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Reaction of Ethyl 4-Bromoacetoacetate with Carbon Disulfide and Active Methylene Compounds

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Reaction of ethyl 4-bromoacetoacetate (**1**) with 2-cyanoethene-1,1-dithiol derivatives (prepared from carbon disulfide and active methylene compounds such as ethyl cyanoacetate and malononitrile in the presence of sodium hydride) gave 2-substituted 4-hydroxy-1,3-dithiolane-4-acetates, **2a** and **2b**.

On the other hand, reaction of **1** with 2-cyano-1-methylthioethene-1-thiol derivatives (prepared from 2-cyanoethene-1,1-dithiol derivatives and methyl iodide) gave 4-substituted 3-amino-5-methylthiothiophene-2-(3-oxo)propionates, **5a** and **5b**.

Keywords——ethyl 4-bromoacetoacetate; carbon disulfide; ethyl cyanoacetate; malononitrile; 1,3-dithiolane-4-acetate; 1,3-dithiole-4-acetate; 2-thiophenepropionate

We have recently reported the reaction of ethyl 4-bromoacetoacetate (**1**) with phenyl isothiocyanate and active methylene compounds such as ethyl cyanoacetate, malononitrile, and cyanoacetamide in the presence of sodium ethoxide to give thiazolidine-4-acetates and thiophene-2-(3-oxo)propionates.[1] In a continuation of our study on the syntheses of heterocycles using ethyl 4-haloacetoacetate,[2-4] we now wish to report the reaction of ethyl 4-bromoacetoacetate (**1**) with carbon disulfide in the presence of active methylene compounds such as ethyl cyanoacetate and malononitrile.

When ethyl 4-bromoacetoacetate (**1**) was allowed to react with 2-cyanoethene-1,1-dithiol disodium salt A[5] prepared *in situ* from carbon disulfide and ethyl cyanoacetate in the presence of sodium hydride, ethyl 2-cyano(ethoxycarbonyl)methylene-4-hydroxy-1,3-dithiolane-4-acetate (**2a**) was obtained in 79% yield. Similarly, reaction of **1** with carbon disulfide and malononitrile in the presence of sodium hydride gave the corresponding 1,3-dithiolane derivative **2b** in 37% yield. Compounds **2a** and **2b** were also obtained in 60 and 52% yields by reaction of monosodium salts A′,[5,6] generated by treatment of A with 1 eq of hydrochloric acid, with compound **1**. Elemental analyses and spectroscopic data for **2a** and **2b** were consistent with these structures, as detailed in the experimental section.

Treatment of compound **2a** with acetic anhydride afforded ethyl 2-cyano(ethoxycarbonyl)methylene-1,3-dithiole-4-acetate (**3**) in 60% yield. On the other hand, treatment of compound **2b** with acetic anhydride gave the 4-acetoxy-1,3-dithiolane derivative **4** in 32% yield.

1,1-Dithiol disodium salt derivatives A were treated with an equivalent amount of methyl iodide to yield *S*-monomethylated intermediates, which reacted with **1** to give ethyl 3-amino-4-ethoxycarbonyl-5-methylthiothiophene-2-(3-oxo)propionate (**5a**) and ethyl 3-amino-4-cyano-5-methylthiothiophene-2-(3-oxo)propionate (**5b**) in 36 and 42% yields, respectively. Elemental analyses and spectroscopic data for **5a** and **5b** were consistent with these structures, as detailed in the experimental section.

Concerning the formation of compounds **2a**, **2b**, **5a**, and **5b**, a likely mechanism is as follows; reaction of carbon disulfide with the sodium salt of active methylene compounds gives

