A CONVENIENT SYNTHESIS OF 3-CINNAMOYL-5-HYDROXY-2-STYRYL-CHROMONES BY A MODIFIED BAKER-VENKATARAMAN TRANSFORMATION

Diana C. G. A. Pinto, Artur M. S. Silva and José A. S. Cavaleiro*
Department of Chemistry, University of Aveiro, 3810 Aveiro, Portugal.

ABSTRACT

A new synthesis of 3-cinnamoyl-5-hydroxy-2-styrylchromones is reported. The procedure involves a one-step modified Baker-Venkataraman rearrangement of 2',6'-dicinnamoyloxyacetophenones into the title compounds.

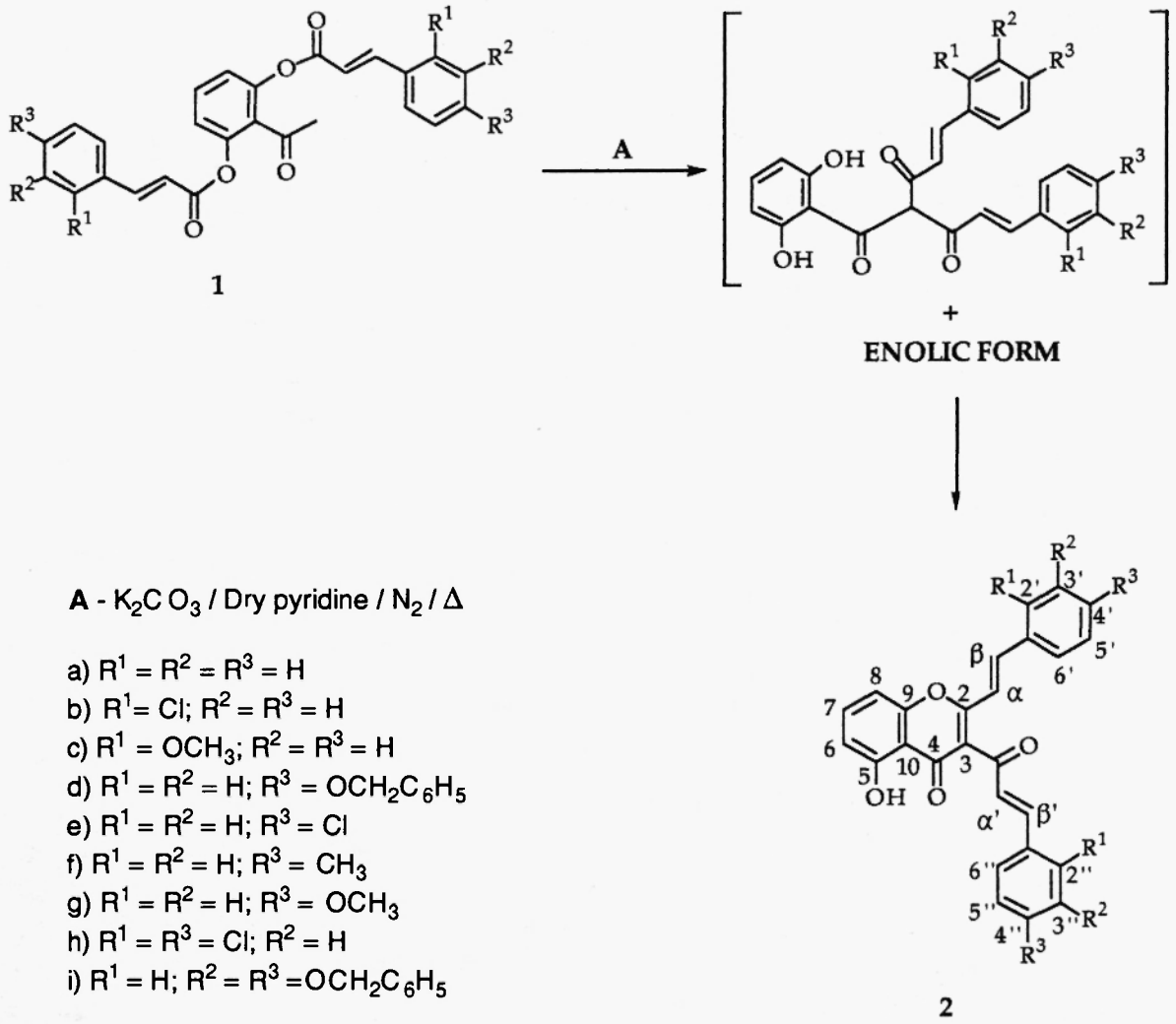
INTRODUCTION

The pharmacological activities and potential medicinal uses of natural and synthetic 2-styrylchromones are well known (1,2,3). Several of these compounds have exhibited significant levels of anti-allergic activity (1); more recently it was demonstrated that some derivatives have anti-tumour activity against colon 38 tumours (2). Our interest on the synthesis (4,5) and further biological assessment of 2-styrylchromones prompted us to look for new methods for synthesis of such compounds. Currently there are a few methods available for synthesis of 2-styrylchromones (6). Nevertheless, so far as we are aware 2-styrylchromones with 3-cinnamoyl substituents are unknown.

RESULTS AND DISCUSSION

In this communication we report a new synthesis of 3-cinnamoyl-5-hydroxy-2-styrylchromones, using a modification of the Baker-Venkataraman approach (7,8). In this method the 2',6'-dihydroxyacetophenone is first converted into a dicinnamoyl ester, by treating the hydroxylated acetophenone with carboxylic acid in the presence of N,N-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine (9). As a result of this transformation the dicinnamoyl ester derivatives 1 (10) were obtained in good yields (76-92 %).

