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SYNTHESIS OF BIOACTIVE POLYHETEROCYCLES: REGIOSELECTIVE CYCLISATION OF 5-CYCLOHEX-2-ENYL-6-HYDROXY[1]BENZOPYRAN-2-ONE

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Abstract: 5-Cyclohex-2-enyl-6-hydroxycoumarin (**4**) was synthesised in 80 % yield alongwith 4% of 7-cyclohex-2-enyl-6-hydroxycoumarin (**5**) by the thermal sigmatropic rearrangement of 6-cyclohex-2-enyloxycoumarin (**3**) in refluxing N,N-diethylaniline. Treatment of **4** with *m*-chloroperoxybenzoic acid in refluxing benzene for 4 h gave 8-hydroxy-7a,8,9,10,11,11a-hexahydrobenzofuro[3,2-*f*]benzopyran-3-one (**6**) in 90 % yield which was then dehydrogenated to benzofuro[3,2-*f*]benzopyran-3-one (**7**) with excess of DDQ. Compound **4** was also cyclised with pyridine hydrotribromide or hexamine hydrotribromide to 2-bromo-1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one (**8**) in 88 % or 95 % yield respectively. Compound **4** when treated with cold conc. H_2SO_4 at 0-5 ^{0}C for 4 h furnished the cyclised 1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one (**10**) in 90 % yield.

Coumarin[1] and its derivatives[2] are interesting owing to their physiological activity. The biological activity[3,4] of 4-alkyl and 3-alkyl coumarins has made their syntheses[5] an important target. In this context we have been working on the regioselective synthesis of 3, 4-fused pyrano- and furocoumarins[6]. Our continued

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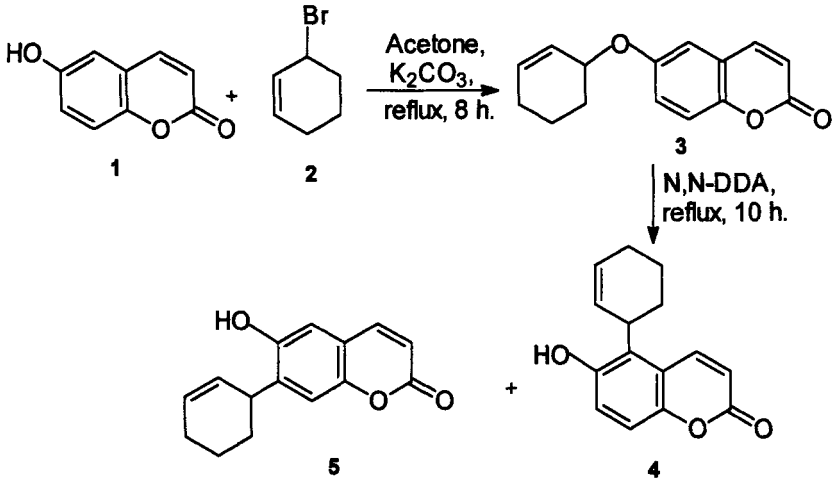

Scheme 1

interest in this area prompted as to undertake a programme for the synthesis of polyheterocycles containing pyran/furan ring fused with benzene ring of coumarin derived from 5-cyclohex-2-enyl-6-hydroxycoumarin (**4**). Here we report the results of this investigation.

This starting material for this study, 5-cyclohex-2-enyl-6-hydroxycoumarin (**4**) was synthesised by the thermal [3s, 3s] sigmatropic rearrangement of 6-cyclohex-2-enyloxycoumarin (**3**) in refluxing N,N-diethylaniline for 10 h. The ether **3** in turn was prepared by the reaction of 3-bromocyclohexene, (**2**) with 6-hydroxycoumarin, (**1**) in refluxing acetone in the presence of anhydrous potassium carbonate. This reaction also gave the other isomer 7-cyclohex-2-enyl-6-hydroxy coumarin (**5**) in ~ 4 % yield (**Scheme 1**).

