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A novel and convenient synthetic method for producing α-(trifluoromethyl)styrenes (**3**)

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Abstract

The Suzuki-type coupling reaction of arylboronic acids (**1**) with 2-bromo-3,3,3-trifluoropropene (**2**) in the presence of a catalytic amount of dichlorobis(triphenylphosphine)palladium {$PdCl_2(PPh_3)_2$} and a base can easily give α-(trifluoromethyl)styrenes (**3**) in good yields. It was also found that 1,2-dibromo-3,3,3-trifluoropropane (**4**) underwent dehydrobromination in the presence of KOH, and subsequently, palladium-catalyzed cross-coupling with **1** to directly afford **3** in a one pot manner in excellent yields.

Keywords: α-(trifluoromethyl)styrenes; Suzuki-type coupling; Arylboronic acid; 2-bromo-trifluoropropene; 1,2-dibromo-3,3,3-trifluoropropane

1. Introduction

As we know, trifluoromethylated compounds have become increasingly important for a large number of industrial applications, such as pharmaceuticals, agrochemicals, polymers, and so on [1]. Just because of their unique physical and biological properties, there is an increasing interest in the convenient synthetic method for specifically trifluoromethylated organic molecules [2–6]. There are two ways of introducing the trifluoromethylated group in general: (i) direct substitution, such as fluorination, the halogen exchanging reaction etc. in a late stage of the synthesis [7–12]; and (ii) using trifluoromethyl-substituted building blocks derived from readily available starting materials [13–25]. However, the former route is not so satisfactory because of low reactivity and low selectivity. The latter one is now becoming an important strategy for the preparation of trifluoromethylated molecules because it allows us to obtain these CF_3-substituted compounds under milder conditions and with tolerant functionalities.

There have been many reported methods using α-(trifluoromethyl)styrenes (**3**) to synthesize *gem*-difluoroalkene [26–28] in recent years because difluoroalkene can be used as a versatile building block to synthesize many compounds with biological activity [29,30]. Thus, it is meaningful to look for a novel convenient synthetic method for **3**. A number of synthetic methods for the preparation of **3** have been reported in the past years [31–33]. Although these methods have their own excellent qualities, they still have many limitations. For instance, the fluoro materials cannot be easily obtained [31,32,34] or the operation is inconvenient because of sensitivity to water and air [31–33].

The palladium-catalyzed coupling reaction of organoboron compounds with electrophiles in the presence of a base (the 'Suzuki reaction' [35,36]) has many attractive features: high yields, milder condition, many functional groups surviving under reaction conditions, and the ability to remain unaffected in the presence of water. Additionally, 2-bromo-3,3,3-trifluoropropene (**2**) could be obtained easily by dehydrobromination of 1,2-dibromo-3,3,3-trifluoropropane (**4**), one of the readily available and economically feasible fluoro materials, with a base in high yield [37]. Thus, firstly, we have studied the coupling reaction of arylboronic acids (**1**) with **2** to give **3**, and herein, we wish to report the experimental results.

2. Results and discussion

Initially, α-naphthylboronic acid and **2** were used as the starting materials for optimizing the coupling conditions ((1); summarized in Table 1).

As $PdCl_2(PPh_3)_2$ can be stored and handled in the presence of air without any special precaution, we selected it

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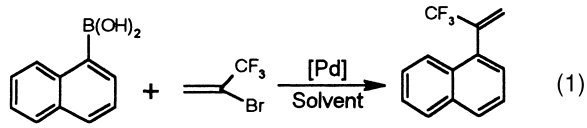
Table 1
The coupling of α-naphthylboronic acid with 2-bromo-3,3,3-trifluoropropene



(1)

Entry[a]	Solvents	Catalysts	Temperature (°C)/time (h)	Base (aq, 2M)	Yields (%)[b]
1	THF	$Pd(PPh_3)_4$	20/10	Na_2CO_3	0
2	DME	$PdCl_2(PPh_3)_2$	20/12	Na_2CO_3	10
3	THF	$Pd(PPh_3)_4$	70/10	Na_2CO_3	50
4	Benzene	$Pd(PPh_3)_4$	80/11	Na_2CO_3	0
5	DME	$PdCl_2(PPh_3)_2$	85/12	Na_2CO_3	65
6	DME	$PdCl_2(PPh_3)_2$	75/12	KOH	70
7	DME–THF (1 : 1, v/v)	$PdCl_2(PPh_3)_2$	70/11	KOH	94

[a] All reactions were carried out in nitrogen atmosphere using a catalyst (3 mmol%), α-naphthylboronic acid (1 mmol), **2** (1.5 mmol), a base (2 ml), $AsPh_3$ (15 mmol%) in a solvent (3 ml).
[b] Isolated yields based on α-naphthylboronic acid.

rather than $Pd(PPh_3)_4$ as the catalyst. Table 1 demonstrates that in the presence of KOH and when using $PdCl_2(PPh_3)_2$ as the catalyst and a mixture of DME–THF (1 : 1, v/v) as a solvent, the Suzuki-type coupling of α-naphthylboronic acid with **2** could undergo easily (entry 7).

