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PROTECTION OF HYDROXY GROUPS BY INTRAMOLECULAR OXIDATIVE FORMATION OF METHOXYBENZYLIDENE ACETALS WITH DDQ

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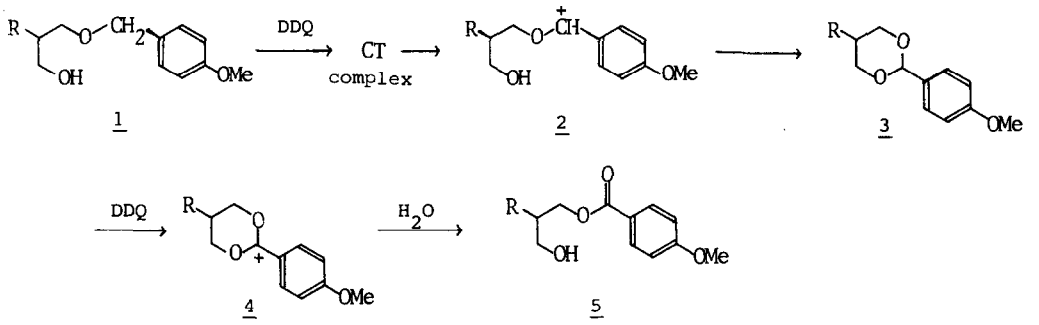
Summary. On DDQ oxidation under anhydrous conditions, hydroxy groups located at α or β position to methoxybenzyl ether groups were readily protected by the intramolecular oxidative formation of acid-sensitive methoxybenzylidene acetals, which were further oxidized to alkali-sensitive hydroxy esters in the presence of H_2O.

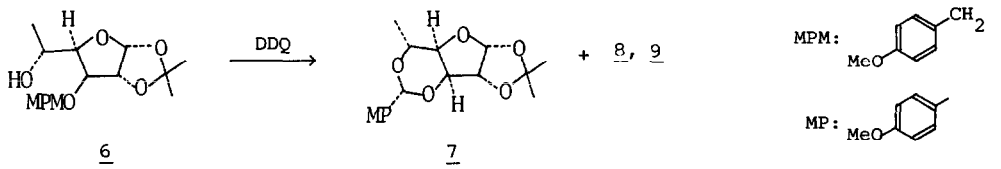
In the preceding paper it was demonstrated that O-methoxybenzyl (MPM)[1] groups were readily and selectively removed by the 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation under neutral conditions, and hence would be widely useful for the protection of alcohols.[2] In the present paper we report an extended application of the benzylic oxidation with DDQ involving a methoxybenzylidene protection of an additional hydroxy group and its further oxidative conversion to hydroxy esters.

Cyclic acetal and ketal groups are the most common for the protection of 1,3- and 1,2-diol systems.[3] If a MPM ether containing an additional hydroxy group located in 1,3- or 1,2-position such as 1 is oxidized with DDQ under anhydrous conditions, a methoxybenzylidene acetal containing a 1,3-dioxan (3) or 1,3-dioxolan system is expected to form by an intramolecular attack of the hydroxy group to an intermediary benzyl cation (2) formed via a charge-transfer (CT) complex.[4]

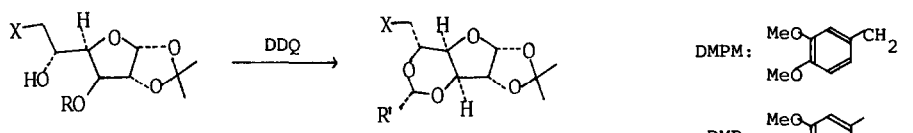
This conversion has at least two characteristics: one is that a hydroxy group at α or β position to the MPM ether group in a multistep synthesis can be protected by a methoxybenzylidene group, and the other is that the acid-resistant MPM group can be converted to the acid-sensitive methoxybenzylidene acetal which is selectively removable under very mild acidic conditions.[5] Further oxidation of 3 with DDQ in the presence of H_2O will give a hydroxy ester (5) via 4. The methoxybenzoyl group in 5 can be removed in alkaline solution instead of acidic solution.



