The "Trivial" Mechanism for the Photo-Fries Reaction of Phenyl Acetate and Biphenylyl Acetates

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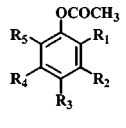
The mechanism for the photo-Fries rearrangement of phenyl acetate and biphenylyl acetates were reinvestigated in phenol (or phenol derivatives) containing media. The results showed that the phenol (or phenol derivatives) which is the most common by-product of Fries reaction reacts with acyl radical to give Fries-product. These phenol (or phenol derivatives) contributions to the Fries-products were suggested as the Trivial mechanism for the photo-Fries reaction.

Introduction

Many reports[1] have appeared during the last decade in connection with the mechanism of the photo-Fries reaction. These contributions have confirmed that photo-Fries reaction occurs through C-O homolytic cleavage from its singlet excited state, followed by radical recombination. In-cage recombination affords the migration products while hydrogen abstraction by the aryloxy radical leads to the formation of phenol derivatives. However, a few reports[2] have been made concerning to the photochemical reaction of biphenyl system such as biphenylyl acetate which is an active metabolite of fenbufen.[3,4]

In spite of the considerable interest attracted by the photochemistry of phenol derivatives not only from the fundamental but also from the applied point of view,[5] a little is known about the photo-Fries reaction process in phenol containing media.[6,7]

Herein we report photo-Fries reaction of phenyl acetates (**1a**, **1b**, **1c**) and biphenylyl acetates (**1d**, **1e**) under presence of phenol or phenol derivatives which are the most common by-product of Fries reaction to investigate the phenol effect on the mechanism of photo-Fries reaction.



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a, $R_1 \sim R_5 = H$
b, $R_1 \sim R_5 = D$
c, $R_2 \sim R_4 = H$, $R_1 = R_5 = Me$
d, $R_2 \sim R_5 = H$, $R_1 = Ph$
e, $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Ph$

Experimental section

Materials and general methods. All solvents were freshly distilled and dried before use according to standard procedures. All other reagents were used as received unless otherwise specified.

Absorption spectra were measured on a Shimadzu UV-2600 or Varian Cary 300 spectrometer. Gas chromatography-mass spectrometry (GC-MS) measurements were made on a Hewlett-Packard 5980 gas chromatograph with a Hewlett-Packard 5988 mass spectrometer (EI 70 eV) using an Ultra-1 (25 m), Ultra-2 (50 m), Pona (50 m) and DB-1 (30 m) capillary column.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-300 or Bruker AMX-500 spectrometer. IR spectra were recorded on a Jasco IR-810 or Perkin-Elmer 2000 spectrophotometer. Mass analyses were carried out on a Jeol JMX-AX 505 instrument.

Irradiations were carried out in quartz cell with a Hanovia 450 W, medium pressure Hg-Arc lamp or a Rayonet photoreactor equipped with 16 RPR 254 nm lamps.

Synthesis of phenyl acetate derivatives (1b, 1c). Acetyl chloride (3.2 mL, 0.045 mol) was added dropwise to phenol-d_6 (3.03 g, 0.03 mol) and the mixture was stirred for 1.0 h at 40 °C. After addition of 10% hydrochloric acid to make homogeneous solution, the mixture was transferred to a separatory funnel and extracted with diethyl ether.

The combined extracts were washed with 5% hydrochloric acid, dilute sodium hydroxide solution and distilled water. The extracts were dried over magnesium sulphate and the solvent was removed *in vacuo*. The residual colorless oil was chromatographed on silica gel to obtain 2.48 g (58%) of phenyl-d_5 acetate (**1b**): ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.5, 121.6, 126.0, 129.6, 151.0, 169.9. IR (neat): 1764 cm^{-1} GC-MS: *m e* 141, 99, 71. HRMS (EI^+) Calc. For $C_8H_3D_5O_2$: 141.0838. Found: 141.0836.

To the mixture of 2,6-dimethylphenol (10.07 g, 0.082 mol) and acetic anhydride (13.0 g, 0.127 mol) was added a few drops of concentrated sulphuric acid. The mixture was stirred for 1.5 h at 60 °C and cooled to room temperature with 50 mL of water and then extracted with diethyl ether. The combined extracts were washed with distilled water and dried over magnesium sulphate. The solvent was removed in vacuo and the residual liquid was chromatographed on silica gel to afford 10.56 g (78%) of 2,6-dimethylphnyl acetate (**1c**): ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 6H), 2.4 (s, 3H), 7.1 (m, 3H). ^{13}C (300 MHz, $CDCl_3$): δ 16.6, 20.8, 126.2, 129.0, 130.5, 148.7, 169.0. IR (neat): 1760 cm^{-1}. GC-MS: *m e* 164, 122, 107, 91, 77. HRMS (EI^-) Calc. For $C_{10}H_{12}O_2$: 164.0837. Found 164.0833.