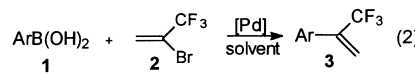
As given in Table 1, we selected the best condition (entry 7) to proceed with the coupling of **1** with **2** (2), and the results are summarized in Table 2.

It can be seen in Table 2 that various **3** could be obtained readily by the Suzuki-type coupling of **2** with the corresponding **1** in good yields under milder conditions. The reaction procedure might be a novel method for preparing **3**, one of the useful CF_3-substituted compounds.

As **2** can be prepared easily from **4** using KOH as a base in high yield [37], and the Suzuki-type reaction was generally proceeded with under similar conditions, it was possible to finish the coupling directly using **4** in place of **2** as the starting material (3). The results of the experiment are summarized in Table 3. The results shown in Table 3 indicate that **3** could be obtained directly by the reaction of **1** and **4** using THF–DME–H_2O (1 : 1 : 1, v/v/v) as a solvent in the presence of $PdCl_2(PPh_3)_2$, KOH and $AsPh_3$ in a one pot manner in high yields. This might be a more convenient method for preparing **3**.

In summary, we have provided a novel and convenient synthetic method of producing **3** by the coupling of **1** with **2** (or directly with **4**). The method has many attractive advantages: high yields, milder conditions, the ability to remain unaffected in the presence of water, the usage of economical and available fluoro materials, and convenience (especially, **3** could be obtained from **4** in a one pot manner).

Table 2
Palladium-catalyzed cross-coupling of arylboronic acids with 2-bromo-3,3,3-trifluoropropene



(2)

Entry[a]	Arylboronic acids		Temp. (℃)/ time (hr)	Products[b]		Yields (%)[c]
1		1a	74/12		3a	82
2		1b	70/10		3b	94
3		1c	74/12		3c	84
4		1d	74/12		3d	83
5		1e	74/12		3e	84
6		1f	70/10		3f	71
7		1g	70/10		3g	70

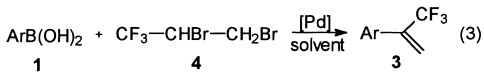
[a] The coupling reaction of arylboronic acids (1.0 mmol) with **2** (1.5 mmol) proceeded with using THF-DME (1 : 1, v/v, 3 ml) as a solvent in the presence of $PdCl_2(PPh_3)_2$ (3 mmol%), KOH (aq, 2M, 2 ml) and $AsPh_3$ (15 mmol%).
[b] All the products were fully characterized by IR ^1H NMR, ^{19}F NMR, MS, and C, H elemental analyses or HRMS.
[c] Isolated yields based on arylboronic acids.

3. Experimental

Infrared spectra were obtained on a Shimadzu IR-440 spectrometer using films. ^1H NMR spectra were recorded on a Varian EM-360A spectra with TMS as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid as an internal standard, and downfield shifts were designated as negative. Mass spectra were done on a Finnigan 4021 GC/MS/DC instrument.

The general procedure for the coupling of **1** with **2**: To a solution of **2** (1.5 mmol) in THF–DME (1 : 1; v/v; 3 ml) and KOH (aq, 2M, 2 ml), **1** (1.0 mmol), $PdCl_2(PPh_3)_2$

Table 3
The Synthesis of α-(trifluoromethyl)styrenes from arylboronic acids and 1,2-dibromo-3,3,3-trifluoropropane



Entry[a]	Arylboronic acids		Temp. (℃)/ time (hr)	Products		Yields (%)[b]
1		1a	74/12		3a	78
2		1b	70/10		3b	85
3		1c	74/12		3c	81
4		1d	74/12		3d	80
5		1e	74/12		3e	82
6		1f	70/10		3f	67
7		1g	70/10		3g	71

[a] The mixture of **1** (1.0 mmol), **4** (1.5 mmol), KOH (6 mmol), $AsPh_3$ (15 mmol%), $PdCl_2(PPh_3)_2$ (4 mmol%) in THF–DME–H_2O (1 : 1 : 1, v/v/v) in a nitrogen atmosphere was stirred at 0–5°C for 5 min, and then reacted at the given temperature for the given time.
[b] Isolated yields based on **1**.

(3 mmol%) and $AsPh_3$ (15 mmol%) were added in a nitrogen atmosphere. The reaction mixture was stirred at 70–74°C for 11–12 h (see Table 2). After being cooled to room temperature, water (10 ml) was added, then the mixture was extracted with ether (2 × 10 ml). The combined organic layer was washed with brine (3 × 10 ml) and dried over $MgSO_4$. After removing the solvent in *vacuo*, the residue was purified by short-path distillation under reduced pressure (for compounds **3a**, **3c**, **3d**, **3e**) or by silica gel chromatography, eluting with petroleum ether–ethyl acetate (100 : 1, v/v) (for **3b**, **3f**, **3g**).

