Synthesis of angular furano- or pyrano-fused coumarins from natural scopoletin

K Nagaih, G L David Krupadananb & G Srinummarayana*

a Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India
b Department of Chemistry, Osmania University, Hyderabad 500 007, India

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Starting from natural coumarin, scopoletin, the syntheses of 8-methyl-6-methoxy-2H-furo[2,3-b]benzopyran-2-one 4, 10-dihydro-9-hydroxy-6-methoxy-2H-benzo[1, 2-b] [3, 4-e]dipyran-2-one 7, 8-hydroxy-6-methoxy-2H, 8H-benzo[1, 2-b]3, 4-b]dipyran-2-one 8 and 6-methoxy-2H, 9H-benzo[1, 2-b]3, 4-b]dipyran-2,8-dione 9 have been reported.

Natural coumarins are biosynthesized in plants as phytoalexins in response to pathogenic attack.1 Many pyrano- and furanocoumarins are isolated from natural source and are reported to have a variety of biological activities.2,3 Trioxsalen has photodynamic activity and used in the treatment of leucoderm.2 Furocoumarins such as pimpinellin, isopimpinellin, bergapten, isobergapten show high insect-antifeedant activity.4

From the bark of Xeromphis uliginosa, syn. Randia ulinium (Rubiacae), a coumarin disaccharide, 7-O-(β-D-apiofuranoxyyl)-6-methoxyxoumarin was isolated in high yield (2.2%) in our laboratories.5 This was also earlier reported as xeroboside6, or hymexelins.7,5 After hydrolysis of the disaccharide, the aglycone was identified as scopoletin (7-hydroxy-6-methoxyxoumarin 2). It was also isolated from the chloroform extract of X. uliginosa in (0.2%) yield.5 It is interesting to note that scopoletin is produced to report hypotension.5

In this paper we report the synthesis of some angular furano-or pyrano-coumarins starting from the natural scopoletin 2. Propargylation of scopoletin 2 yielded 7-O-propargylxoumarin 3, which was subjected to Claisen rearrangement and subsequent cyclisation5 by refluxing at 210°C to yield 8-methyl-6-methoxy-2H-furo (2, 3-h) [1] benzopyran-2-one 4 (Scheme 1). In 1H NMR (CDCl3) spectrum furano methyl group at C3 observed as a broad singlet at δ 2.50 and C3-proton appeared at δ 6.72 as a singlet (br). A three proton singlet at δ 3.90 is due to methoxyl. The C5 and C6 protons appeared as a doublet at δ 6.35 and 7.70 (J=10 Hz) respectively. MS spectrum showed M+ at m/z 230 as a base p. The fragment ions due to M-CH3 (m/z 215) and CO (m/z 202) were also found. Satisfactory microanalysis and spectral data were obtained.

Scopoletin 2 was allylated with allyl bromide giving corresponding 7-O-allylscopoletin 5 in 5% yield. This compound on Claisen rearrangement of N′-diethylamino afforded 8-allylscopoletin 6 in 5% yield. Equimolar amount of 8-allylscopoletin 6 and chloroperoxidebenzoic acid were dissolved in benzene and refluxed for 6 hr. Work-up of mixture gave a semi-solid which was chromatographed over a column of silica gel using pet-eth chloroform (4:6 v/v) to give 9, 10-dihydro-9-hydroxy-6-methoxy-2H,8H-benzo[1, 2-b]3, 4-b]dipyran-2,8-dione 9 have been reported.

Note

In MS, it showed the molecular ion at m/z 248 a base peak. The fragment ions at m/z 247 due to N [M-H], 229 (M-H2O), 204 (M-C2H5O), 220 (C0) and 176(M-C2H4O) were also found. T fragment ion at m/z 229, is a pyrillium ion, which highly characteristic of hydroxylhydroxypyralone system. The formation of hydroxyhydroxypyrone oxidation of 8-allyl-7-hydroxy-4-methylcoumarin m-CPBA was reported5 from our laboratories.

