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(Methyl Difluoroacetate)copper Reagent. Remarkable Solvent Effect on the ^{19}F-NMR Spectrum, Stability and Reactivity

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The ^{19}F-NMR spectrum, thermal stability and reactivity of (methyl difluoroacetate)copper reagent were found to differ remarkably depending on the solvent (DMSO, DMF,or HMPA) used. With allylic bromide or alkynyl halide a crucial solvent effect for the coupling reactions was observed.

In our previous paper, an efficient method for the preparation of various 2,2-difluoroesters through the reaction of iododifluoroacetate-copper system with organic halides in aprotic solvent was reported.$^{1)}$ However, the nature of (methyl difluoroacetate)copper reagent (**2**), the reactive intermediate, was not fully clarified and reactions of **2** with certain halides such as alkynyl halides gave unsatisfactory results.

In this paper, we report the remarkable solvent effects on the structure, stability and reactivity of (methyl difluoroacetate)copper (**2**), and a high yield coupling reaction with alkynyl bromide.

$$\underset{\mathbf{1}}{ICF_2COOMe} + Cu \longrightarrow \underset{\mathbf{2}}{\left[CuCF_2COOMe\right]_n} \xrightarrow{R\text{-}X} \underset{\mathbf{3}}{RCF_2COOMe}$$

R= alkenyl, aryl, allyl, benzyl   X= I, Br

Among the aprotic solvents examined, DMSO, DMF, or HMPA were used for the characterization of the copper reagent (**2**), all of which provided satisfactory results in coupling reactions with alkeny iodides.$^{1)}$ The reaction of the iodide (**1**) with copper powder was monitered by ^{19}F-NMR. It was shown that **1** was completely consumed within 40 min in DMSO, 1 h in HMPA and 4 h in DMF at room temperature to give new signals, respectively (Fig. 1). These newly formed signals may possibly correspond to the organocopper intermediate (**2**),$^{2)}$ since the addition of alkenyl iodide caused the disappearance of these signals and the formation of the signal corresponding to the coupling product. The yield of the reactive species based on the iodide (**1**) was estimated as about 50% in DMSO and about 80% in HMPA or DMF, respectively.

Followings are characteristic features of **2** in each solvent. As shown in Fig. 1, the spectrum of the copper reagent in DMSO or DMF consists of two signals,$^{3)}$ while that in HMPA a singlet. The two signals (A and B, integral ratio of A:B=1:2) in DMF were found coupled to each other (J=11 Hz) by decoupling.

Thus, when the signal A was irradiated, the triplet signal B changed to a singlet. On adding 2,2'-dipyridyl to **2** in DMF, the signals were slightly shifted, and showed a similar integral ratio and coupling pattern to that of **2** formed in DMF. The broadened signal A, however, changed to a clear quinttet (J=7.5 Hz) as shown in Fig. 1. These results show that **2** in DMF possibly has three CF_2COOMe groups in a unit structure, one unequivalent and two equivalent CF_2COOMe groups. That is, **2** may have a non-equivalent polynuclear structure more than trimer.[4-7] Furthermore, the addition of either HMPA to **2** formed in DMF or DMF to **2** formed in HMPA did not bring about any appreciable change in either chemical shifts or coupling pattern. Thus, the differences in the spectra depending on the solvents reflect the differences in the basic structure.

