PHOTOLYSIS OF CYCLIC ACETALS OF ARYL BENZOYLACETATES AS THE KEY STEP IN A NEW SYNTHESIS OF FLAVONES

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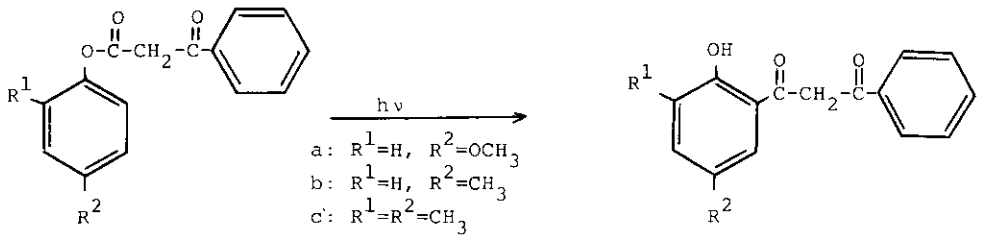
Abstract - Although the yields found for the photo-Fries rearrangement of the aryl benzoylacetates 1 are poor, blocking of the carbonyl group, as in the related acetal derivatives 3, results in a substantial preparative improvement. Thus, the o-hydroxydibenzoylmethanes 2 are obtained from 1 with an average yield of 18%, while the corresponding acetals 4 are obtained from 3 with an average yield of 58%. Compounds 4 are efficiently converted into flavones 8 by means of wet silica gel, through hydrolysis of the acetal moiety and subsequent cyclization of the resulting o-hydroxydibenzoylmethanes 2.

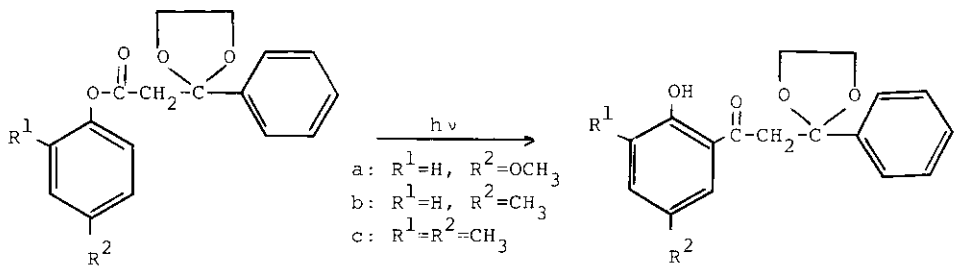
The photo-Fries rearrangement of aryl cinnamates has been explored in the search for new entries to the basic flavone structure.[1-4] The reaction has been found to be of wide applicability, although unfortunately the preparative yields in o-hydroxychalcones are rather unsatisfactory, partially due to the waste of energy through a competing cis-trans photoisomerization of the double bond.

This has prompted related studies dealing with aryl epoxy-, dihydro-, and dibromocinnamates,[5,6] but up to now there has been no report on the photolysis of aryl benzoylacetates such as 1, which could afford the o-hydroxydibenzoylmethanes 2, a type of compound well known as direct flavone precursors and as synthetic intermediates in the classical reactions of Baker-Venkataraman and Allan-Robinson.[7,8]



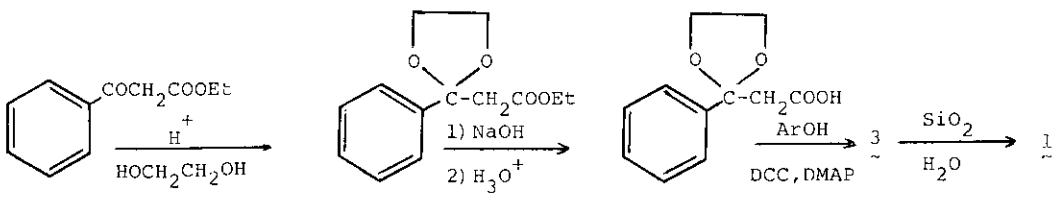
1 2

This prompted us to perform the preparation and photolysis of the ketoesters 1a-c. For comparative purposes, we also decided to carry out the synthesis and irradiation of the related acetal derivatives 3a-c, in order to establish the influence of this carbonyl blocking group on the degree of photorearrangement.[9]



