

AN ELEGANT SYNTHESIS OF 6H-BENZOFURO[3,2-c][1] BENZOPYRAN-6-ONES

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Abstract - Etherification of 4-hydroxy-2H-1-benzopyran-2-ones with 2-bromocyclohexan-1-one and cyclisation with PPA followed by dehydrogenation with DDQ affords 6H-benzofuro[3,2-c][1] benzopyran-6-ones in overall good yield.

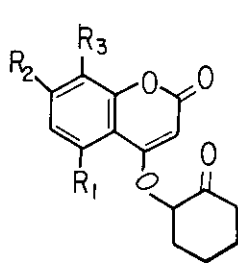
6H-Benzofuro[3,2-c][1] benzopyran-6-ones (coumestans) constitute a well defined group of naturally occurring substances such as coumestrol¹, tephrosol², coumestrin³ etc. They are of structure interest because they are related to substances of 3-aryl-2H-1-benzopyran-2-one type. Many of them are well known to possess estrogenic⁴, antibacterial⁵ and insecticidal⁶ activities. They are also reported² as fish toxic agents. A versatile method for the synthesis of propyl substituted benzofurocoumarins has recently been developed⁷ in our laboratory. This method has now been extended for the synthesis of 6H-benzofuro[3,2-c][1] benzopyran-6-ones involving the condensation of 4-hydroxy-2H-1-benzopyran-2-ones with 2-bromocyclohexan-1-one followed by ring closure with polyphosphoric acid and subsequent dehydrogenation with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ). Earlier, 6H-benzofuro[3,2-c][1] benzopyran-6-ones have been prepared by few methods⁸⁻¹⁰ but they are tedious and in general yields are low.

As a test case, 4-hydroxy-2H-1-benzopyran-2-one when condensed with 2-bromocyclohexan-1-one¹¹ in dry acetone in the presence of anhydrous potassium carbonate gave a solid product, C₁₅H₁₄O₄. The compound responded to DNP test indicating the presence of ketonic group and in its IR spectrum, two bands at 1720 cm⁻¹ (C=O) and 1630 cm⁻¹ (C=C) confirmed the presence of coumarin moiety. The ¹H NMR spectra showed the multiplets at δ 2.00-2.45 and 2.62-2.87 integrating for six and two protons respectively for four methylene protons of cyclohexanone ring and a triplet (J= 7Hz) at δ 5.16 of one proton was assignable to methineoxy group along with other signals. The above spectral data led us assign the structure of 4-(2-oxo-cyclohexanyloxy)-2H-1-benzopyran-2-one (1a) to the product. Compound 1a on heating with polyphosphoric acid

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(PPA) at 95-100°C for 2h gave a product $C_{15}H_{12}O_3$. It did not give any DNP test. Its IR showed absorption at 1720, 1620 cm^{-1} and 1H NMR, in the aliphatic region, indicated two multiplets at δ 1.75-2.05 and 2.64-2.86 each integrating for four protons whereas signals due to C_3 proton disappeared. Therefore, it was assigned the structure 7,8,9,10-tetrahydro-6H-benzofuro[3,2-c][1]benzopyran-6-one (2a). Dehydrogenation of 2a with DDQ in anhydrous benzene furnished 6H-benzofuro[3,2-c][1]benzopyran-6-one (3a). The structure of 3a was established on the basis of its elemental analysis and 1H NMR spectral data (Table-1).

Similar results were obtained when the reaction of 2-bromocyclohexan-1-one was extended to other 4-hydroxy-2H-1-benzopyran-2-ones. Thus, 4-hydroxy-7-methoxy-2H-1-benzopyran-2-one gave the ether 1b. Cyclisation of 1b with PPA afforded 2b which underwent dehydrogenation with DDQ to give 3b. Similarly, 4-hydroxy-7,8-dimethoxy-2H-benzopyran-2-one when reacted with 2-bromocyclohexan-1-one yielded 1c which was cyclised to 2c and 4-hydroxy-5,7-dimethoxy-2H-1-benzopyran-2-one yielded 1d which in turn was cyclised to 2d. All these products were characterised on the basis of elemental analysis, IR and 1H NMR spectral data. Dehydrogenation of 2c and 2d with DDQ gave 3c and 3d respectively.



1

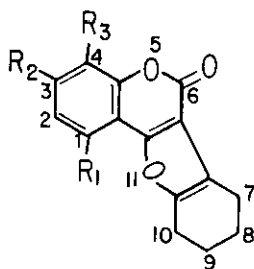
R_1

a, H

b, H

c, H

d, OCH_3



2

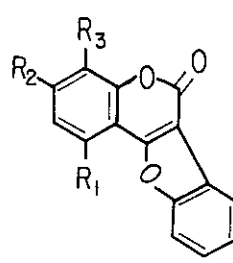
R_2

H

OCH_3

OCH_3

OCH_3



3

R_3

H

H

OCH_3

H

EXPERIMENTAL

All melting points are uncorrected and in degree centigrade. Light petroleum had boiling range 60-80°C; silica gel was used for column chromatography and TLC. IR spectra were measured on a Perkin-Elmer Infracord Spectrophotometer; ^1H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer. Table-1 summarises the yield, mp and spectral data for all the new compounds

4-(2-Oxo-cyclohexanyloxy)-2H-1-benzopyran-2-one (1a): General procedure

A mixture of 4-hydroxy-2H-1-benzopyran-2-one (2g, 12.3 mM), 2-bromocyclohexan-1-one¹¹ (2.18g, 12.3mM), anhydrous potassium carbonate (5g) and dry acetone (60 ml) was refluxed for 30h and the inorganic salts were filtered off. After evaporation of the solvent, the residue was treated with crushed ice to give a solid product (1a) which crystallised from ethanol as colourless needles (2.54 g), mp 229-230°C.