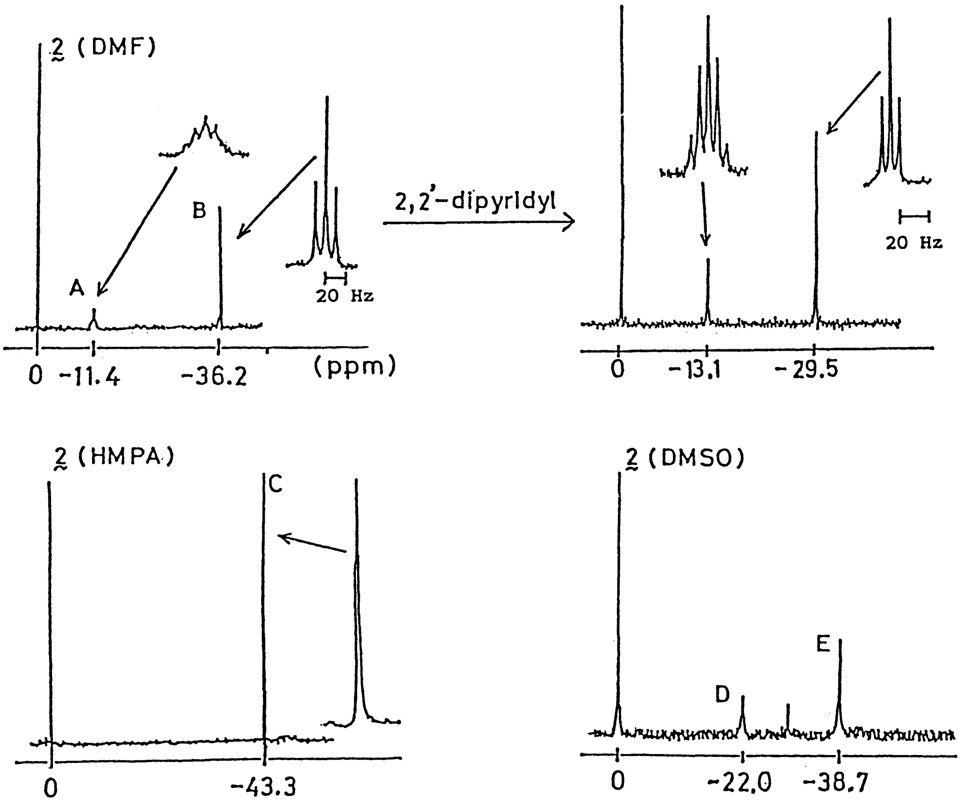
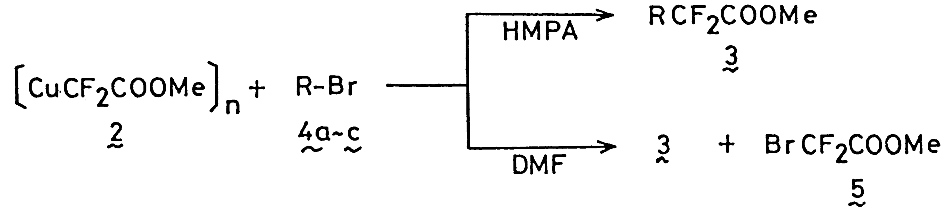


Fig. 1. ^{19}F-NMR spectra of (methyl difluoroacetate)copper (**2**) in DMF, HMPA and DMSO. Spectra were recorded on a Varian EM 360L spectrometer with benzotrifluoride as an internal standard (0 ppm). The expanded signals magnified 10 times are shown in each spectrum.

The thermal stability of **2** was found to vary remarkably depending on the solvent. The stability of **2** decreases in the order, HMPA, DMF, DMSO with half lives at room temperature of about 40 h, 20 h, 5h, respectively.[8] As the major decomposition product, methyl difluorofumalate was detected in DMSO and HMPA.[1] On the other hand, in DMF the major product was not methyl difluorofumarate, but methyl difluoroacetate, probably formed via radical intermediate ($\cdot CF_2COOMe$).

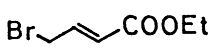
Furthermore, a notable difference was found for the chemical reactivity of the copper reagent (2) depending on the solvent with certain halides. In HMPA, signal C converted to the signal corresponding to the coulpling product nearly quantitatively by the addition of benzyl bromide (4a), ethyl 4-bromocrotonate (4b) or the bromoacetylene (4c). On the other hand, in DMF, reaction of 2 with 4a-4c was rather complicated to provide the coupling product (3) accompanying the formation of the bromoester (5), probably by halogen-metal exchange reaction.[9,10] Results are summarized in Table 1.

While reactions of organocopper with haloacetylenes usually do not give the coupling product because of the preferential halogen-metal exchange, the copper reagent (2) reacts with the bromoacetylene (4c) in HMPA to give the coupling product (3c) in good yield. In the case of the iodoacetylene (4d), halogen-metal exchange occurs to some extent even in HMPA. The degree of halogen-metal exchange in DMF varies depending on the halide (4); with the bromoacetylene (4c) the ratio of 3c and 5 was 1:9 as determined by ^{19}F-NMR.

