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# Facile Stereoselective Syntheses of Aryl Substituted α,β-Unsaturated Esters Containing a Trifluoromethyl Group

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ABSTRACT: *The Suzuki-type cross-coupling reaction of arylboronic acids* **3** *with ethyl (Z)-3-iodo-4,4,4-trifluoro-2-butenoate* **2**, *which was generated by hydroiodination of available ethyl 4,4,4-trifluoro-2-butynoate* **1**, *to afford ethyl (E)-3-aryl-4,4,4-trifluoro-2-butenoates* **4**, *was studied for the first time. It was found that under the optimum conditions the cross-coupling reaction could readily give* **4** *as the sole E-isomer in 76–91% yields.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:287–290, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10032

## *INTRODUCTION*

Trifluoromethylated compounds, especially trifluoromethyl substituted α,β-unsaturated esters, have attracted the attention of synthetic chemists, because of their unique physiologic and bioactivities [1] and potential in synthetic organic chemistry [2]. Among the approaches to trifluoromethylated organic compounds, halogen exchange reaction [3] and trifluoromethylation [4] are possible methods, but these suffer from low reactivity and selectivity. As a convenient strategy for the preparation and application of trifluoromethylated building blocks [5], Qing et al. reported a new method for the synthesis of ethyl (*Z*)-3-iodo-4,4,4-trifluoro-2-butenoate **2** and its alkynylation by the Sonogashira reaction [6]; Gildas et al. [7] described a stereoselective access to functional dienes containing the trifluoromethyl group *via* the Stille coupling of the compound **2**. Recently, two papers contained a report of the stereoselective syntheses of trifluoromethyl substituted retinoates and their analogues [8,9] by use of the compound **2** as a key intermediate. However, the arylation of compound **2** has not been reported. We also described a novel and convenient method for producing α-(trifluoromethyl)styrenes by the arylation of 2-bromo-3,3,3-trifluoro-propene *via* the Suzuki-type coupling [10]. As a continuous development of our previous research on the methodology for preparing various derivatives bearing the trifluoromethyl group, herein we wish to report a facile stereoselective synthesis of aryl substituted α,β-unsaturated esters containing the trifluoromethyl group by the arylation of **2** via the Suzuki cross-coupling reaction.

## *RESULTS AND DISCUSSION*

### *Synthesis of Ethyl (Z)-3-iodo-4,4,4-trifluoro-2-butenoate* **2**

According to either the Qing or Gildas procedures [6,7], respectively, ethyl (*Z*)-3-iodo-4,4,4-trifluoro-

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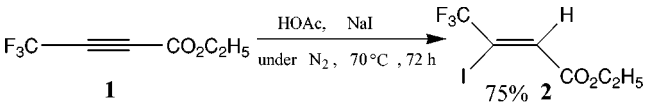
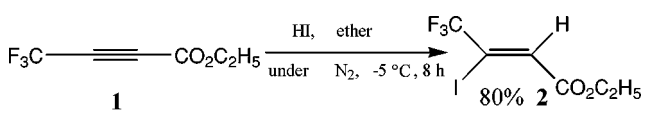



SCHEME 1

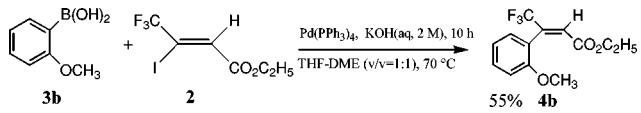
2-butenoate was prepared (Schemes 1 and 2). It was found that both the methods provided the sole stereoisomer, which was proved by the data of $^{19}F$ NMR, HPLC, and GC to be the compound **2**. The single peak of the $CF_3$ group in **2** ($\delta_F = -10.2$ for $CF_3CO_2H$ utilized as an external standard, upfield being positive) at $\delta = -10.0$ demonstrated that the $CF_3$ and $CO_2C_2H_5$ groups were trans oriented [11]. However, Qing's procedure required a relatively long reaction time (72 h) and the yield was somewhat lower than that obtained by the Gildas procedure.

