Seiji Yamaguchi*, Akihito Saitoh, and Yoshiyuki Kawase

Department of Chemistry, Faculty of Science, Toyama University, Gofuku, Toyama 930, Japan

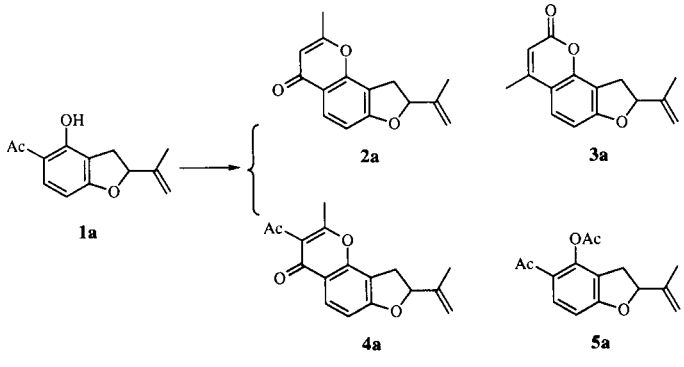
Received July 13, 1994
Revised September 20, 1994

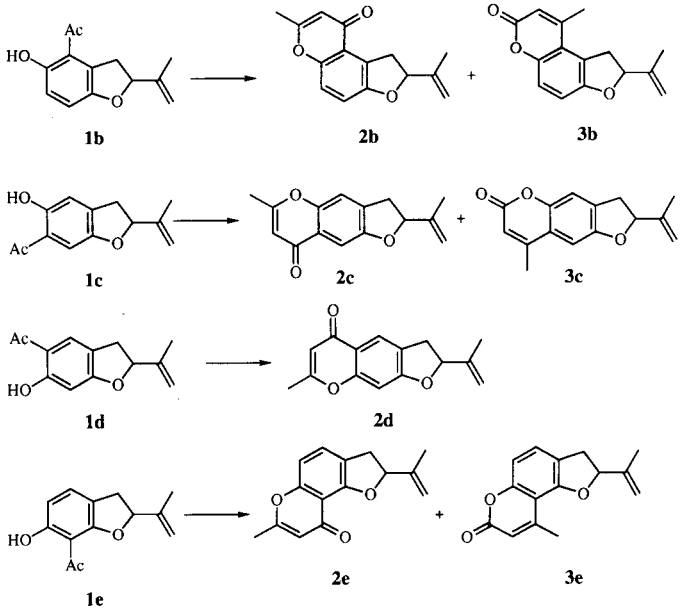
A pyrone-ring formation using *N,N*-dimethylacetamide dimethyl acetal in refluxing xylene converted some *o*-hydroxyacetophenone derivatives **1a-e** to the corresponding dihydrofuro[1]benzopyranones **2a-e**.

J. Heterocyclic Chem., **32**, 511 (1995).

In our previous paper [1], we described a new pyrone-ring formation of salicylaldehydes having a 2-isopropenyl-2,3-dihydrobenzofuran structure. In the ring-closure of the salicylaldehyde derivatives only one cyclized product (the corresponding coumarin derivative) was possible. A similar effective pyrone-ring formation of *o*-hydroxyacetophenone derivatives having a 2-isopropenyl-2,3-dihydrobenzofuran structure was needed for a synthesis of natural umtain (2-isopropenyl-2,3-dihydro-5*H*-furo-[3,2-*g*][1]benzopyran-5-one) [2]. But, in this pyrone-ring formation two types of cyclized products (a coumarin derivative and a chromone derivative) might be possible. In this paper we will describe a study of the pyrone-ring formation of *o*-hydroxyacetophenone derivatives having a 2-isopropenyl-2,3-dihydrobenzofuran structure for some isopropenyldihydrofuro[1]benzopyranones.

