E-(3-Trifluoromethyl-1,3-butadienyl)di-isopropoxyborane as a potentially useful CF₃-containing building block: synthesis and palladium-promoted coupling with aryl halides

Fuqiang Jin, Yuanyao Xu* and Biao Jiang

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032 (China)

Abstract

The title compound was synthesized from a trifluoroisopropenyl–zinc reagent and E-(2-bromoethenyl)di-isopropoxyborane. As a potentially useful building block for trifluoromethylated compounds, this trifluoromethyl-containing boron reagent underwent a palladium-catalyzed stereospecific coupling reaction with aryl halides to afford E-1-aryl-3-trifluoromethyl-1,3-butadienes.

Introduction

Because of the unique physical and biological properties imparted by the CF₃ group, there is at present an increasing interest in the synthesis of specifically trifluoromethylated organic molecules [1]. Although direct conversions of certain functional groups to the CF₃ group are available for the synthesis of trifluoromethylated aromatic compounds [2], the preparation of trifluoromethylated aliphatic compounds is often not straightforward because of the requirement for mild reaction conditions and because of the limited intrinsic reactivity of various trifluoromethylating reagents. An attractive alternative preparation for this kind of compound could be via versatile intermediates carrying a CF₃ group. Hence, the search for new trifluoromethylated building blocks and their further utilization for the synthesis of desired CF₃-containing aliphatic compounds are significant to organofluorine chemistry.

Recently, we have reported the synthesis of a trifluoroisopropenyl–zinc reagent (1) and its application as a useful α-(trifluoromethyl)ethenyl carbanion synthetic equivalent [3]. As part of our continuing studies on the utilization of 1, we have synthesized the E-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane (2) from 1 which, as a new versatile CF₃-containing building block, underwent cross-coupling reactions with aryl halides in the presence of a palladium catalyst.

Results and discussion

In the presence of a palladium catalyst, the trifluoroisopropenyl–zinc reagent 1 reacted with E-(2-bromoethenyl)di-isopropoxyborane (3) to afford E-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane (2) [eqn. (1)]. The optimum conditions for the synthesis of 2 have been examined and the results indicate that the best yield (68%) could be achieved in THF by the reaction of 1 with 3 (1.5:1 mole ratio) in the presence of 3 mol% of Pd(PPh₃)₄. Interestingly, 2 could not be obtained if the reaction was performed in Et₂O.

$$\text{(1)}$$
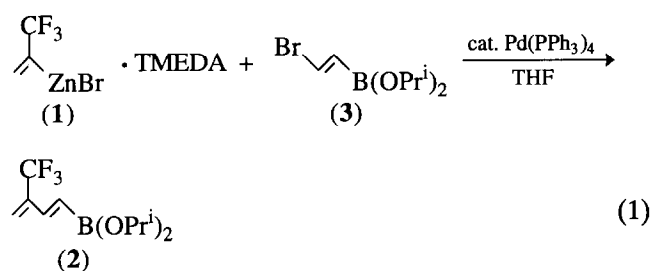
Cross-coupling of organoboron reagents with various electrophiles in the presence of a catalytic amount of palladium has been shown to be an effective method for the formation of a carbon–carbon bond [4]. To demonstrate the synthetic utility of 2, its cross-coupling with aryl halides was examined [eqn. (2)]. The results are depicted in Table 1.

$$\text{(2)}$$

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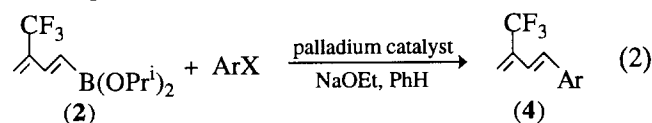
*To whom all correspondence should be addressed.

TABLE 1. Synthesis of E-1-aryl-3-trifluoromethyl-1,3-butadienes (4)^a

Entry No.	ArX	Reaction conditions Temp. (°C)/ time (h)	Products (4)	Yield^b (%)
1	O_2N-C₆H₄-I (4-nitrophenyl)	80/2	4a	86
2	C₆H₄(NO₂)-I (3-nitrophenyl)	80/2.5	4b	89
3	pyridyl-Br	r.t./8	4c	77
4	naphthyl-I	r.t./8, then 80/1	4d	81
5	naphthyl-Br	r.t./8, then 80/1	4e	85
6	C₆H₅-I (iodobenzene)	60/4	4f	48 / 20 (5a)
7	Cl-C₆H₄-I	60/3	4g	55 / 17 (5b)
8	biphenyl-Br	80/2.5	4h	58

^aThe reaction was conducted by using 1.1 equiv. of 2 and 1 equiv. of ArX in benzene in the presence of 3 mol% of PdCl₂(PPh₃)₂ or Ph(PPh₃)₄ and 2 equiv. of NaOEt in EtOH.
^bIsolated yield based on aryl halide.

