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5-Hydroxy-2-(Phenyl or Styryl)chromones: One-Pot Synthesis and C-6, C-8 ^{13}C NMR Assignments

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Abstract: A new procedure to synthesise 5-hydroxy derivatives of 2-phenyl- and 2-styrylchromones is reported. The assignments of their C-6 and C-8 atoms, made by proton-coupled ^{13}C and selective INEPT NMR spectroscopy, show that the literature data for such carbon centres must be interchanged.

2-Phenylchromones are a group of flavonoids widely occuring in plants, where they play several biological functions.[1] Potential applications as agrochemicals,[2] antioxidants[3] and pharmaceutical drugs[4] have been considered for such compounds, in particular the 5-hydroxy derivatives.

2-Styrylchromones, another group of flavonoid type compounds, have been synthesised for some time.[5] However it was only during the last decade that the first two natural 5-hydroxy-2-styrylchromones were obtained from the blue-green algae[6] *Chrysophaeum taylori*. These compounds show potent *in vitro* cytotoxic activity against leukemia cells.[6]

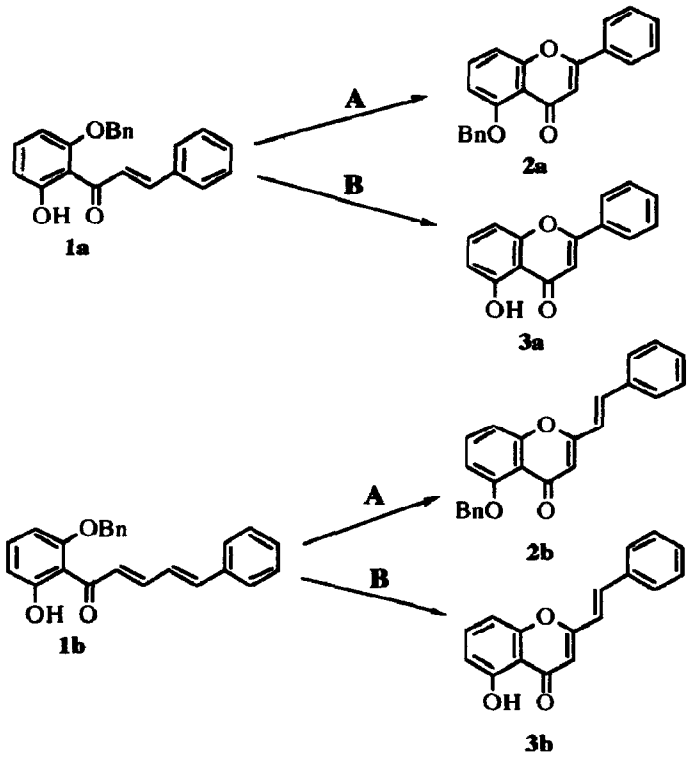
Several methods are available to synthesise 5-hydroxy-2-(phenyl or styryl)chromones. They are based on the use of 2',6'-dihydroxyacetophenones and benzoic or cinnamic acid derivatives (the Baker-Venkataraman procedure) or appropriate 2',6'-dihydroxy-acetophenones and benzoyl or cinnamoyl anhydrides in presence of sodium or potassium benzoate or cinnamate (the Allan-Robinson method) or using the oxidative cyclization of chalcones or cinnamilydeneacetophenones with selenium dioxide. However such procedures usually give low yields of the required compounds and also allow formation of by-products.

The biological and industrial significance of such flavonoids led us to study a convenient synthesis of 5-hydroxy-2-phenyl- and 5-hydroxy-2-styrylchromones.

Refluxing 2'-hydroxychalcone (**1a**) or 2'-hydroxycinnamylideneacetophenone (**1b**), in DMSO, with a catalytical amount of iodine, leads, respectively, to the formation of chromones (**2a**), 92%, and (**2b**), 71%, or (**3a**), 89%, and (**3b**), 81%, depending on the reflux period (scheme 1).

The formation of products (**3a**) and (**3b**) indicates that each reaction mixture, heated at reflux for 2 hours, affords in one step the oxidative cyclization of the starting compound

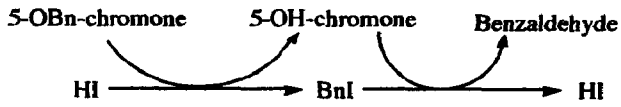
and also the debenzylation of the 5-substituent. However chromones such as (**2a**) and (**2b**) can be obtained in a shorter reflux period (30 minutes).



A - DMSO/I_2, reflux 30 minutes. **B** - DMSO/I_2, reflux 2 hours.
Bn = $CH_2C_6H_5$

SCHEME I

The 5-debenzylation is probably due to the action of hydrogen iodide which is formed in catalytic amounts during the cyclization steps.[7] Hydrogen iodide can form benzyl iodide, which, after being oxidized by DMSO to benzaldehyde, generates other hydrogen iodide molecules to continue the debenzylation process.



This proposal was corroborated with the results obtained in the following experiments: a) ^1H NMR analysis of a product mixture obtained from submitting chalcone (**1a**) to the **B**

reaction conditions (scheme 1), has revealed signals due not only to (**3a**) but also to benzaldehyde; b) refluxing benzyl chloride in DMSO during two hours, followed by work-up and ^{1}H NMR analysis, gave the expected benzaldehyde.[8]

The ^{1}H and ^{13}C NMR studies on flavonoids are well documented.[9,10] The assignments made for C-6 and C-8 in the ^{13}C NMR spectra of several substituted 5,7-dihydroxy-2-phenylchromones show that the resonance of C-6 occurs at a higher frequency than C-8. The opposite conclusion has been put forward for identical centres of 6,7,8-unsubstituted chromones. However the present work has shown that for such 6,7,8-unsubstituted chromones the assignments of C-6 and C-8 must be interchanged.[11] The proton-coupled ^{13}C NMR spectra of (**3a**) and (**3b**), in DMSO, have made it possible to assign the resonances of all carbon centres. In particular, C-6 exhibits spin-spin coupling not only with H-6, but also with the 5-OH and H-8 protons; a double triplet is assigned to such a carbon centre. On the other hand H-8 and H-6 are coupled with C-8 and a double doublet is originated in this case.[12]

The assignments of the C-6 and C-8 were also facilitated by the observation of the following selective INEPT NMR enhancements[13] on irradiation of the corresponding 5-O<u>H</u>: (**3a**), C-5 (δ, 159.9), C-6 (δ, 111.0) and C-10 (δ, 110.2); (**3b**), C-5 (δ, 159.9), C-6 (δ, 110.9) and C-10 (δ, 110.3).

The C-6 and C-8 resonances in the ^{13}C NMR spectra of 6,7,8-unsubstituted 5-hydroxy-2-phenyl- or 2-styrylchromones can then be assigned without ambiguity:[11] the one due to C-6 appears at a higher frequency than that for C-8.

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11. ^{1}H and ^{13}C NMR spectra were determined at 300 MHz and 75 MHz, respectively. The chemical shifts (δ, ppm from TMS) of C-6 and C-8 are the following: **3a** 111.0 and 107.6; **3b** 110.9 and 108.7.
12. The C-7 signal, at δ 135-136 ppm, appears as a doublet due to the coupling with H-7. Coupling of C-7 with the vicinal protons is not observed; the same conclusion applies to C-6 and C-8 with H-7.
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