Synthesis of 2-biphenylyl acetate (1d). To the mixture of 2-phenylphenol (10.2 g, 0.06 mol) and acetic anhydride (9.0 mL, 0.095 mol) was added a few drops of concentrated sul-

phuric acid. The mixture was stirred for 1.5 h at 60 °C and cooled to room temperature with 40 mL of water. This mixture was transferred to a separatory funnel and extracted with diethyl ether. The combined extracts were washed with cold water and dried over magnesium sulphate. The solvent was removed *in vacuo* and the residual oil was chromatographed on silica gel to give 11.8 g (93%) of 2-biphenylyl acetate (**1d**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H), 7.19 (dd, J = 8.0, 1.2 Hz, 1H) 7.35~7.47 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.3, 123.2, 126.9, 127.9, 128.7, 129.0, 129.3, 131.3, 135.3, 138.0, 148.2, 169.9. IR (neat) 1760 cm^{-1}. GC-MS: *m e* 212, 170, 169, 141, 139, 115. HRMS (EI$^+$) Calc. For $C_{14}H_{12}O_2$: 212.0837. Found 212.0837

Irradiation of phenyl acetate (1a) with phenol-d_5. A solution of 141 mg (1.04 mmol) of **1a** and 38 mg (0.38 mmol) of phenol-d_5 in methanol (26.0 mL) was transferred into a quartz cell and degassed with purified nitrogen. The sample was irradiated with Hg-Arc lamp (450 W, medium pressure) for 15 h. The solvent was then evaporated *in vacuo* to obtain yellow liquid. Silica gel chromatography gave 15 mg (23%) of phenol, 35 mg of a mixture of 2-hydroxyacetophenone (**2**) and 2-hydroxyacetophenone-d_4 (**4**) (mixture I), 34 mg of a mixture of 4-hydroxyacetophenone (**3**) and 4-hydroxyacetophenone-d_4 (**5**) (mixture II), and 46 mg of recovered starting material (67% conversion). Since the mixtures of deuterated and non-deuterated photoproducts were not separated by silica gel chromatography, the composition of the mixtures were analyzed by ^{1}H NMR and (or) mass spectral abundance of a particular peak. Spectral analyses showed that the mixture I contained 34 mg (35.7%) of **2** and 0.7 mg (0.7%) of **4**. Mixture II contained 33 mg (34.6 %) of 3 and 1.1 mg (1.1%) of **5**. Spectral data for **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H), 12.17 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.0, 118.4, 118.8, 120.0, 130.7, 136.0, 162.7, 204.9. GC-MS: *m e* 140, 125, 97, 69. Spectral data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 8.30 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.7, 115.5, 130.1, 130.6, 161.3, 198.4. GC-MS: *m e* 140, 125, 97, 69.

Irradiation of phenyl-d_5 acetate (1b) with phenol. A solution of 78 mg (0.55 mmol) of **1b** and 21 mg (0.22 mmol) of phenol in methanol (18.0 mL) was transferred into a quartz cell and degassed with purified nitrogen. The sample was irradiated with Hg-Arc lamp for 15 h. The solvent was then removed in vacuo to obtain a pale yellow oil. Silica gel chromatography and quantitative spectral analyses gave 11 mg (27%) of phenol-d_5, 0.9 mg (1.7%) of **2**, 1.4 mg (2.6%) of **3**, 18 mg (32%) of **4**, 17 mg (30%) of **5** and 22 mg of recovered starting material (72% conversion).

Irradiation of 2,6-dimethylphenyl acetate (1c) with phenol. A solution of 71 mg (0.43 mmol) of **1c** and 15.0 mg (0.16 mmol) of phenol in methanol (17 mL) was transferred into a quartz cell and degassed with purified nitrogen. The sample was irradiated with Hg-Arc lamp for 12 h. After evaporation of the solvent, silica gel chromatography and quantitative spectral analyses gave 6.8 mg (23%) of 2,6-dimethylphenol, 7.0 mg (18%) of 3,5-dimethyl-4-hydroxyacetophenone, trace (0.5%) of **2**, trace (2.1%) of **3** and 31 mg of starting material (56% conversion). Spectral data for 3,5-dimethyl-4-hydroxyacetophenone: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.3 (s, 6H), 2.6 (s, 3H), 5.2 (s, 1H), 7.7 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 16.3, 26.7, 123.3, 130.0, 130.1, 157.2, 197.9. IR (neat) 3600, 1670 cm^{-1}. MS: *m e* 164, 149, 121, 91, 77.

