APPLICATION OF THE PHOTO-FRIES REARRANGEMENT OF ARYL DIHYDROCINNAMATES TO THE SYNTHESIS OF FLAVONOIDS

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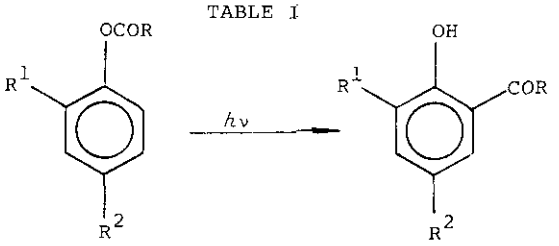
Abstract - The photo-Fries rearrangement of aryl dihydrocinnamates is compared with that of the analogous cinnamates from a preparative point of view. The former proceeds with higher conversions, giving the corresponding 2´-hydroxydihydrochalcones in acceptable yields. This process, combined with well established reactions, provides an alternative entry to the synthesis of flavonoids.

The flavonoids are widely occurring natural polyphenolic compounds, [1,2] whose biosynthesis, although not completely established, is accepted to involve the intermediacy of 2´-hydroxychalcones and the isomeric flavanones. [2]
Much effort has been devoted to the synthesis of the basic flavonoid skeleton. [1]
A priori, one of the most attracting approaches would consist in the Lewis acid--catalyzed acylation of phenols or their alkyl ethers with cinnamoyl chlorides, due to its resemblance to the biosynthetic route. However, the yields obtained in this way are usually low (less than 20%) and, very often, the strongly acidic conditions give rise to the formation of undesired by-products. [3]
In principle, the above difficulties could be avoided by making use of the equivalent photochemical Fries rearrangement of phenyl cinnamates. Some interesting contributions concerning this reaction have been already published, [4-7] mainly by Obara an his group; however, as an important limitation, the preparative yields in 2´-hydroxychalcones are within the range 5-31% (average value: 15%) and considerable amounts of the starting esters are recovered.
The apparent poor conversions achieved by this method could be partially attributed to a competing cis-trans photoisomerization of the double bond. [8] On

the basis of this hypothesis, and as a continuation of our previous work on the photochemical synthesis of chromanones and related oxygen heterocycles, [9] we have tried to establish a comparison between the photochemical behavior of some phenyl cinnamates (1a-c) and that of their saturated analogues (1d-g), where the cis--trans photoisomerization is not possible.

The results obtained from these studies are summarized in the following table :

TABLE I



(1) (2)

R	R^1	R^2	Substrate	Product	Yield %
CH=CH-Ph	H	OCH_3	(1a)	(2a)	20
CH=CH-Ph	H	CH_3	(1b)	(2b)	19
CH=CH-Ph	CH_3	CH_3	(1c)	(2c)	15
CH_2CH_2-Ph	H	OCH_3	(1d)	(2d)	54
CH_2CH_2-Ph	H	CH_3	(1e)	(2e)	50
CH_2CH_2-Ph	CH_3	CH_3	(1f)	(2f)	50
CHBrCHBr-Ph	H	OCH_3	(1g)	(2a)	22

It becomes evident that the presence of a conjugated double bond in the acyl group R (and, therefore, the possibility of undergoing cis-trans isomerization) has an important influence on the degree of photorearrangement. Thus, the average yield of chalcones from cinnamates is 18%, being increased to a 48% in the case of the corresponding dihydro compounds. Furthermore, the recovered cinnamates (approximately 50% of the starting amount) are mixtures of the trans-cis isomers in the ratio 36/62, as shown by the ^{1}H-nmr analysis of the acids obtained by saponification. It is particularly worth mentioning the fact that the cinnamate (1a) and its dibromo derivative (1g) give rise to the same photoproduct (2a) with similar yields. This can be justified by admitting the occurrence of a photochemical debromination of (1g) before the photorearrangement, for which there are some reasonably related precedents in the literature. [10,11]

In connection with the above observations, and specially with the differences due

to the involvement of competitive photochemical processes such as cis-trans isomerization and debromination, it can be interesting to establish comparisons at less advanced stages of the reaction. For this purpose, we have included in the table II data concerning the situation after 1 h and also those corresponding to the end of the irradiation, taking as substrates the different esters derived from 4-methoxyphenol (1a, 1d and 1g).

TABLE II

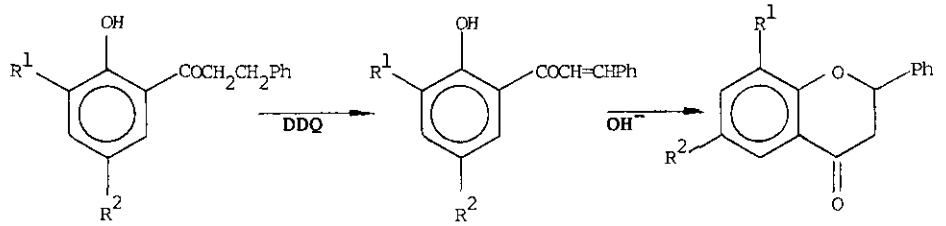
Substrate	Product	Yield 1 h [a]	Yield 8 h [b]
(1a)	(2a)	1	1.5
(1d)	(2d)	3.8	4.0
(1g)	(2a)	0.2	1.8

[a] Measured by uv, at λ=380 nm, taking as unity the yield in chalcone (2a) from its precursor (1a), after 1 h irradiation.

