# The 2*H*-Cyclohepta[*b*]furan-2-one Formation from 2,4-Dichloro-5-methoxytropone with Dimethyl Malonate and Methyl Acetoacetate

Hitoshi Takeshita,* Akira Mori, and Tomoyoshi Minami
*Research Institute of Industrial Science, 86, Kyushu University, Sakamoto, Kasuga, Fukuoka 816*

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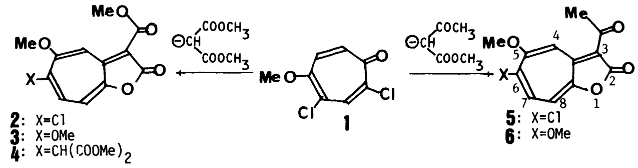
**Synopsis.** 2,4-Dichloro-5-methoxytropone afforded 3,5,6-trisubstituted 2*H*-cyclohepta[*b*]furan-2-one derivatives by condensation with dimethyl malonate and methyl acetoacetate in an exclusive *ciné*-condensation mode in various solvents.

Recently, we have reported[1] a solvent effect on the condensation of 2,5-disubstituted tropones with dimethyl malonate (DM); a concomitant formation of *ciné*- and normal condensates in the 2*H*-cyclohepta[*b*]furan-2-one (oxazulanone) formation from 5-chloro-2-methoxytropone (**A**) was a characteristic feature. In connection to our recent synthesis of the 1*H*-cyclohepta[1,2-*d*;3,4-*d'*]- and 1*H*-cyclohepta[1,2-*d*;4,5-*d'*]diimidazoles,[2] same ring systems to unique metabolites from marine organisms, paragracine[3] and zoanthoxanthins,[4] from 2,4-dichloro-5-methoxytropone (**1**), we thought it would be worthwhile to examine the further cyclohepta[*b*]furanone formation by condensation of **1**[5] with active methylene derivatives.[6] Since the intermediates possess the two leaving groups in the conjugated positions, two different products could be formed by the *ciné*-condensation reaction. In this paper, we wish to describe the results.

When **1** was allowed to react with DM in methanol, a rapid reaction occurred at 15 °C to give two products, **2** and **3**, both yellow crystals, in sum of *ca.* 50 to 60% yields. The major product, **3**, was shown to be a secondary product derived from **2** and sodium methylate. The NMR of **2** showed a small but characteristic long-range coupling between the methoxyl signal at $\delta$[7]=4.13 and an aromatic proton signal at $\delta$=8.55, but other than this, no spin-spin interaction was detectable for this signal. Since these cycloheptafuranones exhibited a clear meta-coupling between $H_4$–$H_6$ in the 5-substituted derivatives,[1] the chlorine must be located on C-6. The $J_{vic}$ value of the other two aromatic protons, 10.5 Hz, is compatible to that of $H_7$–$H_8$ in view of the bond alternation in this conjugated system. Therefore, **2** is 6-chloro-5-methoxy-3-methoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-one, and not the alternative, **2a**, 7-chloro-6-methoxy-3-methoxycarbonyl derivative.[1] On the other hand, the NMR spectrum of **3** showed a close resemblance to that of **2**. Both methoxyl signals revealed a long-range spin-spin splitting with the protons on the seven-membered ring. The condensation of **1** with DM for a prolonged time afforded another product, **4**, which was independently prepared by further reactions of **2** or **3** with DM. The malonyl group of **4** was deduced to be at C-6; the NMR signal of C-4 proton at $\delta$=8.48 resembled those at 8.55 and 8.58 of **2** and **3**, while the *AB*-doublets were moved to $\delta$=7.16 and 7.46 ($J$=10 Hz) from 6.79 and 7.20 ($J$=10.5Hz) in **3**. As expected, **3** was undetectable in the reaction of **1** in benzene. The yields of **2** were most satisfactory in dimethyl sulfoxide (DMSO).

Similarly, **1** was treated with methyl acetoacetate (MA) in methanol at 15 °C; the products were again the *ciné*-products, 6-chloro-5-methoxy derivative (**5**) and 5,6-dimethoxy derivative (**6**). According to the NMR analysis, the position of the methoxy group of **5** was at C-5, because the same long-range splitting behavior was found. A further treatment of **5** under the reaction conditions gave **6**. The reaction features in the different solvents of **1** with MA was parallel to those of **1** with DM.

