NIS OR NBS MEDIATED FORMATION OF HALO ACETALS. A CONVENIENT METHOD FOR THE ONE POT DISUBSTITUTION OF 1,4-BENZODIOXIN

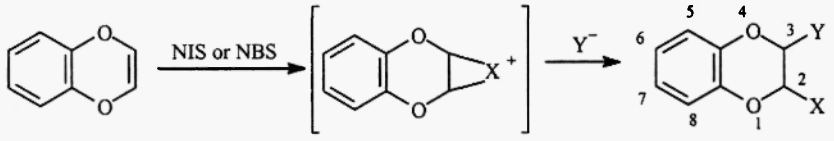
A. Sergi Capilla, Nathalie Hernández, and Mª Dolors Pujol.*

Laboratori de Quimica Farmaceutica. Facultat de Farmacia. Universitat de Barcelona. Av. Diagonal 643, 08028 Barcelona, Spain. Fax: 93 403 59 41

Abstract: 2,3-Substituted-1,4-benzodioxins are easily obtained under mild conditions in one-pot reaction from 1,4-benzodioxin with electrophilic halogen as iodine (NIS) or bromine (NBS) and the appropriate alcohol or phenol, in dichloromethane.

Introduction

Although much has been written on the substructure of 2-substituted and 2,3-disubstituted 2,3-dihydro-1,4-benzodioxin as parts of compounds of considerable medicinal interest[1], reports on the one-pot preparation of 2,3-substituted benzodioxins are rare. Few synthetic methods are available for their preparation from 1,4-benzodioxin, though their alkylation with alkyllithium reagents[2] has received considerable attention. In order to enlarge the reactivity of this dioxygenated heterocycle and as part of our studies on dioxygenated compounds, we report here a simple one-pot procedure by which 1,4-benzodioxin and related compounds were converted into 2-halo acetals or 2,3-disubstituted systems (Scheme 1).



1 **2a** X = I, **2b** X = Br **3a-k** X = I, Br or Y; Y = OR

Scheme 1

The parent 1,4-benzodioxin (**1**) employed in this study was obtained from the saturated compound using the standard method in the literature.[3] The treatment of **1** with NIS or NBS gave the cyclic three-membered ring intermediates (**2**) obtained *in situ*, which was then treated with an appropriate nucleophile. Direct nucleophilic attack gave the 2,3-disubstituted compounds. The products obtained were purified by column chromatography on silica gel, eluting with hexane-ethyl acetate mixtures. In all cases, only one isomer was obtained, deduced from ^{1}H-NMR data. These conditions are mild and should prove useful for the preparation of a wide variety of halo acetals and halo aminoacetals.

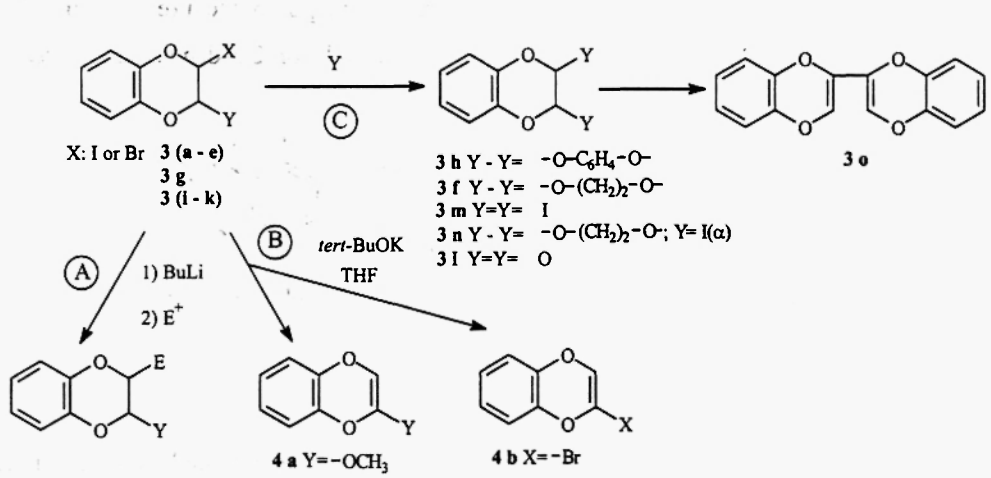
* To whom correspondence should be addressed. E-mail: mdpujol@farmacia.far.ub.es

Reaction conditions for each compound are given in Table 1. Several solvents (THF, dioxane, DME, or other solvents) were tested, but CH_2Cl_2 is our solvent of choice for this transformation, whereas THF reacted with the intermediate (**2**) and led to the corresponding alkylated compound.

