

Synthesis of Alkenyl- and Aryldifluoroacetate Using a Copper Complex from Ethyl Bromodifluoroacetate¹⁾

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Ethyl bromodifluoroacetate reacted with alkenyl or aryl iodides in the presence of copper powder in dimethyl sulfoxide (DMSO) to give the corresponding alkenyl- or aryldifluoroacetates in moderate to good yields.

Key words cross coupling; bromodifluoroacetate; alkenyl iodide; aryl iodide; copper; alkenyldifluoroacetate

Many organic fluorine compounds have been used as medicines based on many interesting characteristics due to high electronegativity and the small van der Waals radius of the fluorine atom.²⁾ Therefore, organic fluorine compounds have attracted much attention in biomedicinal and/or agrochemical fields, and many new methodologies for their synthesis have been developed. Some of these compounds possess a difluoromethylene group.³⁾ For the introduction of a difluoromethylene group, a Reformatsky reaction⁴⁾ using bromo- or iododifluoroacetate or an aldol type reaction⁵⁾ of enolate or ketene acetal from the above acetate have been widely used. These reactions give α -hydroxydifluoromethylene compounds. However, the α -hydroxy group of a difluoromethylene group is quite unreactive and very difficult to remove due to the high electronegativity of the fluorine atoms. Therefore, synthesis of difluoromethylene compounds without a hydroxy group in the α -position is rather difficult. For this purpose, cross coupling of the above acetate with halogen compounds seemed suitable. One example of this type of reaction was reported by Kobayashi *et al.* using a copper complex from methyl difluoroiodoacetate.^{6,7)} This method can be applied to a wide range of halogen compounds. However, methyl difluoroiodoacetate is not commercially available and must be synthesized from bromodifluoroacetate; three moles were used with one mole of halogen compounds. Here, we would like to report the cross coupling reaction of commercially available ethyl bromodifluoroacetate (**1**) with some halogen compounds in the presence of copper powder.

Since Kobayashi *et al.* have reported that hexamethylphosphoric triamide (HMPA) is the best solvent for a coupling reaction of this type,⁷⁾ three equivalents of **1** were reacted with (*E*)-1-iodohexene (**2**) in the presence of Cu

powder⁸⁾ in HMPA at 55 °C, and ethyl (*E*)-3,3-difluoro-3-octenoate (**3**) was obtained, but the yield was only 25%, and the formation of a fairly large amount of 1-bromohexene (**4**) was confirmed by GC-MS (Chart 1).

The formation of **4** seemed to be the reason for the low yield of **3**. To lower the formation of **4**, we examined the solvent effect. Dimethyl sulfoxide (DMSO) gave a much better yield (42%) of **3** in a shorter reaction time. However, another byproduct was obtained in this solvent, the structure of which was assigned as diethyl 4-butyl-2,5,5-trifluoro-2-hexenedioate (**5**), based on its spectral data. A large F—H coupling shows the *E* configuration of the double bond. This seemed to be formed by the reaction of **3** with an excess of the copper reagent. To confirm this point, **3** was treated with **1** in the presence of Cu powder, then **5** was obtained (Chart 2).

To avoid the formation of **5**, one equivalent of **1** was used, then **3** was obtained in 64% yield. The results of this reaction in other solvents [*N,N*-dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), dimethoxyethane (DME) and pyridine (Py)] are shown in Table 1.

Kobayashi *et al.* obtained a fairly stable univalent copper complex from difluoroiodoacetate in HMPA.⁷⁾ To examine the stability of the complex in our reaction, **1** was stirred with Cu powder in DMSO at 55 °C for 12 h, then **2** was

Table 1. Investigation of Solvent Effect

BrCF ₂ COOEt (eq)	Solv.	Time (h) ^{a)}	Yield (%) ^{b)}	3 : 4 ^{c)}
3	HMPA	48	25	100 : 20
3	DMSO	12	42 ^{d)}	100 : 1.8
1	DMSO	12	64	100 : 1.5
1	DMF	36	15	100 : 75
1	DMI	84	2	100 : 200
1	DME	24	No reaction	—
1	Py	24	0 ^{e)}	—

a) Time until the peak of **1** was no longer detected by GC. b) Isolation yield of **3**. c) Area ratio on GC. d) **5** (15%) was isolated. e) Formation of **4** was confirmed by GC.

