Monatshefte für Chemie 112, 119—124 (1981)

Monatshefte für Chemie

A Convenient Synthesis of Linear Pyranocoumarins. Xanthyletin and 3-Phenylxanthyletin

V. K. Ahluwalia*, K. Bhat, Chandra Prakash, and **Manjula Khanna**

Department of Chemistry, University of Delhi, Delhi-7, India

(Received 19 December 1979. Accepted 16 January 1980)

A convenient synthesis of linear pyranocoumarins, viz., 8,8-dimethyl-2*H*,8*H*-benzo[1,2—b;5,4—b′]dipyran-2-one (xanthyletin, **1**) and 8,8-dimethyl-3-phenyl-2*H*,8*H*-benzo[1,2—b;5,4—b′]dipyran-2-one (3-phenylxanthyletin, **2**) is described. The key steps are blocking the 8-position of appropriate 7-hydroxy-2*H*-1-benzopyran-2-one derivatives with iodine and 1,1-dimethyl-2-propynylation followed by cyclisation.

(Keywords: Pyranocoumarins; Xanthyletin derivatives)

Ein einfacher Syntheseweg zu linearen Pyranocumarinen. Xanthyletin und 3-Phenylxanthyletin

Es wird ein vorteilhafter Weg zur Synthese von linearen Pyranocumarinen am Beispiel von Xanthyletin und 3-Phenylxanthyletin gezeigt. Das Syntheseprinzip besteht in einer Blockierung der 8-Position des entsprechenden 7-Hydroxy-2*H*-1-benzopyran-2-ons mit Jod und einer 1,1-Dimethyl-2-propinylierung mit nachfolgender Cyclisierung.

In an earlier publication[1] we have presented the discovery of a new route for the synthesis of psoralen derivatives (linear furanocoumarins), by blocking the 8-position of the coumarin ring with an easily introducable and removable iodo group; we now see the feasibility of that route for the synthesis of linear pyranocoumarins, since a number of these coumarins have been isolated[2–14] from natural sources. A few syntheses of these coumarins are known[15–21] but these involve a number of steps and the yield is poor.

It has been observed[18, 20, 21] that 7-(1,1-dimethyl-2-propynyl) ethers (prepared by the reaction of 7-hydroxy-2*H*-1-benzopyran-2-one derivatives with 3-chloro-3-methylbut-1-yne in acetone/K_2CO_3) on heating

0026-9247/81/0112/0119/$ 01.20

with N,N-dimethyl aniline cyclised at the reactive 8-position resulting in the formation of angular pyranocoumarins (2*H*,8*H*-benzo[1,2—b; 3,4—b']dipyran-2-one derivatives). But cyclisation takes place at 6-position if the 8-position is substituted[18, 21] and the corresponding 8-substituted pyranocoumarins are obtained. Thus linear pyranocoumarins having the 8-position free could not be prepared by this method. However, these coumarins have been synthesised by very tedious methods[16–19], starting from 7-hydroxy-2,2-dimethylchroman derivatives, which are difficult to prepare. Further in the above methods the pyrone ring was built up on the preformed chromene nucleus but the synthesis, which involves the formation of chromene ring on pyrone skeleton may be closer to the biosynthetic process in plants. Hence a convenient method for the synthesis of these coumarins has been developed starting from 7-hydroxy-8-iodo-2*H*-1-benzopyran-2-one derivatives, reaction with 3-chloro-3-methylbut-1-yne in acetone/K_2CO_3 followed by cyclisation with boiling N,N-dimethylaniline. Using this method the synthesis of 8,8-dimethyl-2*H*,8*H*-benzo[1,2—b; 5,4—b']dipyran-2-one (xanthyletin) (**1**) and 8,8-dimethyl-3-phenyl-2*H*,8*H*-benzo[1,2—b; 5,4—b']dipyran-2-one (**2**) has been carried out. Xanthyletin (**1**) was earlier synthesised[17] by the condensation of 7-hydroxy-2,2-dimethylchroman (obtained by the reaction of CH_3MgI with 7-acetoxydihydrocoumarin) with methyl acrylate in presence of $AlCl_3$/HCl, dihydrogenation over Pd/C, followed by bromination with *NBS* and dehydrobromination with collidine.

