Facile Synthesis of Linear and Angular 2-Methylfurobenzopyranone

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Synopsis. A route for the synthesis of 2-methylfurobenzopyranone by the oxidative cyclization of sodium salt of 7-hydroxy-6 or 8-allyl-4*H*-[1]benzopyran-4-one using $PdCl_2(PhCN)_2$ complex has been developed.

Furo[1]benzopyranones were widely distributed in nature[1,2] and exhibit various biological properties. Khellin a furo[1]benzopyranone, isolated from *Ammi visanaga* (L) is useful in the treatment of angina pectoris, bronchial asthma and as a coronary vasodilator.[3,4] Recently it was also employed for the photochemotherapy of vitilago.[5] The synthesis of naturally occurring furo[1]benzopyranones khellin[6] and visnagin[2] has been reported. Earlier Hosokawa et al., synthesised 2-methylbenzofurans by the oxidative cyclization of sodium salt of *o*-allylphenols with $PdCl_2(PhCN)_2$.[7,8] In view of the interesting biological activity of furo[1]benzopyranones, we have developed a convenient and efficient route for the synthesis of some novel linear and angular 2-methylfuro[1]benzopyranone derivatives by the oxidative cyclization of sodium salt of 7-hydroxy-6 or 8-allyl-4*H*-1-benzopyran-4-one using $PdCl_2(PhCN)_2$ complex.

Results and Discussion

7-Allyloxy-4*H*-1-benzopyran-4-ones (**3a**—**d**) were prepared by the allylation of 7-hydroxy-4*H*-1-benzopyran-4-ones (**2a**—**d**, Table 1). The Claisen rearrangement of **3a**—**d** in refluxing *N*,*N*-diethylaniline (210 °C) afforded 7-hydroxy-6 or 8-allyl-4*H*-1-benzopyran-4-ones (**4a**—**d**, Table 2).

In the rearrangement of **3b** and **c**, the allyl group migrates to 8-position, due to the presence of the halogen substituents at 6-position, whereas in **3d**, due to the presence of methyl at 8-position, the allyl group migrates to 6-position. However, in the Claisen migration of **3a** there is a possibility of the allyl group migrate to 6 or 8-position. Since the aromatic protons of **4a** appeared as AB doublets, it is inferred that the allyl group has migrated to 8-position.

Compounds **4a**—**d** were converted into their corresponding sodium salts (**5a**—**d**). The suspension of the anhydrous sodium salts (**5a**—**d**) in benzene was treated with an equimolar quantity of dichlorobis(benzonitrile)-palladium and refluxed for 2 h. The precipitated metallic palladium was filtered off. The products of the reaction in each case viz., benzonitrile and linear or angular 2-methylfuro[1]benzopyranones (**6a**—**d**, Scheme 1) were separated by column chromatography over silica gel. The yield of reaction product was 95%. There were no traces of starting materials in the crude reaction product. Compared to the other methods available for the synthesis of linear or angular 2-methylfurobenzopyranones,[5,9,10] the present method affords a facile route with high overall yields. Reactions are easy to perform and proceed under mild conditions. The structures of the cyclization products **6a**—**d** of an angular 2,7,8-trimethyl-6*H*-furo[2,3-*h*][1]benzopyran-6-one (**6a**), 4-chloro-2,7,8-trimethyl-6*H*-furo[2,3-*h*][1]benzopyran-6-one (**6b**), 4-bromo-2,7,8-trimethyl-6*H*-furo[2,3-*h*][1]benzopyran-6-one (**6c**), and linear 2,6,7-trimethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**6d**) have been established on the basis of spectral data (Table 3).

Experimental

Melting points were determined in sulfuric acid bath and are uncorrected. IR spectra are recorded in KBr on a Shimadzu-435 spectrometer, ^{1}H NMR spectra were obtained on Varian Gemini-200 MHz spectrometer with TMS as an internal standard. Mass spectra were recorded on Perkin–Elmer Hitachi RDO-62 and MS-30 instrument.

Preparation of 7-Hydroxy-4*H*-1-benzopyran-4-ones (2a—d): General Procedure. 7-Hydroxy-2,3-dimethyl-4*H*-1-benzopyran-4-one[11] (**2a**), 7-hydroxy-2,3,8-trimethyl-4*H*-1-benzopyran-4-one[12] (**2d**) were prepared by reported method.

