

4-NITROBENZYL GROUP FOR PROTECTION OF HYDROXYL FUNCTIONS

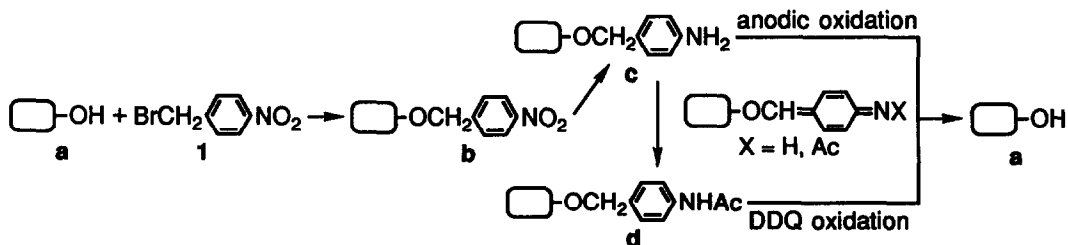
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Summary: Versatile use of 4-nitrobenzyl group for protection of hydroxyl functions is described. It can be removed selectively in the presence of other benzyl-type protecting groups such as benzyl and 4-methoxybenzyl via reduction into 4-aminobenzyl group followed by electrochemical oxidation. Very clean oxidative cleavage of 4-aminobenzyl group could also be effected with 2,3-dichloro-5,6-dicyanobenzoquinone after *N*-acetylation.

Selective protection and deprotection of particular hydroxyl groups play a crucial role in multi-step syntheses of complex carbohydrates and other polyhydroxylated natural compounds. Therefore, considerable efforts have been focused on the development of selectively removable protecting groups. 4-Nitrobenzyl group is an acid-stable group which can be cleaved by catalytic hydrogenolysis. But it has not been used frequently because of the lack of particular advantages over the simple benzyl group. In the present study, we found that 4-nitrobenzyl group can also be used for both versatile temporary and persistent protection of hydroxyl functions. Since benzyl ethers having an electron-releasing substituent such as 4-methoxybenzyl (MPM) ethers were shown to readily undergo side-chain oxidation to the corresponding aldehydes to liberate deprotected alcohols,¹⁾ we anticipated that the 4-nitrobenzyl function would be removed via reduction of the nitro group into an amino group followed by anodic oxidation of the resulting 4-aminobenzyl derivative as shown in the scheme. Furthermore, selective cleavage of a 4-aminobenzyl function from other benzyl-type protecting groups by anodic oxidation could be expected in view of the very low oxidation potential of the former.



We first attempted to find a facile method for 4-nitrobenzylation of hydroxyl functions, since 4-nitrobenzyl bromide (1) rapidly decomposed by a typical procedure for the formation of benzyl ethers with strong bases such as sodium

hydroxide, sodium hydride, or barium hydroxide in *N,N*-dimethylformamide (DMF). As shown in Table 1, however, 4-nitrobenzyl group could be readily introduced by use of 4-nitrobenzyl bromide and silver oxide (Ag_2O) in CH_2Cl_2 , cyclohexane, and benzene (entry 1-5). The bromide decomposed even with Ag_2O in polar solvents such as DMF and THF. The combination of 4-nitrobenzyl bromide and silver trifluoromethanesulfonate (silver triflate, AgOTf) was also effective for introduction of a 4-nitrobenzyl group (entry 6,7) by application of the procedure developed by Berry et al.²⁾ The use of 4-nitrobenzyl triflate, prepared *in situ* from 4-nitrobenzyl alcohol with trifluoromethanesulfonic anhydride, caused considerable *N*-alkylation of 2,6-lutidine or 2,4,6-collidine used as the base to promote the reaction, giving 4-nitrobenzyl ether only in lower yields (entry 8,9).^{2,3)} Other methods for the formation of 4-nitrobenzyl ethers were also reported previously by others, *i.e.*, by *O*-monoalkylation via *O*-stannylene acetal with 4-nitrobenzyl bromide in the presence of cesium fluoride,⁴⁾ and by the reductive cleavage of 4-nitrobenzylidene acetals using $\text{Zn}(\text{BH}_4)_2$ in the presence of trimethylsilyl chloride.⁵⁾

