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The Fries Rearrangement of *bz*-Benzoyloxybenzofuran Derivatives and the Synthesis of the Furo Derivatives of 4-Phenyl-2*H*-chromen-2-one

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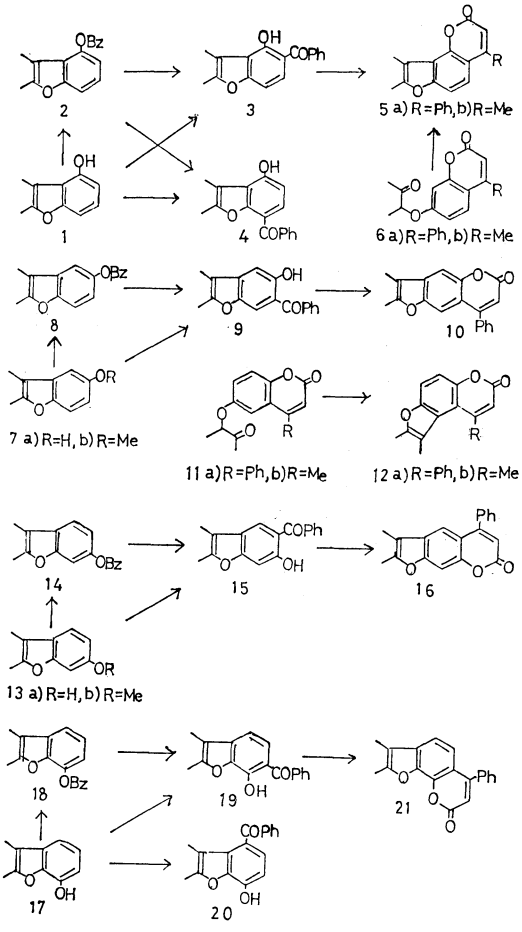
Synopsis. The Fries rearrangement of 4-, 5-, 6-, and 7-benzoyloxy-2,3-dimethylbenzofurans gave exclusively or mainly the corresponding *o*-hydroxy ketones, which were converted to the dimethylfuro derivatives of 4-phenyl-2*H*-chromen-2-one.

In a previous paper, the Fries rearrangement of *bz*-acetoxy-2,3-dimethylbenzofurans to the corresponding *o*-hydroxy ketones accompanied by small amounts of para isomers in some cases was reported.[1] In the present experiments, the reaction of *bz*-benzoyloxy-2,3-dimethylbenzofurans was studied. In order to investigate their spectra and biological activity, the products were converted into the dimethylfuro derivatives of 4-phenyl-2*H*-chromen-2-one.

In the Fries rearrangement of benzoyloxybenzofuran derivatives, Shah and Shah[2] reported that 6-benzoyloxy-3-methylbenzofuran-2-carboxylic acid gave the corresponding 7-benzoyl-6-hydroxy compound. Royer *et al.*[3] reported the synthesis of the furo derivatives of 4-phenyl-2*H*-chromen-2-one, some of which were prepared by the Pechmann reaction of 2,3-dimethyl-*bz*-hydroxybenzofurans and ethyl benzoylacetate.



The Fries rearrangement of 4- (**2**), 5- (**8**), 6- (**14**), and 7-benzoyloxy-2,3-dimethylbenzofuran (**18**) was carried out at 120—130 °C. The reaction of **2** with aluminium chloride gave 5-benzoyl-4-hydroxy-2,3-dimethylbenzofuran (**3**) and some amounts of the 7-benzoyl isomer (**4**). The direct benzoylation of 4-hydroxy-2,3-dimethylbenzofuran (**1**) by benzoic acid and polyphosphoric acid (PPA) gave **2**, **3**, and a small amount of **4**. The Fries reaction of **8** and **14** gave 6-benzoyl-5-hydroxy- (**9**) and 5-benzoyl-6-hydroxy-2,3-dimethylbenzofuran (**15**), which were also prepared by the Friedel-Crafts benzoylation of 5- (**7b**) and 6-methoxy-2,3-dimethylbenzofuran (**13b**). The benzoylation of 5- (**7a**) and 6-hydroxy-2,3-dimethylbenzofuran (**13a**) with benzoic acid and PPA gave only **8** and **14**; in the case of acetylation or phenylacetylation, the hydroxy ketone was obtained.[4,5] The Fries reaction of **18** gave 6-benzoyl-7-hydroxy-2,3-dimethylbenzofuran (**19**) as compared to the benzoylation of 7-hydroxy-2,3-dimethylbenzofuran (**17**) with benzoic acid and PPA which gave **19** and some amounts of the para isomer (**20**).

