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Note

A mild and efficient procedure to remove acetal and dithioacetal protecting groups in carbohydrate derivatives using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

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Cleavage of carbohydrate acetals is usually accomplished by acid-catalysed hydrolysis [1–4]. Iodine in methanol has been proposed [5] as a mild deprotection reagent, but a mixture of methyl glycosides instead of the unprotected sugar is obtained when the deacetalation reaction involves the anomeric position. Among the methodologies available for the deprotection of dithioacetals, acid-catalysed and transition metal-induced hydrolysis as well as oxidative and alkylative procedures are widely used [6,7]. In view of the importance of both acetals and dithioacetals in synthetic carbohydrate chemistry, the search for newer and milder reagents to effect the deprotection is worthwhile.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a well-known electron acceptor and forms charge-transfer (CT) complexes with a variety of donors [8]. This capability allows a number of useful synthetic applications in the carbohydrate field including catalytic acetalation [9], glycosidation [10], and deprotection of *p*-methoxybenzyl and 3,4-dimethoxybenzyl protecting groups [11]. Recently, the use of DDQ for deprotection of acetal [12] and dithioacetal [13] derivatives of simple alcohol and carbonyl compounds has been reported. In connexion with previous synthetic work, we have been

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Table 1
Reaction of sugar-derived acetals and dithioacetals with DDQ

Entry	Substrate	Ref	Solvent–water (9:1)	DDQ (equiv)	T (° C)	Reaction time (h)	Product	Yield (%)	Work up [a]
1	**1a**		MeCN	0.1	20	4	**2a**	~100	A
2	**1a**		MeOH	0.1	20	4	**2a**	~100	A
3	**1a**		EtOAc	0.1	20	16	**2a**	~100	A
4	**1a**		MeCN	0.4	20	48	D-glucose	~100	B
5	**1a**		MeCN	0.4	40	4	D-glucose	90	B
6	**1a**		MeOH	0.4	40	4	D-glucose	~100	B
7	**1b**	[16]	MeCN	0.2	20	4	**2b** [b]	~100	A
8	**1b**	[16]	MeCN	0.2	40	48	D-glucose	~100	B
9	**1b**	[16]	MeCN	0.2	80	5	D-glucose	~100	B
10	**1c**	[16]	MeCN	0.2	20	5	**2c**	85	A
11	**1c**	[16]	MeCN	0.2	80	4	D-glucose (3-*O*-Bz)	87	B
12	**1d**	[17]	MeCN	0.1	20	16	**2d**	95	A
13	**1d**	[17]	MeCN	0.1	80	4	D-glucose (3-*O*-Bzl)	92	B
14	**1e**	[16]	MeCN	0.1	40	24	**2e**	92	A
15	**1e**	[16]	MeCN	0.1	80	24	D-glucose (3-*O*-Ts) [c]	~100	B
16	**3**	[18]	MeCN	0.2	20	4	**4**	~100	A
17	**3**	[18]	MeCN	0.2	80	4	D-allose	~100	B
18	**5**	[19]	MeCN	0.4	80	4	D-galactose	~100	B
19	**5**	[19]	MeOH	0.4	40	96	D-galactose	70 [d]	B
20	**6**	[20]	MeCN	0.4	40	16	**7**	30 [e]	B
21	**6**	[20]	MeCN	0.4	80	4	D-fructose	80 [f]	B
22	**8**	[20]	MeCN	0.2	20	4	**9**	95	A
23	**8**	[20]	MeCN	0.2	80	4	D-fructose	80 [f]	B
24	**10**	[21]	MeCN	0.1	20	16	unreacted **10**	~100	B
25	**10**	[21]	MeCN	0.1	80	4	**11**	~100	B
26	**12**	[22]	MeCN	0.2	20	24	**2a**	95	A
27	**12**	[22]	MeCN	0.2	80	4	D-glucose	90	B
28	**13**	[23]	MeCN	0.2	20	24	**14**	~100	B
29	**15**	[24]	MeCN	0.1	20	2	**16**	90	B
30	**17**	[6]	MeCN	2.0	80	24	D-glucose	95	B
31	**18**	[6]	MeCN	2.0	80	24	D-galactose	92	B
32	**19**	[6]	MeCN	2.0	80	24	D-galactose	87	B
33	**20**	[6]	MeCN	2.0	80	24	D-mannose	43 [g]	B
34	**21**	[6]	MeCN	2.0	80	48	unreacted **21**	~100	B

[a] See Experimental section.

[b] *O*-3 → *O*-6 Acetyl migration was observed (^{13}C NMR).

[c] Ts = *p*-toluenesulfonyl.

[d] Simultaneous formation of a mixture of methyl galactosides was observed.

[e] Unreacted **6** (~20%) and D-fructose (~30%) were also present in the reaction mixture.

