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Fluorous Synthesis of Hydantoins and Thiohydantoins

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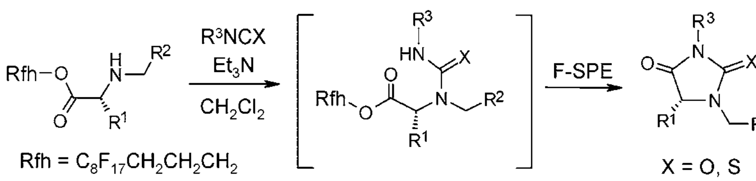
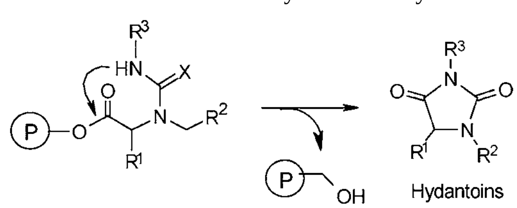
ABSTRACT



A fluorous synthesis of hydantoins is introduced. The reaction of perfluoroalkyl (Rfh)-tagged amino esters with an isocyanate is followed by the cyclization of ureas and simultaneous cleavage of the fluorous tag to afford hydantoins. The product purification is performed by solid-phase extraction over Fluoro*Flash* cartridges, and no fluorous solvent is involved in either the reaction or the separation processes. The same method applies to synthesis of thiohydantoins.

Hydantoins and their bi- and tricyclic derivatives represent an important class of biologically active molecules that have broad medicinal[1] (anticancer, anticovulsant, antimuscarinic, antiulcer, and antiarrythmic) and agrochemical[2] (herbicidal and fungicidal) applications. Numerous hydantoin synthesis, both in the solution phase[3] and on solid supports,[4] have been reported in the literature. One of the first examples of cyclization-assisted cleavage of polymer support was developed in the synthesis of hydantoins (Scheme 1).[5] The cyclization−cleavage strategy combines linker cleavage and ring formation in a single reaction step.[6]

Scheme 1. Solid-Phase Synthesis of Hydantoins



Fluorous synthesis is a complementary type of liquid-phase synthesis that has the character of solution-phase reactivity and a solid-phase type of separation.[7] Fluorous synthesis is

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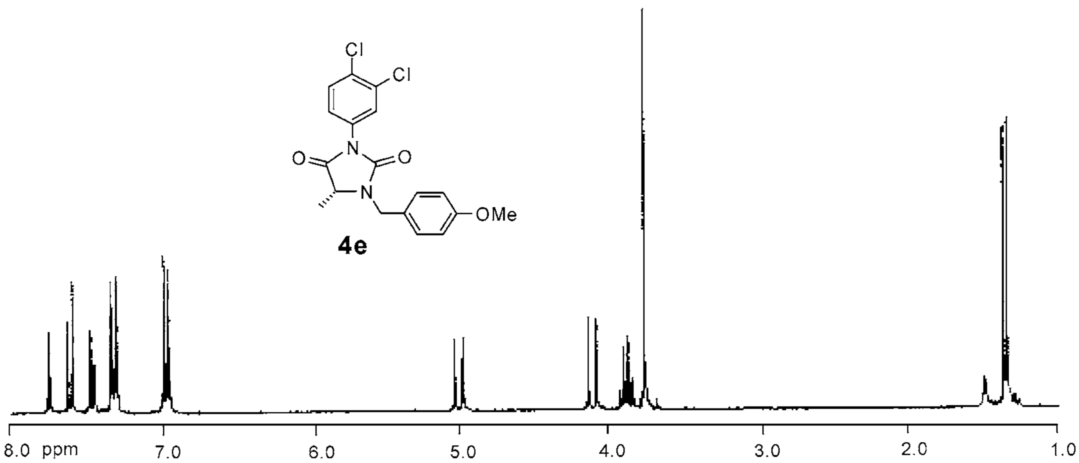
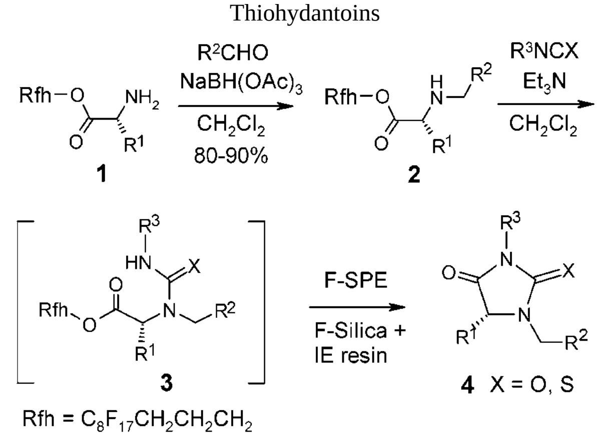


Figure 1. ^{1}H NMR ($CDCl_3$) spectrum of product **4e** after F-SPE.

