Reductive Cupration of Cyanoketene Dithioacetals. Generation of Functionalized (*E*)-Vinylcopper Reagents and Their Reactions with Electrophiles

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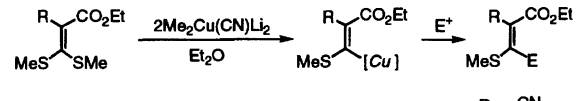
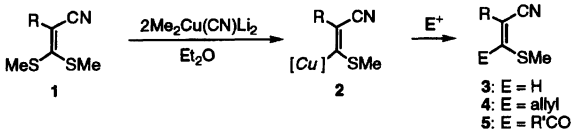
Synopsis. Functionalized (*E*)-vinylcopper species, selectively generated by the effective reduction of cyanoketene dithioacetals with two equimolar amounts of cuprates, react with electrophiles such as water, allyl bromide, and acid chlorides to give the corresponding substitution products in good yields.

Ketene dithioacetals possessing two electron-withdrawing groups such as alkoxycarbonyl, carbonyl, cyano, and sulfonyl groups at α positions are widely applied for the synthesis of heterocycles while the use of ketene dithioacetals with one cyano group at α position as synthetic intermediates has not been reported.[1] In the course of our study to draw out the novel reactivities of ketene dithioacetals,[2] we previously found the reduction of (alkoxycarbonyl)ketene dithioacetals using dimethylcuprate derived from CuCN and methyllithium to generate (*Z*)-vinylcopper species in which reductive C–S bond cleavage was induced by two equimolar amounts of cuprate (Eq. 1).[3] This reduction is selective (reduction vs. addition) and efficient (molar ratio of substrate to cuprate) for the generation of functionalized vinylcopper reagents.[4] In such a context we are interested in the reduction of α-cyano-substituted ketene dithioacetals bearing an electron-withdrawing group except for the alkoxycarbonyl group. We report herein the reduction of cyanoketene dithioacetals **1** with the cuprate and the reduction of stereoselectively generated (*E*)-vinylcopper species **2** toward electrophiles (Eq. 2).





In this cyano-substituted case, reduction proceeds somewhat sluggishly compared to alkoxycarbonyl-substituted case and after several trial experiments the satisfactory results were obtained when the reactions of **1** with two equimolar amounts of $Me_2Cu(CN)Li_2$ in ether were conducted at 0 °C or in a range of 0—10 °C for 4—5 h followed by quenching with sat. NH_4Cl ($E^+=H^+$). The results of the reduction yielding the corresponding vinyl sulfides **3** are summarized in Table 1. The stereoselectivity concerning on the carbon–carbon double bond of **3** was $E/Z=21$—$0/79$—100 and interestingly this *Z*-selectivity was opposite to that in the alkoxycarbonyl-substituted cases (Table 1). The E/Z ratio was determined by ^{1}H NMR integration of the olefinic proton. The stereochemistry around the olefinic linkage of the major isomer of **3a** was determined to be *Z* by NOE experiments between allylic methylene protons and a vinyl proton. The *J* value of **3** was generally observed to be $J_{major} > J_{minor}$.

Table 1. Reduction of Ketene Dithioacetals **1** to VInyl Sulfides **3**

Entry	Substrate **1** R		Conditions	Product **3** %Yield[a]	E/Z[b]
1	Et	(**1a**)	0 °C, 4.5 h then 10 °C, 0.5 h	81	16/84
2	Bu	(**1b**)	0 °C, 5 h	94	15/85
3	Allyl	(**1c**)	0 °C, 4.5 h then 10 °C, 0.5 h	81	21/79
4	Ph	(**1d**)	0 °C, 4.5 h then 10 °C, 0.5 h	84	—[c]
5	Me_3Si	(**1e**)	0 °C, 4.5 h then 10 °C, 0.5 h	61	0/100

a) Isolated yield by column chromatography. b) Isomeric ratio was determined by NMR integration of olefinic protons. c) Not determined.