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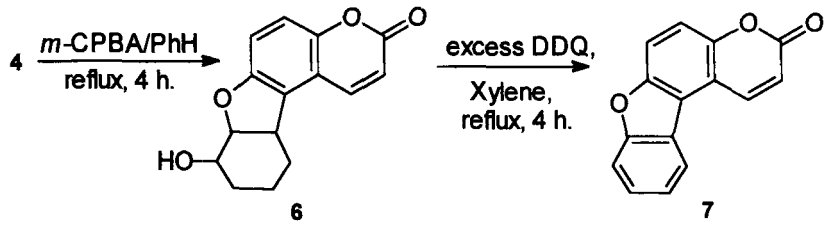

Scheme 2

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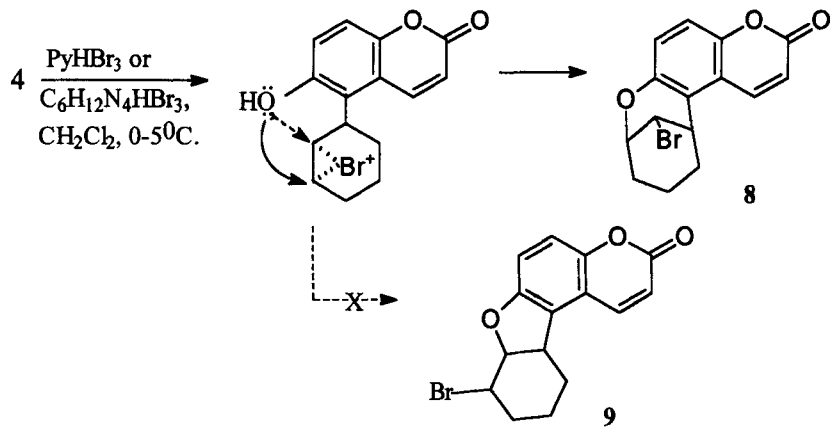
Results and Discussion.

Altogether four different approaches were made for the heterocyclisation of the substrate, 5-cyclohex-2-enyl-6-hydroxy[1]benzopyran-2-one (**4**). Recently there has been a lot of interest on the intramolecular epoxidative cyclisation of suitably substituted alkenes for the synthesis of various furo heterocycles[7] and pyrano heterocycles[8] as well as strategic molecules *e.g.*, lonomycin A[9], lasalocids and monensins[10]. This prompted us to treat our substrate 5-cyclo-hex-2-enyl-6-hydroxy[1]benzopyran-2-one (**4**) with one equivalent of *m*-chloroperoxybenzoic acid in boiling benzene for 4 h. A colorless crystalline solid was obtained in 90 % yield. This was characterised as the hydroxy polyheterocycle 8-hydroxy-7a,8,9,10,11,11a-hexahydrobenzo-furo[3,2-*f*]benzopyran-3-one (**6**) from its elemental analysis and spectral data. This product **6** was subjected to dehydrogenation with excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling dry xylene for 4 h to give the fully aromatised heterocycle benzofuro[3,2-*f*]benzopyran-3-one (**7**) in 75% yield (**Scheme 2**).



Scheme 3

The pyridine hydrobromide perbromide have recehtly been successfullyutilised for the heterocyclisation of suitably substituted *ortho*-cyclohexenyl phenols[11] in excellent yields. We have applied the same methodology for the cyclisation of substrate **4**. Consequently substrate **4** was treated with pyridine hydrotribromide in dichloromethane at 0-5 ^{0}C for 25 min. to give **9** in 88% yield. When hexamethylene tetramine hydrobromide perbromide[12] was used reaction time was reduced to 15 min. and the yield of product was almost quantitative (95 %) (**Scheme 3**). The product resisted dehydrobromination when treated with β-collidine. This rules out structure **9** for the product and indicates its bicyclic nature as in 2-bromo-1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one (**8**). However, a linear product was reported earlier from the reaction of 4-cyclohex-2-enyl-3-hydroxy-1-methylquinolin-2(1H)-one with pyridine hydrotribromide or hexamethylene tetramine hydrotribromide[13].