There are six types of *o*-hydroxyacetophenone derivatives having a 2-isopropenyl-2,3-dihydrobenzofuran structure. Three of them were prepared by the one-step procedure, already reported [3], from dihydroxyacetophenones and 1,4-dibromo-2-methyl-2-butene; 5-acetyl-2-isopropenyl-2,3-dihydro-4-benzofuranol **1a** was prepared from 2,4-dihydroxyacetophenone, 4-acetyl-2-isopropenyl-2,3-dihydro-5-benzofuranol **1b** was from 2,5-dihydroxyacetophenone, and 7-acetyl-2-isopropenyl-2,3-dihydro-6-benzofuranol **1e** was from 2,6-dihydroxyacetophenone. The other two were prepared by the multi-step procedure, already reported; 6-acetyl-2-isopropenyl-2,3-dihydro-5-benzofuranol **1c** was prepared from 5-methoxy-2-isopropenyl-2,3-dihydrobenzofuran in four step reactions (formylation-methylation-oxidation-demethylation) [4]





and 5-acetyl-2-isopropenyl-2,3-dihydro-6-benzofuranol **1d** was from 6-methoxy-2-isopropenyl-2,3-dihydrobenzofuran in two step reaction (acetylation-demethylation) [5]. But, the last 6-acetyl-2-isopropenyl-2,3-dihydro-7-benzofuranol could not be prepared by any method.

Refluxing *o*-hydroxyacetophenones with acetic anhydride and sodium acetate is an old famous procedure for the preparation of the corresponding chromones. But, the yields were usually low. By using **1a** the pyrone-ring formation was checked in three procedures; A: refluxing with acetic anhydride and sodium acetate for 10 hours, B: refluxing with acetic anhydride and 1,8-diazabicyclo[5.4.0]uncec-7-ene (DBU) for 15 hours, and C: refluxing with *N,N*-dimethylacetamide dimethyl acetal (DMA dimethyl acetal) in xylene, and the results are summarized in Table 1. Procedure A did not give any type of cyclized products. Procedure B was carried out under three different conditions, treating with 1 mole of DBU (Procedure B_1), with 2 moles of DBU and dry toluene (Procedure B_2), or with 3 moles of DBU (Procedure B_3).

Procedure B gave a mixture of a chromone derivative **2a**, a coumarin derivative **3a**, and none of the cyclized 5-acetyl-2-isopropenyl-2,3-dihydro-4-benzofuranyl acetate

Table 1

Pyrone-Ring Formation of Acetylisopropenyldihydrobenzofuranols **1a-e**

Starting Compound	Procedure	Chromone	Coumarin	*C*-Acetylated Chromone	Non-Cyclized Acetate	Recovery
1a	A	—	—	—	—	**1a**: 94%
1a	B_1	**2a**: 17%	**3a**: 6%	—	**5a**: 4%	**1a**: 43%
1a	B_2	**2a**: 11%	**3a**: 9%	**4a**: 23%	**5a**: 9%	**1a**: 35%
1a	B_3	**2a**: 22%	**3a**: 7%	**4a**: 17%	**5a**: 12%	—
1a	C	**2a**: 52%	—	—	—	—
1b	C	**2b**: 4%	**3b**: 2%	—	—	—
1c	C	**2c**: 24%	**3c**: 13%	—	—	—
1d	B_3	**2d**: 10%	—	—	—	**1d**: 43%
1d	C	**2d**: 21%	—	—	—	—
1e	B_1	—	**3e**: 11%	—	—	**1e**: 24%
1e	B_2	—	**3e**: 12%	—	—	**1e**: 49%
1e	C	**2e**: 18%	**3e**: 13%	—	—	—

Table 2

Some Physical Data and Elemental Analyses of Dihydrofuro[1]benzopyranones **2** and **3**