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A solution of 8-allylscopoletin 6 (1 mole) was oxidised with 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) (3 moles) and refluxed for 10 hr. TLC examination revealed the formation of two products. The crude reaction product was chromatographed over silica gel. Elution with chloroform : ethyl acetate (7:3 v/v) afforded one major product (40% yield) and chloroform : ethyl acetate (6:4 v/v) afforded a minor product (15% yield). The major compound was assigned structure 8-hydroxy-6-methoxy-2H, 8H-benzo-
[1, 2-b;3, 4-b]dipyran-2-one 8, m.p. 214°C, analyzed for C_{13}H_{10}O_{5}, and M' 246. The minor compound 6-methoxy-2H, 9H-benzo[1, 2-b;3, 4-b]dipyran-2, 8-dione 9, m.p. 234°C, analyzed for C_{13}H_{10}O_{5}, and M' 246.

The IR (KBr) spectrum of major compound 8 showed carbonyl at 1720 cm\(^{-1}\) and newly formed alcoholic-OH at 3375 cm\(^{-1}\). Its \(^1\)H NMR (CDCl\(_3\); 1 drop DMSO-\(d_6\); 200 MHz) spectrum showed the presence of a new structural segment H-C-H=CH as a part of a fused ring. The doublet at \(\delta 7.35 (J_{H,H}=10 \text{ Hz})\) is due to olefinic proton at C$_6$. The doublet at \(\delta 6.07 (J_{H,H}=10 \text{ Hz}; J_{H,H}=3 \text{ Hz})\) is due to allylic C$_3$ proton. The singlet at \(\delta 3.55\) is due to the allylic alcoholic OH. The AB doublet at \(\delta 6.32 (J=10 \text{ Hz})\) and 7.64 (J=10Hz) are due to C$_3$ and C$_4$ protons respectively. The singlet at \(\delta 6.86\) is due to the C$_5$. The three proton singlet at \(\delta 3.95\) is due to C$_6$-OCH$_3$. Its MS showed m/z 246 (M'\(^+\)) and 218 (M-CO). Thus the spectral data established the structure as 8.

The minor compound 9 in its IR spectrum (KBr) showed two carbonyl peaks at 1725 and 1720 cm\(^{-1}\) both characteristic of coumarin carboxyls. Its \(^1\)H NMR (CDCl\(_3\); 1 drop DMSO-\(d_6\), 200 MHz) spectrum showed the absence of allyl group, but revealed one pair of AB doublets at \(\delta 7.25\) (C$_3$-H or C$_9$-H, J=10Hz) and 6.90 (C$_3$-H or C$_9$-H) (J=10Hz) another pair of AB doublet as at \(\delta 7.65\) (C$_9$-H or C$_4$-H, J=10Hz) and 6.28 (C$_3$-H or C$_1$-H) (J=10Hz) integrating one proton each. The three proton singlet at \(\delta 3.98\) is due to C$_6$-OCH$_3$. The singlet at \(\delta 7.35\) is due to the C$_3$. Its MS showed m/z 244 (M'\(^+\)) and 216 (M-CO) and 186 (M-CO-CO). Thus from analytical and spectral data, the structure of the compound was assigned as 9. Earlier from our laboratory, the formation of coumarin ring system was reported by oxidative cyclisation of 2-allylphenols by DDQ.\(^{10,11}\)

The compounds 1 to 9 (9 to 1000 ppm in acetonitrile) were tested for insect-antifeedant activity for 8 hr, prestarved larva of IV larval of Spinopeda litera F, on fresh castor leaf disc, by non-choice test method.\(^{12}\) The percentage of insect antifeedant activity was calculated by the formula of Singh and Panth.\(^{13}\) The compounds 1 and 2 showed moderate antifeedant activity (75 to 50%) and 3 to 9 showed high insect-antifeedant activity (82 to 99%). Generally the compounds that exhibit above 75% antifeedant activity are considered to have high insect-antifeedant activity with potential to control agricultural pests while those with 75 to 50% antifeedant activity are considered to have moderate activity and below 50% poor antifeedant activity respectively.

**Experimental Section**

**General.** Melting points were taken in open capillary on sulphuric acid bath and are uncorrected. \(^1\)H NMR spectra (200 or 300 MHz) were recorded or Varian Gemini 200 and R.C. Bruker AM 300 MHz spectrometer in DMSO-\(d_6\) and or CDCl$_3$. Chemical shifts are reported in δ (ppm) relative to TMS as internal standard, coupling constants(J) were expresssed in Hertz. IR spectra were recorded on Perkin-Elmier Infrared model 337 in KBr pellet and UV spectrum in methanol on a Shimadzu UV-VIS 200 spectrometer Mass spectra were taken on a Finnigan Mat-121 double focussing spectrometer. Purification of compounds were done by silica gel (ACME, 200 mesh column).

