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CYCLIC ACETALS AS CARBONYL BLOCKING GROUPS IN THE PHOTO-FRIES REARRANGEMENT OF ACYL SUBSTITUTED ARYL ESTERS.

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Abstract - The ethylene acetals of o and p-acetoxyacetophenone **3a,b**, prepared from the corresponding hydroxyacetophenones by treatment with acetic anhydride in pyridine and subsequently with ethylene glycol and p-toluenesulphonic acid, give upon irradiation the expected photo-Fries products **4a,b** (from **3a**) or **6** (from **3b**). These compounds are converted in part into diacetylphenols **5a,b** as a consequence of a deacetalization, occurring to some extent during the irradiation and further in the chromatographic workup. The yields of the photoproducts and the ortho/para ratio (in the case of **3a**) are very similar to those given in the literature for phenyl acetate. By contrast, the acetoxyacetophenones **2a,b** do not undergo any appreciable change upon irradiation, showing the deactivating effect of the acetyl side chain. Therefore, it is concluded that cyclic acetals are suitable carbonyl blocking groups in order to circumvent the deactivating effect of acyl substituents on the photo-Fries rearrangement of aryl esters.

INTRODUCTION

Polyacylated aromatic hydrocarbons are in general difficult to prepare, because the Friedel-Crafts reaction stops cleanly after the introduction of the first acyl group,[1] due to the known deactivating effect of this type of substituents towards further electrophilic attacks.

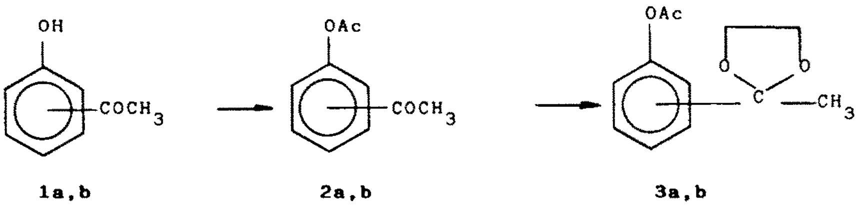
Likewise, the polyacylation of phenolic rings cannot be usually accomplished by the Lewis acid-catalyzed Fries rearrangement of aryl esters,[2,3] nor by the equivalent photochemical process,[4-6] since in both cases the reaction ceases after the first rearrangement has taken place.

In principle, the above difficulties could be avoided by blocking each carbonyl group before the next acylation step. This strategy presents serious limitations when applied to the classical acylation procedures, due to the requirement of strongly acidic conditions. However, it appears that the neutral media and the mild temperatures characteristic of the photochemical reactions could allow to assay the necessary carbonyl blocking with reasonable possibilities of success.

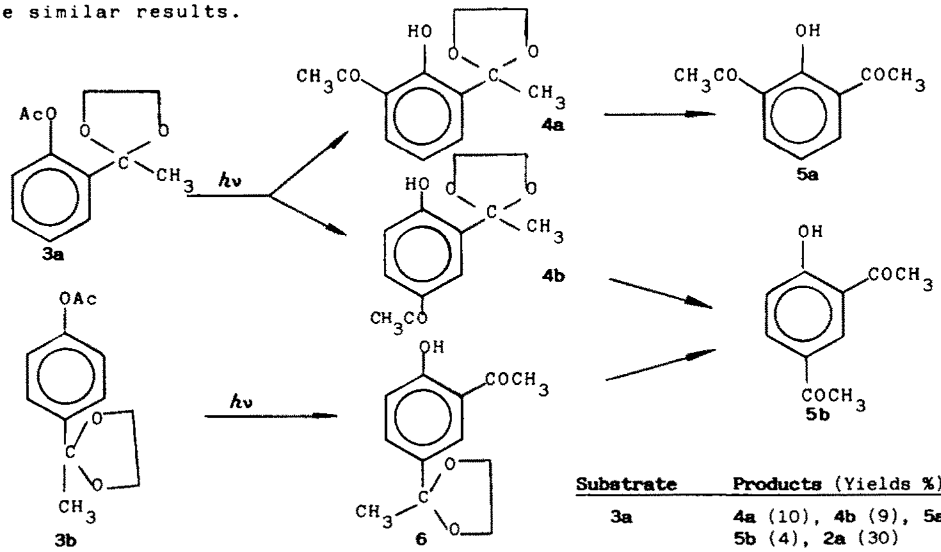
In this context, we have already shown that enol acetylation enhances in some cases the photo-Fries rearrangement of acyl substituted aryl esters,[7] although the method is not generally applicable because of the high photoreactivity of the enol ester moiety.[8,9] As an extension of this idea, we wish now to report on the results obtained when cyclic acetals are used as carbonyl blocking groups in connection with the polyacylation of phenols.

