4-Azidobutyryl Group for Temporary Protection of Hydroxyl Functions

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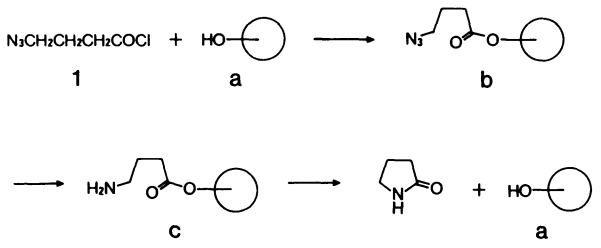
Synopsis. 4-Azidobutyryl esters formed from hydroxyl compounds and 4-azidobutyryl chloride were shown to be cleaved via reduction to 4-aminobutyrate followed by intramolecular O→N-acyl migrations to regenerate the free hydroxyl groups. High susceptibility of azide group to reduction enables the selective removal of this acyl group leaving many other functional groups unchanged.

In the synthetic studies on complex carbohydrates and other polyhydroxylated natural products, selective protection of particular hydroxyl groups is always required. For this purpose, various protecting groups have been proposed. However, during our recent synthetic studies on complex glycolipids, we realized that new types of protecting groups other than known ones are still required to facilitate the synthesis. We thus examined the use of 4-azidobutyryl group and found that this acyl group is versatile for temporary protection of hydroxyl functions.



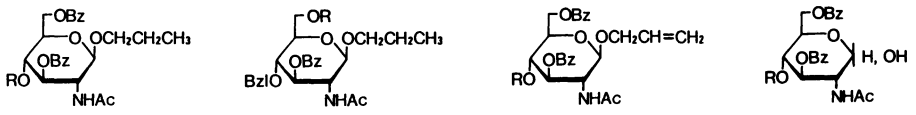
As the reagent for the introduction of 4-azidobutyryl group, the corresponding 4-azidobutyryl chloride (**1**) was prepared from γ-butyrolactone in four steps. Thus, opening of the γ-lactone[1] afforded ethyl 4-chlorobutyrate (**2**), which was then converted to ethyl 4-azidobutyrate (**3**).[2] Alkaline hydrolysis of **3** followed by reaction with thionyl chloride gave the desired chloride **1** as a colorless oil.[3]

Acylation of hydroxyl groups with this chloride (**1**) proceeded readily. The yields of the reaction with several substrates are summarized in Table 1.

We anticipated that the 4-aminobutyryl function which is formed on reduction of 4-azidobutyryl group would cause facile intramolecular O→N-acyl migration to regenerate the free hydroxyl group as shown in the scheme.[4] The only by-product formed thereby would be 2-pyrrolidinone which could be removed readily. Paulsen et al. described acylation of a trisaccharide with the chloride **1** and reduction of the resulting 4-azidobutyrate. However, they did not attempted the cleavage of the amino acyl group formed.[5]

One of the 4-azidobutyryl derivatives (**4b**) listed in Table 1 was then subjected to hydrogenolysis with palladium catalyst. TLC analysis revealed the presence of a small amount of the deacylated product (**4a**) in the reaction mixture together with the 4-aminobutyrate which gave a ninhydrin-positive spot. This indicated that the spontaneous deacylation certainly occurred even at room temperature, though the reaction rate was slow. The reaction was accelerated in boiling ethanol and completed within 1.5 h. The yield of deacylation step was 91% from **4b** as determined by HPLC analysis.

Owing to the high susceptibility of azide to catalytic hydrogenolysis, 4-azidobutyryl group can be selectively reduced and thus removed without affecting *O*-benzyl function in the same molecule as demonstrated in the deprotection of compound **5b**. Since benzyl ether is frequently employed as a persistent protecting group in many synthetic works, use of 4-azidobutyryl group would provide much flexibil-



a R : H b R : $COCH_2CH_2CH_2N_3$ Bz : C_6H_5CO Bzl : $C_6H_5CH_2$

Table 1. Introduction and Removal of 4-Azidobutyryl Group

Compound	Introduction Yield/% (a→b)	Removal		
		Reduction (b→c)	Cleavage (c→a)	Yield/% (b→a)
4	96	H_2/Pd in EtOH[a]	Reflux in EtOH 1.5 h	91[b]
5	95	H_2/Pd in EtOH[a]	Reflux in EtOH 2.5 h	93
6	85	H_2S in Pyr-H_2O 2d[a]	Reflux in EtOH 2.0 h	95[b]
		PPh_3 in dioxane, reflux 2.5 h then 80°C 1.5 h		78[b]

a) At room temperature. b) Determined by HPLC (see experimental section).

ity to the synthetic plan for complex target compounds.