Iodo or bromo derivatives have been used in organic synthesis especially for the introduction of nucleophilic groups by direct displacement or by halogen-metal interchange with alkyllithium reagents followed by condensation with electrophilic groups,[2] as shown in Scheme 2 (Method A).

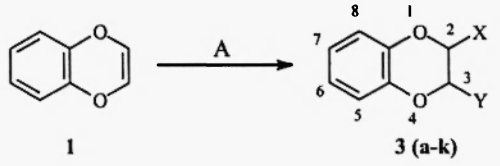
Method B involves the reaction of the halo acetal (**3**) with potassium *tert*-butoxide in THF. The iodo acetals upon treatment with *tert*-BuOK in THF at room temperature underwent iodide elimination and gave 2-substituted-1,4-benzodioxins in good yield (pathway b). Moreover, under the same conditions the bromo derivative (**3i**) underwent methoxy elimination and gave only the 2-bromo-1,4-benzodioxin in a good yield.

The compound (**3a**) was rapidly transformed into **4a** by dehalogenation with *tert*-BuOK, whereas the treatment of **3i** with *tert*-BuOK under the same conditions leads to the formation of **4b**. With reaction of **1** with NIS and ethylenglycol (Entries 6 and 7, Table 1) following method C, a mixture of **3e** and **3f** was obtained and the less stable intermediate (**3n**) resulting from iodination at the 4a-position was also identified. Moreover, in some of these transformations 2-(1,4-benxodioxin-2-yl)-1,4-benzodioxin (**3o**) was formed in low yields (Entries 9 and 10).

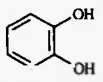
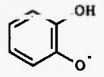
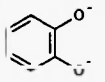
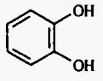
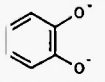


Scheme 2

Table 1. Conditions of synthesis for compounds **3(a-k)** from 1,4-benzodioxin **(1)**



1 3 (a-k)

Entry	A	Conditions		Product 3			Yield% [a]
		Temperature	Time	X	Y	Compound	
1	NIS/CH_3OH	-30°C-rt	1	I	$-OCH_3$	3a	53[b]
2	NIS/CH_3OH	"	24	I	$-OCH_3$	3a	55[b]
3	NIS CH_3CH_2OH	"	1	I	$-OCH_2CH_3$	3b	45[f]
4	NIS $C_6H_5CH_2OH$	"	2	I	$-OCH_2C_6H_5$	3c	73
5	NIS CH_3CH_2COONa	"	2	I	$-OCOCH_2CH_3$	3d	20
6	NIS $HOCH_2CH_2OH$	"	4	I	$HOCH_2CH_2O-$	3e + 3n	45[c]
					$-OCH_2CH_2O-$	3f	27
7	NIS $HOCH_2CH_2OH$	"	6	I	$HOCH_2CH_2O-$	3e + 3n	8[c]
					$-OCH_2CH_2O-$	3f	61
8	NIS 	-15°C-rt	5	I		3g	33[d]
						3h	/
9	NIS 	"	12			3h+3n+3m +3o	40[d-f]
10	NBS CH_3OH	0°C-rt	24	Br	$-OCH_3$	3i+3o	75[f]
11	NIS or I_2 NaOH	0°C-rt	24	I	$-OH$	3j	/
				$-OH$	$-OH$	3k	/
				$-O-$		3l	/
12	NIS or I_2 H_2O	"	52	$-OH$	$-OH$	3k	/

a) Unless otherwise noted, all compounds obtained (**3a-k**) were purified by column chromatography on silica gel and were analysed by high-field proton and ^{13}C NMR. b) The iodo derivative was unstable due to the polymerisation process. c) The iodo derivative (**3n**) was also detected and identified. d) Starting material was also obtained. e) The unstable 2,3-diiodo-1,4-benzodioxin (**3m**) was also detected and identified. f) The 2-(1,4-benzodioxin-2-yl)-1,4-benzodioxin (**3o**) was observed by NMR-spectra.