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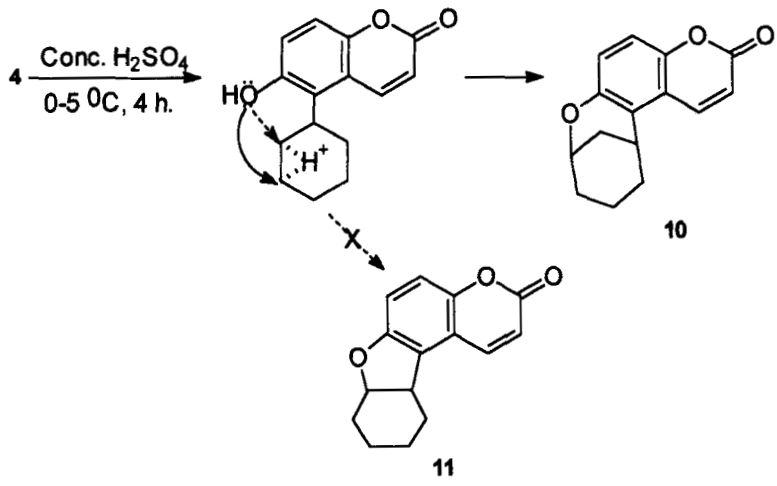

Scheme 4

Another well established methodology[14] for the cyclisation of *ortho*-allylphenols with cold concentrated sulphuric acid was also applied in the present study. The substrate **4** was treated with sulphuric acid at 0-5 ^{0}C for 4 h to give a viscous liquid in 90 % yield. The product 1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one (**10**) resisted dehydrogenation on treatment with excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in boiling xylene for 6 h or 10 % Pd-C in refluxing diphenyl ether for 2 h. This discard structure **11** and 1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one (**10**) may be assigned the structure for this product (**Scheme 4**).

The cyclisation of the substrate **4** was also attempted with mercury(II)acetate in methanol[15] at 25-30 ^{0}C for 12 h. No change of starting material was detected even when the reaction mixture was refluxed for 4 h.

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Experimental.

Melting points are uncorrected. UV absorption spectra were recorded on Hitachi 200-20 spectrometer in absolute ethanol. IR spectra were run for KBr discs on a Perkin-Elmer 1330 apparatus. PMR spectra were determined for solutions in deuteriochloroform with $SiMe_4$ as internal standard on a Jeol Fx-100 (100 MHz) instrument at the Indian Institute of Chemical Biology, Calcutta and Bruker-400 (400 MHz) instrument at the CDRI, Lucknow. Elemental analyses and mass spectra were carried out by RSIC (CDRI), Lucknow. Silica gel (60-120 mesh) was obtained from Spectrochem (India).

6-Cyclohex-2-enyloxycoumarin (3).

A mixture of 6-hydroxy coumarin (0.972g, 6 mmol), 3-bromocyclohexene (0.966 g, 6 mmol) and anhydrous potassium carbonate (3 g) was refluxed in dry acetone (100 mL) on a water bath for 8 h. The reaction mixture was cooled and filtered. The acetone was removed and the residue was extracted with chloroform. The chloroform extract was washed with water (2×25 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a crude mass which was then chromatographed over silica-gel (60-120 mesh). The product **3** was obtained as a white crystalline solid using benzene as eluant.

90 %; m.p.: 142 ^{0}C; UV(EtOH): λ_{max} (log ε) = 223(2.96), 284(2.90) nm; IR(KBr); ν_{max} = 3060, 2880, 1710, 1560 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$, TMS): δ = 1.65-2.13 (m, 6H), 4.79 (d, 1H, J = 1.5 Hz), 5.86 (dd, 1H, J = 8.5, 2 Hz), 5.98-6.04 (m, 1H), 6.42 (d, 1H, J = 8 Hz), 6.96 (d, 1H, J = 2.25 Hz), 7.13 (dd, 1H, J = 7.5, 2.5

Hz), 7.26 (d, 1H, J = 7.5 Hz), 7.65 (d, 1H, J = 8 Hz) ppm; MS: m/z = 242(M^+); $C_{15}H_{14}O_3$; Calc.: C, 74.38; H, 5.79 %; found: C, 74.57; H, 5.90%.