The stereoselectivity is reasonably explained by the relative bulkiness of the electron-withdrawing group (EWG, CN or CO_2R) to the R group in the intermediate (**A**). One of methylthio groups (MeS) rotates across C–R or C–EWG bond prior to the formation of **2**. Then the other methylthio group is eliminated after overlapping with p-orbital. Thus in the case of the CN group, a MeS group rotates clockwise across sterically less hindered C–CN bond rather than C–R bond to reveal the *Z*-selectivity.

Next we tried to introduce carbon electrophiles instead of acidic water to the postulated vinylcopper species **2** as an intermediate. The reaction mixture of **1a** with the cuprate was treated with allyl bromide at 0 ° C for 14 h prior to hydrolysis and an allylated product **4** was obtained in 87% yield. Acid chlorides also reacted with the vinylcopper intermediates **2** and acylated products **5** were obtained in high yields along with the corresponding thiol esters (Table 2).

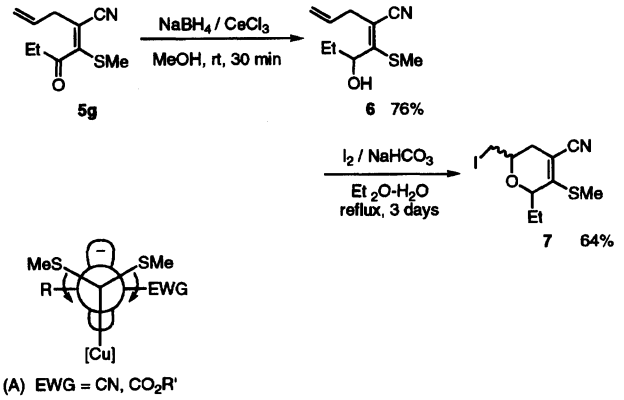
The acylated product **5g** was reduced to the corresponding alcohol and after purification by chromatography a *Z*-isomer **6** was isolated in 76% yield (Eq. 3).[5] This alcohol can be transformed to dihydro-

Table 2. Reductive Acylation of Ketene Dithioacetals **1**[a)]

Entry	Substrate **1** R		Acid chloride R′	Acylation conditions	Product **5**[b)] % Yield[c)]
1	Et	(**1a**)	Et	−20—0 °C, 1 h then 0 °C, 1 h	**5a** 89
2	Et	(**1a**)	*i*-Pr	−20—0 °C, 1 h then 0 °C, 5 h	**5b** 89
3	Et	(**1a**)	*c*-Hex	−20—0 °C, 1 h then 0 °C, 1 h	**5c** 79
4	Et	(**1a**)	*t*-Bu	−20—0 °C, 1 h then 0 °C, 1 h	**5d** 89
5	Et	(**1a**)	Ph	−20—0 °C, 1 h then 0 °C, 1 h	**5e** 79
6	Bu	(**1b**)	Et	−20—0 °C, 1 h	**5f** 95
7	Allyl	(**1c**)	Et	−20—0 °C, 1 h	**5g** 87
8	Ph	(**1d**)	*t*-Bu	−20—0 °C, 1 h then 0 °C, 1 h	**5h** 93

a) Metalation conditions: ketene dithioacetal **1** (1 mmol) was added to the solution of cuprate in ether (2 mmol/14 ml) at −20 °C and the mixture was stirred at 0 °C for 4 h. b) A mixture of geometrical isomers in which the *Z*-isomer was predominant. c) Isolated yield by column chromatography.

pyran derivative **7** in 64% yield as a mixture of diastereomers (1 : 1). In addition to the above chemical evidence, the fact that NOE was observed between allylic methylene protons and a HO–C*H*– proton of **6**, also indicates the *Z* geometry of **6**.



(3)

As shown here cyanoketene dithioacetals **1** are reduced by cuprate efficiently to generate functionalized (*E*)-vinylcopper reagents **2**, otherwise inaccessible, which react with electrophiles to give the corresponding *Z*-rich products. This selectivity is complementary to that of alkoxycarbonyl-substituted cases.

