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Synthesis of α-Fluoro-β-trifluoromethyl Alka-2,4-dienes

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ABSTRACT: *The palladium/copper(I) iodide cocatalyzed coupling reaction of (Z)-α-fluoro-β-trifluoromethylstannanes (***1***) with vinyl iodides (***2***) has been explored giving substituted α-fluoro-β-trifluoromethyl dienes (***3***) in 33–95% yields. In studies we have conducted so far, a larger number of the configurations of the products remained unchanged (cases* **3a, 3e–h***), though in several cases (cases* **3b–d***) two configurations of the products were obtained.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:208–211, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20284

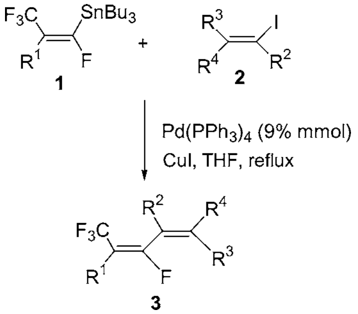
INTRODUCTION

The new methodology for the synthesis of 1,3-dienes and their derivatives have attracted much interest, because a large number of these compounds have been noted as important functionalities in naturally occurring compounds that show biological activity [1]. They are useful intermediates in cycloaddition reactions and Michael-type conjugated additions, and can undergo many synthetic transformations [2], particularly in the synthesis of some natural products [3]. Recently, much attention has been paid to the fluorinated species because they can be employed as useful intermediates for the synthesis of biologically active compounds [4]. Several methods for the synthesis of functionalized trifluoromethyl 1,3-dienes have been reported [5], but they are still limited. The well-known Stille cross-coupling reaction is a widely employed method for the carbon–carbon bond formation [6]. Of late, it has become a useful synthetic approach in organic synthesis, especially for the synthesis of naturally occurring compounds [7].

RESULTS AND DISCUSSION

In our continuing investigation to explore the new methods for the synthesis of functionalized conjugated dienes [8], we found a convenient synthesis of polyfluorinated conjugated dienes via a Stille cross-coupling reaction. The reaction is shown in Scheme 1.

The palladium/copper(I) iodide cocatalyzed coupling reaction of (*Z*)-α-fluoro-β-trifluoromethylstannanes (**1**) with vinyl iodides (**2**) gave substituted α-fluoro-β-trifluoromethyl dienes (**3**) in 33–95%



SCHEME 1

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TABLE 1 Preparation of α-Fluoro-β-trifluoromethyl Alka-2,4-dienes (**3**)

Compound	*R*^{1}	*R*^{2}	*R*^{3}	*R*^{4}	*Yield (%)*^{a}	*2E:2Z*^{b}
3a	4-$CH_3OC_6H_4$	H	CO_2Et	H	73	100:0
3b	4-ClC_6H_4	H	CO_2Et	H	93	86:14
3c	4-ClC_6H_4	H	H	CO_2Et	95	67:33
3d	4-$CH_3OC_6H_4$	H	H	CO_2Et	86	47:53
3e	4-ClC_6H_4	H	H	*n*-C_6H_{13}	62	100:0
3f	4-$CH_3OC_6H_4$	H	H	*n*-C_6H_{13}	33	100:0
3g	4-ClC_6H_4	CH_3	CO_2Me	H	91	100:0
3h	4-$CH_3OC_6H_4$	CH_3	CO_2Me	H	79	100:0

[a] Isolated yields.
[b] The ratios of *E*- to *Z*-isomers were estimated on the basis of NMR data.

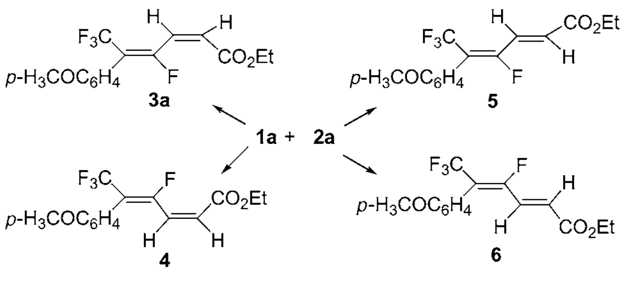
yields. The results are summarized in Table 1. All compounds are new and are characterized by microanalyses (or high-resolution mass spectrometry), IR, NMR, and mass spectroscopy.

It can be assumed that there are four possible isomers **3a, 4, 5**, and **6** that will be obtained in the reaction of **1a** with ethyl (*Z*)-3-iodo-2-propenoate (**2a**) (Scheme 2).