[b] Irradiations for more than 8 h did not lead to an appreciable increase in the absorbance of the resulting solutions.

It can be seen that the differences are more important at lower reaction times, when the perturbations of the absorption due to the filtering effect of chalcones and dihydrochalcones are less significant. Thus, after 1 h, the rearrangement degree of the dihydrocinnamate (1d) is approximately 4 times that of the cinnamate (1a) and 19 times that of the dibromo derivative (1g), whereas these differences are considerably reduced when using more prolonged irradiations.

Turning to the preparative interest of the above transformations, the dihydrochalcones (2d-f) can be quantitatively converted into the corresponding chalcones using dichlorodicyanoquinone (DDQ) as dehydrogenating agent, [12] and the latter compounds (2a-c) undergo a very easy cyclization in the presence of both acids and bases, [13, 14] to give the isomeric flavanones (3a-c).



(2d-f) (2a-c) (3a-c)

As a concluding remark, the photo-Fries rearrangement of aryl dihydrocinnamates could constitute an efficient alternative entry to the synthesis of flavonoids, taking into account that the different types of natural products belonging to this family can be obtained from the chalcone-flavanone isomers by a series of well established reactions. [1]

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 577 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 wavelenght (λ_{max}, nm) and log ε (in brackets).

General esterification procedure

Acid chlorides were prepared treating the corresponding acids with an equimolar amount of thionyl chloride in $CHCl_3$ at room temperature. Solvent evaporation gave the crude chlorides which were refluxed for 2 h in benzene with the corresponding phenols in the presence of Mg. The reaction mixtures were then filtered, washed with 5% NaOH, then with water, and dried with anhydrous Na_2SO_4. Evaporation of the solvent followed by recrystallization from ethanol yielded the esters in pure form.

Bromination of (1a)

Bromine (0.8 g) in 20 ml of CCl_4 was added dropwise to a solution of (1a) (1 g) in 25 ml of CCl_4 at room temperature. The solvent was then evaporated in vacuo and the residue crystallized from ethanol to give (1g) (1.4 g).

Irradiations

A solution of 500 mg of ester in 450 ml of freshly distilled hexane was irradiated for 8 h at room temperature with a 125 W medium pressure mercury lamp inside a quartz immersion well. The photorearranged products were isolated, after removal of the solvent, with silica gel flash-column chromatography using hexane as eluent.

Cyclization of chalcones to flavanones

A solution of 500 mg of chalcone in 200 ml of benzene was stirred at room temperature during 3 h with a mixture of 100 ml of 25% NH_4OH and 20 ml of 20% tetraethylammonium hydroxide in water, the organic layer was then separated and the solvent removed in vacuo. The residue was submitted to silica gel flash column chromatography affording the expected flavanone.

Products

4-Methoxyphenyl trans-cinnamate (1a) (72%), mp 99-100 °C, Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54; Found: C, 75.46; H, 5.53 %, ir 1730 (C=O), ^{1}H-nmr 7.60 (d, J=16Hz, 1H, C_6H_5CH=CH), 7.35 (m, 5H, C_6H_5), 6.92 (m, 4H, $CH_3OC_6H_4$), 6.52 (d, J=16Hz, 1H, CH=CHCO), 3.73 (s, 3H, OCH_3), uv 280 (4.5).

4-Methylphenyl trans-cinnamate (1b) (80%), mp 95-96 °C, Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92; Found: C, 80.71; H, 5.96 %, ir 1735 (C=O), ^{1}H-nmr 7.79 (d, J=16Hz, 1H, C_6H_5CH=CH), 7.35 (m, 5H, C_6H_5), 7.00 (s, 4H, $CH_3C_6H_4$), 6.52 (d, J=16Hz, 1H, CH=CHCO), 2.30 (s, 3H, CH_3), uv 274 (4.5).

2,4-Dimethylphenyl trans-cinnamate (1c) (69%), mp 72-73 °C, Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39; Found: C, 80.85; H, 6.38 %, ir 1735 (C=O), ^{1}H-nmr 7.73 (d, J=16Hz, 1H, C_6H_5CH=CH), 7.60-7.12 (m, 5H, C_6H_5), 6.93 (m, 3H, $(CH_3)_2C_6H_3$) , 6.52 (d, J=16Hz, 1H, CH=CHCO), 2.30 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), uv 274 (4.4).

4-Methoxyphenyl 3-phenylpropanoate (1d) [15] (73%), mp 38-39 °C, ir 1765 (C=O), ^{1}H-nmr 7.50 (m, 5H, C_6H_5), 6.80 (m, 4H, $CH_3OC_6H_4$), 3.71 (s, 3H, OCH_3), 3.30-2.50 (m, 4H, CH_2CH_2), uv 278 (3.3).