Selective cleavage of 4-azidobutyryl group was next attempted in the presence of olefinic double bond. Though the hydrogenolysis of the azide group was faster than saturation of the allyl group in compound **6b**, fully selective reduction of the former was not possible with palladium-black.[6] Several other catalyst such as Raney nickel with absorbed hydrogen or palladium on calcium sulfate were examined but shown to give similar results. Selective reduction was effected chemically as follows. By use of triphenylphosphine, reduction to aminobutyryl group and its cleavage proceeded in boiling dioxane in rather short time in one step. In THF or ethanol, the reaction was slow even at reflux temperature and the yield of the deacylated product decreased due to the formation of an unidentified by-product. Use of hydrogen sulfide gave more satisfactory results. Thus, reduction of **6b** in a mixture of pyridine–water with hydrogen sulfide at room temperature[7] followed by cleavage by heating in ethanol as above gave **6a** in a high yield (Table 1). At higher temperature than 60 °C in the same solvent mixture,[7] reduction and cleavage took place successively but at such temperature the solution colored deeply and the yield of the product was very low.

In addition, the azidobutyryl group proved to survive under reaction conditions employed for cleavage of some other temporary protecting groups. For example, compound **6b** did not changed at all by heating in acetic acid–water (9:1) for 1 h. Thus, isopropylidene and benzylidene groups can be removed without affecting the azidobutyryl group. Furthermore, the allyl group in **6b** was removed through isomerization with an iridium complex,[8] followed by cleavage with iodine[9] to give **7b**, the azidobutyryl group being thereby unaffected.

In conclusion, 4-azidobutyryl group can be used as a new versatile acyl-type protecting group for hydroxyl functions. It can be easily introduced and has sufficient stability as well as a prominent feature to be cleaved preferentially to most of the other known protecting groups.

Experimental

All melting points and boiling points are not corrected. HPLC was performed with Shimadzu LC-5A liquid chromatograph apparatus equipped with a Cosmosil $5C_{18}$ column (4×125 mm); solvent: CH_3CN–H_2O (45:55); detection: absorbance at 254 nm. For quantitative determination of a deprotection product, a known amount of benzophenone was added to the reaction mixture as an internal standard, the peak area determined by use of an integrator (Shimadzu Chromatopac C-R1A) and amount of the product calculated.

Ethyl 4-Azidobutyrate (3). Sodium azide (34.4 g, 0.531 mol) and 15-crown-5 (5.8 g, 0.027 mol) were added to a solution of ethyl 4-chlorobutyrate (**2**)[1] (40 g, 0.266 mol) in CH_3CN (160 ml). The mixture was heated under reflux for 12 h. The completion of the reaction was confirmed with GLC (polyethylene glycol HT, 120 °C), After usual work-up, the product was distilled in vacuo; yield 39.6 g (95%), bp 96.5—98.5 °C/16 mmHg (1 mmHg=133.322 Pa). ^{1}H-NMR and IR spectra of this product were identical to the data given by Keschmann and Zbiral.[2]

4-Azidobutyryl Chloride (1). Azido ester **3** (13.0 g, 82.7 mmol) was heated in a solution of KOH (5.6 g, 100 mmol) in EtOH (270 ml) under reflux for 2 h. After evaporation of the solvent and acidification (HCl), the product was extracted with ether, and worked up as usual. Thionyl chloride (9.0 ml, 123 mmol) was added to a solution of the oily product in benzene. The mixture was stirred at room temperature for 30 min and then heated under reflux for 1.5 h. Evaporation in vacuo followed by vacuum distillation afforded the chloride **1**; yield 9.66 g (79%), bp 90—91 °C/16 mmHg. EI-MS: m/z 147 (M^+). ^{1}H-NMR ($CDCl_3$) δ=1.94 (2H, quintet), 3.02 (2H, t, J=7.1 Hz), and 3.38 (2H, t, J=6.5 Hz).