[f] Formation of significant proportions of α-D-fructofuranose ß-D-fructofuranose 1,2′:2,1′-dianhydride (~5%) and α-D-fructofuranose ß-D-fructopyranose 1,2′:2,1′-dianhydride (~8%) occurred under these conditions (^{13}C NMR anomeric signals at 101.4, 99.5 and 101.5, 95.0, respectively [14]).

[g] Acetylation of the reaction mixture and preparative TLC (1:2 EtOAc–light petroleum ether) of the peracetylated mixture yielded, in addition to the expected peracetyled mannose, ethyl 1-thio-ß-D-mannopyranoside [25] (25%), ethyl 1-thio-α-D-mannopyranoside [25] (16%), and a mixture of ethyl 1-thio-α- and ß-D-mannofuranosides [26] (17%).

interested in checking the potential of this reagent in the case of acetal and dithioacetal derivatives of sugars. Results are summarized in Table 1.

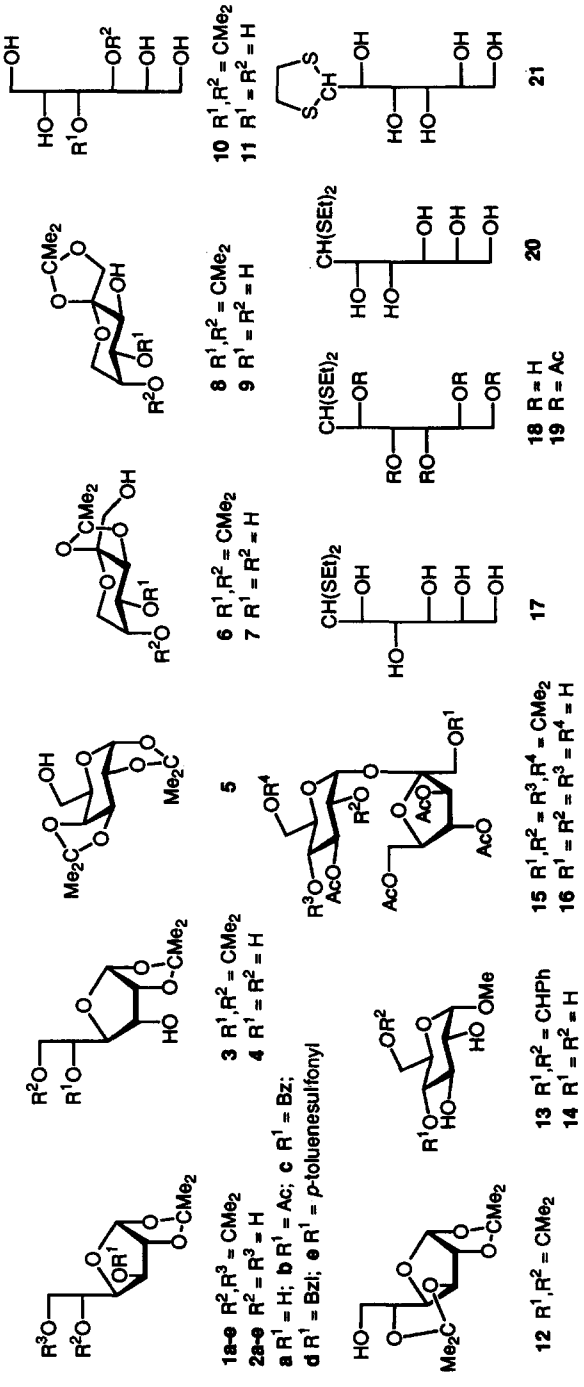
The effect of solvent, equivalent ratio of DDQ and reaction conditions in the cleavage of the isopropylidene groups in 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1a**) are shown in entries 1–6. 9:1 Acetonitrile–water, 9:1 ethyl acetate–water, and 9:1 methanol–water were equally effective for either the selective deacetalation of O-5,6 in **1a** to **2a** or the complete hydrolysis of both isopropylidene groups. Nevertheless, the acetonitrile–water system generally provided faster and cleaner conversion in both cases. On the other hand, the use of methanol–water as solvent was accompanied by formation of methyl glycosides in other examples (e.g. entry 19). The selectivity of the procedure towards other commonly used hydroxyl protecting groups was checked on the 3-*O*-substituted derivatives **1b-1e** (entries 8–15). Benzoyl, benzyl and *p*-toluenesulfonyl groups were stable under reaction conditions for both selective and complete hydrolysis of the acetal groups. The acetyl group in **1b** was stable at room temperature in the presence of DDQ. However, O-3 → O-6 acetyl migration was observed on cleavage of the 5,6-*O*-isopropylidene group. More strenuous reaction conditions resulted in *O*-acetyl hydrolysis, which may be exploited for the selective deprotection of acetyl-protected hydroxyl groups in the presence of benzoates.

