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The trifluoromethylation of 1,1-dibromo-1-alkenes using trifluoromethylcopper (CF_3Cu) generated in situ from methyl fluorosulfonyldifluoroacetate

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Abstract

The trifluoromethylation of 2-aryl-1,1-dibromo-1-alkenes with CF_3Cu under palladium catalysis gave bistrifluoromethylated compounds (**2**), whereas under the same reaction conditions, monotrifluoromethylated products (**3**) were obtained exclusively in the case of 2-alkyl-1,1-dibromo-1-alkenes.

Keywords: Trifluoromethylation; 1,1-Dibromo-1-alkenes; Palladium catalysis

1. Introduction

The introduction of the trifluoromethyl group into an organic compound can bring about remarkable changes in the physical, chemical and biological properties that result in new compounds/materials making them suitable for diverse applications in the areas of materials science, agrochemistry, and biomedical chemistry [1,2]. While a wide variety of methods have been developed for introducing trifluoromethyl groups into organic compounds [3,4], the coupling reaction of alkene halides with in situ generated trifluoromethylcopper (CF_3Cu) is rapidly becoming the method of choice [5]. 1,1-Dibromo-1-alkenes are easily prepared [6,7], and are versatile in organic synthesis. They can form (*Z*)-1-aryl(alkenyl)-1-bromo-1-alkenes, stereospecifically trisubstituted alkenes, disubstituted *cis*-1-bromo-1-alkenes, and 1,3-diynes through coupling with organoboronic acids [8,9], organostannanes [10,11], organozinc and Grignard reagents [12–14], tributyltin hydride [15] and alkynes [16]. Stimulated by these findings we were interested in the investigation of the trifluoromethylation of 1,1-dibromo-1-alkenes in order to obtain a novel type of trifluoromethyl-containing building blocks.

2. Results and discussion

1,1-Dibromo-alkenes were prepared by the reaction of aldehydes with triphenyl phosphorus and carbon tetrabromide in dichloromethane [7]. 1,1-Dibromo-2-(4-nitrophenyl)ethene (**1a**) was chosen as model substrate to couple with in situ generated CF_3Cu. First, the trifluoromethylation of **1a** was carried out using modified Chen's methodology [17,18]. Treatment of **1a** with $FSO_2CF_2CO_2Me$ (5.0 eq.) and CuI (0.3 eq.) in DMF/HMPA at 70°C for 24 h gave a mixture of bistrifluomethylated compound (**2a**), monotrifluoromethylated compounds (*E*)-**3a** and (*Z*)-**3a**, along with unreacted **1a** (Scheme 1). These compounds were very difficult to separate. The ratio of **2a**:(*E*)-**3a**:(*Z*)-**3a** was 2:1:1 as determined by ^{19}F NMR. In an attempt to get a single product and improve the reaction efficiency, we examined the trifluoromethylation under palladium catalysis. When 5 mol% $PdCl_2$ was added to the reaction mixture under similar reaction conditions, **1a** was totally converted and the ratio of **2a**:(*E*)-**3a**:(*Z*)-**3a** was changed to 12:1:1. When the $PdCl_2$ was replaced by $Pd(PPh_3)_4$, we were pleased to find that only a single bistrifluomethylated compound (**2a**) was isolated in 82% yield. These results showed the addition of palladium catalyst greatly improved the bistrifluomethylation. 1,1-Bis(trifluoromethyl)alkenes have been prepared from the reaction of aldehydes with 2,2-dichlorohexafluoropropane [19] or tetrakis(trifluoromethyl)-1,3-dithietane [20] in the presence of triphenyl phosphine.

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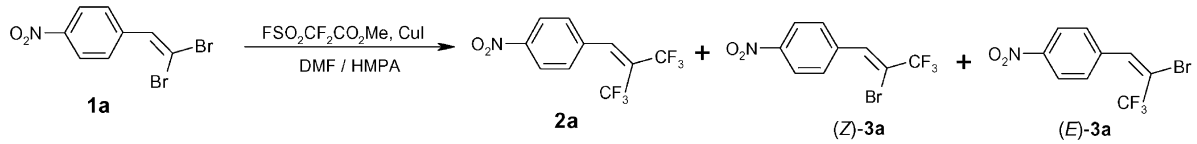
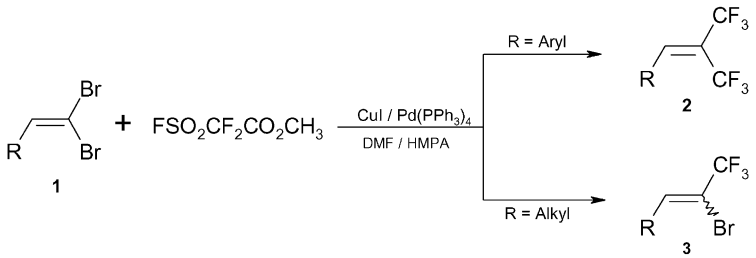


Scheme 1.



