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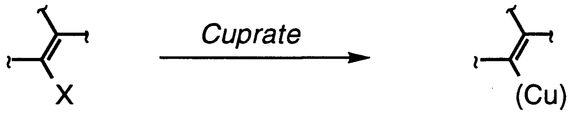
A Novel and Efficient Generation of Functionalized Vinylcopper Reagents and their Reactions with Electrophiles. Synthesis of β-Methylthiobutenolides

Makoto HOJO, Hajime HARADA, and Akira HOSOMI*
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305

Ketene dithioacetals bearing an alkoxycarbonyl group at 2-position are effectively reduced by two equimolar amounts of dimethylcuprate derived from methyllithium and cuprous cyanide to yield the corresponding functionalized vinylcopper species. These organocopper species are efficiently trapped by carbon electrophiles. Formal substitution reactions of a methylthio group in ketene dithioacetals by electrophiles can be attained by one-pot operation. Synthesis of β-thiobutenolides was also achieved.

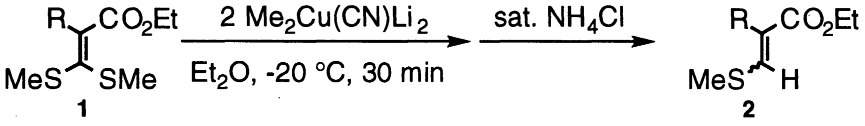
Organocuprates are widely used in carbon-carbon bond formation due to their characteristic reactivities in conjugate additions to α,β-unsaturated carbonyls, in carbocuprations to carbon-carbon triple bonds, and in substitution reactions.[1] In these reactions cuprates serve as nucleophiles. Besides such reactivities, reductive behaviors (metal-halogen exchange reactions) are also known to be another reactivity (Eq. 1). Although such reduction reactions may provide a novel methodology for the direct generation of organocopper reagents, this reductive ability of cuprates is so far recognized as a rather undesired one and the utilization of this process as a metalation reaction, and the reactions of intermediary organocopper species with electrophiles in a synthetic sense have remained still unexplored,[2] possibly because both selectivity (reduction *vs.* addition and/or substitution) and efficiency (molar ratio of substrate to cuprate) are not so high.



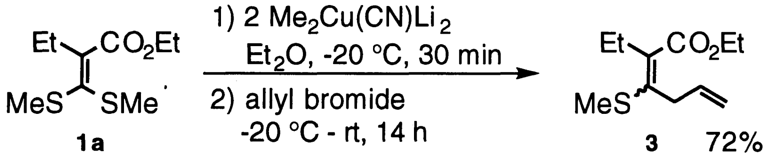
(1)

Previously we found that readily available alkoxycarbonylketene dithioacetals **1**[3] are effectively reduced by two equimolar amounts of dimethylcuprate derived from methyllithium and cuprous cyanide to afford the corresponding vinyl sulfides **2** (E/Z = 85-97/15-3) in high yields after quenching with saturated aq. ammonium chloride, without contamination of any addition products of the methyl group (Eq. 2).[4] In this reduction reaction, however, it is controversial whether an incorporated hydrogen atom in the vinyl sulfide **2** was introduced as a proton or a hydride. Moreover vinyl sulfide **2** may be produced by the nucleophilic addition of copper hydride species at the β-position followed by elimination of a methylthio group.[5] In an extension of our studies, we wish to report herein the evidence demonstrating the stereoselective formation of (Z)-vinylcopper species in Eq. 2 (a hydrogen atom is introduced as a proton) and reactions of these highly functionalized intermediates with carbon electrophiles.[6]

In order to demonstrate that the hydrogen atom of vinyl sulfide **2** was introduced as a proton into the intermediate vinylcopper **5**, deuterium oxide involving deuterium chloride was added to the reaction mixture of **1** with the cuprate, and a deuterated product **2** (94% D-incorporated) was obtained in 78% yield. Moreover by quenching with allyl bromide, an allylated product **3** was obtained in 72% yield after conventional workup (Eq. 3). Apparently a vinylcopper species is generated by a reductive cleavage of a carbon-sulfur bond.