As may be seen from Table 1, compound 2, as a boron reagent, exhibits a normal reactivity and reacts with various aryl halides in the presence of a palladium catalyst and base (NaOEt in the present case) to afford E-1-aryl-3-trifluoromethyl-1,3-butadienes stereospecifically in good yield. Hence, 2 can serve as a useful 3-trifluoromethyl-1,3-butadienyl carbanion synthetic equivalent.

In the case of iodobenzene (Table 1, entry 6) and 1-chloro-4-iodobenzene (Table 1, entry 7), in addition to the normal coupling products 4f and 4g, two other unusual products, 5a and 5b respectively, are obtained. From their ¹⁹F NMR and ¹H NMR spectra, 5a and 5b have been shown to be dimers of 4f and 4g, respectively, resulting from a Diels–Alder reaction. Further studies have revealed that all the compounds 4

Ar = C₆H₅ (5a); Ar = p-ClC₆H₄ (5b)
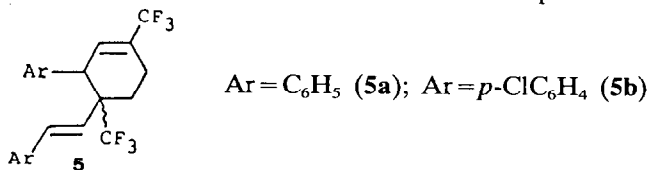
tend to dimerize but 4f and 4g exhibit a marked tendency in this respect which is even greater than that of their fluorine-free analogues, such as 1-phenyl-1,3-butadiene and 1-phenyl-3-methyl-1,3-butadiene [5]. Thus, for example, 12–13% of 1-phenyl-1,3-butadiene dimerized at room temperature and in the dark after 2.5 months [5b], whilst under the same conditions almost 50% of 4f dimerized after 40 d. This unusual tendency of compounds 4 to dimerize may result from the different effects of CF₃ substitution on the diene and the CF₃-substituted double bond. Possibly, the reactivity of the diene as a whole is not greatly affected by CF₃ substitution whereas the dienophilicity of the CF₃-substituted double bond is substantially enhanced.

1-Aryl-1,3-butadienes have been widely studied and serve as dienes in the Diels–Alder reaction [6] and also as precursors of complex molecules [7]. As their fluorine-containing analogues, E-1-aryl-3-trifluoromethyl-1,3-butadienes appear to be potentially useful intermediates for the synthesis of other trifluoromethylated molecules.

In summary, we have prepared a new versatile trifluoromethylated building block and established its usefulness in the synthesis of trifluoromethylated compounds as indicated by the synthesis of E-1-aryl-3-trifluoromethyl-1,3-butadienes.

Further applications of the present boron reagent are in progress.

Experimental

All boiling and melting points were uncorrected. Infrared spectra were obtained on a Shimadzu IR-440 spectrometer using KBr disks for solids and films of liquid products. NMR spectra (chemical shifts in ppm from TMS for ¹H NMR and from external TFA for ¹⁹F NMR; downfield shifts were designated negative in ¹⁹F NMR) were obtained on a Varian EM-360 spectrometer or a XL-200 spectrometer. Mass spectra were recorded on a Finnigan GC–MS 4021 instrument.

Synthesis of E-(3-trifluoromethyl-1,3-butadienyl)-di-isopropoxyborane (2)

To a mixture of E-(2-bromoethenyl)di-isopropoxyborane (5.8 g, 25 mmol) and Pd(PPh₃)₄ (860 mg, 0.75 mmol) was added a THF solution of trifluoropropenyl–zinc reagent [3a] (37.5 mmol). The reaction mixture was heated under reflux for 1 h. After being cooled to room temperature, the solvent was removed under reduced pressure and the residue extracted with anhydrous hexane (4×30 ml). Concentration of the solution followed by distillation under reduced pressure

afforded 4.2 g of the title compound (68% yield, b.p. 45 °C/3 mmHg). All manipulations were carried out under a nitrogen atmosphere. IR(film) (cm^{-1}) 1630; 1590; 1375; 1110; 980; 930. ^{1}H NMR (CCl$_4$) δ: 1.03 (d, $J = 6$ Hz, 12H); 4.35 (hept, $J = 6$ Hz, 2H); 5.48 (s, 1H); 5.62 (s, 1H); 5.95 (d, $J = 18$ Hz, 1H); 6.85 (d, $J = 18$ Hz, 1H) ppm. ^{19}F NMR (CCl$_4$) δ: −10.0(s) ppm.

