STUDIES ON THE SYNTHESIS OF PRECOCENES. THE PHOTO-FRIES REARRANGEMENT OF ESTERS OF α, β-UNSATURATED CARBOXYLIC ACIDS AND META-OXYGENATED PHENOLS

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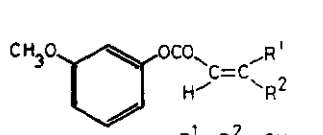
Abstract - The photo-Fries rearrangement of a series of aryl esters of α β-unsaturated carboxylic acids 1a,b and 2 has been investigated, in order to explore the possibilities of this reaction as a key step in the synthesis of precocenes and related compounds. In all cases, the photolysis in hexane does not lead to any observable transformation, but in the presence of potassium carbonate takes place a migration of the acyl group to the two ortho-positions. Additionally, trans-cis photoisomerization occurs with the trans-butenoate 1b. The resulting o-hydroxyketones 4a, 4b, 4c, 5a, 5b, 5c, and 8 are easily and efficiently cyclized to the corresponding 4-chromanones 6a, 6b, 7a, 7b, and 9. A second photo-rearrangement is observed in the case of 9, although the yield is low, due to deactivation by the carbonyl group. Cyclization of 10 gives rise to the tricyclic dichromanone 11. Compounds 6a and 11 are reduced and subsequently dehydrated by known procedures to afford the active chromenes 3 and 12.

In a previous communication[1] we have shown that the photo-Fries rearrangement of phenyl esters of α, β-unsaturated carboxylic acids, combined with basic cyclization, may afford a new entry to 4-chromanones and, after reduction and dehydration, to the corresponding 2H-chromenes. For the sake of simplicity this model study was carried out with esters of p-methoxyphenol, where the para-position was blocked and, therefore, inaccessible to acylation. Now we wish to report on an analogous study on the m-methoxyphenyl esters 1a,b and the resorcine diester 2, whose substitution pattern is interesting in connection with the biological activity, since the expected products could be easily converted into the precocene I (3), which is a well established juvenile hormone inhibitor.[2]



a $R^1 = R^2 = CH_3$
b $R^1 = H$, $R^2 = CH_3$
c $R^1 = CH_3$, $R^2 = H$

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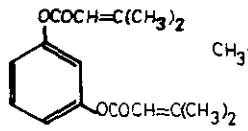

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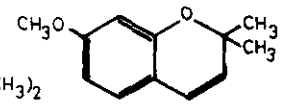

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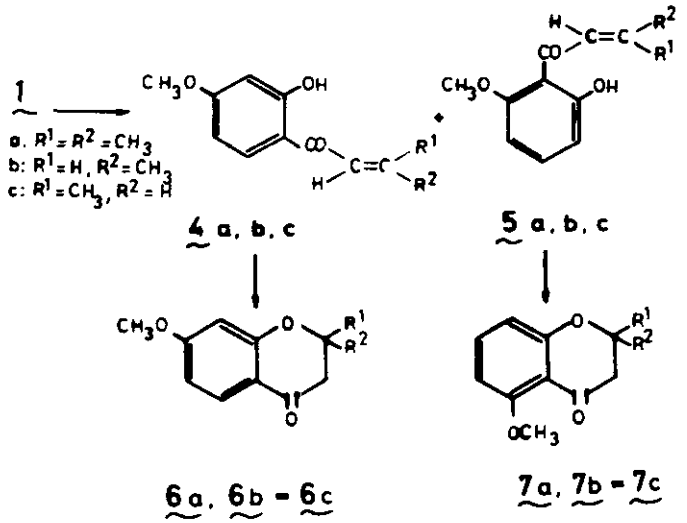
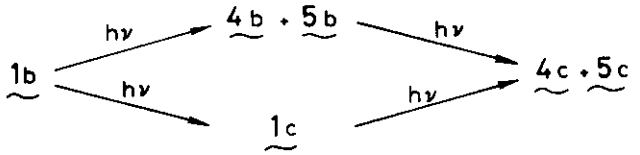
The irradiation of 1a through quartz in hexane with a medium pressure mercury lamp did not produce any observable transformation, even after 20 h.[3] By contrast, when potassium carbonate was added[4] a mixture of the two possible rearrangement products 4a and 5a (ratio 3.5 : 1) was obtained, being the conversion 80% and the product balance 45%. This constitutes a further example of the applicability of this modification of the photo-Fries rearrangement.[4,5] After chromatographie separation (HPLC), the o-hydroxyketones 4a and 5a were cyclized to the chromanones 6a and 7a by means of a two phase system hexane/10% aqueous sodium hydroxide with nearly quantitative yields. Reduction of 6a by means of lithium aluminium hydride, followed by dehydration with hydrochloric acid, afforded as expected the precocene I (3) with 75% yield.

