Acta Chemica Scandinavica, 1994: 48: 80–83
Printed in Belgium – all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Synthesis of Acyclic Carbohydrate Isopropylidene Mixed Acetals Using 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone as a Catalyst

Ove Kjølberg* and Klaus Neumann

Department of Chemistry, University of Oslo, P. O. Box 1033 Blindern, N-0315 Oslo, Norway

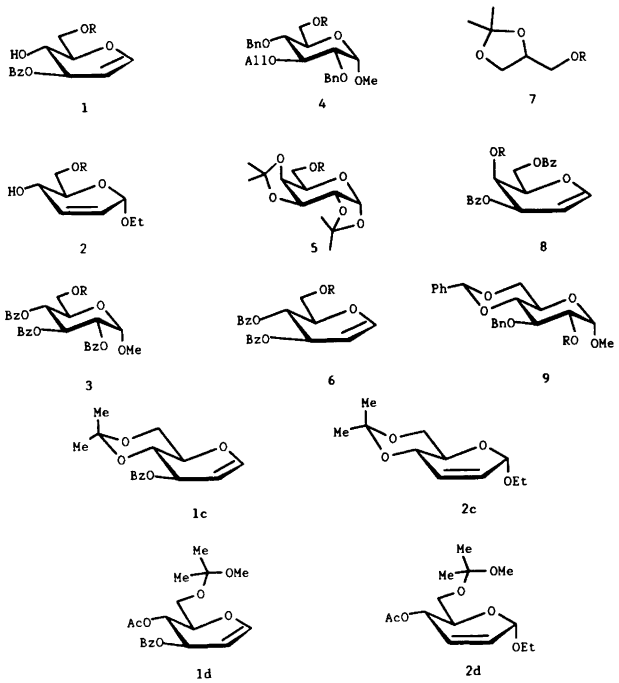
Kjølberg, O. and Neumann, K., 1994. Synthesis of Acyclic Carbohydrate Isopropylidene Mixed Acetals Using 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone as a Catalyst. – Acta Chem. Scand. 48: 80–83. © Acta Chemica Scandinavica 1994.

A new method for the synthesis of isopropylidene mixed acetal derivatives of various carbohydrates using catalytic amounts of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) is reported. Several monohydroxy compounds, as well as some carbohydrate diols, were explored as substrates. The method was found to be especially useful for syntheses starting with acid-sensitive carbohydrate derivatives. Both 2,2-dimethoxypropane (DMP) and 2-methoxypropene were used as reagents in various solvent systems. A short discussion of the mechanism is given.

A variety of acetal functions are often used as protective groups in carbohydrate chemistry. Their formation has been thoroughly investigated and many different catalysts and reagents have been used for this purpose.[1a–c] The use of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as a catalyst for the cleavage of acetal[2] and silyl ether functions[3] in water-containing solvents prompted us to investigate the possibilities for the formation of cyclic and acyclic carbohydrate acetals employing this catalyst under anhydrous conditions. We were particularly interested in a method which could be used for the treatment of acid-sensitive hydroxy compounds. As reported, cyclic carbohydrate acetals[4a] and tetrahydropyranyl ethers[4b] could be synthesized using DDQ as a catalyst in anhydrous solvents. We now report a new method for the synthesis of acyclic carbohydrate isopropylidene mixed acetals [*O*-(1-methoxy-1-methyl)ethyl ethers] using DDQ as a catalyst in the presence of 2,2-dimethoxypropane (DMP) or 2-methoxypropene.

Results and discussion

During the syntheses of the cyclic isopropylidene acetals of the unsaturated carbohydrate derivatives **1a** and **2a**, we observed that the reactions proceeded via intermediates that could be conveniently detected when monitoring the reaction by TLC or NMR spectroscopy. On quenching the reactions (2.0 equiv. of DMP were used) after a few hours, **1b** and **2b** could be isolated in moderate yields (35–45%), together with some starting material as well as with **1c** and **2c**. As reported,[4a] the exclusive formation of the cyclic products **1c** and **2c** (obtained along with some of the starting diols **1a** and **2a**) demands longer reaction times. The acyclic acetals **1b** and **2b** could be acetylated under standard conditions to give derivatives **1d** and **2d** (76% and 81%), respectively. To enhance the yields of the acyclic mixed acetals **1b** and **2b**, we performed the reactions in 1 : 1 mixtures of DMP and acetone at lower temperatures (Table 1). Thus, the synthesis of the cyclic acetals (**1c**,**2c**) could be suppressed and **1b** and **2b** became available in good yields.