RESULTS AND DISCUSSION

The desired acetals **3a** and **3b**, which had been chosen as models to carry out the photochemical studies, were obtained by O-acetylation of the starting hydroxyacetophenones **1a,b** and subsequent treatment of the acetyl derivatives **2a,b** with ethylene glycol in the presence of p-toluenesulphonic acid. This procedure afforded the expected acetals with acceptable yields. By contrast, the alternative synthetic route involving a direct acetalization of the same starting hydroxyacetophenones, followed by acetylation, did not work satisfactorily, confirming the reluctance of phenolic ketones to give acetals under a variety of conditions.[10,11]



Irradiation through quartz of a solution of **3a** in hexane led to the expected photo-Fries products **4a** and **4b**, although, as a consequence of a partial deacetalization, these compounds were converted in part into the diacetylphenols **5a** and **5b**. A considerable amount of the unrearranged starting material was also recovered after undergoing extensive deacetalization to **2a**. Irradiation of **3b** gave similar results.



Substrate	Products (Yields %)
3a	**4a** (10), **4b** (9), **5a** (7), **5b** (4), **2a** (30)
3b	**6** (21), **5b** (12), **2b** (35)

The observed acetal hydrolysis took place in part during the chromatographic workup, but the ^{1}H-nmr spectra of the crude photomixtures revealed that it also ocurred, to an appreciable extent, in the course of the irradiation. The first observation is not surprising, since wet silica gel has been recently found to act as a suitable reagent for quantitative deacetalization.[12] To understand the occurrence of hydrolysis simultaneously to the irradiation, it must be kept in mind that the more difficult is the formation of an acetal, the more easily takes place the reverse hydrolysis. For this reason, ketone acetals are sometimes so sensitive to moisture that are used as one of the best systems to remove traces of water from the medium.[13] In our case, the acetals **4a,b** and **6** would be very difficult to prepare from the corresponding ketonic precursors **5a,b**, since the strong chelation of the carbonyl group in the latter compounds would produce a marked decrease in reactivity.[11] On the other hand, the presence of phenolic hydroxy groups in compounds **4a,b** and **6** could additionally facilitate the acetal hydrolisis through either an inter- or intramolecular mechanism of acid catalysis.[14-16] In this way, the substrates **3a,b** might be also affected by the phenolic hydroxy groups of the photoproducts (whose concentration increases as the irradiation goes on), giving rise to the acetoxyacetophenones **2a,b**.

Concerning the efficiency of ethylene acetals as carbonyl blocking systems in the photo-Fries rearrangement, an evaluation can be made by comparing the above results with those given in the literature for phenyl acetate,[17] where no deactivating substituent is attached to the aromatic ring. Upon irradiation, phenyl acetate gives a mixture containing a 34 % of photorearranged products, the ortho/para ratio being 1.27. These values are very close to those found for the ethylene acetal of o-acetoxyacetophenone **3a** (yield of **4a** + **4b** + **5a** + **5b** : 30 %; ortho/para ratio : 1.3). In the case of the acetal **3b**, where the para position is blocked and therefore inaccesible to the acylation, the overall yield is also very similar (**6** + **5b** : 33 %), but only products of ortho--rearrangement are obviously formed. Instead, the acetoxyacetophenones **2a,b**, which differ from phenyl acetate only by the presence of an acetyl side chain, do not undergo any appreciable change upon irradiation, showing in this way the deactivating effect of the free carbonyl group. This effect might be explained by the fast intersystem crossing characteristic of aromatic ketones. The triplet formation would depopulate the singlet state, which is likely the reactive state involved in the photo-Fries rearrangement.