(2)



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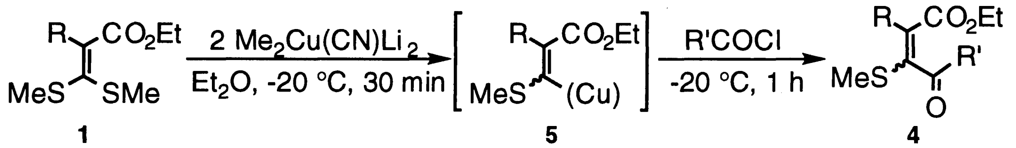
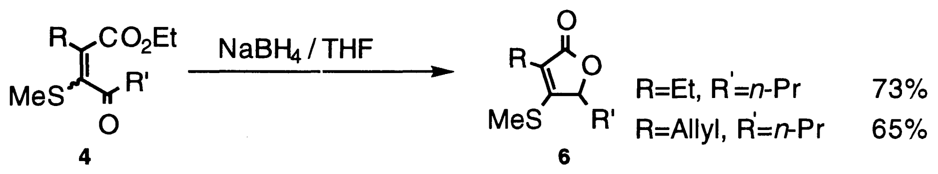


(4)

The above results prompt us to introduce other carbon electrophiles. Acid chlorides also reacted with the expected vinyl intermediates **5** and acylated products **4** at β-position of α,β-unsaturated esters were obtained stereoselectively in high yields along with the corresponding thiol esters derived from copper thiolate and acid chlorides (Eq. 4, Table 1). The E/Z ratios of these acylated products are almost identical with those of reduction products.[4,7] As can be seen in Table 1, several combinations of ketene dithioacetals and acid chlorides gave the corresponding acylated products **4** through one-pot operations. A typical procedure is as follows: to an ethereal solution of the cuprate (2 mmol/10 ml) was added ketene dithioacetal **1a** (220 mg, 1 mmol) at -20 °C and stirred for 30 min. Butyryl chloride (426 mg, 4 mmol) was introduced to the reaction mixture and stirred for further 1 h at the same temperature. After quenching and washing with aqueous ammonium chloride a crude product was obtained. Purification of the crude product by column chromatography on silica gel (hexane/ ethyl acetate = 20/1) gave **4a** (214 mg, 88%) in a ratio of E/Z = 86/14.[8]

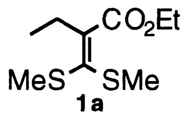
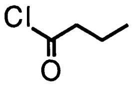
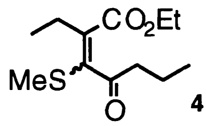
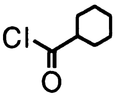
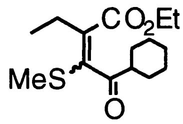
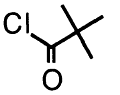
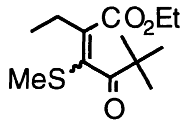
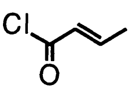
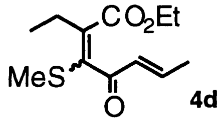
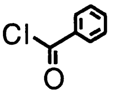
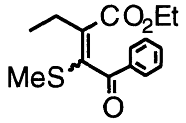
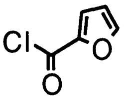
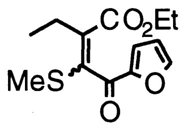
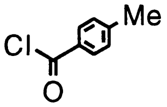
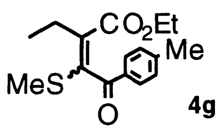
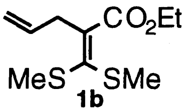
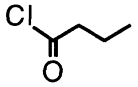
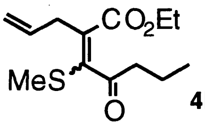
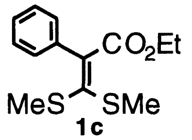
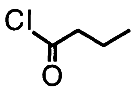
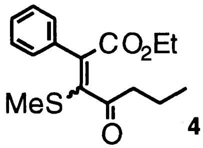
Synthetic utility of this reaction can be demonstrated by further transformation of some of these products **4** to β-thiobutenolides **6** by the reduction with sodium borohydride.[9] The selected examples are shown in Eq. 5. Using this method β-methylthio-substituted butenolides with a variety of substituents can be synthesized by the choice of ketene dithioacetals and acid chlorides.[10]



(5)

Ketene dithioacetals bearing an electron-withdrawing group usually react with nucleophiles *via* addition-elimination pathway to afford a formal substitution product in which one of the methylthio groups at the β-position is replaced by nucleophiles.[11] On the other hand, as shown in this work, ketene dithioacetals are

Table 1. Reduction-Acylation Reaction of Alkoxycarbonylketene Dithioacetals **1** with Acid Chlorides[a)]