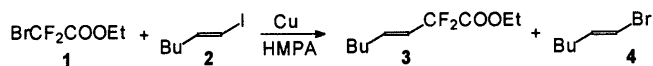


Chart 1

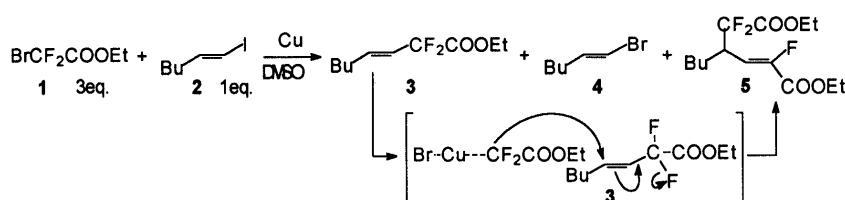


Chart 2

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added and stirred at this temperature for another 12 h, but **3** was not obtained at all. Most of **2** was recovered and the formation of **4** was confirmed by GC-MS. This means the intermediate complex was rather unstable and decomposed to copper bromide, which reacted with **2** to give **4**. On the other hand, **2** was treated with Cu powder, but no decrease in the peak of **2** was observed by GC. By addition of **1** to this mixture, **3** was formed (Chart 3). Namely, **2** did not react with Cu, whereas **1** added later reacted with Cu powder. The complex formed reacted immediately with **2** to give **3**. From these results, we temporarily propose the structure of the complex, which is shown in brackets in Chart 2. Namely, the complex from **1** in DMSO is different from the one in HMPA reported by Kobayashi's group.

Though the mechanism was not clear, we were able to obtain **3** from **1**. We examined the scope and limitation of this method. The results are summarized in Table 2.

As shown in entries 1 and 2, iodides on an sp^2 carbon gave the corresponding ethoxycarbonyldifluoromethyl derivatives stereospecifically in high yields, but iodides on an sp carbon

(entry 3) or on an sp^3 carbon (entry 4) did not give the expected cross coupling products. Compound **8** afforded a homo coupling product, 5,7-dodecadiyne. Aromatic iodides gave good results (entries 5, 7, 8), while a bromide resulted in the recovery of the starting material (entry 6). Nitro compound **13** gave the highest yield. This suggests that the active complex had a character of carbanion and that it reacted with **13**, having a highly electronegative nitro group. α - Or β -methyl groups did not disturb this reaction (entries 9 and 10), while the presence of a larger trimethylsilyl group in the α -position required longer reaction time and gave **22** in a much lower yield. The coupling constants between the fluorines on the CF_2 groups and the methyl (**18**) or the methylene (**20**) protons suggested that these were *cis*. All the products obtained so far were stereoselective, and the structure of **22** was temporarily assigned as *Z*.

In conclusion, ethyl bromodifluoroacetate (**1**) reacts with iodides on sp^2 carbons in the presence of Cu powder in DMSO to give the corresponding ethoxycarbonyldifluoromethyl derivatives stereospecifically in moderate to good yields, while sp or sp^3 analogs or bromides do not react. Thus, this methodology is limited to vinyl or aryl iodides, but **1** is much more easily available than difluoroiodoacetate, and the reaction temperature is easily controllable (55 °C). This method provides another easy access to a special type of difluoromethylene compounds.

Experimental

General Procedures 1H -NMR were recorded on JEOL-FX90Q and JNM-GX400 Spectrometers. Tetramethylsilane was used as an internal standard. ^{19}F -NMR were recorded on Hitachi FT-NMR R-1500 and JEOL-FX90Q Spectrometers. Benzotrifluoride was used as an internal standard.