Scheme 2.

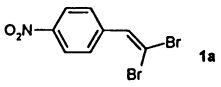
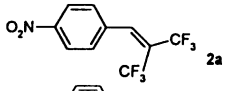
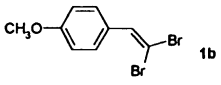
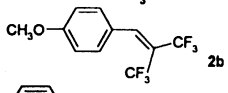
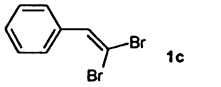
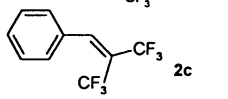
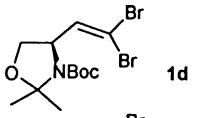
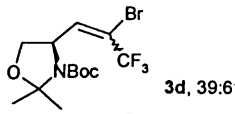
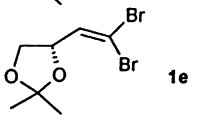
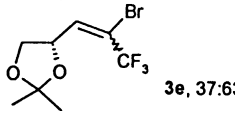
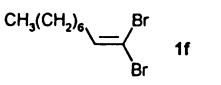
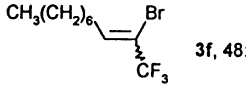
However, the trifluoromethyl-containing starting materials are not readily accessible.

With these results in hand we next performed the trifluoromethylation reaction with a more extensive range of 1,1-dibromo-1-alkenes (Scheme 2 and Table 1). As shown in Table 1, 2-aryl-1,1-dibromo-1-alkenes gave bistrifluoromethylated compounds (**2**) in good yields, with no to small amount of monotrifluoromethylated products (**3**) isolated. Substitutions at the *para* position of the aromatic ring by the electron-donating methoxy group did not affect the trifluoromethylation reaction (entry 2). However, in the case of 2-alkyl-1,1-dibromo-1-alkenes under reaction conditions identical to those used for 2-aryl-1,1-dibromo-1-alkenes (entries 4–6), monotrifluoromethylated products (**3**) were obtained exclusively instead of the bistrifluoromethylated compounds (**2**).

3. Experimental section

^{1}H NMR spectra were recorded on a 300 MHz spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on a 56.4 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in ppm, coupling constants (J) are given in Hz. Mass spectra

Table 1
Trifluoromethylation of 1,1-dibromo-1-alkenes with in situ generated CF_3Cu under $Pd(PPh_3)_4$ catalysis

Entry	Dibromide	Product	Yield (%)[a]
1	 **1a**	 **2a**	82
2	 **1b**	 **2b**	76
3	 **1c**	 **2c**	55
4	 **1d**	 **3d, 39:61**[b]	90[b]
5	 **1e**	 **3e, 37:63**[b]	82[b]
6	 **1f**	 **3f, 48:52**[b]	60[b]

[a] Yields were based on **1**.
[b] The *Z*:*E* ratio was determined by ^{1}H NMR.

were recorded on a Finnigan-MAT-8430 instrument using EI ionization at 70 eV. IR spectra were recorded on a Shimadzu IR-440 spectrometer. 1,1-Dibromo-alkenes (**1**) were prepared using the literature procedure [7].

3.1. Representative procedure for the trifluoromethylation of 1,1-dibromo-alkenes 1

A solution of $FSO_2CF_2CO_2CH_3$ (1.3 ml, 10 mmol) in DMF (5 ml) was added via syringe over a period of 1.5 h to a mixture of dibromide (**1a**) (615 mg, 2 mmol), CuI (115 mg, 0.6 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and HMPA (1 ml) in DMF (10 ml) at 70°C under a nitrogen atmosphere. The reaction was stirred at 70°C for 24 h before being cooled to room temperature. Saturated aqueous NH_4Cl (30 ml) was added and the mixture was extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel and elution with 25:1 hexane ethyl acetate gave compounds **2a** (469 mg, 82% yield).

