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The reaction of substituted ethyl α-bromocinnamates with tetrabutyl ammonium fluoride

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Abstract

The reaction of ethyl α-bromocinnamates with tetrabutyl ammonium fluoride (TBAF) was influenced largely by the position of the substituent at the phenyl ring. While the substrates without an *ortho* substituent at the phenyl ring were transformed to the corresponding β-fluoro ethyl cinnamates under the reaction conditions, the presence of an *ortho* substituent only resulted in the formation of ethyl 3-phenylpropiolate derivatives. The reaction of ethyl 2-bromo-3-(4-methoxyphenyl) acrylate also failed to deliver the hydrofluorination product due to the electron-donating effect of the methoxy group.

Keywords: Tetrabutyl ammonium fluoride; Ethyl α-bromocinnamates; Hydrofluorination; Elimination

Tetrabutyl ammonium fluoride (TBAF) is a useful reagent in organic synthesis. TBAF can act as a weak base in organic reactions. For example, TBAF has been employed to effect the elimination reaction of bromoalkenes, which constitutes a useful protocol for the synthesis of alkynes [1]. Wang et al. reported that TBAF could promote the intramolecular cyclization of 2-(*gem*-dibromovinyl) phenols and 2-(*gem*-dibromovinyl) thiophenols [2]. We found that TBAF was capable of catalyzing the intramolecular hydroalkoxylation of 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates [3].

Monofluorine-containing organic molecules are of synthetic interest due to their potential usefulness as bioactive compounds [4]. In this context, efforts have been made to prepare monofluorinated acrylic esters which are versatile synthons for further structural elaboration [5]. β-Fluoro-α,β-unsaturated esters can be synthesized from the monohydrofluorination of electrophilic alkynes by using a reagent combination of tetrabutylammonium and polymer-supported dihydrogentrifluoride [6] or a biphasic CsF–H_2O–DMF system [7]. Recently, during the course of study on the reactions of vinyl bromides, we found that the reaction of substituted ethyl α-bromocinnamates with TBAF afforded ethyl β-fluoro ethyl cinnamates or elimination product alkynes, depending on the nature of the substituent and its position. Herein we wish to report this result.

The reaction of ethyl α-bromocinnamates **1** [8] with TBAF was carried out in DMF at 60–80 °C. The results are summarized in Table 1. Compound **1** was used mostly as a mixture of *E* and *Z* isomers, with *Z* configuration being the

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Table 1
The reaction of ethyl α-bromocinnamates **1** with TBAF.[a]

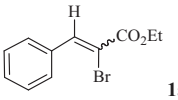
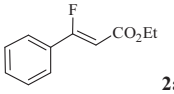
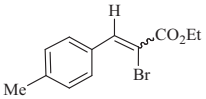
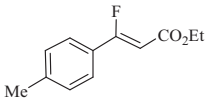
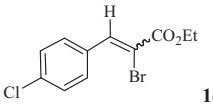
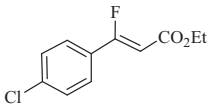
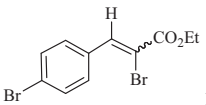
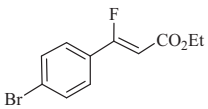
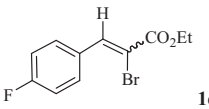
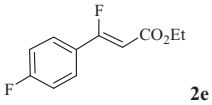
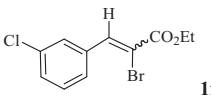
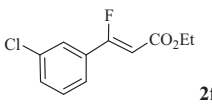
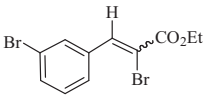
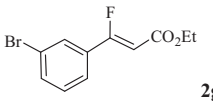
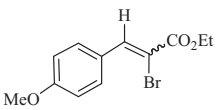
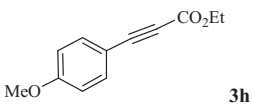
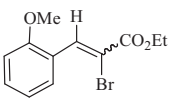
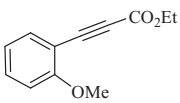
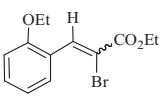
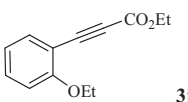
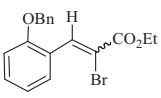
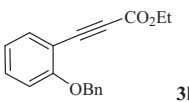
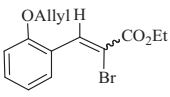
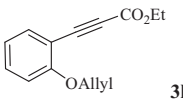
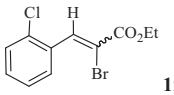
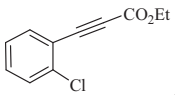
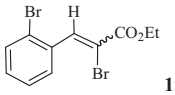
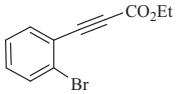
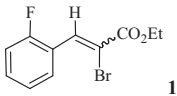
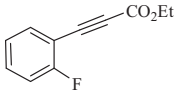
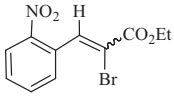
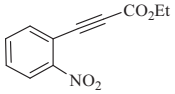
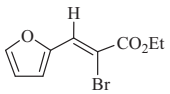
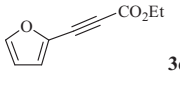
Entry	Substrate **1** (*Z*:*E*)	Product	Yield (%)[b]
1	 **1a** (3.7:1)	 **2a**	89
2	 **1b** (4.3:1)	 **2b**	49[c]
3	 **1c** (>99:1)	 **2c**	92
4	 **1d** (>99:1)	 **2d**	78
5	 **1e** (>99:1)	 **2e**	89
6	 **1f** (>99:1)	 **2f**	75
7	 **1g** (1.6:1)	 **2g**	71
8	 **1h** (4.7:1)	 **3h**	60
9	 **1i** (5.3:1)	 **3i**	63
10	 **1j** (>99:1)	 **3j**	58
11	 **1k** (7.5:1)	 **3k**	70
12	 **1l** (8.6:1)	 **3l**	67