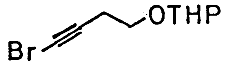


$C_6H_5CH_2Br$

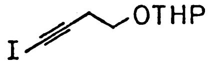
4a



4b



4c



4d

Table 1. Reaction of 2 with Halides (4)[a)]

Entry	RX 4	Solvent	3 Yield /%[b)]	3:5[c)]
1	4a	DMSO	79	d
2	4a	HMPA	75	e
3	4a	DMF	52	2:1
4	4b	HMPA	62	e
5	4b	DMF	37	1:1
6	4c	HMPA	68	e
7	4c	DMF	8	1:9
8	4d	HMPA	37	-
9	4d	DMSO	21	-

a) Molar ratio, 1:Cu:RX=1.5:3.3:1 in HMPA or DMF; 1:Cu:RX=3:6.3:1 in DMSO. b) Isolated yield. c) Determined by ^{19}F-NMR of the reaction mixture. d) 5 was not detected, but unknown fluorine-containing product was also formed. e) 5 was not detected by ^{19}F-NMR of the reaction mixture.

Based on the yield and stability as well as the reactivity of the copper reagent (2) as described above, HMPA was found to be a specific solvent in the coupling reaction with various organic halides.

References

1) T. Taguchi, O. Kitagawa, T. Morikawa, T. Nishiwaki, H. Uehara, H. Endo, and Y. Kobayashi, Tetrahedron Lett., 27, 6103 (1986).

2) ^{19}F-NMR spectra observed for 2 are in agreement with a carbon-metallated structure, since the oxygen-metallated species would be expected to exhibit an AB-quartet for the two unequivalent vinylic fluorines. The ^{19}F-NMR spectrum of 2,2-difluoroketene silyl acetal showed an AB-quartet, while that of the Reformatsky reagent having carbon-zinc bond showed a singlet. O. Kitagawa, T. Taguchi, and Y. Kobayashi, Tetrahedron Lett., 29, 1803 (1988); D. J. Burton and J. C. Easdon, J. Fluorine Chem., 38, 125 (1988).

3) ^{13}C-NMR spectrum of 2 in DMF-d_7 also shows two triplets at 125.6 ppm (J_{C-F}=320 Hz) and 131.3 ppm (J_{C-F}=320 Hz) for CF_2-carbon in a ratio of 1:2.

4) ^{19}F-NMR analysis of trifluorometylcopper complex has been reported by Burton and his coworker. Although the structures of the complexs were not clear, three different [CF_3Cu] species, each of which showed different thermal stability and reactivity were detected. D. M. Wiemers and D. J. Burton, J. Am. Chem. Soc., 108, 832 (1986).

5) It is not clear whether the two signals D and E in Fig. 1 in DMSO derive from a non-equivalent polynuclear structure or different species.

6) As far as we know, no report dealing the structure of the copper compounds of acetate derivatives has been appeared. A high degree of association of cyanomethyl copper is suggested from its insolubility in organic solvents. T. Tsuda, T. Nakatsuka, T. Hirama, and T. Saegusa, J. Chem. Soc., Chem. Commum., 1974, 557; T. Yamamoto, M. Kubota, A. Miyashita, and A. Yamamoto, Bull. Chem. Soc. Jpn., 51, 1835 (1978).

7) It was reported that transmetalation of lithium enolate of ethyl acetate with CuI may possibly form organocopper compound, which reacts with only active allylic bromide. I. Kuwajima and Y. Doi, Tetrahedron Lett., 1972, 1163.

8) The remarkable stability of (trifluoromethyl)copper complex with HMPA has been reported. Y. Kobayashi, K. Yamamoto, and I. Kumadaki, Tetrahedron Lett., 1979, 4071; Ref. 3.

9) With alkenyl iodide (R-I), the coupling product (RCF_2COOMe) was formed nearly quantitatively in each solvent.

10) Copper acetylide formed in the reaction does not react with bromodifluoroacetate.

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