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AN EFFICIENT METHOD FOR THE SYNTHESIS OF NEW SUBSTITUTED CHROMENS

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ABSTRACT

The chromen derivatives can be obtained in excellent yields, in three steps, using first the phase transfer catalysis for the synthesis of phenol ether followed by cyclisation and the Perkin reaction.

KEYWORDS: Lipoxygenase inhibitors, Phase Transfer Catalysis (PTC), Chromens

RESUMO:

Derivados do cromeno foram obtidos com rendimentos excelentes a partir de benzaldeídos em tres etapas usando primeiro catálise por transferência de fase por ciclização e a reação de Perkin.

INTRODUCTION

Inhibitors of the lipoxygenase enzymes and antagonists of leukotrines are now being developed and it remains to be seen if these componds will have the predicted therapeutic value in the treatment of human asthma and inflamation. A general strategy and design for such inhibitors has been under development in our laboratories.

The synthesis of new molecules containing both cinnamic acid and chromene groups is reported in this paper. Such molecules have wide therapeutic possibilities, being able to inhibit the lipoxygenase pathway of arachidonic acid metabolism.

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Conversion of arachidonic acid by the 5 - lipoxygenase enzyme results in the formation of 5 - hydroperoxy - 6, 8, 11, 14 - eicosatetraenoic acid which is subsequently metabolized to a series of highly potent leukotrienes. These oxygenated eicosanoids are implicated in inflammatory and allergic reactions. Little is known at present about the way in which 5 - lipoxygenase acts and any type of information about this mechanism may contribute to the treatment of vascular diseases[1,2].

It has been recentely proved that the caffeic acid[3,4] and a series of chromene derivatives[5] are good inhibitors of 5 - lipoxygenase. In an attempt to understand the physicochemical background of the structural effects of the side chains as well as the ring systems on the inhibition, we synthesized two new compounds that contain a chromene moiety and a cinnamic acid side chain. At the present, only the 2,2 dimethyl - 6 - carboxyethenyl - 2H - 1 - benzopyran is known and it was isolated and identified from Brazilian propolis[6] but it was never synthesized *in situ*.

Conventionaly[7] the chromens are synthesized in two steps. The first is the reaction of the 3 - chloro - 3 methylbutyne with a convenient phenolic substrate, in the presence of potassium iodide and potassium carbonate. This step requires aproximately 65 hours and the O - dimethylprop - 2 - ynyl ether is obtained in a rather poor yield (24%). In the second step the O - dimethyl prop - 2 - ynyl ether, heated at 218°C for 2 hours in diethylaniline to give chromen (56%) by means of the acetylene version of the Claisen rearrengement. Besides the poor yield, this method has a number of disadvantages like the long time required for the synthesis of the ether and the laborious chromatographic procedure required for its purification.

This paper reports an efficient procedure to obtain the chromen derivative (figure 1). This synthesis is based on the observations of McKillop[8] who used the phase - transfer catalysis (P.T.C.) for the preparation of the phenol ether. Compared with the classical methods, the new route proposed for the synthesis of the O - dimethylprop - 2 - ynyl ether gave a very good yield (85%), was carried out in a relatively short time (8 - 10 h) and no further purification by chromatographic method was necessary.

EXPERIMENTAL PROCEDURE

A mixture of 50 mL of dichloromethane, 50 mL of water, 10 mmoles of the hydroxy benzaldehyde **1** (Figure1), 20 mmoles of sodium hydroxide, 20 - 30 mmole of 3 - chloro - 3 methylbutyne and 1 - 1.5 mmole of quaternary ammonium bromide was stirred at room temperature for 8 - 10 h. After this time a volume of 25 ml solution of NaOH (1 M) was added and stiring was continued for 15 minutes. The organic layer was separated and the aqueous layer was extracted with methylene chloride. Removal of the solvent yielded the pure ether **2**. This ether was disolved in diethylaniline and the procedure described by

Crombie was applied to obtain the chromene derivative **3**. The product with the cinnamic side chain **4** was obtained (90% yield) using the general procedure of the Perkin reaction[9].