3.2. 1,1-Ditrifluoromethyl-2-(4-nitrophenyl)ethene (*2a*)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, $J = 8.7$ Hz, 2H), 7.74 (s, 1H), 7.55 (d, $J = 8.7$ Hz, 2H); ^{19}F NMR (56.4 MHz, $CDCl_3$): δ −20.8 (s, 3F), −14.6 (s, 3F); IR (KBr) 2985, 1672, 1527, 1351, 1284, 1194, 1164 cm^{-1}; MS *m/z* 285 (M^+, 94), 318 (100), 169 (96), 89 (11); anal. calcd for $C_{10}H_5F_6NO_2$: C, 42.12; H, 1.77; N, 4.91. Found: C, 42.45; H, 1.94; N, 5.21%.

3.3. 1,1-Ditrifluoromethyl-2-(4-methoxyphenyl)ethene (*2b*)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.48 (d, $J = 8.9$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 3.80 (s, 3H); ^{19}F NMR (56.4 MHz, $CDCl_3$): δ −19.8 (s, 3F), −14.6 (s, 3F); IR (thin film) 2966, 1608, 1516, 1289, 1176, 1154 cm^{-1}; MS *m/z* 271 ($M^+ + 1$, 14), 270 (M^+, 100); anal. calcd for $C_{11}H_8F_6O$: C, 48.90; H, 2.99. Found: C, 48.70; H, 2.96%.

3.4. 1,1-Ditrifluoromethyl-2-phenylethene (*2c*)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 − 7.20 (m); ^{19}F NMR (56.4 MHz, $CDCl_3$): δ −17.6 (s, 3F), −9.8 (s, 3F); IR (thin film) 3033, 1275, 1216, 1138 cm^{-1}; MS *m/z* 241 ($M^+ + 1$, 12), 240 (M^+, 100), 171 (28), 151 (74); HRMS calcd for $C_{10}H_6F_6$: C, 240.0337. Found: 240.0373.

3.5. (Z)/(E)-tert-butyl (4S)-4-(2′-bromo-2′-trifluoromethyleth-1′-enyl)-2,2-dimethoyyloxazolidine-3-carboxylate (*3d*)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, $J = 8.9$ Hz, 0.39H), 6.46 (d, $J = 8.9$ Hz, 0.61H), 4.84 (m, 1H), 4.12 (m, 1H), 3.78 (m, 1H), 1.74 − 1.38 (m, 15H); ^{19}F NMR (56.4 MHz, $CDCl_3$): δ −17.8 (s, 1.83F), −10.6 (s, 1.17F); IR (thin film) 2984, 1709, 1378, 1175, 1155 cm^{-1}; MS *m/z* 373 (M^+, 5), 274 (43), 57 (100); anal. calcd for $C_{13}H_{19}BrF_3NO_3$: C, 41.73; H, 5.12; N, 3.74. Found: C, 41.91; H, 5.28; N, 3.99%.

3.6. 1-Bromo-1-trifluoromethyl-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]ethene (*3e*)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, $J = 7.5$ Hz, 0.37H), 6.56 (d, $J = 7.5$ Hz, 0.63H), 5.04 − 4.90 (m, 1H), 4.34 (m, 0.37H), 4.18 (m, 0.63H), 3.72 (m, 1H), 1.48 − 1.36 (m, 6H); ^{19}F NMR (56.4 MHz, $CDCl_3$): δ −17.2 (s, 1.89F), −9.8 (s, 1.11F); IR (thin film) 2992, 1374, 1179, 1149, 1066 cm^{-1}; MS *m/z* 275 ($M^+ + 1$, 15), 259 (73), 43 (100); anal. calcd for $C_8H_{10}BrF_3O_2$: C, 34.93; H, 6.67. Found: C, 34.99; H, 6.67%.

3.7. 1-Bromo-1-trifluoromethylnon-1-ene (*3f*)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (t, $J = 7.0$ Hz, 0.37H), 6.44 (t, $J = 7.0$ Hz, 0.63H), 3.72 (m, 1H), 2.38 − 2.24 (m, 2H), 1.54 − 1.26 (m, 10H), 1.48 − 1.36 (m, 6H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{19}F NMR (56.4 MHz, $CDCl_3$): δ −17.2 (s, 1.56F), −9.8 (s, 1.44F); IR (thin film) 2959, 2930, 1289, 1172, 1143 cm^{-1}; MS *m/z* 272 (M^+, 15), 69 (61), 43 (100); anal. calcd for $C_{10}H_{16}BrF_3$: C, 43.97; H, 5.90. Found: C, 43.72; H, 5.63%.

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