The ^{1}H NMR data of **3a** show that the coupling constant ($^3J_{HH}$) of vinyl protons is equal to 12.4, indicating that the configuration of the double bond containing two hydrogen groups remained unchanged. Thus, proposed structures **5** and **6** should be ruled out.

On the basis of F-CF_3 coupling constants across the double bond reported in the literature [9], if the trifluoromethyl group was trans with respect to the F group, the $^4J_{FFtrans}$ ranged from 7 to 13 Hz, though for those *cis* with respect to the F group, the $^4J_{FFcis}$ ranged from 21 to 31 Hz. In our case, the coupling constant ($^4J_{FF}$) of **3a** is equal to 11.2 Hz, showing that the retention of the configuration of the double bond containing the trifluoromethyl and fluorine groups occurred. Thus the configuration of **3a** was ascertained as 2*E*, 4*Z*.

The Stille cross-coupling reaction of fluorinated vinylstannanes has been reported previously with retention of configuration [8a, 10]. In studies we have conducted so far, a larger number of the configurations of the products remained unchanged (Table 1, cases **3a, 3e–h**), though in several cases (Table 1, cases **3b–d**) two configurations of the products were obtained. The detailed mechanism for the explanation of this phenomenon is being pursued.



SCHEME 2

In conclusion, a new methodology of palladium/copper(I) iodide cocatalyzed coupling reaction of (*Z*)-α-fluoro-β-trifluoromethylstannanes (**1**) with vinyl iodides (**2**) has been explored giving substituted α-fluoro-β-trifluoromethyl dienes (**3**). In studies we have conducted so far, a larger number of the configurations of the products remained unchanged (Table 1, cases **3a, 3e–h**), though in several cases (Table 1, cases **3b–d**) two configurations of the products were obtained. The title compounds would be expected to be useful intermediates in the synthesis of polyfluorinated biologically active compounds.

EXPERIMENTAL

The IR spectra of liquid products were obtained as films on a Digilab FTS-20E spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm from tetramethylsilane, in $CDCl_3$, J values are given in Hz). ^{19}F NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer (δ in ppm from external trifluoroacetic acid, in $CDCl_3$, positive for upfield shifts). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer. High-resolution mass spectrometry data were obtained on a Finnigan-Mat 8430 high-resolution mass spectrometer.

(*Z*)-α-Fluoro-β-trifluoromethylvinylstannanes (**1**) was prepared according to the method reported in the literature [11a].

Ethyl (*Z*)-3-iodo-2-propenoate (**2a**) was prepared according to the known method [11b].

Ethyl (*E*)-3-iodo-2-propenoate (**2c**) was prepared according to the method reported in the literature [12].

(*E*)-1-Iodo-2-octene (**2e**) was prepared according to the known method [13].

Ethyl (*Z*)-3-iodo-3-methyl-2-propenoate (**2g**) was prepared according to the method reported [14].

*General Procedure for the Preparation of Functionalized Polyfluorinated Alka-2,4-dienes (***3***)*

A mixture of (*Z*)-α-fluoro-β-trifluoromethylvinylstannane (**1**) (0.21 mmol), vinyl iodide (**2**) (0.21 mmol), tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.018 mmol), and Cu(I) (21 mg, 0.11 mmol) in THF (5 mL) was heated at refluxing temperature for 24 hr. Thin-layer chromatography showed that the starting material had disappeared. The reaction mixture was poured into diethyl ether (40 mL), washed with water (3 × 10 mL), and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography, eluting with petroleum ether (60–90°C) to give the product **3**.

*5-Ethoxycarbonyl-1,1,1,3-tetrafluoro-2-(4-methoxyphenyl)-penta-2E,4Z-diene (***3a***)*

Yield: 73%; oil; 2*E*,4*Z*:2*Z*,4*Z* = 100:0. IR (film) (cm^{-1}): 1730, 1610, 1510, 1340, 1250, 1170, 1120, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 7.28–7.20 (m, 2H), 6.94–6.85 (m, 2H), 6.72 (ddq, $J = 23.0$, 12.4, 2.4 Hz, 1H), 6.16 (dd, $J = 12.4$, 2.1 Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 3.83 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): δ −20.5 (d, $J = 11.2$ Hz, 3F), 19.2 (q, $J = 11.3$ Hz, 1F). MS *m/z* (rel. int.): 318 (M$^+$, 61), 298 (5), 273 (36), 245 (100), 225 (49), 213 (9), 201 (16). Anal. Calcd for $C_{15}H_{14}F_4O_3$ (318.26): C, 56.61%; H, 4.43%. Found: C, 56.78%; H, 4.52%.

