CHEMISTRY LETTERS, pp. 445-446, 1991.

Synthesis of (E)-2-Styrylchromones

José A. S. CAVALEIRO, José ELGUERO,† M. Luísa JIMENO,† and Artur M. S. SILVA
Centro de Química do Meio Aquático, INIC, University of Aveiro, 3800 Aveiro, Portugal
†Instituto de Química Médica y Centro Nacional de Química Orgánica, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain

A new synthesis of (E)-2-styrylchromones has been developed in paralell with synthetic studies on several flavone derivatives.

Chromones, flavones and related compounds are widely distributed in the plant kingdom, where they act in several biological functions. In humans, some of those naturally occurring compounds have shown important biological effects[1] and also significant phytopharmaceutical activity has been found for some analogues.[2]

A styrylchromone, hormothamnione **1**, has recently been isolated from a blue green alga.[3] This natural styrylchromone to be firstly reported has shown potent cytotoxic activity in vitro against several human leukemia cells.[3] The biological significance of the mentioned compounds and the known biocidal action of many organic halides, led us to the synthesis of several chlorinated flavones and of the corresponding chalcone intermediates in order to be tested at a later stage.

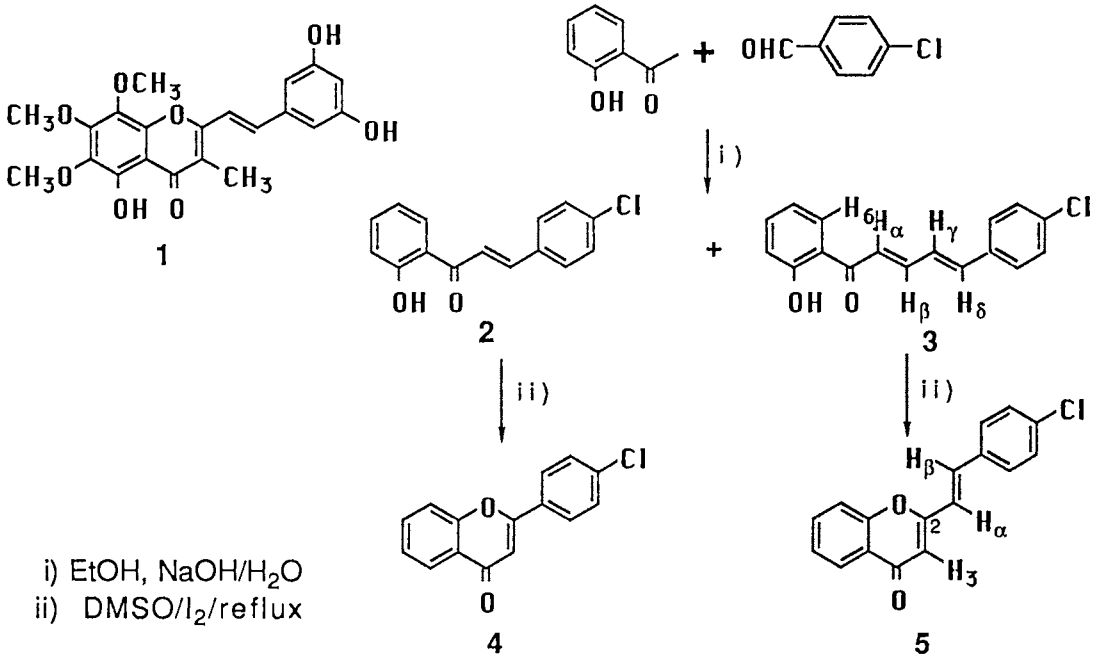
As a result of such studies a new synthesis of (E)-2-styrylchromones has been found.

Typically aldol condensation of o-hydroxyacetophenone with p-chlorobenzaldehyde in ethanol containing sodium hydroxide, gives not only the expected chalcone **2** (55% yield) but also 1-p-chlorophenyl-4-(o-hydroxybenzoyl)-(1E,3E)-butadiene **3** (20% yield). The formation of this compound, which has two extra carbon units in its structure, is interesting and opens a new route to the synthesis of styrylchromones. In fact, the oxidative cyclisations of **2** and **3** in dimethylsulphoxide with a catalytic amount of iodine give, respectively, the flavone **4** and the new styrylchromone **5**. We have already established[4] that such two extra carbon units are derived from acetaldehyde. In this way it is envisaged that under the alkaline conditions of the initial condensation ethanol is oxidized to acetaldehyde by an Oppenauer process. Compound **3** will then arise from the condensation of o-hydroxyacetophenone with acetaldehyde, followed by condensation of the resultant product with p-chlorobenzaldehyde. The reactions reported in Scheme 1 are general and have been extended to several benzaldehydes.[4]

The stereochemistry of compounds **3** and **5** was determined by ^{1}H and ^{13}C NMR. The assignments were established unequivocally by homo and hetero bidimensional

experiments. Proton coupling constant and chemical shift values were obtained by means of iterative computer calculations of spectra.

The main characteristics of compound **3** are : i) The values of vicinal coupling constants ^3J (H_α,H_β)=14.7 Hz; ^3J (H_γ,H_δ)=15.6 Hz indicate a *trans -trans* configuration; ii) NOE experiments have shown spacial proximity between H_6 and H_α. On the other hand, ^3J (H_β,H_γ)=11.3 Hz indicates a s-*trans* arrangement in the C_β-C_γ bond. These results allow the establishment of the stereochemistry of **3** as shown in Scheme 1. The main characteristics of styrylchromone **5** are: i) The value of vicinal coupling constant ^3J (H_α,H_β)=16.1 Hz indicates a *trans* configuration; ii) there are two possible isomers taking into account the C_2–C_α isomerism. NOE experiments have shwon the proximity between H_3 and H_α, thus establishing the stereochemistry of **5**, as seen in Scheme 1.



Scheme 1.

Thanks are due to "Instituto Nacional de Investigacão Científica" and to "Portuguese-Spanish Integrated Actions" for funding this work.

References

1) P. E. Schurr, *J. Med. Chem.*, **26**, 1672 (1983); T. G. Fourie and F. O. Snyckers, *J. Nat.*, **47**, 1057 (1984).
2) M. B. Hogale, B. N. Pawar, and B. P. Nikam, *J. Indian Chem.*, **LXIV**, 486 (1987).
3) W. H. Gerwick, A. Lopez, G. D. Van Duyne, J. Clardy, W. Ortis, and A. Baez, *Tetrahedron Lett.*, **27**, 1979 (1986).
4) Work in progress has already shown that the type-**3** compounds can be synthetized by using other mono- and dichlorobenzaldehydes and other alcohols (but not methanol; in this case only the expected chalcones are obtained).

(Received October 6, 1990)