It has been noted that, in the cyclohepta[*d*]imidazole formation,[2] the introduction of substituents, such as halogens or methoxy group, on the seven-membered ring caused a diminishment of the reactivity toward nucleophilic attack; the present results however disagree for **1** gave the condensates in good yields.



Scheme 1.

## Experimental

*The Condensation of 1 and Dimethyl Malonate with NaOMe. a)*: To an anhydrous MeOH solution (8 cm³) of DM (160 mg) containing NaOMe (55 mg), **1** (60 mg) was added in dropwise at 10—15 °C. Instantly, dark yellow color developed in the solution. After 2 h, the mixture was poured into ice-water, acidified with dil HCl, and extracted with $CHCl_3$. The major product, **2**, obtained by silica gel column chromatography (hexane:ethyl acetate, 9:1) was further purified by fractional recrystallizations from benzene to give yellow needles, mp 249—250 °C (decomp), 29 mg (55%) [Found: C, 53.64; H, 3.37%. Calcd for $C_{12}H_9O_5Cl$: C, 53.65; H, 3.38%. $\delta$=3.92 (3H, s), 4.13 (3H, br. s), 7.04 (1H, d, $J$=10.5 Hz), 7.72 (1H, d, $J$=10.5 Hz), and 8.55 (1H, br. s). $\nu$: 1755, 1683, 1580, 1520, 1242, 895, 790, 760 cm⁻¹. $\lambda_{\max}^{\text{MeOH}}$: 294 nm ($\varepsilon$=25000), 306 (25000), 402 (19000)], together with a trace amount of **3**, yellow needles, mp 259—260 °C (from benzene) [Found: C, 58.85; H, 4.47%. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58%. $\delta$=3.92 (3H, s), 3.98 (3H, s), 4.12 (3H, br. s), 6.79 (1H, d, $J$=10.5 Hz), 7.20 (1H, d, $J$=10.5 Hz), and 8.58 (1H, br. s). $\nu$: 1743, 1675, 1583, 1538, 1470, 1240, 695 cm⁻¹. $\lambda_{\max}^{\text{MeOH}}$: 278 nm ($\varepsilon$=23000), 294 (21000), 402 (18000)]. The recovered **1**, 14 mg (24%), was obtained from the fractions eluted by hexane: ethyl acetate (1:1).

*b)*: Similarly, **1** (30 mg) was allowed to react with DM (80 mg) and NaOMe (25 mg) in methanol (4 cm³) for 22 h. Similar work-up yielded **2**, 22%, and **3**, 28%, together with some of the recovered **1**.

*c)*: To an anhydrous benzene dispersion (10 cm³) of DM (130 mg) and NaOMe (45 mg), **1** (50 mg) was added under stirring for 20 min at 10—15 °C. The mixture was then diluted with water, acidified with dil HCl, and was $CHCl_3$ extracted. Purification by silica gel column chromatography of the extracts yielded **2**, 32.5 mg (61.5%), and the recovered **1**, 4.3 mg (8.6%).

*d)*: Similarly, **1** (50 mg) was treated with DM (130 mg) and NaOMe (45 mg) in benzene (10 cm$^3$) at 10—15 °C for 20 min. The products were isolated by silica-gel column chromatography to give **2**, 36.7 mg (61.3%).

*e)*: Similarly, a mixture of **1** (50 mg), DM (130 mg), and NaOMe (40 mg) in benzene (10 cm$^3$) was kept at 10—15 °C for 2 d. The mixture was chromatographed on a silica-gel column; the yield of **2** has dropped to 2 mg (3%) and another product, **4**, pale yellow needles, mp 209.5—210 °C (from benzene) [Found: C, 55.82; H, 4.38%. Calcd for $C_{17}H_{16}O_9$: C, 56.04; H, 4.43%. $\delta$=3.77 (6H, s), 3.92 (3H, s), 4.05 (3H, s), 5.09 (1H, s), 7.16 (1H, d, $J$=10 Hz), 7.46 (1H, d, $J$=10 Hz), and 8.48 (1H, s). $\nu$: 1758, 1680, 1590, 1518, 1470, 1405, 1250, 890, 765 cm$^{-1}$. $\lambda_{\max}^{\mathrm{MeOH}}$: 283 nm ($\varepsilon$=25000), 294 (25000), 393 (19000)] was obtained, 16 mg (18%).

