Chem. Pharm. Bull. 26(12)3880—3883(1978)

UDC 547.446.6.04 : 547.461.3.04

Reaction of Ethyl 4-Halo-3-oxobutanoate with Diethyl Malonate, Methyl Cyanoacetate, and Malononitrile

Tetsuzo Kato, Hitoshi Kimura, and Kenichi Tanji

Pharmaceutical Institute, Tohoku University[1]

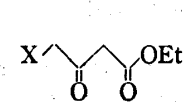
(Received June 3, 1978)

Ethyl 4-bromo (and chloro)-3-oxobutanoate (**1** and **2**) reacts with diethyl malonate in the presence of sodium hydride to give diethyl 5-ethoxycarbonyl-3-oxohexanedioate (**3**) and diethyl 5-carboxy-3-oxohexanedioate (**4**). Similarly, reaction of the haloester (**1**, **2**) with methyl cyanoacetate gives 1-ethyl methyl 5-cyano-3-oxohexanedioate (**6**) and 1-ethyl hydrogen 5-cyano-3-oxohexanedioate (**7**). On the other hand, **1** reacts with malononitrile in the presence of triethylamine to give ethyl 5-amino-4-cyanofuran-2-acetate (**8**) and ethyl 3-amino-2,4,4-tricyano-2-cyclopenten-1-ylideneacetate (**9**).

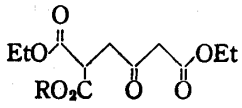
Keywords——ethyl 4-bromo-3-oxobutanoate; active methylene compound; β-ketoadipinic acid derivative; furanacetic acid; selective hydrolysis

It is reported that methyl γ-bromoacetoacetate (4-bromo-3-oxobutanoate) reacted with ethyl acetoacetate to give 1-ethyl methyl 2-methyl-4-oxo-2-cyclopentene-1,3-dioate.[2] The reaction involves the condensation of the bromoacetoacetate with the active methylene of ethyl acetoacetate accompanied with cyclization to give the cyclopentenone derivative. As a continuation of our studies[3] of some potential uses of ethyl 4-halo-3-oxobutanoate, which is most readily prepared from diketene,[4] we are interested in its reaction with active methylene compounds such as diethyl malonate, methyl cyanoacetate, and malononitrile, which is the subject of the present paper.

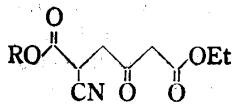
When diethyl malonate was allowed to react with ethyl 4-bromo-3-oxobutanoate (**1**) in tetrahydrofuran (THF) in the presence of sodium hydride, diethyl 5-ethoxycarbonyl-3-oxohexanedioate (**3**) and diethyl 5-carboxyl-3-oxohexanedioate (**4**) were obtained in 37 and 29% yields, respectively. The acid **4** was converted to the methyl ester (**5**) by methylation with diazomethane.



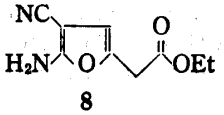
1: X=Br
2: X=Cl



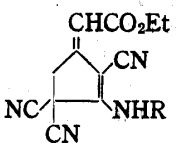
3: R=Et
4: R=H
5: R=Me



6: R=Me
7: R=H



8



9: R=H
10: R=Ac

Chart 1

1) Location: *Aobayama, Sendai 980, Japan.*
2) L.J. Dolby, C. A. Elliger, S. Esfandiari, and K.S. Marshall, *J. Org. Chem.*, **33**, 4508 (1968).
3) T. Kato, T. Chiba, and H. Kimura, *Chem. Pharm. Bull.* (Tokyo), **25**, 203 (1977); T. Kato, M. Sato, and H. Kimura, *J. Chem. Soc. Perkin I*, in press.
4) F. Chick and N.T.M. Wilsmore, *J. Chem. Soc.*, **97**, 1978 (1910).

Table I. Reactions of Haloester ($XCH_2COCH_2CO_2Et$) with Active Methylene Compounds

Active methylene compounds	Reaction products	Yields (%) X=Br	Yields (%) X=Cl
$EtO_2CCH_2CO_2Et$	**3**	37	25
	4	29	50
$NCCH_2CO_2Me$	**6**	22	13
	7	16	18

Similarly, methyl cyanoacetate reacted with the bromoester **1** under the same condition to give 1-ethyl methyl 5-cyano-3-oxohexanedioate (**6**) and 1-ethyl hydrogen 5-cyano-3-oxohexanedioate (**7**) in 22 and 16% yields, respectively. Reaction of malononitrile with the bromoester **1** under the same condition resulted in the formation of the resinous products.