similar to solid-phase synthesis in terms of tag strategy, but very different in practice. In fluorous synthesis, perfluoroalkyl chains (Rfh) are used as the phase-tag to facilitate the separation. Reactions can be conducted in organic solvents under a homogeneous environment with favorable reaction kinetics. The capability of monitoring the reaction process by HPLC, MS, and NMR is another major advantage. The separation of fluorous reaction mixtures can be achieved by solid-phase extraction (SPE) or HPLC over Fluoro*Flash* silica gel.[8] Applications of fluorous reagents,[9] scavengers,[10] protecting groups,[11] and tags[12] in parallel and mixture synthesis[13] have been reported in the literature. Described in this paper is a new method for the synthesis of hydantoins by the combination of the cylization−cleavage reaction and F-SPE separation. A similar fluorous tag cleavage strategy has been employed by the Wipf group in the synthesis of dihydropyridazinones[14a] and by the Bannwarth group in the synthesis of quinazoline-2,4-diones.[14b] In both cases, the products were purified by fluorous liquid−liquid extraction.

The fluorous synthesis of hydantoins is outlined in Scheme 2. Fluorous (L)-α-amino esters **1** (1.0 equiv) were subjected to reductive amination with aldehydes (1.1 equiv) under the standard solution-phase conditions.[15] Purification of intermediate **2** was conducted by SPE over Fluoro*Flash* cartridges.[16,17] The non-fluorous byproducts and unreacted aldehyde were collected in the first fraction of 80:20 MeOH/H_2O, while the fluorous product were collected in the second fraction of 100% MeOH. Intermediates **2** (1.1 equiv) were reacted with isocyanates (1.0 equiv) in the presence of triethylamine as a base to promote the cyclization. The resulting ureas **3** underwent spontaneous cyclization to displace the fluorous tag and form the hydantoin ring. The hydantoin products **4** were purified over the modified Fluoro*Flash* cartridge charged with fluorous silica gel and weak acidic ion-exchange resin (Amberlite G-50).[12,18] The nonfluorous final product was collected in the first fraction of 80:20 MeOH/H_2O. The cleaved fluorous species, unreacted fluorous amine **2**, and urea **3** (if any) were retained by the fluorous silica gel. Triethylamine and the salt were retained by the ion-exchange resin. A typical ^{1}H NMR spectrum of the final product after F-SPE is shown in Figure 1. To achieve the best SPE separation results, fluorous amino ester **1** was the limiting reagent for the first reaction so that amine **2** is the only fluorous compound in the reaction mixture, while the isocyanate was the limiting reagent for the second reaction to prevent contamination of the final products from the unreacted isocyanate.

Scheme 2. Fluorous Synthesis of Hydantoins and Thiohydantoins



The reaction scope of fluorous synthesis was demonstrated by the preparation of 10 hydantoins and thiohydantoins with a three-point diversity backbone by using three amino esters

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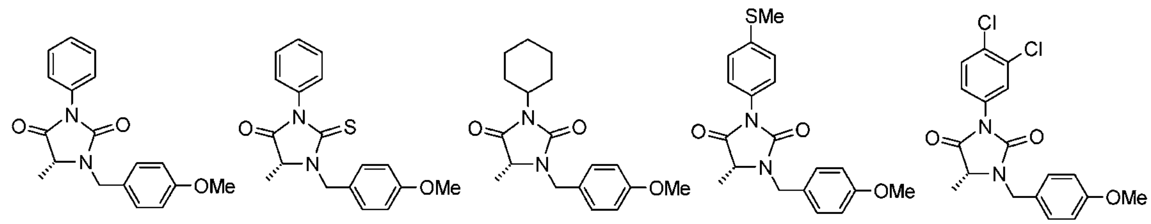
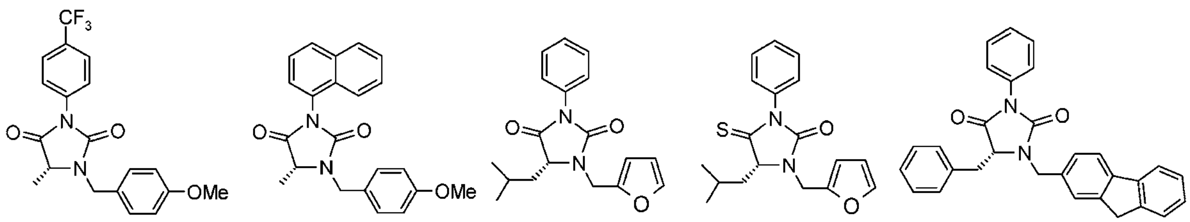
Table 1. Structures, Yields (Purities) of Hyantoins and Thiohydantoins



4a 98% (95%) **4b** 94% (95%) **4c** 89% (89%) **4d** 96% (95%) **4e** 98% (95%)

