EPOXIDATION OF 3-(3'-BUTENYL)-4-HYDROXYCOUMARINS AND INTRAMOLECULAR 6-EXO CYCLIZATION TO 3,4-DIHYDRO-2-HYDROXYMETHYL-2H,5H-PYRANO[2,3-b][1]BENZOPYRAN-5-ONES

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Abstract - Several 3-(3'-butenyl)-4-hydroxycoumarins were synthetized and oxidized with m-chloroperbenzoic acid. 3,4-Dihydro-2-hydroxymethyl-2H,5H-pyrano[2,3-b][1]benzopyran-5-ones were obtained through an intramolecular 6-Exo cyclization of intermediate epoxide.

Several oxygen heterocycles have been synthesized utilizing the intramolecular attack of oxygen nucleophiles on oxiranes. Three[1], four[2], five[3], six[4], and seven[5] membered oxygen heterocycles have been obtained in good yields and generally with high regio and stereoselectivity. Although such reactions are influenced by several factors, depending on substrate (stereoelectronic or steric factors) and on reaction medium (solvent, pH), in most cases Exo cyclization process prevails on Endo one[6].

At present we are investigating the ring forming reactions involving some 3-(3',4'-epoxybutyl)-4-hydroxycoumarins (3). Control of regioselectivity in our case is particularly difficult since both the oxygen in position 4 and that in position 2 of the coumarins can act as nucleophiles on epoxide intermediate both in an Endo and an Exo process. We have previously reported[7] that epoxides (3), obtained as labile intermediates by reacting dimethylsulphoxonium methylide on ketones (1), cyclize preferentially to 3,4-dihydro-2-hydroxymethyl-2H,5H-pyrano[3,2-c][1]benzopyran-5-ones (5) directly in the basic forming conditions. We now report a successfull almost regiocontrolled conversion of the same epoxide intermediates to isomeric 3,4-dihydro-2-hydroxymethyl-2H,5H-pyrano[2,3-b][1]benzopyran-5-ones (4).

Michael adducts (1), obtained by condensing 4-hydroxycoumarins with α,β-unsaturated ketones[8,9], were reacted with triphenylphosphonium methylide in dimethyl solfoxide/tetrahydrofuran solutions and olefins (2) were isolated in high yields[10] (Scheme).

The double bond was oxidized by addition of a slight excess of m-chloroperbenzoic acid in one hour period of time to a solution of (2) in dichloromethane at room temperature and in the presence of 0.1 - 0.2 molar equivalents of p-toluenesulfonic or trifluoroacetic acid. Removal of acids and of the excess of peracid with a slightly basic aqueous solution gave a crude reaction mixture from which pure 3,4-dihydro-2-hydroxymethyl-2H,5H-pyrano[2,3-b][1]benzopyran-5-ones (4) were isolated by chromatography on silica gel[11]. High regioselectivity in the

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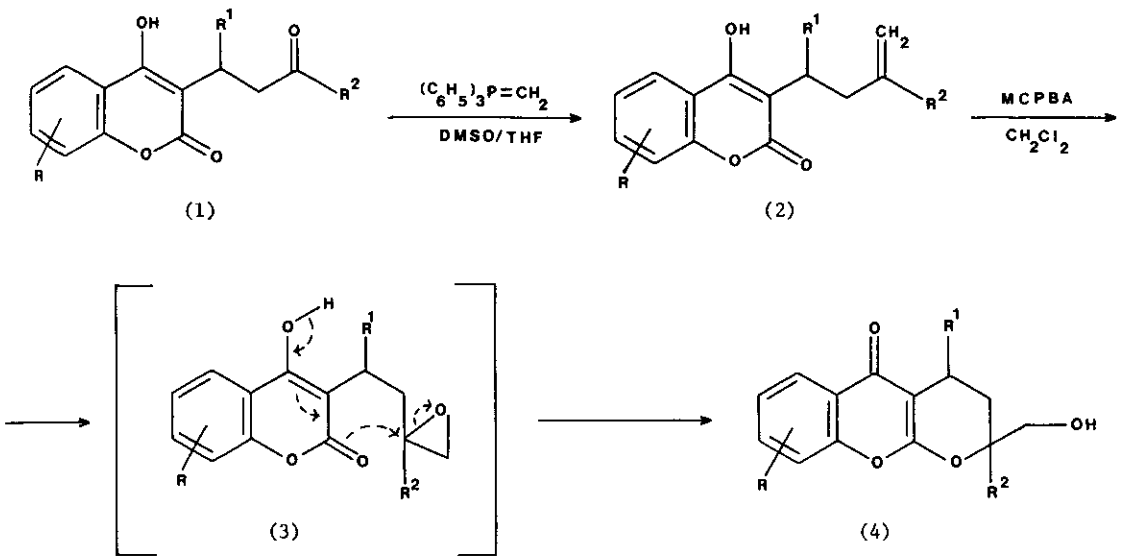

the intramolecular nucleophilic attack on intermediate epoxides (3) was usually observed under these reaction conditions (see Table). Formation of the six membered[12] linear isomers (4) was in fact significantly favoured with respect to the angular ones (5)[7] while varying preferences for one of the two cis-trans diastereoisomers were observed[14]. Conversion and regioselectivity were not significantly altered when strong acids were not added (Table, run 3); on the contrary they diminished dramatically when a molar amount of base was present in the reaction medium (Table, run 2,6)[15].