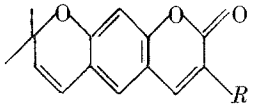
The synthesis of **1** has now been effected as follows: Propynylation of 7-hydroxy-8-iodo-2*H*-1-benzopyran-2-one[1] (prepared by iodination of 7-hydroxy-2*H*-1-benzopyran-2-one with iodine and periodic acid) with 3-chloro-3-methylbut-1-yne in acetone/K_2CO_3 gave 7-O-(1,1-dimethyl-2-propynyl)-2*H*-1-benzopyran-2-one (**3**) which on heating with N,N-dimethyl-aniline afforded **1**. Its NMR spectral data showed the presence of aromatic protons at C_5 and C_{10} which indicates that cyclisation takes place at 6-position and iodine is released. Further, it was found to be different from its angular isomer, viz., 8,8-dimethyl-2*H*,8*H*-benzo[1,2—b; 3,4—b']dipyran-2-one[24] (Seselin) (**4**).

Similarly, iodination of 7-hydroxy-3-phenyl-2*H*-1-benzopyran-2-one[25] with iodine/periodic acid gave 7-hydroxy-8-iodo-3-phenyl-2*H*-1-benzopyran-2-one (**5**). Its structure was confirmed by the NMR spectral data of its acetate, which showed the presence of two AB system of doublets ($J = 9.5$ Hz) for *ortho*-coupled H_5 and H_6 protons.

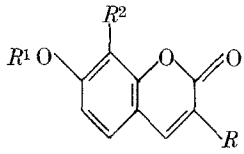
Propyneation of **5** with 3-chloro-3-methylbut-1-yne in acetone/K_2CO_3 followed by cyclisation of the 7-O-(1,1-dimethyl-2-propynyl)-8-iodo-3-phenyl-2*H*-1-benzopyran-2-one (**6**) with N,N-dimethylaniline afforded **2**. It was also found to be different from its angular isomer 8,8-dimethyl

3-phenyl-2*H*,8*H*-benzo[1,2—b; 3,4—b']dipyran-2-one (**7**) (3-phenylseselin), which was prepared by heating of 7-O-(1,1-dimethyl-2-propynyl)-2*H*-1-benzopyran-2-one (**8**) with N,N-dimethylaniline.

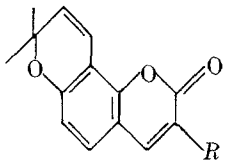
The method has wider application for the synthesis of other linear pyranocoumarins.



1 $R = H$
2 $R = —C_6H_5$



3 $R = H$; $R^1 = —C(CH_3)_2—C\equiv CH$; $R^2 = I$
5 $R = —C_6H_5$; $R^1 = H$; $R^2 = I$
6 $R = —C_6H_5$; $R^1 = —C(CH_3)_2—C\equiv CH$; $R^2 = I$
7 $R = —C_6H_5$; $R^1 = —C(CH_3)_2—C\equiv CH$; $R^2 = H$



4 $R = H$
8 $R = —C_6H_5$

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. The NMR spectra were measured on a R-32 spectrometer with $SiMe_4$ as internal reference.

