Synthesis of 4,4-Dimethyl-5-methylene-4,5-dihydrofurans

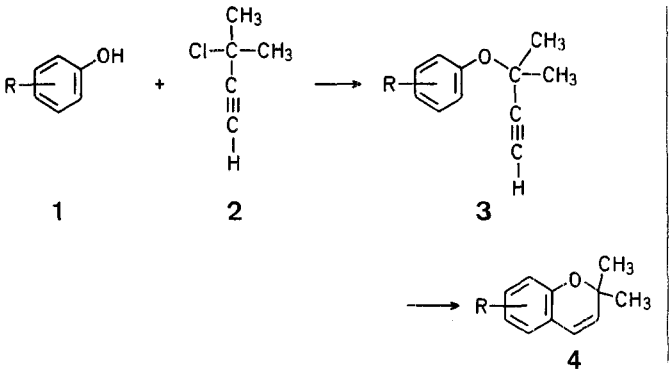
Robert CHÊNEVERT*, Jocelyne PAGÉ, Raymond PLANTE, Dominique BEAUCAGE

Département de Chimie, Faculté des Sciences et de Génie, Université Laval, Québec, Canada G1K 7P4

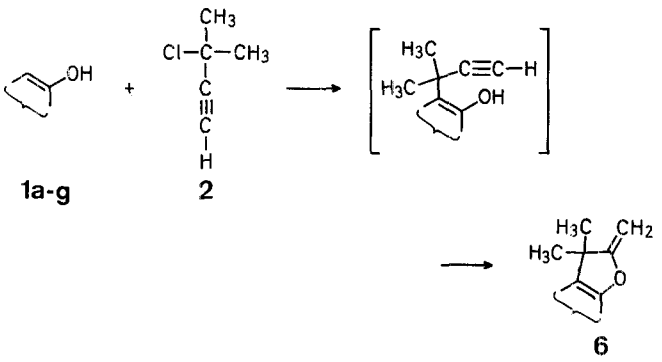
The *O*-alkylation of phenols **1** by 3-chloro-3-methylbutyne **(2)** followed by thermal rearrangement of the propargyl phenyl ethers **3** gives 2*H*-1-benzopyrans **4**, also called chromenes (Scheme **A**). Discovered by Iwai and Ide[1], the method has been applied in the synthesis of a large number of naturally occurring 2,2-dimethyl-2*H*-1-benzopyrans[2].

While using this method for the preparation of precocene analogs[3], we found that some phenols give furan derivatives along with chromene derivatives. We now report the applica-

0039-7881/82/0132-0075 $ 03.00



Scheme A



Scheme B

tion of this reaction to the synthesis of 4,4-dimethyl-5-methylene-4,5-dihydrofurans **6**, a class of compounds of which very few examples have been reported[4,5,6]. There is no general method of preparation for these compounds and the reported cases were unexpected side reaction products.

The enols **1a–g** were treated with 3-chloro-3-methylbutyne **(2)** in absolute ethanol in the presence of potassium carbonate and potassium iodide. The phenols **1a, b** reacted to give a mixture of furans **6** and chromenes **4** while the diketones **1c–g** gave exclusively furan compounds (Table). Yields are in the range 52–83%. The products were characterized by microanalysis and spectral methods (Table). Particularly, the ^{1}H-N.M.R. spectra of compounds **6a–g** are characteristic: the protons on the *exo*-double bond appear as two doublets ($J = 3$ Hz) at high field (between 4–5 ppm). Compounds **4a** and **4b** have been previously reported in the literature[7,8]. The furan compounds are almost certainly formed by *C*-alkylation followed by cyclisation of the intermediate ynol (Scheme **B**).

