Selective Dealkylation of Methoxyanthraquinones *via* Difluoro[1-hydroxymethoxyanthraquinonato-O^1,O^9]boron Chelates: Synthesis of Hydroxymethoxyanthraquinones

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1,8-, 1,5-, 1,2-, and 1,4-Dimethoxyanthraquinones have been treated with boron trifluoride–diethyl ether to give difluoro(anthraquinonato)boron chelates (1a—d) respectively. 1,4,5-Trimethoxyanthraquinone was similarly converted separately in benzene and toluene into the mono- (2) and bis-difluoroboron(3)-chelates respectively, and 2,2',4,4'-tetramethoxybenzophenone was converted by $BF_3{\cdot}Et_2O$ in toluene into the boron adduct (4). Treatment of these derivatives, (1a—d) and (2)—(4), with methanol gave the following uncomplexed derivatives in good yield respectively: 1-hydroxy-8-methoxyanthraquinone, 1-hydroxy-5-methoxyanthraquinone, 1-hydroxy-2-methoxyanthraquinone, 1-hydroxy-4-methoxyanthraquinone, 4-hydroxy-1,5-dimethoxyanthraquinone, 1,4-dihydroxy-5-methoxyanthraquinone, and 2-hydroxy-2',4,4'-trimethoxybenzophenone.

The commercial success of adriamycin [1] as an antitumour agent † has led to a renewed interest in the synthesis of unsymmetrically functionalised anthraquinone derivatives with special regard to compounds bearing hydroxy and methoxy groups; useful synthetic intermediates in this respect are 1-hydroxy-4,5-dimethoxyanthraquinone [2], 4-hydroxy-1,5-dimethoxyanthraquinone,[3] and 1,4-dihydroxy-5-methoxyanthraquinone.‡

In this paper we describe a simple, high-yield synthesis of hydroxymethoxyanthraquinones from inexpensive di- and tri-methoxyanthraquinones.

The procedure involves the initial conversion of 1-methoxyanthraquinones into isolable difluoro(1-hydroxymethoxyanthraquinonato-O^1,O^9)boron chelates by treating the former with boron trifluoride–diethyl ether in benzene or toluene. For example, 1,8-dimethoxyanthraquinone is converted under these conditions (C_6H_6 solvent) into the difluoroboron chelate (1a), and related compounds (1c—d) are formed in high yield (>90%) from 1,5-, 1,2-, and 1,4-dimethoxyanthraquinones. Compounds of this type are high-melting solids, stable in air, but difficult to obtain analytically pure because of their extreme insolubility. Compounds in this category are well documented in anthraquinone chemistry [5] but are usually prepared from hydroxy rather than methoxy derivatives; bis(diacetoxy)boron chelates have been used to activate 1,4-dihydroxyanthraquinones to [4 + 2] cycloaddition [6] and, interestingly in the light of this work, to protect two hydroxy groups during a synthetic procedure leading to 4-hydroxy-1,5-dimethoxyanthraquinone.[3]

Treatment of the difluoroboron chelates (1a—d) with methanol at *ca.* 50 °C for *ca.* 10 min effects removal of the difluoroboron moiety, and the appropriate 1-hydroxymethoxyanthraquinones are formed in high yield (>90%). We believe this method to be superior for the preparation of 1-hydroxy-5-methoxyanthraquinone and 1-hydroxy-8-methoxyanthraquinone to the method involving the selective dealkylation of dimethoxyanthraquinones by conc. sulphuric acid/oleum [7a,§] and suggest it as an alternative to the selective methylation by diazomethane of hydroxyanthraquinones.[8] The principle of the method is not new [*cf.* selective demethylation in the $AlCl_3$-induced conversion of 1,2-$(MeO)_2$-3-$EtCOC_6H_3$ into 1-MeO-2-HO-3-$EtCOC_6H_3$] [9] and related processes [10] but there are advantages to our modified approach: the reaction conditions are relatively moderate; yields are excellent; the intermediate Lewis acid chelate can be obtained in a reasonably pure state prior to conversion into the hydroxy derivative; and finally, the method can be used for the *selective* successive replacement of methoxy groups *via* intermediate mono- and bis-difluoroboron chelates.