3 4

The aryl benzoylacetates 1a-c were best prepared by selective hydrolysis of their acetals 3a-c with wet silica gel,[10] while the latter compounds were obtained in turn from ethyl benzoylacetate (5),[11] by treatment with ethylene glycol in the presence of catalytic amount of p-toluenesulphonic acid, subsequent saponification of the resulting acetal 6, and final esterification of the acid 7 with the respective phenols by means of N,N´-dicyclohexylcarbodiimide and 4-dimethylaminopyridine.[11]

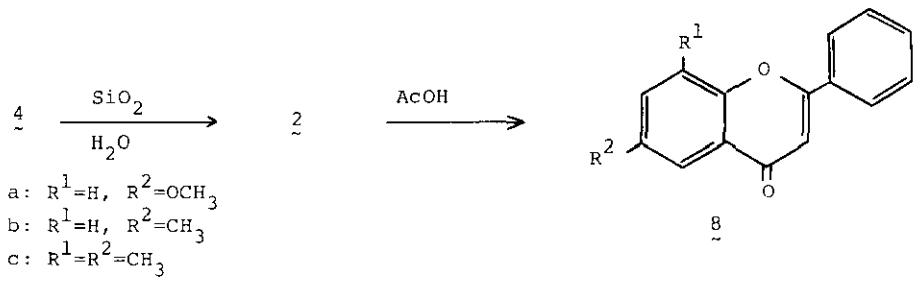


5 6 7

As expected, the irradiation of 1a-c afforded the photo-Fries products 2a-c, although the average yield was only 17%. This value is very close to that found for the photorearrangement of the analogous aryl cinnamates (ca. 18%),[6] what is not surprising if one considers that the esters 1 exist predominantly as the enol tautomers, whose structure can be viewed as that of a 3-hydroxycinnamate. Furthermore, it is well known that enolizable 1,3-dicarbonyl compounds are markedly reluctant to photochemical α-cleavage, due to the existence of an efficient energy wasting channel, provided by the keto-enol interconversion.[13]

By contrast, the acetal derivatives 3a-c gave upon irradiation the corresponding photo-Fries products 4a-c with an average yield of 58%, 3.5 times higher than that found for the photochemical transformation of 1a-c into 2a-c, showing in this way the preparative advantages of blocking the carbonyl group prior to the irradiation.

Finally, the synthesis of the flavones 8a-c from their precursors 4a-c was efficiently accomplished by means of wet silica gel, through one-pot hydrolysis of the acetal moiety accompanied by cyclization of the o-hydroxydibenzoylmethanes 2a-c.



a: R^1=H, R^2=OCH_3
b: R^1=H, R^2=CH_3
c: R^1=R^2=CH_3

Thus, the photo-Fries rearrangement of cyclic acetals of aryl benzoylacetates, followed by treatment of the photoproducts with wet silica gel, constitutes a new and expedient synthesis of flavones.

EXPERIMENTAL

Melting points are uncorrected. Combustion analyses were performed at the Instituto de Química Bio-Orgánica of the CSIC (Barcelona). Ir spectra were determined in CCl_4, with a Perkin-Elmer 781 spectrometer; absorptions ($\bar{\nu}$, cm^{-1}) are given only for the main bands. ^{1}H-nmr spectra were measured with a Varian 360

EM instrument, using CCl_4 as solvent; chemical shifts are reported in ppm downfield (δ) from TMS. The uv spectra were determined in ethanol with a Varian 634 spectrophotometer; absorbed radiation is defined by its wavelength (λ_{max}, nm) and log ε (in brackets).

Preparation of the esters 3

A mixture of ethyl benzoylacetate (5) (10 g), with 5 g of ethylene glycol and 0.5 g of p-toluenesulphonic acid was heated in 100 ml of benzene using a Dean-Stark system, until no more water was formed. Then, the crude solution was washed with water, concentrated in vacuo and submitted to saponification with 50 ml of 10% aqueous NaOH. After heating for 1 h, the mixture was neutralyzed and thoroughly extracted with ethyl ether, giving 3-(ethylenedioxy)-3-phenylpropanoic acid (7), which was recrystallized from CCl_4. To a solution of 7 (1.0 g, 4.8 mmol), the corresponding phenols (4.8 mmol) and catalytic amount of 4-dimethylaminopyridine in $CHCl_3$ was added dropwise an equimolar amount of N,N´-dicyclohexylcarbodiimide (1.0 g) in $CHCl_3$; the mixture was stirred for 15 min at room temperature, then filtered to remove the precipitated N,N´-dicyclohexylurea, concentrated in vacuo and purified by chromatography to give the esters 3.

