Michael-type Reaction of Ethyl Bromodifluoroacetate with α,β-Unsaturated Carbonyl Compounds in the Presence of Copper Powder

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We have reported that the reaction of ethyl bromodifluoroacetate (1) with alkenyl iodides in the presence of copper powder gives ethyl alkenyldifluoroacetates. As an extension of this reaction, reaction of 1 with Michael acceptors in the presence of copper powder was examined and found to give 1,4-addition products selectively, unless the acceptor has a group stabilizing a radical intermediate, such as a phenyl group.

Key words bromodifluoroacetate; copper; α,β-unsaturated carbonyl compound; Michael acceptor; 1,4-addition; δ-oxodifluoroacetate

Organofluorine compounds are now drawing much attention in biomedicinal fields, since many of them are used as medicines.[1] Among them, difluoromethylene (CF_2) analogs of bioactive compounds have been synthesized to modify their biological activities,[2] and various methods have been developed for the introduction of a CF_2 group.[3] In conjunction with this field, we have reported the cross-coupling reaction of ethyl bromodifluoroacetate (**1**) with alkenyl or aryl iodides in the presence of copper powder, providing a convenient route to aryl- or alkenyldifluoroacetates.[4] As an extension of this reaction, now we would like to report the 1,4-addition reaction of **1** with various Michael acceptors in the presence of copper powder.

Taguchi and his colleagues reported the atom-transfer reaction of methyl difluoroiodoacetate with olefins in the presence of Cu powder. They postulated that the reactive intermediate might be a difluoroacetate radical.[5,6] Although their reaction proceeded with olefins, it did not proceed with α,β-unsaturated carbonyl compounds. We have suggested, however, that the reactive intermediate is anionic in our reaction.[4] Therefore, we expected that the anionic intermediate would react with Michael acceptors to afford α,α-difluorocarboxylates with electron-withdrawing substituents at δ-position. So, 2-cyclohexen-1-one (**2**) was treated with **1** in the presence of Cu powder in DMSO at 55 °C. As we expected, ethyl 2,2-difluoro-2-(3-oxocyclohexyl)acetate, a Michael adduct (**3**), was obtained in the isolation yield of 45% (Chart 1). In this reaction, we could obtain neither an atom-transfer product nor a 1,2-adduct. This result strongly suggests that the reactive intermediate in this reaction is anionic.

To improve the yield of this reaction, we examined the solvent effect. In DMSO, **3** was obtained in the isolation yield of 45%, while the yield was estimated to be 63% by ^{1}H-NMR. The results obtained using other solvents are shown in Table 1.

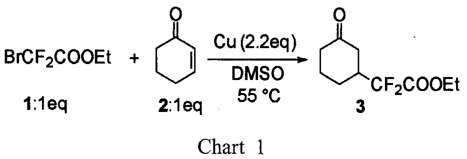

Chart 1

Next, we examined the effect of temperature using DMSO as the solvent. The results are shown in Table 2. The reaction proceeded even at room temperature, but it was very slow and gave only a poor yield of **3**. The best result was obtained at 55 °C, as in the previous reactions with alkenyl iodides.[4]

These results suggested that the best condition for this reaction is to use DMSO as a solvent and to carry it out at 55 °C. Using this condition, we examined the reaction with various Michael acceptors. The results are shown in Table 3.

At first, the effects of electron withdrawing groups of Michael acceptors were investigated (entries 1 to 4). An α,β-unsaturated ketone (**4**) gave the best result, while an ester (**6**) was much less reactive. A nitrile (**8**) and a sulfone (**10**) were comparable to **4** and much better than **6** as a Michael acceptor of this reaction. Thus, the relative activating power of various groups is as follows: ketone>nitrile~sulfone≫ester. Taguchi and his colleagues reported that 2,2-difluoroketene silyl acetal, generated from methyl difluoroiodoacetate, reacted with α,β-unsaturated carbonyl compounds to give

Table 1. Investigation of Solvent Effect

Solv.	Time[a] (h)	Yield[b] (%)
DMSO	3	63
HMPA	24	7[c]
DMF	56	56
CH_3CN	1 week	ND[d]
THF	1 week	ND[d]

a) Until the peak of **1** was no longer detected by GLC. *b*) ^{1}H-NMR yield (Internal standard is 1,4-dioxane). *c*) HMPA was eliminated by column chromatography. *d*) No products were detected by GLC.