Compound	Melting Point	IR (cm^{-1})	MS (m/z)	Elemental Analysis [a] Found C (%)	H (%)
2a	159-160	1645	242 (M^+), 227, 187	74.24	5.92
2b	78-80	1635	242 (M^+), 227, 199	74.53	6.00
2c	170-180 (6 mm Hg) [b]	1630	242 (M^+), 227, 225	74.09	5.91
2d	98-100	1635	242 (M^+), 227, 199	74.15	5.88
2e	230-240 (3 mm Hg) [b]	1640	242 (M^+), 227, 201	74.32	6.04
3a	120-122	1720	242 (M^+), 227, 199	74.34	5.78
3b	173-175	1720	242 (M^+), 227, 199	74.07	6.13
3c	132-134	1720	242 (M^+), 227, 199	74.65	5.80
3e	76-78	1720	242 (M^+), 227, 199	74.65	5.92

[a] Calcd. data for $C_{15}H_{14}O_3$: C, 74.36; H, 5.80. [b] Boiling point.

Table 3

PMR Spectral Data of Isopropenyldihydrofuro[1]benzopyranones, δ/ppm (J/Hz) [a]

Compound	Dihydrofuran-Ring H_A	H_B	H_X	Pyrone-Ring Me	Olefinic	Aromatic Proton	
2a	3.1 (dd, 16, 8)	3.5 (dd, 16, 9)	5.3 (dd, 9, 8)	2.3 (s)	6.0 (s)	6.8 (d, 8)	8.0 (d, 8)
2b	3.5 (dd, 17, 8)	4.0 (dd, 17, 8)	5.3 (t, 8)	2.3 (s)	6.0 (s)	7.0 (d, 8)	7.2 (d, 8)
2c	3.1 (dd, 18, 8)	3.5 (dd, 18, 9)	5.2 (dd, 9, 8)	2.3 (s)	6.1 (s)	7.2 (s)	7.4 (s)
2d	3.0 (dd, 16, 8)	3.5 (dd, 16, 9)	5.2 (dd, 9, 8)	2.3 (s)	6.0 (s)	6.8 (s)	7.0 (s)
2e	3.0 (dd, 15, 8)	3.2 (dd, 15, 9)	5.3 (dd, 9, 8)	2.3 (s)	5.8 (s)	6.6 (d, 8)	7.2 (d, 8)
3a	3.1 (dd, 16, 9)	3.5 (dd, 16, 10)	5.3 (dd, 10, 9)	2.3 (s)	5.9 (s)	6.6 (d, 8)	7.3 (d, 8)
3b	3.5 (dd, 18, 8)	3.5 (dd, 18, 10)	5.3 (dd, 10, 8)	2.3 (s)	6.0 (s)	7.0 (d, 8)	7.2 (d, 8)
3c	3.0 (dd, 16, 8)	3.5 (dd, 16, 10)	5.2 (dd, 10, 8)	2.3 (s)	6.0 (s)	6.8 (s)	7.0 (s)
3e	3.0 (dd, 15, 9)	3.4 (dd, 15, 8)	5.3 (dd, 9, 8)	2.5 (s)	6.0 (s)	6.7 (d, 8)	7.2 (d, 8)

[a] Isopropenyl signals are the same in all samples; 1.8 (s, Me), 4.9 and 5.1 (two br s, olefinic).

5a under all conditions. The two most severe conditions in procedure B_2 and B_3 gave a *C*-acetylated chromone, 7-acetyl-2-isopropenyl-8-methyl-1,2-dihydrofuro[2,3-*h*]-[1]benzopyran-6-one **4a**. Procedure C gave the chromone derivative **2a** only. We already reported a similar pyrone-ring formation of salicylaldehyde derivatives in refluxing ether [1]. But, the higher reaction temperature (in refluxing xylene) was needed for this pyrone-ring formation. These results are summarized in Table 1.

