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Studies on Ketene and Its Derivatives. CX.[1] Synthesis of 1,3-Dimethoxyfluoren-9-ones

JUN NAKANO,[a] NOBUYA KATAGIRI,[b] and TETSUZO KATO[b],*

Kakenyaku-kako, Kyoto Research Laboratories,[a] 14 Shinomiya Minami Kawara-cho, Yamashina-ku, Kyoto, 607, Japan and
Pharmaceutical Institute, Tohoku University,[b]
Aobayama, Sendai, 980, Japan

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The synthesis of 1,3-dimethoxyfluoren-9-ones (**7a**—**f**) from ethyl 2-aryl-4,6-dihydroxybenzoates (**4a**—**d**), prepared by the reaction of diketene with ethyl 3-aryl-3-oxopropionates (**3a**—**d**), is described. Reaction of diketene with **3a**—**d** in the presence of sodium hydride in tetrahydrofuran gave **4a**—**d**. Methylation of **4a**—**d** with methyl iodide, followed by treatment with alcoholic sodium hydroxide, gave 2-aryl-4,6-dimethoxybenzoic acids (**6a**—**d**). Cyclization of **6a**—**d** with trifluoroacetic anhydride gave **7a**—**f**.

Keywords——ethyl 3-aryl-3-oxopropionates; diketene; ethyl 2-aryl-4,6-dihydroxybenzoates; cyclization; 1,3-dimethoxyfluoren-9-ones

Fluorene, which is a hydrocarbon having a bridged active methylene group at the 9-position, and related compounds have been extensively investigated because of their unusual properties.[2] For example, 2,7-bis(*N*,*N*-diethylaminoethoxy)fluoren-9-one (Tilorone) is an interferon inducer and exhibits antiviral activity, while some fluorenylidene and fluorenone derivatives are photosensitive.

Preparation of fluorenones by cyclization of biphenyl-2-carboxylic acids is a well-known synthetic method for fluorene skeletons. The method is very useful in cases where biphenyl derivatives are readily available.[3]

On the other hand, we found a one-step synthesis of ethyl orsellinate (**1**) from diketene and ethyl acetoacetate,[4] and reported the syntheses of various natural products from compound **1**.[5] In the preceding paper,[1] we reported the synthesis of naturally occurring anthracene-9,10-diones using this versatile reaction of diketene. In the present paper we wish to describe the synthesis of 1,3-dimethoxyfluoren-9-ones from biphenyl-2-carboxylic acids prepared by the reaction of diketene with benzoyl acetates.

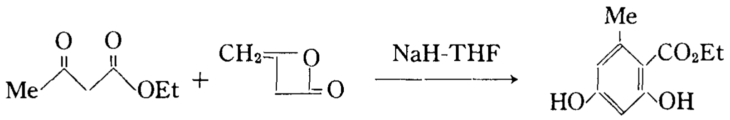

Chart 1

According to the procedures of Mori *et al.*,[6] the starting materials, β-keto esters (**3a**—**d**), were obtained in *ca.* 70% yield by the reaction of diethyl carbonate with acetophenones (**2a**—**c**) or acetylnaphthalene (**2d**) in the presence of sodium hydride. When **3** was allowed to react with diketene in tetrahydrofuran (THF) in the presence of sodium hydride, a crystalline product was obtained. Purification by silica gel column chromatography followed by recrystallization gave ethyl biphenyl-2-carboxylate (**4**) in *ca.* 30% yield. The results are summarized in Table I.

Usually, cyclization of biphenyl-2-carboxylic acid to fluoren-9-one proceeds under acidic conditions. However, a carboxylic acid, which could be derived from compound **4** and has hydroxyl groups at the 2- and 4-positions, would undergo decarboxylation under such conditions.[4a)] Therefore, **4** was methylated with methyl iodide to give the dimethoxy derivative

TABLE I. Ethyl 2-Aryl-4,6-dihydroxybenzoates (**4a**—**d**)