**Scopoletin (7-hydroxy-6-methoxycoumarin) 2**

7-O-(β-D-Apiofuranosyl(1→6)-β-D-glucopyranosyl)-6-methoxycoumarin\(^3\) 1 (10 g) was hydrolysed by methanolic sulphuric acid (500 mL) to yield scopoletin (5.4 g) as reported in the literature.\(^2\)

**7-O-Propargylscoopletin (7-propargyloxy-6-methoxycoumarin) 3**

A mixture scopoletin 2 (1.86 g, 0.01 mole), propargyl bromide (1.30 g, 0.011 mole) and K$_2$CO$_3$ (20g) in acetone (100mL) was refluxed or steam bath for 6 hr. The acetone was removed under reduced pressure and then crushed ice was added to the residue. The solution was filtered and distilled. The crude product was recrystallised from dry chloro form to give 7-O-propargylscoopletin 3 as light yellow low crystals. m.p. 210-12°C (2.16g, yield 98%); If (KBr): 2130, 1710 cm\(^{-1}\); \(^1\)H NMR (CDCl$_3$, 200 MHz) \(\delta 2.49\) (t, J=2.5 Hz, 1H, =CH), 4.70 (d, J=2.5 Hz -CH$_3$), 6.29 (d, J=9.5 Hz, C$_1$-H, 7.93 (d, J=9.5 Hz, C$_6$-H), 7.26 (s, 1H, C$_3$-H), 7.78 (s, 1H, C$_5$-H), 3.78 (s, 3H -OCH$_3$); MS: m/z (%) 230(100), 215(5), 191(60), 16 (58), 135 (45). Anal. Calcd for C$_{13}$H$_{15}$O$_5$: C, 67, 84 H, 4.38; Found: C, 67.82, H, 4.37%.

**8-Methyl-6-methoxy-2H-furo[2, 3-b]1-benzopy ran-2-one 4**

7-O-Propargyl scopoletin 3 (2.0 g 0.01mole) was dissolved in N, N'-diethylanilin (25mL) was refluxed for 5 hr at 210 °C in oil bath. The crude product was chromatographed over silicagel (ACME 200 mesh) and eluted with pet,ether benzene(2:8) to give 4, m.p. 169°C (0.80 g, yield 68%); UV (MeOH) (log ε): 340nm (3.77), 304 (3.99); 251(4.52), 219 (4.54); IR (KBr): 1715 cm\(^{-1}\); \(^1\)H NMI (CDCl$_3$, 300 MHz): 82.58 (s, 1H, =C$_3$-H).
The resulting product 7-allylscopoletin that separated was filtered, washed thoroughly with water, dried and recrystallised from benzene as colorless needles as 5, m.p. 128°C. (3.24 g, yield 98%); UV (MeOH) (log e): 210 nm (4.50), 248 (4.48), 255(4.36), 325 (3.76); IR (KBr): 3075, 1715 cm^{-1}; ^1H NMR (CDCl$_3$, 200 MHz): δ 7.35 (d, 1H, $J_{	ext{H1,H2}}=10$ Hz, C$_6$-H), 6.07 (dd, 1H, $J_{	ext{H1,H2}}=10$ Hz, $J_{	ext{H2,H3}}=3$ Hz, C$_7$-H), 5.78 (d, 1H, $J_{	ext{H1,H2}}=3.0$ Hz, C$_8$-H), 3.58 (s, 3H, C$_9$-OCH$_3$), 6.32 (d, 1H, $J_{	ext{H1,H2}}=9.0$ Hz, C$_{10}$-H), 7.60 (d, $J_{	ext{H1,H2}}=10$ Hz, C$_9$-H), 7.79 (s, 1H, C$_8$-H), 6.79 (s, 1H, C$_7$-H), 3.98 (s, 3H, C$_6$-OCH$_3$). Anal. Calcd for C$_{13}$H$_9$O$_3$: C, 63.41, H, 3.02%.

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References