The last feature is exemplified using 1,4,5-trimethoxyanthraquinone in which a subtle difference in reactivity toward boron trifluoride can be harnessed. Treatment of the trimethoxy derivative with boron trifluoride–diethyl ether under reflux with benzene as solvent gives an intermediate mono-(4,8-dimethoxyanthraquinonato-O^1,O^9)boron chelate (2) whereas when toluene is used as solvent, the bis-boron chelate (3) can be isolated. Ensuing solvolysis of (2) and (3) gives 4-hydroxy-1,5-dimethoxyanthraquinone and 1,4-dihydroxy-5-methoxyanthraquinone respectively, in high yield. This synthesis of the former is shorter than previously reported routes from 2-chloro-7-methoxynaphthoquinone [11] or 1,4,5-trihydroxyanthraquinone,[3] whilst this route to 1,4-dihydroxy-5-methoxyanthraquinone obviates the use of expensive oxidants (*e.g.* AgO) [4] for 1,4,5-trimethoxyanthraquinone.¶ It should be noted that the regiochemical outcome of the reaction of 1,4,5-trihydroxyanthraquinone with boron triacetate is temperature dependent.[3] The product bis[diacetoxy-(anthraquinonato)boron] complexes may form as a mixture of 1,4-[*cf.* 3; OH for OMe)] and 1,5-bis-chelates under conditions of thermodynamic control or entirely in the 1,5-mode under conditions of kinetic control. It is not clear in the present work why the 1,4-chelate (3) is formed exclusively but we assume that its formation is thermodynamically

† Marketed by Montedison as doxorubicin hydrochloride.

‡ Useful as an alternative starting material for the anthradiquinone derivative.[4]

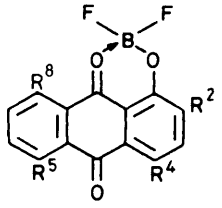
§ We successfully prepared 1-hydroxy-5-methoxyanthraquinone by this method [7a] (79% yield) but could not obtain 1-hydroxy-8-methoxyanthraquinone by the recommended procedure.[7a] Difficulties in partially demethylating 1,5-dimethoxyanthraquinone by the method of ref. 7*a* and in partially methylating 1,5-dihydroxyanthraquinone encouraged Baldwin and Rajeckas to devise a new synthesis of 1-hydroxy-5-methoxyanthraquinone from 1,5-dimethoxyanthraquinone *via* an anthrone derivative.[7b]

¶ The selective methylation of 1,4,5-trihydroxyanthraquinone by diazomethane is the method of choice for 1,4-dihydroxy-5-methoxyanthraquinone.[8]

Table. Preparation of hydroxymethoxyanthraquinones *via* difluoroboron chelates

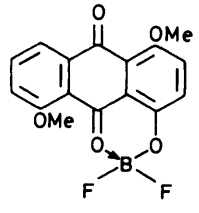
Anthraquinone deriv. (3.7 mmol)	Mol equiv. $BF_3{\cdot}Et_2O$	Solvent (ml)	BF_2 chelate [g, %, m.p. (°C)]	Hydrolysis product [%, m.p. (°C), (lit. m.p.)]
1,2-$(MeO)_2$	4.0	C_6H_6 (20)	(1c) [1.07, 95, 260—270 (decomp.)] [a,b]	1-OH,2-MeO: [93, 232—233 (232—233) [d]]
1,4-$(MeO)_2$	2.5	C_6H_6 (20)	(1d) [0.96, 85, 268 (decomp.)] [a,b]	1-OH,4-MeO [93, 167—168 (167—168) [e]]
1,5-$(MeO)_2$	6.0	*o*-$Cl_2C_6H_4$ (50)	(1b) [1.06, 94, 265 (decomp.)] [a,b]	1-OH,5-MeO [91, 181—183 (181—183) [7]]
1,8-$(MeO)_2$	4.0	C_6H_6 (15)	(1a) [1.04, 92, 270 (decomp.)] [a,b,c]	1-OH,8-MeO [90, 196—197 (196) [7]]

[a] ν_{max}/cm^{-1} Values: (1a) 1 670, 1 615, 1 580, 1 560, 1 522, 1 453, 1 285, 1 252, 1 052, and 750; (1b) 1 660, 1 610, 1 585, 1 562, 1 522, 1 455, 1 295, 1 280, 1 258, 1 155, 1 050, 1 012, 810, 768, and 705; (1c) 1 665, 1 615, 1 585, 1 540, 1 475, 1 450, 1 380, 1 335, 1 290, 1 270, 1 145, 1 060, 1 035, 985, 850, and 710; (1d) 1 663, 1 625, 1 583, 1 521, 1 468, 1 438, 1 285, 1 262, 1 238, 1 133, 1 060, 1 020, 833, and 728. [b] λ_{max}/nm ($CHCl_3$) Values: (1a) 253, 275, and 410; (1b) 253, 275, and 398; (1c) 248, 275, and 432; (1d) 249, 272, and 452. [c] Analysis: Found: C, 58.7; H, 3.15. $C_{15}H_9BF_2O_4$ requires C, 59.60; H, 2.98%. [d] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, vol. 1, p. 59. [e] H. Laatsch, *Liebigs Ann. Chem.*, 1980, 814.

