Photo-Fries Rearrangement: Synthesis of Alkyl Hydroxyaryl Ketones

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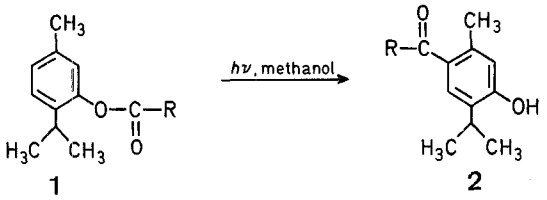
The photo-Fries migration has been extensively studied[1-8] and used preparatively[9,10]. From the available data it appears that, in certain cases, a mixture of *o*- and *p*-migrated products is obtained while, in other cases, it is exclusively either *o*- or *p*-product. The factors governing the formation of *o*- or *p*-products are not clear though, in some cases, steric reasons have been assigned[11]. Photo-Fries migration of phenyl acetate[8] gave a mixture of *o*- and *p*-hydroxyacetophenones while 1-naphthyl acetate and its derivatives gave exclusively 2-acetyl-1-naphthol[11]. In order to confirm the steric effects, the study of the following compounds was undertaken: thymyl esters[12] **(1a-d)** of pentanoic, 3-methylbutanoic, 2-methylbutanoic, and acetic acids, resorcinol diacetate **(3)**, and 4-methylphenyl acetate **(6)**.

The thymyl esters **1** were prepared from thymol and the corresponding acyl chlorides. Irradiation of these esters in methanol lead to photo-Fries rearrangement with the exclusive formation of the *p*-substitution products **2** (in addition to thymol and unchanged educt).

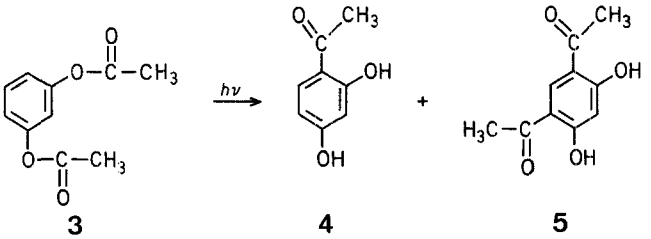


1 2

1,2	a	b	c	d
R	*n*-C_4H_9–	*i*-C_3H_7–CH_2–	C_2H_5–CH(–CH_3)–	H_3C–

The structures of products **2a-d** were assigned on the basis of analytical and spectral data. The exclusive *p*-substitution is probably caused by the fact that the *o*-position is sterically more shielded than the *p*-position.

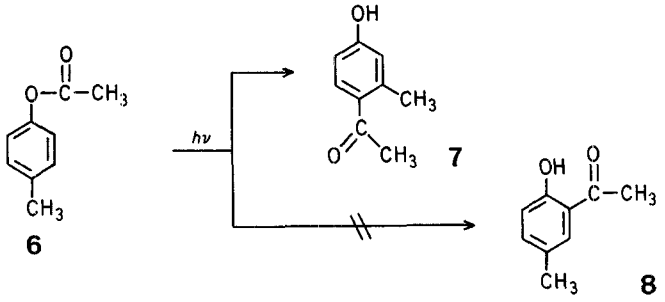
Irradiation of resorcinol diacetate under the same conditions affords 4-acetylresorcinol **(4)** and 4,6-diacetylresorcinol **(5)**.



3 4 5

The formation of products **4** and **5** supports a mechanism which involves fragmentation of **3** into free radicals[8]. The other possible product, 2,4-diacetylresorcinol, is most probably not formed due to steric reasons.

In the case of 4-methylphenyl acetate **(6)** which has a blocked *p*-position, irradiation does not afford the expected product **8**[13]; instead, 4-hydroxy-2-methylacetophenone **(7)** is obtained.



6 7 8

To our knowledge, 1,2-migration of a methyl group under the conditions used by us is not known. Methyl group 1,2-migration has been reported to occur in the acetylation of *o*-xylene, however[15]. We explain the formation of **7** by the following mechanism:

Table. Rearrangement Products **2a-d** and **7**

Product	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c] or m.p. [°C] reported	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
2a	32	86°	$C_{15}H_{22}O_2$ (234.3)	3240 (br, OH); 1640 (C=O)	7.58 (s, 1 H_{arom}); 7.1 (s, 1 H, OH[d]); 6.6 (s, 1 H_{arom}); 3.06-3.42 [m, 1 H, Ar—CH(CH$_3$)$_2$]; 2.91 (t, 2 H, J=8.5 Hz, CH_2—CO—); 2.43 (s, 3 H, Ar—CH_3); 1.4-1.8 (m, 4 H, CH_2—CH_2—CH_3); 1.27 [d, 6 H, J=8.5 Hz, Ar—CH(CH$_3$)$_2$]; 0.94 (t, 3 H, J=8 Hz, CH_2—CH_3)
2b	28	119°	$C_{15}H_{22}O_2$ (234.3)	3260 (br, OH); 1645 (C=O)	7.5 (s, 1 H_{arom}); 7.06 (s, 1 H, OH[d]); 6.62 (s, 1 H_{arom}); 3.1-3.45 [m, 1 H, Ar—CH(CH$_3$)$_2$]; 2.84 (d, 2 H, J=7 Hz, CH_2—CO—); 2.5 (s, 3 H, Ar—CH_3); 2.14-2.4 (m, 1 H, CH_2—CH(CH$_3$)$_2$; 1.35 (d, 6 H, J=9 Hz, Ar—CH(CH$_3$)$_2$); 1.12 [d, 6 H, J=9 Hz, CH(CH$_3$)$_2$]
2c	16	126°	$C_{15}H_{22}O_2$ (234.3)	3245 (br, OH); 1645 (C=O)	7.48 (s, 1 H_{arom}); 7.2 (s, 1 H, OH[d]); 6.58 (s, 1 H_{arom}); 3.15-3.4 [m, 1 H, Ar—CH(CH$_3$)$_2$]; 2.55-2.85 (m, 1 H, CH—CO); 2.47 (s, 3 H, Ar—CH_3); 1.5-1.85 (m, 2 H, CH_2—CH_3); 1.33 (d, 3 H, J=8.5 Hz, CH—CH_3); 1.25 [d, 6 H, J=9 Hz, Ar—CH(CH$_3$)$_2$]; 1.05 (t, 3 H, J=8.5 Hz, CH_2—CH_3)
2d	41	135°	$C_{12}H_{16}O_2$ (192.3)	3020 (br, OH); 1630 (C=O)	7.95 (s, 1 H_{arom}); 7.6 (s, 1 H, OH[d]); 6.68 (s, 1 H_{arom}); 3.1-3.4 [m, 1 H, Ar—CH(CH$_3$)$_2$]; 2.58 (s, 3 H, CO—CH_3); 2.47 (s, 3 H, Ar—CH_3); 1.27 [d, 6 H, J=8.5 Hz, Ar—CH(CH$_3$)$_2$]
7	26	128-130°	128°[14]	3310 (br, OH); 1750 (C=O)	7.68 (d, J=9.5 Hz, 1 H_{arom}); 6.65 (dd, J=9.5 and 2 Hz, 1 H_{arom}); 6.48 (d, J=2.5 Hz, 1 H_{arom}); 2.56 (s, 3 H, CO—CH_3); 2.38 (s, 3 H, Ar—CH_3)

[a] Yield of pure isolated product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C, ±0.25; H, ±0.21.
[d] Exchangeable with deuterium.

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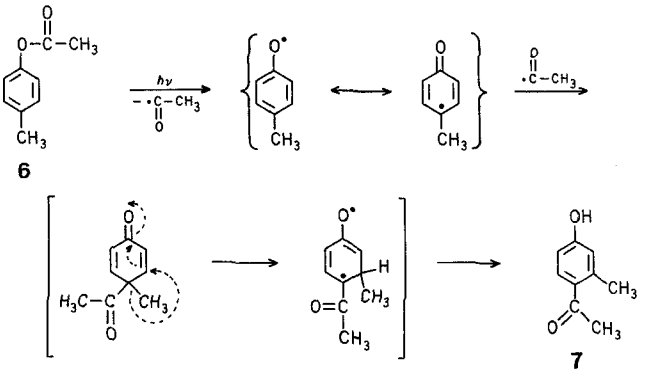

6

7

Photo-Induced Fries Rearrangement of Phenyl Carboxylates; General Procedure:

A solution of the ester **1** (20 mmol) in methanol (600 ml) is divided into 4 equal portions. Each portion is irradiated at 25 °C under a nitrogen atmosphere for 6 h at a low wavelength using a 450 W Ace-Hanovia U.V. lamp (Model 6515). The portions are then combined, the solvent is evaporated in vacuo, and the residue is dissolved in ethyl acetate (250 ml) and worked up as follows:

Work-up of Products **2a–d**: The ethyl acetate is extracted with aqueous 5% sodium hydroxide (100 ml). The aqueous phase is saved and the organic phase is dried with sodium sulfate, passed through a small column of silica gel, and evaporated to give the educt **1**. The aqueous phase is acidified with dilute hydrochloric acid and extracted with ether (2 × 100 ml). The ether extract is dried with sodium sulfate and the solvent removed in vacuo. The residual solid is fractionally crystallized from methanol/acetone (**2c** from ethanol/acetone) to give thymol and product **2**.

Work-up of Product **7**: The ethyl acetate extract is washed with water (3 × 50 ml) and extracted with aqueous 7% sodium hydroxide (70 ml). The aqueous layer is acidified with dilute hydrochloric acid and extracted with ether (300 ml). The ether is removed in vacuo and the residue chromatographed on silica gel using light petroleum (b.p. 60–80 °C) with increasing amounts of ethyl acetate as eluent to give 4-methylphenol and colorless product **7**.

Work-up of Products **4** *and* **5** is done by column chromatography using light petroleum (b.p. 60–80 °C) with increasing amounts of ethyl acetate as eluent.

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