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The Photo-Fries Rearrangement of 2,5-Disubstituted Phenyl Acetates

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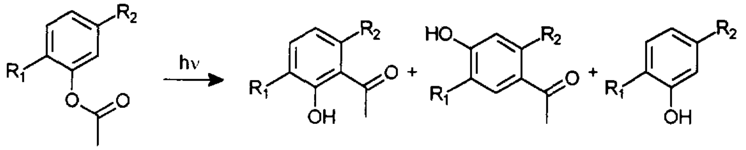
Abstract: In a homogeneous solution, the photo-Fries rearrangement of 2,5-disubstituted phenyl acetates gives *ortho*-hydroxyacetophenones as major photoproducts. The *ortho/para* ratio can be increased by using a highly viscous medium or restricted spaces such as those in zeolites. On the other hand, micellar solutions have little effect.

The preparation of polysubstituted aromatic rings continues to be a great challenge in synthetic organic chemistry. Snieckus[1] has reviewed methods for the regioselective synthesis of benzenes bearing adjacent substituents (1,2-, 1,2,3- and 1,2,3,4-). In combination with the more versatile directed *ortho* metalation, some molecular migrations, particularly the Claisen rearrangement[2] and the photochemical variant of the Fries reaction[3] have found synthetic application. Our interest in the preparation of 1,2,3,4-tetrasubstituted benzene derivatives as intermediates for complex natural products prompted us to explore the synthetic potential of the photo-Fries rearrangement of acetates derived from 2,5-disubstituted phenols.

The photo-Fries reaction of phenyl acetate is known to afford both *ortho-* and *para*-hydroxyacetophenones in addition to phenol,[4] by C-O homolytic cleavage from its singlet excited state, followed by radical recombination.[5] The product distribution, which is strongly dependent on the reaction conditions, usually results in *ortho/para* ratios close to unity. However, substituents at positions 2 and 5 must influence the recombination and alter the selectivity.

Irradiation of 2,5-dimethylphenyl acetate (**1a**) in methanol at 254 nm led to the formation of 2-hydroxy-3,6-dimethylacetophenone (**2a**)[6] as the major product, together with 4-hydroxy-2,5-dimethylacetophenone (**3a**) and phenol (**4a**). As expected,[7] increasing the polarity and viscosity of the solvent [(2:1) MeOH/H_2O] also increased the *o/p* ratio while diminishing the phenol concentration as a result of the stronger solvent cage surrounding the radical pair (table, entries 1 and 2). In order to asses the steric effect from substituents at positions 2 and 5, the isomeric carvacryl acetate (**1b**) and thymyl acetate (**1c**) were irradiated. With the isopropyl group at position 5, a decreased yield of the rearranged products (**2b** and **3b**) was observed that resulted in an increase in the carvacrol yield (**4b**) (entries 3 and 4). These results suggest the influence of a bulk substituent at position 5 which hinders radical recombination and favours *out-of-cage* processes.



1a-d **2a-d** **3a-d** **4a-d**

1-4	R_1	R_2
a	CH_3	CH_3
b	CH_3	$CH(CH_3)_2$
c	$CH(CH_3)_2$	CH_3
d	OCH_3	CH_3

The size of the substituent at position 2 is less influential as shown by the fact that photoreaction of **1c** gave product distribution similar to that observed for **1a**.[8] Also, *in cage* reactivity (*ortho* plus *para*) was favoured over *out-of-cage* reactivity (entries 5 and 6). Although the electronic effect of subtituents in the course of the photo-Fries reaction is poorly documented, some influence of an alkoxy group was anticipated, particularly on a singlet π-π^* reaction.[9] Acetate **1d**, with a methoxy group at C-2, was thus selected. In fact, the product distribution was similar to that observed in previous experiments (entries 7 and 8). Compound **1d** makes a significant substitution model as it allows one to prepare *ortho*-methoxy phenols, which occur in many natural compounds, especially those resulting from L-dopa[10] metabolism. This prompted us to try to improve the results, by increasing the *o/p* ratio and diminishing phenol formation.

In order to assess the potential effect of the medium viscosity on the outcome of the radical recombination, acetate **1d** was irradiated in a glycerol solution (entry 9). The enhanced regioselectivity obtained (*ortho/para* > 30) was accompanied by an unusually high proportion of phenol (**4d**) that was ascribed to the low homolytic dissociation energy of this medium.