Irradiation of 2-biphenylyl acetate (1d). A solution of 283 mg of **1d** in 106 mL of ethanol was transferred into 5 quartz cells and degassed with purified nitrogen. The sample was irradiated with 16 RPR 254 nm lamps for 5 h. After evaporation of the solvent, silica gel chromatography gave 38 mg (13.4%) of 2-hydroxy-3-phenyl acetophenone (**6**), 20 mg (7.1%) of 4-hydroxy-3-phenyl acetophenone (**7**) and 48 mg (21%) of 2-phenylphenol. Spectral data for **6** : ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H), 7.0~7.8 (m, 8H), 12.9 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.4, 119.2, 120.2, 127.9, 128.6, 129.8, 130.5, 131.6, 137.4, 137.7, 160.2, 205.4. IR (neat) 3200, 1640 cm^{-1}. MS: *m e* 212, 197, 141, 115, 98, 63, 43. Spectral data for **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3H), 5.85 (s, 1H), 7.05~7.94 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.9, 116.3, 128.5, 128.9, 129.5, 129.9, 130.5, 130.9, 131.7, 136.3, 157.3, 197.4. IR (CCl_4): 3550, 3300, 1680 cm^{-1}. MS: *m e* 212, 197, 168, 141, 115, 98, 43.

Irradiation of 4-biphenylyl acetate (1e). A solution of 123 mg of **1e** in 46 mL of ethanol was transferred into 2 quartz cells and degassed with purified nitrogen. The samples were irradiated with 16 RPR 254 nm lamps for 4 h. The solvent was then evaporated in vacuo and the residue was separated by silica gel chromatography to give 75 mg (61%) of 2-hydroxy-5-phenyl acetophenone (**9**) and 35 mg (35%) of 4-phenylphenol. Spectral data for **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72 (s, 3H), 7.07~7.94 (m, 8H), 12.3 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.0, 119.3, 120.2, 127.1, 127.7, 129.4, 132.6, 135.6, 140.3, 162.3, 205.1. IR (CCl_4): 3500~2800, 1640 cm^{-1}. MS: *m e* 212, 197, 169, 141, 139, 115, 99, 84, 63, 43.

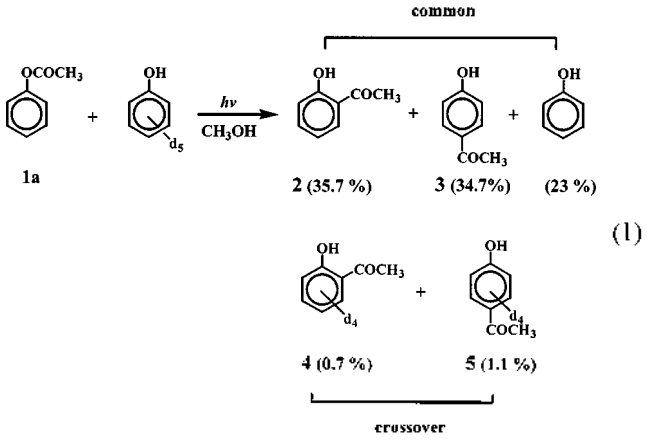
Acid catalyzed Fries reaction of 4-biphenylyl acetate (1e). A mixture of **1e** (2.1g, 10 mmol) and aluminum trichloride (1.5 g) in 1,1,2,2-tetrachloroethane (15 mL) was stirred at 140 °C for 2h. The reaction was quenched with 10%-hydrochloric acid (20 mL) and extracted with chloroform several times. The combined chloroform solution was extracted with 10%-aqueous sodium hydroxide. The extracts were acidified by 10%-hydrochloric acid and extracted with dietylether. The ether layer was dried over magnesium sulphate and the solvent was removed *in vacuo*. The residual liquid was chromatographed on silica gel to obtain 0.3 g (1.42 mmol, 14%) of **9**, 0.13g (0.76 mmol, 7.6%) of 4-phenylphenol and 9 mg (0.035 mmol, 0.35%) of **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H), 2.74 (s, 3H), 7.12~8.05 (m, 7H), 12.35 (s, 1H). IR (neat): 3600~3100, 1690, 1650 cm^{-1}. GC-MS: m/e 254, 239, 168, 139, 112, 98, 84, 63.