Compd. No.	Yield (%)	mp (°C)	Formula	Analysis(%) Calcd (Found) C	H	IR ν_{max}^{Nujol} cm^{-1}	MS *m/e* (M$^+$)	^{1}H-NMR (CDCl$_3$)δ (ppm) 3,5-Ring H	4,6-OH	Others
4a	28.5	118—119[a]	$C_{15}H_{14}O_4$	69.75 (69.94	5.46 5.71)	3320, 1643	258	6.29 (d, $J=2$ Hz) 6.46 (d, $J=2$ Hz)	5.80 (br s) 11.11 (s)	0.78 (3H, t, $J=7.5$ Hz) 3.94 (2H, q, $J=7.5$ Hz) 7.18—7.37 (5H, m)
4b	30.9	120—122	$C_{16}H_{16}O_5$	66.66 (66.74	5.59 5.61)	3320, 1642	288	6.32 (d, $J=2$ Hz) 6.48 (d, $J=2$ Hz)	6.16—6.50 (br s) 11.03 (s)	0.78 (3H, t, $J=7.5$ Hz) 3.83 (3H, s) 3.99 (2H, q, $J=7.5$ Hz) 6.84—6.99 (3H, m) 7.18—7.34 (1H, m)
4c	30.5	126	$C_{16}H_{16}O_4$	70.57 (70.68	5.92 6.04)	3300, 1641	272	6.23 (d, $J=2$ Hz) 6.38 (d, $J=2$ Hz)	5.72—6.08 (br s) 10.98 (s)	0.74 (3H, t, $J=7.5$ Hz) 2.34 (3H, s) 3.91 (2H, q, $J=7.5$ Hz) 6.93—6.98 (2H, m) 7.05—7.20 (2H, m)
4d	30.9	146—147	$C_{19}H_{16}O_4$	74.01 (74.27	5.23 5.53)	3540, 3300 1648	308	6.42 (d, $J=2.5$ Hz) 6.55 (d, $J=2.5$ Hz)	5.51—6.15 (br s) 11.16 (s)	0.53 (3H, t, $J=7.5$ Hz) 3.90 (2H, q, $J=7.5$ Hz) 7.42—7.66 (3H, m) 7.73—8.01 (4H, m)

a) Lit.[4a] mp 127—128°C.

TABLE II. Ethyl 2-Aryl-4,6-dimethoxybenzoates (**5a**—**d**)

Compd. No.	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	IR ν_{max}^{neat} cm^{-1}	MS *m/e* (M$^+$)	^{1}H-NMR (CDCl$_3$) δ (ppm) 3,5-Ring H	Others
5a	92.5	$C_{17}H_{18}O_4$	71.31 (71.27	6.34 6.36)	1723	286	6.50 (2H, s)	0.93 (3H, t, $J=7.5$ Hz) 3.83 (3H, s), 3.85 (3H, s) 4.03 (2H, q, $J=7.5$ Hz) 7.33 (5H, br s)
5b	93.0	$C_{18}H_{20}O_5$	68.34 (68.17	6.37 6.44)	1723	316	6.48 (2H, s)	0.96 (3H, t, $J=7.5$ Hz) 3.77 (3H, s), 3.79 (3H, s) 3.82 (3H, s) 4.05 (2H, q, $J=7.5$ Hz) 6.83—7.01 (3H, m) 7.20—7.26 (1H, m)
5c	92.0	$C_{18}H_{20}O_4$	71.98 (71.80	6.71 6.83)	1726	300	6.40 (2H, s)	0.94 (3H, t, $J=7.5$ Hz) 2.32 (3H, s) 3.74 (3H, s), 3.78 (3H, s) 3.99 (2H, q, $J=7.5$ Hz) 7.05—7.22 (4H, br s)
5d	90.5	$C_{21}H_{20}O_4$	74.98 (74.81	5.99 6.05)	1723	336	6.52 (d, $J=2$ Hz) 6.59 (d, $J=2$ Hz)	0.82 (3H, t, $J=7.5$ Hz) 3.79 (3H, s), 3.82(3H, s) 4.00 (2H, q, $J=7.5$ Hz) 7.40—7.60 (3H, m) 7.80—7.90 (4H, m)

5, which was then hydrolyzed with alkali to give the carboxylic acid **6**.

The cyclization of **6** to the fluoren-9-one **7** was then carried out. Thus, **6** was treated with conc. sulfuric acid or polyphosphoric acid (PPA) to give **7** in very poor yield. However, when **6** was treated with trifluoroacetic anhydride in chloroform, **7** was obtained in good yield.