Experimental

Boiling points listed in the section for compound data were determined with Kugelrohr distillation apparatus. ^{1}H NMR spectra at 60 MHz was determined on a JEOL PMX-60si instrument with tetramethylsilane as an internal standard. Infrared spectra were measured with a Shimadzu IR-460 spectrometer. Mass spectra were measured on a Shimadzu GCMS-QP2000 instrument. Microanalyses were performed by the Analysis Center of University of Tsukuba. Analyses agreed with the calculated values within 0.3%.

Solvents and Reagents. Unless otherwise specified, the following solvents and reagents (reagent grade) were used without further purification: Copper(I) cyanide, methyllithium/diethyl ether solution (Kanto Chem. Co.), ethyl acetate, and hexane. Diethyl ether were dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Acid chlorides were dried over $CaCl_2$ and distilled under nitrogen atmosphere. Ketene dithioactals were prepared according to the reported procedure.

General Procedure for Reduction of Ketene Dithioacetals 1 to Vinyl Sulfide 3. A solution of methyllithium in ether (4 mmol) was added to the suspension of copper(I) cyanide in ether (2 mmol/10 ml) at −20 °C and the mixture was stirred for 30 min. To this solution was introduced cyanoketene dithioacetals **1** (1 mmol) via a syringe. The mixture was stirred for 5 h in a range of 0—10 °C. After quenching with saturated aq NH_4Cl at −20 °C and extraction with ethyl acetate (×3) combined organic layer was washed with saturated aq $NaHCO_3$. After drying (Na_2SO_4) and evaporation a crude mixture was obtained. This mixture was subjected to purification by column chromatography (3% deactivated alumina, hexane–ethyl acetate).

2-Cyano-1-butyl Methyl Sulfide 3a: Bp 100 °C (40 Pa). ^{1}H NMR ($CDCl_3$) δ=1.13 (t, J=7 Hz, 3H), 1.97—2.40 (m, 2H), 2.43 (s, 0.84H), and 6.93 (s, 0.16H); IR (neat film) 2400 (s), 1575 (s), 1530 (m), 1485 (m), and 850 (s) cm^{-1}; MS *m/z* (rel intensity) 127 (m$^+$; 39), 112 (78), 85 (30), and 45 (100).

2-Cyano-1-hexenyl Methyl Sulfide 3b: Bp 120 °C (93 Pa). ^{1}H NMR ($CDCl_3$) δ=0.65—1.13 (m, 3H), 1.13—1.80 (m, 4H), 2.03—2.38 (m, 2H), 2.3 (s, 3H), 6.70 (s, 0.85H), and 6.97 (s, 0.15H); IR (neat film) 2200 (s), 1682 (m), 1568 (s), 1460 (m), and 1430 (m) cm^{-1}; MS *m/z* (rel intensity) 155 (m$^+$; 30), 112 (100), and 45 (39).

2-Cyano-1,4-pentadienyl Methyl Sulfide 3c: Bp 115 °C (93 Pa). ^{1}H NMR ($CDCl_3$) δ=2.47 (s, 3H), 2.97 (d, J=7 Hz, 2H), 4.85—5.40 (m, 2H), 5.60 (ddt, J=17, 9, and 7

Hz, 1H), 6.77 (s, 0.79H), and 7.03 (s, 0.21H); IR (neat film) 2200 (s), 1640 (s), 1570 (s), 1430 (s), 990 (m), 925 (m), and 840 (m) cm^{-1}; MS *m/z* (rel intensity) 139 (m^+; 45), 124 (100), 97 (63), 65 (43), and 45 (97).

2-Cyano-2-phenylvinyl Methyl Sulfide 3d: Bp 150 °C (120 Pa). ^1H NMR ($CDCl_3$) δ=2.50 (s, 1.59H), 2.57 (s, 1.41H), and 7.03—7.73 (m, 6H); IR (neat film) 3020 (m), 2900 (m), 2200 (s), 1580 (m), 1540 (s), 1495 (m), and 1540 (s) cm^{-1}; MS *m/z* (rel intensity) 175 (m^+; 100), 160 (96), 133 (31), 89 (26), and 51 (30).

2-Cyano-2-(trimethylsilyl)vinyl Methyl Sulfide 3e: Bp 120 °C (93 Pa). ^1H NMR ($CDCl_3$) δ=0.22 (s, 9H), 2.52 (s, 3H), 6.97 (s, 1H); MS *m/z* (rel intensity) 171 (m^+; 28), 156 (76), 105 (100), 73 (83), and 43 (51).