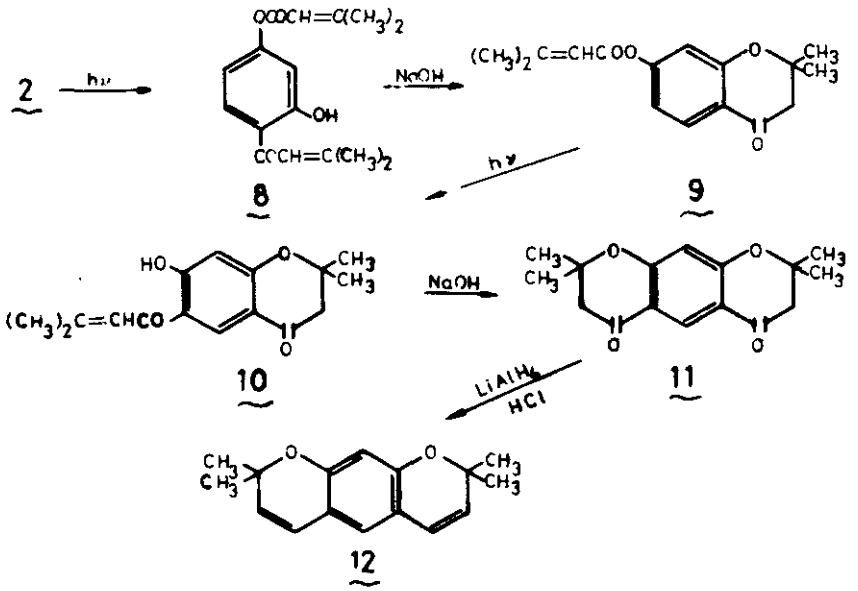


Likewise, irradiation of trans-m-methoxyphenyl crotonate 1b in the presence of potassium carbonate resulted in a photochemical acylation of the same ring positions, although in this case the photomixture was more complex, due to an accompanying trans-cis photoisomerization. Thus, the products isolated after separation by HPLC were 4b (18%), 4c (6%), 5b (4%) and 5c (7%). Besides, unreacted starting material 1b (29%) and a small amount of the cis-crotonate 1c (2%) were also isolated. In principle, two alternative reaction pathways could account for the formation of the cis-ketones 4c and 5c as minor products: i) trans-cis photoisomerization of 1b, followed by photo-Fries rearrangement of the cis-isomer 1c or ii) a combination of the same individual processes, but in the inverse sequence, i.e.,photo-rearrangement to 4b and 5b, followed by trans-cis photoisomerization of these compounds. In this context, the isolation of the cis-ester 1c constitutes a clear evidence in favour of the first reaction pathway, although the second one cannot be ruled out on this basis, and we feel that both mechanisms could be actually operating.



The cyclization of the isolated o-hydroxyketones 4b, 4c, 5b and 5c was efficiently accomplished by the same reaction system used in the case of 4a and 5a, affording the chromanones 6b and 7b.

Finally, we tried the photolysis of the resorcine diester 2. As in the previous cases, no transformation was observed when a solution of the substrate in hexane was irradiated during 20 h. However, when potassium carbonate was added a clear rearrangement to the photo-Fries product 8 (isolated yield 20%) was observed, being also recovered a part of the starting material 2 (32%). The corresponding chromanone 9, obtained by cyclization in the usual way, was also submitted to irradiation, in order to know the relative ease of the second acyl group migration.



