Glycosidation of Glycals by 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as a Catalytic Promoter

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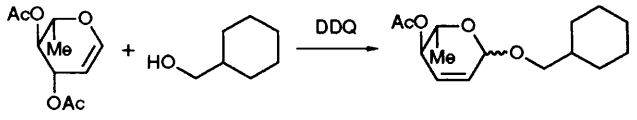
O-Glycosidations of glycals **1, 8** and **9** with several alcohols by using a catalytic amount of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under neutral conditions proceeds smoothly to give the corresponding 2,3-unsaturated glycosides in high yields.

2,3-Unsaturated glycosides[1] are versatile synthetic intermediates, and 2,3-dideoxy sugars, which are easily derived from the 2,3-unsaturated glycosides, are common structural units in many bioactive substances such as antibiotics[2]. Although Lewis acid-catalysed allylic rearrangement of glycals is well known as the Ferrier reaction[3] and widely employed to obtain the 2,3-unsaturated glycosides, a strong acid catalyst such as boron trifluoride–ether[3,4] or tin(IV) chloride[5] is generally required. Very recently, Fraser-Reid *et al.* announced an oxidative alternative to the Ferrier rearrangement by using 3-*O*-pentenoyl glycals and iodonium dicollidinium perchlorate under mild conditions.[6] In this communication, we report a novel and neutral method for glycosidations of glycals which afford the corresponding 2,3-unsaturated glycosides *via* an allylic rearrangement. Thus, *O*-glycosidations of glycals **1, 8** and **9** with several alcohols by using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as a catalytic activator in MeCN under neutral conditions were found to proceed smoothly to afford the corresponding 2,3-unsaturated glycosides in high yields.

DDQ is widely used as a neutral oxidative reagent and a deprotecting agent of the *p*-methoxybenzyl group[7]. Also, DDQ was very recently found to be a good promoter for the ring-opening reaction of epoxides with an alcohol,[8] tetrahydropyranylation of alcohols[9] and effective cleavage of acetals[10] and silyl ethers.[11] Since DDQ behaved just like a Lewis acid in the latter cases, we pursued the utilization of such DDQs properties in glycosidation reactions. Therefore, we

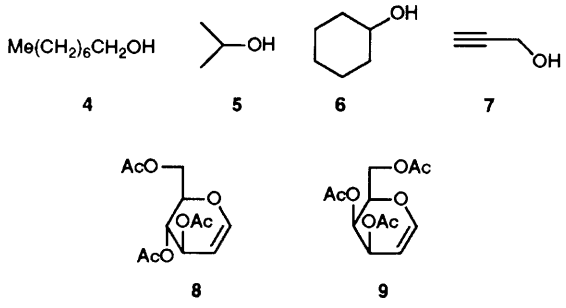
Table 1 Glycosidations of **1** with cyclohexylmethanol **2** by DDQ[a]



1 **2** **3**

Entry	Solvent	DDQ (mol%)	*T*/°C	*t*/h	Yield (%)[b]
1	CH_2Cl_2	100	40[c]	24	66
2	PhH	100	50	24	7
3	Et_2O	100	35[c]	24	0
4	THF	100	50	24	10
5	Dioxane	100	50	24	0
6	MeCN	100	50	24	85
7	MeCN	100	25	72	74
8	MeCN	100	70	4	83
9	MeCN	50	50	24	86
10	MeCN	10	50	24	88

[a] All reactions were carried out by use of 1.5 equiv. of the alcohol to the glycosyl donor. [b] Isolated yields after purificaiton by column chromatography. [c] The reaction was carried out under reflux.



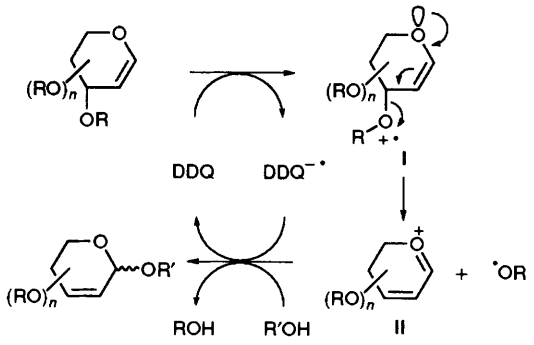
4 **5** **6** **7**

8 **9**

Table 2 Glycosidations of glycals with several alcohols by DDQ as a catalyst[a]