6-Chloro-7-hydroxy-2,3-dimethyl-4*H*-1-benzopyran-4-one (**2b**), 6-bromo-7-hydroxy-2,3-dimethyl-4*H*-1-benzopyran-4-one (**2c**) have now been prepared by refluxing **1b**—**c**, acetic anhydride and sodium acetate at 180 °C for 6 h and subsequent hydrolysis with 5% MeOH/HCl. **2a**, mp 281 °C; **2b**, mp 294 °C. **2b**: Calcd for $C_{11}H_9O_3Cl$: C, 58.78; H, 4.04%. Found: C, 58.72; H, 4.01%. **2c**: Calcd for $C_{11}H_9O_3Br$: C, 49.24; H, 3.38%. Found: C, 49.19; H, 3.32%.

Preparation of 7-Allyloxy Chromones (3a—d): General Procedure. 7-Allyloxy-2,3,8-trimethyl-4*H*-1-benzopyran-4-one[5] (**3d**) was prepared by reported method.

7-Allyloxy-2,3-dimethyl-4*H*-1-benzopyran-4-one (**3a**) 7-allyloxy-6-chloro-2,3-dimethyl-4*H*-1-benzopyran-4-one (**3b**), 7-allyloxy-6-bromo-2,3-dimethyl-4*H*-1-benzopyran-4-one (**3c**), have now been prepared by refluxing **2a**, **2b**, and **2c** respectively, with allyl bromide in acetone K_2CO_3 medium. **3a**: Calcd for $C_{14}H_{14}O_3$: C, 73.00; H, 6.13%. Found: C, 72.98; H, 6.11%. **3b**: Calcd for $C_{14}H_{13}O_3Cl$: C, 63.49; H, 4.95%. Found: C, 63.46; H, 4.93%. **3c**: Calcd for $C_{14}H_{13}O_3Br$: C, 54.53; H, 4.25%. Found: C, 54.51; H, 4.21%.

Preparation of 6 or 8-Allyl-7-hydroxy-4*H*-1-benzopyran-4-ones (4a—d): General Procedure. 6-Allyl-7-hydroxy-2,3,8-trimethyl-4*H*-1-benzopyran-4-one[6] (**4d**) was prepared by reported method.

8-Allyl-7-hydroxy-2,3-dimethyl-4*H*-1-benzopyran-4-one (**4a**), 8-allyl-6-chloro-7-hydroxy-2,3-dimethyl-4*H*-1-benzopyran-4-one (**4b**), 8-allyl-6-bromo-7-hydroxy-2,3-dimethyl-

Table 1. Physical Constants and Spectral Data of 7-Allyloxy-4*H*-1-benzopyran-4-ones (**3a**—**d**)

