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SPECIFIC REMOVAL OF O-METHOXYBENZYL PROTECTION BY DDQ OXIDATION

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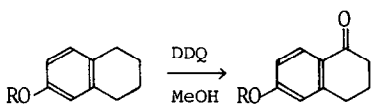
Summary. Methoxybenzyl protecting groups of alcohols were readily and efficiently removed with DDQ in CH_2Cl_2-H_2O at room temperature. Under these neutral conditions, other usual protecting groups, isopropylidene, methoxymethyl, benzyloxymethyl, tetrahydropyranyl, acetyl, t-butyldimethylsilyl, benzyl, benzoyl, and tosyl, as well as functional groups, epoxide, double bond, and ketone, were remained unchanged.

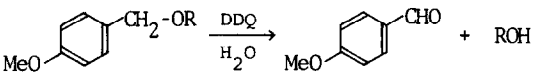
It is very important how to protect hydroxy groups in multistep syntheses of complex natural products, especially in syntheses using carbohydrates as chiral templates, and numerous reports on the hydroxy protection have been published.[1] The benzyl group is one of the most useful protecting groups, because it is stable to acid, alkali, and a number of other usual reagents, and is readily removed by catalytic hydrogenation or by sodium in liquid NH_3. The benzyl protection, however, may not be applied to the alcohols having additional reducible functional groups. During the course of a chiral synthesis of macrolides from carbohydrates, it becomes desirable to have a new benzyl deprotection in a neutral solution other than the reductive methods.

Benzylic oxidation by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been well studied by Becker,[2] Turner,[3] Oikawa,[4] and many other groups.[5] For example, when a MeOH solution of 1 was treated with DDQ, the benzylic position para to an electron-donating group (OH, OMe) was readily oxidized to give 2 in a high yield.[6] Therefore, a p-methoxybenzyl (MPM)[7] ether (3) was expected to undergo oxidative cleavage and to give p-methoxybenzaldehyde (4) and an alcohol (5).

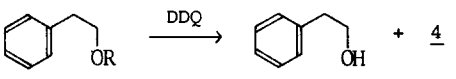
When a MeOH solution of 6 was treated with an equimolar amount of DDQ at room temperature by a method similar to that described by Becker[8] and Turner,[6] a brownish green color of the initially formed charge-transfer (CT) complex between the electron-donating MPM group in 6 and the electron-attracting DDQ slowly faded into light brownish yellow. After 24 hr, 4 and phenethyl alcohol (7)



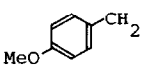
1: R=H,Me 2

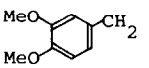


3 4 5



6: R=MPM 7
23: R=DMPM

MPM: 

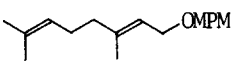
DMPM: 

were isolated in excellent yields. Similarly, the reaction in THF-H_2O (10:1)[9] proceeded efficiently but also very slowly.

$CHCl_3$ and CH_2Cl_2 are reported to be good solvents for DDQ dehydrogenation.[10] Actually, addition of CH_2Cl_2 to the MeOH solution markedly accelerated the reaction, and the reaction rate increased with increasing the proportion of CH_2Cl_2. In CH_2Cl_2 containing a small amount of H_2O instead of MeOH, the deep green CT Complex faded rapidly to colorless and the reaction was completed in 40 min at room temperature. This procedure has an additional merit, namely, as the reaction proceeded, 2,3-dichloro-5,6-dicyanohydroquinone (DDQH) precipitated because DDQH is almost insoluble in both CH_2Cl_2[11] and H_2O, and consequently, the reaction medium was kept almost neutral all through the reaction. This is very important for the deprotection of substrates containing other acid-sensitive functional and protecting groups. A stoichiometric amount of DDQ was sufficient for the reaction, but 10% excess of DDQ brought about a considerable reduction in reaction time, and the reaction was completed only in 20 min.

Similarly, MPM ethers containing an allylic double bond (8) and an acid-sensitive isopropylidene group (9) also readily lost the MPM group to give the corresponding primary alcohols. The deprotection of 10 containing two isopropylidene groups was unusually slow, but could be speeded up by use of 1.5 equiv. of DDQ. Compound 11 derived from a secondary alcohol also containing two isopropylidene groups exhibited a similar behavior. Additional compounds containing benzoyl and tosyl (12), epoxide (13), unsaturated (14), and keto (15) groups also gave good results.