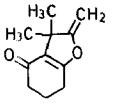
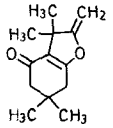
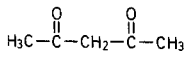
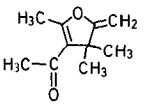
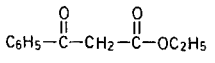
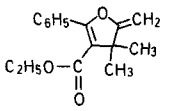
Similar ring closures of ynols by addition of a hydroxy group on the triple bond have been described in the literature[9,10]. The intermediate ynol has never been isolated under our experimental conditions. *A priori*, the intermediate could give a furan (*5-exo-dig*) or a pyran ring (*6-endo-dig*); according to the set of empirical rules proposed by Baldwin[11], both processes are favoured. However, a Dreiding model shows that the six-membered ring formation is sterically unfavorable, the terminal carbon atom on the triple bond being too distant from the oxygen atom. This is a consequence of the presence of an additional double bond in the forming ring.

The method is limited to enols able to give *C*-alkylation products. Since *O*-alkylation is usually predominant with phenols, they give mixtures where the furans are the minor products. Experimental conditions favouring *C*-alkylation over *O*-alkylation increase the yield in furan derivatives. The new compounds described have structures closely related to those of vitamin K antagonists (anti-coagulants) and are currently being tested for such pharmacological activity.

Table. 4,4-Dimethyl-5-methylene-4,5-dihydrofurans **6a–g** prepared

Substrate	Product(s)	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (CCl_4)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]	M.S. *m/e* (M^+)
1a	6a	21	61–62°	$C_{15}H_{14}O$ (210.3)	3035, 2940, 1670, 1620, 1572, 1510, 1450, 1434, 1250, 1190, 1025, 970, 920	1.73 (s, 6H); 4.30 (d, 1H, J=2.5 Hz); 4.72 (d, 1H, J=2.5 Hz); 7.3–8.0 (m, 5H)	210
	4a	62	oil				
1b	6b	20	88–89° (subl.)	$C_{12}H_{12}O_3$ (204.2)	2930, 2895, 1675, 1608, 1468, 1454, 1292, 1160, 1125, 1108, 1030, 930, 835	1.38 (s, 6H); 4.14 (d, 1H, J=2.5 Hz); 4.56 (d, 1H, J=2.5 Hz); 5.87 (s, 2H); 6.44 (s, 1H); 6.56 (s, 1H)	204
	4b	51	oil				
1c	6c	52	oil	$C_{14}H_{12}O_3$ (228.4)	3066, 2965, 2920, 1755, 1670, 1600, 1420, 1247, 1107, 1012, 982, 925	1.57 (s, 6H); 4.46 (d, 1H, J=3 Hz); 4.88 (d, 1H, J=3 Hz); 7.1–7.7 (m, 4H)	228

Table. (Continued)

Substrate	Product(s)	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (CCl_4)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]	M.S. m/e (M^+)
1d 	6d 	71	oil	$C_{11}H_{14}O_2$ (178.2)	2942, 2902, 2865, 1677, 1665, 1400, 1375, 1126, 1061, 1007, 920, 833	1.40 (s, 6H); 2.0 (m, 2H); 2.2–2.5 (m, 4H); 4.19 (d, 1H, J=3 Hz); 4.55 (d, 1H, J=3 Hz)	178
1e 	6e 	74	oil	$C_{13}H_{18}O_2$ (206.3)	2955, 2925, 2865, 2845, 1680, 1405, 1248, 1138, 1060, 1040, 940, 900, 843	1.11 (s, 6H); 1.39 (s, 6H); 2.17 (s, 2H); 2.32 (s, 2H); 4.18 (d, 1H, J=3 Hz); 4.54 (d, 1H, J=3 Hz)	206
1f 	6f 	68	oil	$C_{10}H_{14}O_2$ (166.2)	2990, 2940, 1718, 1690, 1664, 1410, 1390, 1280, 1158, 1085, 1022, 914, 855	1.36 (s, 6H); 2.26 (s, 6H); 4.04 (d, 1H, J=2.5 Hz); 4.40 (d, 1H, J=2.5 Hz)	166
1g 	6g 	83	oil	$C_{16}H_{16}O_3$ (258.3)	2950, 2910, 1714, 1671, 1617, 1398, 1384, 1345, 1232, 1100, 945, 835	1.13 (t, 3H, J=7 Hz); 1.49 (s, 6H); 4.04 (q, 2H, J=7 Hz); 4.14 (d, 1H, J=2.5 Hz); 4.53 (d, 1H, J=2.5 Hz); 7.2 (m, 3H); 7.5 (m, 2H)	258