8,8-Dimethyl-2 H,8 H-benzo[1,2—b; 5,4—b']dipyran-2-one (xanthyletin) (**1**)

(i) *7-O-(1,1-Dimethyl-2-propynyl)-8-iodo-2 H-1-benzopyran-2-one* (**3**)

A solution of 7-hydroxy-8-iodo-2*H*-1-benzopyran-2-one[1] (1 g) in dry acetone (75 ml) was refluxed for 24 h with 3-chloro-3-methylbut-1-yne (4 ml) in presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (1.5 g). The solvent was distilled off and the residue treated with ice. The separated solid was filtered, washed with dilute solution of sodium carbonate (2%), water and crystallized from benzene-petroleum ether as pale yellow shining needles of **3** (0.7 g, 63.6%), m.p. 182-183° (Found C, 47.5; H, 3.2. $C_{14}H_{11}IO_3$ requires: C, 47.4; H, 3.1%). NMR ($CDCl_3$): δ 1.80 [s, 6H, $—C(CH_3)_2$]; 2.71 (s, 1H, $—C\equiv C\mathbf{H}$); 6.32 (d, 1H, $J = 9.5$ Hz, H-3); 7.44 (d, 1H, $J = 9.5$ Hz, H-6); 7.54 (d, 1H, $J = 9.5$ Hz, H-5) and 7.65 (d, 1H, $J = 9.5$ Hz, H-4).

(ii) *8,8-Dimethyl-2 H,8 H-benzo[1,2—b; 5,4—b']dipyran-2-one (xanthyletin)* (**1**)

The above propynyl ether **3** (200 mg) was refluxed with N,N-dimethyl aniline (5 ml) for 6 h. The cooled reaction mixture was poured over ice cold

hydrochloric acid. The solution was extracted thrice with ethyl acetate, washed successively with 5% hydrochloric acid, 5% sodium hydroxide and finally with water and dried (Na_2SO_4). Distillation of ethyl acetate yielded **1** (80 mg) (56.9%) which crystallized from benzene-petroleum ether as yellow needles, m.p. 128–130° (Found C, 73.52; H, 5.34. $C_{14}H_{12}O_3$ requires: C, 73.6; H, 5.26%). NMR ($CDCl_3$): δ 1.43 [s, 6 H, $-C(CH_3)_2$]; 5.62 (d, 1 H, J = 10 Hz, Hβ); 6.18 (d, 1 H, J = 9.5 Hz, H-3); 6.27 (d, 1 H, J = 10 Hz, Hγ); 6.68 (s, 1 H, H 8); 7.02 (s, 1 H, H 5) and 7.52 (d, 1 H, J = 9.5 Hz, H-4).

8,8-Dimethyl-3-phenyl-2 H,8 H-benzo[1,2—b; 5,4—b']dipyran-2-one (3-phenylxanthyletin) (**2**)

(i) *7-Hydroxy-8-iodo-3-phenyl-2 H-1-benzopyran-2-one* (**5**)

7-Hydroxy-3-phenyl-2 *H*-1-benzopyran-2-one[25] (2.0 g) was dissolved in minimum amount of alcohol and to this solution iodine (0.914 g) and periodic acid (0.273 g) were added. The mixture was stirred for 2 h at room temperature and then diluted with water to give the coumarin **5** (2.2 g) (71.24%). It crystallized from alcohol as yellow needles, m.p. 239–240° (Found C, 49.2; H, 3.7. $C_{15}H_9IO_3$ requires: C, 49.5; H, 2.5%). Acetate, m.p. 215—216°. [Methyl ether, m.p. 224—225°. NMR ($CDCl_3$): δ 3.96 (s, 3 H, $-OCH_3$); 6.81 (d, 1 H, J = 9.5 Hz, H-6); 7.46 (d, 1 H, J = 9.5 Hz, H-5); 7.56 (m, 5 H, $-C_6H_5$) and 7.65 (s, 1 H, H-4)].

