An Efficient Synthesis of 2-Acyl-1,4-benzodioxins

Gérald GUILLAUMET*, Michel TRUMTEL

Laboratoire de Chimie Organique, Université d'Orléans, Rue de Chartres, F-45046 Orléans Cedex, France

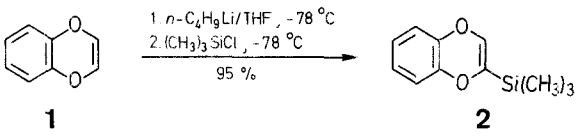
Gérard COUDERT*, Choukri ZEGGAF

Groupe de Recherche en Chimie Hétérocyclique, Université de Nancy I, B.P. 239, F-54506 Vandoeuvre-les-Nancy Cedex, France

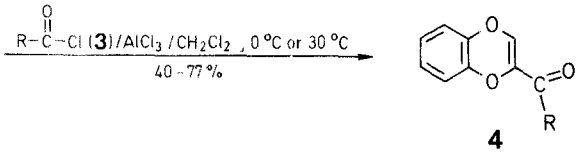
The synthesis of 2-acyl-1,4-benzodioxins from 2-trimethylsilyl-1,4-benzodioxin and acyl chlorides is described.

In the course of our work on the synthesis of therapeutically valuable benzodioxinic compounds[1,2], we needed 1,4-benzodioxins bearing various acyl groups on position 2. Some years ago we published a synthesis of benzodioxins from analogous benzodioxans[3] but, in the present case, this method proved to be inadequate due to the low availability of the required 2-acyl-1-4-benzodioxans. We report here an eminently versatile aliphatic Friedel-Crafts approach to 2-acyl-1,4-benzodioxins which proceeds under extremely mild conditions, relying for its success on the highly efficient acylation of vinyl silanes induced by Lewis acids[4,5,6].

The vinyl-silane **2** is readily prepared by metallation of 1,4-benzodioxin **1** with *n*-butyllithium (1.6 eq) in tetrahydrofuran at −78 °C followed by addition of chlorotrimethylsilane (2 eq.). The product obtained in quantitative yield after isolation is sufficiently pure to be used directly in the subsequent Friedel-Crafts acylation. Treatment of **2** and acetyl chloride (1.1 eq) in dichloromethane at 0 °C with aluminium chloride (1.1 eq) resulted quickly in the complete consumption of the substrate **2** as ascertained by thin layer chromatography. After 20 min, the resulting deep red solution is quenched with water. Isolation using dichloromethane and chromatography afforded pure 2-acetyl-1,4-benzodioxin **(4a)** in a overall yield of 77% from 1,4-benzodioxin. No further improvement in this yield could be obtained by increasing the proportions of acetyl chloride and aluminium chloride employed, by lowering or increasing temperature nor by use of titanium(IV) chloride as Lewis acid.



1 **2**



4

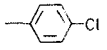
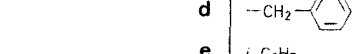
3,4	R	3,4	R
a	CH_3	f	
b	n-C_3H_7	g	
c	n-C_5H_{11}	h	
d			
e	i-C_3H_7		

Table. 2-Acyl-1,4-benzodioxins **4a–h** prepared

Product	Yield [%][a] by Method A	B	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν[cm^{-1}]	^{1}H-N.M.R. (solvent/TMS) δ[ppm]
4a	77	–	114–115°	112°[7]	1660	($CDCl_3$): 2.19 (s, 3H, CH_3); 6.55–7.05 (m, 4H$_{arom}$ + =CH—)
4b	70	–	91–92°	$C_{12}H_{12}O_3$ (204.2)	1665	($CDCl_3$): 0.90 (t, J = 7 Hz, 3H); 1.06–1.87 (m, 2H); 2.40 (t, J = 7 Hz, 2H); 6.20–6.85 (m, 4H$_{arom}$ + =CH—)
4c	66	–	69–70°	$C_{14}H_{16}O_3$ (232.3)	1670, 1675	(CCl_4): 0.85–1.90 (m, 9H); 2.44 (t, J = 7 Hz, 2H); 6.55–7.05 (m, 4H$_{arom}$ + =CH—)
4d	51	–	95–96°	$C_{16}H_{12}O_3$ (252.3)	1640, 1660	($CDCl_3$): 3.67 (s, 2H); 6.27–6.80 (m, 4H$_{arom}$ + =CH—); 6.98 (s, 5H$_{arom}$)
4e	76	–	oil	$C_{12}H_{12}O_3$ (204.2)	1635, 1655[c]	(CCl_4): 1.08 (d, J = 6.5 Hz, 6H); 2.93 (hept, J = 6.5 Hz, 1H); 6.45–7.05 (m, 4H$_{arom}$ + =CH—)
4f	–	60	75–76°	$C_{15}H_{10}O_3$ (238.2)	1635, 1660	(CCl_4): 6.55–6.96 (m, 4H$_{arom}$ + =CH—); 7.25–7.90 (m, 5H$_{arom}$)
4g	–	50	125–126°	$C_{15}H_9ClO_3$ (272.7)	1630, 1655	(CCl_4): 6.50–7.00 (m, 4H$_{arom}$ + =CH—); 7.42 (d, J = 8.6 Hz, 2H$_{arom}$); 7.81 (d, J = 8.6 Hz, 2H$_{arom}$)
4h	–	40	89–90°	$C_{15}H_9ClO_3$ (272.7)	1640, 1655	($CDCl_3$): 6.56 (s, =CH—); 6.65–7.05 (m, 4H$_{arom}$); 7.25–7.55 (m, 4H$_{arom}$)

