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# Facile synthesis and photo-Fries rearrangement of 2-benzoyl-4-benzoyloxyphenol leading to dibenzoyldihydroxybenzene derivatives

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## Abstract

We prepared 2-benzoyl-4-benzoyloxyphenol **1** in 93% yield by reacting 1,4-dimethoxybenzene with benzoyl chloride in the presence of aluminium chloride. Irradiation of **1** with 254 mercury lamps provided 2,5-dibenzoyl-1,4-dihydroxybenzene **4**, 2,3-dibenzoyl-1,4-dihydroxybenzene **5**, and 2-benzoyl-1,4-dihydroxybenzene **6** with 19, 48, and 17% yields, respectively. The structure of the compound **4** was confirmed by single crystal X-ray analysis. Photo-Fries reaction of 1,4-dibenzoyloxybenzene **7** was also re-examined. The reported mp and $^1$H NMR data of **1** and **4** were corrected.

*Keywords:* Photo-Fries rearrangement; 2-Benzoyl-4-benzoyloxyphenol; Dibenzoyldihydroxybenzene

## 1. Introduction

Benzoylhydroxybenzene derivatives are useful intermediates for the synthesis of benzofurans [1], diaroylbiphenyls [2], drugs [3], and polymers [4]. However, very limited number of dibenzoyldihydroxybenzene derivatives have been reported [5,6]. The most frequently used method for the introduction of acyl group to benzene ring is the Friedel-Crafts acylation [7], but this method would not provide dibenzoyldihydroxybenzene derivatives having two benzoyl groups at *o*- or *p*-positions as the benzoyl group already present on the benzene ring strongly direct the position of the incoming second benzoyl group to the *m*-position. Another route for introducing acyl group onto aromatic rings is Fries rearrangement of esters of phenols, which provides *o*- and *p*-acyl-substituted phenol derivatives [8]. Thus, the choice of methods for the synthesis of dibenzoyldihydroxybenzene derivatives would depend on the position of the substituents on the aromatic rings. For example, the Friedel-Crafts reaction of 1,3-dimethoxybenzene with benzoyl chloride in the presence of aluminium chloride provides 1,5-dibenzoyl-2,4-dihydroxybenzene [5], while the corresponding reaction of 1,4-dimethoxybenzene gives 2,5-dimethoxybenzophenone [2]. On the other hand, 2-benzoyl-4-benzoyloxyphenol **1** and 2,5-dibenzoyl-1,4-dihydroxybenzene **4** have been reported to be obtained by photo-Fries rearrangement of 1,4-dibenzoyloxybenzene **7** [6]. We report here simple preparation of 2-benzoyl-4-benzoyloxyphenol **1**, and its facile photo-Fries rearrangement to 2,5-dibenzoyl-1,4-dihydroxybenzene **4**, and 2,3-dibenzoyl-1,4-dihydroxybenzene **5**.

## 2. Results and discussion

For the introduction of benzoyl group to the benzene ring of 1,4-dimethoxybenzene, Friedel-Crafts acylation reaction with benzoyl chloride was attempted in the presence of $AlCl_3$ (Scheme 1). The reaction of 1,4-dimethoxybenzene with ca. 1 eq. of benzoyl chloride and $AlCl_3$ was reported to produce almost exclusively 2,5-dimethoxybenzophenone **3** at 0 °C [2]. We found that the same reaction mixture at refluxing temperature gave a mixture of 2-benzoyl-4-benzoyloxyphenol **1**, 2-hydroxy-5-methoxybenzophenone **2**, and 2,5-dimethoxybenzophenone **3** with 3, 54, and 36% yields, respectively. The reaction with ca. 2 eq. of benzoyl chloride and $AlCl_3$ at room temperature gave a mixture of **1**, **2**, and **3** with 40, 17, and 3% yields, respectively. By heating the same reaction mixture at reflux, we could get almost exclusively the compound **1**: simple washing of the organic residue with hexane gave analytically pure **1** in 93% yield.

