



Radical reactivity of α,β,β -trifluoroacrylic ester: Facile approach to γ -silyloxy- α,β,β -trifluorobutyric acid derivatives involving regioselective nucleophilic radical addition reaction

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ABSTRACT

In this paper are disclosed new aspects for chemical reactivity of benzyl α,β,β -trifluoroacrylate, which is already known to undergo C–C bond formation reactions via nucleophilic addition-elimination reaction or Diels-Alder cycloaddition reaction. The α,β,β -trifluoroacrylate reacted well with nucleophilic radical species, generated from cyclic ethers, to afford the corresponding radical adducts in good to excellent yield as a diastereomeric mixture. The radical addition protocol is successfully evolved into the new synthetic approach to γ -silyloxy- α,β,β -trifluorobutanoic acid derivatives, which fascinates as promising precursors for medicinally as well as pharmaceutically-important organic molecules.

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1. Introduction

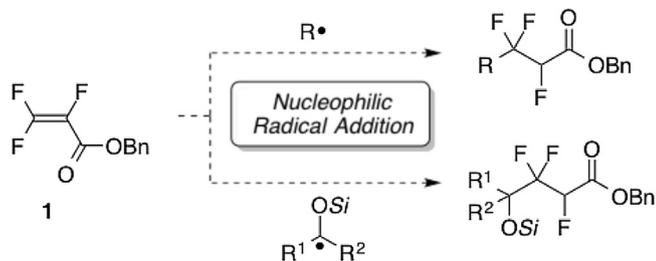
γ -Hydroxybutanoic acid and the derivatives are well-known as bio-active substances and coinstantaneously as one of the most promising synthetic intermediates toward γ -butyrolactone scaffolds that are often found in agrochemicals as well as pharmaceuticals [1]. Recently, much attention has been paid to fluorine-containing materials since fluorine atom(s) incorporated in a molecule can very often impart unique chemical as well as physical properties to the molecule. Consequently, it is not surprising that many efficient synthetic pathways for fluorine-containing γ -hydroxy acid derivatives have been extensively developed so far [2]. Among them, however, little attention has been paid to γ -hydroxy- α,β,β -trifluorobutanoate in spite of high potential synthetic utility. To the best of our knowledge, there have been only a few reports on the syntheses of γ -hydroxy- α,β,β -trifluorobutanoate and its derivatives [3], and therefore synthetic methods for the preparation of such molecules have been highly desirable.

Since several years ago, we intensively studied the chemical reactivity of α,β,β -trifluoroacrylic acid benzyl ester (**1**) as a fluorinated substrate, which is of easy-handling [4] as well as versatile convertibility. Thus, we demonstrated the reaction of **1** with various nucleophiles as well as with dienes, because there were no systematic studies on the chemical reactivity albeit the **1**

was of great significance as a promising entry for not only versatile fluorine-containing organic molecules but also fluorinated polymers. As a consequence, we successfully reported that the **1** underwent stereoselective addition-elimination reaction with organocuprates or regioselective Diels-Alder reaction with various dienes, leading to the corresponding *Z*-*vic*-difluoroacrylate or trifluorinated cyclohexene derivatives in good to excellent yields, respectively [5,6]. During the intensive studies, it was obviously proved that the fluorine(s) on alkene moiety in **1** caused effective lowering of the lowest unoccupied molecular orbital (LUMO) and, therefore, the carbon at β -position was easily susceptible to nucleophilic addition with various nucleophiles. With the deep understandings, our next interest was directed toward nucleophilic radical addition reaction with **1**, which has a significant advantage like high tolerance for active proton or water in contrast to organometallic nucleophiles: the radical addition would be a promising methodology to afford various kinds of fluorine-containing molecules, especially fluorinated γ -hydroxybutanoic acid derivatives. In this paper, we would like to disclose the new aspect of the chemical reactivity of α,β,β -trifluoroacrylate **1** with nucleophilic radicals in detail. Additionally, we would also offer facile approach to γ -silyloxy- α,β,β -trifluorobutyric acid derivatives by means of the regioselective nucleophilic radical addition reaction (Scheme 1).