The procedure for preparing **3** from **4** in a one pot manner: To a solution of **4** (1.5 mmol) in THF–DME–H_2O (1 : 1 : 1; v/v/v; 3 ml), **1** (1.0 mmol), $PdCl_2(PPh_3)_2$ (4 mmol%), $AsPh_3$ (15 mmol%) and KOH (6.0 mmol) were added in a nitrogen atmosphere. The reaction mixture was stirred at 0–5°C for 5 min, and subsequently, the reaction was proceeded with at the given temperature for the given time (see Table 3). Then the work-up was carried out by the above-mentioned procedures.

α-(trifluoromethyl)styrene (**3a**): colorless oil; b.p. 48–50°C 18 mm^{-1} Hg, 82% yield. IR (film) (cm^{-1}): 1580; 1500; 1400; 1350; 1160. ^1H NMR ($CDCl_3$) δ: 5.84 (s, 1H); 6.03 (s, 1H); 7.50 (m, 5H) ppm. ^{19}F NMR ($CDCl_3$) δ: −13.0 (s, 3F) ppm. MS *m/z* (relative intensity): 172 (M, 52); 103 (100); 78 (35). HRMS Calc. for $C_9H_7F_3$: 172.0050. Found: 172.0513.

1-(α-(trifluoromethyl)ethenyl)naphthalene (**3b**): pale yellow oil; 94% yield. IR (film) (cm^{-1}): 1600; 1400; 1350; 1230. ^1H NMR ($CDCl_3$) δ: 5.80 (s, 1H); 6.46 (s, 1H); 7.60 (m, 7H) ppm. ^{19}F NMR ($CDCl_3$) δ: −10.8 (s, 3F) ppm. MS *m/z* (relative intensity): 222 (M, 72); 153 (100); 126 (3). *Anal.* Calc. for $C_{13}H_9F_3$: C, 70.27; H, 4.08%. Found: C, 70.05; H, 4.20%.

2-methyl-α-(trifluoromethyl)styrene (**3c**): pale yellow oil; b.p. 52–53°C 18 mm^{-1} Hg, 84% yield. IR (film) (cm^{-1}): 1600; 1500; 1350; 1240. ^1H NMR ($CDCl_3$) δ: 2.57 (s, 3H); 5.84 (s, 1H); 6.03 (s, 1H); 7.35 (s, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −13.1 (s, 3F) ppm. MS *m/z* (relative intensity): 186 (M, 100); 117 (48); 91 (11). HRMS Calc. for $C_{10}H_9F_3$: 186.0656. Found: 186.0679.

3-methyl-α-(trifluoromethyl)styrene (**3d**): pale yellow oil; b.p. 51–53°C 18 mm^{-1} Hg, 83% yield. IR (film) (cm^{-1}): 1600; 1580; 1350; 1210. ^1H NMR ($CDCl_3$) δ: 2.58 (s, 3H); 5.92 (s, 1H); 6.12 (s, 1H); 7.43 (m, 4H) ppm. ^{19}F NMR (CDCl3) δ: −13.0 (s, 3F) ppm. MS *m/z* (relative intensity): 186 (M, 100); 117 (75); 91 (24). HRMS Calc. for $C_{10}H_9F_3$: 186.0656. Found: 186.0651.

4-methyl-α-(trifluoromethyl)styrene (**3e**): pale yellow oil; b.p. 52–54°C 18 mm^{-1} Hg, 84% yield. IR (film) (cm^{-1}): 1600; 1580; 1350; 1170. ^1H NMR ($CDCl_3$) δ: 2.52 (s, 3H); 5.85 (s, 1H); 6.02 (s, 1H); 7.35 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −13.2 (s, 3F) ppm. MS *m/z* (relative intensity): 186 (M, 84); 117 (100); 91 (37). HRMS Calc. for $C_{10}H_9F_3$: 186.0656. Found: 186.0671.

2-methoxyl-α-(trifluoromethyl)styrene (**3f**): pale yellow oil; 71% yield. IR (film) (cm^{-1}): 1600; 1500; 1350; 1170. ^1H NMR ($CDCl_3$) δ: 4.00 (s, 3H); 5.79 (s, 1H); 6.22 (s, 1H); 7.40 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −12.3 (s, 3F) ppm. MS *m/z* (relative intensity): 202 (M, 100); 187 (32); 133 (46); 105 (54). *Anal.* Calc. for $C_{10}H_9F_3O$: C, 59.41%; H, 4.48%. Found: C, 58.80; H, 4.32%.

3-chloro-α-(trifluoromethyl)styrene (**3g**): pale yellow oil; 70% yield. IR (film) (cm^{-1}): 1600; 1580; 1400; 1350; 1180; 800. ^1H NMR ($CDCl_3$) δ: 5.75 (s, 1H); 5.96 (s, 1H); 7.30 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −12.8 (s, 3F) ppm. MS *m/z* (relative intensity): 206 (M, 100); 137 (50); 102 (32). *Anal.* Calc. for $C_9H_6ClF_3$: C, 52.32; H, 2.93%. Found: C, 52.43; H, 2.99%.

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