Notes

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Synthesis of Furan Derivatives. Synthesis of Furanpolycarboxylic Acid[1]

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5-Ethoxycarbonyl-3,4-dimethoxycarbonyl-2-methylfuran (**6**) was prepared from sulfonium 1-ethoxycarbonylacetonylide (**1**) with dimethyl acetylenedicarboxylate (**2**). It has been made clear by separate synthetical method that the reaction occurred with, 1.3-shift of the acetyl group of the ylid compound (**1**).

Keywords——furanpolycarboxylic acid; ylid reaction; decarboxylation; selective hydrolysis; 1,3-shift of acetyl group

Our main object in this work has been in synthesis of some polycarboxylic acid derivatives of furan as starting materials in Curtius reaction. In the meantime, several reports[3] have been published on the unique synthesis of furanpolycarboxylate using appropriate sulfonium ylids and acetylenic compounds. Especially, the interesting reaction mechanism has been proposed by Mukaiyama[3b] to account for the formation of dimethyl 2,5-dimethyl-3,4-furandicarboxylate from the reaction of dimethylsulfonium 1-methylacetonylide with dimethyl acetylenedicarboxylate (DMA).

In this paper, the results of the study of the reaction of dimethylsulfonium 1-ethoxycarbonylacetonylide (**1**) with DMA (**2**) in the course of the formation of 5-ethoxycarbonyl-3,4-dimethoxycarbonyl-2-methylfuran (**6**) are separately discussed.

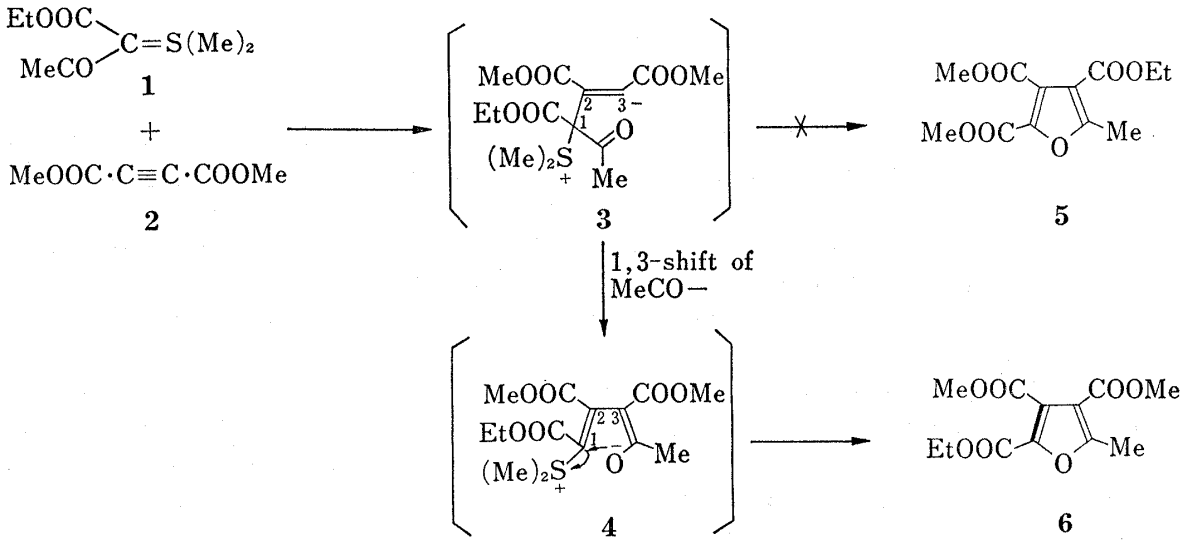

Chart 1

1) Some parts of this work presented at the 23th Local Meeting of the Pharmaceutical Society of Japan at Kyoto, November 1973.

2) Location: *Ikawadani, Tarumi-ku, Kobe, Japan, 673, Japan.*

3) *a*) Y. Hayashi, M. Kobayashi and H. Nozaki, *Tetradedron*, **26**, 4353 (1970); *b*) M. Higo and T. Mukaiyama, *Tetrahedron Letters*, **29**, 2565 (1970); *c*) E. Winterfeldt, *Chem. Ber.*, **1965**, 1110.