The second step in the synthesis of 2 was the base-catalysed transformation, under anhydrous conditions and a nitrogen atmosphere, of the 2',6'-dicinnamoyloxyacetophenones, 1 to afford the 2,2-dicinnamoyl-2',6'-dihydroxy-acetophenone intermediates; these were not isolated but underwent *in situ* cyclodehydration to give the desired products 2, (Scheme I), in good yields (63-81 %), without any acid catalysis. Similar situations have been already reported for 2',6'-dibenzoylacetophenones (11).



A - $K_2C O_3$ / Dry pyridine / N_2 / Δ

a) $R^1 = R^2 = R^3 = H$
b) R^1= Cl; $R^2 = R^3 = H$
c) $R^1 = OCH_3$; $R^2 = R^3 = H$
d) $R^1 = R^2 = H$; $R^3 = OCH_2C_6H_5$
e) $R^1 = R^2 = H$; R^3 = Cl
f) $R^1 = R^2 = H$; $R^3 = CH_3$
g) $R^1 = R^2 = H$; $R^3 = OCH_3$
h) $R^1 = R^3$ = Cl; $R^2 = H$
i) $R^1 = H$; $R^2 = R^3 = OCH_2C_6H_5$

Scheme I

Structures of the 3-cinnamoyl-5-hydroxy-2-styrylchromones **2** were determined by ^1H and ^{13}C NMR spectroscopy , mass spectrometry and elemental analysis (12). A noticeable feature in the ^1H NMR spectra of compounds **2** was the signal due to the resonance of each 5-OH proton, which appears as a singlet at δ 12.24-12.51 ppm.

The unequivocal assignments of the two AB systems corresponding to the H-α, H-β and H-α', H-β' protons in the ^1H NMR spectra of compounds **2** were achieved by performing one-dimensional selective INEPT measurements (13) and also 2D COSY experiments. The INEPT measurements give the connectivity of a selected proton, by irradiation of the corresponding resonance, to the carbon atoms to which it is coupled, and can be optimized for different long-range J (C/H) coupling. In the case of compound 2a (14), irradiation of the proton resonance at δ 7.70 ppm, with a 7 Hz long-range J (C/H) coupling, which give enhancements on the carbon atoms signals two or three bonds away from the irradiated proton, such enhancements were observed for signals at δ 190.8 and 128.8 ppm. Those signals must be due to the resonances of 3-cinnamoyl C=O carbon and of C-2",6" carbon atoms of the phenyl ring. Subsequently with the