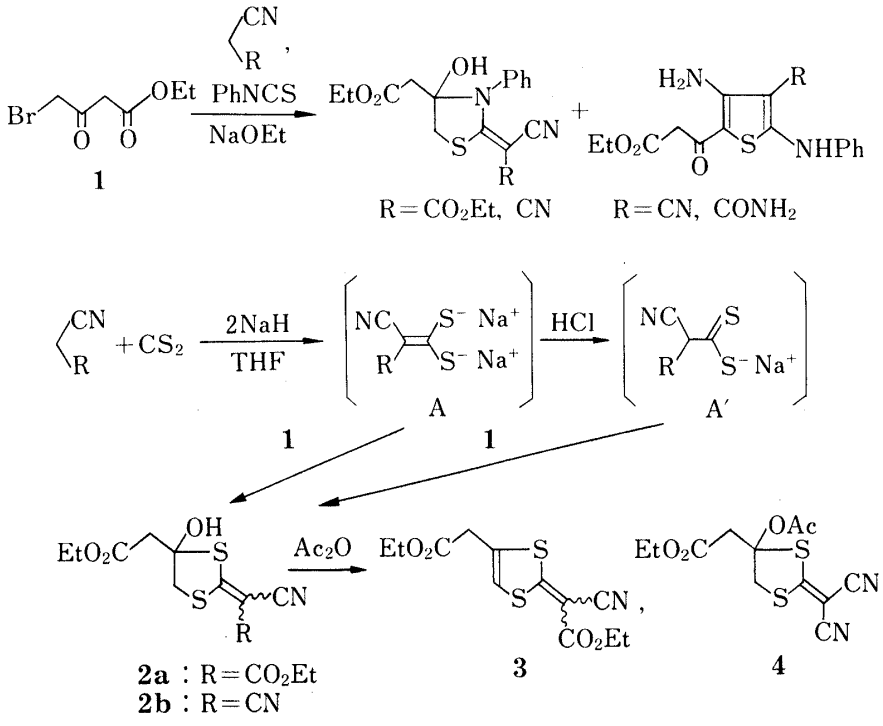

Chart 1

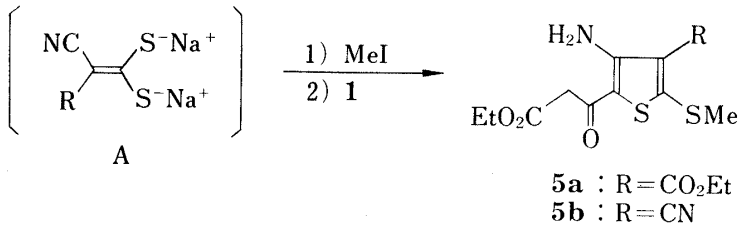

Chart 2

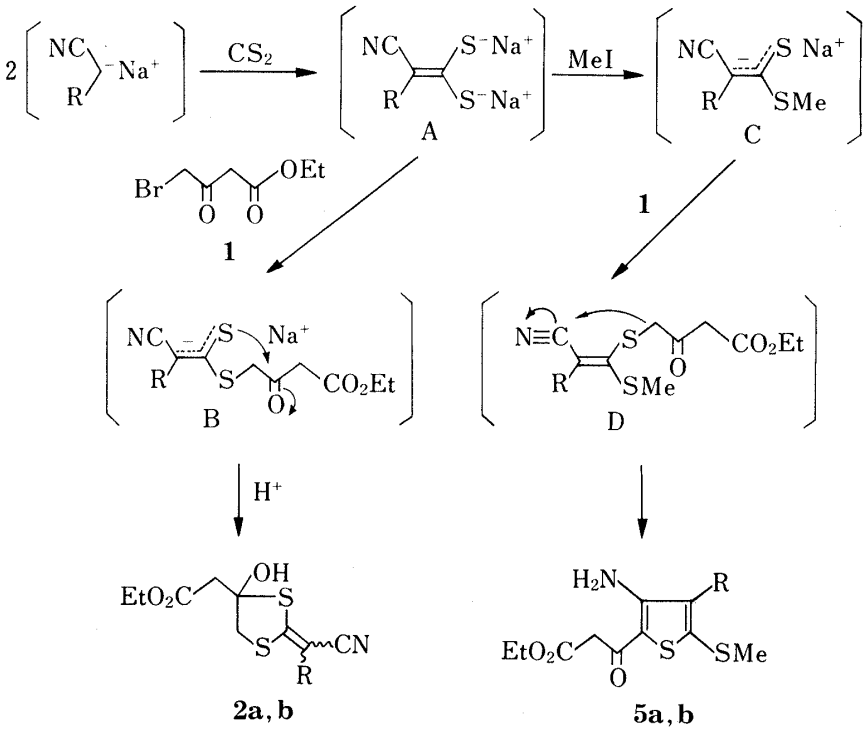

Chart 3

a 2-cyanoethene-1,1-dithiol intermediate A,[5] which reacts with ethyl 4-bromoacetoacetate (**1**) to yield an intermediate B. Ring closure of B gives rise to compounds **2a** and **2b**.

