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p-Anisyloxymethyl Group, a Novel Oxidatively Removable Acetal Type OH-Protecting Group

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Protection of various types of alcohols with p-anisyloxymethyl (p-AOM) chloride gave the corresponding p-AOM ethers which were deprotected with ceric ammonium nitrate efficiently. Chemoselective removal either of p-AOM group or of tetrahydropyranyl group is also reported.

Foreseeing selection of protecting groups for various functional groups is crucial for the successful synthesis of complex molecules. Because of tremendous versatility of hydroxyl groups in organic synthesis a wide variety of methods for protection of hydroxyl groups have been developed.[1)] Recently, p-anisyl (4-methoxyphenyl) group has been introduced by Fukuyama[2)] as the acid- and base-stable and oxidatively removable hydroxyl protecting group.[3)] Although p-anisyl group is a successful protecting group for primary alcohols, introduction of the protecting group into (chiral) secondary alcohols by the reported method[2)] resulted inevitably in the Walden inversion of the configuration at the hydroxylic carbon.

Loubinoux reported the guaiacylmethyl group as the protecting group for various hydroxyl groups.[4)] However, he recognized guaiacylmethyl group merely as one of acetal type OH-protecting groups and therefore, he removed the group with a Lewis acid $ZnBr_2$ and did not try to deprotect under oxidative conditions. Here we wish to present p-anisyloxymethyl (4-methoxyphenoxymethyl) (p-AOM) group as a novel oxidatively removable acetal type OH-protecting group. Protection of alcohols with p-AOM group is featured by (1) easy preparation of the protecting reagent p-anisyloxymethyl chloride (p-AOMCl); (2) facile introduction of this protecting group into various primary, secondary, and tertiary hydroxyl groups; (3) easy oxidative deprotection with ceric ammonium nitrate (CAN); (4) chemoselective removal either of p-AOM group or of tetrahydropyranyl (THP) group, one of the most widely used acetal type OH-protecting groups.

The protecting reagent p-AOMCl has been prepared by a tedious method including the utilization of inaccessible sodium p-anisyloxymethanesulfonate.[5)] We synthesized p-AOMCl (bp 98-102 °C/5 mmHg) in a single step and 66% yield from 1,4-dimethoxybenzene by treatment with 0.2 equiv. mole of PCl_5 [$(PhCO)_2O_2$ (cat.)/CCl_4/reflux/15 h] according to the method which Loubinoux applied to the synthesis of guaiacylmethyl chloride from veratrole.[4)]

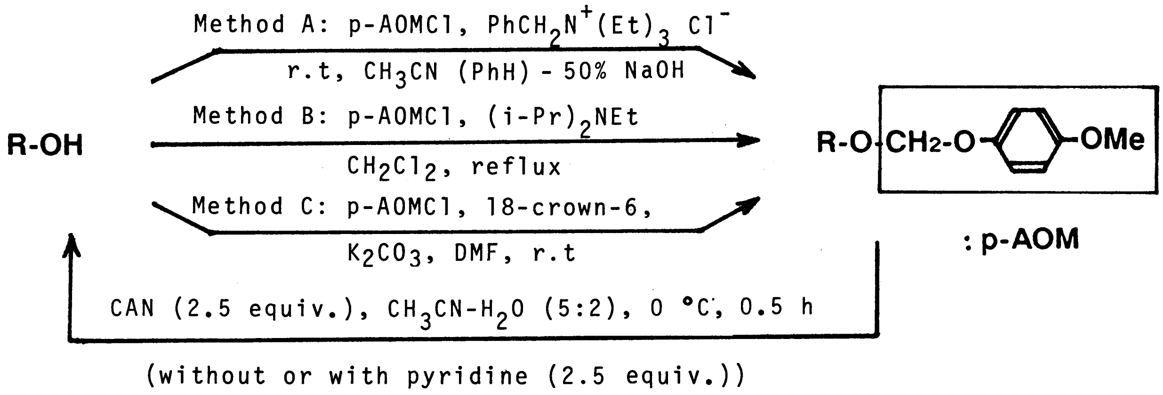


Table 1. Conversion of Alcohols into p-AOM Ethers (Yield/%)[a]