Use of ethyl 4-chloro-3-oxobutanoate (**2**) instead of the bromo ester **1** gave the same products. Results are summarized in Table I.

Similar reaction of diethyl malonate with the bromoester **1** in the presence of triethylamine in place of sodium hydride resulted in the recovery of the starting materials, while methyl cyanoacetate reacted with **1** in the presence of triethylamine, 1-ethyl methyl 5-cyano-3-oxohexanedioate (**6**) was obtained in 67% yield.

Similar reaction of compound **1** with malononitrile gave ethyl 5-amino-4-cyanofuran-2-acetate (**8**) and ethyl 3-amino-2,4,4-tricyano-2-cyclopenten-1-ylideneacetate (**9**) in 21 and 4% yields, respectively. Compound **9** was acetylated with acetic anhydride to give the acetate (**10**) in 85% yield.

The formations of these products can be explained as follows: 1) Compounds **3** and **6**, which are produced from diethyl malonate and ethyl cyanoacetate in the first stage, cyclize giving the furanone derivative (A) as the intermediate, hydrolysis of which gives the acids **4** and **7**. 2) Reaction of malononitrile with **1** would give the intermediate (B), which cyclizes

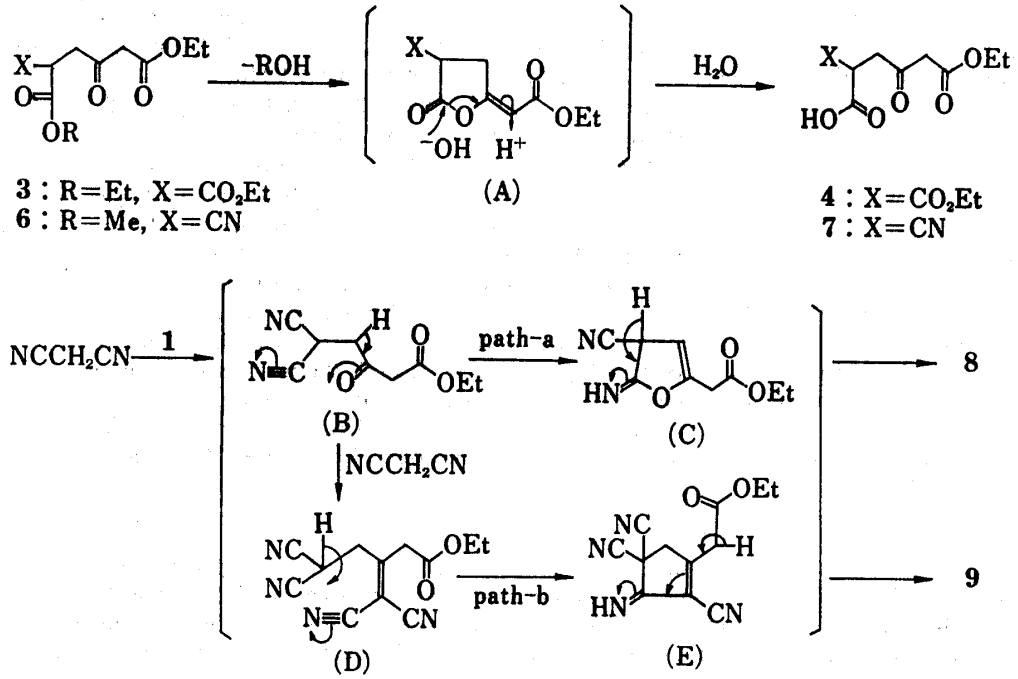


Chart 2

along path-a to give the furan derivative **8** *via* the intermediate (C). 3) Addition of another mole of malononitrile to the intermediate (B) gives the tetracyano intermediate (D), which along path-b cyclizes to the cyclopentene derivative **9** *via* intermediate (E).

Experimental[5]

Reaction of Ethyl 4-Bromo-3-oxobutanoate (1) with Diethyl Malonate——To a stirred suspension of sodium hydride (50% oil, 3.84 g, 0.08 mol)[6] in THF (160 ml), was added dropwise a solution of diethyl malonate (12.8 g, 0.08 mol) in THF (20 ml) under ice-cooling. The mixture was stirred for 30 min, and a solution of compound **1** (8.4 g, 0.04 mol) in THF (20 ml) was added to the solution dropwise with continous stirring, during which time temperature was kept below −10 °. After stirring for additional 2 hr at room temperature, the reaction mixture was condensed *in vacuo*. The residue was added to water (50 ml), and the mixture was extracted with ether. The ether solution was dried, and condensed. The residue was distilled under reduced pressure to give the product **3** as a colorless oil, bp 150—153° (2 mmHg), 4.2 g (37%). *Anal.* Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 54.32; H, 6.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1730. NMR ($CDCl_3$) δ: 1.28 (9H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.17 (2H, d, J=6.5 Hz, 4-CH_2), 3.50 (2H, s, 2-CH_2), 3.87 (1H, t, J=6.5 Hz, 5-CH), 4.20 (6H, q, J=7 Hz, $CH_3C\underline{H}_2O$).