Procedure for Reduction-Allylation Reaction of 1a: To the reaction mixture of ketene dithioacetal **1a** with cuprate described above, was added allyl bromide (5 mmol) at −20 °C. The mixture was stirred at 0 °C for 14 h. After quenching with saturated aq NH_4Cl at −20 °C and extraction with ether (×3), the combined organic layer was dried with Na_2SO_4 and solvents were evaporated. This crude mixture was subjected to column chromatography (3% deactivated alumina, hexane/ethyl acetate=30/1) to give 1-allyl-2-cyano-1-butenyl methyl sulfide **4**. ^1H NMR ($CDCl_3$) δ=1.13 (t, *J*=7 Hz, 3H), 1.80—2.60 (m, 2H), 2.40 (s, 3H), 3.13 (d, *J*=6 Hz, 1.46 H, major), 3.38 (d, *J*=6 Hz, 0.54H, minor), 4.83—5.41 (m, 2H), and 5.67 (m, 1H); MS *m/z* (rel intensity) 167 (m^+; 89), 152 (100), 104 (92), 77 (67), and 45 (78).

General Procedure for Reductive Acylation of Ketene Dithioacetals 1. To the reaction mixture of ketene dihioacetals with cuprate described above, was added acid chloride (4 mmol) at −20 °C instead of quenching with aq NH_4Cl. The temperature was raised to 0 °C during 1 h and the mixture was stirred at 0 °C for 1 h. After quenching with saturated aq NH_4Cl at −20 °C and extraction with ether (×3), the combined organic layer was dried with Na_2SO_4 and solvents were evaporated. This crude mixture was subjected to column chromatography (silica gel, hexane–ethyl acetate).

2-Cyano-1-propionyl-1-butenyl Methyl Sulfide 5a: Bp 110 °C (93 Pa). ^1H NMR ($CDCl_3$) δ=1.17 (t, *J*=8 Hz, 3H), 1.20 (t, *J*=8 Hz, 3H), 2.18 (q, *J*=7 Hz, 2H), and 2.70 (q, *J*=7 Hz, 2H); IR (neat film) 1975 (s), 2205 (s), 1700 (s), 1460 (m), 1430 (m), and 1140 (m) cm^{-1}; MS *m/z* (rel intensity) 183 (m^+; 13), 168 (19), 112 (13), and 57 (100). Anal. Found: C, 58.89; H, 7.15; N, 7.52%. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64%.

2-Cyano-1-isobutyryl-1-butenyl Methyl Sulfide 5b: Bp 115 °C (67 Pa). ^1H NMR ($CDCl_3$) δ=1.17 (d, *J*=7 Hz, 6H), 1.18 (t, *J*=7 Hz, 3H), 1.97—2.55 (m, 2H), 2.23 (s, 3H), and 3.03 (sep, *J*=7 Hz, 1H); IR (neat film) 2980 (s), 2200 (s), 1690 (s), 1580 (s), 1460 (s), 1330 (m), and 1130 (m) cm^{-1}; MS *m/z* (rel intensity) 197 (m^+; 13), 182 (12), 112 (19), 81 (39), and 43 (100). Anal. Found: C, 60.86; H, 7.58; N, 7.08%. Calcd for $C_{10}H_{15}NOS$: C, 60.87; H, 7.67; N, 7.10%.

2-Cyano-1-cyclohexylcarbonyl-1-butenyl Methyl Sulfide 5c: ^1H NMR ($CDCl_3$) δ=1.00—2.10 (m, 14H), 2.10—2.46 (m, 2H), and 2.23 (s, 3H); IR (neat film) 2950 (s), 2200 (s), 1690 (s), 1480 (m), 1180 (m), and 1150 (m) cm^{-1}; MS *m/z* (rel intensity) 237 (m^+; 17), 112 (32), 83 (100), 55 (58), and 41 (39). Anal. Found: C, 65.52; H, 8.06; N, 5.85%. Calcd for $C_{13}H_{19}NOS$: C, 65.77; H, 8.07; N, 5.90%.