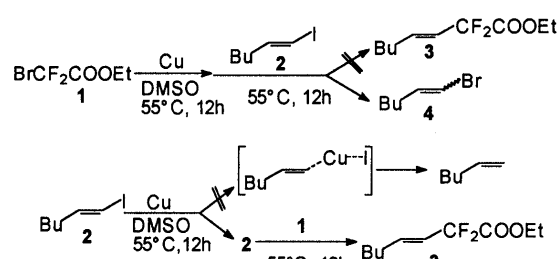
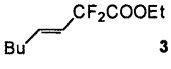
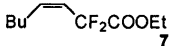
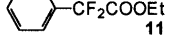
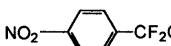
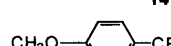
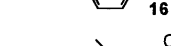
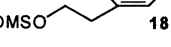
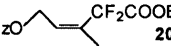


Chart 3

Table 2. Reaction of **1** with Various Halogen Compounds in the Presence of Cu in DMSO at 55 °C

Entry	R-X	Time (h)	R-CF ₂ COOEt	Yield (%)
1	 2	12	 3	64
2	 6	12	 7	69
3	 8	—	—	^{a)}
4	 9	6	—	No reaction
5	 10	5	 11	53
6	 12	5	—	No reaction
7	 13	9	 14	66
8	 15	5	 16	55
9	 17	9	 18	62
10	 19	8	 20	60 ^{d)}
11	 21	30	 22	21

^{a)} Homo coupling occurred at r.t. ^{b)} Synthesized according to the literatures (9, 10, 11). ^{c)} $BzOCH_2CH=CH_2$: $BzOCH_2CH=CH_2$ = 8.3:1. ^{d)} $BzOCH_2CH=CH_2$ isolated yield.

Mass spectra were obtained by JEOL JMS-DX-300. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. The melting point was measured on an Ishii Shoten Melting Point Apparatus. Gas-liquid chromatography (GLC) was carried out on a Hitachi 263-50 gas chromatograph (column, 5% SE-30 3 mm $\times$ 2 m; carrier, N₂ at 30 ml/min). Peak areas were calculated on a Hitachi D-2000 chromatointegrator.

Ethyl (E)-2,2-Difluoro-3-octenoate (3) 1) Using 3 eq of Ethyl Bromodifluoroacetate (**1**) in HMPA: In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**, 0.77 ml, 6.0 mmol) and (E)-1-iodo-1-hexene (420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in HMPA (10 ml), and the mixture was stirred at 55 °C for 24 h. After this time, **1** was not detected by GLC. The mixture was poured into a mixture of ice and saturated NH₄Cl, then extracted with Et₂O. The Et₂O layer was washed with saturated NH₄Cl and saturated NaCl, then dried over MgSO₄. After evaporation of the solvent, the residue was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **3** (105 mg, 25%). **3**: Colorless oil, MS *m/z*: 206 (M⁺); HRMS Calcd C₁₀H₁₆F₂O₂: 206.112 (M⁺). Found: 206.112. IR (neat) cm⁻¹: 2968, 2936, 2880, 1772, 1678, 1302, 1230, 1084. ¹H-NMR (CDCl₃) δ : 6.27 (dt, 1H, *J*=15.9, 7.0, 2.5 Hz), 5.67 (dt, 1H, *J*=15.9, 11.0, 1.5 Hz), 4.32 (q, 2H, *J*=7.0 Hz), 2.15 (m, 2H), 1.28–1.46 (m, 4H), 1.34 (t, 3H, *J*=7.0 Hz), 0.90 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –40.1 (dq, 2F, *J*=11.0, 2.5 Hz).

2) In DMSO: In an atmosphere of Ar, **1** (0.77 ml, 6.0 mmol) and **2** (420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C. After 12 h, the peak of **1** on GLC was no longer observed. The mixture was worked up as in 1). After concentration of the extract, the residue was separated by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **3** (175 mg, 42%) and diethyl 4-butyl-2,5,5-trifluoro-2-hexenedioate (**5**, 93 mg, 15%). **5**: Colorless oil; MS *m/z*: 310 (M⁺), HRMS Calcd C₁₄H₂₄F₃O₄: 310.139 (M⁺). Found: 310.139. IR (neat) cm⁻¹: 2968, 2880, 1774, 1742, 1688, 1398, 1376, 1322, 1254, 1208, 1132, 1096, 1018. ¹H-NMR (CDCl₃) δ : 5.97 (dd, 1H, *J*=31.1, 11.0 Hz), 4.33 (q, 2H, *J*=7.0 Hz), 4.31 (q, 2H, *J*=7.0 Hz), 3.40 (m, 1H), 1.15–1.52 (m, 6H), 1.35 (t, 3H, *J*=7.0 Hz), 1.34 (t, 3H, *J*=7.0 Hz), 0.89 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –47.7 (dd, 1F, *J*=14.3, 2.4 Hz), –47.9 (dd, 1F, *J*=13.4, 2.4 Hz), –61.8 (d, 1F, *J*=31.1 Hz).