(ii) *7-O-(1,1-Dimethyl-2-propynyl)-8-iodo-3-phenyl-2 H-1-benzopyran-2-one* (**6**)

A solution of **5** (1 g) in dry acetone (75 ml) was refluxed with 3-chloro-3-methylbut-1-yne (4 ml) for 24 h in presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (1.12 g). The solvent was distilled off and the residue treated with ice. The separated solid was filtered, washed with dilute solution of sodium carbonate 2%, water and crystallized from benzene-petroleum either as yellow needles of **6** (0.62 g) (52.54%), m.p. 159–160° (Found C, 55.7; H, 3.6. $C_{20}H_{15}IO_3$ requires: C, 55.8; H, 3.5%). NMR ($CDCl_3$): δ 1.77 [s, 6 H, $-C(CH_3)_2$]; 2.67 (s, 1 H, $-C \equiv CH$); 7.40 (d, 1 H, J = 9.5 Hz, H-6); 7.49 (d, 1 H, J = 9.5 Hz, H-5); 7.57 (s, 1 H, H-4) and 7.70 (m, 5 H, $-C_6H_5$).

(iii) *8,8-Dimethyl-3-phenyl-2 H,8 H-benzo[1,2—b; 5,4—b']dipyran-2-one(3-phenylxanthyletin)* (**2**)

The above propynyl ether **6** (500 mg) was refluxed with N,N-dimethyl aniline (4 ml) for 6 h. The cooled reaction product was poured over ice cold hydrochloric acid. The working up the reaction as in **1** gave **2** which crystallized from benzene-petroleum ether as yellow needles (250 mg) (70.8%), m.p. 169–170° (Found C, 78.8, H, 5.4. $C_{20}H_{16}O_3$ requires: C, 78.9; H, 5.3%). NMR ($CDCl_3$) δ: 1.45 [s, 6 H, $-C(CH_3)_2$]; 5.63 (d, 1 H, J = 10 Hz, Hβ); 6.22 (d, 1 H, J = 10 Hz, Hγ); 6.98,(s, 1 H, H-8); 7.47 (m, 5 H, $-C_6H_5$); 7.55 (s, 1 H, H-5) and 7.60 (s, 1 H, H-4).

Preparation of the angular isomer 8,8-dimethyl-3-phenyl-2 H,8 H-benzo[1,2—b; 3,4—b']dipyran-2-one(3-phenylseselin) (**8**)

(i) *7-O(1,1-Dimethyl-2-propynyl)-3-phenyl-2 H-1-benzopyran-2-one* (**7**)

7-Hydroxy-3-phenyl-2 *H*-1-benzopyran-2-one[25] (0.5 g) in dry acetone (100 ml) was refluxed with 3-chloro-3-methylbut-1-yne (3 ml) in presence of

anhydrous potassium carbonate (1.5 g) and potassium iodide (0.7 g). The solvent was filtered and evaporated and the residue treated with crushed ice to give required aryl propynyl ether (0.45 g) (71.05%) which crystallized from benzene-petroleum ether as yellow needles, m.p. 134–135°. (Found C, 78.8; H, 5.37. $C_{20}H_{16}O_3$ requires: C, 79.0; H, 5.27%). NMR ($CDCl_3$) δ: 1.68 [s, 6 H, $-C(CH_3)_2$]; 2.64 (s, 1 H, $-C\equiv H$); 7.06 (dd, 1 H, $J = 9.5$ Hz, H-6); 7.35 (m, 5 H, $-C_6H_5$); 7.45 (d, 1 H, $J = 2.5$ Hz, H-8); 7.66 (d, 1 H, $J = 9.5$ Hz, H-5) and 7.75 (s, 1 H, H-4).

(ii) *8,8-Dimethyl-3-phenyl-2 H,8 H-benzo[1,2—b; 3,4—b']dipyran-2-one (3-phenyl seselin)* (**8**)