Table 1

Treatment of iodo derivatives with another nucleophilic group afforded the corresponding 2,3-disubstituted compounds by intramolecular displacement of the iodide ion: for example, if a diol was used as a nucleophilic group, the corresponding cyclic system was obtained (Entries 6-9). Under these conditions, the formation of polycyclic compounds may be a consequence of thermodynamic control. When NIS was used as an halogenating agent, prolonged reaction times did not markedly increase the yield (Entry 2 *versus* 1). When 1,4-benzodioxin **(1)** was treated with NBS/methanol in the described conditions, **3i** was obtained in better yield than iodinated **3a** (Entry 10 *versus* 1). The last compound was obtained from **1** by treatment with NIS/methanol. The best yield of **3i** was attributed to the stability of the halogenated intermediate. The iodo derivative is more unstable and more reactive than the corresponding bromo derivatives. In some reactions the undesired 2,3-diiodo-1,4-benzodioxin **(3m)** was obtained in poor yield: this compound was analyzed by ^{1}H-NMR (Experimental section) and decomposed quickly, as confirmed later by spectral data. When **1** was treated with NIS or I_2 in H_2O the corresponding diol **(3k)** was obtained and treatment with NIS or I_2 in NaOH solution led to a mixture of **3j**, **3k** and **3l**. The compounds identified by NMR were unstable and purification was impossible under the usual conditions.

In conclusion, our preliminary results demonstrate that the 1,4-benzodioxin or other enol ethers are the best substrates for nucleophilic substitution. All the structures found are confirmed by their analytical data (Experimental section).

Experimental section

IR spectra were recorded on a FTIR Perkin Elmer 1600 spectrophotometer. MS spectra were recorded on a Hewlett-Packard spectrometer 5988-A (70 eV). The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 (200 MHz ^{1}H and 50.3 MHz ^{13}C) or Varian Gemini 300 (300 MHz ^{1}H and 75.5 MHz ^{13}C) instruments with tetramethylsilane as internal standard and using $CDCl_3$ or CD_3OD as solvent; chemical shifts were expressed in ppm downfield from internal TMS or residual signal of deuterated solvent (δ) and the coupling constants were measured in Hz. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures.

Preparation of halo acetals and diacetals. General Procedure.

A solution of alcohol or phenol (1 mol) and 1,4-benzodioxin **1** (1,1 mol) in CH_2Cl_2 (5 mL) at -30°C or at 0°C (indicated in the Table 1) was added in small portions to NIS or NBS (1 mol), respectively for 5-10 min and was then stirred at rt (see Table 1). The dark mixture was treated with water-CH_2Cl_2 and washed consecutively with aqueous $Na_2S_2O_3$ 10%, saturated solution of $NaHCO_3$ and saturated NaCl.

The organic phase was dried over Na_2SO_4, the solvent removed under reduced pressure, and the residue purified by column chromatography on Merck silica gel (70-230 mesh) eluting with (hexane:ethyl acetate 7/3) to afford the pure compounds. Reaction conditions and yields of isolated products are listed in Table 1. The products were adequately characterized by spectral means and elemental analysis after the workup and purification.

Preparation of 4a and 4b.

A solution of **3a** and **3c** (1 mol) in THF (10 mL) at 0 °C was added, in small portions *tert*-BuOK (1.1 mol) for 10 min and was then stirred at rt for 2 h. This reaction was followed by TLC. The resulting mixture was extracted with ether. The organic phase was dried over Na_2SO_4, the solvent removed under reduced pressure, and the residue purified by column chromatography eluting with (hexane:ethyl acetate 8/2) to afford the pure compounds.

2-Iodo-3-methoxy-2,3-dihydro-1,4-benzodioxin (3a). Colorless oil. IR (neat) ν (cm^{-1}): 1487, 1246, 1089. ^1H NMR δ (ppm): 3.51 (s, 3H, CH_3-O-); 5.39 (s, 1H, H-3); 6.90 (s, 1H, H-2); 6.95 (m, 4H, Ar). ^{13}C NMR δ (ppm): 55.7 (CH_3); 58.9 (CH, C-2); 98.3 (CH, C-3); 117.9 (CH); 118.2 (CH); 122.7 (CH); 124.4 (CH); 138.6 (C); 138.6 (C).