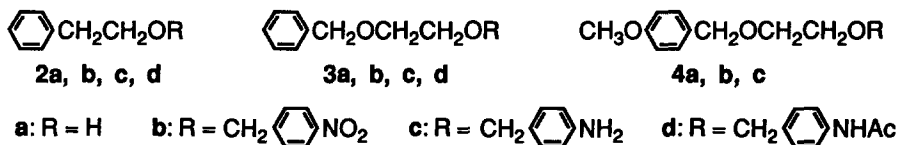


Table 1. Introduction of 4-nitrobenzyl group to hydroxyl functions

entry	alcohol	conditions	solvent	product	yield
1	2a		benzene	2b	94%
2	2a	BrCH ₂ -C ₆ H ₄ -NO ₂ (1) (1.0 eq.) Ag ₂ O (1.0 eq.)	CH ₂ Cl ₂	2b	92
3	2a		cyclohexane	2b	87
4	3a		benzene	3b	87
5	4a		benzene	4b	89
6	2a	1 (1.0 eq.) AgOTf (1.0 eq.)	CH ₂ Cl ₂	2b	91
7	2a	2,4,6-collidine (1.3 eq.)	cyclohexane	2b	88
8	2a	HOCH ₂ -C ₆ H ₄ -NO ₂ (1.5 eq.) } (CF ₃ SO ₂) ₂ O (1.5 eq.) } 2,4,6-collidine (3.5eq.) } 2,6-lutidine (3.5 eq.) }	CH ₂ Cl ₂	2b	56
9	2a		CH ₂ Cl ₂	2b	67

Selective reduction of nitro group in 4-nitrobenzyl ethers (**2b,3b,4b**) could be then carried out by catalytic hydrogenation using palladium black without any changes at benzylic positions to give desired 4-aminobenzyl ethers in good yields (**2c**, 98%; **3c**, 94%; **4c**, 95%). Catalytic transfer hydrogenation of **3b** with palladium black was also effective for the selective reduction of the nitro group (**3c**: HCO_2NH_4 , 96%; HCO_2H , 83%; 1,4-cyclohexadiene, 94%).

Cleavage of 4-aminobenzyl group by anodic oxidation was first investigated using 4-aminobenzyl phenethyl ether (**2c**) in an undivided cell under a constant current using Pt electrodes.⁶⁾ The anodic oxidation under neutral conditions using

tetraethylammonium tosylate, tetraethylammonium tetrafluoroborate, or tetraethylammonium perchlorate as supporting electrolytes gave polymeric brown precipitate but no phenethyl alcohol (2a). Addition of H₂SO₄ to the reaction mixture after electrolysis formed 2a though in low yields. These results suggested that the oxidation of 4-aminobenzyl ether proceeded under the conditions described, whereas the subsequent hydrolysis did not occur. Hence, we carried out the anodic oxidation of 2c using various acids as supporting electrolytes. As shown in Table 2, desired phenethyl alcohol (2a) was satisfactorily obtained under many of the acidic conditions examined.⁶⁾ Suitable solvent systems were dioxane-H₂O (11:4) and *t*-butanol-H₂O (3:1). The use of other solvent systems such as methanol, methanol-H₂O, methanol-H₂O-AcOH, CH₃CN, CH₃CN-H₂O, CH₃CN-H₂O-AcOH, dioxane-methanol-H₂O, and CH₂Cl₂-methanol gave 2a in much lower yields. Stainless steel electrodes were also useful for the present reaction (see the footnote of Table 2), whereas a carbon electrode was not suitable as the anode. In all cases, the aminobenzyl part formed polymeric brown precipitate, which could be easily removed by simple silica-gel column chromatography.

Table 2. Removal of 4-aminobenzyl group of 2c by anodic oxidation

solvent	passed electricity	supporting electrolyte							
		H ₂ SO ₄		HClO ₄		HNO ₃	TFA	HBr	H ₃ PO ₄
		1	2	1	2	2	2	2	2*
dioxane-H ₂ O (11:4)	4.2 F/mol	91%	93% ^a	91%	93% ^c	90%	68%	69%	69%
^t BuOH-H ₂ O (3:1)	10 F/mol		89 ^b	93	90 ^d	89	90	86	80

* Equivalent of acids to amino group of 2c.

