

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

Hermenegildo García,^a Sara Iborra,^a Miguel A. Miranda,^{b*} and
Jaime Primo^a

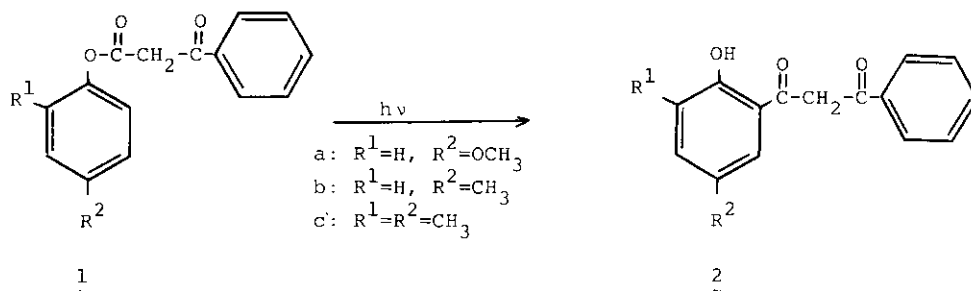
^a Dep. Química, ETSII, Universidad Politécnica, Apartado 22012,
46071-Valencia, Spain

^b Dep. Química Orgánica, Facultad Farmacia, 46010-Valencia, Spain

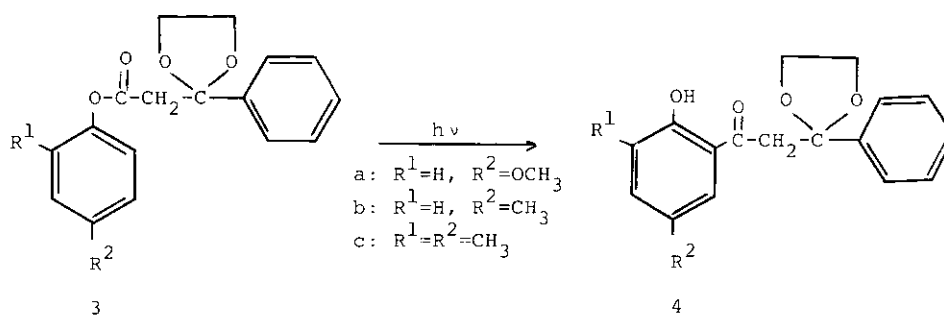
Abstract - Although the yields found for the photo-Fries rearrangement of the aryl benzoylacetates 1 are poor, blocking of the carbonyl group, as in the related acetal derivatives 3, results in a substantial preparative improvement. Thus, the o-hydroxydibenzoylmethanes 2 are obtained from 1 with an average 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.

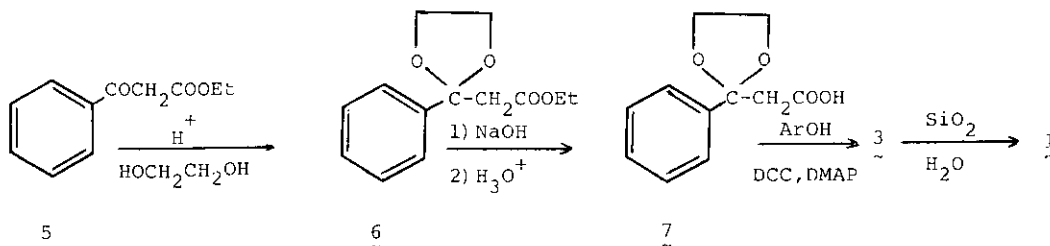
This has prompted related studies dealing with aryl epoxy-, dihydro-, and dibromocinnamates,^{5,6} but up to now there has been no report on the photolysis of aryl benzoylacetates such as 1, which could afford the o-hydroxydibenzoylmethanes 2, a type of compound well known as direct flavone precursors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