*f)*: To anhydrous DMSO solution (10 cm$^3$) of DM (1.05 g) and NaOMe (400 mg), **1** (220 mg) was added. After 40 min, the mixture was diluted with water, and extracted by $CHCl_3$. Silica-gel chromatography gave yellow crystals, **2**, 231 mg (92%), together with the recovered **1** (25 mg, 12%).

*The Reaction of 2 with Dimethyl Malonate.* To an anhydrous MeOH solution (4 cm$^3$) of DM (100 mg) and NaOMe (20 mg), 2 (20 mg) was added at 15 °C and kept 12 h. The mixture was diluted with ice-water, extracted with $CHCl_3$, and purified on a silica-gel column to give **4**, 20 mg (74%).

*The Reaction of 3 with Dimethyl Malonate.* Similarly, **3** (20 mg) was mixed with DM (100 mg) and NaOMe (15 mg) in a MeOH (4 cm$^3$) solution at 15 °C. A similar work-up after 12 h yielded **4**, 15 mg (54%).

*The NaOMe-catalyzed Reaction of 1 with Methyl Acetoacetate.* *a)*: To an anhydrous MeOH solution (8 cm$^3$) of MA (160 mg) and NaOMe (55 mg), **1** (60 mg) was added under stirring at 10—15 °C. After 5 min, the separated crystals were collected by filtration. After fractional recrystallizations from benzene, **5**, yellow needles, mp 235—236 °C, 45 mg (74%) [Found: C, 56.96; H, 3.60%. Calcd for $C_{13}H_9O_4$: C, 57.05; H, 3.59%. $\delta$=2.61 (3H, s), 4.14 (3H, br. s), 7.11 (1H, d, $J$=11.5 Hz), 7.78 (1H, d, $J$=11.5 Hz), and 9.00 (1H, br. s). $\nu$: 1743, 1638, 1515, 1450, 1240 cm$^{-1}$. $\lambda_{\max}^{\mathrm{MeOH}}$: 239 nm ($\varepsilon$=22000), 305 (23000), 410 (20000)], was obtained together with the recovered **1**, 3 mg (5%).

*b)*: Anhydrous benzene dispersion (10 cm$^3$) of MA (160 mg) and NaOMe (55 mg) was mixed with **1** (60 mg) and kept at 10—15 °C for 2 h. Then the mixture was diluted with water and extracted with $CHCl_3$. Silica gel chromatography of the product gave **5**, 54 mg (84%).

*c)*: To an anhydrous DMSO solution (3 cm$^3$) of MA (160 mg) and NaOMe (55 mg), **1** (60 mg) was added, the mixture was kept at 10—15 °C After 5 min, it was chromatographed on a silica-gel column to give **5**, 64 mg (quantitative yield).

*The Conversion of 5 to 6.* **5** (27 mg) was dissolved in a mixture of MeOH (1 cm$^3$) and benzene (7 cm$^3$) containing NaOMe (10 mg) at 15—20 °C for 2 d. Then the mixture was poured into water, and extracted with $CHCl_3$. Silica-gel chromatography of the extracts gave yellow needles, mp 244—245 °C (from benzene), **6**, 22 mg (80%) [Found: C, 63.50; H, 4.94%. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87%. $\delta$=2.60 (3H, s), 3.98 (3H, s), 4.12 (3H, s), 6.85 (1H, d, $J$=11 Hz), 7.26 (1H, d, $J$=11 Hz), and 9.00 (1H, br. s). $\nu$: 1722, 1640, 1623, 1588, 1460, 1243 cm$^{-1}$. $\lambda_{\max}^{\mathrm{MeOH}}$: 285 nm ($\varepsilon$=19000), 301 (20000), 414 (19000)].

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7) The NMR spectra were measured in $CDCl_3$ solutions, and the chemical shifts were expressed in $\delta$ units from the internal $Me_4Si$.