Table III. 2-Aryl-4,6-dimethoxybenzoic Acids (**6a**—**d**)

Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	IR ν_{max}^{Nujol} cm^{-1}	MS m/e (M$^+$)	^{1}H NMR ($CDCl_3$) δ (ppm) 3.5-Ring H	COOH	Others
6a	93.0	165—167	$C_{15}H_{14}O_4$	69.75 (69.64	5.46 5.61)	3410, 1685	258	6.48(2H, s)	10.42(br s)	3.81(3H, s) 3.84(3H, s) 7.37(5H, s)
6b	92.5	111—112	$C_{16}H_{16}O_5$	66.66 (66.50	5.59 5.59)	3400, 1687	288	6.52(2H, s)	10.39(br s)	3.79(3H, s) 3.84(3H, s) 3.88(3H, s) 6.85—7.08(3H, m) 7.31(1H, m)
6c	92.0	136	$C_{16}H_{16}O_4$	70.57 (70.44	5.92 5.98)	3400, 1698	272	6.40(2H, s)	10.54(br s)	2.32(3H, s) 3.74(3H, s) 3.77(3H, s) 7.14(4H, br s)
6d	92.0	163	$C_{19}H_{16}O_4$	74.01 (74.19	5.23 5.11)	3400, 1686	308	6.53 (d, $J=2$ Hz) 6.58 (d, $J=2$ Hz)	Undetected	3.85(3H, s) 3.88(3H, s) 7.42—7.56(3H, m) 7.72—7.91(4H, m)

Table IV. Fluoren-9-ones (**7a**—**f**)

Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	IR ν_{max}^{Nujol} cm^{-1}	MS m/e (M$^+$)	^{1}H-NMR ($CDCl_3$) δ (ppm) 2,4-Ring H	Others
7a	86.0	143—144	$C_{15}H_{12}O_3$	74.99 (74.73	5.03 5.21)	1690	240	6.23 (d, $J=2$ Hz) 6.64 (d, $J=2$ Hz)	3.87 (3H, s), 3.93 (3H, s) 7.23—7.44 (3H, m) 7.54—7.65 (1H, m)
7b	67.2	144—145	$C_{16}H_{14}O_4$	71.10 (71.37	5.22 5.10)	1691	270	6.35 (d, $J=2$ Hz) 6.71 (d, $J=2$ Hz)	3.91 (3H, s), 3.93 (3H, s) 3.97 (3H, s) 6.82 (1H, dd, $J=2, 8$Hz) 7.03 (1H, d, $J=2$ Hz) 7.64 (1H, d, $J=8$ Hz)
7c	12.8	185—186	$C_{16}H_{14}O_4$	71.10 (71.17	5.22 5.11)	1685	270	6.36 (d, $J=2$ Hz) 6.75 (d, $J=2$ Hz)	3.94 (3H, s), 4.00 (3H, s) 4.02 (3H, s) 6.94 (1H, d, $J=8$ Hz) 7.16 (1H, d, $J=8$ Hz) 7.49 (1H, t, $J=8$ Hz)
7d	37.2	150	$C_{16}H_{14}O_3$	75.57 (75.63	5.55 5.51)	1692	254	6.14 (d, $J=2$ Hz) 6.50 (d, $J=2$ Hz)	2.31 (3H, s), 3.80 (3H, s) 3.86 (3H, s) 6.97 (1H, d, $J=8$ Hz) 7.10 (1H, s) 7.39 (1H, d, $J=8$ Hz)
7e	58.7	167	$C_{16}H_{14}O_3$	75.57 (76.69	5.55 5.47)	1683	254	6.15 (d, $J=2$ Hz) 6.52 (d, $J=2$ Hz)	2.55 (3H, s), 3.80 (3H, s) 3.86 (3H, s) 6.88—7.03 (1H, m) 7.09—7.26 (2H, m)
7f	Quant.	201	$C_{19}H_{14}O_3$	78.60 (78.58	4.85 4.80)	1690	290	6.27 (d, $J=2$ Hz) 6.70 (d, $J=2$ Hz)	3.91 (3H, s), 3.98 (3H, s) 7.42—8.01 (5H, m) 9.08 (1H, d, $J=9$Hz)