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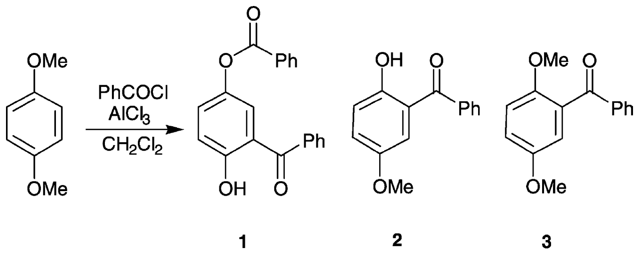


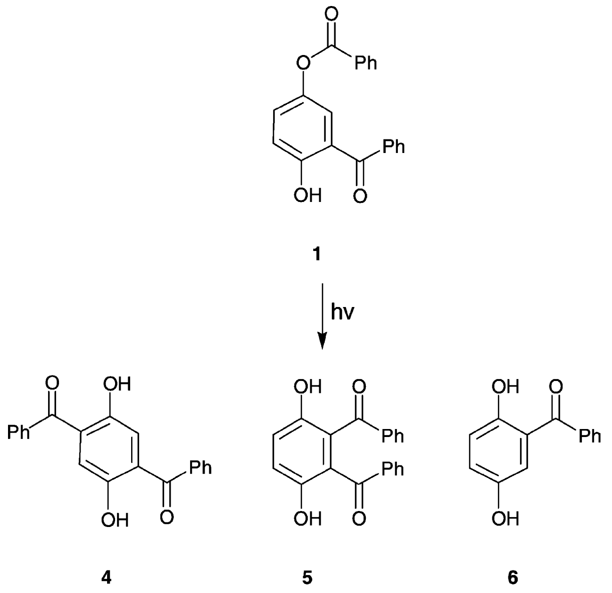
| reaction temp | [PhCOCl] / [C$_6$H$_4$(OMe)$_2$] | yields 1 | 2 | 3 |
|---|---|---|---|---|
| 0 °C | 1.1 | --- | --- | 85 %[ref 2] |
| at reflux | 1.1 | 3 % | 54 % | 36 % |
| 25 °C | 2.2 | 40 % | 17 % | 3 % |
| at reflux | 2.2 | 93 % | --- | --- |

Scheme 1. Reaction of 1,4-dimethoxybenzene with benzoyl chloride in the presence of aluminium chloride.

The structure of **1** was firmly characterized by $^1$H and $^{13}$C NMR and elemental analysis: the observed number of $^{13}$C NMR peaks was one less than the expected number due to overlapping. Our literature survey [9] for **1** revealed that its preparation had once been reported, via photo-Fries rearrangement of 1,4-dibenzoyloxybenzene **7**, with mp of 213–214 °C (in this work, 95–97 °C) and $^1$H NMR (CDCl$_3$) of δ 6.60–6.80 (m, 10H, OCOC$_6$H$_5$ and COC$_6$H$_5$), 6.90 (d, 1H, $J = 10$ Hz), 7.30 (dd, 1H), and 11.20 (s, 1H, –OH) [6]. The NMR data are obviously doubtful since there is one less number of protons and the peaks of benzoyl protons appear at too high field (δ 6.60–6.80) [10]: in this work, they show at δ 7.45–8.16.

The large variation of the reaction products depending on the reaction temperature in the Friedel-Crafts acylation of 1,4-dimethoxybenzene reflects the sensitivity of the extent of demethylation of methyl aryl ether groups on the reaction temperature: both methyl ether groups are stable at 0 °C, while moderately selective demethylation of 2-methoxy group occurs at room temperature. Such selective demethylation of methoxy group *ortho* to carbonyl group had also been reported in the reaction of aryl methyl ether with AlCl$_3$ [2] and BeCl$_2$ [11]. At high temperature both methoxy groups are demethylated and selective *O*-benzoylation of 5-hydroxy group of 2,5-dihydroxybenzophenone leads to the product **1**: 2-hydroxy group of 2,5-dihydroxybenzophenone is hydrogen-bonded to carbonyl and less reactive than 5-OH [12].

Establishment of the simple and efficient method for the preparation of 2-benzoyl-4-benzoyloxyphenol **1** from 1,4-dimethoxybenzene prompted us to utilize **1** for the synthesis of dibenzoyldihydroxybenzene derivatives via photo-Fries rearrangement [13]. Separation of the reaction mixture after 8–10 h of irradiation with 254 nm mercury lamps gave the Fries-rearranged products, **4** and **5** together with the debenzoylated compound **6** (Scheme 2).



| solvent | yields 4 | 5 | 6 |
|---|---|---|---|
| benzene (2.3 mM)[a] | 10 % | 22 % | 10 % |
| methanol (2.3 mM) | 19 % | 48 % | 17 % |
| methanol (10 mM) | 14 % | 24 % | 29% |

[a] In benzene, 20 % of unreacted starting material was recovered.

Scheme 2. Photoreaction of **1** with 254 nm lamps.