General procedure for preparation of E-1-aryl-3-trifluoromethyl-1,3-butadienes (4)

To a stirred solution of an aryl halide (1.6 mmol) in 4 ml of benzene was added PdCl$_2$(PPh$_3$)$_2$ (30 mg, 0.04 mmol), followed by the introduction of E-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane (450 mg, 1.8 mmol) and 2 ml of a 2 M ethanolic solution of NaOEt. The reaction mixture was stirred at room temperature or under heating. After completion of the reaction, 2 ml of a 3 M aqueous solution of NaOH was added. The mixture was then stirred at room temperature for 2 h. Purification by column chromatography on silica gel (petroleum ether(60–90 °C)/ethyl acetate, 100:1) after extraction with hexane gave the product 4 (and 5).

Compound **4a**: m.p. 64–65 °C, 86% yield. IR (KBr) (cm^{-1}): 1590; 1500; 1320; 1150; 1100; 850; 820. ^{1}H NMR (CDCl$_3$) δ: 5.73 (d, $J = 2$ Hz, 1H); 5.87 (d, $J = 2$ Hz, 1H); 6.75 (d, $J = 17$ Hz, 1H); 6.88 (d, $J = 17$ Hz, 1H); 7.49–8.16, centred at 7.84 (A$_2$B$_2$, $J = 9$ Hz, 4H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.2 (s) ppm. MS *m/z* (relative intensity): 243(57); 196(100); 128(94). Analysis: Calc. for C$_{11}$H$_8$F$_3$NO$_2$: C, 54.30; H, 3.30; F, 23.46; N, 5.76%. Found: C, 54.03; H, 3.27; F, 23.42; N, 5.67%.

Compound **4b**: oil, 89% yield. IR(film) (cm^{-1}): 1540; 1460; 1350; 1160; 1130; 830; 800. ^{1}H NMR (CDCl$_3$) δ: 5.69 (d, $J = 1.5$ Hz, 1H); 5.81 (d, $J = 1.5$ Hz, 1H); 6.71 (d, $J = 17$ Hz, 1H); 6.85 (d, $J = 17$ Hz, 1H); 7.40–8.10 (m, 3H); 8.23 (s, 1H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.1 (s) ppm. MS *m/z* (relative intensity): 243 (100); 226 (58); 196 (45); 128 (27). HRMS: Calc. for C$_{11}$H$_8$F$_3$NO$_2$: 243.0507. Found: 243.0520.

Compound **4c**: oil, 77% yield. IR(film) (cm^{-1}): 1610; 1590; 1560; 1160; 1120; 980; 780. ^{1}H NMR (CDCl$_3$) δ: 5.67 (d, $J = 1$ Hz, 1H); 5.76 (d, $J = 1$ Hz, 1H); 6.80 (d, $J = 16.4$ Hz, 1H); 7.02–7.58 (m, 4H); 8.48 (m, 1H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.0 (s) ppm. MS *m/z* (relative intensity): 199 (55); 198 (100); 130 (55), HRMS: Calc. for C$_{10}$H$_8$F$_3$N: 199.0609 Found: 199.0591.

Compound **4d**: oil, 81% yield. IR(film) (cm^{-1}): 1680; 1590; 1490; 1100; 740; 720. ^{1}H NMR (CDCl$_3$) δ: 5.60 (d, $J = 1.4$ Hz, 1H); 5.72 (d, $J = 1.4$ Hz, 1H); 6.62 (d, $J = 16.2$ Hz, 1H); 7.20–8.00 (m, 8H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.0 (s) ppm. MS *m/z* (relative intensity): 248 (66); 179 (100). HRMS: Calc. for C$_{15}$H$_{11}$F$_3$: 248.0813. Found: 248.0814.

Compound **4e**: m.p. 50 °C, 85% yield. IR(KBr) (cm^{-1}) 1690; 1590; 1510; 1120; 780; 770. ^{1}H NMR (CDCl$_3$) δ: 5.64 (d, $J = 1.1$ Hz, 1H); 5.73 (d, $J = 1.1$ Hz, 1H); 6.72 (d, $J = 16.6$ Hz, 1H); 7.02 (d, $J = 16.6$ Hz, 1H); 7.30–7.80 (m, 7H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.2 (s) ppm. MS *m/z* (relative intensity): 248 (58); 179 (100). Analysis: Calc. for C$_{15}$H$_{11}$F$_3$: C, 72.57; H, 4.47; F, 22.96%. Found: C, 72.49; H, 4.43; F, 22.52%.