Glycal + Alcohol		10 mol% DDQ, MeCN, 50 °C		2,3-Unsaturated glycosides	
Entry	Glycal	Alcohol	*t*/h	Yield (%)[b]	α:β Ratio[c]
1	**1**	**2**	24	88	4.8/1
2	**1**	**4**	24	83	5.1/1
3	**1**	**5**	24	81	2.1/1
4	**1**	**6**	24	87	6.2/1
5	**1**	**7**	48	86	5.5/1
6	**8**	**2**	48	91	5.6/1
7[d]	**9**	**2**	48	72	8.4/1

[a] All reactions were carried out by use of 1.5 equiv. of the alcohol to the glycosyl donor. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H NMR (270 MHz) spectroscopy. [d] The reaction was carried out at 70 °C.



Scheme 1 Presumed mechanism of the glycosidation of glycal by DDQ

first examined the glycosidation of 3,4-di-*O*-acetyl-L-rhamnal **1**[5b] with cyclohexylmethanol **2** by DDQ in several solvents. The results summarized in Table 1 as entries 1–6 indicated that the glycosidations using an equimolar quantity of DDQ with **1** in CH_2Cl_2, benzene, tetrahydrofuran (THF) or MeCN worked to give the 2,3-unsaturated glycoside **3**† and MeCN was shown to be superior to the other solvents examined. Next, our attention turned to the effect of temperature and quantity of DDQ used in this reaction. These results were demonstrated as entries 7–10 in Table 1. Although a long reaction time was required at room temperature to get a high yield of **3**, glycosidation by using 10 mol% of DDQ at 50 °C for 24 h gave a satisfactory yield. Therefore, the glycosidations of **1** with other alcohols, **4**, **5**, **6** and **7**, were next examined under such conditions. As shown in Table 2, these glycosidation reactions proceeded smoothly to afford the corresponding 2,3-unsaturated glycosides† in good yields while the stereoselectivities of these glycosidations were moderate and small amounts of a mixture of the corresponding 2-deoxy α- and β-glycosides‡ (2–7%) were also produced[5a] in all cases examined. Since the configuration of the anomeric centre was isomerized by exposure of the single α-isomer of 2,3-unsaturated glycoside to the reaction conditions, the predominant α selectivity§ of the glycosidation must arise from the thermodynamic anomeric effect.[12] Further, other typical glycals, tri-*O*-acetyl-D-glucal **8** and tri-*O*-acetyl-D-galactal **9** were also smoothly glycosidated with **2** under similar conditions to afford the corresponding 2,3-unsaturated glycosides† in similar fashions (entries 6 and 7 in Table 2).

Mechanistically, this glycosidation reaction with DDQ probably proceeds *via* a one-electron transfer with the initial formation of the radical cation **I**[8,11] and the allylic oxonium intermediate **II**[5a] as shown in Scheme 1.

A typical experimental procedure is described for the reaction of **1** and **2**: to a mixture of **1** (0.1 mmol) and **2** (0.15 mmol) in MeCN (0.5 ml) was added DDQ (0.01 mmol). After stirring for 24 h at 50 °C, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with benzene. The extracts were washed with a saturated sodium chloride solution, dried over anhydrous Na_2SO_4 and concentrated to a crude syrup that was chromatographed on silica gel with 6:1 hexane–acetone to afford the 2,3-unsaturated glycosides **3** and the corresponding 2-deoxyglycosides in 88% (α:β = 4.8:1) and 6.5% (α:β = 1:1) yields, respectively.

In conclusion, although high stereoselectivity at the anomeric centre was not realized in this reaction, the present methodology offers a new entry to the glycosidation of glycals which affords the corresponding 2,3-unsaturated glycosides under neutral and catalytic conditions.

† All compounds were purified by silica gel column chromatography and were fully characterized by spectroscopic means.

‡ The ratio of the 2,3-unsaturated glycosides to the corresponding 2-deoxy glycosides in the glycosidation reaction was affected by the protecting groups of the glycal.[5b] When glycals possess a poor leaving group, methoxymethyl, at C-3 position, the ratio of the 2-deoxy glycosides was increased signficantly and the 2,3-unsaturated glycosides and the 2-deoxy glycosides were produced in a ratio 1 (27%):2.1(57%).

§ The configurations of the anomeric positions were confirmed by ^{1}H NMR analyses of the corresponding 2,3-dideoxy glycosides which were obtained by standard hydrogenolysis using H_2 and $Pd(OH)_2$ as a catalyst.

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