When an anhydrous CH_2Cl_2 solution of 6 (30 mg) was treated with DDQ, the oxidative cyclization readily occurred to give the desired methoxybenzylidene acetal (7), but the yield was only 44% and further oxidation products (8, 9; 21%) were concomitantly produced, probably because of contamination by a trace of H_2O. In the presence of powdered molecular sieves (3 Å), this undesirable side reaction was avoidable as exemplified below: when 6 (65 mg) in anhydrous CH_2Cl_2 (distilled over P_2O_5) in the presence of powdered 3 Å molecular sieves (80 mg) was treated with DDQ (1.5 equiv.) for 1.5 hr at room temperature, 7 was isolated as the sole product in 80.2% yield. There are two possible stereoisomers with respect to the benzylic position, but actually the only isomer was obtained. The structure of 7 having the equatorial methoxyphenyl group is both kinetically and thermodynamically favorable.

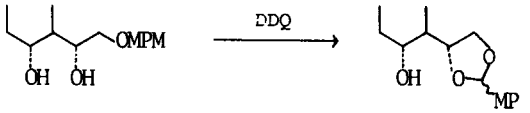


Simllarly, 10 and 12 readily gave 11 and 13, respectively. The oxidative cyclization of a dimethoxybenzyl (DMPM) ether (14) proceeded much faster than that of the corresponding MPM compound (12), and gave a dimethoxybenzylidene product (15) in 83.7% yield.



10: R=MPM,X=TsO
12: R=MPM,X=BzO
14: R=DMPM,X=BzO

11: R'=MP,X=TsO
13: R'=MP,X=BzO
15: R'=DMP,X=BzO



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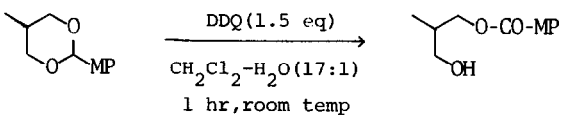
When an open-chain MPM ether (16) containing two hydroxy groups at α and γ positions was oxidized, the only five-membered acetal (17) was isolated in 80% yield, though it was a 2:1 stereoisomeric mixture with respect to the benzylic position.

Table 1. Oxidative formation of methoxybenzylidene acetals from hydroxy ethers with DDQ (1.5 eq) in the presence of molecular sieves

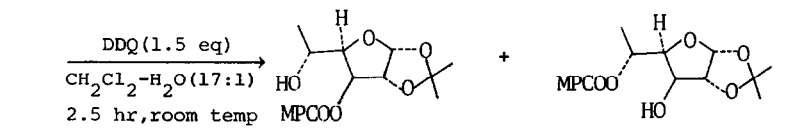
substrate	time(hr)	acetal[a]	yield(%)	mp°C
6	1.5	7	80.2	133.5-135
10	1.5	11	81.4	121.5-123
12	2.5	13	80.1	121-121.5
14	0.5	15	83.7	oil
16	1.0	17	80	oil

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

Although the methoxybenzylidene groups were selectively removed by the treatment with 80% AcOH at room temperature,[5] the oxidative conversion to alkali-sensitive hydroxy esters was next examined. When 18 in CH_2Cl_2-H_2O (17:1) was treated with DDQ (1.5 equiv.) at room temperature for



18 19



8 9

1 hr, the oxidative cleavage of the methoxybenzylidene group readily occurred and a hydroxy ester (19) was isolated in 73.8% yield. The oxidation of 7 gave a similar result, namely, 7 was oxidized under the same conditions as described above for 2.5 hr, a mixture of 8 and 9 in a 7:3 ratio, determined easily by nmr spectroscopy, were isolatated in 86.9% yield.

The oxidation of benzylidene acetals to the corresponding hydroxy esters with ozone has been reported.[6] This ozone oxidation is quite similar to the DDQ oxidation presented in this paper, but naturally lacks the specificity toward the benzylidene acetals. On the other hand, the DDQ oxidation proceeds rapidly only at highly electron-donating groups which can form CT complexes more easily with electron-attracting DDQ.

Some applications of these benzylic oxidation methods with DDQ for a new synthesis of macrolide antibiotics are currently in progress.

REFERENCES AND NOTES

1. Abbreviation: MPM = p-methoxyphenylmethyl.
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