NOVEL (*E*)-3-(2'-BENZYLOXY-6'-HYDROXYPHENYL)-5-STYRYLPYRAZOLES FROM (*E*)-2-STYRYLCHROMONES

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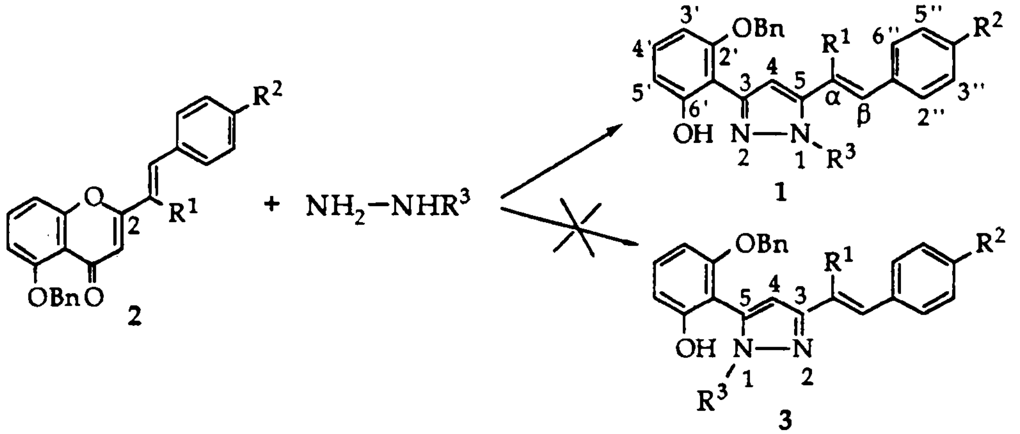
Abstract: Novel (*E*)-3-(2'-benzyloxy-6'-hydroxyphenyl)-5-styrylpyrazoles were obtained from (*E*)-2-styrylchromones and hydrazines. The stereochemistry of each product was established by NOE experiments.

Synthetic routes leading to pyrazole type compounds are being extensively studied. Such studies have been stimulated by some promising applications, which became known for some pyrazole derivatives. In fact, certain pyrazoles can be of great medical interest and others are important intermediates in the agrochemicals' field.[1] Others, like some hydroxyphenylpyrazoles can act as ultraviolet stabilizers[2] and as analytical reagents in the complexation of transition metal ions;[3] also certain vinylpyrazoles have been used in the preparation of other important heterocyclic compounds.[4]

The significance of such applications has pointed out that other pyrazoles, with appropriate substituents (e.g., hydroxyphenyl and styryl moieties), might become important targets to be prepared. Following our previous work on styrylchromones,[5] a programme has been set up aiming the synthesis of pyrazoles from 2-styrylchromones and hydrazine or derivatives. The synthesis of novel (*E*)-3-(2'-benzyloxy-6'-hydroxyphenyl)-5-styrylpyrazoles 1 from (*E*)-2-styrylchromones 2 is now reported. The new products were prepared by treatment of diluted methanolic solutions of (*E*)-2-styrylchromones 2 with hydrazines (Scheme 1).[6,7]

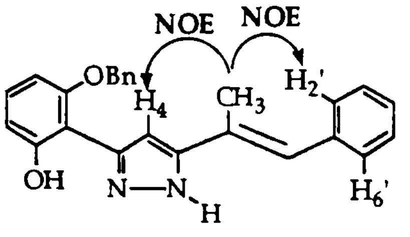
3(5)-(2'-hydroxyphenyl)pyrazoles have been previously obtained from the reaction of simple chromones with hydrazines.[1b,8] In the present work, in each case only one isomer 1g-l has been obtained from the reaction of the corresponding 2-styrylchromone with methylhydrazine. Due to the hydrogen bond between 6'-O*H* and N-2 in each product,[2] there is the formation of only one tautomer 3-(2'-benzyloxy-6'-hydroxyphenyl)-5-styrylpyrazole 1 and not the corresponding 5-(2'-benzyloxy-6'-hydroxyphenyl)-3-styrylpyrazole 3. This fact is confirmed by the high frequency resonance value of the 6'-OH proton in the ^{1}H NMR spectra of these pyrazoles 1, which appear as a singlet at δ 11.79-12.13 ppm.



a) $R^1 = R^2 = R^3 = H$
b) $R^1 = R^3 = H$; $R^2 = CH_3$
c) $R^1 = R^3 = H$; $R^2 = OCH_3$
d) $R^1 = CH_3$; $R^2 = R^3 = H$
e) $R^1 = (CH_2)_5CH_3$; $R^2 = R^3 = H$
f) $R^1 = CH_3$; $R^2 = C(CH_3)_3$; $R^3 = H$
g) $R^1 = R^2 = H$; $R^3 = CH_3$
h) $R^1 = H$; $R^2 = R^3 = CH_3$
i) $R^1 = H$; $R^2 = OCH_3$; $R^3 = CH_3$
j) $R^1 = R^3 = CH_3$; $R^2 = H$
k) $R^1 = (CH_2)_5CH_3$; $R^2 = H$; $R^3 = CH_3$
l) $R^1 = R^3 = CH_3$; $R^2 = C(CH_3)_3$

Scheme 1

Other important features in the ^{1}H NMR spectra of pyrazoles 1 are the following resonances due to: i) the N*H* protons which appear as broad singlets at δ 10.04-10.33 ppm; ii) H-α and H-β protons of pyrazoles 1a-c,g-i, which appear as AB spin systems at δ 6.72-6.89 ppm; and iii) H-β protons of pyrazoles 1d-f,j-l, which appear as broad singlets at δ 6.52-6.85 ppm. The coupling constants $J_{H\alpha\text{-}H\beta}$ ~ 16 Hz of the AB spin systems indicate *trans* configurations for the vinylic systems. However, we can still consider the formation of two isomers, like 3 and 4, taking into account the C_5-C_α isomerism. NOE experiments with 3-(2'-benzyloxy-6'-hydroxyphenyl)-5-(α-methylstyryl)pyrazole 1d have indicated a close proximity of α-CH_3 and H-4 and H-2',6', upon irradiation of the CH_3 resonance. These results indicate that of the two possible arrangements like 3 and 4, only the type structure 3 is present.



