



Preparation of acid-resistant heavy fluorous tags for recycling in synthetic systems



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ABSTRACT

Acid-resistant heavy fluorous tags, in which all three fluorous chains are tethered in a symmetric manner by carbon–carbon linkage, were designed and synthesized from ethyl crotonate. They were designed also to possess a reactive OH group at a central position, not only for conjugation with a target molecule but also for tag recycling. The tag with an alkyl spacer equipped the primary OH group had the greatest reactivity in conjugation reactions with target molecules and could be recovered in the highest yields, implying its potential for use in recycling applications.

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1. Introduction

Fluorous chemistry is based on the unique physicochemical properties of highly fluorinated compounds (heavy fluorous compounds): they are immiscible with the usual organic and inorganic solvents but can be selectively partitioned into fluorous solvents [1]. Techniques of fluorous liquid–liquid extraction (F-LLE) and fluorous-tag synthesis have thus emerged and are being evaluated in chemical studies in a wide range of fields, including catalytic chemistry, combinatorial chemistry, and green chemistry [2]. Synthesis using a heavy fluorous tag that enables reagent recycling [1b] is expected to provide us with an established synthetic methodology comparable to solid-phase synthesis of peptides or polynucleotides [3].

In fluorous-tag synthesis and recycling, a functional tag is required that can react with a targeting molecule, partition the fluorous conjugate into a fluorous phase, tolerate any chemical processes involved in fluorous synthesis, and be released from the final construct at a high recovery yield. Recycling use of fluorous tags is important not only for economic reasons but also from the perspective of green and environmental chemistry. To date, several types of heavy fluorous tags have been proposed in the literature [4]. Also, in our previous study, we reported a symmetric heavy fluorous tag **1** (Fig. 1), which has three perfluorooctyl chains and a

primary OH group [4o,p]. However, this tag was found to be decomposed when treated with strong Lewis acids such as BBr₃. In the present study, acid-resistant heavy fluorous tags were newly designed with the aim of establishing a general fluorous-tag synthetic methodology. We designed and prepared symmetric heavy fluorous tags **2** and **3** with all carbon–carbon connections and a reactive OH group in the central position. Verlhac et al. reported an analogous tag bearing two fluorous chains with C–C connections [5]. Our compounds **2** and **3**, bearing three perfluorooctyl chains, were expected to maintain the high partition and recovery efficiency of our preceding tag **1**. Here, we describe the synthesis of **2**, **3** and their derivatives, as well as their potential as acid-resistant heavy fluorous tags.

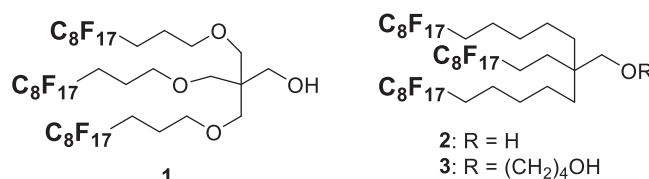


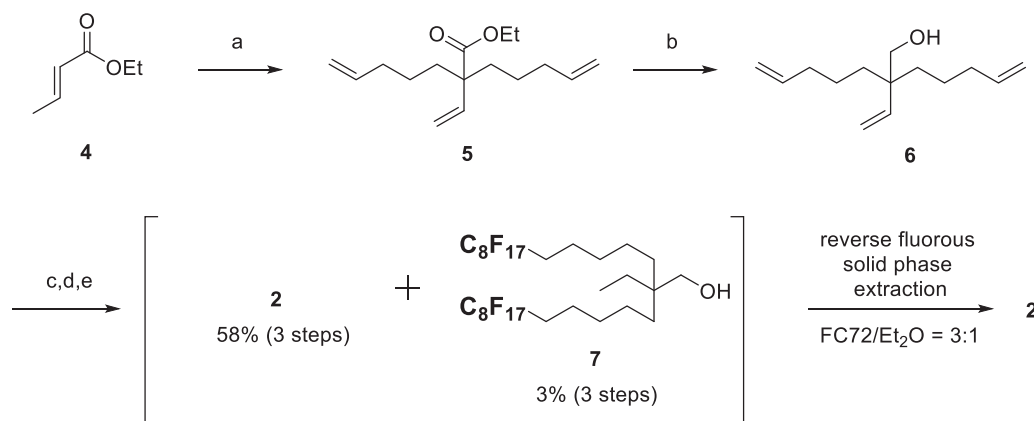
Fig. 1. Structures of heavy fluorous tags 1–3.