Namely, from the reaction of ylid (**1**) with (**2**) in dioxane in the presence of a catalytic amount of triethylamine, the crystalline product, mp 61—62°, either (**5**) or (**6**) was obtained in 77.2% yield. Naturally, judging from the Mukaiyama's announcement,[3b] it suggests us that the structure of the crystalline product (**5**) or (**6**) in above reaction may be not 3-ethoxycarbonyl-4,5-dimethoxycarbonyl-2-methylfuran (**5**), but 5-ethoxycarbonyl-3,4-dimethoxycarbonyl-2-methylfuran (**6**) (Chart 1). However, several attempts to isolate the intermediate (**4**) which be useful to reason out the formation of **6**, were unsuccessful in our experiments.

Hence, in order to determine the structure of **6**, the following steps were taken. All of three ester groups of **6** were readily hydrolyzed under refluxed condition in aqueous potassium hydroxide to afford 2-methylfuran-3,4,5-tricarboxylic acid, mp 246—248°, in 71.4% yield. On the other hand, when the ester group at 2-position of the furan ring of **6** was selectively hydrolyzed with methanolic potassium hydroxide at room temperature, the crystalline product (**7**), mp 151—152°, was afforded in 72.2% yield and also in the nuclear magnetic resonance (NMR) spectrum($CDCl_3$) of product (**7**), the characteristic signals (δ; 3.88 and 3.96) of the methyl ester groups at 3- and 4-positions of the furan ring of **6** were clearly demonstrated. This data and the results of the elementary analysis supported that the hydrolyzed product obtained is 3,4-dimethoxycarbonyl-5-methyl-2-furoic acid (**7**) (Chart 2).

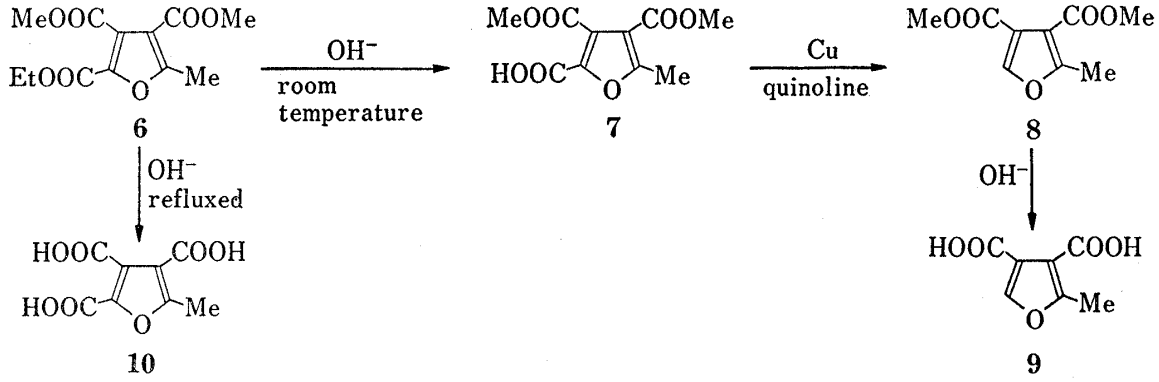

Chart 2

Furthermore, in confirmation of the formation of the above partial acid(**7**), decarboxylation of **7** with copper powder in quinoline solution gave readily 3,4-dimethoxycarbonyl-2-methylfuran (**8**), bp 115—117°/5 mmHg, and the hydrolysis of this ester (**8**) gave 2-methylfuran-3,4-dicarboxylic acid (**9**), mp 231—232° in 68% yield. No mixed melting point determination of **9** with the authentic sample[4], mp 230—231°, obtained by the Alder-Reckert reaction of 2-methylfuran and DMA, did show any depression. Additionaly, the IR spectral data of **9** is identical with that of the above authentic sample (Chart 2).

Accordingly, it is understood clearly from our experiments that dimethylsulfonium 1-ethoxycarbonylacetonylide (**1**) reacts readily with DMA (**2**) to give 2-ethoxycarbonyl-3,4-dimethoxycarbonyl-5-methylfuran (**6**), and also in the course of the formation of **6**, the reaction mechanism of 1,3-shift of acetyl group of **1**, proposed by Mukaiyama,[3b] is quite reasonable.

4) K. Alder and H.G. Rickert, *Chem. Ber.*, 70, 1354 (1937).

