	95^c
15	**c**	**e**	**ce**	74	97^c

[a] Procedure: FCDI and amine were dissolved in DCM (2 mL) under argon at 0 °C. Acid was added, and the mixture was stirred at rt for 3 h. [b] By ^{19}F NMR. [c] By ^{1}H NMR. [d] After flash chromatography.

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(12) Keller, A., Ph.D. Thesis, University of Pittsburgh, 2007. The thesis is archived and openly available from the University of Pittsburgh Library Electronic Thesis Deposition (ETD) site at http://etd.library.pitt.edu/ETD/available/etd-04122007-142347/.

impurities were fluorous as ascertained by ^1H or ^{19}F NMR, and these typically consist of small amounts of the urea, although the presence of other products cannot be ruled out (see below). Even better purities can be obtained by conducting the separation chromatographically (collecting and analyzing fractions); however, the purpose of these experiments was to assess the scope of a fixed SPE procedure across a range of substrates. For this purpose, the general procedure worked well.

Somewhat lower yields were obtained in the reactions involving tetrahydroisoquinoline **9d** as the amine component (entries 4, 9, and 14), but the purities of the products were still very good. However, coupling of acid **8c** with amines **9a** and **9b** gave products in only 85% and 80% purity, respectively. These products are unique by TLC analysis in that they are considerably less polar than the other amide products; presumably they are too close to the fluorous region for adequate SPE separation. The partially pure products were further purified by standard flash chromatography (with fraction collection and TLC analysis) in 3:1 HFE-7100/EtOAc to provide the amide **9a** (57% yield, 99% pure) and **9a**,**b** (45% yield, 96% pure).

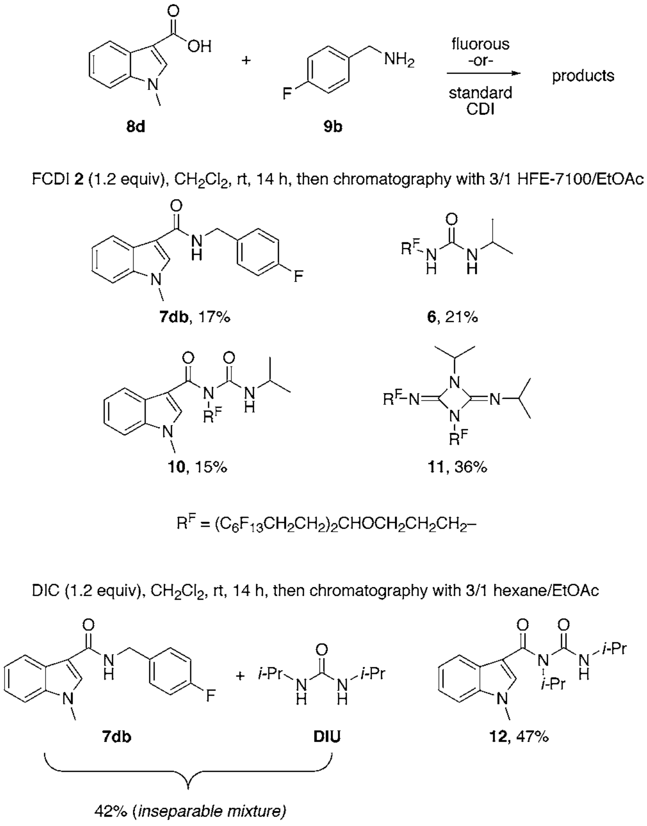
More difficult amide coupling reactions than those shown in Table 1 are not expected to proceed in near-quantitative yields, and accordingly, crude mixtures will contain other byproducts derived from the carbodiimide besides the urea. *N*-Methylindole-3-carboxylic acid **8d** is known to be a recalcitrant participant in carbodiimide-mediated amide coupling reactions,[10a] so we investigated the coupling of this acid with fluorous carbodiimide **2** and diisopropylcarbodiimide (DIC) under conditions where high yields of amide product were not expected. The crude mixtures were purified by flash chromatography with HFE-7100/EtOAc or hexane/ethyl acetate. The results of these experiments are summarized in Scheme 2.

The crude mixture from the fluorous reaction showed four clear spots on TLC. The most polar spot was the target product **7db**, which was isolated in pure form in 17% yield. The other spots, in reverse order of elution, where identified as the fluorous urea **6** (21%), the *N*-acyl urea **10** (15%), and the carbodiimide dimer **11** (36%). The *N*-acyl urea resulting from an *O*- to *N*-acyl shift is a well-known dead end product in carbodiimide couplings, and carbodiimide dimers have also been observed.[14]

In contrast, the reaction mixture with standard DIC showed only two spots on TLC, one of which proved to be the *N*-acyl urea **12** (47%), while the other was a mixture of amide **7db** and diisopropyl urea (DIU).

These results show the potential options for manipulation of the retention times of urea byproducts by using fluorous solvents. In the case at hand, the standard urea DIU and the target product coincidentally have about the same R_f, but the side products from the fluorous reaction are easily separated from **7db**. It is unlikely that amide products could also coincidentally have about the same R_f as the fluorous urea or another fluorous byproduct. However, if this occurs, then separation can probably be established by changing the fluorous solvent of the elution mixture to an organic one, thereby significantly changing the relative retention factors of the fluorous compared to nonfluorous components.

Scheme 2. Separation in a Difficult Coupling Reaction



In summary, a new fluorous carbodiimide **2** has been introduced, and a general procedure for amide coupling reactions has been deployed. Reactions of acids and amines under standard conditions for carbodiimide couplings, followed by simple reverse fluorous solid-phase extraction over standard silica gel, provide the target amide products in good yields and purities. The use of HFE-7100 as a fluorous solvent is crucial for the success of the FSPE. The results suggest that HFE-7100 and related solvents have excellent potential to modulate relative retention factors of organic and fluorous components in both solid-phase extraction and chromatographic applications.

Acknowledgment. We thank the National Institute of General Medical Science of the National Institutes of Health for funding (P50GM067082 and R44GM067326). C.P. thanks the Ministerio de Educación y Ciencia of Spain for a Ramón y Cajal contract.

Supporting Information Available: Experimental procedures for reagent synthesis and amide coupling along with representative spectra of the products following reverse FSPE. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The fluorous urea can be recovered in about 80% (after purification) for reuse.

(14) Hartke, K.; Rossbach, F. *Angew. Chem., Int. Ed.* **1968**, *7*, 72−74.