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APPLICATION OF 4-AZIDOBENZYL GROUP TO PROTECTION OF HYDROXYL FUNCTIONS

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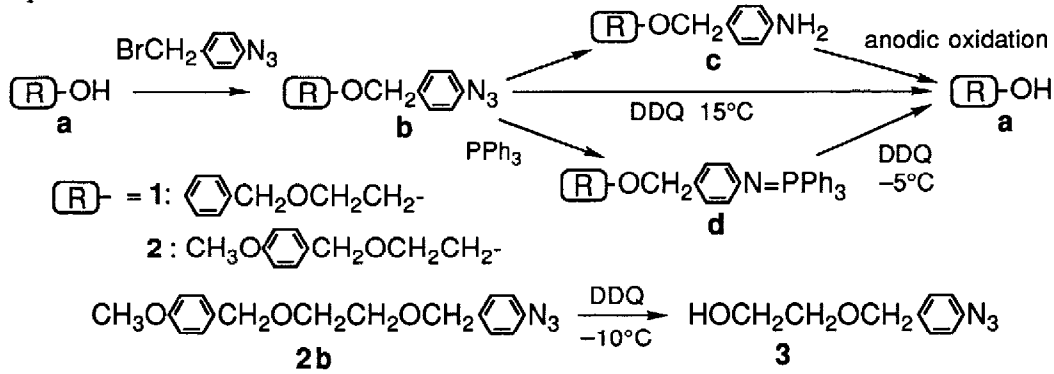
Summary: The 4-azidobenzyl ether can be readily formed and cleaved either by direct oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or by oxidation after conversion to the 4-aminobenzyl ether or the corresponding iminophosphorane derivative. In the latter two-step cleavage methods the azidobenzyl group is removed in preference to the 4-methoxybenzyl (MPM) group, whereas the MPM group can be selectively removed by the direct DDQ oxidation.

For the synthesis of complex polyhydroxylated natural compounds, we have recently devised the use of the 4-nitrobenzyl (4-nitrophenylmethyl, NPM)[1] and the 4-pivaloylaminobenzyl[2] groups for temporary protection of hydroxyl functions. The NPM ether is stable under various reaction conditions but can be removed *via* reduction to 4-aminobenzyl ether followed by anodic oxidation. The 4-pivaloylaminobenzyl ether can be directly cleaved with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) like the 4-methoxybenzyl (MPM) ether.[3] In view of the some possible drawbacks of these groups, *e.g.*, the requirement of a silver salt for the preparation of the former and the presence of the amide proton in the latter, we examined the use of 4-azidobenzyl ether, that is readily formed in a same way as the non-substituted benzyl ether and has been already utilized for photoaffinity labelling experiments.[4]



4-Azidobenzylation of model compounds **1a** and **2a** proceeded smoothly with azidobenzyl bromide[5] and NaH in *N,N*-dimethylformamide (DMF) (**1b**, 92%; **2b**, 98%). Selective reduction of the azide groups was carried out by catalytic hydrogenation using Pd-black to give **1c** (93%) and **2c** (99%) without any cleavage at the benzyl ether linkage. Since the 4-aminobenzyl ethers in **1c** and **2c** were cleaved highly selectively by anodic oxidation in

our previous work (**1a** , 92%; **2a** , 81%),[1] preferential removal of the 4-azidobenzyl group is possible by this route in the presence of the benzyl and MPM groups.

Cleavage of the azidobenzyl group was also effected, without catalytic hydrogenation, by direct oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at room temperature (**1a** from **1b**, 90%).[6] But because of its considerably slower oxidation rate than that of MPM ether, the MPM ether could be cleaved selectively without the change of the 4-azidobenzyl group with DDQ at low temperature (**3** from **2b**, 92%) .[7]

On the other hand, oxidation at the benzylic position could be enhanced by conversion of the azide function to the corresponding iminophosphorane, as expected from the strong electron-donating character of iminophosphoranes.[8] The iminophosphorane **2d** formed by the reaction of 4-azidobenzyl ether **2b** with triphenylphosphine was treated with DDQ without isolation[9] to give the desired **2a** in a good yield (92%). The selectivity of the cleavage of the 4-azidobenzyl group in this method was better than that of the 4-aminobenzyl ether by anodic oxidation.

The stability of the 4-azidobenzyl group to acids lies between those of the MPM and benzyl groups in accordance with the order of their oxidation potentials. The 4-azidobenzyl ether was completely decomposed with TFA at room temperature within 30 min, but stable under the reaction conditions of glycosidation with a glycosyl fluoride and BF_3 etherate[10]. The 4-azidobenzyl ether was also stable during the cleavage of acyl groups with MeONa.

In conclusion, the 4-azidobenzyl group can be used as a new versatile temporary protecting group for hydroxyl functions. It is readily introduced and removed either directly with DDQ or in two steps *via* the aminobenzyl ether or an iminophosphorane.

References and Notes

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4) D. J. Keeling, C. Fallowfield, K. M. W. Lawrie, D. Saunders, S. Richardson, and R. J. Ife, *J. Biol. Chem.*, **264**, 5552 (1989).
5) R. Mornet, N. J. Leonard, J. B. Theiler, and M. Doree, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 879.
6) The direct cleavage of the 4-azidobenzyl ether in **1b** was carried out with DDQ (1.5 eq) in CH_2Cl_2-H_2O (19:1) at 15°C for 23 h. After the completion of the reaction as checked by TLC, excess DDQ was decomposed with a 5% L-ascorbic acid solution in order to avoid the undesirable cleavage of the benzyl group.
7) The reaction was carried out with DDQ (1.5 eq) in CH_2Cl_2-H_2O (19:1) at –10°C for 6h. Excess DDQ was decomposed with L-ascorbic acid as above.
8) Y. Iino and M. Nitta, *J. Syn. Org. Chem. Jpn.*, **48**, 681 (1990).
9) The formation of the iminophosphorane (Staudinger reaction of **2b**) was carried out by using triphenylphosphine (1.2 eq) in THF at room temperature overnight. DDQ (2.0 eq) and H_2O (1 eq) were then added and the solution was stirred at –5°C for 3h. Excess DDQ was decomposed with L-ascorbic acid as above in order to avoid the cleavage of MPM group.
10) H. Kunz, and W. Sager, *Helv. Chim. Acta*, **68**, 283 (1985).

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