Alkylation of an intermediate A with methyl iodide gives an *S*-monomethylated intermediate C, which reacts with **1** to yield an intermediate D. Cyclization of D between the nitrile carbon and the *S*-methylene carbon[6-9] would give a 3-imino-2,3-dihydrothiophene derivative, which, on prototropy, is transformed to compounds **5a** and **5b**.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-PMX 60 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a Hitachi M-52G spectrometer.

Ethyl 2-Cyano(ethoxycarbonyl)methylene-4-hydroxy-1,3-dithiolane-4-acetate (2a)——Method A: A solution of carbon disulfide (0.8 g, 0.01 mol) in anhydrous tetrahydrofuran (10 ml) was added dropwise to a mixture of ethyl cyanoacetate (2.3 g, 0.02 mol) and sodium hydride (60%, 0.8 g, 0.02 mol) in anhydrous tetrahydrofuran (20 ml) under stirring at 0—10 °C. The mixture was stirred at room temperature for 1 h. A solution of ethyl 4-bromoacetoacetate (**1**) (2.1 g, 0.01 mol) in tetrahydrofuran (10 ml) was added dropwise to this mixture under stirring at 0—10 °C. After being stirred at 0 °C for 1 h, the reaction mixture was neutralized with acetic acid. Precipitates were filtered off and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (60 g) column chromatography using chloroform as an eluent to give an oily product, which was crystallized by rubbing with a glass rod in hexane. Crystals thus obtained were recrystallized from hexane–benzene (1 : 2) to afford the product **2a** as colorless needles, mp 101—102 °C. Yield, 2.5 g (79%). *Anal.* Calcd for $C_{12}H_{15}NO_5S_2$: C, 45.41; H, 4.76; N, 4.41; S, 20.20. Found: C, 45.40; H, 4.57; N, 4.70; S, 19.84. IR ($CHCl_3$): 3425, 2220, 1720, 1710, 1690 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ: 1.27 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.34 (2H, s, CH_2CO), 3.95 (2H, br s, CH_2S), 4.20 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.26 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.25—6.56 (1H, br, OH). MS *m/e*: 317 (M^+), 299 (M^+-H_2O).

Method B: After the treatment of carbon disulfide (0.8 g, 0.01 mol) with ethyl cyanoacetate (2.3 g, 0.02 mol) in the presence of sodium hydride (60%, 0.8 g, 0.02 mol) in the manner described above, a solution of concentrated hydrochloric acid (1.0 g, 0.01 mol) in ethanol (10 ml) was added dropwise to the mixture under stirring at 0—10 °C. The mixture was stirred at 0 °C for 1 h. A solution of **1** (2.1 g, 0.01 mol) in tetrahydrofuran (10 ml) was added dropwise to this mixture under stirring at 0—10 °C. After being stirred at 0 °C for 1 h, the reaction mixture was worked up as described in the above run (method A) to give the product **2a**. Yield, 1.9 g (60%).

Ethyl 2-Dicyanomethylene-4-hydroxy-1,3-dithiolane-4-acetate (2b)——Method A: Following the procedure given for **2a** (method A), **1** (2.1 g, 0.01 mol) was allowed to react with carbon disulfide (0.8 g, 0.01 mol), malononitrile (1.3 g, 0.02 mol), and sodium hydride (60%, 0.8 g, 0.02 mol). The reaction mixture was neutralized with acetic acid. Precipitates were filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on a silica gel (60 g) column using chloroform as an eluent to give the product **2b** as colorless needles (recrystallized from benzene), mp 150—151 °C. Yield, 1.0 g (37%). *Anal.* Calcd for $C_{10}H_{10}N_2O_3S_2$: C, 44.43; H, 3.73; N, 10.36; S, 23.72. Found: C, 43.93; H, 3.85; N, 9.94; S, 24.07. IR ($CHCl_3$): 3400, 2225, 1730, 1710 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ: 1.27 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.40 (2H, s, CH_2CO), 4.12, 4.30 (2H, ABq, J=12 Hz, CH_2S), 4.22 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.96 (1H, s, OH). MS *m/e*: 270 (M^+), 252 (M^+-H_2O).

Method B: Following the procedure given for **2a** (Method B), **1** (2.1 g, 0.01 mol) was allowed to react with carbon disulfide (0.8 g, 0.01 mol), malononitrile (1.3 g, 0.02 mol), sodium hydride (60%, 0.8 g, 0.02 mol), and concentrated hydrochloric acid (1.0 g, 0.01 mol). The reaction mixture was worked up as described in the above run (method A) to give the product **2b**. Yield, 1.4 g (52%).