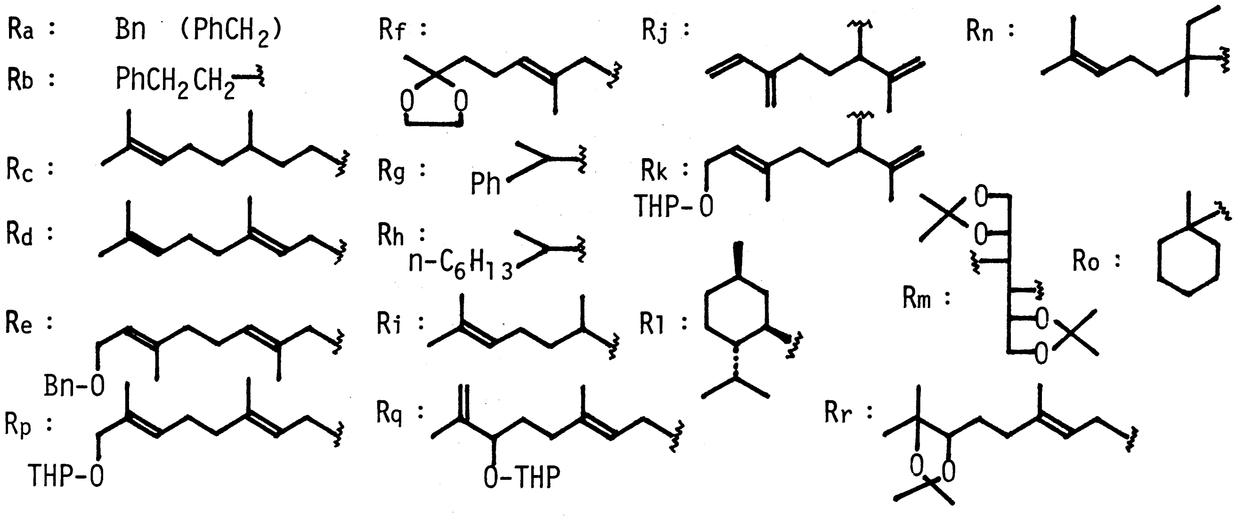
R	Ra	Rb	Rc	Rd	Re	Rf	Rg	Rh	Ri	Rj	Rk	Rl	Rm	Rn	Ro
Method A[b]	76*	82*	80	78	-	52	79 76*	67	55	78	91*	79	0 64*	0	0
Method B	-	75	87	69	75	67	76	78	79	-	51	67	-	63	72
Method C	-	-	-	-	-	46	-	-	60	-	-	-	52	-	-

a) -: Reactions have not been carried out. The symbol is used also in Table 2.
b) *: Benzene was used as organic solvent.

Table 2. Generation of Alcohols from p-AOM Ethers (Yield/%)

R	Rb	Rc	Rd	Rf	Rg	Rh	Ri	Rj	Rk	Rl	Rn	Rp	Rq	Rr
Without py.	79	98	73	42	84	97	79	96	65	96	94	-	60	-
With py.	-	-	-	88	-	-	-	-	95	-	-	86	85	93

