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 A5) prepared in situ from carbon disulfide and ethyl cyanoacetate in the presence of sodium hydride, ethyl 2-cyano(ethoxy carbonylmethylene-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(ethoxy carbonylmethylene)-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-ethoxy carbonyl-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
a 2-cyanoethene-1,1-dithiol intermediate A, which reacts with ethyl 4-bromoacetoacetate (I) 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-monosubstituted intermediate C, which reacts with 1 to yield an intermediate D. Cyclization of D between the nitrile carbon and the S-methylene carbon would give a 3-imino-2,3-dihydropyridine derivative, which, on protopropylation, 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 (1H-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(ethoxy carbonyl)methylene-4-hydroxy-1,3-dithiole-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 (I) (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.* Caled for C7H11NO2S2: 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 (CHCl3): 3425, 2240, 1720, 1710, 1690 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.27 (3H, t, J = 7 Hz, CH₃), 1.29 (3H, t, J = 7 Hz, CH₂CH₃), 3.34 (2H, s, CH₂CO), 3.95 (2H, br s, CH₂S), 4.20 (2H, q, J = 7 Hz, OCH₂CH₃), 4.26 (2H, q, J = 7 Hz, OCH₂CH₃), 6.25—6.56 (1H, br, OH). MS m/e: 317 (M⁺), 299 (M⁺ — H₂O).

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 I (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-dithiole-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.* Caled for C₁₀H₁₄N₂O₃S₂: 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 (CHCl₃): 3400, 2225, 1730, 1710 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.27 (3H, t, J = 7 Hz, CH₃), 3.40 (2H, s, CH₂CO), 4.12, 4.30 (2H, ABq, J = 12 Hz, CH₂S), 4.22 (2H, q, J = 7 Hz, OCH₂CH₃), 6.96 (1H, s, OH). MS m/e: 270 (M⁺), 252 (M⁺ — H₂O).

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(ethoxy carbonyl)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.* Caled for C₁₀H₁₂N₂O₄S₂: 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 (CHCl₃): 2220, 1735, 1675 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.31 (3H, t, J = 7 Hz, CH₃), 3.35 (3H, t, J = 7 Hz, CH₂CH₃), 3.68 (2H, s, CH₂CO), 4.23 (2H, q, J = 7 Hz, OCH₂CH₃), 4.32 (2H, q, J = 7 Hz, OCH₂CH₃), 6.96 (1H, s, 5-H).

**Ethyl 4-Acetoxy-2-dicyanomethylene-1,3-dithiole-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 poured 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.* Caled for C₁₁H₁₂N₂O₄S₂: 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 (CHCl₃): 2225,
1750, 1730 cm\(^{-1}\), \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.28 (3H, t, \(J = 7\) Hz, CH\(_2\)CH\(_3\)), 2.14 (3H, s, COCH\(_3\)), 3.29, 3.73 (2H, ABq, \(J = 14\) Hz, CH\(_2\)CO), 4.16 (2H, s, CH\(_2\)S), 4.22 (2H, q, \(J = 7\) Hz, OCH\(_2\)CH\(_3\)). MS m/e: 312 (M\(^+\)), 252 (M\(^+\) − AcOH).

**Ethyl 3-Amino-4-ethoxycarbonyl-5-methylthioiophene-2-(3-oxo)propionate (5a)** — Following the procedure given for 2a (method B), I (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. Calec for C\(_{14}\)H\(_9\)NO\(_2\)S\(_2\): 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\(_3\)) \(\delta\): 1.28 (3H, t, \(J = 7\) Hz, CH\(_2\)CH\(_3\)), 1.40 (3H, t, \(J = 7\) Hz, CH\(_2\)CH\(_3\)), 2.58 (3H, s, SCH\(_3\)), 3.60 (2H, s, CH\(_2\)CO), 4.21 (2H, q, \(J = 7\) Hz, OCH\(_2\)CH\(_3\)), 4.37 (2H, q, \(J = 7\) Hz, OCH\(_2\)CH\(_3\)), 7.30—8.30 (2H, br, NH\(_2\)). MS m/e: 331 (M\(^+\)).

**Ethyl 3-Amino-4-cyano-5-methylthioiophene-2-(3-oxo)propionate (5b)** — Following the procedure given for 2a (method B), I (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. Calec for C\(_{15}\)H\(_{11}\)N\(_2\)O\(_2\)S\(_2\): 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\(_3\)) \(\delta\): 1.28 (3H, t, \(J = 7\) Hz, CH\(_2\)CH\(_3\)), 2.67 (3H, s, SCH\(_3\)), 3.62 (2H, s, CH\(_2\)CO), 4.23 (2H, q, \(J = 7\) Hz, OCH\(_2\)CH\(_3\)), 6.35—7.10 (2H, br, NH\(_2\)).

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**References**