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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 fluorine tag to afford hydantoins. The product purification is performed by solid-phase extraction over FluoroFlash cartridges, no fluorine 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 which have broad medicinal¹ (anticancer, anticonvulsant, antimuscarinic, antiulcer, and antiarrhythmic) and agrochemical² (herbicidal and fungicidal) applications. Numerous hydantoin synthesis, both in solution phase³ 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

Fluorous synthesis is a complementary type of liquid-phase synthesis that has the character of solution-phase reactivity and solid-phase type of separation.⁷ Fluorous synthesis is 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 FluoroFlash silica gel.⁸ Applications of fluorous reagents,⁹ scavengers,¹⁰ protecting groups,¹¹ and tags¹² in parallel and mixture synthesis¹³ have been reported in the literature. Described in this paper is a new method for the synthesis of hydantoins by the combination of the cyclization-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

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solution-phase conditions.¹⁵ Purification of intermediate **2** was conducted by SPE over FluoroFlash cartridges.^{16,17} The fluorine product were collected in the second fraction of 100% MeOH. The non-fluorine byproducts and unreacted aldehyde were collected in the first fraction of 80:20 MeOH/H₂O. 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 fluorine tag and form the hydantoin ring. The hydantoin products **4** were purified over the modified FluoroFlash cartridge charged with fluorine silica gel and weak acidic ion-exchange resin (Amberlite G-50).^{12,18} The non-fluorine final product was collected in the first fraction of 80:20 MeOH/H₂O. The cleaved fluorine species, unreacted fluorine amine **2**, and urea **3** (if any) were retained by the fluorine silica gel. Triethylamine and the salt were retained by the ion-exchange resin. A typical ¹H NMR spectrum of the final product after F-SPE is shown in Figure 1. To achieve the best SPE separation results, fluorine amino ester **1** was the limiting reagent for the first reaction so that amine **2** is the only fluorine compound in the reaction mixture, while the isocyanate was the limiting reagent for the second reaction to prevent contamination of the final products by the unreacted isocyanate.

The reaction scope of fluorine synthesis was demonstrated by the preparation of 10 hydantoins and thiohydantoins with a three-point diversity backbone by using 3 amino esters (R¹ = Me, *i*-Pr, and benzyl), three kinds of aromatic aldehydes (R² = phenyl, 2-furanyl, and 2-fluorenyl), and three kinds of isocyanates (R³ = 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% (based on the isocyanate). Most products have ¹H 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.

The starting fluorine amino esters were readily prepared by coupling of Fmoc- or Boc-protected amino acids with a fluorine alcohol containing a C₈F₁₇ chain (Scheme 3).¹⁷ The perfluoroalkyl moiety is separated from the hydroxyl group by a propylene spacer to minimize the electronic effect of the fluorine tag. Deprotection of Fmoc or Boc provided fluorine 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 fluorine amino acid derivatives have potential utility in the construction of a broad range of small molecules as well as peptides. The preparation of fluorine 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 fluorine amino esters in the construction of hydantoin and thiohydantoin ring systems. This method can be applied to solution-phase synthesis of related compound libraries.

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

Figure 1.
Structures, yields (purities) of hyantoins and thiohydantoins

Scheme 1.
Solid-phase synthesis of hydantoins

Scheme 2.
Fluorous synthesis of hydantoins and thiohydantoins

Scheme 3.
Synthesis of fluorinated amino esters