Table 2. Temperature Effect

Temp. (°C)	Time[a] (h)	Yield[b] (%)
120	3	52
80	3	61
55	3	63
40	9	62
25	4 days	16

a) Until the peak of **1** was no longer detected by GLC. *b*) Estimated by ^{1}H-NMR: Internal standard is 1,4-dioxane.

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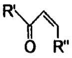
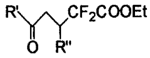
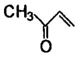
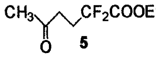
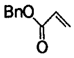
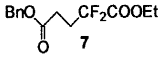
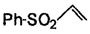
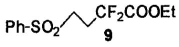
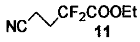
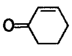
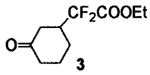
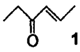
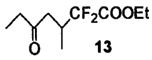
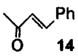
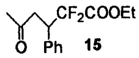
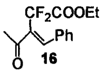
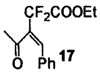
Table 3. Reaction of **1** with Various Michael Acceptors

Entry		Time$^{a)}$ (h)		Yield$^{b)}$ (%)
1	 **4**	5	 **5**	54
2	 **6**	3	 **7**	16
3	 **8**	7	 **9**	40
4	 **10**	5	 **11**	42
5	 **2**	3	 **3**	45
6	 **12**	3	 **13**	49
7	 **14**	8	 **15**	8$^{c,d)}$

a) Until the peak of **1** was no longer detected by GLC. *b*) Isolation yield. *c*) Two equivalents of **1** were used.

d)  **16** and  **17** were obtained as by-products.

Michael type 1,4-addition products.[7)] However, the regioselectivity of this reaction is not high. Thus, some 1,2-addition products were obtained in many cases. Further, this reaction does not proceed with α,β-unsaturated esters or phenyl vinyl sulfone (**8**). Our reaction proceeded not only with benzyl acrylate (**6**) but with **8** to afford the 1,4-addition products (entries 2 and 3). As mentioned above, cyclic enone (**2**) gave the Michael type adduct (**3**). From entry 6, an alkyl group on the β-position did not disturb the reaction, while an aryl group on the β-carbon afforded a poor yield of the Michael adduct (**15**) with larger amounts of **16** and **17**. Hydrogenation of the latter two products gave the same product, ethyl-3-benzyl-2,2-difluoro-4-oxopentanoate (**18**), and seemed to be produced by copper-induced radical addition of bromodifluoroacetate (**1**) followed by elimination of hydrogen bromide. Namely, because of high stability of benzylic radical, a primary radical from **1** attacked the β-carbon from the phenyl group of **14**. In other cases, the radical must have reacted with copper to give the copper reagent ($BrCuCF_2CO_2C_2H_5$) postulated in the previous paper.[4)]

In conclusion, **1** reacted with α,β-unsaturated carbonyl compounds and other Michael acceptors in the presence of copper powder to give 1,4-addition products in the absence of substituents that stabilize a radical intermediate. These results are quite different from the reaction of copper complex from difluoroiodoacetate reported by Taguchi's group. This suggests that the intermediate of our reaction is the one shown above and it behaves as an anionic species with Michael acceptors. Although this reaction is affected by an aryl substituent at β-position, the 1,4-addition proceeds with various Michael acceptors in moderate yields.

Experimentals

General Procedures ^{1}H-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, JEOL-FX90Q and GE-Omega 600 spectrometer. Benzotrifluoride was used as an internal standard. Mass spectra were obtained by JEOL JMS-DX-300. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. Gas-liquid chromatography (GLC) was carried out on a Hitachi 263-50 gas chromatograph (column, 5% SE-30 3 mm×2 m, carrier, N_2 at 30 ml/min). Peak areas were calculated on a Shimadzu C-R5A Chromatopac.

Ethyl 2,2-Difluoro-2-(3-oxocyclohexyl)acetate (3) In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**, 0.25 ml, 2.0 mmol) and 2-cyclohexen-1-one (**2**, 0.19 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 3 h. Thereafter, **1** was not detected by GLC. The mixture was poured into a mixture of ice and saturated NH_4Cl, and extracted with Et_2O. The Et_2O layer was washed with saturated NH_4Cl and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **3** (198 mg, 45%). **3**: A colorless oil; MS *m/z*: 220 (M^+); HRMS Calcd for $C_{10}H_{14}F_2O_3$: 220.091 (M^+). Found: 220.090; IR (neat) cm^{-1}: 2968, 2880, 1766, 1722, 1316, 1266, 1200, 1118, 1082, 1054; ^{1}H-NMR ($CDCl_3$) δ: 4.35 (q, 2H, J=7.0 Hz), 1.90—2.70 (m, 7H), 1.66 (m, 2H), 1.37 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −50.4 (dd, 1F, J=256.4, 14.7 Hz), −51.0 (dd, 1F, J=256.4, 14.7 Hz).