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



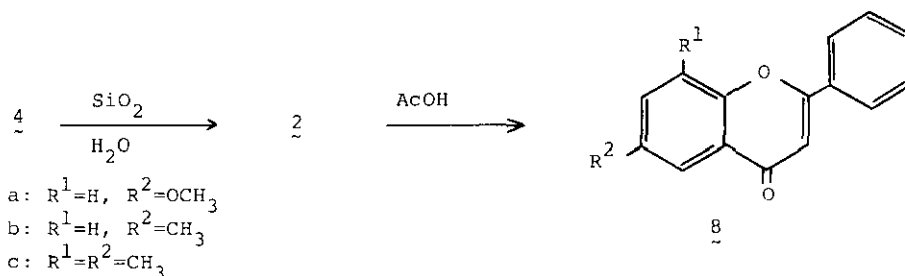
The aryl benzoylacetates 1a-c were best prepared by selective hydrolysis of their acetals 3a-c with wet silica gel,¹⁰ while the latter compounds were obtained in turn from ethyl benzoylacetate (5),¹¹ by treatment with ethylene glycol in the presence of catalytic amount of *p*-toluenesulphonic acid, subsequent 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



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.



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. ^1H -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 $\log \epsilon$ (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 neutralized 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, 1H -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, 1H -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), 1H -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, 1H -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), 1H -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, 1H -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, 1H -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, ^1H -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, CH₃), 2.25 (s, 3H, CH₃).

4-Methoxyphenyl 3-(ethylenedioxy)-3-phenylpropanoate (3a) (70%), mp 72-73 °C, Anal. Calcd. for C₁₈H₁₈O₅: C, 68.78; H, 5.77; Found: C, 68.68; H, 6.05%, ir 1760, ^1H -nmr 7.70-7.19 (m, 5H, C₆H₅), 6.80 (s, 4H, C₆H₄), 4.32-3.78 (m, 4H, OCH₂CH₂O), 3.75 (s, 3H, OCH₃), 3.05 (s, 2H, CH₂), uv 277 (3.3).

4-Methylphenyl 3-(ethylenedioxy)-3-phenylpropanoate (3b) (68%), mp 105-106 °C, Anal. Calcd. for C₁₈H₁₈O₄: C, 72.46; H, 6.08; Found: C, 72.53; H, 6.18 %, ir 1760, ^1H -nmr 7.70-6.60 (m, 9H, ArH), 4.35-3.75 (m, 4H, OCH₂CH₂O), 3.02 (s, 2H, CH₂), 2.34 (s, 3H, CH₃), uv 265 (3.2).

2,4-Dimethylphenyl 3-(ethylenedioxy)-3-phenylpropanoate (3c) (57%), mp 63-64 °C, Anal. Calcd. for C₁₉H₂₀O₄: C, 73.06; H, 6.45; Found: C, 73.08; H, 6.38 %, ir 1760, ^1H -nmr 7.80-7.10 (m, 5H, C₆H₅), 7.05-6.50 (m, 3H, C₆H₃), 4.23-3.50 (m, 4H, OCH₂CH₂O), 3.10 (s, 2H, CH₂), 2.25 (s, 3H, CH₃), 2.00 (s, 3H, CH₃), uv 274 (3.0).

3-(Ethylenedioxy)-1-(2-hydroxy-5-methoxyphenyl)-3-phenyl-1-propanone (4a) (65%), mp 92-93 °C, Anal. Calcd. for C₁₈H₁₈O₅: C, 68.78; H, 5.77; Found: C, 68.83; H, 5.81 %, ir 1640, ^1H -nmr 11.70 (s, 1H, OH), 7.65-6.60 (m, 8H, ArH), 4.20-3.80 (m, 4H, OCH₂CH₂O), 3.75 (s, 3H, OCH₃), 3.45 (s, 2H, CH₂), uv 365 (3.7).