2-Cyano-1-pivaloyl-1-butenyl Methyl Sulfide 5d: Bp 115 °C (67 Pa). ^1H NMR ($CDCl_3$) δ=0.12 (s, 9H), 2.60 (s, 3H), and 3.13 (s, 2H); IR (neat film) 2970 (s), 2200 (s), 1690 (s), 1580 (s), 1480 (s), 1370 (m), and 1120 (s) cm^{-1}; MS *m/z* (rel intensity) 178 (m^+; 11), 163 (23), 105 (47), 73 (100), and 45 (30). Anal. Found: C, 62.27; H, 7.97; N, 6.55%. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 7.98; N, 6.63%.

1-Benzoyl-2-cyano-1-butenyl Methyl Sulfide 5e: Bp 160 °C (333 Pa). ^1H NMR ($CDCl_3$) δ=1.10 (t, *J*=7 Hz, 3H), 1.90—2.47 (m, 2H), 2.17 (s, 3H), and 7.27—8.10 (m, 5H); IR (neat film) 2970 (s), 2200 (s), 1670 (s), 1580 (m), 1450 (s), and 1260 (s) cm^{-1}; MS *m/z* (rel intensity) 231 (m^+; 33), 216 (4), 105 (100), 77 (49), and 51 (21). Anal. Found: C, 67.43; H, 5.69; N, 6.00%. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.67; N, 6.06%.

2-Cyano-1-propionyl-1-hexenyl Methyl Sulfide 5f: Bp 120 °C (93 Pa). ^1H NMR ($CDCl_3$) δ=0.70—1.93 (m, 7H), 1.17 (t, *J*=7 Hz, 3H), 2.25 (s, 3H), 1.93—2.50 (m, 2H), and 2.70 (q, *J*=7 Hz, 2H); IR (neat film) 2960 (s), 2925 (s), 2200 (s), 1715 (s), 1670 (m), 1460 (m), and 1380 (m) cm^{-1}; MS *m/z* (rel intensity) 221 (m^+; 27), 196 (46), 140 (17), 112 (21), 57 (100), and 41 (25). Anal. Found: C, 62.43; H, 8.07; N, 6.60%. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63%.

2-Cyano-1-propionyl-1,4-pentadienyl Methyl Sulfide 5g (*E*/*Z*=24/76): Bp 120 °C (533 Pa). ^1H NMR ($CDCl_3$) δ=1.17 (m, 3H), 2.40—3.27 (m, 4H), 4.90—5.37 (m, 2H), 5.67 (ddt, *J*=17, 9, and 7 Hz, 1H); IR (neat film) 2980 (s), 2205 (s), 1702 (s), 1456 (m), 1431 (s), 1344 (m), 993 (s), and 927(s) cm^{-1}; MS *m/z* (rel intensity) 195 (m^+; 4), 180 (5), 111 (8), 57 (100), and 45 (12). Anal. Found: C, 61.74; H, 6.75; N, 7.23%. Calcd for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; N, 7.17%.

2-Cyano-1-phenyl-1-pivaloylvinyl Methyl Sulfide 5h: Bp 170 °C (533 Pa). ^1H NMR ($CDCl_3$) δ=1.00 (s, 0.97H), 1.26 (s, 0.03H), 2.40 (s, 3H), and 7.33 (s, 5H); IR ($CHCl_3$) 3050 (s), 2360 (m), 2210 (s), 1690 (s), 1470 (m), and 1460 (m) cm^{-1}. Anal. Found: C, 69.61; H, 6.63; N, 5.42%. Calcd for $C_6H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40%.

Reduction of Acylated 5g to Alcohol 6: To the mixture of substrate **5g** (0.27 mmol) and $CeCl_3$ (1.0 mmol) in MeOH (2.5 ml, distilled from CaH_2) was added $NaBH_4$ (1.0 mmol) at room temperature in several portions and the resultant mixture was poured into water and after extraction with ether and drying with $MgSO_4$, crude alcohol **6** was obtained. (*Z*)-**6** was obtained by column chromatography (florisil, hexane/ethyl acetate=3/1; 0.20 mmol, 76%).