Ethyl 2,2-Difluoro-5-oxohexanoate (5) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and methyl vinyl ketone (**4**, 0.17 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 6 h. The mixture was worked up as in the case of **3**. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **5** (208 mg, 54%). **5**: A colorless oil; MS *m/z*: 194 (M^+); HRMS Calcd for $C_8H_{12}F_2O_3$: 194.075 (M^+). Found: 194.076; IR (neat) cm^{-1}: 2992, 2952, 1768, 1726, 1440, 1362, 1196, 1040; ^{1}H-NMR ($CDCl_3$) δ: 4.32 (q, 2H, J=7.0 Hz), 2.69 (t, 2H, J=7.9 Hz), 2.31—2.43 (m, 2H), 2.19 (s, 3H), 1.36 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −40.9 (t, 2F, J=16.1 Hz).

Ethyl Benzyl 2,2-Difluoropentandioate (7) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and benzyl acrylate (**6**, 324 mg, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 3 h. The mixture was worked up as in the case of **3**. The extract was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **7** (90 mg, 16%). **7**: A colorless oil; MS *m/z*: 286 (M^+); HRMS Calcd for $C_{14}H_{16}F_2O_4$: 286.101 (M^+). Found: 286.102; IR (neat) cm^{-1}: 3072, 3044, 2988, 1768, 1744, 1310, 1284, 1186, 1098; ^{1}H-NMR ($CDCl_3$) δ: 7.35 (m, 5H), 5.13 (s, 2H), 4.30 (q, 2H, J=7.0 Hz), 2.60 (m, 2H), 2.37—2.52 (m, 2H), 1.33 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −44.0 (t, 2F, J=17.1 Hz).

Ethyl 2,2-Difluoro-4-(benzenesulfonyl)butanoate (9) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) was added to a suspension of activated Cu powder (280 mg, 4.4 mmol) and phenyl vinyl sulfone (**8**, 336 mg, 2.0 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 6 h. The mixture was worked up as in the case of **3**. The extract was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **9** (236 mg, 40%). **9**: A colorless oil; MS *m/z*: 219 (M^+−COOEt); HRMS Calcd for $C_9H_9F_2O_2S$: 219.029 (M^+−COOEt). Found: 219.029; IR (neat) cm^{-1}: 2992, 2770, 1476, 1312, 1192, 1152, 1090; ^{1}H-NMR ($CDCl_3$) δ: 7.93 (m, 2H), 7.71 (tt, 1H, J=7.6, 1.5 Hz), 7.61 (m, 2H), 4.32 (q, 2H, J=7.0 Hz), 3.30 (m, 2H), 2.53 (m, 2H), 1.35 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −43.1 (t, 2F, J=15.9 Hz).

Ethyl 4-Cyano-2,2-difluorobutanoate (11) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and acrylonitrile (**10**, 0.13 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 5 h. The mixture was worked up as in the case of **3**. The extract was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **11** (150 mg, 42%). **11**: A colorless oil; MS *m/z*: 178 (M^++1); HRMS Calcd for $C_7H_{10}F_2NO_2$: 178.067 (M^++1). Found: 178.067; IR (neat) cm^{-1}: 2992, 2256, 1770, 1446, 1378, 1320, 1222, 1198, 1098; ^{1}H-NMR ($CDCl_3$) δ: 4.37 (q, 2H, J=7.0 Hz), 2.63 (m, 2H), 2.48 (m, 2H), 1.38 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −44.6 (dd, 2F, J=15.9, 14.7 Hz).

Ethyl 2,2-Difluoro-3-methyl-5-oxoheptanoate (13) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and 4-hexen-3-one (**12**, 0.23 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 3 h. The mixture was worked up as in the case of **3**. The extract was purified by column chromatography (SiO_2, Et_2O : hexane = 1 : 9) to give **13** (216 mg, 49%). **13**: A pale yellow oil; MS *m/z*: 222 (M^+); HRMS Calcd for $C_{10}H_{16}F_2O_2$: 222.106 (M^+). Found: 222.105; IR (neat) cm^{-1}: 2988, 2948, 1770, 1724, 1312, 1278, 1142, 1112, 1062; ^{1}H-NMR ($CDCl_3$) δ: 4.32 (q, 2H, J=7.0 Hz), 2.90 (m, 1H), 2.77 (dd, 1H, J=17.7, 4.0 Hz), 2.48 (dq, 1H, J=17.7, 7.3 Hz), 2.41 (dq, 1H, J=17.7, 7.3 Hz), 2.38 (dd, 1H, J=17.7, 9.2 Hz), 1.36 (t, 3H, J=7.0 Hz), 1.07 (t, 3H, J=7.3 Hz), 1.01 (d, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −44.0 (dd, 1F, J=252.0, 13.2 Hz), −49.3 (dd, 1F, J=252.0, 14.7 Hz).