Preparation of the esters 1

20% aqueous H_2SO_4 (0.2 ml) was added with continuous magnetic stirring to a slurry of silica gel Merck 60, 70-230 mesh (3 g) in $CHCl_3$ (10 ml). After disappearing the aqueous phase, the corresponding ester 3 (1 g) was added and stirring continued for 6 h. Then, the solid phase was filtered and washed with $CHCl_3$. Evaporation of the solvent and chromatographic purification gave the esters 1.

Irradiations

A solution of 500 mg of aryl ester in 450 ml of freshly distilled hexane was irradiated for 6 h at room temperature with a 125 W medium pressure mercury lamp inside a quartz immersion well photoreactor. The photorearranged products were isolated, after removal of the solvent, with silica gel flash-column chromatography using hexane as eluent.

Cyclization of 2 to flavones 8

A solution of the corresponding o-hydroxydibenzoylmethane 2 (250 mg) in glacial acetic acid (15 ml) with catalytic amount of H_2SO_4 was refluxed 30 min and, then, poured into ice-water. The resulting suspension was filtered in vacuo and the solid was washed with water and dried to give the flavones 8 quantitatively.

Cyclization of 4 to flavones 8

Following the procedure described for the preparation of the esters 1, the acetals 4 were converted quantitatively to the corresponding flavones 8.

Products

4-Methoxyphenyl benzoylacetate (1a) (92%), mp 69-70 °C, Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; Found: C, 71.03; H, 5.10 %, ir 1660 1620, ^{1}H-nmr 12.60 (s, 1H, OH), 8.10-7.37 (m, 5H, C_6H_5), 7.35-6.77 (m, 4H, C_6H_4), 5.95 (s, 1H, =CH), 3.85 (s, 3H, OCH_3), uv 286 (4.3).

4-Methylphenyl benzoylacetate (1b) (90%), mp 34-36 °C, Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; Found: C, 75.40; H, 5.53 %, ir 1760 1690 1660 1620, ^{1}H-nmr of the enolic tautomer: 12.50 (s, 1H, OH), 8.20-6.75 (m, 9H, ArH), 5.90 (s, 1H, =CH), 2.32 (s, 3H, CH_3), ^{1}H-nmr of the keto tautomer: 8.20-6.75 (m, 9H, ArH), 4.15 (s, 2H, CH_2), 2.32 (s, 3H, CH_3); from the relative intensities the ratio enol/keto was established as 70/30, uv 290 (4.3).

2,4-Dimethylphenyl benzoylacetate (1c) (87%), oil, Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; Found: C, 75.64; H, 6.44 %, ir 1760 1690 1660 1620, ^{1}H-nmr of the enol tautomer: 12.50 (s, 1H, OH), 8.15-6.72 (m, 8H, ArH), 5.89 (s, 1H, =CH), 2.30 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), ^{1}H-nmr of the keto tautomer: 8.15-6.72 (m, 8H, ArH), 4.03 (s, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.03 (s, 3H, CH_3); from the relative intensities the ratio enol/keto was established as 60/40, uv 290 (4.2).

1-(2-Hydroxy-5-methoxyphenyl)-3-phenyl-1,3-propanedione (2a)[14](20%), mp 70-71 °C, ir 1600, ^{1}H-nmr 15.62 (s, 1H, OH), 11.32 (s, 1H, OH), 8.20-6.60 (m, 8H, ArH), 6.75 (s, 1H, =CH), 3.75 (s, 3H, OCH_3).

1-(2-Hydroxy-5-methylphenyl)-3-phenyl-1,3-propanedione (2b)[15] (17%), mp 88-89 °C, ir 1610, ^{1}H-nmr 15.60 (s, 1H, OH), 11.68 (s, 1H, OH), 8.30-6.85 (m, 8H, ArH), 6.70 (s, 1H, =CH), 2.30 (s, 3H, CH_3).

1-(2-Hydroxy-3,5-dimethylphenyl)-3-phenyl-1,3-propanedione (2c)[15] (13%), mp 80-81

°C, ir 1610, H-nmr 15.64 (s, 1H, OH), 12.18 (s, 1H, OH), 8.27-6.97 (m, 7H, ArH), 6.78 (s, 1H, =CH), 2.30 (s, 3H, CH_3), 2.25 (s, 3H, CH_3).

