

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-butenolate **2**, which was generated by hydroiodination of available ethyl 4,4,4-trifluoro-2-butyrate **1**, to afford ethyl (E)-3-aryl-4,4,4-trifluoro-2-butenates **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-butenolate **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

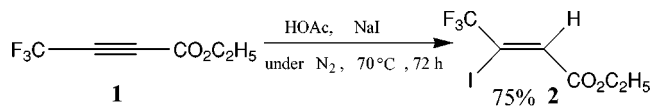
Synthesis of Ethyl (Z)-3-iodo-4,4,4-trifluoro-2-butenolate **2**

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

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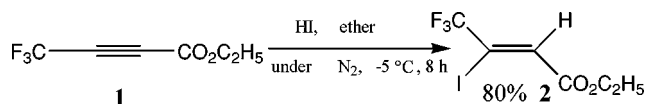


SCHEME 1

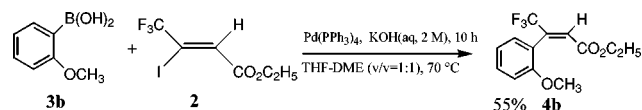
2-butenolate was prepared (Schemes 1 and 2). It was found that both the methods provided the sole stereoisomer, which was proved by the data of ^{19}F NMR, HPLC, and GC to be the compound **2**. The single peak of the CF_3 group in **2** ($\delta_{\text{F}} = -10.2$ for $\text{CF}_3\text{CO}_2\text{H}$ utilized as an external standard, upfield being positive) at $\delta = -10.0$ demonstrated that the CF_3 and $\text{CO}_2\text{C}_2\text{H}_5$ 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-butenates **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 $\text{Pd}(\text{PPh}_3)_4$ is difficult to prepare and preserve because of its instability to air, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ was used instead of $\text{Pd}(\text{PPh}_3)_4$. From many experiments, it was found that using $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ as a catalyst and $\text{K}_3\text{PO}_4 \cdot 3\text{H}_2\text{O}$ 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 spectroscopy. δ_{F} Values of the products **4** at $\delta = -10.0$ revealed that the CF_3 group and $\text{CO}_2\text{C}_2\text{H}_5$ group were trans oriented [11,12]. The chemical shifts (beyond $\delta_{\text{F}} = 6.50$) 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].

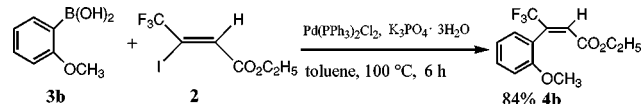
In summary, we have provided a stereoselective synthetic method for producing aryl substituted α,β -unsaturated esters **4** containing a trifluoromethyl group from the arylboronic acids and **2** by the Suzuki cross-coupling reaction. This method has many attractive features: the easily availability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

EXPERIMENTAL

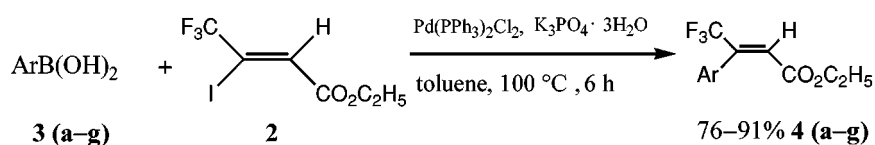
^1H NMR spectra were recorded on a Varian EM-360A spectrometer using CCl_4 as the solvent with TMS as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with $\text{CF}_3\text{CO}_2\text{H}$ as an external standard and an upfield shift was designated as positive. 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].

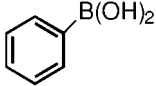
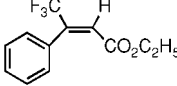
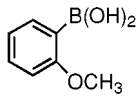
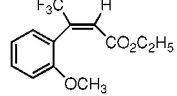
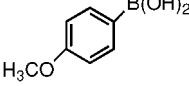
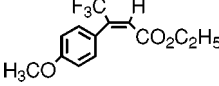
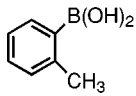
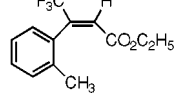
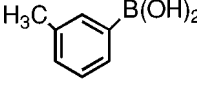
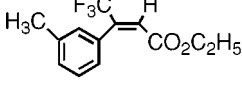
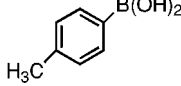
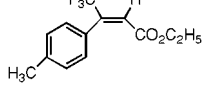
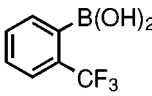
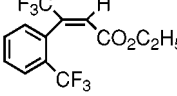
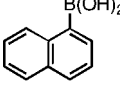
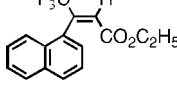
Typical Experimental Procedure for Preparation of **4**

To a solution of ethyl (*Z*)-3-iodo-4,4,4-trifluoro-2-butenolate **2** (0.5 mmol) in toluene (3 ml), the arylboronic acid **3** (0.6 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (11 mg,



SCHEME 4

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

Entry	Arylboronic Acids		Products	δ_F (ppm)	δ_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

^aIsolated yields, based on the compound **2**.^bThe shift of CF₃ on the aryl circle.