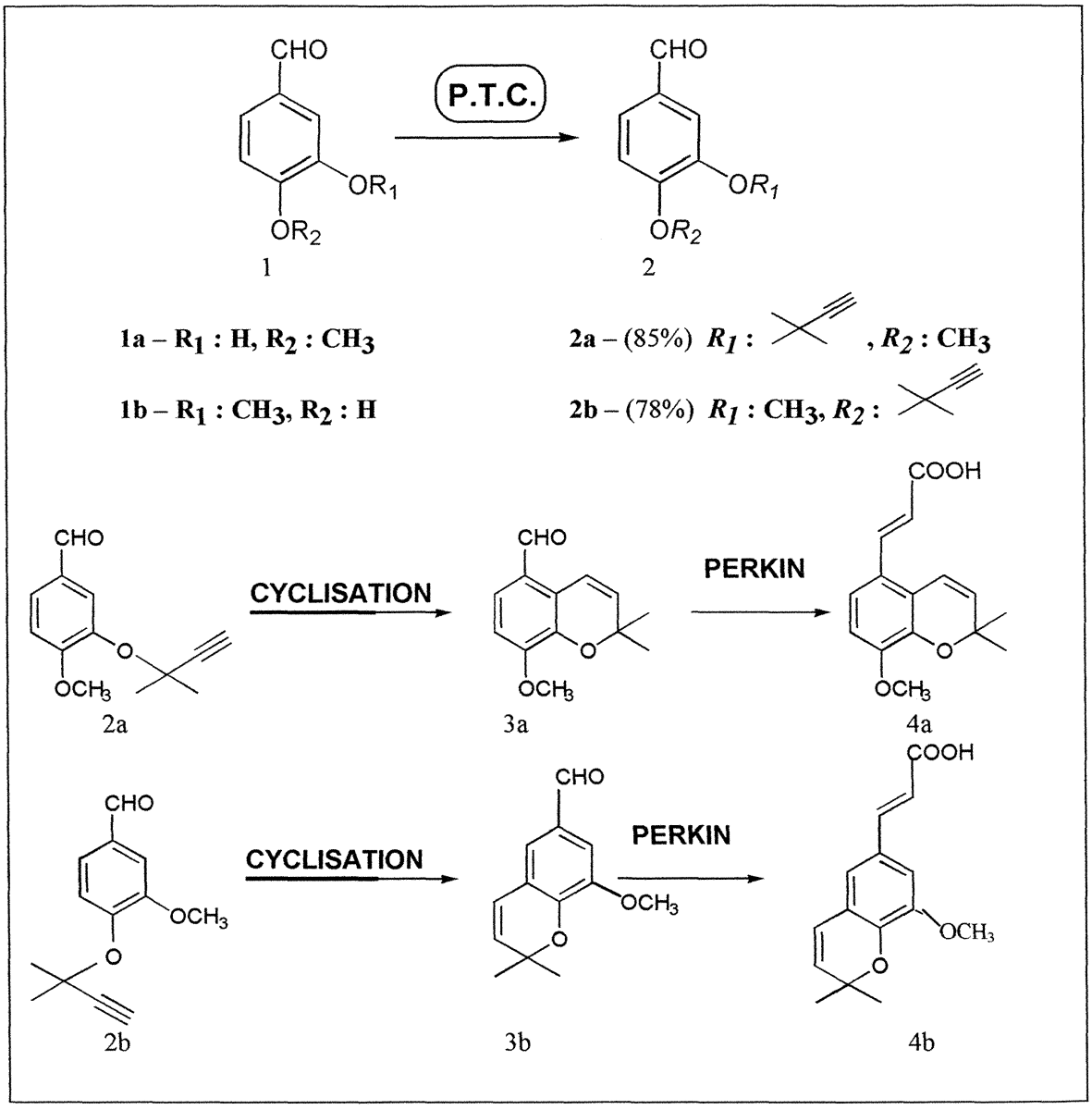

Figure 1. Synhtesis of substituted chromens using the new route proposed

Analytical characterization of the products gave the following results:

3 a : ***5 - formyl - 8 - methoxy - 2,2 dimethyl chromen*** (92%) **^{1}H NMR** ($CDCl_3$) 1,47 ppm (s, 6 H -2x CH_3); 3,90 ppm (s, 3 H - OCH_3); 5,80 ppm (d, 1H, ^3J = 10,13 Hz); 6,87 ppm (d, $1H_{arom}$ ^3J = 8,49 Hz); 7,30 ppm (d, $1H_{arom}$ ^3J= 8,49 Hz); 7,44 ppm (d, 1H ^3J= 10,14 Hz); 9,96 ppm (s, 1H - CHO); **MS m/e** (percent, relative abundance) 218 (M^+, 13,77); 203 (M^+-CH_3, 100); **IR (ν cm^{-1})** 3100 - 2700 (ν_{C-H}); 1690 ($\nu_{C=O}$); 1495 ($\nu_{C-Carom}$).