4-Methylphenyl 3-phenylpropanoate (1e) [16] (82%), mp 32-33 °C, ir 1760 (C=O), ^{1}H-nmr 7.19 (m, 5H, C_6H_5), 6.83 (m, 4H, $CH_3C_6H_4$), 3.09-2.53 (m, 4H, CH_2CH_2), 2.20 (s, 3H, CH_3), uv 265 (2.8).

2,4-Dimethylphenyl 3-phenylpropanoate (1f) (78%), Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13; Found: C, 80.32; H, 7.00 %, ir 1765 (C=O), ^{1}H-nmr 7.51-6.60 (m, 8H, ArH), 3.10-2.52 (m, 4H, CH_2CH_2), 2.20 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), uv 266 (3.1).

4-Methoxyphenyl 2,3-dibromo-3-phenylpropanoate (1g) (87%), mp 114-115 °C, Anal. Calcd. for $C_{16}H_{14}Br_2O_3$: C, 46.41; H, 3.41; Br, 38.60; Found: C, 46.45; H, 3.36; Br, 38.78 %, ir 1775 (C=O), ^{1}H-nmr 7.22 (m, 5H, C_6H_5), 6.83 (m, 4H, $CH_3OC_6H_4$), 5.30 (d, J=12Hz, 1H, CHBrCO), 4.80 (d, J=12Hz, 1H, $CHBrC_6H_5$), 3.70 (s, 3H, OCH_3), uv 292 (4.0).

2'-Hydroxy-5'-methoxychalcone (2a) [17] (20%), ir 1650 (C=O), ^{1}H-nmr 12.40 (s, 1H, OH), 8.00-6.80 (m, 10H, ArH and CH=CH), 3.83 (s, 3H, OCH_3), uv 380 (3.5) 313 (4.2) 249 (4.1).

2'-Hydroxy-5'-methylchalcone (2b) [18] (19%), mp 94-96 °C, ir 1660 (C=O), ^{1}H-nmr 12.50 (s, 1H, OH), 8.00-6.79 (m, 10H, ArH and CH=CH), 2.32 (s, 3H, CH_3), uv 365 (3.8) 311 (4.4).

2'-Hydroxy-3',5'-dimethylchalcone (2c) (15%), mp 70-72 °C, Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39; Found: C, 81.11; H, 6.47 %, ir 1650 (C=O), ^{1}H-nmr 12.50 (s, 1H, OH), 8.21-6.93 (m, 9H, ArH and CH=CH), 2.31 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), uv 376 (3.7) 312 (4.4).

1-(2-Hydroxy-5-methoxyphenyl)-3-phenyl-1-propanone (2d) [19] (54%), ir 1660 (C=O), ^{1}H-nmr 11.60 (s, 1H, OH), 7.24-6.68 (m, 8H, ArH), 3.70 (s, 3H, OCH_3), 3.15-2.96 (m, 4H, CH_2CH_2), uv 360 (3.6) 240 (4.4).

1-(2-Hydroxy-5-methylphenyl)-3-phenyl-1-propanone (2e) [20] (50%), mp 36-38 °C, ir 1660 (C=O), ^{1}H-nmr 12.04 (s, 1H, OH), 7.30-6.64 (m, 8H, ArH), 3.23-2.80 (m, 4H, CH_2CH_2), 2.20 (s, 3H, CH_3), uv 343 (3.5) 254 (3.9).

1-(2-Hydroxy-3,5-dimethylphenyl)-3-phenyl-1-propanone (2f) (40%), Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13; Found: C, 80.13; H, 7.54 %, ir 1645 (C=O), ^{1}H-nmr 12.15 (s, 1H, OH), 7.35-6.92 (m, 7H, ArH), 3.22-2.82 (m, 4H, CH_2CH_2), 2.20 (s, 6H, $2CH_3$), uv 350 (3.5) 259 (3.9).

6-Methoxyflavanone (3a) [21] (75%), mp 139-141 °C, ir 1695 (C=O), ^{1}H-nmr 7.40--6.80 (m, 8H, ArH), 5.30 (dd, J_{cis}=6Hz, J_{trans}=11Hz, 1H, CHPh), 3.72 (s, 3H, OCH_3), 3.20-3.00 (m, 2H, CH_2), uv 350 (3.9).

6-Methylflavanone (3b) [22] (68%), mp 104-106 °C, ir 1695 (C=O), ^{1}H-nmr 7.73--6.70 (m, 8H, ArH), 5.32 (dd, J_{cis}=6Hz, J_{trans}=11Hz, 1H, CHPh), 3.10-2.62 (m, 2H, CH_2), 2.29 (s, 3H, CH_3).

6,8-Dimethylflavanone (3c) (40%), mp 69-71 °C, Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39; Found: C, 80.85; H, 6.41 %, ir 1710 (C=O), ^{1}H-nmr 7.52-6.82 (m, 7H, ArH), 5.23 (dd, J_{cis}=6Hz, J_{trans}=10Hz, 1H, CHPh), 2.94-2.69 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), uv 337 (3.4) 261 (3.8).

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