0.015 mmol), and K₃PO₄·3H₂O (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 MgSO₄. After removal of the solvent on a rotary evaporator, the residue was purified by flash silica gel chromatography (petroleum 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-butenate **4a**. A light yellow oil; yield, 83%; ¹H NMR: δ_H 1.06 (t, 3H),

4.06 (q, 2H), 6.52 (s, 1H), 7.10–7.60 (m, 5H); ¹⁹F NMR: δ_F −10.4 (s, CF₃); 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 C₁₂H₁₁F₃O₂: C, 59.02; H, 4.54; Found: C, 59.21; H, 4.63.

Ethyl (E)-3-(2-methoxyphenyl)-4,4,4-trifluoro-2-butenate **4b**. A light yellow oil; yield, 84%; ¹H NMR: δ_H 1.06 (t, 3H), 3.74 (s, 3H), 4.0 (q, 2H), 6.54 (s, 1H), 6.70–7.50 (m, 4H); ¹⁹F NMR: δ_F −10.6 (s, CF₃); 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 C₁₃H₁₃F₃O₃: C, 56.94; H, 4.78; Found: C, 56.89; H, 4.61.

Ethyl (E)-3-(4-methoxyphenyl)-4,4,4-trifluoro-2-butenolate 4c. A light yellow oil; yield, 89%; ^1H NMR: δ_{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: δ_{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 $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}_3$: C, 56.94; H, 4.78; Found: C, 57.15; H, 4.72.

Ethyl (E)-3-(2-methylphenyl)-4,4,4-trifluoro-2-butenolate 4d. A light yellow oil; yield, 91%; ^1H NMR: δ_{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: δ_{F} –10.0 (s, CF_3); MS (m/z): 259 ($\text{M}^+ + 1$, 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 $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}_2$: C, 60.47; H, 5.07; Found: C, 60.32; H, 4.99.

Ethyl (E)-3-(3-methylphenyl)-4,4,4-trifluoro-2-butenolate 4e. A light yellow oil; yield, 89%; ^1H NMR: δ_{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: δ_{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 $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}_2$: C, 60.46; H, 5.07; Found: C, 60.74; H, 4.92.

Ethyl (E)-3-(4-methylphenyl)-4,4,4-trifluoro-2-butenolate 4f. A light yellow oil; yield, 89%; ^1H NMR: δ_{H} 1.06 (t, 3H), 2.40 (s, 3H), 4.0 (q, 2H), 6.52 (s, 1H), 7.15 (s, 4H); ^{19}F NMR: δ_{F} –10.6 (s, CF_3); MS (m/z): 259 ($\text{M}^+ + 1$, 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 $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}_2$: C, 60.46; H, 5.07; Found: C, 60.91; H, 5.02.

Ethyl (E)-3-(2-trifluoromethylphenyl)-4,4,4-trifluoro-2-butenolate 4g. A light yellow oil; yield, 85%; ^1H NMR: δ_{H} 1.10 (t, 3H), 4.06 (q, 2H), 6.70 (s, 1H), 7.20–7.86 (m, 4H); ^{19}F NMR: δ_{F} –10.2 (s, olefinic CF_3), –15.4 (s, aryl CF_3); MS (m/z): 311 ($\text{M}^+ - 1$, 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 $\text{C}_{13}\text{H}_{10}\text{F}_6\text{O}_2$: C, 50.01; H, 3.23; Found: C, 50.34; H, 3.29.

Ethyl (E)-3-(1-naphthyl)-4,4,4-trifluoro-2-butenolate 4h. A light yellow oil; yield, 76%; ^1H NMR: δ_{H} 0.65 (t, 3H), 3.70 (q, 2H), 6.76 (s, 1H), 7.10–7.90 (m, 7H); ^{19}F NMR: δ_{F} –10.6 (s, CF_3); MS (m/z): 295 ($\text{M}^+ + 1$, 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 $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_2$: C, 65.30; H, 4.45; Found: C, 65.75; H, 4.53.

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