Benzyl ethers such as 16 were almost unreactive to DDQ under these conditions,[12] and hence only the MPM group was selectively removed from 17 containing both the MPM and the benzyl groups. As shown in the oxidative deprotection of 18-22, some other typical protecting groups of alcohols, such as tetrahydropyranyl (THP), methoxymethyl (MM), benzyloxymethyl (BM), acetyl (Ac), and t-butyldimethylsiliyl (TBDMS) groups, which are frequently used, were quite unaffected.



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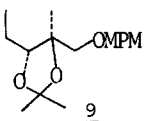

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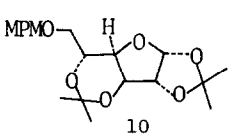

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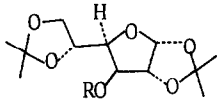
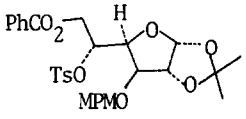


11: R=MPM

24: R=DMPM



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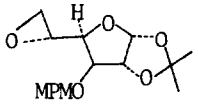

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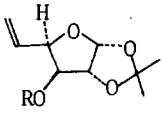
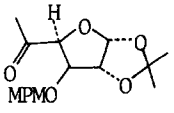


14: R=MPM

16: $R=C_6H_5CH_2$



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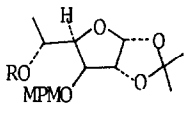


17: $R=C_6H_5CH_2$

18: $R=C_5H_9O$(THP)

19: $R=CH_3OCH_2$

20: $R=C_6H_5CH_2OCH_2$

21: $R=CH_3CO$

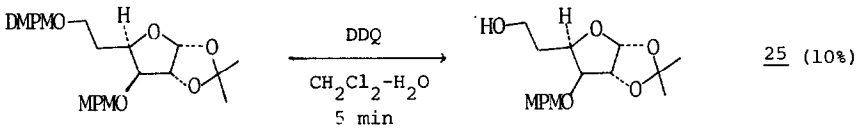
22: $R=Me_3CSiMe_2$

Table 1. Oxidative cleavage of methoxybenzyl ethers with DDQ at room temperature

ether	DDQ equiv	solvent	reaction time	alcohol[a] yield,%	mp°C
6	1.0	MeOH	24 hr	86.3	oil
"	"	THF-H_2O(10:1)	"	84.9	"
"	"	CH_2Cl_2-MeOH(4:1)	6 hr	86.5	"
"	"	CH_2Cl_2-MeOH(9:1)	3.5 hr	80.3	"
"	"	CH_2Cl_2-H_2O(18:1)	40 min	89.2	"
"	1.1	"	20 min	83.8	"
23	"	"	15 min	86.0	"
8	"		1 hr	81.9	"
9	"	"	30 min	86.6	"
10	"	"	4 hr	93.0	"
"	1.5	"	1 hr	91.5	"
11	1.1	"	5 hr	86.2	108-109
"	1.5	"	3 hr	86.2	"
24	1.1	"	2.5 hr	86.3	"
"	1.5	"	1 hr	87.4	"
12	"	"	2 hr	86.1	139-140
13	"	"	2.5 hr	83.7	130-131
14	"	"	"	89.3	oil
15	"	"	7 hr	83.5	94-95.5
17	"	"	1.5 hr	84.8	oil
18	"	"	2 hr	85.7	"
19	"	"	1.5 hr	90.4	"
20	"	"	"	86.5	"
21	"	"	2.5 hr	84.9	59.5-61
22	"	"	45 min	87.0	oil

[a] All alcohols were identified by satisfactory nmr and mass spectra, and/or elemental analyses.

Because 1,2-dimethoxybenzene has a lower oxidation potential and hence more reactive for the CT complex formation than anisole,[13] the 3,4-dimethoxybenzyl (DMPM) group was expected to afford a more reactive protecting group to DDQ. Whereas, only a small difference in reactivity between 23 and 6 derived from the primary alcohol (7) was observed, a DMPM ether (24) derived from the secondary alcohol, however, was clearly more reactive than the corresponding MPM compound (11). The DMPM protection could be selectively removed from 25 by the oxidation with 1.1 equiv. of DDQ only for 5 min.



25 (10%)

25 26 (78.2%)

There are several precedents for the oxidative cleavage of MPM ethers.[14-16] The oxidation with tritylfluoroborate proceeds very rapidly but is not specific to the MPM groups.[14] The oxidation with stable radical cations of triarylamines[15] and the electrochemical oxidation[16] also appear to be promising, but only simple examples have been published, and therefore, it is still uncertain whether many other functional and protecting groups are affected under these conditions or not.

In conclusion, the DDQ oxidation in this communication may provide an alternative but more simple and versatile oxidative deprotection method of the MPM groups, which may become much more useful for the protection of alcohols. An extension and some applications of this method in natural product syntheses will be reported soon.

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