Structure assignments rest mainly on spectroscopic data. ^{13}C NMR spectra of linear isomers (4) showed a signal at 175.0 - 180.0 ppm, as already observed in 2-alkoxy or 2-aryloxy chromones[16]. In ^{1}H NMR spectra the CH_2CH mojety of cis diastereoisomers (4) (see onwards) gives rise to an ABX system in which H_A and H_B are almost isochronous (1.9 - 2.1 ppm). One of them shows a long range coupling with the methyl group in position 2 which is characteristic for a W pattern (0.8 Hz in 4a, d, and e) and another coupling with the vicinal H_X proton (10 Hz in previous substrates) typical for a trans diaxial position. These facts imply that the hydroxymethyl group and the substituent in position 4 are in a cis relationship. In the trans diastereoisomers (4) (in which the above cited ring substituents are trans each other) the CH_2CH group gives rise to an AMX system (H_A and H_M show chemical shift differences of about 0.4 - 0.6 ppm). In the ν(C=O) - ν(C=C) region of IR spectra both diastereoisomers of compounds (4) show two bands (ca. 1610 and 1555 cm^{-1}) while compounds (5) show three absorptions (ca. 1680, 1610, and 1570 cm^{-1})[7].

TABLE - Yields and physical data of compounds (4).

Run	Starting material	R	R^1	R^2	Reaction conditions[a]	Yields %[b] 4cis+trans	5cis+trans	4cis (mp°C;solv.)[c]	4trans (mp°C;solv.)[c]
1	2a	H	CH_3	CH_3	A	72	4	26 (d,e)	46 (136-137;C)
2	2a	H	CH_3	CH_3	B	32	22	10	22
3	2a	H	CH_3	CH_3	N	70	5	26	44
4	2b	H	C_6H_5	C_6H_5	A	49	5	-	49 (209-210;D)[f]
5	2c	H	CH_3	C_6H_5	A	33	6	10 (d,g)	23 (liquid)[h]
6	2c	H	CH_3	C_6H_5	B	7	22		
7	2d	H	C_6H_5	CH_3	A	73	6	39 (192-193;D)	34 (191;D)
8	2e	5,7-$(CH_3)_2$	C_6H_5	CH_3	A	62	5	36 (183;D)	26 (211;D)

(a) A: 0.1 - 0.2 molar equivalents of a strong acid were added to reaction mixture before addition of MCPBA; B: 1.0 molar equivalent of sodium bicarbonate or potassium carbonate was added; N: no addition was made. (b) No attempts were made to maximize yields and selectivity. (c) Uncorrected values; C = n-hexane/AcOEt; D = acetone. (d) No pure sample of this stereoisomer could be obtained; its presence in the proper chromatographic fractions was ascertained throug ^{1}H NMR (300 MHz) spectroscopy. (e) ^{1}H NMR ($CDCl_3$): 1.91-1.85 (CH_2), 1.41-1.43 ($2CH_3$), 8.08 (C(6)H); IR (nujol) 1610, 1555. (f) 31% yield of furtherly oxidized products as described in note 11 were isolated. (g) ^{1}H NMR ($CDCl_3$): 1.45 (CH_3); ^{13}C NMR ($CDCl_3$): 177.7 (C=O). (h) ^{1}H NMR ($CDCl_3$): 0.78 (CH_3CH); ^{13}C NMR ($CDCl_3$): 177.5 (C=O), 19.6 (CH_3); IR ($CHCl_3$) 1610, 1565.

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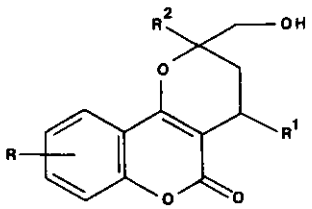

(5)

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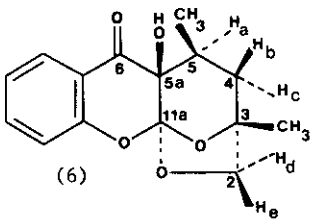
9. Products (1) were obtained and used as mixtures of cyclic hemiketals and open chain tautomer. In the synthesis of (1e), opening of B coumarin ring and decarboxilation occurred. The corresponding 1,5-diketone was obtained as a by product.

10. Yields and melting points (C_6H_6) of compounds (2): (2a): 95%, 141-142°C; (2b): 85%, 150-151°C; (2c): 90%, 130-131°C; (2d): 65%, 160-161°C; (2e): 66%, 145-146°C.

11. Olefins (2), in acid solution and in the absence of oxidizing agents, tend to cyclize and to give 3,4-dihydro-2-methyl-2H,5H-pyrano[2,3-b][1]benzopyran-5-ones and 3,4-dihydro-2-methyl-2H,5H-pyrano[3,2-c][1] benzopyran-5-ones. Otherwise, when a great excess of oxidizing agent is used and long reaction times are employed consistent amounts of further oxidation products having policyclic structures like (6) are formed.



(6)

^{1}H NMR (acetone-d_6): 1.69 (H_b, ^3J = 12.4 Hz), 1.80 (H_c, ^3J = 6.1 Hz), 2.51 (H_a), 3.65 (H_e, $^4J_{(Hb)(He)}$ = 2.2 Hz), 4.01 (H_d).

^{13}C NMR (acetone-d_6): 30.08 (C(5)), 41.51 (C(4)), 73.64 (C(2)), 74.18 (C(3)), 82.58 (C(5a)), 122.28 (C(11a), $^3J_{(\underline{C}(11a))(C(2)\underline{H})}$ = 5.0 Hz), 192.92 (C(6)).

12. The formation of 3-hydroxyoxepin isomers through a 7-Endo intramolecular cyclization of intermediate epoxide (3)[13] was ruled out as all isolated compounds showed a broad triplet for the hydroxyl signal in ^{1}H NMR spectra.

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14. The cis to trans ratio of compounds (4) probably depends on the diastereoisomer ratio of epoxides (3) formed. Attempts to isolate intermediates (3) or to have some rigorous experimental evidence of their formation has jet failed.

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