(*Z*)-**6**: ^1H NMR ($CDCl_3$) δ=0.96 (t, *J*=7.6 Hz, 3H), 1.56—1.78 (m, 2H), 2.15 (bs, 1H), 2.56 (s, 3H), 3.12 (dt, *J*=6.3 and 1.3 Hz, 2H), 4.50 (dd, *J*=7.9, 5.9 Hz, 1H), 5.16—5.23 (m, 2H), and 5.82 (ddt, *J*=17.5, 9.9, and 6.3 Hz, 1H); MS *m/z* (rel intensity) 197 (m^+; 2), 179 (33), 164 (44), 150 (32), 124 (26), 104 (24), 97 (60), 92 (40), 47 (25), 45 (57), and 41 (100).

Intramolecular Transformation of 6 to Dihydropyran Derivatives 7: To the mixture of alcohol (*Z*)-**6** (0.25 mmol) and $NaHCO_3$ (2.0 mmol) in ether–H_2O (1.3 ml—0.5 ml), I_2 (0.67 mmol) was added and the mixture was stirred for 3 d at refluxing temperature. The reaction mixture was

washed with saturated Na_2SO_3, aq HCl (1 mol dm^{-3}) and saturated $NaHCO_3$. After drying and evaporation, a crude mixture was obtained. Purification by chromatography on silica gel gave a mixture of diastereomers **7** (1/1).

One isomer, ^{1}H NMR ($CDCl_3$) δ=1.14 (t, J=7.6 Hz, 3H), 1.72 (ddq, J=15.2, 10.2, and 7.6 Hz, 1H), 1.93 (ddq, J=15.2, 2.6, and 7.6 Hz, 1H), 2.31 (ddd, J=16.5, 9.6, and 1.7 Hz, 1H), 2.40 (s, 3H), 2.46 (dd, J=16.8 and 3.6 Hz, 1H), 3.19 (dd, J=10.2 and 6.3 Hz, 1H), 3.23 (dd, J=10.2 and 4.6 Hz, 1H), 3.76 (m, 1H), and 4.29 (ddd, J=10.2, 2.6, and 1.7 Hz, 1H).

Another isomer, ^{1}H NMR ($CDCl_3$) δ=0.98 (dd, J=7.3 and 7.3 Hz, 3H), 1.70 (ddq, J=14.3, 7.3, and 7.3 Hz, 1H), 1.97 (ddq, J=14.3, 3.0, and 7.3 Hz, 1H), 2.35 (ddd, J=16.5, 10.2, and 3.6 Hz, 1H), 2.50 (ddd, J=16.5, 3.0, and 3.0 Hz, 1H), 2.53 (s, 3H), 3.23 (dd, J=10.9 and 5.6 Hz, 1H), 3.24 (dd, J=10.9 and 5.9 Hz, 1H), 3.51—3.59 (m, 1H), and 4.27 (dddd, J=7.3, 3.6, 3.0, and 3.0 Hz, 1H).

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4) The reductive reactivity of cuprates (metal–halogen exchange reaction) is so far recognized to be rather undesired because the reduction occurs as a side reaction in substitution reactions using a cuprate as a nucleophile. The cases in which only a reduction reaction proceeds are rare and the efficiency (molar ratio of substrate to cuprates) is not so high. N. Krause and G. Handke, *Tetrahedron Lett.*, **32**, 7229 (1991), and references cited therein.

5) The E/Z ratio was determined by ^{1}H NMR integration of the olefinic proton. The stereochemistry around the olefinic linkage of the major isomer of **3a** was determined to be Z by NOE experiments between allylic methylene protons and a vinyl proton. The J value of **3** was generally observed to be $J_{major} > J_{minor}$. Under conditions during this conversion shown in Eq. 3, the E/Z isomerization was not found.

6) Unfortunately, it was very hard to determine precisely the ratio of geometrical isomers of allylated and acylated products, **4** and **5**, respectively, by spectroscopic and chromatographic analyses. However in the case of **5g**, the ratio was determined to be E/Z=24/76 by NMR.