3b : ***6 - formyl - 8 - methoxy - 2,2 dimethyl chromen*** (88%) **^{1}H NMR** ($CDCl_3$) 1,44 ppm (s, 6 H -2x CH_3); 3,85 ppm (s, 3 H - OCH_3); 5,62 ppm (d, 1H, ^3J = 9,90 Hz); 6,28 ppm (d, 1H, ^3J = 9,90 Hz); 7,09 ppm (d, $1H_{arom}$ ^3J = 1,72 Hz); 7,24 ppm (d, $1H_{arom}$ ^3J = 1,69 Hz); 9,78 ppm (s, 1H, CHO); **MS m/e** (percent, relative abundance) 218 (M^+, 16,27); 203 (M^+-CH_3, 100); **IR (ν cm^{-1})** 3000 - 2800 (ν_{C-H}); 1695 ($\nu_{C=O}$); 1460 ($\nu_{C-Carom}$).

4a : ***5 - carboxyethenyl - 8 - methoxy - 2,2 dimethyl chromen*** (90%) **^{1}H NMR** ($CDCl_3$) 1,50 ppm (s, 6 H -2x CH_3); 3,88 ppm (s, 3 H - OCH_3); 5,78 ppm (d, 1H, ^3J = 10,04 Hz); 6,28 ppm (d, 1H, ^3J = 15,72 Hz); 6,70 ppm (d, 1H, ^3J= 10,09 Hz); 6,80 ppm (d, $1H_{arom}$ ^3J = 8,68 Hz); 7,17 ppm (d, $1H_{arom}$ ^3J = 8,64 Hz); 8,01 ppm (d, 1H, ^3J = 15,72 Hz); **MS m/e** (percent, relative abundance) 260 (M^+, 18,19); 245 (M^+-CH_3, 100); **IR (ν cm^{-1})** 3600 - 2890 (ν_{O-H} et ν_{C-H}); 1690 ($\nu_{C=O}$); 1490 ($\nu_{C-Carom}$).

4b : ***6 - carboxyethenyl - 8 - methoxy - 2,2 dimethyl chromen*** (85%) **^{1}H NMR** ($CDCl_3$) 2,10 ppm (s, 6 H -2x CH_3); 3,90 ppm (s, 3 H - OCH_3); 5,60 ppm (d, 1H, ^3J = 9,86 Hz); 6,22 ppm (d, 1H, ^3J = 9,62 Hz); 6,25 ppm (d, 1H, ^3J= 15,72 Hz); 6,83 ppm (s, 1 H_{arom}); 6,94 ppm (s, 1 H_{arom}); 7,66 ppm (d, 1H, ^3J = 15,83 Hz); 11,58 ppm (s, 1 H, COOH); **^{13}C NMR** ($CDCl_3$) 15,1 ppm (q, CH_3); 25,6 ppm (q, CH_3); 28,1 ppm (q, CH_3); 30,2 ppm (d, CH); 56,2 ppm (d, CH); 65,9 ppm (d, CH); 111,2 ppm (d, CH); 114,4 ppm (d, CH); 120,2 ppm (d, CH); 121,7 ppm (s, C); 123,5 ppm (s, C); 131,4 ppm (s, C); 147,2 ppm (s, C); 149,2 ppm (s, C); 175,0 ppm (s, C); **MS m/e** (percent, relative abundance) 260 (M^+, 18,07); 245 (M^+-CH_3, 100); **IR (ν cm^{-1})** 3600 - 2500 (ν_{O-H} et ν C-H); 1690 ($\nu_{C=O}$); 1420 ($\nu_{C-Carom}$).

Summarising, a simple, rapid and highly eficient procedure for the synthesis of chromen derivatives is now available.

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