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1,4-Addition reaction of ethyl bromodifluoroacetate to Michael acceptors in the presence of copper powder Improvement of the reaction using TMEDA as an additive

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Abstract

Reaction of ethyl bromodifluoroacetate with a variety of Michael acceptors was tremendously improved by the addition of TMEDA. Using this additive, 1,4-adducts were formed exclusively, and any 1,2-adducts or radical adducts were not obtained. THF or other low boiling solvents can be used as a solvent. This simplifies the work-up of the reaction effectively.
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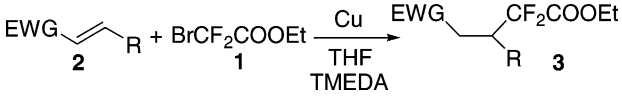
Keywords: Fluorine; Bromodifluoroacetate; Organocopper reagent; 1,4-Addition; TMEDA

1. Introduction

Organofluorine compounds have highly distinguished properties from other organic compounds and they are used in various fields, such as medicines, agricultural chemicals and electronic materials [1]. Therefore, the method for introducing a fluorine functional group to an organic compound has been widely investigated [2]. $BrCF_2COOEt$ (**1**) is supposed to be a good starting material to introduce a fluorine functional group to organic compounds, since **1** has a CF_2 and an ester moieties, which could be modified to other functional groups. One of the most useful reaction of **1** is the Reformatsky reaction [3] with carbonyl compounds or aldol reaction [4] of the enolate and/or the ketene acetals derived from **1**. These reactions are very useful to synthesize β-hydroxy-α, α-difluoro esters, but the hydroxyl group of the products is too stable to be modified to other functional groups due to the high electronegativity of fluorine. To solve this difficulty, we have developed a cross-coupling reaction [5], 1,4-addition reaction [6] and radical addition reaction [7] of **1** in the presence of active Cu powder [8]. These reactions gave those compounds that have no hydroxyl group on the α-position to the CF_2 group.

In the previous work [6], we reported that the 1,4-addition reaction of **1** with some Michael acceptors proceeded in good yields. However, in order to obtain the 1,4-adducts, Me_2SO must be used as a solvent. Further, when a substrate had a substituent which stabilizes a radical intermediate, radical adducts were obtained mainly besides a small amount of the 1,4-adduct. This seemed to limit application of this reaction. So, we searched an additive that would make the 1,4-addition reaction proceed more smoothly, and found that the 1,4-addition reaction of **1** with Michael acceptors was promoted by the addition of TMEDA (Scheme 1). Here, we would like to report our results.



Scheme 1.

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2. Results and discussion

First, we examined some additives that would help the 1,4-addition reaction. After various trials, we found that TMEDA was the best additive to promote the 1,4-addition reaction in THF (Table 1).

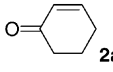
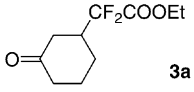
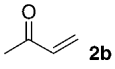
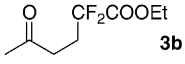
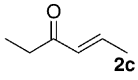
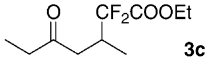
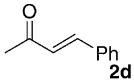
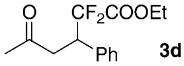
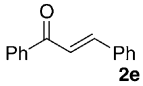
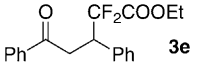
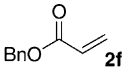
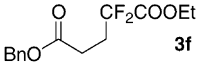
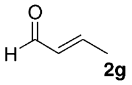
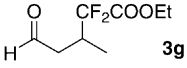
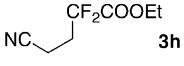
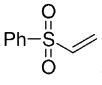
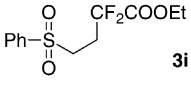
Namely, when TMEDA was added to a solution of **1**, Cu and 2-cyclohexen-1-one (**2a**) in boiling THF, the corresponding

Table 1
Examination of reaction condition

Entry	Additive	**1**:**2a**:additive (eq.)	Temperature (°C)	Time (h)	Yield (%)[a]
1	diPy	1:1:1	r.t.	48	(3)[b]
2	DIPHOS	1:1:1	r.t.	48	(NR)[b]
3	DME	1:1:1	r.t.	48	(NR)[b]
4	TMEDA	1:1:1	r.t.	7	(14)[b]
5	TMEDA	1:1:1	Reflux	1	(36)[b]
6	TMEDA	1:1:2	Reflux	1	(21)[b]
7	TMEDA	1:1:0.3	Reflux	24	55 (66)[b]
8	TMEDA	3:1:0.3	Reflux	7	70
9	TMEDA	3:1:0.9	Reflux	7	73

[a] Isolated yield.
[b] ^{19}F-NMR yield (internal standard is benzotrifluoride).

Table 2
Reaction of ethyl bromodifluoroacetate (**1**) with various Michael acceptors (**2**)

Entry	**2**	Temperature (°C)	Time (h)	**3**	Yield of **3** (%)[a]
1	 **2a**	Reflux	7	 **3a**	73
2	 **2b**	r.t.	5	 **3b**	62
3	 **2c**	Reflux	2	 **3c**	68
4	 **2d**	Reflux	2	 **3d**	21
5	 **2e**	Reflux	1	 **3e**	23
6	 **2f**	r.t.	5	 **3f**	60
7	 **2g**	Reflux	3	 **3g**	23
8	 **2h**	r.t.	2	 **3h**	40
9	 **2i**	Reflux	1	 **3i**	73

[a] Isolated yield.