### *Preparation of Ethyl (E)-3-aryl-4,4,4-trifluoro-2-butenoates* **4**

The arylboronic acids **3** are easily available and handled, because of their stability to moisture and air. The Suzuki-type coupling of the arylboronic acids **3** with compound **2** to obtain aryl substituted α,β-unsaturated esters **4** with a trifluoromethyl group was investigated. Initially, *o*-methoxyphenylboronic acid **3b** was used as a starting material to optimize the coupling conditions. It was found, that under our previous conditions, the coupling reaction of **3b** with **2** could take place to produce the cross-coupling product **4b** in 55% yield (Scheme 3). Considering that $Pd(PPh_3)_4$ is difficult to prepare and preserve because of its instability to air, $Pd(PPh_3)_2Cl_2$ was used instead of $Pd(PPh_3)_4$. From many experiments, it was found that using $Pd(PPh_3)_2Cl_2$ as a catalyst and $K_3PO_4 \cdot 3H_2O$ as a base in toluene, the cross-coupling of *o*-methoxyphenylboronic acid **3b** with **2** readily takes place at 100°C to produce, in 84% yield, the product **4b** (Scheme 4). Under these optimum conditions, the cross-coupling of the various arylboronic acids **3** with **2** were accomplished and the results are shown in Table 1. The data of Table 1 demonstrates that all the reaction of arylboronic acids **3** with **2** afforded the corresponding coupling products **4** in high yields. Thus, the reaction procedure is a generally facile method for producing aryl substituted α,β-unsaturated esters bearing a trifluoromethyl group.




SCHEME 2




SCHEME 3

The configurations of the cross-coupling reaction products were characterized by $^{19}F$ NMR and $^1H$ NMR spectrascopy. $\delta_F$ Values of the products **4** at $\delta = -10.0$ revealed that the $CF_3$ group and $CO_2C_2H_5$ group were trans oriented [11,12]. The chemical shifts (beyond $\delta_F = 6.50$) of the olefinic H of all of the products also proved that the $CF_3$ group and the proton of the vinyl group were present on the same side of the double bond in **4** [13]. Therefore, the configuration of the compound **2** was retained in the cross-coupling reaction, the same as that of other Suzuki-type couplings [14,15].

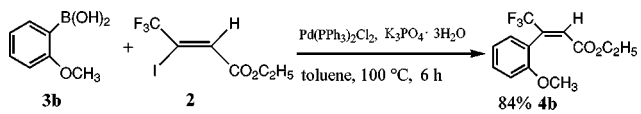
In summary, we have provided a stereoselective synthetic method for producing aryl substituted α,β-unsaturated esters **4** containing a trifluoromethyl group from the arylboronic acids and **2** by the Suzuki cross-coupling reaction. This method has many attractive features: the easily availability of starting materials, mild conditions, high yields, and effective stereoselectivity.

## *EXPERIMENTAL*

$^1H$ NMR spectra were recorded on a Varian EM-360A spectrometer using $CCl_4$ as the solvent with TMS as an internal standard. $^{19}F$ NMR spectra were obtained on a Varian EM-360L spectrometer with $CF_3CO_2H$ as an external standard and an upfield shift was designated as positive. Infrared spectra were taken on a *Shimadzu* IR-440 spectrometer using films. Mass spectra were taken on a HP5989A Mass spectrometer using EI (70 eV). Elemental analyses were determined on a Foss-Heraeus Vario EL instrument. The compound **2** was prepared according to the Qing and Gildas methods, respectively [6,7].

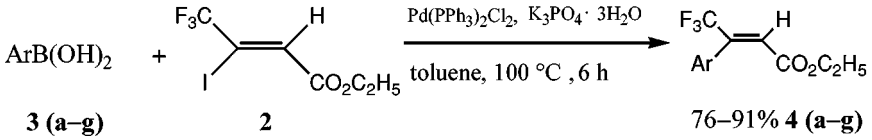
### *Typical Experimental Procedure for Preparation of* **4**

To a solution of ethyl (*Z*)-3-iodo-4,4,4-trifluoro-2-butenoate **2** (0.5 mmol) in toluene (3 ml), the arylboronic acid **3** (0.6 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg,

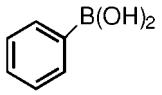
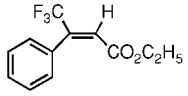
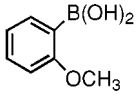
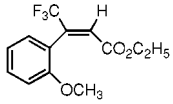
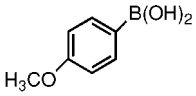
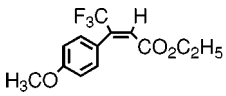
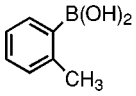
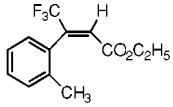
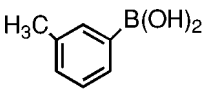
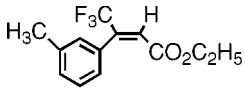
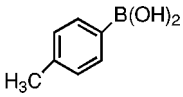
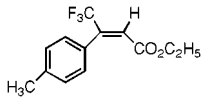
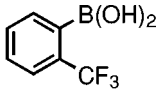
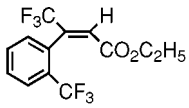
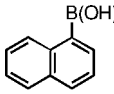
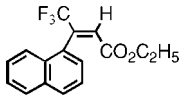