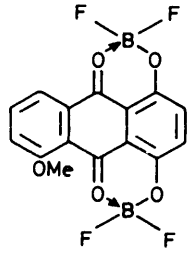


(1)

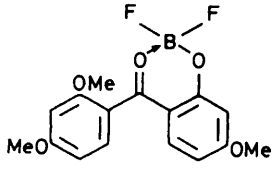
	R^2	R^4	R^5	R^8
a;	H	H	H	MeO
b;	H	H	MeO	H
c;	MeO	H	H	H
d;	H	MeO	H	H



(2)



(3)



(4)

controlled. Further work is required to determine the conditions necessary for modifying the direction of demethylation by careful selection of the boron derivative and of the reaction conditions.

It is likely that the present method can be applied to a variety of *o*-acyl- and *o*-aroyl-methoxyarenes. For example, treatment of 2,2′,4,4′-tetramethoxybenzophenone with boron trifluoride–diethyl ether gives an isolable difluoroboron chelate (4) which is transformed in high yield by methanol into 2-hydroxy-2′,4,4′-trimethoxybenzophenone. The selectivity achieved in this reaction may be contrasted with the problem associated with the use of aluminium trichloride *in situ*: whereas a single product is obtained in this work, 2,2′,4,4′-tetramethoxybenzophenone [from 1,3-$(MeO)_2C_6H_4$, $COCl_2$, $AlCl_3$] is transformed (67 °C, 6—8 h) *in situ* into a mixture of hydroxymethoxybenzophenones and tetrahydroxybenzophenone.[10e]

Experimental

Benzene and toluene were dried (Na) and distilled before use. Preparative reactions using boron trifluoride–diethyl ether (B.D.H.) were carried out under an atmosphere of dry nitrogen.

General Procedure for the Preparation of Di- and Trimethoxyanthraquinones.—The di- or tri-hydroxyanthraquinone derivative (0.04 mol) in *o*-dichlorobenzene (500 ml) was heated under reflux with methyl toluene-*p* sulphonate (0.16—0.24 mol) and sodium carbonate (0.09 mol) for 2—24 h. Volatile materials were evaporated under reduced pressure and the residue was recrystallised [compound, yield (%), solvent of recrystallisation, and m.p. given]: 1,4-dimethoxyanthraquinone, 86, benzene, 170—171 °C (lit.,[12] 170—171 °C); 1,5-dimethoxyanthraquinone, 85, ethanol, 236—237 °C (lit.,[13] 236 °C); 1,8-dimethoxyanthraquinone, 87, methanol, 218—220 °C (lit.,[13] 219 °C); 1,4,5-trimethoxyanthraquinone, 80, butan-2-ol, 208—209 °C (lit.,[14] 209 °C).

General Procedure for the Preparation of Hydroxymethoxyanthraquinones via *Difluoroboron Chelates* (1a—d) (*see Table*).—Dimethoxyanthraquinones were heated with boron trifluoride–diethyl ether under reflux for 2 h in either benzene or *o*-dichlorobenzene. When the mixture was cooled, a precipitate of relatively pure difluoroboron chelate was formed. It proved unnecessary to obtain materials analytically pure, but satisfactory analytical data were obtained from (1a). The chelates (1a—d) were converted into hydroxymethoxyanthraquinones by heating them in methanol for 10 min at 50 °C.

Preparation of 4-*Hydroxy*-1,5-*dimethoxyanthraquinone.*—1,4,5-Trimethoxyanthraquinone (1.0 g, 3.3 mmol), benzene (20 ml), and boron trifluoride–diethyl ether (1.67 ml, 4 mol equiv.) were heated under reflux for 0.5 h. The reaction was terminated when all starting material was consumed and a new spot (R_F 0.54) appeared on t.l.c. analysis [silica gel, ethyl acetate–light petroleum (2 : 1) as eluant). The mixture was cooled to precipitate impure dark red-brown difluoro (4-hydroxy-1,5-dimethoxyanthraquinonato-O^1,O^{10})boron (2) (1.0 g, 89%), m.p. 286 °C (decomp.) $\nu_{max.}$ (KBr) 1 653, 1 618,

1 587, 1 523, 1 438, 1 246, and 1 060 cm^{-1}. This material (0.5 g, 1.5 mmol) and methanol (10 ml) were heated at 50 °C for 10 min. The mixture was cooled to precipitate orange-red 4-hydroxy-1,5-dimethoxyanthraquinone (0.42 g, 94%), m.p. 248—250 °C [from dichloromethane–light petroleum (b.p. 40—60 °C)] (lit.,[11] 248—250 °C).