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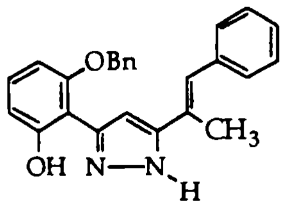

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The ^{13}C assignments in the ^{13}C NMR spectra of pyrazoles 1 were carried out by using 2D COSY and HETCOR experiments and also one-dimensional selective INEPT measurements.[9]

In the case of compounds 1g-l the assignment of the C-5 carbon resonance was made for each one by using a one dimensional selective INEPT experiment [7 Hz long-range *J* (C/H) coupling]: on irradiation of the N-CH_3 protons resonances, enhancements were observed in the resonances at δ 140.6-146.3 ppm, which were then attributed to C-5. The resonances at δ 146.8-147.3 ppm were assigned to the C-3 carbon atoms. For pyrazole 1d the assignment of C-5 was also made by using a one dimensional selective INEPT and 2D HETCOR experiments; upon irradiation of the H-β resonance [*J* (C/H) = 7 Hz], enhancements were observed in the resonances at δ 15.9, 129.2 and 144.9 ppm. These were assigned, respectively, to the α-CH_3, C-2′,6′ and C-5 carbon resonances. The resonance at δ 149.7 ppm was also assigned to the C-3 carbon atom. For the other NH pyrazoles 1a-c,e-f the assignments of the C-3 and C-5 carbon resonances[10] were made by comparison with those of compound 1d.

The formation of products 1 must involve a selective attack by hydrazine or methylhydrazine at C-2 of the 2-styrylchromone, with subsequent heterocyclic ring opening, followed by hydrazone formation and transformation into the final pyrazoles.

ACKNOWLEDGEMENTS

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6. **Experimental procedures:**

   To a methanolic solution (50 ml) of the appropriate 2-styrylchromone 2 (1 mmol), was added hydrazine hydrate (0.2 ml, 4.1 mmole) or methylhydrazine (0.4 ml, 8.2 mmlole) and the reaction mixture was heated at reflux (70-75 °C) during 24 hours. After this period the solvent was evaporated to dryness; the residue was taken in chloroform (50 ml), washed with water and purified by silica gel column chromatography, using chloroform as eluent, giving (*E*)-3-(2'-benzyloxy-6'-hydroxyphenyl)-5-styrylpyrazoles 1 (1a, 40%; 1b, 65%; 1c, 67%; 1d, 66%; 1e, 53%; 1f, 66%; 1g, 40%; 1h, 40%; 1i, 40%; 1j, 38%; 1k, 37%; 1l, 39%).
7. Characterization of 1a as an example of the set of compounds 1: Anal. Calcd. for $C_{24}H_{20}O_2N_2$; C, 78.24%; H, 5.47%; N, 7.60%; Found; C, 77.98%; H, 5.67%; N, 7.20%; m.p. 88-90 °C; ^{1}H NMR (300 MHz; $CDCl_3$; δ, ppm from TMS; *J* Hz) 5.20 (2'-OCH_2C$_6$H$_5$, s), 6.59 (H-3', d, *J* 8.2 Hz), 6.72 (H-5', d, *J* 8.2 Hz), 6.89 (H-α,β, AB, *J* 16.4 Hz), 7.16 (H-4, s), 7.16 (H-4', t, *J* 8.2 Hz), 7.27-7.48 (H-2'',3'',4'',5'',6'' and H-3,4,5 of 2'-OCH$_2$C$_6$$H_5$, m), 7.54 (H-2,6 of 2'-OCH$_2$C$_6$$H_5$, d, *J* 7.9 Hz), 10.04 (N*H*, s), 11.79 (6'-O*H*, s); ^{13}C NMR (75 MHz; $CDCl_3$; δ, ppm from TMS) 70.7 (2'-OCH$_2$C$_6$H$_5$), 103.1 (C-3'), 105.0 (C-4), 106.5 (C-1'), 110.4 (C-5'), 114.5 (C-α), 126.6 (C-2'',6''), 128.0 (C-2,6 of 2'-OCH$_2$C$_6$H$_5$), 128.2 (C-4 of 2'-OCH$_2$C$_6$H$_5$), 128.5 (C-4''), 128.6 (C-3,5 of 2'-OCH$_2$C$_6$H$_5$), 128.8 (C-3'',5''), 129.0 (C-4'), 131.7 (C-1''), 136.9 (C-1 of 2'-OCH$_2$C$_6$H$_5$), 137.8 (C-β), 141.0 (C-5), 149.6 (C-3), 157.2 (C-2'), 158.0 (C-6'); IEMS (int. rel) 368 ($M^{+\cdot}$, 100), 367 (40), 351 (12), 291 (37), 277 (17), 264 (14), 262 (14), 249 (21), 238 (10), 219 (14), 218 (13), 162 (7), 115 (10), 103 (6), 91 (93), 77 (7), 65 (13).
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10. ^{13}C resonances (δ, ppm from TMS) of C-3 and C-5 are the following: 1a 149.6 and 141.0; 1b 150.0 and 141.2; 1c 149.9 and 141.4; 1e 149.6 and 144.6; 1f 150.3 and 145.1.

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