The yields obtained with stainless steel electrodes: a, 78%; b, 95%; c, 91%; d, 93%.

Oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) which is satisfactorily employed for cleavage of MPM groups⁷⁾ was also applied to the aminobenzyl group. The reaction of 2c and 3c with DDQ actually proceeded, but the yields of the resulting alcohols 2a (84%) and 3a (70%) were lower than those by anodic oxidation. In contrast, after *N*-acetylation with acetic anhydride and pyridine, the resultant 4-acetamidobenzyl ethers (2d, 98%; 3d, 96%) were cleaved in good yields (2a, 97%; 3a, 92%) on oxidation with the same reagent.

Having established the conditions for the electrooxidative removal of 4-aminobenzyl group, we then attempted the selective cleavage of 4-aminobenzyl group in

Table 3. Selective removal of 4-aminobenzyl group in the presence of Bzl and MPM groups

entry	compound	solvent	passed electricity	supporting electrolyte	product	yield
1	3c	^t BuOH-H ₂ O (3:1)	10 F/mol	H ₂ SO ₄ (2.0eq.)	3a	89%
2	3c	dioxane-H ₂ O (11:4)	4.2 F/mol	H ₂ SO ₄ (2.0eq.)	3a	92
3	3c	dioxane-H ₂ O (11:4)	4.2 F/mol	H ₂ SO ₄ (1.0eq.)	3a	92
4	4c	^t BuOH-H ₂ O (3:1)	10 F/mol	H ₂ SO ₄ (2.0eq.)	4a	81
5	4c	dioxane-H ₂ O (11:4)	4.2 F/mol	H ₂ SO ₄ (2.0eq.)	4a	48

the presence of Bzl and MPM groups by use of 3c and 4c as substrates. The electro-oxidation was carried out under a constant current of 13 mA/cm² using Pt electrodes. As shown in Table 3, 4-aminobenzyl group of 3c was selectively removed without causing any oxidation of benzyl group (entry 1,2,3). Selective cleavage of 4-aminobenzyl group of 4c was achieved similarly even in the presence of MPM group in *t*-butanol-H₂O (3:1) solution (entry 4).

4-Nitrobenzyl group proved to survive under reaction conditions employed for cleavage of many other temporary protecting groups. For example, 4-nitrobenzyl group was of course stable under various acidic conditions and also stable during the cleavage of acyl-type protecting groups.⁸⁾ The 4-nitrobenzyl function in 4b remained unchanged when the MPM group was removed by DDQ oxidation.

In conclusion, 4-nitrobenzyl group can be used as a new versatile benzyl-type protecting group for hydroxyl functions. It is readily introduced, enough stable unless reducing reagents are used, but can be removed either in one step by hydrogenolysis or highly selectively by electrochemical or DDQ oxidations after reductive conversion into the corresponding 4-aminobenzyl group.

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References and Notes

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- 2) In the present study, 2,4,6-collidine was used as the base instead of expensive 2,6-di-*t*-butylpyridine which was used in the original paper: J.M. Berry and L.D. Hall, *Carbohydr. Res.*, **47**, 307 (1976).
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- 6) A typical electrooxidation procedure is as follows. A solution of 2c (177 mg, 0.780 mmol) and H₂SO₄ (42 μ l, 0.780 mmol) in the mixture of dioxane (11 ml) and H₂O (4 ml) was placed in an undivided cell equipped with platinum electrodes (each 3 cm²). The mixture was electrolyzed at room temperature under a constant current of 13 mA/cm² until 4.2 F/mol of electricity was passed. The yield of resulting phenethyl alcohol 2a was determined with HPLC (column: Cosmosil 5C₁₈, 4 x 250 mm; solvent: CH₃CN-H₂O, gradient: 30-50%(2%/min); flow rate: 1.0 ml/min; detection: UV at 220 nm). The yields of all other cleavage reactions were determined by HPLC analyses under similar conditions as well.
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- 8) 4-Nitrobenzyl ethers are stable under usual conditions for ester hydrolysis in alcohol but decomposed rapidly by alkaline treatment in DMF.