3) Using 1 eq of **1** in DMSO: In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and **2** (420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 12 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **3** (263 mg, 64%).

4) In Other Solvents: The same reaction as above using DMF, DMI, DME or pyridine were examined. Amount of **4** was estimated by GLC. The results are shown in Table 2.

Ethyl (Z)-2,2-Difluoro-3-octenoate (7) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (Z)-1-iodo-1-hexene (**6**, 420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 12 h. The mixture was worked up as in the case of **2**, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **7** (284 mg, 69%). **7**: Colorless oil, bp 77 °C/8 mmHg, MS *m/z*: 206 (M⁺), HRMS Calcd C₁₀H₁₆F₂O₂: 206.112 (M⁺). Found: 206.111. IR (neat) cm⁻¹: 2964, 2936, 2876, 1770, 1662, 1302, 1090. ¹H-NMR (CDCl₃) δ : 5.93 (dt, 1H, *J*=11.6, 7.9, 1.8 Hz), 5.58 (tdt, 1H, *J*=14.3, 11.6, 1.5 Hz), 4.32 (q, 2H, *J*=7.0 Hz), 2.29 (m, 2H), 1.28–1.44 (m, 4H), 1.34 (t, 3H, *J*=7.0 Hz), 0.90 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –36.0 (dd, 2F, *J*=14.3, 1.8 Hz).

Ethyl 2,2-Difluoro-2-phenylacetate (11) In an atmosphere of Ar, **1** (0.10 ml, 0.8 mmol) and iodobenzene (**10**, 0.09 ml, 0.8 mmol) were added to a suspension of activated Cu powder (140 mg, 2.2 mmol) in DMSO (4.0 ml), then the mixture was stirred at 55 °C for 5 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **11** (84 mg, 53%). **11**: Colorless oil, MS *m/z*: 200 (M⁺), HRMS Calcd C₁₀H₁₀F₂O₂: 200.065 (M⁺). Found: 200.064. IR (neat) cm⁻¹: 2992, 1768, 1374, 1268, 1104. ¹H-NMR (CDCl₃) δ : 7.61 (m, 2H), 7.47 (m, 3H), 4.30 (q, 2H, *J*=7.0 Hz), 1.30 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –41.1 (s, 2F).

Ethyl 2,2-Difluoro-2-(4-nitrophenyl)acetate (14) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) was added to a suspension of activated Cu powder (353 mg, 5.6 mmol) and 4-nitroiodobenzene (**13**, 500 mg, 2.0 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 9 h. The mixture was worked up as above, and the product was purified by column chro-

matography (SiO₂, Et₂O:hexane=1:9) to give **14** (321 mg, 66%). **14**: Pale yellow crystals, mp 47–48 °C, MS *m/z*: 245 (M⁺), HRMS Calcd C₁₀H₉F₂NO₄: 245.050 (M⁺). Found: 245.050. IR (KBr) cm⁻¹: 3128, 3096, 3068, 2996, 2948, 2872, 1770, 1528, 1348, 1298, 1268, 1142, 1122, 1104. ¹H-NMR (CDCl₃) δ : 8.32 (m, 2H), 7.82 (m, 2H), 4.32 (q, 2H, *J*=7.0 Hz), 1.32 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –41.6 (s, 2F).

Ethyl 2,2-Difluoro-2-(4-methoxyphenyl)acetate (16) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) was added to a suspension of activated Cu powder (353 mg, 5.6 mmol) and 4-iodoanisole (**15**, 468 mg, 2.0 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 5 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **16** (255 mg, 55%). **16**: Colorless oil, MS *m/z*: 230 (M⁺), HRMS Calcd C₁₁H₁₂F₂O₃: 230.075 (M⁺). Found: 230.076. IR (neat) cm⁻¹: 2988, 2944, 2848, 1770, 1618, 1520, 1256, 1180, 1140, 1102, 1022. ¹H-NMR (CDCl₃) δ : 7.53 (m, 2H), 6.95 (m, 2H), 4.29 (q, 2H, *J*=7.0 Hz), 3.83 (s, 3H), 1.30 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –39.8 (s, 2F).