Compound **4f**: oil, 48% yield. IR(film) (cm^{-1}): 1480; 1440; 1110; 740; 680. ^{1}H NMR (CDCl$_3$) δ: 5.57 (d, $J = 1$ Hz, 1H); 5.68 (d, $J = 1$ Hz, 1H); 6.58 (d, $J = 17$ Hz, 1H); 6.79 (d, $J = 17$ Hz, 1H); 7.15–7.38 (m, 5H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.2 (s) ppm. MS *m/z* (relative intensity): 198 (51); 129 (100). HRMS: Calc. for C$_{11}$H$_9$F$_3$: 198.0656. Found: 198.0666.

Compound **4g**: oil, 55% yield. IR(film) (cm^{-1}): 1590; 1490; 1460; 1130; 810; 720; 700. ^{1}H NMR (CDCl$_3$) δ: 5.66 (s, 1H); 5.80 (s, 1H); 6.62 (d, $J = 16.7$ Hz, 1H); 6.84 (d, $J = 16.7$ Hz, 1H); 7.30–7.50, centred at 7.40 (A$_2$B$_2$, $J = 9$ Hz, 4H) ppm. ^{19}F NMR (CCl$_4$) δ: −10.7 (s) ppm. MS *m/z* (relative intensity): 232 (100); 197 (45); 177 (22); 111 (51). HRMS: Calc. for C$_{11}$H$_8$ClF$_3$: 232.0266. Found: 232.0256.

Compound **4h**: m.p. 117 °C, 58% yield. IR (KBr) (cm^{-1}): 1590; 1480; 1350; 960; 820; 760; 710; 680. ^{1}H NMR (CDCl$_3$) δ: 5.55 (d, $J = 1$ Hz, 1H); 5.65 (d, $J = 1$ Hz, 1H); 6.58 (d, $J = 17$ Hz, 1H); 6.81 (d, $J = 17$ Hz, 1H); 7.16–7.60 (m, 9H) ppm. ^{19}F NMR (CCl$_4$) δ: −11.2 (s) ppm. MS *m/z* (relative intensity): 274 (81); 205 (100). Analysis: Calc. for C$_{17}$H$_{13}$F$_3$: C, 74.44; H, 4.78; F, 20.78%. Found: C, 74.46; H, 4.74; F, 20.63%.

Compound **5a**: oil, 20% yield. IR (film) (cm^{-1}): 1720; 1680; 1590; 1480; 1440; 740; 690; 680. ^{1}H NMR (CDCl$_3$) δ: 2.18 (m, 2H); 2.39 (m, 2H); 3.76 (m, 1H); 5.90 (d, $J = 16.4$ Hz, 1H); 6.25 (m, 1H); 6.34 (d, $J = 16.4$ Hz, 1H); 7.00–7.40 (m, 10H) ppm. ^{19}F NMR (CCl$_4$) δ: −5.3 (s, 3F); −8.0 (s, 3F) ppm. MS *m/z* (relative intensity): 396 (15); 198 (100); 129 (90). HRMS: Calc. for C$_{22}$H$_{18}$F$_6$: 396.1312. Found: 396.1332.

Compound **5b**: oil, 17% yield. IR(film) (cm^{-1}): 1730; 1680; 1580; 1480; 960; 930; 820; 790. ^{1}H NMR (CDCl$_3$) δ: 2.26 (m, 2H); 2.47 (m, 2H); 4.02 (m, 1H); 5.92 (d, $J = 16$ Hz, 1H); 6.28 (m, 1H); 6.40 (d, $J = 16$ Hz, 1H); 7.24–7.48, centred at 7.36 (A$_2$B$_2$, $J = 8$ Hz, 4H); 7.26–7.54, centred at 7.40 (A$_2$B$_2$, $J = 8$ Hz, 4H) ppm. ^{19}F NMR (CCl$_4$) δ: −5.5 (s, 3F); −8.0 (s, 3F) ppm. MS *m/z* (relative intensity): 464 (4.3); 233 (100). Analysis: Calc. for C$_{22}$H$_{16}$Cl$_2$F$_6$: C, 56.93; H, 3.47%. Found: C, 56.80; H, 3.39%.

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