Pyrone-ring formations of the other four isopropenyldihydrobenzofuranols **1b-e** were similarly carried out by procedure C, and the results are also summarized in Table 1. The corresponding chromone derivatives **2b-e** were obtained in all cases. In cases of **2b**, **2c**, and **2e**, the corresponding coumarin derivatives **3b**, **3c**, and **3e** were also obtained, but their yields were lower than those of the

corresponding chromone derivatives. Pyrone-ring formation of **1d** was also tried by procedure B_3 and the corresponding chromone derivative **2d** was only obtained in 10% yield. However, interestingly, two types of the pyrone-ring formations of **1e** gave the corresponding coumarin derivative **3e** only in 11% (by procedure B_1) and 12% (procedure B_2). The reason why the coumarin derivative was favorable only in the pyrone-ring formation of **1e** by method B_2 and B_3 remain to be studied [6].

Some physical data of the dihydrofuro[1]benzopyranones **2** and **3**, thus obtained, are listed in Table 2, and their pmr spectral data are in Table 3. There is no remarkable difference between the chromone derivatives and the corresponding coumarin derivatives in the pmr spectra, but their ir spectra showed a remarkable difference; chromone derivatives showed their carbonyl absorption around 1640 cm^{-1} while the coumarin derivatives showed them around 1720 cm^{-1}.

EXPERIMENTAL

All melting points and boiling points are uncorrected. The ir spectra were measured on a Hitachi 260-50 spectrometer in liquid films or potassium bromide disks. The pmr spectra were recorded on a JEOL PMX-60Si or FX-90Q NMR spectrometer in carbon tetrachloride or chloroform solutions, and the mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer.

Cyclization of **1a** with Acetic Anhydride-Sodium Acetate (Procedure A).

To a solution of **1a** (0.980 g, 4.50 mmoles) in acetic anhydride (1.36 g, 13.5 mmoles) was added anhydrous sodium acetate (1.42 g, 19.7 mmoles), and the mixture was refluxed for 10 hours under stirring. After cooling, the mixture was treated with excess amounts of aqueous sodium carbonate solution, stirred for 1 hour to complete the hydrolysis of acetic anhydride, and then extracted with ether. The ether layer was washed with aqueous saturated sodium carbonate solution and with aqueous saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the ether, the residual oil was distilled and the starting **1a** (0.92 g, 94%) was recovered as the fraction boiling at 145-156° (6 mm Hg).

General Procedure for Cyclization with Acetic Anhydride-DBU (Procedure B).

To a solution of **1a** (*ca.* 1 g, *ca.* 5 mmoles) in acetic anhydride (*ca.* 1.5 g, *ca.* 15 mmoles) was added DBU (1,8-diazabicyclo[5.4.0]uncec-7-ene) (5, 10, or 15 mmoles). Only in the case using 2 equivalents of DBU dry toluene (5 ml) was also added to prevent getting a tary mixture. The mixture was refluxed for 15 hours, and the mixture was treated with excess aqueous saturated sodium carbonate solution and stirred for 1 hour to hydrolyze the remaining acetic anhydride. The residual mixture was then extracted with ether, and the ether layer was washed with aqueous saturated sodium carbonate solution and aqueous saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatogramed with hexane-ethyl acetate elution. The corresponding chromone derivative **2a** and the coumarin derivative **3a**, the *C*-aceylate chromone derivative **4a**, and the non-cyclized **5a** were obtained as the fractions eluted by hexane-ethyl acetate (8:2), and the starting material **1a** was recovered as the fractions eluted by hexane-ethyl acetate (9:1). By a similar procedure **1d** (0.650 g, 3.00 mmoles) was reacted with acetic anhydride (2.20 g, 21.0 mmoles) and DBU (2.30 g, 15.1 mmoles) and the corresponding chromone derivative was only obtained. A similar reaction of **1e** (0.75 g, 3.50 mmoles) was reacted with acetic anhydride (1.20 g, 12.0 mmoles) and DBU (0.55 g, 3.6 mmoles), and the corresponding coumarin derivative **3e** was only obtained. The data for the dihydrofuro[1]benzopyranones are summarized in Table 1.