*5-Ethoxycarbonyl-3,1,1,1-tetrafluoro-2-(4-chlorophenyl)-pentadiene (***3b***)*

Yield: 93%; oil; 2*E*,4*Z*:2*Z*,4*Z* = 86:14. IR (film) (cm^{-1}): 1760, 1490, 1340, 1210, 1170, 1130, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 7.42–7.37 (m, 2H), 7.31–7.24 (m, 2H), 6.71 (ddq, $J = 21.5$, 12.3, 2.5 Hz, 1H), 6.20 (dd, $J = 12.4$, 2.2 Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 1.29 (t, $J = 7.2$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): δ −21.6 (d, $J = 11.2$ Hz, 0.86 × 3F), −18.3 (d, $J = 23.3$ Hz, 0.14 × 3F), 30.2 (q, $J = 11.5$ Hz, 0.86 × 1F), 32.8 (q, $J = 23.3$ Hz, 0.14 × 1F). MS *m/z* (rel. int.): 324 (M$^+$ + 2, 12), 322 (M$^+$, 33), 303 (7), 277 (53), 249 (55), 229 (100). Anal. Calcd for $C_{14}H_{11}ClF_4O_2$ (322.68): C, 52.11%; H, 3.44%. Found: C, 52.26%; H, 3.52%.

*5-Ethoxycarbonyl-3,1,1,1-tetrafluoro-2-(4-chlorophenyl)-pentadiene (***3c***)*

Yield: 95%; oil; 2*E*,4*E*:2*Z*,4*E* = 67:33. IR (film) (cm^{-1}): 1720, 1490, 1330, 1310, 1290, 1200, 1170, 1130, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 7.62 (ddq, $J = 27.8$, 15.4, 1.2 Hz, 1H), 7.44–7.38 (m, 2H), 7.28–7.22 (d, $J = 8.4$ Hz, 2H), 6.48 (d, $J = 15.5$ Hz, 1H), 4.29 (q, $J = 7.3$ Hz, 2H), 1.35 (t, $J = 8.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): δ−21.6 (d, $J = 11.3$ Hz, 0.67 × 3F), −18.8 (d, $J = 23.3$ Hz, 0.33 × 3F), 30.2 (q, $J = 11.5$ Hz, 0.67 × 1F), 32.7 (q, $J = 23.3$ Hz, 0.33 × 1F). MS *m/z* (rel. int.): 324 (M$^+$ + 2, 7), 322 (M$^+$, 20), 302 (3), 277 (31), 249 (64), 229 (100). Anal. Calcd for $C_{14}H_{11}ClF_4O_2$ (322.68): C, 52.11%; H, 3.44%. Found: C, 52.09%; H, 3.57%.

*5-Ethoxycarbonyl-3,1,1,1-tetrafluoro-2-(4-methoxyphenyl)-pentadiene (***3d***)*

Yield: 86%; oil; 2*E*,4*E*:2*Z*,4*E* = 53:47. IR (film) (cm^{-1}): 1720, 1610, 1330, 1310, 1250, 1210, 1170, 1130, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 7.63 (ddq, $J = 27.9$, 15.4, 1.3 Hz, 1H), 7.27–7.21 (m, 2H), 6.96–6.91 (d, $J = 7.9$ Hz, 2H), 6.43 (d, $J = 15.4$, 1H), 4.30 (q, $J = 7.3$ Hz, 2H), 3.85 (s, 0.47 × 3H), 3.84 (s, 0.53 × 3H), 1.34 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): δ−21.6 (d, $J = 11.1$ Hz, 0.47 × 3F), −18.7 (d, $J = 23.3$ Hz, 0.53 × 3F), 32.0 (q, $J = 11.5$ Hz, 0.47 × 1F), 34.3 (q, $J = 23.2$ Hz, 0.53 × 1F). MS *m/z* (rel. int.): 318 (M$^+$, 53), 298 (4), 273 (34), 245 (100), 225 (52), 213 (8), 201 (17). Anal. Calcd for $C_{15}H_{14}F_4O_3$ (318.27): C, 56.61%; H, 4.43%. Found: C, 56.91%; H, 4.64%.