Several authors have irradiated aryl esters in restricted spaces such as cyclodextrin,[11] micellar solutions[12] and silica surfaces[13] to modify the *ortho/para* ratio. Most of these environments hinder mass transfer of the radical pair produced in the cage, thus acting similarly to highly viscous solvents. A micellar solution of **1d** containing the surfactant sodium dodecylsulfate (SDS) was irradiated (entry 10). Surprisingly, the product distribution was not substantially different from that observed in the homogeneous solution. Moreover, attempts at increasing cage effects by changing the micelle concentration[14] produced no better results.[15]

One alternative way of limiting the mobility of the reactants/intermediates is using a heterogeneous medium such as zeolite.[16] The photochemistry in zeolite-solvent slurries results in significantly improved selectivity, particularly in reactions involving radical intermediates.[17] However,

Table. Product distribution in the photo-Fries rearrangement of acetates **1a-d**^{a}.

Entry	Substrate	Solvent	% Conversion^b	% Yield^c	Product distribution^b		
1	**1a**	MeOH	82	96	**2a** (50)	**3a** (30)	**4a** (20)
2		MeOH/H_2O(2:1)	52	97	(68)	(20)	(12)
3	**1b**	MeOH	81	92	**2b** (48)	**3b** (20)	**4b** (32)
4		MeOH/H_2O(2:1)	91	97	(58)	(16)	(26)
5	**1c**	MeOH	83	95	**2c** (54)	**3c** (30)	**4c** (16)
6		MeOH/H_2O(2:1)	74	96	(68)	(24)	(8)
7	**1d**	MeOH	84	98	**2d** (46)	**3d** (26)	**4d** (28)
8		MeOH/H_2O(2:1)	53	97	(68)	(20)	(12)
9		Glycerol	72	70	(64)	(<2)	(34)
10		SDS/H_2O	70	80	(66)	(18)	(16)
11		Zeolite/hexane	49	66	(53)	(<0.1)	(46)

(a) All irradiations were carried out in Vycor tubes by using a cylindrical photochemical reactor equipped with eight-low pressure Hg lamps (Sylvania G8T5), under N_2 at r.t. Entries 1-8: acetates **1a-d** (3.3 mmol) were dissolved in the pertinent solvent (100 ml). Entry 9: A few drops of MeOH were necessary to completely dissolve **1d** (0.6 mmol) in glycerol (40 ml). Entry 10: a suspension of **1d** (1 mmol) in a SDS detergent solution (0.4 M, 50 ml) was sonicated to complete dissolution. Entry 11: a hexane (25 ml) solution of **1d** (0.55 mmol) was stirred with activated NaX zeolite (zeolite 13X, Linde, 1 g) until no guest ester was detected in solution (GC/MS). Reaction mixtures were separated by vacuum chromatography (Silica gel, hexane/CH_2Cl_2). (b) Measured by GC/MS and ^1H NMR. Values are the averages of at least six experiments. (c) Yields are given in terms of starting material consumed.

no applications have so far been reported for the photo-Fries reaction. A hexane slurry of acetate **1d** included in NaX-type zeolite[18] was irradiated (entry 11). The reaction developed with a high *ortho*-regioselectivity, but required a long irradiation time to obtain a conversion of *ca.* 50%. Recovering the photoproducts from the zeolite cavity was rather difficult (refluxing MeOH); in fact, the amount recovered never exceeded 70% of the starting ester.

In summary, limiting the mobility of the radical pair by increasing the solvent viscosity or modifying mass transfer phenomena allows one obtain good enough yields of 3,6-disubstituted *ortho*-hydroxyacetophenones by photo-Fries rearrangement of 2,5-disubstituted phenyl esters for synthetic use. One major drawback is the yield of phenol, which apparently depends not only on *out-of-cage* processes, but also on *in-cage* hydrogen abstraction from the solvent or the acetyl radical to produce ketene.[19] Variants based on the glycerol and guest-zeolite-solvent systems are currently being tested in order to overcame this drawback.

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19. No ester solvolysis is involved in the phenol formation, as shown in parallel dark experiments.

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