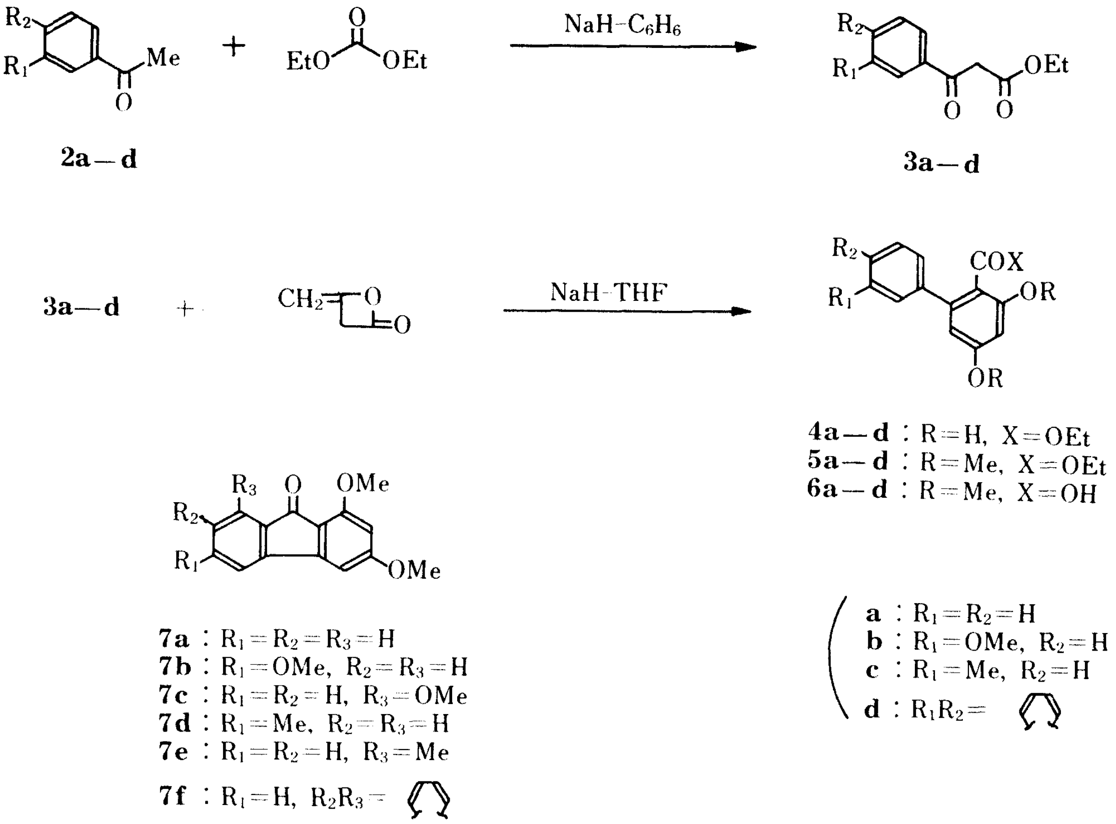

Chart 2

Cyclization of **6b** and **6c** under similar conditions gave **7b**, **c** and **7d**, **e** in ratios of 5.3: 1 and 1: 1.6, respectively. On the basis of spectral data, compound **7f** obtained from **6d** was assigned the angular structure, 1,3-dimethoxybenzo[*a*]fluoren-11-one. Namely, its proton nuclear magnetic resonance (^{1}H-NMR) spectrum in $CDCl_3$ showed the signal due to the ring proton (C_{10}-H) at abnormally low field (9.08 ppm). Therefore, cyclization of **6d** had occurred exclusively at the α-position of the naphthalene ring.

Substituted fluorenes, except for those substituted at the 2- or 7-position, are usually difficult to prepare because electrophilic reactions of fluorene take place predominantly at the 2- or 7-position. Therefore, our present method is useful for the preparation of fluoren-9-ones bearing methoxy groups at the 1- and 3-positions.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu model IR 430 spectrometer; ^{1}H-NMR spectra were recorded using tetramethylsilane as an internal standard on a JEOL model PS-100 spectrometer at 100 MHz; mass spectra (MS) were recorded on a Hitachi model M-52 machine. Merck Kieselgel 60 and Merck Kieselgel 60F 254 were employed for column chromatography and thin-layer chromatography (TLC), respectively.