The aqueous solution was acidified with 10% hydrochloric acid, and the mixture was extracted with ether. The ether solution was dried over sodium sulfate and condensed to dryness. The residue was purified by silica gel column chromatography using $CHCl_3$ as an eluant to give a viscous colorless oil **4**, 3 g (29%). *Anal.* Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.63; H, 6.29. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (br), 1735, 1717. NMR ($CDCl_3$) δ: 1.25 (6H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.02—3.24 (2H, m, 4-CH_2), 3.43 (2H, s, 2-CH_2), 4.17 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.19 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 8.35 (1H, br, OH).

Diethyl 5-Methoxycarbonyl-3-oxohexanedioate (5)——To compound **4** (1.5 g, 0.05 mol) was added a solution of excess diazomethane in ether. The reaction mixture was condensed, and the residue was distilled to give the product **5** as a colorless oil, bp 150° (2 mmHg), 0.9 g (66%). *Anal.* Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.49; H, 6.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742 (sh), 1732. NMR ($CDCl_3$) δ: 1.28 (6H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.20 (2H, d, J=7.5 Hz, 4-CH_2), 3.52 (2H, s, 2-CH_2), 3.77 (3H, s, CH_3O), 3.91 (1H, t, J=7.5 Hz, 5-CH), 4.23 (4H, q, J=7 Hz, $CH_3C\underline{H}_2O$).

Reaction of Ethyl 4-Bromo-3-oxobutanoate (1) with Methyl Cyanoacetate——1) To a stirred suspension of sodium hydride (50% oil, 0.96 g, 0.02 mol) in THF (40 ml), was added methyl cyanoacetate (2.0 g, 0.02 mol) under ice-cooling. To the mixture, was added dropwise a solution of compound **1** (2.1 g, 0.01 mol) in THF (10 ml) at −10° with stirring. After stirring for 3 hr at room temperature, the mixture was condensed *in vacuo*. The residue was poured into water (30 ml), and the mixture was extracted with ether. The ether solution was dried and condensed to give an oil, which was distilled under reduced pressure to give an oil, methyl cyanoacetate, bp 50—52° (2 mmHg), 0.4 g (40%). The distilled residue was purified by silica gel column chromatography using $CHCl_3$ as an eluant to give a crystalline substance, which was recrystallized from ether–petroleum ether to colorless needles **6** of mp 51—52°. *Anal.* Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.88; H, 5.70; N, 6.35. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240, 1760, 1735. NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.27 (2H, d d, J=6.3 Hz and 2.8 Hz, 4-CH_2), 3.52 (2H, s, 2-CH_2), 3.82 (3H, s, OCH_3), 3.80—4.15 (1H, m, 5-CH), 4.21 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$).

The aqueous layer was acidified with 10% hydrochloric acid, and the mixture was extracted with ether. The ether solution was evaporated, and crystals obtained were collected. Recrystallization from ethyl acetate–benzene gave the acid **7** as colorless prisms, mp 115—117°, 0.3 g (16%). *Anal.* Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.73; H, 5.29; N, 6.40. IR ν_{max}^{KBr} cm^{-1}: 3040, 2240, 1730, 1695. NMR (DMSO-d_6) δ: 1.21 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.26 (2H, d, J=5.5 Hz, 4-CH_2), 3.69 (2H, s, 2-CH_2), 4.12 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.26 (1H, t, J=5.5 Hz, 5-CH), 7.25 (1H, br, OH).

2) To a solution of methyl cyanoacetate (1.0 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in THF (20 ml), was added dropwise a solution of **1** (2.1 g, 0.01 mol) in THF (20 ml) with stirring under ice-cooling. The mixture was stirred at the same temperature for 1 hr, then at room temperature for additional 5 hr. Triethylamine hydrobromide separated was filtered off, and the filtrate was condensed *in vacuo*. The resulting oily residue was purified by silica gel column chromatography using $CHCl_3$ as an eluant to give the product **6**, 1.5 g (67%).