Scheme 1. Synthesis of the carbohydrate isopropylide mixed acetals **1b**–**9b**, the cyclic acetals **1c** and **2c** and the acylated derivatives **1d** and **2d**. In the **a**-series R = H and in the **b**-series R = $C(Me)_2OMe$.

Table 1. Reaction conditions for the synthesis of the acyclic carbohydrate acetals **1b–9b**.

Sugar	Run	Method	eq. DMP[a]	Solvent	*t*/h	*T*/°C	Yield (%)[b]
1a	1	A	Solvent	Acetone	4.5	0	67
2a	2	A	Solvent	Acetone	24	−15	85
3a	3	A	Solvent	Acetone	2	22	80
	4	B	Solvent	DMF	2	22	68
4a	5	A	Solvent	Acetone	24	0	88
5a	6	A	Solvent	Acetone	4.5	0	90
	7	B	Solvent	DMF	2	0	72
	8	C	1.05	CH_2Cl_2	0.5	−15	85
6a	9	A	Solvent	Acetone	1.5	22	71
	10	B	Solvent	DMF	1	22	68
	11	C	1.05	CH_2Cl_2	0.5	−15	78
7a	12	A	Solvent	Acetone	5	22	96
8a	13	A	Solvent	Acetone	4	22	47
	14	B	Solvent	DMF	3.5	22	45
	15	C	1.05	CH_2Cl_2	0.5	−15	51
9a	16	A	Solvent	Acetone	2	22	38
	17	B	Solvent	DMF	2	22	35

[a] In methods A and B, 2,2-dimethoxypropane was used in a 1:1 mixture with the stated solvent. 2-Methoxypropene was used as a reagent in method C. [b] The total yield of recovered material and product was ⩾90% in all cases. All yields are isolated yields and refer to the amount of starting material.

The carbohydrate derivatives **3a–9a** were treated under the same conditions (method A) using 0.1 equivalents of DDQ in all the reactions. The primary alcohols **3a–7a** gave the respective acyclic acetals **3b–7b** in high yields when the transformations were performed in a DMP–acetone 1:1 mixture. The use of secondary alcohols such as **8a** and **9a**, on the other hand, resulted in only moderate yields of the desired products **8b** and **9b**. In all cases, some of the starting material could be recovered and no other products could be detected (TLC and NMR). The reactions were quenched simply by adding triethylamine to the reaction mixture and the catalyst could easily be removed by flash chromatography.

In attempts to remove the liberated methanol from the reaction vessel, we treated some of the monohydroxy compounds in DMP–DMF 1:1 mixtures under a stream of nitrogen (method B). The yields were slightly lower in all these cases and the transformations were more difficult to control because the total removal of DMP had to be avoided. For example, quenching the reaction using **5a** (run 7, Table 1) gave **5b** in a 72% yield after work-up, whilst after 18 h the starting material **5a** could be recovered nearly quantitatively. This indicated that DDQ also catalyzed the removal of the acyclic mixed acetal moiety (Scheme 2) from **5b**. On the other hand, this method had the advantage that the extractive work-up procedure allowed the direct use of the crude *O*-(1-methoxy-1-methyl)ethyl derivatives without further purification.

The alternative reagent, 2-methoxypropene was used in CH_2Cl_2 solutions (method C) using the same catalytic amount of DDQ. The acyclic acetals **5b**, **6b** and **8b** could thus be synthesized in high yields. These reactions proceeded with very high rates and had to be performed at temperatures not higher than −15°C, using only a small excess of reagent (1.05 equiv.), to prevent the formation of side products. The work-up procedure for these transformations was as described for method A. In general, during the work-up procedures and flash chromatography, the use of solvents containing traces of acid had to be avoided. NMR and $[\alpha]_D$ measurements were, for that reason, performed in acid-free CD_2Cl_2, and CH_2Cl_2 solutions, respectively, and chromatographic separations were performed with diethyl ether–hexane–triethylamine (100:80:1) mixtures.