In fact, the photolysis of 9 in the presence of potassium carbonate led to the expected product 10, although the preparative yield was only 9%, presumably due to the deactivating efect of the ketone carbonyl group.[7] Reduction and subsequent dehydration of the dichromanone 11 by standard methods led to the dichromene 12, which has shown some activity in the precocious metamorphosis test on insects.[6]

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 ($\tilde{\nu}$, 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.

Preparation of the Esters 1a and 1b

Acid chloride (0.1 mol) was added to a solution of m-methoxyphenol (12.4 g, 0.1 mol) in 50 ml of benzene in the presence of Mg. The reaction mixture was refluxed for 11 h, filtered, washed with 5% NaOH, then with water and dried (Na_2SO_4). Evaporation of the solvent yielded the esters in pure form.

Preparation of the Ester 2

To a solution of resorcine (9 g, 0.081 mol) in pyridine (10 ml) was added 3-methyl-2-butenoyl chloride (19.4 g, 0.163 mol). The reaction mixture was refluxed for 3 h. The cooled solution was then poured into a mixture of concentrated hydrochloric acid (30 ml) and ice (100 g), and then extracted with ethyl acetate. The extracts were washed with aqueous sodium hydroxide (10%), dried and evaporated.

Irradiations

A solution of the ester (500 mg) in hexane (400 ml) with or without anhydrous potassium carbonate (2 g) was irradiated for 20 h with magnetic stirring, using a 125 W medium pressure mercury lamp inside a quartz immersion well. After irradiation the potassium carbonate was filtered off and washed thoroughly with chloroform. The organic solutions were

combined and concentrated in vacuo to give an oil. The photoproducts were *isolated with silica gel* flash-column chromatography using hexane as eluent and subsequently by HPLC.

Cyclization to Chromanones

A solution of the o-hydroxyaryl ketone (200 mg) in hexane (100 ml) together with aqueous sodium hydroxide (10%, 25 ml) was stirred at room temperature for 4 h. The organic layer was washed with water, dried and evaporated to give the pure chromanone. Yields were nearly quantitative in all cases.

Reduction/Dehydration of Chromanones to Chromenes

To a solution containing 500 mg (0.013 mol) of lithium aluminium hydride in 25 ml of ether was added dropwise with stirring a solution containing the corresponding chromanone (6a : 2.06 g, 0.01 mol; 11 : 1.37 g, 0.005 mol) in 30 ml of ether. The resulting mixture was heated to reflux for 1 h and then filtered. To the resulting filtrate was added acetone (20 ml) to decompose the excess lithium aluminium hydride, and then 6M hydrochloric acid (10 ml). After boiling the mixture during 10 min, 50 ml of water were added and the solvent was evaporated. The remaining aqueous phase was extracted with methylene chloride. The organic extract was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on a short silica gel column using methylene chloride as eluent.

Products

m-Methoxyphenyl 3-Methyl-2-butenoate (1a)[3] (85%), oil, ir 1740, ^{1}H-nmr 7.15 (d, J = 8 Hz, 1H, 6-ArH), 6.86 - 6.53 (m, 3H, ArH), 5.90 (s, 1H, HC=), 3.73 (s, 3H, OCH_3), 2.20 (s, 3H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$), 1.93 (s, 3H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$).

trans-m-Methoxyphenyl 2-Butenoate (1b)[8] (75%), oil, ir 1740, ^{1}H-nmr 7.50 - 6.93 (m, 5H, ArH, $=CHCH_3$), 6.00 (d, J = 14 Hz, 1H, COCH=), 3.76 (s, 3H, OCH_3), 1.93 (d, J = 6Hz, 3H, CH_3).

cis-m-Methoxyphenyl 2-Butenoate (1c) (2%), oil, Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; Found: C, 69.02; H, 6.21%, ir 1735, ^{1}H-nmr 7.20 (d, J = 6Hz, 1H, 6-ArH), 7.00 - 6.30 (m, 4H, ArH, $=CHCH_3$), 5.96 (d, J = 10Hz, 1H, COCH=), 3.80 (s, 3H, OCH_3), 2.20 (d, J = 7Hz, 3H, CH_3).

Resorcine Di(3-methyl)-2-butenoate (2) (60%), oil, Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; Found: C, 69.66; H, 6.82%, ir 1735, ^{1}H-nmr 7.50 - 6.80 (m, 4H, 4ArH), 5.85 (br s, 2H, COCH=), 2.20 (s, 6H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$), 1.97 (s, 6H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$).

