4-Azido-3-chlorobenzyl Ether, New Protection for Hydroxy Functions

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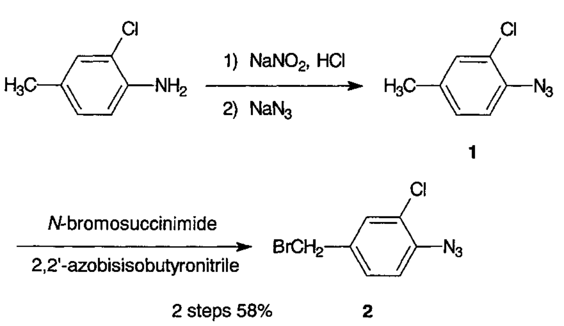
Received 25 February 1997

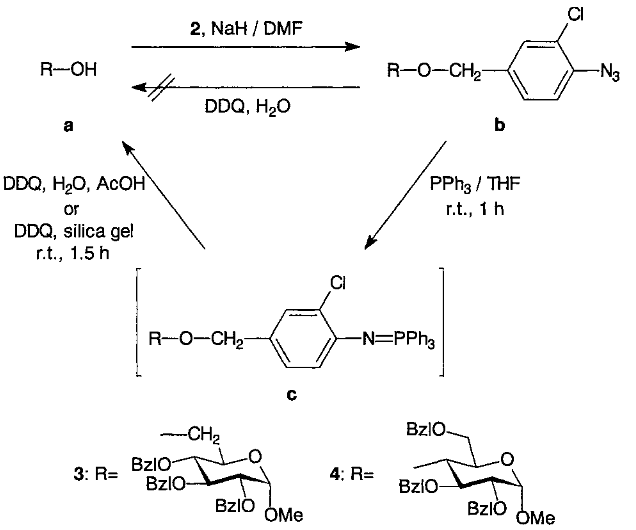
Abstract: The 4-azido-3-chlorobenzyl (Cl-Azb) group was readily introduced to hydroxy functions by the use of a crystalline reagent, 4-azido-3-chlorobenzyl bromide, which was prepared from commercially available 2-chloro-4-methylaniline in two steps. Cl-Azb ethers have improved acid stability as compared to the corresponding parent 4-azidobenzyl (Azb) ether. Cl-Azb ethers were stable to direct 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation, but were cleaved smoothly by DDQ oxidation after conversion to the corresponding iminophosphorane derivative.

Acid-stable temporary protecting groups are particularly of importance for synthesis of oligosaccharides and glycoconjugates since most glycosidation reactions are carried out under acidic conditions. The 4-methoxybenzyl (MPM) ether, which can be cleaved by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation, is one of the most versatile protecting groups for hydroxy functions.[1] MPM ethers are, however, sometimes cleaved under glycosidation conditions using strong Lewis acids as activators of glycosyl donors. We recently described the use of 4-azidobenzyl (Azb) groups for protection of hydroxy functions.[2] The Azb group is readily introduced and removed via a safety catch procedure, i.e., conversion of the azido function to the corresponding iminophosphorane followed by DDQ oxidation. The Azb ether is stable under various reaction conditions including glycosidation catalyzed by Lewis acids, e.g., reactions of glycosyl fluorides in the presence of BF_3 etherate and triethylamine. The Azb ether, however, was partially cleaved by treatment with an excess amount of BF_3 etherate in dichloromethane (ca. 25% cleavage with 2 eq. of BF_3 etherate at r.t. for 6 h), though it is much more stable to acids than the MPM ether. In order to further increase the acid stability of the Azb ether, we examined the introduction of an electron-withdrawing chloro-substituent to the Azb function.

Thus, a reagent for the formation of 4-azido-3-chlorobenzyl (Cl-Azb) ethers, 4-azido-3-chlorobenzyl bromide **2**, was prepared from commercially available 2-chloro-4-methylaniline as shown in the scheme.[3] The bromide **2** is crystalline and can be stored in a desiccator at room temperature without decomposition for months.

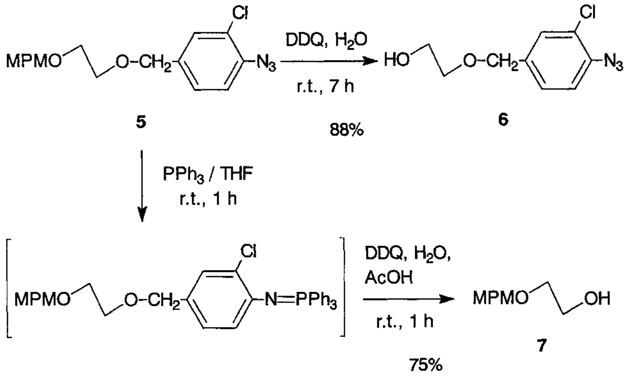


The Cl-Azb group was readily introduced to the hydroxy group of model compounds **3a** and **4a** by the use of Cl-Azb bromide **2** and NaH in *N,N*-dimethylformamide (DMF) (**3b**, 94%; **4b**, 90%). In fact, the Cl-Azb ether had improved stability to acids as expected: the Cl-Azb ether was stable under the above conditions (2 eq. of BF_3 etherate, at r.t., 6 h) where the corresponding Azb ether was cleaved partially. But in neat trifluoroacetic acid at room temperature the Cl-Azb ether was decomposed completely.