The formation[5] and the use[6] of *O*-(1-methoxy-1-methylethyl) ethers has been reported in only a few cases. Their use as a protective group, in both organic synthesis and carbohydrate chemistry, demands methods for their easy and selective introduction and removal. We found,

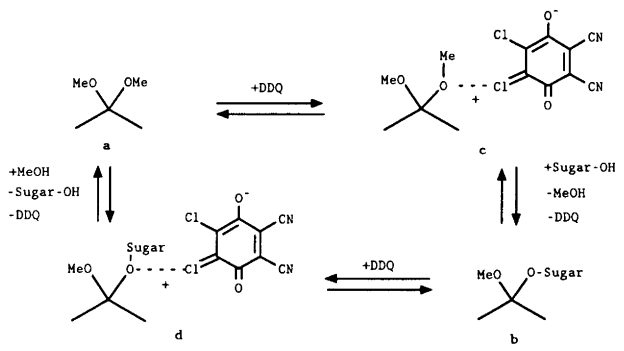
Table 2. Selected spectroscopic data for the synthesized acyclic acetals **1b–9b**, the cyclic isopropylidene acetals **1c** and **2c**, and derivatives **1d** and **2d**.

	δ_C			
Sugar	OCH_3	CH_3	CMe_2	$\delta_H(OCH_3)$
1b	49.0	24.7, 24.9	100.3	3.21
2b	48.8	24.8	100.1	3.21
3b	48.7	24.7	99.7	3.16
4b	48.7	24.9, 25.0	100.0	3.12
5b	48.6	24.5	100.6	3.15
6b	48.7	24.6	100.4	3.14
7b	48.6	24.6	100.0	3.16
8b	49.9	25.1, 25.2	101.7	3.26
9b	49.4	25.7	101.6	3.25
1c		19.7, 29.4	99.6	
2c		19.4, 29.5	100.0	
1d	48.8	24.8	100.5	3.18
2d	48.6	24.8, 24.9	99.8	3.15

that the acyclic acetal moiety could conveniently be removed from **5b** and **6b** by the action of catalytic amounts of pyridinium toluene-4-sulfonate (PPTS)[7] in 1:1 mixtures of methanol and chloroform at +5°C to give the alcohols **5a** and **6a** (94% and 90%), respectively.

For the characterization of the products ^1H and ^{13}C NMR spectroscopy proved to be very valuable. The acyclic acetals **1b–9b** showed very typical ^1H and ^{13}C NMR resonances for the methyl groups, the methoxy group and the acetal carbon (Table 2). The chemical shifts for the atoms involved varied only slightly in all the compounds investigated. This enabled an unequivocal structure assignment of the acetal moiety and an elegant method for the discrimination of acyclic and cyclic acetal derivatives[8] as demonstrated in the case of **1b**, **2b** and compounds **1c** and **2c**, respectively.

So far, the mechanism of this reaction is not understood fully. In particular the role of the catalyst needs to be considered in more detail. Oku *et al.*[2] have recently given an interesting discussion about the possible mechanisms for the removal of cyclic acetals in water-containing solvents. Among other things, they discussed the possibility that DDQ could function as a Lewis acid. We suggest that DDQ can act in a similar manner under anhydrous conditions, generating an ethereal oxonium-ion-type species **c** (as indicated in Scheme 2).



Scheme 2. Proposed mode of complexation between DDQ and ethereal oxygen atoms in the synthesis of carbohydrate acetals.

The UV spectroscopic investigation of the reaction, using the alcohol **5a** (see below), showed a distinct rise in absorption at 347 nm ($\varepsilon = 2980$ after 2 h). This increase was obviously caused by an interaction between DDQ and the ether oxygen of DMP. The mode of complexation may be described in terms of DDQ acting as a 'positive-halogen'-containing molecule. These are known to form complexes with various types of base and nucleophile.[9] Thus, the interaction of DDQ with the oxygen donor atom could possibly proceed via such a positive halogen complex **c**. However, it is difficult to give a more detailed interpretation of the observed UV transitions and the chemical species that are involved. Another possible mechanism, via initial single electron transfer (SET),[3,10] has found no experimental support in our hands so far.[11]

The use of DDQ as a catalyst has allowed us to synthesize the partially or fully protected carbohydrate derivatives **1b–9b**. Particularly useful is the application of this reaction to highly acid-sensitive compounds such as the hex-1-enitols **1a**, **6a** and **8a**. The acyclic *O*-(1-methoxy-1-methylethyl) acetals can be introduced and removed, using a variety of derivatives, in a selective and easy manner. Thus, these acetals should be candidates for further use as a protecting group in organic synthesis as well as in carbohydrate chemistry.