The *o*-hydroxy ketones (**3**, **9**, **15**, and **19**) thus obtained were converted to the corresponding furo derivatives of 4-phenyl-2*H*-chromen-2-one (**5a**, **10**, **16**, and **21**) by the action of acetic anhydride and 1,8-diazabicyclo-[5.4.0]undecene-7 (DBU); in this reaction, anhydrous sodium acetate instead of DBU only gives the acetates. The cyclization of 7-(1-methyl-2-oxopropoxy)-4-phenyl-2*H*-chromen-2-one (**6a**) gave also **5a**. It is interesting to note that the furan ring formation of 6-(1-methyl-2-oxopropoxy)-4-phenyl-2*H*-chromen-2-one (**11a**) gave **12a** instead of the isomeric **10**, the furan ring having closed at the hindered position. The furo derivatives of 4-methyl-2*H*-chromen-2-one (**5b**[3] and **12b**) were also prepared through the analogous route in order to compare the spectra. Royer *et al.*[3] have reported the Pechmann reaction of the hydroxybenzofurans (**1** and **17**) gave the furochromenones (**5a**, **5b**, and **21**) compared to the reaction of **7a** which gave a mixture of **10** and **12a**. These were not however, separated into the pure components.

The structures of all the compounds were determined by means of IR, NMR spectroscopy and elemental analysis. In the NMR spectra, it was observed that the chemical shift of the 1-methyl protons of **12a** appeared at δ 1.01, a much higher magnetic field than that (δ 2.20) of the 3-methyl protons of **10**. This characteristic shift is analogous to the 4-phenyl-2*H*-chromen-2-one derivatives,[6,7] and appears due to the anisotropic shielding effect of the phenyl ring at the 9-position.[7] The chemical shift of the 1-methyl protons of **12b** appeared at δ 2.64, a lower field than those of

Table 1. The MP, IR, and elemental analysis of the new compounds

Compd	Mp °C (solv.a))	ν_{CO}^{KBr}	Found		Calcd	
			C%	H%	H%	C%
2	118—119(Et)	1745	76.44	5.13	76.67	5.30
3	87—88(Et)	1635	76.42	5.41	76.67	5.30
4	207.5—208.5(Et)	1645	76.44	5.58	76.67	5.30
6a	117—119(Et)	1725(broad)	73.86	5.28	74.01	5.23
6b	99—101(Et)	1725, 1710	68.08	6.00	68.28	5.73
8	84—85(Et)	1745	76.82	5.27	76.67	5.30
9	118—120(Et)	1650	76.45	5.12	76.67	5.30
10	164—165(Me)	1710	78.49	4.81	78.60	4.85
11a	117.5—120(Et)	1720(broad)	74.24	5.40	74.01	5.23
11b	78—79(Et)	1735, 1715	68.44	5.45	68.28	5.73
12a	168—171(Et)	1720	78.56	5.01	78.60	4.85
12b	218—219(Et)	1710	73.69	5.58	73.67	5.30
14	120—121(Et)	1730	76.55	5.01	76.67	5.30
15	153—154.5(Et)	1630	76.48	5.45	76.67	5.30
16	192—193(Et)	1710	78.88	4.93	78.60	4.85
18	65.5—66.5(Et)	1745	76.64	5.22	76.67	5.30
19	127—128(Me)	1655	76.41	5.02	76.67	5.30
20	195—196(Pr)	1615	76.71	5.50	76.67	5.30

a) Et: ethanol, Me: methanol, and Pr: propanol.

the corresponding methyl protons of other compounds; this appears due to the effect of the 9-methyl group.

Experimental[8]

The bz-*Benzoyloxy-2,3-dimethylbenzofurans (2, 8, 14, and 18).* These compounds were prepared from *bz*-hydroxy-2,3-dimethylbenzofurans[9] (**1**, **7a**, **13a**, and **17**) by the benzoyl chloride-pyridine method (about 60% yields).