The Cl-Azb ether was inert to direct oxidation with DDQ, whereas an Azb ether was cleaved readily. Cleavage of the Cl-Azb ether was thus effected via conversion to the corresponding iminophosphorane derivative followed by DDQ oxidation. The iminophosphoranes **3c** and **4c** were formed smoothly by the reaction of **3b** and **4b** with triphenylphosphine in THF. The resulting iminophosphoranes were then treated with DDQ without isolation in the presence of H_2O and acetic acid to give alcohol **3a** (95%) and **4a** (92%).[4] Addition of acetic acid was essential to complete the DDQ oxidation within a reasonable period. Addition of silica gel, instead of acetic acid, was also effective (**3b** to **3a**, 90%).

Interestingly, the acceleration effect by acids was only observed in the particular case of iminophosphorane substituted benzyl ethers formed from the Cl-Azb ethers: addition of acetic acid or silica gel did not influence the reaction rate of the cleavage of MPM ethers. The rate of cleavage of an iminophosphorane benzyl ether was faster than that of an MPM ether: selective removal of the Cl-Azb group of **5** was thus effected in the presence of an MPM group by DDQ oxidation after conversion to the corresponding iminophosphorane to yield **7**.[5] By contrast, selective cleavage of the MPM ether in the presence of the Cl-Azb group was carried out at room temperature by direct DDQ oxidation (**5** to **6**, 88%) by virtue of the stability of the Cl-Azb ether to this reagent.[6]



In conclusion, the Cl-Azb group can be used as a new versatile protecting group for hydroxy functions. Since the Cl-Azb ether has improved stability under acidic conditions but is more readily cleaved than the MPM ether via a 2-step procedure, the Cl-Azb group is expected to be applicable to the solid-phase synthesis of oligosaccharides.

References and Notes

(1) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885.

(2) Fukase, K.; Hashida, M.; Kusumoto, S. *Tetrahedron Lett.* **1991**, 32, 3557.

(3) **4-azido-3-chlorotoluene 1:** To a solution of 2-chloro-4-methylaniline (14.2 g, 0.10 mol) in a mixture of conc. HCl (50 ml), DMF (100 ml), and water (400 ml) was added an aqueous solution (50 ml) of $NaNO_2$ (6.9g, 0.10 mol) dropwise during 20 min under ice-salt cooling. After stirring for 10 min, an aqueous solution (50 ml) of NaN_3 (6.5 g, 0.10 mol) was added dropwise to the mixture during 20 min. The mixture was further stirred for 1.5 h under ice-salt cooling, then extracted with three 150 ml portions of diethyl ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and then concentrated *in vacuo* to give **1** as a brown oil: yield 17.1 g (quant.). The product was used for subsequent reaction without further purification.

4-azido-3-chlorobenzyl bromide 2: A suspension of **1** (17.1 g, 0.10 mol), *N*-bromosuccinimide (19.6 g, 0.11 mol), and 2,2'-azobisisobutyronitrile (1.64 g, 0.01mol) in dry benzene (80 ml) was refluxed for 10 h. Water (100 ml) was added and the mixture was filtered. The organic layer was separated and the aqueous layer was washed with ether (50 ml). The combined organic phase was washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane) to afford **2** as orange crystals: yield 14.2 g (58%), m.p. 74-77, after recrystallization from acetone.

(4) A typical procedure for the cleavage of a Cl-Azb ether is as follows. To a solution of **3b** (126 mg, 0.20 mmol) in THF (1 ml) was added triphenylphosphine (63 mg, 0.24 mmol). After the solution was stirred at room temperature for 1 h, water (10 μL), glacial acetic acid (10 μL), and DDQ (68 mg, 0.30 mmol) were added and the mixture was further stirred at room temperature for 1.5 h. The mixture was diluted with ethyl acetate and washed with 5% aqueous L-ascorbic acid solution, saturated $NaHCO_3$ solution, and brine. After drying over Na_2SO_4, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel (dichloromethane-ethyl acetate 40:1) to give **3a** as a colorless oil: yield 88 mg (95%). Instead of water and acetic acid, addition of silica gel (100 mg, containing 6.5% of water) was also effective: yield 84mg (90%).

(5) The iminophosphorane was formed by the reaction of **5** with triphenylphosphine (1.2 eq.) in THF and then treated with DDQ (1.4 eq.) at room temperature for 1 h in the presence of H_2O and acetic acid.

(6) The reaction was carried out with DDQ (1.5 eq.) in THF-H_2O (20:1) at room temperature for 7 h.