Experimental

Physical data of all the products were in accordance with the assigned structures. All the starting materials were prepared according to literature procedures except for **8a**.[12] NMR experiments were run in CD_2Cl_2 solutions at room temperature and mass spectra were recorded under electron impact conditions at 70 eV (EI). TLC and flash chromatography were performed using diethyl ether–hexane–triethylamine (100:80:1) mixtures unless otherwise stated. For further experimental details see elsewhere.[13] UV spectroscopy was performed with a Shimadzu UV-260 spectrometer using 2×10^{-4} M DDQ solutions in CH_2Cl_2, giving λ_{max} (ε): 279 (11 850), 286 (12 300) and 387 (1050) nm. The reaction of alcohol **5a** and DMP (both 2×10^{-3} M) with DDQ (2×10^{-4} M) was followed by the use of UV spectroscopy. After 2 h no further change in the absorption spectra could be observed; λ_{max} (ε): 268 (7270), 282 (6550) and 347 (2980) nm. A similar spectrum was obtained when equilibrating DDQ and DMP (using the same molar concentrations as above) in CH_2Cl_2 solution for 2 h.

Typical procedure A. 1,2;3,4-Di-O-isopropylidene-6-O-(1-methoxy-1-methylethyl)-α-D-galactopyranoside (**5b**). The alcohol **5a** (215 mg) was dissolved in 6 ml of acetone–DMP (1:1) and cooled to 0°C, and DDQ (19 mg) was added in one portion. After 5 h at the same temperature the mixture was quenched with triethylamine and evaporated, and the remainder was purified by flash chromatography on SiO_2 to yield **5b** (247 mg, 90%) as a colorless syrup ($R_f = 0.73$), $[\alpha]_D - 59.4°$ (*c* 0.75, CH_2Cl_2). ^1H NMR: δ 1.29, 1.39 and 1.48 (3 s, 18 H, $6 \times CH_3$), 3.15 (s, 3 H, OMe), 3.49 (m, 2 H), 3.84 (ddd, 1 H, *J* 1.8, 3.2, 4.4 Hz, H-5), 4.22 (dd, 1 H, *J* 1.8, 8.0 Hz, H-4), 4.26 (dd, 1 H, *J* 2.4, 5.0 Hz, H-2), 4.56 (dd, 1 H, *J* 2.4, 8.0 Hz, H-3), 5.46 (d, 1 H, *J* 5.0 Hz, H-1). ^{13}C NMR: δ 24.5–26.2 ($6 \times CH_3$), 48.6 (OMe), 60.2, 67.6, 2×71.2 and 71.7 (C-2, C-3, C-4, C-5 and C-6), 96.9 (C-1), 100.5 (CMe_2OMe), 108.9 and 109.5 ($2 \times CMe_2$).

Typical procedure B. The alcohol **5a** (204 mg) was dissolved in 4 ml of DMF–DMP (1:1) and DDQ (18 mg)

was added at room temperature. The mixture was stirred vigorously for 2 h under a stream of N_2 to remove the liberated methanol, diluted with 5 ml of CH_2Cl_2, and washed with 0.05 M $NaHCO_3$ (2 × 5 ml). The organic phase was dried with $MgSO_4$ and evaporated *in vacuo* to yield **5b** (190 mg, 72%). The crude product could be used without further purification. A purified sample showed the same physical data as described above.

Typical procedure C. A solution of **5a** (150 mg) in CH_2Cl_2 (5 ml) was cooled to −15°C and 2-methoxypropene (43 mg) and DDQ (13 mg) were added. The mixture was kept at the same temperature for 30 min and then quenched with triethylamine. Removal of the volatiles and purification of the residue by flash chromatography yielded 160 mg (85%) of **5b** as a colorless syrup giving the same physical data as described above.

4-O-Acetyl-1,5-anhydro-3-O-benzoyl-2-deoxy-6-O-(1-methoxy-1-methylethyl)-D-arabino-*hex-1-enitol* (**1d**). The alcohol **1b** (50 mg) was acetylated with Ac_2O–pyridine in the usual manner to yield 42 mg (76%) of **1d** as a chromatographically homogeneous syrup ($R_f = 0.54$) after flash chromatography, $[\alpha]_D - 128.2°$ (*c* 0.6, CH_2Cl_2). ^1H NMR: δ 1.31 (s, 6 H, 2 × CH_3), 2.06 (s, 3 H, OAc), 3.18 (s, 3 H, OMe), 3.62 (dd, 1 H, *J* 3.6, 11.0 Hz, H-6a), 3.76 (dd, 1 H, *J* 6.4, 11.0 Hz, H-6b), 4.29 (ddd, 1 H, *J* 3.6, 6.4, 6.8 Hz, H-5), 4.97 (dd, 1 H, *J* 3.6, 6.2 Hz, H-2), 5.37 (t, 1 H, *J* 6.8 Hz, H-4), 5.46 (dd, 1 H, *J* 3.6, 6.8 Hz, H-3), 6.54 (d, 1 H, *J* 6.2 Hz, H-1), 7.41–8.03 (3 m, 5 H, ArH). ^{13}C NMR: δ 21.5 (OAc), 24.8 (2 × CH_3), 48.8 (OMe), 59.4 (C-6), 2 × 68.0, 75.7 (C-3, C-4 and C-5), 98.1 (C-2), 100.1 (CMe_2OMe), 127.9–132.6 (Ph), 145.3 (C-1), 164.8 and 168.4 (C=O). MS (EI): Calc. for $C_{18}H_{21}O_7$ ($M-15$): 349.1287. Found ($M^+ - 15$) = 349.1283. *m/z* (%): 349 (5), 332 (7), 290 (5) 275 (40), 201 (14), 150 (8), 122 (63), 105 (100), 97 (11), 81 (24), 77 (53), 73 (38), 51 (21), 43 (84).