Ethyl 2,2-Difluoro-5-oxo-3-phenyl-hexanoate (15), Ethyl (*Z*)- and (*E*)-3-Acetyl-2,2-difluoro-4-phenyl-3-butenoate (16 and 17) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) was added to a suspension of activated Cu powder (280 mg, 4.4 mmol) and benzalacetone (**14**, 290 mg, 2.0 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 6 h. After this time, **1** (0.25 ml, 2.0 mmol) was added to the mixture, since **14** was detected by GLC, and the mixture was stirred for further 2 h. At this time, **14** was not detected by GLC. The mixture was worked up as in the case of **3**. The extract was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **15** (41 mg, 8%), **16** (86 mg, 16%) and **17** (54 mg, 10%). **15**: A colorless oil; MS *m/z*: 270 (M^+); HRMS Calcd for $C_{14}H_{16}F_2O_3$: 270.106 (M^+). Found: 270.106; IR (neat) cm^{-1}: 3044, 2992, 1772, 1726, 1268, 1110; ^{1}H-NMR ($CDCl_3$) δ: 7.29 (m, 5H), 4.12 (q, 2H, J=7.0 Hz), 4.05 (dddd, 1H, J=22.0, 12.2, 9.2, 4.3 Hz), 3.16 (dd, 1H, J=17.7, 4.3 Hz), 3.03 (dd, 1H, J==17.7, 9.2 Hz), 2.10 (s, 3H), 1.13 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −42.9 (dd, 1F, J=251.5, 12.2 Hz), −51.0 (dd, 1F, J=251.5, 22.0 Hz). **16**: A colorless oil; MS *m/z*: 268 (M^+); HRMS Calcd for $C_{14}H_{14}F_2O_3$: 268.091 (M^+). Found: 268.091; ^{1}H-NMR ($CDCl_3$) δ: 7.92 (s, 1H), 7.49 (m, 2H), 7.41 (m, 3H), 4.27 (q, 2H, J=7.0 Hz), 2.49 (s, 3H), 1.30 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −35.8 (s, 2F). **17**: A colorless oil; MS *m/z*: 268 (M^+); HRMS Calcd for $C_{14}H_{14}F_2O_3$: 268.091 (M^+). Found: 268.091; ^{1}H-NMR ($CDCl_3$) δ: 7.51 (t, 1H, J=1.83 Hz), 7.41 (m, 3H), 7.30 (m, 2H), 4.39 (q, 2H, J=7.0 Hz), 2.08 (s, 3H), 1.37 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −42.0 (s, 2F).

Ethyl 3-Acetyl-2,2-difluoro-4-phenylbutanoate (18) A solution of **16** (54 mg, 0.2 mmol) in THF (5 ml) was shaken overnight in the presence of 10% Pd–C (80 mg) in an atmosphere of H_2 at room temperature. After filtration of the catalyst, the solvent was evaporated under vacuum, and the residue was purified by column chromatography (SiO_2, Et_2O : hexane = 1 : 4) to give **18** in a quantitative yield. **18**: A colorless oil; MS *m/z*: 270 (M^+); HRMS Calcd for $C_{14}H_{16}F_2O_3$: 270.107 (M^+). Found: 270.107; ^{1}H-NMR ($CDCl_3$) δ: 7.16—7.33 (m, 5H), 4.30 (q, 2H, J=7.0 Hz), 3.66 (ddt, 1H, J=14.7, 12.2, 7.3 Hz), 3.08 (d, 2H, J=7.3 Hz), 2.00 (s, 3H), 1.35 (t, 3H, J=7.0 Hz); ^{19}F-NMR ($CDCl_3$) ppm: −44.20 (dd, 2F, J=361.4, 12.2 Hz), −44.59 (dd, 2F, J=361.4, 14.7 Hz). A similar reaction of **17** gave the same product in a quantitative yield.

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