irradiation of the proton resonance at δ 7.80 ppm, with the same long-range J (C/H) coupling value, enhancements of the signals of C-2 (δ 162.5 ppm) and of C-2',6' (δ 128.3 ppm) carbon atoms were observed. The first proton resonance at 7.70 ppm was then assigned to the H-β' proton, while the second at 7.80 ppm was assigned to the H-β proton. The assignments of H-α and H-α' proton resonances at, respectively, δ 7.17 and 7.24 ppm, were performed from the 2D COSY experiments. The coupling constants ($^3J_{H\alpha-H\beta}$ ~ 16 Hz) indicate a *trans* configuration for the vinylic systems. The higher frequency values of the H-β and H-β' resonances are due to the deshielding mesomeric effect of the carbonyl groups. Similar experiments were also carried out for the other compounds **2b-g** and **2i**, allowing us to assign the corresponding resonances.

In the ^{13}C NMR spectra of compounds **2a-g** and **2i** the assignments of the C-6 and C-8 carbon atoms were carried out by using 2D COSY and HETCOR experiments; the following values of frequencies were found: δ 111.7-112.1 and 106.7-107.1 ppm. However, these experiments do not allow the assignment of C-6 and C-8. This problem was solved using also one-dimensional selective INEPT measurements (7 Hz long-range J (C/H) coupling): on irradiation of the signal of 5-OH proton (δ 12.35-12.51 ppm), enhancements of the signals of C-5 (δ 160.9-161.0 ppm) and C-10 (δ 110.4-110.6 ppm) carbon atoms were observed; identical results were obtained with the signal at δ 111.7-112.1 ppm, which is then assigned to the resonance of C-6 carbon atom. In compounds **2** the resonance due to C-6 appears at higher frequency than that for the C-8 carbon atom (14, 15).

EXPERIMENTAL

NMR spectra, in deuteriochloroform and using tetramethylsilane as internal reference, were recorded on a Bruker AMX 300 spectrometer.

Experimental procedure for the synthesis of 2',6'-dicinnamoyloxyacetophenones 1a-i:

To a solution of 2',6'-dihydroxyacetophenone (0.76 g, 5 mmol) in dichloromethane (30 mL), was added the appropriate cinnamic acid (10 mmol), 4-pyrrolidinopyridine (0.15 g, 1 mmol) and N,N-dicyclohexylcarbodiimide (2.06 g, 10 mmol). The mixture was stirred, at room temperature, during 1 hour. After this period the expected 1,3-dicyclohexylurea was filtered off, washed with dichloromethane (2 x 10 mL) and discarded. The organic layer was passed through anhydrous sodium sulfate and the solvent was evaporated to dryness. The residue was purified by silica gel (Merck, 70-230 mesh ASTM) column chromatography, using a mixture of dichloromethane:petroleum ether (8:2) as eluent. Finally the compound, in each case, was crystallized from ethanol. The following yields were obtained: **1a** (1.59 g, 77 %); **1b** (1.94 g, 81 %); **1c** (1.96 g, 83 %); **1d** (2.50 g, 80 %); **1e** (1.83 g, 76 %); **1f** (2.03 g, 92 %); **1g** (1.94 g, 82 %); **1h** (2.48 g, 90 %); **1i** (3.47 g, 83 %).

Experimental procedure for the synthesis of 3-cinnamoyl-5-hydroxy-2-styrylchromones 2a-i:

To a solution of 2',6'-dicinnamovloxvacetophenones **1a-i** (2 mmol) in dry pyridine (25 mL), was added anhydrous potassium carbonate (0.55 g, 4 mmol). The mixture was heated (115-120 °C), under nitrogen, during 1 hour, and after this period it was poured into a mixture of ice (100 g) and concentrated hydrochloric acid (pH adjusted to ~3). The solid obtained was filtered, dissolved in chloroform (75 mL), and washed with a saturated solution of sodium hydrogen carbonate (3 x 50 mL). The organic layer was collected, dried through anhydrous sodium sulfate and the solvent was evaporated to dryness. The residue was purified by silica gel (Merck, 70-230 mesh ASTM) column chromatography, using dichloromethane as eluent. Finally the compound, in each case, was crystallized from ethanol. The yields

obtained were as follows: 2 a (615 mg, 78 %); 2 b (582 mg, 63 %); 2 c (727 mg, 80 %); 2 d (972 mg, 80 %); 2 e (583 mg, 63 %); 2 f (667 mg, 79 %); 2 g (736 mg, 81 %); 2 h (798 mg, 75 %); 2 i (1311 mg, 80 %).