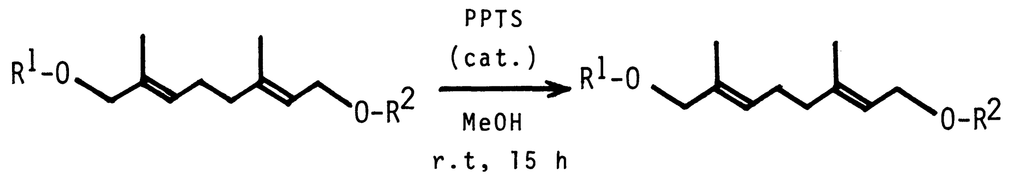
Ra : Bn (PhCH$_2$)
Rb : PhCH$_2$CH$_2$-



Conversion of a hydroxyl group into the corresponding p-AOM ether was carried out mainly by the following two methods. Method A: Stirring an alcohol with 1.5-2.0 equiv. mole of p-AOMCl in 50% NaOH and CH_3CN (or benzene) (1:1) in the presence of 0.1 equiv. mole of $PhCH_2N^+(C_2H_5)_3\ Cl^-$ at the room temperature (r.t) for 15 h.[4] Method B: Refluxing a solution of an alcohol with 1.5-2.0 equiv. mole of p-AOMCl and $(i\text{-}Pr)_2NC_2H_5$ (2 equiv.) in CH_2Cl_2 for 15 h.[6] Another procedure (Method C) using 18-crown-6 as catalyst in dimethylformamide (DMF) with K_2CO_3 as the base (r.t/15 h) also proved to be useful on the limited cases although the procedure has not been investigated extensively. As summarized in Table 1, protection of various types of alcohols using p-AOMCl proceeds successfully to give corresponding allylic and non-allylic, and primary to tertiary p-AOM ethers. With tertiary alcohols, protection was achieved by Method B, although unsuccessful by Method A.[4]

Removal of the p-AOM group was carried out in high yields as summarized in Table 2 by treatment with 2.5 equiv. mole of CAN in aqueous CH_3CN at 0 °C analogously to the deprotection of p-anisyl ethers.[2] Oxidation of 1,4-dialkoxybenzene derivatives with CAN mechanistically generates acidic protons (H^+) in the reaction media together with 1,4-benzoquinone.[7] As a result, yields reduced when the substrates possess the acid-labile functional groups such as THP and acetal group. The yields were much improved by the addition of pyridine (py.) in the equivalent amount to CAN used.

The p-AOM ethers are expected to be stable under basic or alkalline conditions, and on the contrary, labile under acidic conditions. Stability and lability of the p-AOM ethers were exemplified on p-AOM protected geraniol (R = Rd), which was stable and recovered unchanged under the following conditions: 10% NaOH-EtOH (1:1)/ r.t/15 h; n-BuLi (1 equiv.)/THF/-70 °C/1 h, and deprotected to give geraniol in high yields under the following conditions: p-TsOH (cat.)/MeOH/r.t/24 h; 70% AcOH/ 60 °C/15 h; 4% $HClO_4$ - CH_3CN (1:2)/0 °C - r.t/15 h, although stable under the transacetalization conditions: BF_3-Et_2O (cat.)/Me_2CO/CH_2Cl_2/0 °C/2 h; p-TsOH (cat.)/$Me_2C(OMe)_2$/Me_2CO/55 °C/15 h. The p-AOM ether moiety was intact under several oxidation conditions: m-chloroperbenzoic acid/CH_2Cl_2/0 °C/1 h; SeO_2/py./ EtOH/80 °C/3.5 h; CrO_3 - py./CH_2Cl_2/0 °C/1 h; CrO_3 - H_2SO_4/Me_2CO/0 °C/0.5 h.



1 R^1 : THP, R^2 : P-AOM

2 R^1 : p-AOM, R^2 : THP

3 R^1 : H, R^2 : p-AOM (95%)

4 R^1 : p-AOM, R^2 : H (87%)

In the extensive trials we found the conditions for selective removal of THP group in the substrates containing both THP and p-AOM protecting groups. Thus, protected alcohols 1 and 2 were treated with a catalytic amount (0.05 equiv.) of pyridinium p-toluenesulfonate (PPTS)[8] in MeOH at r.t for 15 h to give the p-AOM protected alcohols 3 and 4 in 95 and 87% yield, respectively. It should be worth noting that p-AOM protecting group is more stable than THP group under acidic conditions and easily removed by oxidative treatment with CAN, and appears to be a novel, useful, and promising protecting group for alcohols.

References

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