From this work, it can be concluded that, within the general preparative limitations of the reaction, cyclic acetals can be used as suitable carbonyl blocking groups, in order to circumvent the deactivating effect that acyl substituents exert on the photo-Fries rearrangement of aryl esters.

EXPERIMENTAL

General. M.ps were determined with a Büchi 510 apparatus and are uncorrected. Ir-spectra were obtained in CCl_4 solns with a Perkin-Elmer Model 557 spectrometer; $\bar{\nu}_{max}$ (cm^{-1}) is given only for the carbonyl absorption bands. ^{1}H-nmr spectra were measured in CCl_4 with a 60-MHz Varian 360 EM instrument; chemical shifts are reported in δ (ppm) values, using TMS as internal standard. Uv-spectra were determined in hexane with a Varian 634 spectrophotometer; absorbed radiation is defined by its wavelenght (λ_{max}, nm) and log ϵ (in brackets). Elemental analyses were performed at the Instituto de Química Bio-Orgánica de C.S.I.C., Barcelona. Isolation and purification were done by column chromatography on silica gel Merck 60, 70-230 mesh and the solid substances were recrystallized from hexane before submission to the elemental analysis. Yields are given in percentages and measured on isolated products.

Preparation of the substrates.
Acetoxyacetophenones **2a** *and* **2b**. A mixture of 3 g (22.1 mmol) of hydroxyacetophenone and 2.3 g

(22.5 mmol) of acetic anhydride in 15 ml of pyridine was refluxed during 30 min and then poured into 100 ml of ice-water. The resulting solid was filtered in vacuo, dried and used without further purification. The yields were almost quantitative.

General procedure for the preparation of acetals. 3 g (16.9 mmol) of acetoxyacetophenone, with 1.2 g (19.4 mmol) of ethylene glycol and 0.1 g of p-toluenesulphonic acid were heated in 100 ml of benzene using a Dean-Stark system, until no more water was formed. Then, the crude soln was washed with water, dried with K_2CO_3, concentrated in vacuo and purified by column chromatography, using a 3 : 1 mixture of hexane and ether as eluent.

Yields, spectral and analytical data of the acetals

2-(2-acetoxyphenyl)-2-methyl-1,3-dioxolane **3a**. 2.1 g (9.8 mmol, 58 %) with m.p 58-59 °C; analysis : C 64.86 H 6.60 % (Calcd for $C_{12}H_{14}O_4$: C 64.85 H 6.35 %); ir : 1780 (ester); ^{1}H-nmr : δ=7.70-6.71 (m, 4H, aromatic H), 4.01-3.40 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$), 2.22 (s, 3H, $OCOC\underline{H}_3$), 1.63 (s, 3H, $C\underline{H}_3$); uv : 282 (2.9) 274 (3.0). *2-(4-acetoxyphenyl)-2-methyl-1,3-dioxolane* **3b**. 2.5 g (11.3 mmol, 67 %) with m.p 57-58 °C; analysis : C 64.92 H 6.23 % (Calcd for $C_{12}H_{14}O_4$: C 64.85 H 6.35 %); ir : 1775 (ester); ^{1}H-nmr : δ=7.44 (d, 2H, aromatic H at C-2 and C-6, J=9Hz), 6.91 (d, 2H, aromatic H at C-3 and C-5, J=9Hz), 4.06-3.67 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$), 2.27 (s, 3H, $OCOC\underline{H}_3$), 1.69 (s, 3H, $C\underline{H}_3$); uv : 267 (2.9).

Irradiations

General procedure. A soln of 500 mg of the substrate in 300 ml of distilled hexane was placed in an immersion well photoreactor, provided with a quartz sleeve and a 125 W medium pressure Hg lamp , and irradiated for 6 h. The resulting soln was evaporated at reduced pressure and the residue was submitted to column chromatography, using a 3 : 1 mixture of hexane and ether as eluent.