5) All melting points and boiling points were uncorrected. Infrared (IR) spectra were recorded with a JASCO model IR-S spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a Hitachi R-20 Spectrometer using TMS as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Mass spectra were measured on a Hitachi Double Focusing Mass Spectrometer RMU-7L.

6) Commercial sodium hydride (50% dispersed in mineral oil) was used after washing with petroleum ether.

Reaction of Ethyl 4-Chloro-3-oxobutanoate (2) with Diethyl Malonate——To a suspension of sodium hydride (50% oil, 0.96 g, 0.02 mol) in THF (100 ml), was added a solution of diethyl malonate (3.2 g, 0.02 mol) in THF (10 ml) under ice-salt-cooling. After stirring for 30 min, the mixture was cooled below −10° and a solution of compound **2** (1.64 g, 0.01 mol) in THF (10 ml) was added dropwise to the mixture. After stirring at room temperature for 7 hr, the mixture was heated on a water bath at reflux for 2 hr. Similar treatment as above gave compound **3** and **4** in 25% (0.7 g) and 50% (1.2 g) yields, respectively.

Reaction of Ethyl 4-Chloro-3-oxobutanoate (2) with Methyl Cyanoacetate——Following the similar fashion given for compounds **6** and **7** from compound **1** and methyl cyanoacetate, compound **2** (1.64 g, 0.01 mol) was allowed to react with methyl cyanoacetate (2.0 g, 0.02 mol) in the presence of sodium hydride (50% oil, 0.96 g, 0.02 mol) in THF to give 0.3 g (13%) of compound **6** and 0.35 g (18%) of compound **7**.

Reaction of Ethyl 4-Bromo-3-oxobutanoate (1) with Malononitrile ——To a solution of malononitrile (0.73 g, 0.011 mol) and triethylamine (1.1 g, 0.011 mol) in THF (50 ml), was added dropwise a solution of **1** (2.1 g, 0.01 mol) in THF (20 ml) with stirring under ice-cooling. After stirring for 4 hr at the same temperature, crystals separated (triethylamine hydrobromide, 1.73 g), were collected by suction. The filtrate was condensed *in vacuo*. The residue was dissolved in benzene (40 ml), and the solution was washed with water (50 ml). The benzene solution was dried, and condensed to dryness. The residue was purified by silica gel column chromatography using $CHCl_3$ as an eluant. The first elution gave 0.1 g of recovered **1**. The subsequent elution gave the product **8** as colorless prisms (from benzene), mp 92—93°, 0.4 g (21%). *Anal.* Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.78; H, 5.09; N, 14.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3430, 2220, 1735, 1635. NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.48 (2H, s, CH_2), 4.15 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.90 (2H, br, NH_2), 6.11 (1H s, ring-H).

The water soluble fraction was allowed to stand overnight to give a crystalline substance, which was collected and recrystallized from methanol to give the product **9** as colorless prisms, mp 230° (dec.), 0.1 g (4%). *Anal.* Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.71; H, 4.24; N, 22.93. IR ν_{max}^{KBr} cm^{-1}: 3260, 3110, 2230, 1680, 1670. NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.92 (2H, d, J=2 Hz, CH_2), 4.10 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$). 5.10 (1H, t, J=2 Hz, CH=), 9.20 (2H, m, NH_2). MS m/e: 242 (M^+).

Ethyl 3-Acetylamino-2,4,4-tricyano-2-cyclopenten-1-ylideneacetate (10)——To a solution of compound **8** (0.24 g, 1 mmol) in pyridine (20 ml), was added acetic anhydride (0.5 ml) with ice-cooling. After allowing to stand at room temperature for 18 hr, the mixture was poured into ice-water (20 ml). Crystals separated were collected by suction. Recrystallization from methanol gave the acetate **10** as colorless prisms, mp 210° (dec.), 0.24 g (85%). *Anal.* Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71. Found: C, 59.20; H, 4.29; N, 19.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240, 1740, 1705, 1613. NMR ($CDCl_3$-2% DMSO-d_6) δ: 1.32 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 2.33 (3H, s, CH_3CO), 4.06 (2H, d, J=2 Hz, CH_2), 4.24 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 6.08 (1H, t, J=2 Hz, olefinic H), 11.54 (1H, br, NH).

Acknowledgement The authors are indebted to Mrs. A. Sato, Mrs. C. Koyanagi, Miss K. Mushiake, Miss H. Koizumi and Mr. K. Kawamura of the central analysis room of this Institute for the elemental analyses and spectral measurements.