The above aryl propynyl ether (0.2 g) was refluxed with N,N-dimethyl aniline (3 ml) for 5–6 h. The cooled reaction mixture was poured over crushed ice cold hydrochloric acid (30 ml). The solid separated was taken up in ethyl acetate, washed with hydrochloric acid (5%, 60 ml) and finally with water and dried (Na_2SO_4). Distillation of ethyl acetate yielded **8** (0.15 g) (75%). It crystallised from benzene-petroleum ether as yellow plates, m.p. 143–144° (Found C, 78.8; H, 5.4. $C_{20}H_{16}O_3$ requires: C, 78.9; H, 5.3%). NMR ($CDCl_3$) δ: 1.44 [s, 6 H, $-C(CH_3)_2$]; 5.64 (d, 1 H, $J = 10$ Hz, Hβ); 6.64 (d, 1 H, $J = 9$ Hz, H-6); 6.82 (d, 1 H, $J = 10$ Hz, Hγ); 7.15 (d, 1 H, $J = 9$ Hz, H-5); 7.29–7.54 (m, 5 H, C_6H_5) and 7.58 (s, 1 H, H-4).

Acknowledgement

The authors express their sincere thanks to the Council of Scientific and Industrial Research and the University Grants Commission (New Delhi) for financial help.

References

1 *V. K. Ahluwalia, C. Prakash,* and *S. Bala,* Mh. Chem., in press.
2 *H. A. Jones,* J. Amer. Chem. Soc. **56**, 1247 (1934).
3 *S. A. Harper,* J. Chem. Soc. **1942**, 181.
4 *S. Krishna* and *T. P. Ghose,* Indian Forest Leaflet No. 2 (1942).
5 *E. P. Clarke,* J. Org. Chem. **8**, 489 (1943).
6 *H. A. Jones* and *H. L. Haller,* J. Org. Chem. **8**, 493 (1943).
7 *P. K. Bose* and *A. Mookerjee,* J. Ind. Chem. Soc. **21**, 181 (1944).
8 *A. Mookerjee,* J. Ind. Chem. Soc. **23**, 41 (1946).
9 *L. H. Briggs,* and *R. H. Locker,* J. Chem. Soc. **1951**, 3131.
10 *F. E. King, J. R. Housley,* and *T. J. King,* J. Chem. Soc. **1954**, 1392.
11 *M. P. Hegarty* and *F. N. Lahey,* Aust. J. Chem. **9**, 120 (1956).
12 *T. R. Govindachari, B. R. Pai, P. S. Subramanian,* and *N. Muthu-Kumar-Swamy,* Tetrahedron **24**, 753 (1968).
13 *W. D. Ollis, A. J. East,* and *R. E. Wheeler,* J. Chem. Soc. (C) **1969**, 365.
14 *C. P. Falshan, R. A. Harmer, W. D. Ollis, R. E. Wheeler, V. R. Lalitha,* and *N. V. Subba Rao,* J. Chem. Soc. (C) **1969**, 374.
15 *E. Späth* and *R. Hillel,* Ber. **72 B**, 2093 (1939).
16 *A. K. Ganguli, B. S. Joshi, V. N. Kamat,* and *A. H. Manmade,* Tetrahedron **23**, 4777 (1967).
17 *A. K. Dasgupta* and *K. R. Das,* J. Chem. Soc. (C) **1969**, 33.

[18] *J. Hlubuck*, *E. Ritchie*, and *W.C. Taylor*, Tetrahedron Lett. **1969**, 1369.
[19] *C. Mercier*, Chem. Abst. **73**, 55993 (1970).
[20] *A.C. Jain* and *S.M. Jain*, Tetrahedron **29**, 2803 (1973).
[21] *D. Mowat* and *R.D.H. Murray*, Tetrahedron **29**, 2943 (1973).
[22] *P.S. Sampathkumar*, *V.V.S. Murti*, and *T.R. Seshadri*, Ind. J. Chem. **9**, 1319 (1971).
[23] *V.K. Ahluwalia*, *C. Prakash*, and *R.P. Singh*, Ind. J. Chem. **15B**, 1033 (1979).
[24] *J.O. Hlubuck*, *E. Ritchie*, and *W.C. Taylor*, **17**, 1369 (1969).
[25] *B.B. Dey* and *K.K. Row*, J. Ind. Chem. Soc. **1**, 122 (1924).