Irradiation of **3a**. Following products were isolated : *o-acetoxyacetophenone* **2a**. (120 mg, 30 %). *2-(3-acetyl-2-hydroxyphenyl)-2-methyl-1,3-dioxolane* **4a**. (30 mg, 10 %). Oil; analysis : C 65.42 H 6.52 % (Calcd for $C_{12}H_{14}O_4$: C 64.85 H 6.35 %); ir 1645 (ketone); ^{1}H-nmr : δ=12.66 (s, 1H, $O\underline{H}$), 7.82-6.54 (m, 3H, aromatic H), 4.16-3.52 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$), 2.54 (s, 3H, $COC\underline{H}_3$), 1.66 (s, 3H, $C\underline{H}_3$); uv 334 (3.5) 259 (3.8) 253 (3.8). *2-(5-acetyl-2-hydroxyphenyl)-2-methyl-1,3-dioxolane* **4b**. (45 mg, 9 %) with m.p 78-80 °C; analysis : C 65.26 H 6.36 % (Calcd for $C_{12}H_{14}O_4$: C 64.85 H 6.35 %); ir : 1690 (ketone); ^{1}H-nmr : δ=8.38 (s, 1H, $O\underline{H}$), 7.79 (broad s, 1H, aromatic H at C-6), 7.69 (d, 1H, aromatic H at C-4, J=8Hz), 6.78 (d, 1H, aromatic H at C-3, J=8Hz), 4.30-3.64 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$), 2.44 (s, 3H, $COC\underline{H}_3$), 1.67 (s, 3H, $C\underline{H}_3$); uv : 264 (3.9). *1,3-diacetyl-2-hydroxybenzene* **5a**. (30 mg , 7 %) with m.p 71-73 °C; analysis : C 67.32 H 5.59 % (Calcd for $C_{10}H_{10}O_3$: C 67.41 H 5.66 %); ir : 1695 and 1655 (C=O); ^{1}H-nmr : δ=13.28 (s, 1H, $O\underline{H}$), 8.03-6.69 (m, 3H, aromatic H), 2.62 (s, 6H, $2COC\underline{H}_3$); uv 340 (3.5). *2,4-diacetyl-1-hydroxybenzene*[18] **5b**. (15 mg, 4 %) with m.p 90-92 °C (lit[18] 86 °C); ir : 1695 and 1655 (C=O); ^{1}H-nmr : δ=12.48 (s, 1H, $O\underline{H}$), 8.24 (d, 1H, aromatic H at C-3, J=2Hz), 7.92 (dd, 1H, aromatic H at C-5), 6.89 (d, 1H, aromatic H at C-6, J.8Hz), 2.67 and 2.48 (s and s, 6H, $2COC\underline{H}_3$).

Irradiation of **3b**. After irradiation were isolated the following products : *p-acetoxyacetophenone* **2b**. (140 mg, 35 %). *2-(3-acetyl-4-hydroxyphenyl)-2-methyl-1,3-dioxolane* **6**. (105 mg, 21 %) with m.p 56-57 °C; analysis : C 65.06 H 6.41 % (Calcd for $C_{12}H_{14}O_4$: C 64.85 H 6.35 %); ir : 1665 (ketone); ^{1}H-nmr : δ=12.02 (s, 1H, $O\underline{H}$), 7.73 (d, 1H, aromatic H at C-2, J=2Hz), 7.48 (dd, 1H, aromatic H at C-6), 6.80 (d, 1H, aromatic H at C-5, J=9Hz), 4.06-3.51 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$), 2.59 (s, 3H, $COC\underline{H}_3$), 1.59 (s, 3H, $C\underline{H}_3$); uv : 330 (3.2) 257 (3.5) 250 (3.6) 242 (3.6). *2.4-diacetyl-1-hydroxybenzene* **5b**. (50 mg, 12 %).

Irradiation of **2a** *and* **2b**. Acetoxyacetophenones **2a** and **2b** were irradiated according to the general procedure. Periodic controls made by ^{1}H-nmr spectroscopy showed no appreciable variation and after 6 h, workup of the irradiated solns led to a complete recovering of the starting acetophenones.

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