2. Results and discussion

Synthesis of **2** was done as shown in Scheme 1. Dialkylation of ethyl crotonate **4** [6] with LDA and HMPA gave β,γ-unsaturated

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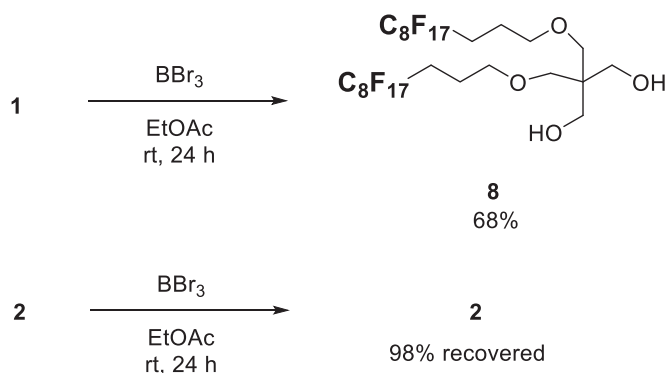
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Scheme 1. Preparation of heavy fluorous tag **2**. Reagents and conditions: (a) 5-bromo-1-pentene, LDA, HMPA, THF, -78°C to rt, 22 h, 76%; (b) LAH, Et_2O , 0°C , 1.5 h, 95%; (c) $\text{C}_8\text{F}_{17}\text{I}$, Et_3B in *n*-hexane, O_2 , FC72, *n*-hexane, 60°C , 28 h; (d) DBU, THF, rt, 17 h; (e) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, AcOH, EtOAc , EtOH , rt, 6 days, 58% (3 steps).

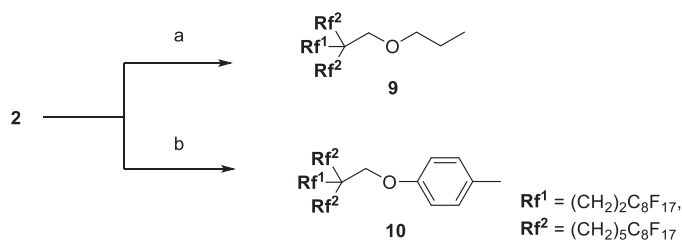
ester **5** [7], which was reduced into a triantennary olefin **6**. Radical addition of **6** to perfluorooctyl iodide [8], followed by elimination and hydrogenation, gave **2** together with a bisfluoroalkyl byproduct **7**. The mixture of **2** and **7** was barely separable on silica gel column chromatography (eluent: ethyl acetate and *n*-hexane), but they could be separated by a reverse fluorous solid-phase extraction method reported by Matsugi and Curran [9]. The structure of **2** was confirmed by means of ^1H , ^{13}C , ^{19}F NMR and mass spectroscopy.

For each of **1** and **2**, chemical stability was tested by using BBr_3 in ethyl acetate (Scheme 2). In the former, one of the three ether linkages was cleaved to afford **8** as a major product of decomposition (68%). In contrast, the new tag **2** tolerated the same conditions, showing its stability under the strong acidic conditions used to cleave the ether bonds.

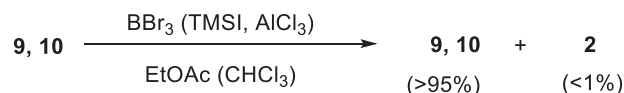


Scheme 2. Chemical stability of heavy fluorous tag.

The acid-resistant fluorous tag **2** was subjected to *O*-alkylation and *O*-phenylation reactions to obtain the corresponding ether derivatives **9** and **10** (Scheme 3). Both of these reactions were very sluggish, and the yields after 48 h were not satisfactory. Moreover, attempts to recover **2** from these products failed, because no apparent reaction occurred under any of the acidic conditions examined (Scheme 4). The low reactivities of **2**, **9**, and **10** likely arose from steric hindrance at the quaternary carbon in the center, as well as from the electron-withdrawing effect of the three perfluoroalkyl groups. It was obvious that compound **2** needed



Scheme 3. *O*-alkylation and *O*-phenylation of **2**. Reagents and conditions: (a) 1-bromopropane, NaH, NaI, 15-Crown-5, THF, rt, 48 h, 55%; (b) *p*-cresol, 1,1'-(azodicarbonyl)dipiperidine, PPh_3 , THF, reflux, 48 h, 70%.



Scheme 4. Acid treatment of ether derivatives **9** and **10**.

chemical modifications to gain chemical reactivity for application in fluorous-tag-assisted synthesis.

Next, another tag, **3**, with an elongated spacing group between the quaternary carbon and the reaction site, was designed and prepared from **2** (Scheme 5) in the following manner. *O*-allylation of **2**, followed by olefin cross-metathesis reaction with *cis*-2-butene-1,4-diol diacetate, afforded the crude product **11**, which was hydrogenated with Pd/fibroin and de-*O*-acylated to give **3**.

The derived tag **3** was subjected to *O*-alkylation and *O*-phenylation reactions to afford **12** (74%) and **13** (99%), respectively (Scheme 6). When **12** was treated with BBr_3 , the terminal propyl group was removed to afford a bromide derivative **14** exclusively. This product was easily converted to the starting tag **3** in reactions with sodium acetate and sodium methoxide in high yields (Entry 1 in Table 1). In contrast, the terminal *O*-phenyl group in **13** could not be removed with any of the Lewis acids used here (Entries 2–4). Obviously, the phenyl ether linkage was more stable than the alkyl ether one in the reaction with BBr_3 . Also, in the case of **16**, which possessed an ethylene glycol spacer, the bromide derivative **14** was obtained near-quantitatively in the same reaction, meaning that BBr_3 caused a site-selective cleavage at the internal alkyl ether junction in **16** (Entry 5 in Table 1).

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