ACKNOWLEDGEMENTS

Sincere thanks are due to JNICT, Lisbon, for a grant to purchase the Bruker AMX 300 NMR spectrometer. One of us (D. C. G. A. P.) is also grateful to JNICT/Praxis XXI for the award of a student's grant.

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10. Compounds 1 gave satisfactory elemental analysis. As an example, 1a: Anal. Calcd. for $C_{26}H_{20}O_5$: C, 75.72; H, 4.89; Found: C, 75.52; H, 4.79
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12. 2a Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.18; H, 4.60; Found: C, 79.09; H, 4.64; 2b Anal. Calcd. for $C_{26}H_{16}O_4Cl_2$: C, 67.40; H, 3.48; Found: C, 67.55; H, 3.62; 2c Anal. Calcd. for $C_{28}H_{22}O_6$: C, 74.00; H, 4.88; Found: C, 73.92; H, 4.92; 2d Anal. Calcd. for $C_{40}H_{30}O_6.1/2H_2O$: C, 78.03; H, 5.08; Found: C, 77.99; H, 4.86; 2 e Anal. Calcd. for $C_{26}H_{16}O_4Cl_2$: C, 67.40; H, 3.48; Found: C, 67.29; H, 3.66; 2f Anal. Calcd. for $C_{28}H_{26}O_4$: C, 79.60; H, 5.25; Found: C, 79.56; H, 5.35; 2g Anal. Calcd. for $C_{28}H_{22}O_6$: C, 74.00; H, 4.88; Found: C, 73.76; H, 5.12; 2 h Anal. Calcd. for $C_{26}H_{14}O_4Cl_4$: C, 58.68; H, 2.65; Found: C, 58.33; H, 2.74; 2i Anal. Calcd. for $C_{54}H_{42}O_8 1/2H_2O$: C, 78.34; H, 5.24; Found: C, 78.11; H, 5.03
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14. 2a: ^{1}H NMR (δ, ppm from TMS; J Hz) 6.84 (H-6, d, J 8.3), 7.03 (H-8, d, J 8.4), 7.17 (H-α, d, J 15.9), 7.24 (H-α', d, J 16.0), 7.39-7.42 (H-3', 3", 4', 4", 5', 5", m), 7.56-7.63 (H-2', 2", 6', 6", 7), 7.70 (H-β', d, J 16.0), 7.80 (H-β, d, J 15,9), 12.41 (5-OH, s); ^{13}C NMR (δ, ppm from TMS) 106.9 (C-8), 110.5 (C-10), 111.9 (C-6), 117.4 (C-α), 120.8 (C-3), 127.1 (C-α'), 128.3 (C-2',6'), 128.8 (C-2", 6"), 128.9 (C-3",5"), 130.6 (C-4'), 130.9 (C-4"), 134.4 (C-1'), 134.6 (C-1"), 136.0 (C-7), 140.8 (C-β), 144.8 (C-β'), 155.3 (C-9), 161.0 (C-5), 162.5 (C-2), 181.7 (C-4) and 190.8 (C=O of the 3-cinnamoyl group)
15. The chemical shifts (δ, ppm from TMS) of C-6 and C-8 in compounds 2b-g and 2i are the following: 2b 112.1 and 107.1; 2c 111.7 and 107.0; 2d 111.7 and 106.7; 2e 112.1 and 106.8; 2f 111.8 and 106.8; 2g 111.7 and 106.8; 2i 111.7 and 106.8

Received November 29, 1995