3-Ethoxy-2-iodo-2,3-dihydro-1,4-benzodioxin (3b). Colorless oil. IR (neat) ν (cm^{-1}): 1490, 1253, 1095. ^1H NMR δ (ppm): 1.19 (t, J = 7.2, 3H, CH_3); 3.68 (q, J = 7.2, 1H; CH-O); 3.98 (q, J = 7.2, 1H, CH-O); 5.44 (s, 1H, CH-O); 6.81 (s, 1H, CH-I); 6.99 (m, 4H, Ar).^{13}C NMR δ (ppm): 15.1 (CH_3); 59.6 (CH, CH-I); 64.4 (CH_2, CH_2-O); 97.3 (CH, C-3); 117.9 (CH); 118.2 (CH); 122.5 (CH); 122.6 (CH); 138.8 (C) 138.9 (C).

3-Benzyloxy-2-iodo-2,3-dihydro-1,4-benzodioxin (3c). Yellow oil. IR (neat) ν (cm^{-1}): 1500, 1240, 1100. ^1H NMR δ (ppm): 4.75 (dd, J_1= 12, J_2 = 15, 2H CH_2-O); 5.45 (s, 1H, H-3); 6.81 (s, 1H, H-2); 6.89 (m, 4H, Ar); 7.25 (m, 5H, Ar). ^{13}C NMR δ (ppm): 59.4 (CH, CH-I); 69.7 (CH_2); 95.9 (CH, C-3); 117.9 (CH); 118.3 (CH); 122.8 (CH); 124.5 (CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 136.1 (C); 138.7 (C); 139.0 (C).

3-(Ethylcarbonyloxy)-2-iodo-2,3-dihydro-1,4-benzodioxin (3d). Colorless oil. IR (neat) ν (cm^{-1}): 1740, 1490. ^1H NMR δ (ppm): 1.09 (t, J = 7.2, 3H, CH_3); 2.32 (q, J = 7.2, 2H; CH_2); 5.43 (s, 1H, CH-O); 6.33 (s, 1H, CH-I); 6.95 (m, 4H, Ar).^{13}C NMR δ (ppm): 8.7 (CH_3); 27.4 (CH_2); 86.9 (CH, CH-I); 87.6 (CH, C-3); 117.6 (CH); 117.8 (CH); 122.5 (CH); 123.0 (CH); 139.4 (C); 175.0 (C, C=O).

3-(2-Hydroxyethoxy)-2-iodo-2,3-dihydro-1,4-benzodioxin (3e). Colorless oil. IR (neat) ν (cm^{-1}): 3590, 1243, 1100. ^1H NMR δ (ppm): 1.91 (bs, 1H, -OH); 3.72 (t, J = 7.1, 2H, CH_2-O); 3.79 (m, 2H, CH_2-O); 5.50 (s, 1H, H-3); 6.80 (s, 1H, H-2); 6.94 (m, 4H, Ar) ^{13}C NMR δ (ppm): 58.7 (CH_2); 61.6 (CH_2); 70.0 (CH, C-2); 97.2 (CH, C-3); 115.2 (CH); 118.2 (CH); 120.8 (CH); 122.9 (CH); 125.5 (CH); 142.8 (C); 143.9 (C).

2,3-(Ethylendioxy)-2,3-dihydro-1,4-benzodioxin (3f). Colorless oil. IR (neat) ν (cm^{-1}): 1245, 1112. ^1H NMR δ (ppm): 3.80 (m, 2H, CH_2-O); 3.85 (m, 2H, CH_2-O); 5.24 (s, 2H, CH-O); 6.93 (m, 4H, Ar). ^{13}C NMR δ (ppm): 66.9 (CH_2 CH_2-O); 97.2 (CH); 115.2 (CH); 120.8 (CH); 143.9 (C). MS (EI) *m/z*: 194 (M^+); 110; 86.

3-(2-Hydroxyphenoxy)-2-iodo-2,3-dihydro-1,4-benzodioxin (3g). Pale yellow oil. IR (neat) ν (cm^{-1}): 3300, 1498, 1240, 1100. ^1H NMR δ (ppm): 5.61 (s, 1H, H-3); 6.58 (s, 1H, H-2); 6.86 (m, 8H, Ar).

5a,11a-Dihydro-1,4-benzodioxino[2,3-*b*]-1,4-benzodioxin (3h). Pale yellow oil. IR (neat) ν (cm^{-1}): 1245, 1112. ^1H NMR δ (ppm): 6.64 (s, 2H); 7.03 (m, 4H, Ar); 7.08 (m, 4H, Ar). ^{13}C NMR δ (ppm): 76.8 (CH); 118.4 (CH); 124.8 (CH).