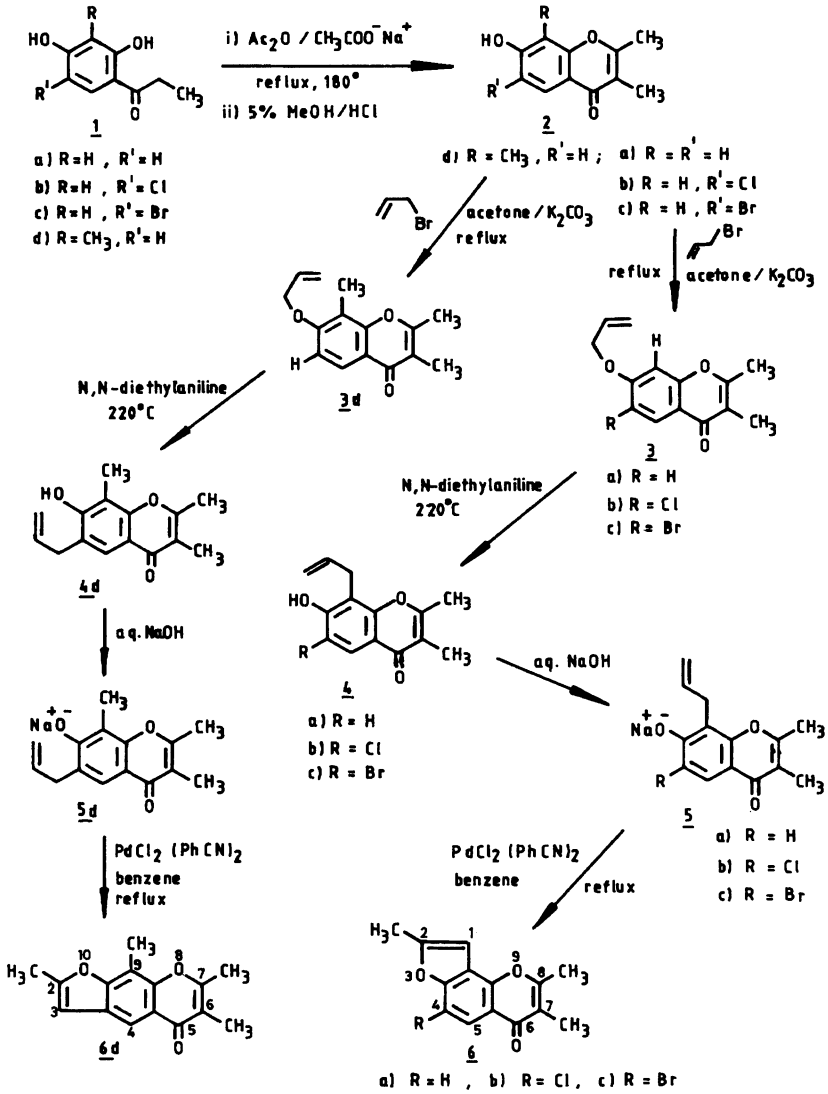
Entry	Compound	Mp/°C (lit, mp/°C)	IR ν (cm^{-1}) >C=O	IR ν (cm^{-1}) >C=C<	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200 MHz)
1	**3a**	97	1640	1615	2.43 (s,3H,H_3C-2); 2.11 (s,3H,CH_3-3); 8.12 (d,1H,H-5); 6.77—6.93 (m,2H,H6 and H-8); 4.65 (dd,2H,H-1′,J=6.0 and 11.0 Hz); 6.13 (m,1H,H-2′); 5.40 (m,2H,H-3′).
2	**3b**	138	1635	1615	2.35 (s,3H,CH_3-2); 2.05 (s,3H,CH_3-3); 8.15 (s,1H,H-5); 6.81 (s,1H,H-8); 4.65 (dd,2H,H-1′,J=6.0 and 1.0 Hz); 6.10 (m, 1H,H-2′); 5.40 (m,2H,H-3′).
3	**3c**	147	1640	1620	2.38 (s,3H,CH_3-2); 2.08 (s,3H,CH_3-3); 8.12 (s,1H,H-5); 6.80 (s,1H,H-8); 4.66 (dd,2H,H-1′,J=6.0 and 1.0 Hz); 6.11 (m,1H,H-2′); 5.38 (m,2H,H-3′).
4	**3d**	134 (132—134)	1645	1620	2.42 (s,3H,CH_3-2); 2.10 (s,3H,CH_3-3); 8.05 (d,1H,H-5, J=10.0 Hz); 6.95 (d,1H,H-6,J=10.0 Hz); 2.32 (s,3H,CH_3-8); 4.68 (dd,2H,H-1′,J=6.0 and 1.0 Hz); 6.10 (m,1H,H-2′); 5.40 (m,2H,3-H′).

Table 2. Physical Constants and Spectral Data of 7-Hydroxy-6 or 8-allyl-4*H*-1-benzopyran-4-ones (**4a**—**d**)

Entry	Compound	Mp/°C (lit, mp/°C)	IR ν (cm^{-1}) O–H	IR ν (cm^{-1}) >C=O	IR ν (cm^{-1}) >C=C<	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200 MHz)
1	**4a**	241	3280	1640	1620	2.35 (s,3H,CH_3-2); 1.95 (s,3H,CH_3-3); 7.65 (d,1H,H-5, J=10.0 Hz); 6.92 (d,1H,H-6,J=10.0 Hz); 3.52 (m,2H, H-1′); 5.90 (dd,2H,H-3′,J=10.0 and 1.0 Hz); 4.95 (dd,2H, H-3′,J=16.0 and 1.0 Hz); 10.20 (s,1H,O–H).
2	**4b**	258	3250	1640	1620	2.38 (s,3H,CH_3-2); 1.96 (s,3H,CH_3-3), 7.62 (s,1H,H-5, J=10.0 Hz); 3.59 (m,2H,H-1′); 5.91 (m,1H,H-2′); 5.10 (dd,2H,H-3′,J=10.0 and 1.0 Hz); 4.99 (dd,2H, H-3′,J=16.0 and 1.0 Hz).
3	**4c**	261	3270	1645	1615	2.39 (s,3H,CH_3-2); 1.97 (s,3H,CH_3-3); 7.64 (s,1H,H-5, J=10.0 Hz); 3.49 (m,2H,H-1′); 5.90 (m,1H,H-2′); 5.12 (dd,2H,H-3′,J=10.0 and 1.0 Hz); 4.99 (dd,2H, H-3′,J=16.0 and 1.0 Hz).
4	**4d**	193 (192)	3260	1640	1615	2.46 (s,3H,CH_3-2); 2.10 (s,3H,CH_3-3); 7.80 (s,1H,H-5, J=10.0 Hz); 2.30 (s,3H,CH_3-8); 3.50 (m,2H,H-1′); 6.08 (m,1H,H-2′); 5.30 (dd,2H,H-3′,J=10.0 and 1.0 Hz); 5.09 (dd,2H,H-3′,J=16.0 and 1.0 Hz).