5) Melting point were determined on a Yanagimoto melting point test apparatus, and uncorrected. Infrared (IR) spectra were obtained on a Hitachi 215 spectrometer, NMR spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as an internal standard, and UV spectra were determined on a Hitachi 323 spectrometer.

6) R. Oda and Y. Hayashi, *Nippon Kagaku Zasshi*, **87**, 1110 (1966) [*C. A.*, **66**, 85416 (1967)].

7) E.H. Hunterss, T.E. Lesslie, and J. Bornstein, "Org. Syn.," Coll. Vol. 4, John wiley & Sons, Inc., New York, 1963, p. 329.

Experimental[5]

2-Ethoxycarbonyl-3,4-dimethoxycarbonyl-5-methylfuran (6)——To a dioxane solution (10 ml) of dimethylsulfonium 1-ethoxycarbonylacetonylide[6] (1.9 g, 0.01 mole) and DMA[7] (1.5 g, 0.01 mole), was added triethylamine (3 drops) with stirring and cooling. The resulting mixture was stirred at 100° for 6 hours. After removal of dioxane under reduced pressure, the residual reaction mixture was chromatographed on a column of silicic acid using benzene. The product formed was recrystallized from benzene; colorless prisms, yield, 2.1 g (77.2%), mp 61—62°. *Anal.* Calcd. for $C_{12}H_{14}O_7$: C, 53.33; H, 5.22. Found: C, 53.44; H, 5.27. IR ν_{max}^{KBr} cm^{-1}: 1740, 1715. UV λ_{max}^{EtOH} mμ (ε): 255 (12800). NMR ($CDCl_3$) δ: 2.65 (3H, s, $-CH_3$), 3.84 and 3.94 (each 3H, s, $-COOCH_3$), 4.35 (2H, q, $-COO\underline{CH_2}CH_3$), 1.37 (3H, t, $-COOCH_2\underline{CH_3}$).

3,4-Dimethoxycarbonyl-5-methyl-2-furoic Acid (7)——Methanolic 6N KOH (2 ml) was added to a solution **6** (2.5 g, 0.015 mole) in methanol (10 ml). The reaction mixture was allowed to stand at room temperature overnight. After evaporating methanol under reduced pressure, the residual solution was acidified with 6 N hydrochloric acid. Precipitated crystals were recrystallized from cyclohexane; colorless prisms, yield, 1.6 g (72.2%), mp 151—152°. *Anal.* Calcd. for $C_{10}H_{10}O_7$: C, 49.59; H, 4.16. Found: C, 49.77; H, 4.25. IR ν_{max}^{KBr} cm^{-1}: 1720, 1695. UV λ_{max}^{EtOH} mμ(ε): 250 (12250). NMR ($CDCl_3$): 2.68 (3H, s, $-CH_3$), 3.88 and 3.96 (each 3H, s, $-COOCH_3$), 11.45 (1H, s, -COOH).

3,4-Dimethoxycarbonyl-2-methylfuran (8)——A mixture of 7 (6 g, 0.034 mole), 5 ml of quinoline and 1 g of copper powder was heated by means of an electric mantle (170—180°) for one hour, and then poured into an ice-water. The solution was acidified with 6N hydrochloric acid and extracted with ether. The ether solution was washed with water, and dried over sodium sulfate. After the ether was removed distillation yields 4.3 g (86.9%) of colorless (**8**), bp 115—117°/5 mmHg. *Anal.* Calcd. for $C_9H_{10}O_5$: C, 54.55; H, 5.05. Found: C, 54.36; H, 5.12. IR ν_{max}^{Liquid} cm^{-1}: 1720.

2-Methylfuran-3,4,5-tricarboxylic Acid (10)——(6) (1.5 g, 0.059 mole) was suspended in 20 ml of 1.25 N KOH, and this suspention was refluxed for 2 hours. After cooling, the solution was acidified with 6 N hydrochloric acid. The acidified solution was extracted with ether. The ether solution was washed with a minimum of cold water and dried over sodium sulfate. The ether was removed, the residue was recrystallized from benzene–acetone (1: 1), colorless needles, yield, 0.9 g (71.4%), mp 246—247°. *Anal.* Calcd. for $C_8H_6O_7$: C, 44.87; H, 2.86. Found: C, 44.58; H, 2.62. IR ν_{max}^{KBr} cm^{-1}: 1720.

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