1,4-addition product (**3a**) was obtained in 73% yield (entry 1). This was better than that obtained by the reaction in Me_2SO. Results on other substrates are shown in Table 2.[1]

The 1,4-addition reaction proceeded in good yield as shown entries 1–3, although **3b** was isolated in moderate yield due to its high volatility. **2d** or **2e** have a phenyl group, which would stabilize a radical intermediate, and afforded radical products in our previous work. However, in the presence of TMEDA, both gave only the 1,4-adducts in poor yields (entries 4 and 5), and none of 1,2-adducts or radical products were formed at all. This suggested that if the substituent on β-carbon became larger, 1,4-addition was more difficult to proceed. In fact, **2b**, which has no substituent on β-carbon, gives **3b** even at room temperature.

Next, the effect of the electron-withdrawing groups of the Michael acceptors was investigated. α,β-Unsaturated ester and nitrile gave the 1,4-adducts in moderate to good yields, while the aldehyde gave a poor yield (entries 6–8). The reaction of an α,β-unsaturated sulfone proceeded smoothly (entry 9). For all of Michael acceptors, no 1,2-adducts and radical products were formed as in the case of α,β-unsaturated ketones by this modification.

[1] The typical procedure is as follows: under an Ar atmosphere, **1** (0.77 ml, 6 mmol) and **2a** (0.19 ml, 2 mmol) were added to a suspension of active Cu powder (839 mg, 13.2 mmol) in THF (6 ml). The mixture was refluxed under stirring for 1 h. Then, TMEDA (0.27 ml, 1.8 mmol) was added to the mixture, and then the mixture was stirred at same temperature for 7 h. The mixture was worked-up as usual, followed by column chromatographic purification to give ethyl 2,2-difluoro-2-(3-oxocyclohexyl)acetate (**3a**, 322 mg, 73%). **3a**: colorless oil; MS *m/z*: 220 (M^+); HRMS Calcd. $C_{10}H_{14}F_2O_3$: 220.091 (M^+). Found: 220.090; ^{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); ^{13}C-NMR ($CDCl_3$) δ: 208.1, 163.4 (t, $J = 32.4$ Hz), 115.7 (t, $J = 252.6$ Hz), 63.1, 42.4 (t, $J = 23.4$ Hz), 40.9, 39.7 (t, $J = 3.6$ Hz), 24.0, 23.4 (t, $J = 4.2$ Hz), 14.0; ^{19}F-NMR ($CDCl_3$) δ: −47.4 (d, $J = 13.2$ Hz); IR (neat) cm^{-1}: 2968, 2880, 1766, 1722, 1316, 1266, 1200, 1118, 1082, 1054. New products given in this reports are **3e** and **3g**. **3e**: colorless crystals; mp 64–66 °C; MS *m/z*: 332 (M^+); HRMS Calcd. $C_{19}H_{18}F_2O_3$: 332.122 (M^+). Found: 332.122; ^{1}H-NMR ($CDCl_3$) δ: 7.93 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 7.36 (m, 2H), 7.28 (m, 3H), 4.14 (m, 2H), 3.67 (s, 1H), 3.65 (d, 1H, $J = 2.4$ Hz), 1.14 (t, 3H, $J = 7.6$ Hz); ^{13}C-NMR ($CDCl_3$) δ: 195.9, 163.3 (dd, $J = 33.2$, 31.6 Hz), 136.4, 135.0, 134.9, 133.3, 129.3, 128.6, 128.5, 128.1, 128.0, 116.4 (dd, $J = 256.1$, 253.5 Hz), 62.8, 45.1 (dd, $J = 22.7$, 20.9 Hz), 37.5 (m), 13.7; ^{19}F-NMR ($CDCl_3$) δ: −39.3 (dd, 1F, $J = 250.5$, 11.7 Hz), −47.8 (dd, 1F, $J = 250.5$, 20.5 Hz); IR (KBr) cm^{-1}: 3072, 1766, 1690, 1280, 1178. **3g**: a colorless oil; MS *m/z*: 194 (M^+); HRMS Calcd. $C_8H_{12}F_2O_3$: 194.075 (M^+). Found: 194.075; ^{1}H-NMR ($CDCl_3$) δ: 9.78 (s, 1H), 4.35 (q, 2H, $J = 7.1$ Hz), 2.93 (m, 1H), 2.84 (dd, 1H, $J = 18.1$, 4.2 Hz), 2.47 (dd, 1H, $J = 18.1$, 9.0, 1.6 Hz), 1.37 (t, 3H, $J = 7.1$ Hz), 1.08 (d, 3H, $J = 6.8$ Hz); ^{13}C-NMR ($CDCl_3$) δ: 198.9, 163.5 (t, $J = 33.0$ Hz), 116.8 (dd, $J = 253.6$, 251.0 Hz), 63.0, 43.5 (t, $J = 3.4$ Hz), 32.5 (t, $J = 21.8$ Hz), 13.9, 13.1 (t, $J = 4.4$ Hz); ^{19}F-NMR ($CDCl_3$) δ: −43.3 (dd, 1F, $J = 254.9$, 13.2 Hz), −49.5 (dd, 1F, $J = 254.9$, 16.1 Hz); IR (neat) cm^{-1}: 2848, 2744, 1770, 1732, 1312, 1142, 1060. The spectral data of other products are given in the previous paper [6].

3. Conclusion

In conclusion, **1** reacted with various Michael acceptors to give **3** in moderate to good yields, when TMEDA was used as an additive. The reaction proceeded regio-specific; neither 1,2-addition products nor radical products were obtained under this condition. THF was the best solvent among many other solvents examined. This makes this reaction useful, since the work-ups become more convenient than the previous one using Me_2SO as a solvent. Thus, this 1,4-addition reaction became more useful methodology to introduce difluoro functional group into organic molecule by this improvement using TMEDA as an additive.

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