1-(2-Hydroxy-4-methoxyphenyl)-3-methyl-2-buten-1-one (4a)[9] (28%), mp 48°C (lit. oil), ir 1635, ^{1}H-nmr 13.05 (s, 1H, OH), 7.70 (d, J = 10Hz, 1H, 6-ArH), 6.70 (s, 1H, COCH=), 6.43 (m, 2H, 3,5-Ar-H), 3.85 (s, 3H, OCH_3), 2.20 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$), 2.03 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$).

trans-1-(2-Hydroxy-4-methoxyphenyl)-2-buten-1-one (4b)[10] (18%), mp 90°C (lit. 89°C), ir 1650, ^{1}H-nmr 13.26 (s, 1H, OH), 7.70 (d, J = 10Hz, 1H, 6-ArH), 7.25 - 6.95 (m, 2H, CH=CH), 6.40 (m, 2H, 3,5-ArH), 3.83 (s, 3H, OCH_3), 1.97 (d, J = 6Hz, 3H, CH_3).

cis-1-(2-Hydroxy-4-methoxyphenyl)-2-buten-1-one (4c) (6%), mp 82-83°C, Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; Found: C, 68.63; H, 6.59%, ir 1630, ^{1}H-nmr 13.20 (s, 1H, OH), 7.60 (d, J = 10Hz, 1H, 6-ArH), 6.76 (d, J = 10Hz, 1H, COCH=), 6.00 - 6.50 (m, 3H, 3,5-ArH, $=CHCH_3$), 3.80 (s, 3H, OCH_3), 2.05 (d, J = 5Hz, 3H, CH_3).

1-(2-Hydroxy-6-methoxyphenyl)-3-methyl-2-buten-1-one (5a) (8%), oil, Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; Found: C, 69.93; H, 6.86%, ir 1630, ^{1}H-nmr 12.70 (s, 1H, OH), 7.30 (t, 1H, 4-ArH), 6.87 (s, 1H, COCH=), 6.63-6.30 (m, 2H, 3,5-ArH), 3.90 (s, 3H, OCH_3), 2.20 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$), 2.00 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$).

trans-1-(2-Hydroxy-6-methoxyphenyl)-2-buten-1-one (5b) (4%), oil, Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; Found: C, 69.00, H, 6.12%, ir 1640, ^{1}H-nmr 13.20 (s, 1H, OH), 7.60 - 6.40 (m, 5H, ArH, CH=CH), 3.95 (s, 3H, OCH_3), 2.03 (d, J = 4Hz, 3H, CH_3).

cis-1-(2-Hydroxy-6-methoxyphenyl)-2-buten-1-one (5c) (7%), oil, Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; Found: C, 68.82; H, 6.38%; ir 1640, ^{1}H-nmr 13.03 (s, 1H, OH), 7.50 - 7.30 (m, 1H, 4-ArH), 7,00 (d, J = 10Hz, 1H, COCH=), 6.70 - 6.10 (m, 3H, 4,6-ArH, $=CHCH_3$), 3.90 (s, 3H, OCH_3), 2.15 (d, J = 6 Hz, 3H, CH_3).

7-Methoxy-2,2-dimethyl-4-chromanone (6a)[11] (98%), mp 81°C (lit. 81°C), ir 1680, ^{1}H-nmr 7.86 (d, J = 8Hz, 1H, 5-ArH), 6.60 (m, 2H, 6,8-ArH), 3.85 (s, 3H, OCH_3), 2.70 (s, 2H, CH_2), 1.45 (s, 6H, CH_3).

7-Methoxy-2-methyl-4-chromanone (6b)[10] (96%), mp 77°C (lit. 77°C), ir 1685, ^{1}H-nmr 7.80 (d, J = 8Hz, 1H, 5-ArH), 6.60 - 6.30 (m, 2H, 6,8-ArH), 4.50 (m, 1H, $CHCH_3$), 3.83 (s, 3H, OCH_3), 2.60 (d, J = 8Hz, 2H, CH_2), 1.45 (d, J = 6Hz, 3H, CH_3).