7,8,9,10-Tetrahydro-6H-benzofuro[3,2-c][1] benzopyran-6-one (2a): General procedure

Compound 1a (10g, 3.87 mM) was heated with PPA (5ml) on a boiling water bath (95-100°C) for 2h. Crushed ice was added to the cooled reaction mixture, the solid separated, was filtered, washed with aq. Na_2CO_3 (5%) and water. It was purified by column chromatography and eluting with benzene-petroleum ether (1:9) gave 2a. It crystallised from benzene-petroleum ether as colourless needles (0.65g), mp 190-191°C.

6H-Benzofuro[3,2-c][1] benzopyran-6-one (3a) : General procedure

A mixture of 2a (0.2g, 0.82 mM) and DDQ (0.35g, 1.4mM) in dry benzene (25 ml) was refluxed for 36h. The reaction mixture was filtered, the filtrate washed successively with aq. Na_2CO_3 (10%), water, dried and solvent distilled off. The residue was subjected to column chromatography while elution of column with benzene-petroleum ether (1:4) gave 3a. It crystallised from benzene-petroleum ether as colourless needles (0.17g), mp 187-188°C.

Table -1 Compounds prepared

Product ^a	Yield (%)	mp (°C)	IR KBr max (cm ⁻¹)	¹ H NMR (CDCl ₃ /TMS) δ (ppm)
1a	80	229-30	1720, 1630	2.00-2.45(m, 6H), 2.62-2.87(m, 2H), 5.16(t, J=7Hz, 1H), 5.98(s, 1H), 7.31-7.74(m, 3H), 7.98(dd, J=9Hz, 2.5Hz, 1H).
1b	78	204-5	1720, 1620	1.71-2.15(m, 6H), 2.36-2.62(m, 2H), 3.81(s, 3H), 4.85(t, J=7Hz, 1H), 5.34(s, 1H), 6.61-6.83(m, 2H), 7.68(dd, J=9Hz, 2.5Hz, 1H).
1c	80	212-13	1730, 1620	1.87-2.17(m, 6H), 2.40-2.66(m, 2H), 3.90(s, 6H), 5.27(s, 1H), 6.78(d, J=9Hz, 1H), 7.52(d, J=9Hz, 1H).
1d	77	213-14	1730, 1630	1.84-2.10(m, 6H), 2.52-2.70(m, 2H), 3.84(s, 6H), 4.75(t, J=7Hz, 1H), 5.22(s, 1H), 6.25(d, J=2.5Hz, 1H), 6.37(d, J=2.5Hz, 1H).
2a	69	190-91	1720, 1620	1.75-2.05(m, 4H), 2.64-2.86(m, 4H), 7.17-7.43(m, 3H), 7.72(d, J=9Hz, 1H).
2b	70	164-65	1720, 1615	1.70-1.95(m, 4H), 2.55-2.79(m, 4H), 3.78(s, 3H), 6.61-6.79(m, 2H), 7.44(d, J=9Hz, 1H).
2c	68	190-91	1730, 1630	1.75-1.95(m, 4H), 2.57-2.77(m, 4H), 3.88(s, 3H), 3.93(s, 3H), 6.82(d, J=9Hz, 1H), 7.33(d, J=9Hz, 1H).
2d	69	218-19	1730, 1625	1.70-1.95(m, 4H), 2.60-2.82(m, 4H), 3.80(s, 3H), 3.92(s, 3H), 6.25(d, J=2.5Hz, 1H), 6.43(d, J=2.5Hz, 1H).
3a	89	187-88	1730, 1620	7.24-7.59(m, 6H), 7.78-8.03(m, 2H).
3b	88	198-99	1730, 1630	3.75(s, 3H), 6.71-6.89(m, 2H), 7.20-7.55(m, 4H), 7.73(d, J=9Hz, 1H).
3c	90	189-90	1740, 1630	3.97(s, 3H), 4.05(s, 3H), 6.95(d, J=9Hz, 1H), 7.30-7.53(m, 4H), 7.65(d, J=9Hz, 1H).
3d	87	257-58	1730, 1620	3.73(s, 3H), 3.85(s, 3H), 6.20(d, J=2.5Hz), 6.34(d, J=2.5Hz, 1H), 7.15-7.60(m, 4H).

^a Satisfactory microanalysis obtained for all the products.

ACKNOWLEDGEMENTS

We are thankful to the University Grants Commission, New Delhi for financial help.

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Received, 6th December, 1984