Photo-Fries rearrangement is generally believed to be a singlet reaction that occurs through homolytic cleavage of the carbonyl–oxygen bond, to give a caged radical pair. In-cage recombination affords the acyl migration products, while hydrogen abstraction by the aryloxy radical leads to the formation of phenols, which are the most common byproducts [13]. Plank [13c] reported that polar solvents such as methanol favor the rearrangement, and nonpolar solvents favor phenol formation, but Pitchumani et al. [13d] found that both methanol and benzene gave almost same yields of the rearranged products. In our case, the combined yields of the photo-rearranged products **4** and **5** were more than double in methanol than those in benzene. Raising the concentration to 10 mM lowered the yields of **4** and **5** with increased amount of the debenzoylated product **6**. Regioselectivity between two *ortho*-rearrangement products were observed in both solvents, favoring **5** over **4**. The clarification of the origin for the favored formation of **5** over **4** is beyond the scope of this work. However, it would be worthwhile to mention that energy calculation by *CS Chem 3D Pro* shows that **5** is energetically more favorable by 3.7 kcal/mol than **4**.

The compounds **4** and **5** have very similar structural features and their $^1$H and $^{13}$C NMR spectral data were not

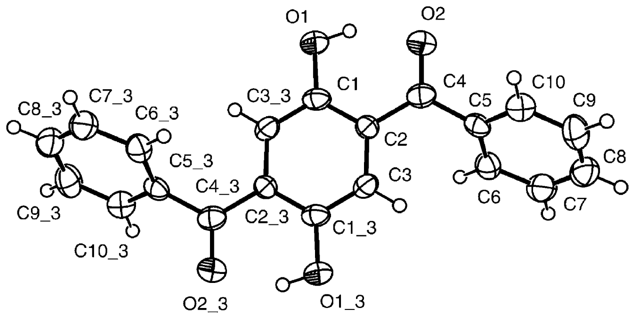
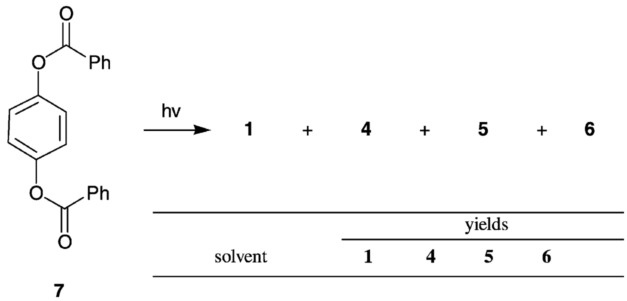


Fig. 1. ORTEP drawing of the X-ray structure of 2,5-dibenzoyl-1,4-dihydroxybenzene **4**. An additional ‘_3’ symbol refers to atoms at equivalent position $(2 - x, -y, 2 - z)$.



**7**

| solvent | yields 1 | 4 | 5 | 6 |
|---|---|---|---|---|
| benzene (2.3 mM) | 26 % | 7% | 10 % | 15 % |
| methanol (2.3 mM) | --- | 8 % | 13 % | 40 % |
| benzene (33 mM)$^{a}$ | 24 % | --- | 4 % | 9 % |
| benzene (33 mM)$^{ref\ 6}$ | 30 %$^{ref\ 6}$ | 10 %$^{ref\ 6}$ | --- | --- |

$^{a}$18 % of unreacted starting material was recovered.

Scheme 3. Photoreaction of **7** with 254 nm lamps.

sufficient to assign their structures: both **4** and **5** showed eight $^{13}$C NMR peaks due to their symmetrical nature. We obtained single crystals of **4** by slow evaporation of its dichloromethane solution and X-ray diffraction analysis provided its firm structural assignment. The ORTEP drawing of **4** is shown in Fig. 1. The compound **4** lies about an inversion center.

Inspection of $^{1}$H NMR data of **4** and **5** shows interesting features. Benzoyl protons of **5**, which appears at 7.03 (dd, 4H, *o*-), 7.16 (t, 4H, *m*-) and 7.39–7.43 (m, 2H, *p*-), are quite up-field shifted compared to benzoyl protons of **4** whose chemical shifts are in the normal range [10], 7.74–7.77 (m, 4H, *o*-), 7.52–7.56 (m, 4H, *m*-) and 7.62–7.67 (m, 2H, *p*-). This can be ascribed to the fact that two phenyl groups of **5** are in close proximity to each other and shielded due to ring current effect of the neighboring one. The compound **4** has been prepared previously [6], but mp and $^{1}$H NMR data are considerably different from this work: the reported mp is 172–173 °C (in this work, 203–205 °C) and the chemical shifts of benzoyl protons were reported as $\delta$ 6.90–7.15 (in this work, $\delta$ 7.52–7.77).