Preparation of 1,4-*Dihydroxy-5-methoxyanthraquinone*.—1,4,5-Trimethoxyanthraquinone (1.0 g, 3.3 mmol), toluene (50 ml), and boron trifluoride–diethyl ether (3.35 ml, 8 mol equiv.) were heated under reflux for 3 h. The reaction was terminated when t.l.c. analysis [silica gel, ethyl acetate–light petroleum (2 : 1) as eluant] indicated consumption of the starting material and a new spot at R_F 0.80. The mixture was cooled, and filtered to give air-sensitive blue-black tetrafluoro(1,4-dihydroxy-5-methoxyanthraquinonato-O^1,O^4,-O^9,O^{10}) diboron(3) (0.22 g). This material was immediately treated with methanol (10 ml) at 50 °C for 10 min. The solvent was evaporated under reduced pressure and the residual red tar was recrystallised from ethyl acetate to give orange 1,4-dihydroxy-5-methoxyanthraquinone (0.14 g), m.p. 231—233 °C (lit.,[15] 231—233 °C) identical (i.r. and n.m.r.) with a sample prepared from 1,4,5-trimethoxyanthraquinone by silver(I) oxide oxidation. The filtrate from above was poured into 2M-HCl (50 ml) and extracted with diethyl ether (2 × 50 ml). The extract was dried ($MgSO_4$) and evaporated to leave a red residue which provided (from ethyl acetate) a further 0.64 g of product; total yield of 1,4-dihydroxy-5-methoxyanthraquinone 0.78 g (86%).

Preparation of 2-*Hydroxy*-2′,4,4′-*trimethoxybenzophenone*.—2,2′,4,4′-Tetramethoxybenzophenone (1.0 g, 3.3 mmol), toluene (40 ml), and boron trifluoride–diethyl ether (1.65 ml, 4 mol equiv.) were heated under reflux for 0.5 h. The product was added to 2M-hydrochloric acid and extracted with diethyl ether (2 × 20 ml). The extract was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to leave a dark yellow oil, recrystallisation of which gave the yellowish green difluoroboron chelate (4) (0.96 g, 86%), m.p. 160—161 °C (from $CHCl_3$–Et_2O), $\nu_{max.}$ (KBr) 3 010, 2 980, 2 950, 2 820, 1 615, 1 570, 1 555, 1 455, 1 445, 1 425, 1 385, 1 290, 1 255, 1 225, 1 160, 1 130, 1 035, 1 010, 970, 950, 845, 835, 825, and 765 cm^{-1}; δ($CDCl_3$) 3.72 (3 H, s, MeO), 3.86 (6 H, s, 2 × OMe), 6.2 (4 H, s, ArH), and 7.3 (2 H, m, ArH); $\lambda_{max.}$ ($CHCl_3$) 306 and 382 nm (Found: C, 57.5; H, 4.75; B, 3.6%. $C_{16}H_{15}BF_2O_5$ requires C, 57.14; H, 4.46; B, 3.27%). This compound (4) (0.5 g, 1.88 mmol) and methanol (10 ml) were heated at 50 °C for 10 min. The solvent was evaporated under reduced pressure to leave a yellow residue, recrystallisation of which gave colourless 2-hydroxy-2,4,4′-trimethoxybenzophenone (0.41 g, 95%), m.p. 108—109 °C (from methanol), $\nu_{max.}$ (KBr) 2 930, 1 620, 1 595, 1 495, 1 455, 1 412, 1 365, 1 340, 1 302, 1 260, 1 205, 1 155, 1 130, 1 105, 1 040, 1 020, 965, 930, 845, 830, and 800 cm^{-1}; δ($CDCl_3$) 3.68 (3 H, s, OMe), 3.76 (3 H, s, OMe) 3.78 (3 H, s, OMe), 6.2 (4 H, m, ArH), 7.12 (2 H, ArH), and 13.98 (1 H, s, exch OH) (Found: C, 66.6; H, 5.97. $C_{16}H_{16}O_5$ requires C, 66.66; H, 5.55%).

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