Procedure for the rearrangement of compound 3.

Compound **3** (1.0 g) was refluxed in N,N-diethylaniline (10 mL) for 10 h. The reaction mixture was cooled, poured into ice-cold dil. HCl (1:1) and extracted with chloroform (3×25 mL). Chloroform layer was washed with dil. HCl (3×25 mL) and water (2×25 mL). The chloroform layer was dried(Na_2SO_4) and the solvent was removed to give a crude mass. This was chromatographed over silica-gel (60-120 mesh). The column eluted with benzene and chloroform to give products **4** and **5** respectively.

5-Cyclohex-2-enyl-6-hydroxycoumarin 4: 80 %; m.p.: 202 ^{0}C; UV(EtOH): λ_{max} (log ε) = 224(3.31), 340(2.80) nm; IR(KBr): ν_{max} = 3400, 2860, 1710, 1585 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$, TMS): δ = 1.77-2.24 (m, 6H), 4.00 (brs., 1H), 5.93 (d, 1H, J = 6.5 Hz), 6.23 (brs, 2H), 6.43 (d, 1H, J = 8 Hz), 7.06 (d, 1H, J = 7.5 Hz), 7.16 (d, 1H, J = 7.5 Hz), 7.99(brs., 1H) ppm; MS: m/z = 242(M^+); $C_{15}H_{14}O_3$; Calc.: C, 74.38; H, 5.79 %; found: C, 74.57; H, 5.82 %.

7-cyclohex-2-enyl-6-hydroxycoumarin 5: 4 %; m.p.: 240 ^{0}C; UV(EtOH): λ_{max} (log ε) = 228(3.09), 290(3.04) nm; IR(KBr): ν_{max} = 3420, 2840, 1710, 1580 cm^{-1}; ^{1}H-NMR (100 MHz, $CDCl_3$, TMS): δ = 1.73-2.20 (m, 6H), 4.11 (brs., 1H), 5.88 (d, 1H, J = 6.5 Hz), 6.22 (brs., 2H), 6.43 (d, 1H, J = 8 Hz), 7.10 (s, 1H), 7.22 (s, 1H), 8.04 (d, 1H, J = 8 Hz) ppm; MS: m/z = 242(M^+); $C_{15}H_{14}O_3$; Calc.: C, 74.38; H, 5.79 %; found: C, 74.42; H, 5.86 %.

8-hydroxy-7a,8,9,10,11,11a-hexahydrobenzo-furo[3,2-*f*]benzopyran-3-one 6.

The compound **4** (0.121g, 0.5 mmol) was refluxed with *m*-CPBA (0.18g, 50%, 0.5 mmol) in thiophene free dry benzene (100 mL) for 4 h. The reaction mixture was cooled, washed with saturated sodiumbicarbonate solution to make the benzene layer free from *m*-chlorobenzoic acid. The organic layer was then washed with water (2×25 mL) and dried(Na_2SO_4). Removal of solvent gave a crude gummy mass which was subjected to column chromatography over silica-gel (60-120 mesh). The product **6** was obtained wen the column was eluted with ethylacetate-benzene (1:3).

90 %; m.p.: 190 ^{0}C; UV(EtOH): λ_{max} (log ε) = 224(3.12), 310(2.91) nm; IR(KBr): ν_{max} = 3450, 2940, 1690, 1450 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): δ = 1.40-2.10 (m, 7H), 3.55-3.80 (m, 1H), 4.15-4.30 (m, 1H), 4.58 (dd, 1H, J = 7, 2.5 Hz), 6.45 (d, 1H, J = 8 Hz), 7.00 (d, 1H, J = 7.5 Hz), 7.15 (d, 1H, J = 7.5 Hz), 7.73 (d, 1H, J = 8 Hz) ppm; MS: m/z = 258(M^+); $C_{15}H_{14}O_3$; Calc.: C, 69.77; H, 5.43 %; found: C, 69.89; H, 5.53 %.

Benzofuro[3,2-*f*]benzopyran-3-one 7.