Table 3. Physical Constants and Spectral Data of Angular and Linear 2-Methylfuro[1]benzopyranones (**6a**—**d**)

Entry	Compound	Mp/°C (lit, mp/°C)	IR ν_{max} (cm^{-1}) >C=O	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200 MHz)	Mass M^+
1	**6a**	231	1640	2.55 (s,3H,CH_3-2); 2.01 (s,3H,CH_3-6); 2.45 (s,3H, CH_3-5); 6.70 (s,1H,H-3); 8.05 (d,1H,H-8,J=9.0 Hz); 7.43 (d,1H,H-9,J=9.0 Hz).	228
2	**6b**	253	1640	2.52 (s,3H,CH_3-2); 2.43 (s,3H,CH_3-5); 2.06 (s,3H,CH_3-6); 6.68 (s,1H,H-3); 7.98 (s,1H,H-8).	262
3	**6c**	261	1645	2.51 (s,3H,CH_3-2); 2.42 (s,3H,CH_3-5); 2.04 (s,3H,CH_3-6); 6.68 (s,1H,H-3); 7.97 (s,1H,H-8).	306
4	**6d**	239 (239—241)	1645	2.56 (s,3H,CH_3-2); 2.08 (s,3H,CH_3-6); 2.48 (s,3H,CH_3-8); 6.46 (s,1H,H-3); 8.15 (s,1H,H-4); 2.45 (s,3H,CH_3-9).	242



Scheme 1.

4*H*-1-benzopyran-4-one (**4c**) were prepared by Claisen rearrangement of **3a**—**c** respectively in *N*,*N*-diethylaniline at 210 °C. **4a**: Calcd for $C_{14}H_{14}O_3$: C, 73.00; H, 6.13%. Found: C, 72.98; H, 6.11%. **4b**: Calcd for $C_{14}H_{13}O_3Cl$: C, 63.49; H, 4.95%. Found: C, 63.45; H, 4.93%. **4c**: Calcd for $C_{14}H_{13}O_3Br$: C, 54.33; H, 4.25%. Found: C, 54.51; H, 4.21%.

Preparation of Linear (6d) and Angular (6a—c) 2-Methylfuro[1]benzopyranones: General Procedure. A suspension of sodium salt (**5a**—**d**, 0.001 mol) in benzene (200 ml) containing $PdCl_2(PhCN)_2$ (0.001 mol) was stirred at room temperature for 30 min. The suspension became clear and developed intense red color during stirring. The clear red solution was refluxed for 2 h when metallic palladium separated out and the solution turned colorless. Palladium was filtered off the filtrate concentrated, and the products in each case (2-methylfurobenzopyranones and benzonitrile) were separated by column chromatography on silica gel (200 mesh, ACME). Elution with benzene gave benzonitrile and subsequent elution with chloroform gave the 2-methylfurobenzopyranones (**6a**—**d**) which recrystallised from benzene as colorless prisms. The yields of **6a**—**d** are 95%. **6a**: Calcd for $C_{14}H_{12}O_3$: C, 73.65; H, 5.30%. Found: C, 73.62; H, 5.27%. **6b**: Calcd for $C_{14}H_{11}O_3Cl$: C, 63.98; H, 4.22%. Found: C, 63.95; H, 4.19%. **6a**: Calcd for $C_{14}H_{11}O_3Br$: C, 54.89; H, 1.38%. Found: C, 54.86; H, 1.35%.

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