2-Bromo-3-methoxy-2,3-dihydro-1,4-benzodioxin (3i). Yellow oil. IR (neat) ν (cm^{-1}): 1488, 1248, 1090. ^1H NMR δ (ppm): 3.53 (s, 3H, CH_3-O); 5.23 (s, 1H, H-3); 6.43 (s, 1H, H-2); 6.98 (m, 4H, Ar). ^{13}C NMR δ (ppm): 55.3 (CH_3); 60.1 (CH, C-2); 97.2 (CH, C-3); 118.0 (CH); 118.1 (CH); 122.9 (CH); 125.2 (CH); 139.0 (C); 139.1 (C).

2,3-Diiodo-2,3-dihydro-1,4-benzodioxin (3m). Brown oil. ^1H NMR δ (ppm): 7.11 (m, 2H, Ar); 7.26 (m, 2H, Ar); 7.68 (s, 2H, H-2 and H-3); 7.73.^{13}C NMR δ (ppm): Not available because of its instability.

4a-Iodo-2,3,4a,10a-tetrahydrodioxino[2,3-*b*]benzodioxin (3n). Brown oil. ^1H NMR δ (ppm): 3.81 (m, 2H, CH_2-O); 4.06 (m, 2H, CH_2-O); 5.23 (s, 1H, H-3); 6.95 (m, 4H, Ar). MS (IE) *m/z*: 321 (M^+, 1).

2-(1,4-Benzodioxin-2-yl)-1,4-benzodioxin (3o). Stiff oil. IR (neat): 1500, 1230, 1090. ^1H NMR δ (ppm): 6.83 (m, 8H, Ar); 6.97 (s, 2H, H-3). MS (EI) *m/z*: 266 (M^+); 210; 110.

2-Methoxy-1,4-benzodioxin (4a). Colorless oil. Yield 30%. IR (neat) ν (cm^{-1}): 1599, 1255, 1077. ^1H NMR δ (ppm): 3.52 (s, 3H, CH_3-O); 5.85 (s, 1H, H-3); 6.92 (m, 4H, Ar).

2-Bromo-1,4-benzodioxin (4b). This compound was described by Lee[4] et al.

Acknowledgements

Were are grateful for the support for this research received from the Generalitat de Catalunya (QF 95-4704). We also wish to thank the GRQ 97-0140. One of us (N.H.) would like to thank the E.U. for a Leonardo fellowship.

References

(1) a) T. V. Lee, J. A. Leigh, and C. B. Chapleo, *Tetrahedron* **46**, 921-934 (1990).
b) M. T. Vázquez, G. Rosell, and M. D. Pujol, *Eur. J. Med. Chem.* **32**, 529-534 (1997).
c) T. Ganesh, C. H. Kumar, and G. L. Krupadanam, *Synth. Commun.* **29**, 2069-2078 (1999).

(2) a) W. Adam, E. Schmidt, and K. Takayama, *Synthesis* 322-324 (1982).
b) N. Ruiz, M.D. Pujol, G. Coudert, and G. Guillaumet, *Synth. Commun.* **26**, 2057-2066 (1996).

(3) a) G. Farina and G. Zecchi, *Synthesis* 755-755 (1977).
b) G. Coudert, G. Guillaumet, and B. Loubinoux, *Tetrahedron Lett.* 1059-1062 (1978).
c) G. Coudert, G. Guillaumet, and B. Loubinoux, *Tetrahedron Lett.* 4379-4382 (1979).
d) Y. Satho, C. Powers, L. Toledo, T. J. Kowalski, P. A. Peters, and E. F. Kimble, *J. Med. Chem.* **38**, 68-75 (1995).
e) C. Davrinche, E.N.T. Xuong, Y.E. Hamed, P. Reynaud, P. Rinjard, and G. Tran, *Eur. J. Med. Chem.* **27**, 765-778 (1992).
f) W. Quaglie, M. Pigini, S. K. Tayebati, A. Piergentili, M. Giannella, G. Marucci, and C. Melchiorre, *J. Med. Chem.* **36**, 1520-1528 (1993).

(4) T. V. Lee, J. A. Leigh, and C. B. Chapleo, *Synthesis* 208-209 (1989).

Received on January 15, 2001