Table 1 (*Continued*)

Entry	Substrate **1** (*Z*:*E*)	Product	Yield (%)[b]
13	 **1m** (>99:1)	 **3m**	92
14	 **1n** (>99:1)	 **3n**	73
15	 **1o** (18:1)	 **3o**	89
16	 **1p** (10:1)	 **3p**	89
17	 **1q** (2:1)	 **3q**	71

[a] General reaction procedure: a mixture of 0.2 mmol of ethyl α-bromocinnamates **1** and 0.6 mmol of TBAF (1.5 mol/l in THF) in 1 ml of DMF was stirred at 60–80 °C for 22 h. The reaction mixture was then cooled to the room temperature, and the product was extracted with EtOAc (15 ml ×2). The combined organic layer was washed with brine (20 ml ×3) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual was treated with silica gel chromatography to give product **2** or **3**.

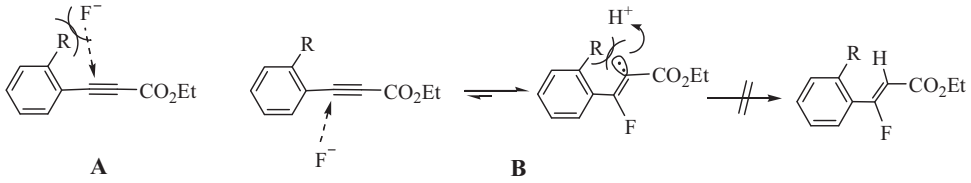
[b] Isolated yield.

[c] The reaction time was 30 h. Besides **2b**. There were 11% of recovered **1b** and 7% of elimination product alkyne.

dominant. Unsubstituted compound **1a** was converted to β-fluoroethylcinnamate **2a** in yield of 89% under the reaction conditions. Compounds **1b**–**1g**, which incorporated a substituent at the *para*- or *meta*-position of the phenyl ring reacted in the same way, giving rise to the corresponding fluorination products **2b**–**2g**. The ratio of *E* to *Z* configuration in the reactants did not have obvious influence on the result. It is noteworthy that compounds **2** were obtained exclusively in *Z*-configuration [9]. This result is comparable to that concerning the mono-hydrofluorination of electrophilic alkynes by using the CsF–H_2O–DMF system, in which case a *Z:E* stereoselectivity of 95:5 was observed for the formation of compound **2a** [7]. However, when compound **1h** was subjected to the reaction conditions, only elimination product **3h** was obtained after reaction.

On the other hand, when the substituents were at the *ortho*-position of the phenyl ring, as in the cases of **1i**–**1p**, the reaction products were exclusively alkynes **3** (Table 1, entries 9–16). As aforementioned, TBAF can act as base to effect the elimination reaction of bromoalkenes [5]. The formation of **3h**–**3p** is consistent with this reaction pattern. However, the reaction of **1a**–**1g** gave a different result. We believed that compounds **2** resulted from the hydrofluorination of **3**. This mechanism is supported by the observation that during the course of the reaction of **1b**, elimination product **3b** formed firstly, but disappeared at the end of reaction time. In addition, control experiment showed that **3a** can be converted to **2a** by treatment with TBAF.

It is interesting to see that the nature and position of the substituent played a critical role in determining the final reaction consequence. In the absence of the *ortho*-substituent, compound **2** was formed exclusively in its *Z* configuration, whereas in the presence of it, the formation of compound **2** became largely disfavored, and **3** was obtained exclusively. These results indicate that in the present cases, the addition of HF to the electrophilic triple bond is greatly influenced by the steric effect. We believe that the trajectory of fluoride attack on the triple bond falls in the plane of phenyl ring and triple bond to keep the conjugated system, and a substituent at the *ortho*-position would render the reaction much unfavorable (Scheme 1). By contrast, the elimination of HBr from **1** is not sensitive to the position of substituent. The only exception to this scenario is ethyl 2-bromo-3-(4-methoxyphenyl) acrylate (**2h**), in which case the product was **3h** rather than the fluorination product. The reason why **1h** failed to be transformed to the corresponding **2h** is probably due to the strong electron-donating methoxy group renders the triple bond unreactive



Scheme 1. Illustration of the steric hindrance caused by the *ortho*-substituent.

towards hydrofluorination. To test this hypothesis, we treated compound **1q** with TBAF under the present conditions, and as expected, only obtained elimination product **3q** after reaction.

In summary, this work demonstrated that the reaction of ethyl α-bromocinnamates **1** with TBAF was largely influenced by the electronic nature and the position of the substituent at the phenyl ring. When the substituent was at the *para* and *meta* position, the reaction generated (*Z*) ethyl β-fluorocinnamates **2** following a consecutive elimination/addition process. When the substituent was at the *ortho* position, only elimination product alkynes **3** were obtained. Compound **1h** cannot be converted to the hydrofluorination product either due to the strong electron-donating effect of the methoxy group.

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[8] X. Zhang, F.L. Qing, Y. Yu, J. Org. Chem. 65 (2000) 7075.
[9] The *Z* configuration was determined by the *J* value (32.8–33.6 Hz) of vinyl hydrogen in ^{1}H NMR spectra (in $CDCl_3$).