*3,1,1,1-Tetrafluoro-2-(4-chlorophenyl)-undeca-2E,4E-diene (***3e***)*

Yield: 62%; oil; 2*E*,4*E*:2*Z*,4*E* = 100:0. IR (film) (cm^{-1}): 2930, 1660, 1490, 1350, 1220, 1160, 1130, 1090, 950. ^{1}H NMR ($CDCl_3$/TMS): δ 7.39–7.34 (m, 2H), 7.22 (d, $J = 8.6$ Hz, 2H), 6.48–6.40 (m, 2H), 2.25 (q, $J = 6.9$ Hz, 2H), 1.50–1.11 (m, 8H), 0.90 (t, $J = 6.5$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): δ−21.8 (d, $J = 11.5$ Hz, 3F), 28.4 (q, $J = 11.5$ Hz, 1F). MS *m/z* (rel. int.): 336 (M$^+$ + 2, 11), 334 (M$^+$, 31), 322 (7), 307 (7), 249 (41), 215 (100), 195 (65). Anal. Calcd for $C_{17}H_{19}ClF_4$ (334.78): C, 60.99%; H, 5.72%. Found: C, 61.15%; H, 5.91%.

*3,1,1,1-Tetrafluoro-2-(4-methoxyphenyl)-undeca-2E,4E-diene (**3f**)*

Yield: 33%; oil; $2E,4E:2Z,4E = 100:0$. IR (film) (cm^{-1}): 2930, 1660, 1610, 1510, 1470, 1290, 1250, 1160, 1120. ^{1}H NMR ($CDCl_3$/TMS): δ 7.18 (d, $J = 8.6$ Hz, 2H), 6.90–6.85 (m, 2H), 6.51–6.26 (m, 2H), 3.81 (s, 3H), 2.22 (q, $J = 7.3$ Hz, 2H), 1.56–1.14 (m, 8H), 0.93 (t, $J = 7.5$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta -21.6$ (d, $J = 12.0$ Hz, 3F), 30.4 (q, $J = 12.0$ Hz, 1F). MS m/z (rel. int.): 330 (M^+, 48), 311 (3), 275 (2), 259 (9), 245 (100), 225 (10). HRMS: m/z calcd for $C_{18}H_{22}F_4O$ (330.36): 330.1607; found 330.1564.

*5-Methoxycarbonyl-4-methyl-3,1,1,1-tetrafluoro-2-(4-chlorophenyl)-penta-2E,4Z-diene (**3g**)*

Yield: 91%; oil; $2E,4Z:2Z,4Z = 100:0$. IR (film) (cm^{-1}): 1730, 1690, 1640, 1610, 1510, 1440, 1360, 1330, 1290, 1250, 1120, 1040, 960. ^{1}H NMR ($CDCl_3$/TMS): δ 7.40–7.37 (m, 4H), 6.03 (br.s, 1H), 3.77 (s, 3H), 2.18–2.16 (m, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta -18.4$ (d, $J = 10.0$ Hz, 3F), 10.1 (q, $J = 10.0$ Hz, 1F). MS m/z (rel. int.): 324 ($M^+ + 2$, 5), 322 (M^+, 15), 291 (11), 275 (5), 263 (48), 253 (100), 243 (62), 227 (21). Anal. Calcd for $C_{14}H_{11}ClF_4O_2$ (322.68): C, 52.11%; H, 3.44%. Found: C, 52.49%; H, 3.86%.

*5-Methoxycarbonyl-4-methyl-3,1,1,1-tetrafluoro-2-(4-methoxyphenyl)-penta-2E,4Z-diene (**3h**)*

Yield: 79%; oil; $2E,4Z:2Z,4Z = 100:0$. IR (film) (cm^{-1}): 1730, 1610, 1510, 1340, 1250, 1170, 1120, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 7.35 (d, $J = 8.4$ Hz, 2H), 6.93–6.89 (m, 2H), 6.01 (br.s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.17–2.15 (m, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta -17.4$ (d, $J = 9.6$ Hz, 3F), 12.6 (q, $J = 9.8$ Hz, 1F). MS m/z (rel. int.): 318 (M^+, 21), 298 (2), 287 (11), 259 (100), 249 (26), 239 (39), 215 (12), 190 (69). Anal. Calcd for $C_{15}H_{14}F_4O_3$ (318.26): C, 56.61%; H, 4.43%. Found: C, 56.88%; H, 4.54%.

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