7-Acetyl-2-isopropenyl-8-methyl-1,2-dihydro[2,3-*h*][1]benzopyranone (**4a**).

This compound had mp 86-88°; ir (potassium bromide): 1680 and 1630 cm^{-1}; pmr (deuteriochloroform): 1.8 (3H, s), 2.3 (3H, s), 2.5 (3H, s), 3.0 (1H, dd, J = 16 and 8 Hz), 3.4 (1H, dd, J = 16 and 10 Hz), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.3 (1H, dd, J = 10 and 8 Hz), 6.7 (1H, d, J = 8 Hz), 7.8 ppm (1H, d, J = 8 Hz); ms: (m/z) 284 (M^+), 269, 227, 203, 187. This *C*-acetylated chromone **4a** was readily converted to the corresponding chromone **2a** by refluxing with aqueous saturated sodium carbonate solution for 1 hour.

5-Acetyl-2-isopropenyl-2,3-dihydro-4-benzofuranyl Acetate (**5a**).

This compound had bp 180-200° (5 mm Hg) (bath temperature); ir (liquid film): 1770 and 1680 cm^{-1}; pmr (deuteriochloroform): 1.7 (3H, s), 2.3 (3H, s), 2.5 (3H, s), 2.9 (1H, dd, J = 14 and 8 Hz), 3.3 (1H, dd, J = 14 and 10 Hz), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.2 (1H, dd, J = 10 and 8 Hz), 6.7 (1H, d, J = 9 Hz), 7.6 ppm (1H, d, J = 9 Hz); ms: (m/z) 260 (M^+), 218, 203.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.30; H, 6.17.

General Procedure for Cyclization with *N,N*-Dimethylacetamide Dimethyl Acetal (Procedure C).

To a solution of **1a** (0.903 g, 4.14 mmoles) in dry xylene (5 ml) was added *N,N*-dimethylacetamide dimethyl acetal (0.650 g, 4.68 mmoles), and the mixture was refluxed for 2 hours under continuous removal of the generated methanol. After cooling, the mixture was treated with 10% hydrochloric acid and extracted with ether. The organic layer was washed with aqueous saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was chromatogramed on a silica-gel column. The fractions eluted with hexane-ethyl acetate (3:2) were recrystallized from ether to give **2a** (525 mg, 52%). The reaction of other benzofuranols with 1.5 molar equivalents of *N,N*-dimethylacetamide dimethyl acetal was carried out similarly, and **1b**, **1c**, and **1e** gave mixtures of the corresponding chromone derivative and the coumarin derivative, which were separated on a silica-gel column with hexane-ethyl acetate (8:2) elution, and **1d** gave the corresponding chromone derivative **2d** only. These data were summarized in Table 1.

REFERENCES AND NOTES

[1] S. Yamaguchi, R. Miyakawa, S. Yonezawa, and Y. Kawase, *Bull. Chem. Soc. Japan*, **62**, 3593 (1989).

[2] F. M. Dean, B. Parton, A. W. Price, N. Somvichein, and D. A. H. Taylor, *Tetrahedron Letters*, 2737 (1967).

[3] S. Yamaguchi, A. Saitoh, and Y. Kawase, *Bull. Chem. Soc. Japan*, **59**, 3983 (1986).

[4] S. Yamaguchi, T. Nitta, T. Hosaka, Y. Nishino, and Y. Kawase, *Bull. Chem. Soc. Japan*, **63**, 3230 (1990).

[5] S. Yamaguchi, K. Sugiura, R. Fukuoka, K. Okazaki, M. Takeuchi, and Y. Kawase, *Bull. Chem. Soc. Japan*, **57**, 3607 (1984).

[6] There is a dipole repulsion between the C-O bond of the dihydrofuran ring and the C=O double bond of the pyrone. Thus, more severe conditions might lead the kinetically controlled reaction to the thermodynamically controlled one favoring stable coumarin derivative.