Sharma and Khanna [6] reported that photo-Fries rearrangement of 1,4-dibenzoyloxybenzene **7** provided 2-benzoyl-4-benzoyloxyphenol **1** and 2,5-dibenzoyl-1,4-dihydroxybenzene **4**, of which mp and $^{1}$H NMR data are doubtful (vide supra). Thus, we reexamined the reaction (Scheme 3). In addition to the compounds **1** and **4** [6], we obtained two more products, **5** and **6**. It is naturally expected that Fries rearrangement of one of the two benzoyloxy groups of **7** would produce **1** and further reaction of **1** gives the products **4**, **5**, and **6** (vide supra).[1] Lowering the concentration and changing the solvent from benzene to methanol increased the yields of the doubly Fries-rearranged products **4** and **5**.

In summary, we found that 2-benzoyl-4-benzoyloxyphenol **1** can be prepared in excellent yield by reacting 1,4-dimethoxybenzene with benzoyl chloride in the presence of aluminium chloride, and **1** provides, via photo-Fries rearrangement, dibenzoyldihydroxybenzenes **4** and **5** in much better yields than 1,4-dibenzoyloxybenzene **7** does.

## 3. Experimental

### 3.1. General

All reagents were purchased from Aldrich and used as received. Melting points are uncorrected. $^{1}$H NMR and $^{13}$C NMR spectra were obtained at 400/100 MHz using tetramethylsilane as an internal standard. NMR measurements and elemental analyses were performed at the Central Research Facilities of Chungnam National University.

### 3.2. Synthesis of 2-benzoyl-4-benzoyloxyphenol 1

A solution of dimethoxybenzene (3.0 g, 21.7 mmol) and benzoyl chloride (6.7 g, 47.7 mmol) in 50 ml of dichloromethane was added slowly to a suspension of aluminium chloride (7.0 g, 52.4 mmol) in 130 ml of dichloromethane, and the reaction mixture was heated at reflux for 26 h. The resulting mixture was poured over a mixture of cold water (90 ml) and conc. HCl (30 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 ml × 100 ml). The organic layers were combined, dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was washed with hexane three times to provide 6.45 g (93% yield) of **1**: mp 95–97 °C; $^{1}$H NMR ($CDCl_3$) $\delta$ 7.14 (d, 1H, $J = 9$ Hz, ArH *ortho* to OH), 7.36–7.39 (m, 1H, ArH *meta* to OH), 7.45–7.63 (m, 7H, ArH), 7.70–7.73 (m, 2H, ArH *ortho* to C=O in $C_6H_5CO$–), 8.14–8.16 (m, 2H, ArH *ortho* to COO in PhCOO–), 11.95 (s, 1H, OH); $^{13}$C NMR $\delta$ 118.77, 119.34, 125.63, 128.49, 128.58, 129.10, 129.17, 130.12,

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[1] The compound **6** may also be produced by photo-Fries reaction of 4-benzoyloxyphenol which can be a product of photochemical reaction of **7**. This could be a reason of high yield of **6** from **7**, compared to that from **1**.

132.19, 133.75, 137.41, 141.96, 160.94, 165.31, 200.81. Anal. Found: C, 75.08; H, 4.47. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43.

The same reaction was also carried out at room temperature for 50 h, and worked up as described above. The residue was subjected to silica gel column chromatography (eluent, 1:1 $CH_2Cl_2$:hexane). 2-Hydroxy-5-methoxybenzophenone **2** (mp 82–84 °C: 82–84 °C (lit.) [11], 83.5 °C (lit.) [2]) and 2,5-dimethoxybenzophenone **3** (mp 51 °C: 51 °C (lit.) [2,11]) were obtained with 17 and 3% yields, respectively, in addition to **1** with 40% yield.

### 3.3. *Photoreaction of 2-benzoyl-4-benzoyloxyphenol* ***1***

A methanol solution (800 ml) of **1** (0.600 g, 1.88 mmol) contained in quartz vessel was purged with nitrogen for 1 h and then irradiated under nitrogen with 254 nm mercury lamp for 6–7 h using RPR-100 photochemical reactor (Southern New England Ultraviolet Company). After the reaction was complete, the solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (eluent, 1:1 $CH_2Cl_2$:hexane) to afford 2,5-dibenzoyl-1,4-dihydroxybenzene **4**, 2,3-dibenzoyl-1,4-dihydroxybenzene **5**, and 2-benzoyl-1,4-dihydroxybenzene **6** with 19, 48, and 17% yields, respectively.