5-Methoxy-2,2-dimethyl-4-chromanone (7a)[12] (98%), mp 120°C (lit. 123.5-124°C), ir 1685, ^{1}H-nmr 7.30 (t, J = 8Hz, 1H, 7-ArH), 6.76 (m, 2H, 6,8-ArH), 3.90 (s, 3H, OCH_3), 2.70 (s, 2H, CH_2), 1.43 (s, 6H, CH_3).

5-Methoxy-2-methyl-4-chromanone (7b) (95%), mp 92-93°C, Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; Found: C, 69.03; H, 6.50%, ir 1690, ^{1}H-nmr 7.33 (t, J = 8Hz, 1H, 7-ArH), 6.35 (m, 2H, 6,8-ArH), 4.50 (m, 1H, $CHCH_3$), 3.80 (s, 3H, OCH_3), 2.47 (d, J = 7Hz, 2H, CH_2), 1.40 (d, J = 6Hz, 3H, CH_3).

1-[2-Hydroxy-4-(3-methyl-2-butenoyloxy)phenyl]-3-methyl-2-buten-1-one (8) (20%) mp 47-48°C. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; Found: C, 69.64; H, 6.86%, ir 1735, 1635, ^{1}H-nmr: 12.87 (s, 1H, OH), 7.67 (d, J = 8Hz, 1H, 6-ArH), 6.66 (m, 3H, 3,5-ArH, COCH=), 5.80 (br s, 1H, OCOCH=), 2.15 (s, 6H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$), 1.93 (s, 6H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$).

7-(3-Methyl-2-butenoyloxy)-2,2-dimethyl-4-chromanone (9) (97%), mp 94-95°C, Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; Found: C, 70.51; H, 6.90%, ir 1735, 1685, ^{1}H-nmr 7.90 (d, J = 8Hz, 1H, 5-ArH), 6.76 (m, 2H, 6,8-ArH), 5.93 (s, 1H, CH=), 2.73 (s, 2H, CH_2), 2.27 (s, 3H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$), 2.03 (s, 3H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$), 1.43 (s, 6H, CH_3).

7-Hydroxy-6-(3-methyl-2-butenoyl)-2,2-dimethyl-4-chromanone (10) (9%), mp 88-89°C, Anal Calcd. for $C_{16}H_{18}O_4$: C, 70.05, H, 6.61; Found: C, 69.80; H, 6.53%, ir 1690, 1620, ^{1}H-nmr 13.50 (s, 1H, OH), 8.46 (s, 1H, 5-ArH) 6.80 (br s, 1H, COCH=), 6.40 (s, 1H, 8-ArH), 2.70 (s, 2H, CH_2), 2.20 (s, 3H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$) 2.06 (s, 3H, $H\diagup C = C\diagdown^{CH_3}_{CH_3}$), 1.43 (s, 6H, CH_3).

2,2,8,8-Tetramethyl-2,3,7,8-tetrahydro-4H,6H-benzo[1,2-b:5,4-b']dipyrane-4,6-dione (11) (99%), mp 179-180°C, Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; Found: C, 70.09; H, 6.86%, ir 1690, ^{1}H-nmr 8.33 (s, 1H, 5-ArH) 6.30 (s, 1H, 10-ArH), 2.60 (s, 4H, CH_2) 1.45 (s, 12H, CH_3).

2,2,8,8-Tetramethyl-2H,8H-benzo[1,2-b: 5,4-b']dipyran (12)(70%), mp 77-79°C, ir 1620, ^{1}H-nmr 6.50 (s, 1H, 10-ArH), 6.15 and 5.36 (AB, J = 10Hz, 4H, CH = CH), 6.16 (s, 1H, 5-ArH), 1.40 (s, 12H, CH_3).

7-Methoxy-2,2-dimethylchromene (3)[11] (75%), oil, ir 1600, ^{1}H-nmr, 6.80 (d, J = 8Hz, 1H, 6-ArH), 6.30 (m, 2H, 5,8-ArH), 6.20 and 5.40(AB, J = 10Hz, 2H, CH = CH), 3.70 (s, 3H, OCH_3) 1.40 (s, 6H, CH_3).

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Received, June 25, 1987