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.16, Cl ±0.25.
[c] Neat.

Importantly compound **2** also reacted efficiently in the presence of aluminium chloride at 0°C with a range of other aliphatic acyl chlorides. In each case the appropriate 2-acyl-1,4-benzodioxin **4b–e** is obtained rapidly. During the acylation of **2** with aromatic acyl chlorides it proved necessary to keep the reaction mixture at 30°C and to increase the amount of aluminium chloride to reach satisfactory yields of **4f–h**.

In summary, this new approach provides superior access in terms of efficiency and convenience to benzodioxinyl ketones.

2-Trimethylsilyl-1,4-benzodioxin (2):
A 1.6 molar solution of *n*-butyllithium in hexane (20 ml, 32 mmol) is added dropwise over a period of 20 min to a stirred solution of 1,4-benzodioxin[3] (**1**; 2.68 g, 20 mmol) in dry tetrahydrofuran (40 ml) at −78°C under argon. After 2 h, chlorotrimethylsilane (4.34 g, 40 mmol) is added, and the mixture is further stirred for 2 h at −78°C. The cooling bath is removed and the mixture allowed to come to room temperature. After hydrolysis with water (30 ml), the product is extracted with ether (3 × 35 ml), the ether phase is dried with magnesium sulfate, and evaporated to give a yellow oil; yield: 3.92 g (95%); n_D^{25}: 1.5143.

$C_{11}H_{14}O_2Si$ (206.3) calc. C 64.04 H 6.84
found 63.89 6.93

I.R. (film): ν = 1645 cm^{-1} (C=C).

^{1}H-N.M.R. (CCl_4/TMS): δ = 0.14 [s, 9H, $OSi(CH_3)_3$]; 5.71 (s, 1H$_{ethylenic}$); 6.30–6.80 ppm (m, 4H$_{arom}$).

2-Acyl-1,4-benzodioxins 4; Typical Procedures:

Method A, R = alkyl: Under a nitrogen atmosphere, a solution of acyl chloride **3** (4.4 mmol) in dry dichloromethane (5 ml) is added at 0°C to a stirred suspension of anhydrous aluminium chloride (586 mg, 4.4 mmol) in dry dichloromethane (20 ml). After a few minutes the solid disappears and a solution of 2-trimethylsilyl-1,4-benzodioxin (**2**; 825 mg, 4 mmol) in dry dichloromethane (5 ml) is added dropwise with stirring. The addition rate is maintained so that the temperature of the reaction mixture does not exceed 5°C. The dark mixture is stirred at 0°C for 20 min and then quenched with ice/water (10 ml). The organic layer is washed with water (2 × 5 ml) and dried with magnesium sulfate. The solvent is removed in vacuo and the residue is chromatographed on silica gel using ether/petroleum ether as eluent to give **4**.

Method B, R = aryl: The procedure B differs from A only in the reaction temperature and molar rations. The reaction is conducted at 30°C with 8.8 mmol of acyl chloride, 8.8 mmol of aluminium chloride for 4 mmol of **2**.

Received: July 22, 1985

[1] Lalloz, L., Loppinet, V., Coudert, G., Guillaumet, G., Loubinoux, B., Labrid, C., Beaughard, M., Dureng, C., Lamar, J.C. *J. Med. Chem.* **1981**, *24*, 994.
[2] Regnier, G., Poignant, J.C. *European Patent* 84 993 (1983) ADIR; *C.A.* **1983**, *99*, 194 980 g.
[3] Coudert, G., Guillaumet, G., Loubinoux, B. *Tetrahedron Lett.* **1978**, 1059.
[4] Colvin, E. *Silicon in Organic Synthesis*, Butterworths, London, 1981, p. 70.
[5] Fleming, I., Pearce, A. *J. Chem. Soc. Chem. Commun.* **1975**, 633.
[6] Gill, M. *Tetrahedron* **1984**, *40*, 621.
[7] Farina, G., Zechi, G. *Synthesis* **1977**, 755.