**4**. mp 203–205 °C, $^1H$ NMR ($CDCl_3$) $\delta$ 7.33 (s, 2H, ArH *ortho* to OH), 7.52–7.56 (m, 4H, ArH *meta* to C=O in $C_6H_5CO$), 7.62–7.67 (m, 2H, ArH *para* to C=O in $C_6H_5CO$), 7.74–7.77 (m, 4H, ArH *ortho* to C=O in $C_6H_5CO$), 10.87 (s, 2H, OH); $^{13}C$ NMR $\delta$ 121.84, 124.28, 128.58, 129.43, 132.76, 137.11, 153.34, 200.73. Anal. Found: C, 75.50; H, 4.53. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43.

**5**. mp 189–190 °C, $^1H$ NMR ($CDCl_3$) $\delta$ 7.03 (dd, 4H, $J$ = 8, 1 Hz, ArH *ortho* to C=O in $C_6H_5CO$), 7.16 (t, 4H, $J$ = 8 Hz, ArH *meta* to C=O in $C_6H_5CO$), 7.31 (s, 2H, ArH *ortho* to OH), 7.39–7.43 (m, 2H, ArH *para* to C=O in $C_6H_5CO$), 10.29 (s, 2H, OH); $^{13}C$ NMR $\delta$ 118.47, 125.82, 128.33, 128.70, 132.70, 139.61, 153.58, 198.24. Anal. Found: C, 75.15; H, 4.63. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43.

**6**. mp 122–124 °C (mp 121–123 °C (lit.) [14], 122–124 °C (lit.) [15]), $^1H$ NMR ($CDCl_3$) δ 5.37 (s, 1H), 6.93–7.07 (m, 3H), 7.44–7.65 (m, 5H), 11.57 (s, 1H).

The same reaction was carried out in benzene and it gave **4**, **5**, and **6** in 10, 22, and 10% yields, respectively, with 20% of the starting material recovered.

### 3.4. *Crystal structure determination of compound* ***4***

Single crystals of **4** suitable for X-ray diffraction were obtained by slow evaporation of its dichloromethane solution.

#### 3.4.1. *Crystal data*

$C_{20}H_{14}O_4$, $M = 318.31$, monoclinic, $a = 5.7789(7)$ Å, $b = 20.994(4)$ Å, $c = 6.7385(19)$ Å, $\beta = 112.775(18)^\circ$, $U = 753.8(3)$ Å$^3$, $T = 293(2)$ K, space group $P2_1/n$, $Z = 2$, $\mu$ (Mo K$\alpha$) $= 0.098\,\mathrm{mm}^{-1}$, 1515 reflections measured, 1397 unique ($R_{\mathrm{int}} = 0.092$; $R[F^2 > 2\sigma(F^2)] = 0.071$). The final $wR(F^2)$ was 0.169 (all data).

### 3.5. *Photoreaction of 1,4-dibenzoyloxybenzene* ***7***

The diester **7** [16,17] was prepared by reacting hydroquinone in 10% aq NaOH solution with benzoyl chloride: mp 206–207 °C (207 °C (lit.) [16]), $^1H$ NMR ($CD_2Cl_2$) $\delta$ 7.21 (s, 4H), 7.46 (t, 4H, $J$ = 8 Hz), 7.59 (t, 2H, $J$ = 8 Hz), 8.12 (dd, 4H, $J$ = 8, 1 Hz). A benzene solution (800 ml) of **7** (0.600 g, 1.88 mmol) was photo-irradiated in the same manner as described for the photoreaction of **1**. Silica gel column chromatography (eluent, 1:1 $CH_2Cl_2$:hexane) of the concentrated reaction mixture afforded 3-benzoyl-4-hydroxyphenyl benzoate **1**, 1,4-dibenzoyl-2,5-dihydroxybenzene **4**, 2,3-dibenzoyl-1,4-dihydroxybenzene **5**, and 1-benzoyl-2,5-dihydroxybenzene **6** with 26, 7, 10, and 15% yields, respectively. The same reaction in methanol gave **4**, **5**, and **6** in 8, 13, and 40% yields, respectively. The reaction of 33 mM benzene solution resulted in the formation of **1**, **5**, and **6** with 24, 4, and 9% yields, respectively.

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