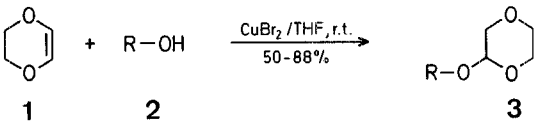
1,4-Dioxan-2-yl: A New Protective Group for Alcohols

Marcel FETIZON*, Issam HANNA

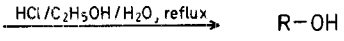
Laboratoire de Synthèse Organique, Ecole Polytechnique, F-91128 Palaiseau Cedex, France

The acid-catalyzed addition of dihydropyran to hydroxy groups has been extensively used for the protection of alcohols[1]. However, the signals of the methylene protons of the tetrahydropyranyl moiety may blur the ^{1}H-N.M.R. spectra between 0.5 and 2 ppm, especially at low field (60–100 MHz). This inconvenience is expected to be avoided when dihydropyran is replaced by dihydro-1,4-dioxin[2] (**1**) since each proton of the new protecting group is bonded to a carbon bearing an oxygen atom, and therefore gives rise to signals shifted downfield, in the range of 4 ppm.

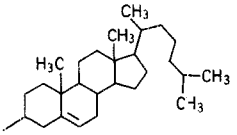
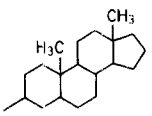
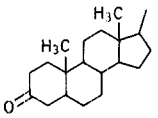
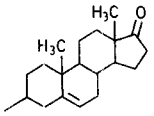
We report the preparation of 1,4-dioxan-2-yl derivatives **3** of some alcohols **2**. It is interesting to note that treatment of alcohols **2** with dihydro-1,4-dioxin (**1**) in the presence of a catalytic amount of *p*-toluenesulphonic acid led[3] to a *mixture* of the expected ether **3** and the formate **4** (as confirmed by a direct comparison of the ^{1}H- and ^{13}C-N.M.R. spectra with those of authentic samples). No feasible explanation for this can be given at present. Pyridinium *p*-toluenesulphonate was ineffective as catalyst.



1 2 3



2

2,3	R	2,3	R
a		d	
b		e	
c			

4

On screening various Lewis acids [copper(II) fluoride, silver tetrafluoroborate, copper(II) bromide, copper(II) chloride] we found that copper(II) bromide was the most effective. Thus, treatment of an alcohol **2** (1 mmol) with excess dihydro-1,4-dioxin (**1**; 4 mmol) at room temperature in the presence of copper(II) bromide (0.1 mmol) in tetrahydrofuran led to the desired 1,4-dioxan-2-yl derivatives **3** (Table). As can be seen from the Table, the highest yields are obtained with unhindered alcohols. This new protective group, which is stable towards lithium aluminium hydride and organolithium reagents can be removed by refluxing the compound **3** with acidified aqueous ethanol.

Dihydro-1,4-dioxin (**1**) is readily prepared by refluxing diethylene glycol in the presence of copper chromite/hydrogen potassium sulfate[2]; it is stable, and can be stored for several months in a refrigerator.

Addition of Alcohols 2 to Dihydro-1,4-dioxin (1); General Procedure: To a stirred solution of an alcohol **2** (1 mmol) and copper(II) bromide (22.3 mg, 0.1 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise a solution of dihydro-1,4-dioxin (**1**; 0.34 g, 4 mmol) in tetrahydrofuran (1 ml). The mixture is stirred at room temperature until the starting alcohol has completely disappeared (monitored by T. L. C.). It is then diluted with diethyl ether (20 ml), washed with sodium hydrogen carbonate in water (1 × 5 ml), and finally with a saturated solution of sodium chloride (1 × 10 ml). The

Table. 1,4-Dioxan-2-yl Derivatives **3** of Alcohols **2** prepared

Product	Reaction Time	Yield [%][a]	m.p. [°C][b] and/or $[\alpha]_D$ (*c*, $CHCl_3$)	Molecular Formula[c]	I.R. (CCl_4) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$) δ [ppm]
3a	20 h	85	oil	$C_{10}H_{18}O_3$ (186.2)	–	0.86–2.20 (m, 10H); 3.23–4.20 (m, 7H); 4.61 (2d, J = 7 Hz, 13 Hz, 1H);	23.8; 24.0; 25.3; 31.4; 33.3; 61.9; 65.8; 69.2; 75.3; 93.8
3b	20 h	88	119–121° +40° (3.9)	$C_{23}H_{38}O_3$ (362.5)	–	0.68 (s, 3H); 0.85 (s, 3H); 3.25–4.16 (m, 7H); 4.66 (m, 1H)	62.0; 66.0; 69.4; 76.9; 94.3
3c	28 h	80	153–154° +20° (2.2)	$C_{23}H_{34}O_4$ (374.5)	1745	0.87 (s, 3H); 1.03 (s, 3H); 3.26–4.16 (m, 7H); 4.67 (m, 1H); 5.37 (m, 1H)	62.1; 66.1; 69.5; 77.1; 94.3; 121.0; 141.0; 220.7
3d	62 h	75	105–106° −28° (2.3)	$C_{31}H_{52}O_3$ (472.2)	–	3.25–4.2 (m, 7H); 4.65 (m, 1H); 5.31 (m, 1H)	62.0; 66.0; 69.4; 77.3; 94.2; 121.7; 140.5
3e	72 h	50	121–122° +2° (2.2)	$C_{23}H_{36}O_4$ (376.5)	1715	0.80 (s, 3H); 1.0 (s, 3H); 3.26–4.20 (m, 7H); 4.50 (m, 1H)	(62.0, 62.2); 66.0; (69.1, 69.8); (85.8, 87.6); (94.8, 96.7)

[a] Yield of product isolated by flash chromatography.
[b] Recrystallization from methanol.
[c] All solid compounds gave satisfactory microanalysis: C ± 0.20, H ± 0.15. Purity of the oily compound **3a** was ≥ 98% as determined by ^{13}C-N.M.R. spectroscopy.

organic layer is dried with magnesium sulphate and concentrated. The crude product is purified by flash chromatography (ethyl acetate/pentane 1 : 9) on silica gel 60 (0.040–0.063 mm).

Removal of the 1,4-Dioxan-2-yl Protecting Group; Typical Procedure: A mixture of the 1,4-dioxan-2-yl derivative of cholesterol (**3d**; 250 mg, 0.53 mmol), ethanol (10 ml), water (1 ml), and 3 drops of 6 normal hydrochloric acid is refluxed for 2 h. Cholesterol (**2d**), which precipitates on cooling, is collected by filtration: yield: 184 mg (90%).

Received: November 27, 1984

[1] Green, T.W. *Protective Groups in Organic Chemistry*, John Wiley and Sons, New York, 1981, p. 10.
[2] Moss, R.D., Page, J. *J. Chem. Eng. Data* **1967**, *12*, 452.
[3] Gandolfi, C., Amendola, M., Doria, G., Guidobono, F., Agresta, G., Mandelli, V. *Farmaco Ed. Sci.* **1973**, *28*, 186; *C.A.* **1973**, *78*, 148106.