Compound **6** (0.05g) was refluxed with excess DDQ in dry xylene (2 mL) for 4 h.The reaction mixture was cooled. It was then subjected to column chromatography over silica-gel (60-120 mesh). Xylene was removed by eluting the column with pet-ether (60-80 ^{0}C) and the dehydrogenated product **7** was obtained when benzene was used as eluant.

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75 %; m.p.: 186 ^{0}C; UV(EtOH): λ_{max} (log ε) = 228(3.27), 289(3.21) nm; IR(KBr): ν_{max} = 1725, 1600, 1530 cm^{-1} ; ^{1}H-NMR (100 MHz, $CDCl_3$, TMS): δ = 6.68 (d, 1H, J = 8 Hz), 7.40-7.88 (m, 5H) 8.08-8.24 (m, 1H), 8.54 (d, 1H, J = 8 Hz); MS: m/z = 236(M^+); $C_{15}H_8O_3$; Calc.: C, 76.27; H, 3.39 %; found: C, 76.31; H, 3.44 %.

2-bromo-1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one 8.

The brominating agent solid $PyHBr_3$ (0.16g, 0.5 mmol) was added slowly to a dichloromethane solution (25 mL) of the compound **4** (0.12g, 0.5 mmol). The reaction mixture was stirred for 25 min. at 0-5 ^{0}C (when $HMTAHBr_3$ was used in the same condition the reaction was completed within 15 min.). The reaction muxture was washed with 5 % $NaHCO_3$ solution (2×25 mL), water (2×25 mL) and dried(Na_2SO_4). The residual mass after removal of solvent was subjected to column chromatography over silica-gel using benzene-pet. ether (60-80 ^{0}C) (1:1) as eluant to give the solid.

95 %; m.p.: 170 ^{0}C; UV(EtOH): λ_{max} (log ε) = 228(3.09), 294(2.86) nm; IR(KBr): ν_{max} = 3080, 2950, 1720, 1580 cm^{-1} ; ^{1}H-NMR (100 MHz, $CDCl_3$, TMS): δ = 1.54-2.22 (m, 6H), 3.54-3.82 (m, 1H), 4.66-4.98 (m, 2H), 6.46 (d, 1H, J = 8 Hz), 7.08 (d, 1H, J = 7.5 Hz), 7.24 (d, 1H, J = 7.5 Hz), 7.70 (d, 1H, J = 8 Hz); MS: m/z = 322, 320(M^+); $C_{15}H_{13}BrO_3$; Calc.: C, 56.07; H, 4.05 %; found: C, 56.19; H, 3.98 %.

1,3-propano-1,2,3-trihydropyrano[3,2-*f*]benzopyran-8-one 10.

Compound **4** (0.2 g) was added to well-stirred cold conc. H_2SO_4 (2 mL) at 0-5 ^{0}C and the stirring was continued for 4 h at this temparature. The reaction mixture

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was poured into crushed ice and extracted with chloroform. The chloroform extract was washed with saturated $NaHCO_3$ solution to make the chloroform layer free from acid, then with water (3×25 mL) and dried (Na_2SO_4). Removal of solvent gave a viscous liquid which was subjected to column chromatography over silica-gel (60-120 mesh). The product **10** was obtained using benzene as eluant.

90 %; gummy mass; UV(EtOH): λ_{max} (log ε) = 223(3.05), 319(2.89) nm; IR(KBr): ν_{max} = 2820, 1710,1560 cm^{-1} ; ^{1}H-NMR (100 MHz, $CDCl_3$, TMS): δ = 1.56-2.12 (m, 8H), 3.32-3.52 (brs., 1H), 4.56-4.76 (brs., 1H), 6.44 (d, 1H, J = 8 Hz), 7.00 (d, 1H, J = 7.5Hz), 7.16 (d, 1H, J = 7.5 Hz), 7.88 (d, 1H, J = 8 Hz) ppm; MS: m/z = 242(M^+); $C_{15}H_{14}O_3$; Calc.: C, 74.38; H, 5.79 %; found: C, 74.42; H, 5.85 %.

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