Examination of the reaction of the D-allose (**3**), D-galactose (**5**), D-fructose (**6** and **8**) and D-mannitol (**10**) isopropylidene derivatives with a catalytic amount of DDQ (entries 16–25) led to the conclusion that monosubstituted dioxolane rings are, in general, more readily hydrolysed than bicyclic, spiro and disubstituted systems. Except in the case of the D-*galacto* derivative **5**, if two acetal groups are present in the molecule, one of them can be removed selectively. Total deprotection in the fructose derivatives **6** and **8** at 80° C (entries 21 and 23) was accompanied by formation of difructose dianhydrides [14].

Acetal derivatives of 1,3-diol systems (e.g. **12**, **13** and **15**) could be hydrolysed with DDQ (entries 26–29) under milder conditions as compared to derivatives of 1,2-diol systems. In the case of the sucrose derivative **15**, both isopropylidene groups could be removed (→ **16**) without acetyl migration or hydrolysis of the acid-sensitive interglycosidic bond.

Removal of diethyl dithioacetal groups (entries 30–33) in aldose derivatives (**17–20**) required 2 equiv of DDQ and 80° C. Acetyl protecting groups were simultaneously removed under these conditions (entry 32). Nevertheless, the outcome of the reaction was dependent on the sugar configuration. Thus, the D-glucose (**17**) and D-galactose (**18**, **19**) derivatives afforded the corresponding reducing sugars in quantitative yield, whereas the D-*manno* isomer **20** gave a significant proportion of ethyl 1-thiomannosides. A higher tendency to form thioglycosides in the case of D-mannose dithioacetals upon hydrolysis, as compared with other sugar configurations, has been previously reported [15]. Under the same reaction conditions, the cyclic ethylene dithioacetal **21** did not react (entry 34).

Some controversy still exists about the mechanism of action of DDQ in these types of reactions. Both electron-transfer and controlled formation of hydrogen chloride have been suggested as the key reaction step [12,13]. In any case, the set of results presented in Table 1 show that the use of DDQ is a very convenient alternative procedure for the selective removal of acetal and dithioacetal protecting groups in carbohydrate deriva-


1a–e R²,R³ = CMe₂
2a–e R² = R³ = H
a R¹ = H; b R¹ = Ac; c R¹ = Bz;
d R¹ = Bzl; e R¹ = p-toluenesulfonyl
3 R¹,R² = CMe₂
4 R¹ = R² = H
5
6 R¹,R² = CMe₂
7 R¹ = R² = H
8 R¹,R² = CMe₂
9 R¹ = R² = H
10 R¹,R² = CMe₂
11 R¹ = R² = H
12 R¹,R² = CMe₂
13 R¹,R² = CHPh
14 R¹ = R² = H
15 R¹,R² = R³,R⁴ = CMe₂
16 R¹ = R² = R³ = R⁴ = H
17
18 R = H
19 R = Ac
20
21

tives. The method is compatible with acetyl, benzoyl, benzyl, and tosyl protecting groups and requires only a filtration and evaporation process for product isolation.

1. Experimental

Typical procedure for the selective removal of acetal groups in carbohydrate derivatives using DDQ.—To a solution of the corresponding acetal derivative (100 mg) in acetonitrile–water (9:1, 3 mL) was added DDQ (Fluka AG, recrystallized from benzene–hexane, 0.1–0.4 equiv, see Table 1), and the dark red reaction mixture was stirred under the reaction conditions stated in Table 1 (entries 1–29), with monitoring by TLC (3:1 EtOAc–light petroleum ether). When the reaction was complete, the solvents were evaporated and the residue was purified by one of the two following protocols: (A) the residue was dissolved in EtOAc (5 mL), washed with water (2 × 5 mL) and the organic layer was decolourized by passing it through a charcoal layer (3 × 1 cm) and concentrated; (B) the residue was dissolved in water or water–methanol (5 mL) and filtered through charcoal. In the cases of reaction products bearing aromatic substituents (i.e. **1c–1e**), the charcoal layer was subsequently extracted with methanol (5 mL) and boiling methanol (5 mL). In all cases, the structure of the products of hydrolysis was established by ^{1}H and ^{13}C NMR as well as comparison with authentic samples.

Typical procedure for the cleavage of dithioacetal groups in carbohydrate derivatives using DDQ.—To a solution of the corresponding dithioacetal (100 mg) in 9:1 acetonitrile–water (3 mL) was added DDQ (2 equiv), and the reaction mixture was stirred at 80° C until the starting material was consumed (TLC, Table 1, entries 30–34). During the reaction, the initial dark-red colour of the solution faded to pale yellow. The solvents were evaporated and the residue purified by filtering through charcoal (protocol B, see above).

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