4-Methoxyphenyl 3-(ethylenedioxy)-3-phenylpropanoate (3a) (70%), mp 72-73 °C, Anal. Calc. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77; Found: C, 68.68; H, 6.05%, ir 1760, ^{1}H-nmr 7.70-7.19 (m, 5H, C_6H_5), 6.80 (s, 4H, C_6H_4), 4.32-3.78 (m, 4H, OCH_2CH_2O), 3.75 (s, 3H, OCH_3), 3.05 (s, 2H, CH_2), uv 277 (3.3).

4-Methylphenyl 3-(ethylenedioxy)-3-phenylpropanoate (3b) (68%), mp 105-106 °C, Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08; Found: C, 72.53; H, 6.18 %, ir 1760, ^{1}H-nmr 7.70-6.60 (m, 9H, ArH), 4.35-3.75 (m, 4H, OCH_2CH_2O), 3.02 (s, 2H, CH_2), 2.34 (s, 3H, CH_3), uv 265 (3.2).

2,4-Dimethylphenyl 3-(ethylenedioxy)-3-phenylpropanoate (3c) (57%), mp 63-64 °C, Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; Found: C, 73.08; H, 6.38 %, ir 1760, ^{1}H-nmr 7.80-7.10 (m, 5H, C_6H_5), 7.05-6.50 (m, 3H, C_6H_3), 4.23-3.50 (m, 4H, OCH_2CH_2O), 3.10 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), uv 274 (3.0).

3-(Ethylenedioxy)-1-(2-hydroxy-5-methoxyphenyl)-3-phenyl-1-propanone (4a) (65%), mp 92-93 °C, Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77; Found: C, 68.83; H, 5.81 %, ir 1640, ^{1}H-nmr 11.70 (s, 1H, OH), 7.65-6.60 (m, 8H, ArH), 4.20-3.80 (m, 4H, OCH_2CH_2O), 3.75 (s, 3H, OCH_3), 3.45 (s, 2H, CH_2), uv 365 (3.7).

3-(Ethylenedioxy)-1-(2-hydroxy-5-methylphenyl)-3-phenyl-1-propanone (4b) (64%), mp 56-57 °C, Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08: Found: C, 72.49; H, 5.94 %, ir 1635, ^{1}H-nmr 11.90 (s, 1H, OH), 7.69-6.60 (m, 8H, ArH), 4.01-3.62 (m, 4H, OCH_2CH_2O), 3.45 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), uv 346 (3.8).

3-(Ethylenedioxy)-1-(2-hydroxy-3,5-dimethylphenyl)-3-phenyl-1-propanone (4c) (46%), mp 84-85 °C, Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; Found 72.82; H, 6.76 %, ir 1630, ^{1}H-nmr 12.40 (s, 1H, OH), 7.69-6.92 (m, 7H, ArH), 4.21-3.62 (m, 4H, OCH_2CH_2O), 3.43 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), uv 349 (3.5).

3-(Ethylenedioxy)-3-phenylpropanoic acid (7) (38%), mp 90-92 °C, Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; Found: C, 63.67; H, 5.84 %, ir 1715, ^{1}H-nmr 7.78-7.10 (m, 5H, ArH), 4.35-3.60 (m, 4H, OCH_2CH_2O), 2.95 (s, 2H, CH_2), uv 246 (2.6).

6-Methoxyflavone (8a)[16], mp 150-153 °C (lit. 152-154 °C),ir 1640, ^{1}H-nmr 8.10-7.28 (m, 8H, ArH), 6.77 (s, 1H, H at C-3), 3.92 (s, 3H, OCH_3).

6-Methylflavone (8b)[17], mp 118-120 °C (lit. 118-120 °C), ir 1650, ^{1}H-nmr

8.20-7.25 (m, 8H, ArH), 6.70 (s, 1H, H at C-3), 2.45 (s, 3H, CH_3).

6,8-Dimethylflavone (8c)[18], mp 163-164 °C, ir 1650, ^{1}H-nmr 8.50-7.24 (m, 7H, ArH), 6.70 (s, 1H, H at C-3), 2.55 (s, 3H, CH_3), 2.40 (s, 3H, CH_3).

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