Ethyl (E)-2,2-Difluoro-4-methyl-6-(tert-butyldimethylsilyloxy)-3-hexenoate (18) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (E)-4-(tert-butyldimethylsilyloxy)-1-iodo-2-methyl-1-butene⁹⁾ (**17**, 653 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 9 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **18** (402 mg, 62%). **18**: Colorless oil, MS *m/z*: 277 (M⁺–C₂H₅O), 265 (M⁺–^{*t*}Bu). HRMS Calcd C₁₃H₂₃F₂O₂Si: 277.144 (M⁺–C₂H₅O), C₁₁H₁₉F₂O₃Si: 265.107 (M⁺–^{*t*}Bu). Found: 277.143 (M⁺–C₂H₅O), 265.107 (M⁺–^{*t*}Bu). IR (neat) cm⁻¹: 2960, 2864, 1770, 1676, 1298, 1258, 1200, 1102. ¹H-NMR (CDCl₃) δ : 5.47 (ttq, 1H, *J*=14.0, 1.2, 1.2 Hz), 4.32 (q, 2H, *J*=7.0 Hz), 3.72 (t, 2H, *J*=6.4 Hz), 2.28 (tt, 2H, *J*=6.4, 2.1, 1.2 Hz), 1.88 (td, 3H, *J*=2.7, 1.2 Hz), 1.34 (t, 3H, *J*=7.0 Hz), 0.88 (s, 9H), 0.04 (s, 6H). ¹⁹F-NMR (CDCl₃) ppm: –36.0 (dq, 2F, *J*=14.0, 2.7, 2.1 Hz).

Ethyl (Z)-5-Benzoyloxy-2,2-difluoro-3-methyl-3-pentenoate (20) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (Z)-2-iodo-2-butenyl benzoate¹⁰⁾ (**19**, 604 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 8 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **20** (358 mg, 60%). **20**: Colorless oil, MS *m/z*: 298 (M⁺), HRMS Calcd. C₁₅H₁₆O₄F₂: 298.101 (M⁺). Found: 298.102. IR (neat) cm⁻¹: 3072, 2992, 1772, 1724, 1606, 1270, 1118, 1072, 1040, 1028. ¹H-NMR (CDCl₃) δ : 8.05 (m, 2H), 7.57 (tt, 1H, *J*=7.4, 1.2 Hz), 7.44 (m, 2H), 5.88 (tqt, 1H, *J*=6.1, 1.5, 0.6 Hz), 5.07 (dtq, 2H, *J*=6.1, 3.1, 1.5 Hz), 4.35 (q, 2H, *J*=7.0 Hz), 1.91 (q, 3H, *J*=1.5 Hz), 1.35 (t, 3H, *J*=7.0 Hz). ¹⁹F-NMR (CDCl₃) ppm: –36.9 (td, 2F, *J*=3.1, 0.6 Hz).

Ethyl 2,2-Difluoro-3-trimethylsilyl-3-octenoate (22) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (Z)-(1-iodo-1-hexenyl)trimethylsilane¹¹⁾ (**21**, 532 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 30 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO₂, Et₂O:hexane=1:9) to give **22** (118 mg, 21%). **22**: Colorless oil, MS *m/z*: 263 (M⁺–CH₃), HRMS Calcd C₁₂H₂₁F₂O₂Si: 263.128 (M⁺–CH₃). Found: 263.128 (M⁺–CH₃). IR (neat) cm⁻¹: 2968, 2876, 1766, 1618, 1288, 1252, 1182, 1132, 1092. ¹H-NMR (CDCl₃) δ : 6.10 (t, 1H, *J*=7.3 Hz), 4.28 (q, 2H, *J*=7.0 Hz), 2.24 (m, 2H), 1.25–1.40 (m, 4H), 1.32 (t, 3H, *J*=7.0 Hz), 0.89 (t, 3H, *J*=7.0 Hz), 0.17 (s, 9H). ¹⁹F-NMR (CDCl₃) ppm: –28.1 (s, 2F).

References and Notes

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