Irradiation of 2-biphenylyl acetate (1d) with 4-phenylphenol. A solution of 631 mg of **1d** and 131 mg of 4-phenylpnenol in 152 mL of ethanol was transferred into 10 quartz cells and degassed with purified nitrogen. The samples were irradiated with 16 RPR 254 nm lamps for 12 h.

The solvent was evaporated *in vacuo* and the residue was separated by silica gel chromatography to obtain 66 mg (10.5%) of **6**, 38 mg (6%) of **7**, 173 mg (34.5%) of 2-phenylphenol and 5 mg of starting material (99% conversion). The crossover products, **8** (6 mg, 1%) and **1e** (1 mg, 0.16%) were also obtained.

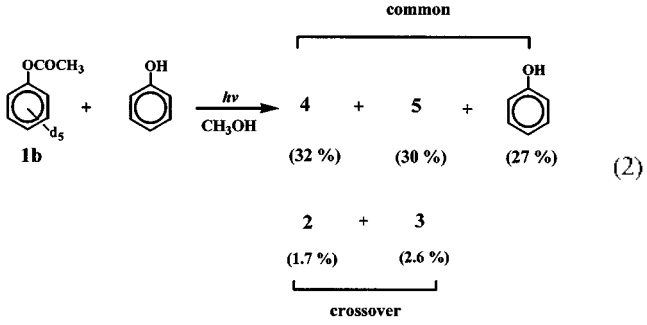
Results and Discussion

Phenol effect on the photochemistry of phenyl acetates (1a, 1c). Since the phenol which is the most common by-product of photo-Fries reaction might react with acyl radical to give crossover Fries-product, phenyl acetate (**1a**) was irradiated under presence of phenol-d_5 to distinguish the crossover products from the common Fries-rearranged products (Eq. (1)). As expected, crossover products **4** and **5** were obtained as minor product under presence of phenol-d_5.



(1)

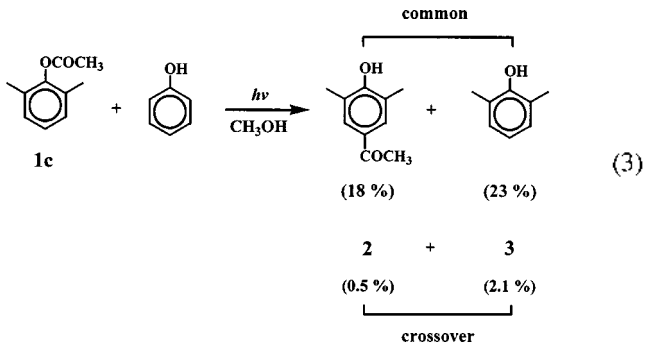
Irradiation of phenyl-d_5 acetate (**1b**) under presence of phenol also gave the crossover products (**2**, **3**), and the relative yields of the crossover products were slightly increased (Eq. (2)) (Table 1).



(2)

Recently Haruo Shizuka **8** reported that 1,3-sigmatropic hydrogen shift of photo-Fries reaction by Laser Flash photolysis showed kinetic isotope effect ($k_H/k_D = 3.8$). This isotope effect was thought to increase the relative yields of the crossover products, **2** and **3**.

Irradiation of 2,6-dimethyl acetate (**1c**) under presence of phenol did not increase the relative yields of the crossover products (**2**, **3**) as much as expected even though two ortho-

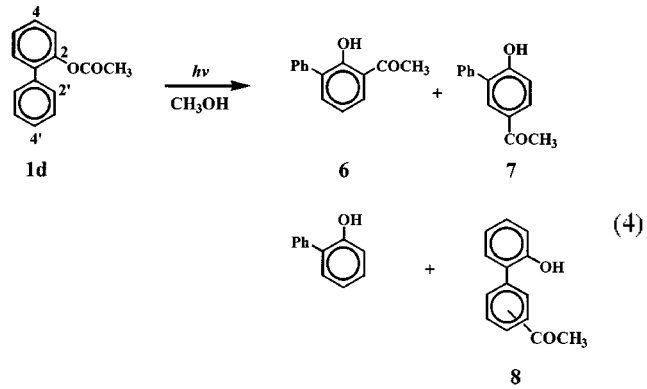


(3)

positions were blocked by methyl groups (Table 1).