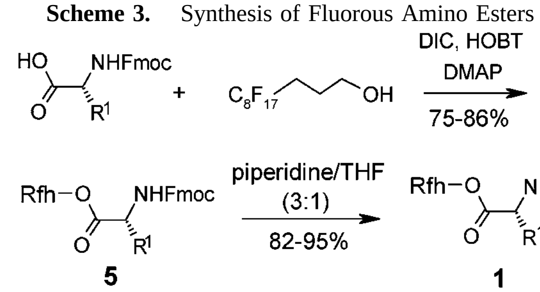


4f 95% (95%) **4g** 93% (95%) two diastereomers (1:1) **4h** 90% (95%) **4i** 46% (95%) **4j** 60% (90%)

(R^1 = Me, *i*-Pr, and benzyl), three kinds of aromatic aldehydes (R^2 = phenyl, 2-furanyl, and 2-fluorenyl), and three kinds of isocyanates (R^3 = phenyl, 1-naphthyl, and cyclohexyl).[19] Structures, yields, and purities of the final products are listed in Table 1. Yields for the last step were in the range of 46–98% (on the basis of the isocyanate). Most products have ^{1}H NMR purities greater than 90%. Because the naphthyl group restricted the free rotation of the C–N bond, product **4g** is axially chiral.[20] It was detected as a 1:1 diastereomeric mixture by ^{1}H NMR at room temperature.

The starting fluorous amino esters were readily prepared by coupling of Fmoc- or Boc-protected amino acids with a fluorous alcohol containing a C_8F_{17} chain (Scheme 3).[17] The perfluoroalkyl moiety is separated from the hydroxyl group by a propylene spacer to minimize the electronic effect of the fluorous tag. Deprotection of Fmoc or Boc provided fluorous amino esters **1**. Both reaction steps were carried out under traditional solution-phase conditions. Compounds **5** and **1** can be purified by F-SPE or flash column chromatography with normal silica gel. The fluorous amino acid derivatives have potential utility in the construction of a broad range of small molecules as well as peptides. The preparation

Scheme 3. Synthesis of Fluorous Amino Esters



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(15) **General Procedure for Reductive Amination.** To a solution of fluorous amino ester **1** (1.2 mmol) and an aldehyde (1.3 mmol) in 10 mL of CH_2Cl_2 was added $NaBH(OAc)_3$ (1.8 mmol). After being stirred at 25 °C for 2 h, the reaction mixture was extracted with EtOAc and washed with aqueous $NaHCO_3$. The concentrated organic layer was loaded onto a Fluoro*Flash* cartridge containing 10 g of fluorous silica gel. The cartridge was eluted with 20 mL of 80:20 MeOH/H_2O followed by 20 mL of MeOH. The MeOH fraction was concentrated to give desired product **2** in 80–90% yields.

(16) For more information about F-SPE, see: Fluourous Technologies, Inc. http://fluorous.com/download/fspe.pdf.

(17) Fluoro*Flash* cartridges and $C_8F_{17}CH_2CH_2CH_2OH$ are available from Fluourous Technologies, Inc.: www.fluorous.com.

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(19) **General Procedure for the Preparation of Hydantoins by the Cyclization Cleavage of the Fluorous Tag.** To a solution of **2** (R^1 = Me, R^2 = *p*-MeOPh, 31 mg, 0.046 mmol) and isocyanate **3** (R^3 = Ph, 4.6 μL, 0.042 mmol) in 0.3 mL of CH_2Cl_2 was added Et_3N (6.0 μL, 0.043 mmol) at 25 °C. After the mixture was stirred at this temperature for 2 h, the reaction was complete as monitored by GC. The reaction mixture was directly loaded onto a Fluorou*Flash* cartridge containing 5 g of fluorous silica gel and 100 mg of Amberlite G-50 ion-exchange resin. The cartridge was eluted with 10–15 mL of 80:20 MeOH/H_2O. The fraction was collected and concentrated to give 12.7 mg of hydantion **4a**: ^{1}H NMR ($CDCl_3$) δ 1.48 (d, J = 6.9 Hz, 3H), 3.83 (s, 3H), 3.94 (q, J = 6.9 Hz, 1H), 4.17 (d, J = 15.3 Hz, 1H), 5.04 (d, J = 15.3 Hz, 1H), 6.92 (d, J = 6.7 Hz, 2H), 7.20–7.55 (7H); ^{13}C NMR ($CDCl_3$) δ 15.4, 44.2, 54.5, 55.4, 114.4 (2C), 126.0 (2C), 127.6, 128.1, 129.0 (2C), 129.7 (2C), 131.8, 155.1, 159.5, 172.5. LRMS (APCI) 310.9 (M^+ + H).

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of fluorous Cbz-protected amino acids and their synthetic application have been recently reported by the Curran group.[21]

In short, we have demonstrated the synthetic utility of the fluorous amino esters in the construction of hydantoin and thiohydantoin ring systems. This method can be applied to solution-phase synthesis of related compound libraries.

Acknowledgment. We thank the National Institutes of General Medical Sciences for the SBIR funding (1R43GM066415-01).

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