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Scheme 1. Nucleophilic radical addition reaction of **1** undertaken in this study.

2. Results and discussion

2.1. Radical addition reaction of α,β,β -trifluoroacrylate with cyclic ethers

Initially, we started with nucleophilic radical addition of benzyl α,β,β -trifluoroacrylate (**1**), which can be easily handled by higher boiling point than the corresponding methyl or ethyl esters as previously mentioned [4], with cyclic ethers, e.g. tetrahydrofuran, 1,3-dioxolane, and 1,4-dioxane. The benzyl ester **1** was obtained by a vacuum distillation (160–162 °C/20 mmHg) according to our previous reports with a slight modification [5]. The results for the radical addition reaction are summarized in Table 1.

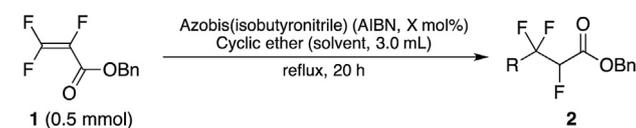
Thus, on treating **1** (0.5 mmol) with 3 mL of tetrahydrofuran as a reactant/solvent in the presence of 10 mol% of azobis(isobutyronitrile) (AIBN) as a radical initiator at reflux temperature for 20 h, the radical reaction proceeded smoothly to give the corresponding radical adduct **2a** in 82% yield as a diastereomeric mixture in a ratio of 55:45 (Entry 1, Table 1) [7]. In this case, 15% of the starting ester **1**

still remained unreacted. Increasing the amount of AIBN loading from 10 mol% to 30 mol% led to a significant decrease of the yield of **2a** as well as 28% recovery of **1** (Entry 2). On the other hand, a stepwise addition of AIBN at 10 h interval resulted in a significant improvement of the reaction efficacy, affording the desired adduct **2a** quantitatively (Entry 3). With a similar manner, 1,3-dioxolane and 1,4-dioxane as a reactant/solvent could also participate very well in the nucleophilic radical addition reaction, giving rise to the corresponding addition products **2b** and **2c** quantitatively (Entries 4 and 5).

2.2. Radical addition reaction of α,β,β -trifluoroacrylate with ketyl radical *in situ* generated from various carbonyl compounds

As mentioned above, we have reported the specific chemical reactivity of α,β,β -trifluoroacrylate **1** toward nucleophiles or dienes due to the low electron density on the β -carbon triggered by electrostatic p - π repulsion between lone pairs on fluorine atoms and π -electrons on the sp^2 -hybridized carbon [8]. It means that it is difficult to incorporate functional groups including a hydroxyl group in the structure of **1**. In the aforementioned radical addition reaction, however, the fluorinated alkene **1** was found to accept radicals at β -position through C–C bond formation reactions. At the viewpoint, we envisioned that the radical reaction would be one of the most suitable methodologies to incorporate functional moieties, especially a hydroxy group in the fluorinated molecule **1**. Therefore, we next carried out radical addition reactions of **1** with ketyl radicals *in situ* generated from various carbonyl compounds [9]. We initially began with an optimization of reaction conditions for radical addition of **1** with benzaldehyde-ketyl radical, generated from benzaldehyde (**3a**),

Table 1
Nucleophilic radical addition reaction of α,β,β -trifluoroacrylate (**1**) with cyclic ethers.



Entry	Cyclic ether (Solvent)	Amount of AIBN (X mol%)	Product	Yield ^a /% [d.r.] of 2	Recovery ^a /% of 1
1		10		82 [55:45]	15
2		30		65 [56:44]	28
3	(37 mmol/ b.p. 66 °C)	10 + 10 ^b		quant (93) [56:44]	0
4		10 + 10 ^b		quant (89) [–]	0
5	(43 mmol/ b.p. 75 °C)	10 + 10 ^b		quant (83) [55:45]	0
		10 + 10 ^b			

^a Determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard. Values in parentheses and brackets are the isolated yield and the diastereomeric ratio, respectively.

^b AIBN (10 mol% each) was stepwise added into the reaction mixture at 10 h interval.

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