*Ethyl 4-O-acetyl-2,3-dideoxy-6-O-(1-methoxy-1-methylethyl)-α-*D-erythro-*hex-2-enopyranoside* (**2d**). The alcohol **2b** (95 mg) was acetylated with Ac_2O–pyridine and processed as usual to yield **2d** (90 mg, 81%) as a chromatographically homogenous syrup ($R_f = 0.54$), $[\alpha]_D + 126.0°$ (*c* 0.35., CH_2Cl_2). ^1H NMR: δ 1.22 (t, 3 H, CH_3), 1.31 (s, 6 H, 2 × CH_3), 3.15 (s, 3 H, OMe), 3.50 (m, 4 H), 4.00 (m, 1 H, H-5), 5.00 (br s, 1 H, H-1), 5.28 (dd, 1 H, *J* 7.0, 9.6 Hz, H-4), 5.84 (m, 2 H). ^{13}C NMR: δ 16.0 (CH_3), 21.6 (OAc), 24.7 and 24.8 (2 × CH_3), 48.7 (OMe), 60.5, 64.2, 66.2 and 68.3 (CH_2O-1, C-4, C-5, C-6), 94.0 (C-1), 99.8 (CMe_2OMe), 127.8 and 128.5 (C-2 and C-3), 169.2 (C=O).

Acknowledgments. This work was supported by a grant from the Royal Norwegian Council for Scientific and Industrial Research (ST.72.157.221479-Deminex 18910). Thanks are due to to Prof. L. Eberson (Lund, Sweden) for an instructive discussion on the complexation mode of DDQ.

References

1. For reviews, see (a) De Belder, A. N. *Adv. Carbohydr. Chem. Biochem. 34* (1977) 179; (b) Clode, D. M. *Chem. Rev. 79* (1979) 491; (c) Gelas, J. *Adv. Carbohydr. Chem. Biochem. 39* (1981) 71.
2. Oku, A., Kinugasa, M. and Komada, T. *Chem. Lett.* (1993) 165.
3. Tanemura, K., Suzuki, T. and Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* (1992) 2997.
4. (a) Kjølberg, O. and Neumann, K. *Acta Chem. Scand. 47* (1993) 843; (b) Tanemura, K., Horaguchi, T. and Suzuki, T. *Bull. Chem. Soc. Jpn. 65* (1992) 304.
5. Catelani, G., Colonna, F. and Marra, A. *Carbohydr. Res. 182* (1988) 297 and references cited herein.
6. Pietraszkiewicz, M. and Sinäy, P. *Tetrahedron Lett.* (1979) 4741.
7. Miyashita, N., Yoshikoshi, A. and Grieco, P. A. *J. Org. Chem. 42* (1977) 3772.
8. Buchanan, J. G., Chacón-Fuertes, M. E., Edgar, A. R. Moorhouse, S. J., Rawson, D. I. and Wightman, R. H. *Tetrahedron Lett. 21* (1980) 1793.
9. For a review, see Eberson, L. *Pure Appl. Chem. 63* (1991) 205 and references cited herein.
10. For the alcoholysis of epoxides via an SET mechanism, see Iranpoor, N. and Baltork, I. M. *Tetrahedron Lett. 31* (1990) 735.
11. For spectroscopic data of $DDQ^{\bullet -}$, see Pradella, F., Scoponi, M. and Sostero, S. *J. Organomet. Chem. 412* (1991) 137.
12. Kjølberg, O. and Neumann, K. *Unpublished results.*
13. Kjølberg, O. and Neumann, K. *Acta Chem. Scand. 46* (1992) 877.

Received May 28, 1993.