The Fries Rearrangement. A mixture of benzoyloxy-2,3-dimethylbenzofuran (1.3 g) and powdered anhydrous aluminium chloride (0.8 g) was heated for 1 h at 120—130 °C. The cooled mixture was decomposed with dilute hydrochloric acid, and extracted with ether. The ethereal solution was washed with 5% aqueous sodium hydroxide solution. The *o*-hydroxy ketones were obtained from the ethereal solution and the *p*-hydroxy ketone was obtained from the alkaline solution. Products(yields %): **3**(26.0) and **4**(8.3) from **2**, **9**(16.7)from **8**, **15**(15.4) from **14**, and **19**(15.0) from **18**.

The Benzoylation of bz-*Hydroxy-2,3-dimethylbenzofurans.* A mixture of the hydroxybenzofuran (4 g), benzoic acid (3.4 g), and PPA (n=1.5, 60 g) was heated for 1 h at 90—100 °C. The cooled mixture was decomposed with water, and extracted with chloroform. The chloroform solution was washed with 5% aqueous sodium hydroxide solution and the benzoyloxy compounds or/and the *o*-hydroxy ketones were obtained from the chloroform solution. In the case of **1**, **2**, and **3** were separated by chromatography on silica gel with benzene–hexane (1:9) as a solvent. The *p*-hydroxy ketones were obtained from the alkaline solution. Products(yields %): **2**(20.2), **3**(31.2), and **4**(1.1) from **1**, **8**(36.5) from **7a**, **14**(36.5) from **13a**, and **19**(15.5) and **20**(6.2) from **17**.

The Benzoylation of bz-*Methoxy-2,3-dimethylbenzofurans.* Anhydrous aluminium chloride (4.5 g) was added to a solution of methoxy-2,3-dimethylbenzofuran[9] (3.8 g) and benzoyl chloride (3.6 g) in benzene (30 ml) with cooling and stirring. The mixture stirred for 2 h at room temperature and then refluxed for 10 min. The usual treatment gave the *o*-hydroxy ketones. Products(yields %): **9**(44.6) from **7b**, and **15**(40.6) from **13b**.

The Preparation of the Furo Derivatives of Chromenone. A mixture of the hydroxy ketone (1 g), acetic anhydride (0.8 g), and DBU (0.4 g) was heated for 8 h at 180 °C. The cooled mixture was treated with water, allowed to stand overnight, and then extracted with chloroform. The chloroform solution was washed with 5% aqueous sodium hydroxide solution, and the product from the chloroform solution recrystallized. 8,9-Dimethyl-4-phenyl-2*H*-furo[2,3-*h*]chromen-2-one (**5a**); mp 124.5—125.5 °C (from ethanol), (lit,[3] mp 123 °C), ν_{CO}^{KBr} 1715 cm^{-1}, Anal. C, 78.45; H, 4.86%. Products(yields %): **5** (26.6) from **3**, **10**(40.4) from **9**, **16**(40.1) from **15**, and **21**(21.8) from **19**. 2,3-Dimethyl-6-phenyl-8*H*-furo[3,2-*h*]chromen-8-one (**21**); mp 151.5—152.5 °C (from methanol), (lit,[3] mp 146 °C), ν_{CO}^{KBr} 1725 cm^{-1}, Anal. C, 78.31; H, 4.64%.

The Preparation of the Furo Derivatives of Chromenones from Hydroxychromenones. *a*) Anhydrous potassium carbonate (3.5 g) was added to a mixture of hydroxy-2*H*-chromen-2-one[10] (2 g), 3-chloro-2-butanone (0.9 g), and acetone (10 ml), and the mixture was refluxed for 8 h. The cooled mixture was treated with water, extracted with chloroform, and the chloroform solution was washed with 5% aqueous sodium hydroxide solution. The product from the chloroform solution recrystallized to give 6- and 7-(1-methyl-2-oxopropoxy) derivatives of chromenones (**6a**, **6b**, **11a**, and **11b**), respectively (about 50% yields). *b*) A mixture of the alkoxychromenone (1 g) and PPA (n=2.5, 20 g) was heated for 4 h at 130 °C. The cooled mixture was treated with water, and the precipitates recrystallized to give the product. Products(yields %): **5a**(55.9) from **6a**, **5b**(67.3) from **6b**, **12a**(56.9) from **11a**, and **12b**(56.9) from **11b**. 4,8,9-Trimethyl-2*H*-furo[2,3-*h*]chromen-2-one (**5b**); mp 155—156 °C (from ethanol), (lit,[3] mp 155—156 °C), ν_{CO}^{KBr} 1710 cm^{-1}, Anal. C, 73.89; H, 5.43%.

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