3-(Ethylenedioxy)-1-(2-hydroxy-5-methylphenyl)-3-phenyl-1-propanone (4b) (64%), mp 56-57 °C, Anal. Calcd. for C₁₈H₁₈O₄: C, 72.46; H, 6.08; Found: C, 72.49; H, 5.94 %, ir 1635, ^1H -nmr 11.90 (s, 1H, OH), 7.69-6.60 (m, 8H, ArH), 4.01-3.62 (m, 4H, OCH₂CH₂O), 3.45 (s, 2H, CH₂), 2.29 (s, 3H, CH₃), 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 C₁₉H₂₀O₄: C, 73.06; H, 6.45; Found: C, 72.82; H, 6.76 %, ir 1630, ^1H -nmr 12.40 (s, 1H, OH), 7.69-6.92 (m, 7H, ArH), 4.21-3.62 (m, 4H, OCH₂CH₂O), 3.43 (s, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.15 (s, 3H, CH₃), uv 349 (3.5).

3-(Ethylenedioxy)-3-phenylpropanoic acid (7) (38%), mp 90-92 °C, Anal. Calcd. for C₁₁H₁₂O₄: C, 63.45; H, 5.81; Found: C, 63.67; H, 5.84 %, ir 1715, ^1H -nmr 7.78-7.10 (m, 5H, ArH), 4.35-3.60 (m, 4H, OCH₂CH₂O), 2.95 (s, 2H, CH₂), uv 246 (2.6).

6-Methoxyflavone (8a)¹⁶, mp 150-153 °C (lit. 152-154 °C), ir 1640, ^1H -nmr 8.10-7.28 (m, 8H, ArH), 6.77 (s, 1H, H at C-3), 3.92 (s, 3H, OCH₃).

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

8.20-7.25 (m, 8H, ArH), 6.70 (s, 1H, H at C-3), 2.45 (s, 3H, CH₃).
6,8-Dimethylflavone (8c)¹⁸, mp 163-164 °C, ir 1650, ¹H-nmr 8.50-7.24 (m, 7H, ArH),
 6.70 (s, 1H, H at C-3), 2.55 (s, 3H, CH₃), 2.40 (s, 3H, CH₃).

ACKNOWLEDGEMENTS

We wish to thank the CAICYT for financial support (project 1303/83) and for a postgraduate fellowship to S.I.

REFERENCES

1. V.T. Ramakrishnan and J. Kagan, J. Org. Chem., 1970, 35, 2901.
2. H. Obara and H. Takahashi, Bull. Chem. Soc. Japan, 1967, 40, 1012.
3. H. Obara, H. Takahashi and H. Hirano, Bull. Chem. Soc. Japan, 1969, 42, 560.
4. J. Onodera and H. Obara, Bull. Chem. Soc. Japan, 1974, 47, 240.
5. V.T. Ramakrishnan and J. Kagan, J. Org. Chem., 1970, 35, 2898.
6. H. García, S. Iborra, M.A. Miranda and J. Primo, Heterocycles, 1985, 23, 1983.
7. G.P. Ellis in: 'Chromenes, Chromanones and Chromones', G.P. Ellis Ed., Wiley-Interscience, New York, 1977, p. 495.
8. H. Wagner and L. Farkas in: 'The Flavonoids', J.B. Harborne Ed., Academic Press, New York, 1975, p. 138.
9. H. García, R. Martínez-Utrilla and M.A. Miranda, Tetrahedron, 1985, 41, 3131.
10. F. Huet, A. Lechevalier, M. Pellet and J.M. Conia, Synthesis, 1978, 63.
11. J.M. Straley and A.C. Adams, 'Org. Synth.', Coll. Vol. IV, 1963, p. 415.
12. E. Haslam, Tetrahedron, 1980, 36, 2409.
13. P. Markov, Chem. Soc. Rev., 1984, 13, 69.
14. C.J.P. Becket and G.P. Ellis, J. Chem. Research., 1978, 47.
15. S.V. Kulkarni and K.A. Thakar, J. Indian Chem. Soc., 1976, 53, 283.
16. R.S. Varma and M. Varma, Synth. Commun., 1982, 12, 927.
17. P.K. Jain, J.K. Makrandi and S.K. Grover, Synthesis, 1982, 221.
18. H. García, S. Iborra, M.A. Miranda and J. Primo, J. Org. Chem. in press.

Received, 4th April, 1986