SCHEME 4

**TABLE 1** The Synthesis of Ethyl (*E*)-3-Aryl-4,4,4-trifluoro-2-butenoates **4**




**3 (a–g)** **2** 76–91% **4 (a–g)**

| *Entry* | *Arylboronic Acids* | | *Products* | | $\delta_F$ *(ppm)* | $\delta_H$ *(ppm) (ole nic H)* | *Yields*[a] *(%)* |
|---|---|---|---|---|---|---|---|
| 1 |  | **3a** |  | **4a** | −10.4 | 6.52 | 83 |
| 2 |  | **3b** |  | **4b** | −10.6 | 6.54 | 84 |
| 3 |  | **3c** |  | **4c** | −10.6 | 6.52 | 89 |
| 4 |  | **3d** |  | **4d** | −10.0 | 6.56 | 91 |
| 5 |  | **3e** |  | **4e** | −10.6 | 6.50 | 89 |
| 6 |  | **3f** |  | **4f** | −10.6 | 6.52 | 89 |
| 7 |  | **3g** |  | **4g** | −10.2 (−15.4[b]) | 6.70 | 85 |
| 8 |  | **3h** |  | **4h** | −10.6 | 6.76 | 76 |

[a]Isolated yields, based on the compound **2**.
[b]The shift of $CF_3$ on the aryl circle.

0.015 mmol), and $K_3PO_4{\cdot}3H_2O$ (400 mg, 1.5 mmol) were added under a nitrogen atmosphere. The reaction mixture was stirred at 100°C for 6 h. The mixture was allowed to cool to room temperature, water (10 ml) was added, and the mixture was extracted with ether (3 × 5 ml). The combined organic layer was washed with brine (3 × 5 ml) and dried over $MgSO_4$. After removal of the solvent on a rotary evaporator, the residue was purified by flash silica gel chromatography (petroluem ether : ethyl acetate = 15 : 1, v/v as the eluant) to yield **4a–h** as light yellow oils.

*Ethyl (E)-3-phenyl-4,4,4-trifluoro-2-butenoate* **4a**. A light yellow oil; yield, 83%; $^1$H NMR: $\delta_H$ 1.06 (t, 3H), 4.06 (q, 2H), 6.52 (s, 1H), 7.10–7.60 (m, 5H); $^{19}$F NMR: $\delta_F$ − 10.4 (s, $CF_3$); MS (*m/z*): 244 ($M^+$, 75.5), 215 (78.1), 199 (100.0), 171 (25.3), 151 (57.1), 102 (15.9); IR ($cm^{-1}$) 1730, 1280–1120, 700; Anal Calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54; Found: C, 59.21; H, 4.63.

*Ethyl (E)-3-(2-methoxyphenyl)-4,4,4-trifluoro-2-butenoate* **4b**. A light yellow oil; yield, 84%; $^1$H NMR: $\delta_H$ 1.06 (t, 3H), 3.74 (s, 3H), 4.0 (q, 2H), 6.54 (s, 1H), 6.70–7.50 (m, 4H); $^{19}$F NMR: $\delta_F$ − 10.6 (s, $CF_3$); MS (*m/z*): 274 ($M^+$, 39.3), 229 (35.8), 215 (100.0), 151 (10.3), 131 (25.6); IR ($cm^{-1}$) 1730, 1280–1120, 750; Anal Calcd for $C_{13}H_{13}F_3O_3$: C, 56.94; H, 4.78; Found: C, 56.89; H, 4.61.

*Ethyl (E)-3-(4-methoxyphenyl)-4,4,4-trifluoro-2-butenoate* **4c**. A light yellow oil; yield, 89%; $^1$H NMR: $\delta_H$ 1.10 (t, 3H), 3.75 (s, 3H), 4.04 (q, 2H), 6.52 (s, 1H), 6.70–7.25 (m, 4H); $^{19}$F NMR: $\delta_F$ − 10.6 (s, $CF_3$); MS (*m/z*): 274 ($M^+$, 100.0), 245 (10.5), 229 (56.6), 201 (21.6), 181 (12.7), 133 (10.4); IR ($cm^{-1}$) 1730, 1280–1120, 830; Anal Calcd for $C_{13}H_{13}F_3O_3$: C, 56.94; H, 4.78; Found: C, 57.15; H, 4.72.