Ethyl 2-Cyano(ethoxycarbonyl)methylene-1,3-dithiole-4-acetate (3)——A solution of **2a** (1.6 g, 5 mmol) in acetic anhydride (5 ml) was heated at 110 °C for 4 d. The reaction mixture was poured into water (20 ml). Crystals thus obtained were collected and subjected to silica gel (40 g) column chromatography using benzene as an eluent to give the product **3** as slightly yellow leaves (recrystallized from hexane–benzene (1 : 1)), mp 125—126 °C. Yield, 0.9 g (60%). *Anal.* Calcd for $C_{12}H_{13}NO_4S_2$: C, 48.15; H, 4.38; N, 4.68; S, 21.42. Found: C, 47.86; H, 4.30; N, 4.59; S, 21.51. IR ($CHCl_3$): 2220, 1735, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$),1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.68 (2H, s, CH_2CO), 4.23 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.32 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.96 (1H, s, 5-H).

Ethyl 4-Acetoxy-2-dicyanomethylene-1,3-dithiolane-4-acetate (4)——A solution of **2b** (1.35 g, 5 mmol) in acetic anhydride (5 ml) was heated at 90 °C for 1.5 d. The reaction mixture was pouted into water (20 ml) and the oily layer was extracted with chloroform (20 ml × 3). The chloroform layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on a silica gel (40 g) column using benzene as an eluent to give the product **4** as colorless needles (recrystallized from hexane–benzene (1 : 1)), mp 81—82 °C. Yield, 0.5 g (32%). *Anal.* Calcd for $C_{12}H_{12}N_2O_4S_2$: C, 46.14; H, 3.87; N, 8.97; S, 20.53. Found: C, 46.51; H, 3.81; N, 8.84; S, 20.88. IR ($CHCl_3$): 2225,

1750, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.14 (3H, s, $COCH_3$), 3.29, 3.73 (2H, ABq, J=14 Hz, CH_2CO), 4.16 (2H, s, CH_2S), 4.22 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e*: 312 (M^+), 252 ($M^+ - AcOH$).

Ethyl 3-Amino-4-ethoxycarbonyl-5-methylthiothiophene-2-(3-oxo)propionate (5a)——Following the procedure given for **2a** (method B), **1** (2.1 g, 0.01 mol) was allowed to react with carbon disulfide (0.8 g, 0.01 mol), ethyl cyanoacetate (2.3 g, 0.02 mol), sodium hydride (60%, 0.8 g, 0.02 mol), and methyl iodide (1.4 g, 0.01 mol). Precipitates were filtered off and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (60 g) column chromatography using chloroform as an eluent to give an oily product, which was crystallized by rubbing with a glass rod in petroleum ether. Crystals thus obtained were recrystallized from ether to afford the product **5a** as slightly brown leaves, mp 88—89 °C. Yield, 1.2 g (36%). *Anal.* Calcd for $C_{13}H_{17}NO_5S_2$: C, 47.11; H, 5.17; N, 4.23; S, 19.35. Found: C, 46.86; H, 5.43; N, 3.86; S, 19.84. IR ($CHCl_3$): 3475, 3350, 1730, 1720, 1690, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.40 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.58 (3H, s, SCH_3), 3.60 (2H, s, CH_2CO), 4.21 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.37 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.30—8.30 (2H, br, NH_2). MS *m/e*: 331 (M^+).

Ethyl 3-Amino-4-cyano-5-methylthiothiophene-2-(3-oxo)propionate (5b)——Following the procedure given for **2a** (method B), **1** (2.1 g, 0.01 mol) was allowed to react with carbon disulfide (0.8 g, 0.01 mol), malononitrile (1.3 g, 0.02 mol), sodium hydride (60%, 0.8 g, 0.02 mol), and methyl iodide (1.4 g, 0.01 mol). Precipitates were filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel (60 g) using chloroform as an eluent to give the product **5b** as slightly yellow prisms (recrystallized from benzene), mp 150—151 °C (dec.). Yield, 1.2 g (42%). *Anal.* Calcd for $C_{11}H_{12}N_2O_3S_2$: C, 46.46; H, 4.26; N, 9.85; S, 22.55. Found: C, 46.19; H, 4.22: N, 9.65; S, 22.59. IR ($CHCl_3$): 3500, 3350, 2225, 1730, 1720, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.67 (3H, s, SCH_3), 3.62 (2H, s, CH_2CO), 4.23 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.35—7.10 (2H, br, NH_2).

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