[a] The microanalysis were in satisfactory agreement with the calculated values (C ±0.29, H ±0.23), performed by Dr. C. Daesslé, Organic Microanalyses, Montreal, Canada H3R 1K8.

[b] Beckman IR-12 spectrophotometer.

[c] Bruker HX-90 spectrometer.

4,4-Dimethyl-5-methylene-4,5-dihydrofurans 6a–g; General Procedure: The 3-chloro-3-methylbut-1-yne (**2**) is readily obtained from commercially available 3-hydroxy-3-methylbut-1-yne[12]. A mixture of the enol **1** (10 mmol), 3-chloro-3-methylbut-1-yne (**2**; 1.025 g, 10 mmol), potassium carbonate (1.750 g, 12.3 mmol), and potassium iodide (2.750 g, 16.5 mmol) in absolute ethanol (30 ml) is stirred under reflux for 2 h. An additional portion of compound **2** (10 mmol) is added and the reflux resumed for another 2 h. After cooling, ether (50 ml) is added, the salts are filtered off, washed with ether, and the combined filtrate and washings evaporated. The crude product is chromatographed on a short column of silica gel with dichloromethane as eluent. The pure compounds **6** are stable at room temperature and have a peculiar, coumarin-like odor.

Separation of 4a/6a and 4b/6b:
Separations are performed with a Waters System 500 preparative liquid chromatograph using two Prep. PAK-500 silica cartridges (5.7 × 30 cm).

4a/6a: Retention times **4a:** 32.0 min, **6a:** 8.5 min [solvent: 85:15 petroleum ether (35–60 °C)/dichloromethane; flow rate: 0.20 l/min].

4b/6b: Retention times **4b:** 7.5 m, **6b:** 6.0 min [solvent: 75:25 petroleum ether (38–49.5 °C)/dichloromethane: flow rate: 0.35 l/min.]

Financial supports from the Natural Sciences and Engineering Research Council of Canada and the Ministère de l'Education du Québec are gratefully acknowledged.

Received: July 28, 1981

[1] I. Iwai, J. Ide, *Chem. Pharm. Bull.* **11**, 1042 (1963).
[2] E. E. Schweizer, D. Meeder-Nyez, *Chromenes, Chromanones, and Chromones*, Wiley-Interscience, New York, 1977.
[3] R. Chênevert et al., *Experientia* **36**, 379 (1980).
[4] T. Hosokawa, H. Okkata, I. Moritani, *Bull. Chem. Soc. Jpn.* **48**, 1533 (1975).
[5] D. Plouin, C. Coeur, R. Glénat, *Bull. Soc. Chim. Fr.* **1973**, 1043.
[6] J. W. Huffman, T. M. Hsu, *Tetrahedron Lett.* **1972**, 141.
[7] R. Livingstone, D. Miller, R. B. Watson, *J. Chem. Soc.* **1958**, 2422.
[8] G. Sartori, G. Casiraghi, L. Bolzoni, G. Casnati, *J. Org. Chem.* **44**, 803 (1979).
[9] G. Büchi, H. Wüest, *J. Org. Chem.* **34**, 857 (1969).
[10] S. Holand, F. Mercier, N. Le Goff, R. Epsztein, *Bull. Soc. Chim. Fr.* **1972**, 4357.
[11] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734.
[12] G. F. Hennion, A. P. Boiselle, *J. Org. Chem.* **26**, 725 (1961).

0039-7881/82/0132-0077 $ 03.00