*Ethyl (E)-3-(2-methylphenyl)-4,4,4-trifluoro-2-butenoate* **4d**. A light yellow oil; yield, 91%; $^1$H NMR: $\delta_H$ 1.0 (t, 3H), 2.20 (s, 3H), 3.94 (q, 2H), 6.56 (s, 1H), 6.90–7.30 (m, 4H); $^{19}$F NMR: $\delta_F$ − 10.0 (s, $CF_3$); MS (*m/z*): 259 ($M^+ + 1$, 12.8), 258 ($M^+$, 8.0), 213 (98.1), 184 (51.7), 165 (89.2), 133 (15.3), 115 (100.0); IR ($cm^{-1}$) 1730, 1280–1120, 720; Anal Calcd for $C_{13}H_{13}F_3O_2$: C, 60.47; H, 5.07; Found: C, 60.32; H, 4.99.

*Ethyl (E)-3-(3-methylphenyl)-4,4,4-trifluoro-2-butenoate* **4e**. A light yellow oil; yield,89%; $^1$H NMR: $\delta_H$ 1.04 (t, 3H), 2.36 (s, 3H), 3.96 (q, 2H), 6.50 (s, 1H), 6.74–7.52 (m, 4H); $^{19}$F NMR: $\delta_F$ − 10.6 (s, $CF_3$); MS (*m/z*): 258 ($M^+$,89.1), 243 (55.6), 229 (46.2), 213 (100.0), 199 (21.7), 165 (52.2), 145 (18.2), 115 (59.4); IR ($cm^{-1}$) 1730, 1280–1120, 780, 720; Anal Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07; Found: C, 60.74; H, 4.92.

*Ethyl (E)-3-(4-methylphenyl)-4,4,4-trifluoro-2-butenoate* **4f**. A light yellow oil; yield, 89%; $^1$H NMR: $\delta_H$ 1.06 (t, 3H), 2.40 (s, 3H), 4.0 (q, 2H), 6.52 (s, 1H), 7.15 (s, 4H); $^{19}$F NMR: $\delta_F$ − 10.6 (s, $CF_3$); MS (*m/z*): 259 ($M^+ + 1$,12.8), 258 (8.0), 243 (9.3), 229 (1.3), 213 (98.1), 199 (3.3), 184 (51.7), 165 (89.2), 164 (52.8), 145 (24.8), 115 (100.0); IR ($cm^{-1}$) 1730, 1280–1120, 820; Anal Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07; Found: C, 60.91; H, 5.02.

*Ethyl (E)-3-(2-trifluoromethylphenyl)-4,4,4-trifluoro-2-butenoate* **4g**. A light yellow oil; yield, 85%; $^1$H NMR: $\delta_H$ 1.10 (t, 3H), 4.06 (q, 2H), 6.70 (s, 1H), 7.20–7.86 (m, 4H); $^{19}$F NMR: $\delta_F$ − 10.2 (s, olefinic $CF_3$), −15.4 ( s, aryl $CF_3$); MS (*m/z*): 311 ($M^+ - 1$, 53.3), 283 (100.0), 263 (37.2), 235 (8.1), 169 (11.5), 91 (5.1); IR ($cm^{-1}$) 1730, 1310–1125, 800, 750; Anal Calcd for $C_{13}H_{10}F_6O_2$: C, 50.01; H, 3.23; Found: C, 50.34; H, 3.29

*Ethyl (E)-3-(1-naphthyl)-4,4,4-trifluoro-2-butenoate* **4h**. A light yellow oil; yield, 76%; $^1$H NMR: $\delta_H$ 0.65 (t, 3H), 3.70 (q, 2H), 6.76 (s, 1H), 7.10–7.90 (m, 7H); $^{19}$F NMR: $\delta_F$ − 10.6 (s, $CF_3$); MS (*m/z*): 295 ($M^+ + 1$, 8.2), 294 ($M^+$, 37.0), 249 (15.0), 221 (28.5), 201 (100.0), 152 (35.8); IR ($cm^{-1}$) 1725, 1280–1125, 795, 775; Anal Calcd for $C_{16}H_{13}F_3O_2$: C, 65.30; H, 4.45; Found: C, 65.75; H, 4.53.

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