Entry	Substrate **1**	Acid Chloride	Product **4** [b)]	%Yield [c,d)]
1	 **1a**		 **4a**	88 (86 : 14)
2	**1a**		 **4b**	83
3	**1a**		 **4c**	93 (89 : 11)
4	**1a**		 **4d**	72
5	**1a**		 **4e**	93
6	**1a**		 **4f**	72
7	**1a**		 **4g**	85
8	 **1b**		 **4h**	79
9	 **1c**		 **4i**	71 (84 : 16)

a) Acylation conditions: acid chloride was added at -20 °C to the metalated mixture and the resulting mixture was stirred for 1 h at the same temperature. b) A mixture of geometrical isomers in which the (*E*)-isomer was predominant. c) Isolated yield by column chromatography. d) The *E*/*Z* ratio shown in the parenthesis was determined by ^{1}H NMR using isomeric SMe peaks.

effectively reduced by $Me_2Cu(CN)Li_2$ to generate vinylcopper species which subsequently react with electrophiles such as a proton, allyl bromide, and acyl chlorides yielding vinyl sulfides **2**, an allylated product **3**, and acylated products **4**, respectively. Thus the present reduction reaction provides a novel and effective method for the generation of new functionalized organocopper reagents **5** and formal substitution reactions of a methylthio group by electrophiles can be attained.

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2) N. Krause and G. Handke, *Tetrahedron Lett.*, **32**, 7229 (1991) and references cited therein.

3) R. K. Dieter, *J. Org. Chem.*, **46**, 5031 (1981).

4) M. Hojo and S. Tanimoto, *J. Chem. Soc., Chem. Commun.*, **1990**, 1284.

5) Copper hydride species that may be generated by β-elimination of the ligand on a copper atom is postulated in the reduction reaction using organocuprates. C. Sahlberg and A. Claesson, *J. Org. Chem.*, **49**, 4120 (1984). In the present reaction the ligand on a copper atom is methyl and therefore such a possibility is ruled out. Recently dimethylcuprate-promoted reductive cleavage of an oxirane ring was also reported. M. Mitani, H. Matsumoto, N. Gouda, and K. Koyama, *J. Am. Chem. Soc.*, **112**, 1286 (1990).

6) E.g., C. Jubert and P. Knochel, *J. Org. Chem.*, **57**, 5425 (1992), and references cited therein.

7) The E/Z ratio of the acylated products was almost in accord with the E/Z ratio for the corresponding reduction products which was determined by the ^1H NOE experiment as shown in ref. 4.

8) **4a** (as an E/Z mixture): bp 170 °C (1.3×10^2 Pa); $R_f = 0.33$ (hexane/ethyl acetate = 20/1). ^1H NMR ($CDCl_3$) (as a major isomer) δ 0.99 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 7.6 Hz, 3H), 1.26 (t, J = 7.3 Hz, 3H), 1.73 (sept, J = 7.3 Hz, 2H), 2.18 (s, 3H), 2.47 (q, J = 7.6 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 4.17 (q, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 13.8 (CH_3), 14.1 (CH_3), 14.7 (CH_3), 16.6 (CH_2), 22.9 (CH_2), 44.4 (CH_2), 61.0 (CH_2), 128.3 (q), 150.6 (q), 165.1 (q), 202.3 (q); IR (neat film) 1135 (s), 1175 (s), 1245 (s), 1295 (s), 1365 (m), 1460 (m), 1580 (s), 1700 (s) cm^{-1}; MS *m/z* (rel intensity) 244 (M^+, 11), 198 (26), 173 (32), 97 (41), 71 (60), 43 (100). Anal. Found: C, 59.11; H, 8.15 %. Calcd for $C_{12}H_{20}O_3S$: C, 58.99; H, 8.25%.

9) An E/Z-mixture was subjected to a reduction reaction. **6** (R=Et, R'=*n*-Pr): ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.6 Hz, 3H), 1.35-1.65 (m, 3H), 1.90-2.05 (m, 1H), 2.33 (m, 2H; change to AB system by irr. at 1.09, 2.33 d, J = 13.5 Hz and 2.39 d, J = 13.5 Hz), 2.44 (s, 3H), 4.93 (dd, J = 8.3, 4.6 Hz, 1H); IR (neat film) 960 (m), 1045 (m), 1240 (m), 1340 (m), 1460 (m), 1615 (m), 1740 (s) cm^{-1}; MS *m/z* (rel intensity) 200 (M^+, 58), 185 (31), 171 (16), 157 (62), 153 (66), 129 (58), 101 (100), 85 (51).

10) Thiobutenolides are useful intermediates in organic synthesis. See G. J. Hollingworth and J. B. Sweeney, *Tetrahedron Lett.*, **33**, 7049 (1992) and references cited therein.

11) For a review, see, M. Kolb, *Synthesis*, **1990**, 171.

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