General Procedure for the Synthesis of Ethyl 3-Aryl-3-oxopropionates (3a—d)——Sodium hydride (50% dispersion, 24 g, 0.5 mol) was added with stirring to a solution of diethyl carbonate (60 ml) in dry benzene (200 ml). A solution of aryl methyl ketone (**2a**—**d**) (0.2 mol) in diethyl carbonate (25 g) was then added dropwise, and the whole was refluxed for 1 h with stirring, then cooled. A small amount of ethanol was added to the reaction mixture to destroy excess NaH. The resulting mixture was poured into a mixture of 10% aq. HCl (200 ml) and ice (200 g) and extracted with ether (300 ml × 2). The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to leave an oily residue. The residue was purified by distillation under reduced pressure. **3a** (74%): bp 115°C (1.3 mmHg) (lit.[7a] bp 142—146°C (6 mmHg), lit.[7b] bp 132—137°C (4 mmHg)). **3b** (75%): bp 123°C (0.3 mmHg) (lit.[8] bp 162—166°C (2.5 mmHg)). **3c** (75%): bp 128°C (1.7 mmHg) (lit.[8] bp 116—118°C (0.5 mmHg)). **3d** (73%): viscous oil, IR ν_{max}^{neat} cm^{-1}: 1736, 1686.

General Procedure for the Synthesis of Ethyl 2-Aryl-4,6-dihydroxybenzoates (4a—d)——Sodium hydride (50% dispersion, 0.55 g, 0.011 mol) was added to a solution of ethyl aroylacetate (**3a**—**d**) (0.01 mol) in abs. THF (20 ml) with stirring and cooling. The mixture was stirred for 10 min, then a solution of diketene (0.93 g, 0.011 mol) in abs. THF (5 ml) was added dropwise. The whole was stirred for 1 h at room temperature, and then poured into a mixture of conc. HCl (2 ml) and ice (30 g). The resulting mixture was extracted with ether (50 ml × 2). The ether fraction was washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crystalline residue. Purification by silica gel column chromatography (100 g) using a mixture of *n*-hexane and ether (4: 1) as an eluent gave the product **4** (recrystallized from benzene–*n*-hexane (2: 1)). The results are summarized in Table I.

General Procedure for the Synthesis of Ethyl 2-Aryl-4,6-dimethoxybenzoates (5a—d)——Potassium carbonate (0.035 mol) was added to a solution of **4** (0.015 mol) in acetone (30 ml). The mixture was refluxed with vigorous stirring for 30 min. Methyl iodide (10 g) was added to the reaction mixture, and the whole was refluxed with vigorous stirring for 48 h. After the addition of water (20 ml), the mixture was extracted with ether (50 ml × 2). The ether fraction was washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave an oily residue which was purified by silica gel column chromatography (50 g) using a mixture of *n*-hexane and ether (7: 1) as an eluent to give the product **5** as a colorless oil. The results are summarized in Table II.

General Procedure for the Synthesis of 2-Aryl-4,6-dimethoxybenzoic Acids (6a—d)——A solution of **5** (0.02 mol) in 10% ethanolic NaOH (50 ml) was refluxed for 1 h. The mixture was adjusted to pH 3—4 with conc. HCl under cooling, and extracted with ether (50 ml × 3). The extract was washed with 1 N aq. NaOH (20 ml × 2). The washings were adjusted to pH 3—4 with conc. HCl under cooling, and the mixture was extracted with ether (50 ml × 2). The ethereal layer was washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crystalline residue, which was recrystallized from benzene to give the product **6**. The results are summarized in Table III.

General Procedure for the Synthesis of 1,3-Dimethoxyfluoren-9-ones (7a—f)——Trifluoroacetic anhydride (5 ml) was added dropwise to a solution of **6** (4 mmol) in $CHCl_3$ (15 ml) at room temperature. The mixture was stirred for 30 min and poured onto ice (30 g). The resulting mixture was made alkaline with K_2CO_3 and extracted with dichloromethane (20 ml × 2). The dichloromethane fraction was washed with water and dried over $MgSO_4$. Removal of the solvent gave a crystalline residue which was recrystallized from benzene to give the product **8**. Reactions of **6b** and **6c** with trifluoroacetic anhydride gave a mixture of **7b** and **7c** and a mixture of **7d** and **7e**, respectively. These compounds were separated from one another by silica gel column chromatography [50 g, CH_2Cl_2–ether (5: 1)]. The results are summarized in Table IV.

References and Notes

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