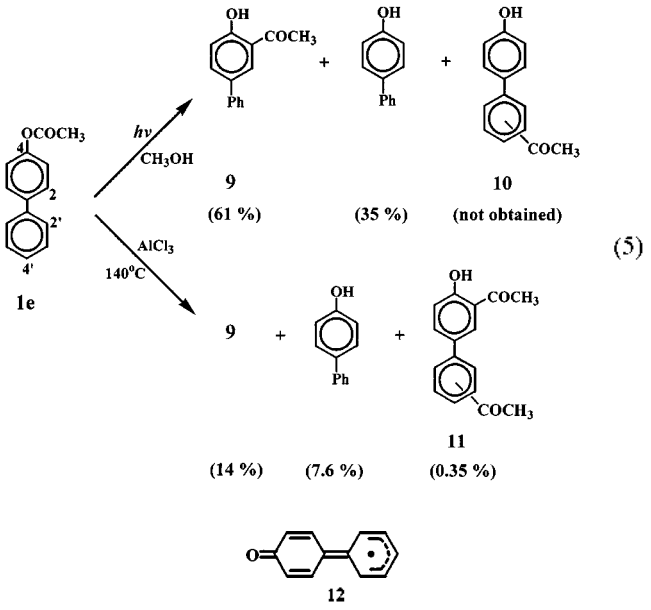
The photo-Fries reaction of phenyl acetate is known to afford both ortho- and para- hydroxyacetophenone in addition to phenol. This is a singlet reaction that occurs through homolytic cleavage of the carbon-oxygen bond to give a caged radical pair. In-cage recombination affords the acyl migration products, while hydrogen abstraction by phenoxy radical leads to the formation of phenol. As the reaction proceeds, the concentration of phenol increases (~50%, depends on the reaction condition.) and this phenol can be attacked by acyl radical to give the crossover products.

Photo-Fries reaction of biphenylyl acetates (1d, 1e). The photolysis of biphenylyl acetates were undertaken in order to investigate the possibility of acyl transfer not only to ortho- and para-position but also to carbon-2' and 4' position. Irradiation of 2-biphenylyl acetate (**1d**) gave the common Fries-product **6** (13.4%) and **7** (7.1%) in addition to 2-phenylphenol (1%). The products **8** from acyl transfer to carbon-2' or (and) 4' position, however, were not obtained (Eq. (4)).



(4)

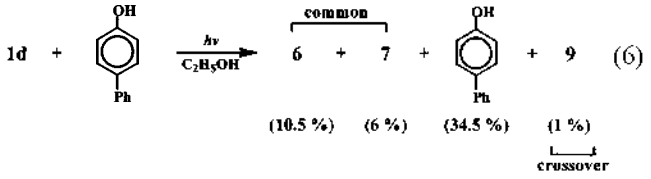
Irradiation of 4-biphenylyl acetate (**1e**) produced a common Fries-product **8** (61%) and 4-phenylphenol (35%). The product, **10** from acyl transfer to carbon-2' or (and) 4' position was not obtained (Eq. (5)) presumably due to restricted geometry of an intermediate **12** at the irradiation temperature (40 °C). However, reaction of **1e** with aluminum trichloride at 140 °C produced **11**.



(5)

In thermal Fries-reaction of **1e**, high temperature (140 °C) of the reaction media might overcome the unfavorabole geometry of **12**.

Phenol effect on the photochemistry of 2-biphenylyl acetate (1d). Irradiation of **1d** under presence of 4-phenylphenol afforded the common Fries-products **6** and **7** in addition to crossover product **9** (Eq. (6)).



(6)

The "Trivial" mechanism for the photo-Fries reaction. Since the photo-Fries reaction is always accompanied by the formation of phenol or phenol derivatives, these phenol effects on the photo-Fries reaction were examined with added phenol which gives crossover product.

As Fries reaction proceeds, the concentration of phenol increases and this phenol reacts intermolecularly with acyl radical to afford Fries-product which cannot be distinguished from the common Fries-product. This undistinguishable crossover products are not negligible even though the contribution is small, because the crossover products are produced by mechanistically different process from the common Fries-reaction mechanim. This minor contribution (2~12%) (Table 1) to the photo-Fries reaction is suggested as the "Trivial" mechanism.

Table 1. Relative yields of photo-Fries products (common *vs.* crossover)

Entry	Starting Compounds	Relative yields (%)			
		ortho-		*para-*	
		common	crossover	common	crossover
1	**1a**	98	2	97	3
2	**1b**	94.7	5.3	91.3	8.7
3	**1c**	94.5	5.5	88.3	11.7
4	**1d**	93.9	6.1	–	–

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