Propyl 2-Acetamido-3,6-di-*O*-benzoyl-2-deoxy-β-D-glucopyranoside (4a). Allyl 2-acetamido-3,6-di-*O*-benzoyl-2-deoxy-β-D-glucopyranoside (**6a**)[10] (300 g, 6.39 mmol) was hydrogenated with Pd-black in EtOH (150 ml) at room temperature and recrystallized from EtOAc; yield 2.35 g (78%), mp 180—182 °C. Found: C, 63.42; H, 6.18; N, 2.95%. Calcd for $C_{25}H_{29}NO_8$: C, 63.88; H, 6.20; N, 2.95%.

Propyl 2-Acetamido-4-*O*-(4-azidobutyryl)-3,6-di-*O*-benzoyl-2-deoxy-β-D-glucopyranoside (4b). To an ice-cooled solution of **4a** (500 mg, 1.06 mmol) and pyridine (0.17 ml, 2.1 mmol) in CH_2Cl_2 (25 ml) was added the chloride **1** (235 mg, 1.59 mmol). The mixture was stirred at room temperature for 4.5 h. The mixture was worked up as usual and the product recrystallized from EtOAc–hexane; yield 590 mg (95%); mp 142—144 °C, IR (nujol) 2100 cm^{-1} (N_3); $[\alpha]_D^{15}$ +0.40° (c 1.00, $CHCl_3$). Found: C, 59.66; H, 5.83; N, 9.52%. Calcd for $C_{29}H_{34}N_4O_9$: C, 59.79; H, 5.88; N, 9.62%.

Propyl 2-Acetamido-3-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (5a). Allyl 2-acetamido-3-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside[10] (494 mg, 1.08 mmol) was hydrogenated as described for **4a**. The completion of the reaction was checked by HPLC. After usual work-up the product was recrystallized from EtOAc; yield 437 mg (88%); mp 171—172 °C; $[\alpha]_D^{24}$ −46.9° (c 1.00, $CHCl_3$). Found: C, 65.53; H, 6.85; N, 3.08%. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06%.

Propyl 2-Acetamido-6-*O*-(4-azidobutyryl)-3-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (5b). Compound **5a** was acylated with 4-azidobutyryl chloride (**1**) and pyridine in CH_2Cl_2 as described above for the preparation of **4b**. The product was recrystallized from EtOAc–hexane; yield 1.19 g (96%); mp 110 °C; IR (nujol) 2100 cm^{-1} (N_3); $[\alpha]_D^{24}$ −15.3° (c 1.00, $CHCl_3$). Found: C, 61.26; H, 6.35; N, 9.80%. Calcd for $C_{29}H_{36}N_4O_8$: C, 61.26; H, 6.38; N, 9.85%.

Allyl 2-Acetamido-4-*O*-(4-azidobutyryl)-3,6-di-*O*-benzoyl-2-deoxy-β-D-glucopyranoside (6b). Compound **6a**[10] was acylated with the chloride **1** as described above. The product was recrystallized from EtOAc–hexane; yield 739 mg (85%); mp 127—128 °C; $[\alpha]_D^{24}$ −1.20° (c 1.00, $CHCl_3$). Found: C, 60.05; H, 5.52; N, 9.62%. Calcd for $C_{29}H_{39}N_4O_9$: C, 59.99; H, 5.56; N, 9.65%.

Removal of 4-Azidobutyryl Group of 4b and 5b via Catalytic Hydrogenolysis. a) Compound **4b** (290 mg, 0.500 mmol) was dissolved in EtOH (10 ml) and hydrogenolyzed in the presence of Pd-black (50 mg) at room temperature under atmospheric pressure of H_2. After 3 h disappearance of the starting material was confirmed by TLC. The catalyst was filtered off, and the filtrate was heated under reflux for 1.5 h. Yield of **4a** was 91% as determined by HPLC (see above). Isolation yield after recrystallization from EtOAc–hexane was 195 mg (83%); mp 178—180 °C. The product was identified with an authentic specimen of **4a** by means of TLC and ^{1}H-NMR.

b) Compound **5b** (569 mg, 1.00 mmol) was hydrogenolyzed and heated in ethanol as described above for **4b**.

Recrystallization from EtOAc gave a product which was identical with an authentic specimen of **5a**; yield 428 mg (93%); mp 169—171 °C.

Removal of 4-Azidobutyryl Group of 6b. a) With Triphenylphosphine: Triphenylphosphine (24.3 mg, 0.12 mmol) was added to a solution of **6b** (58.0 mg, 0.10 mmol) in dioxane (10 ml) heated under reflux. Heating was continued for 2.5 h.[11] The mixture was then kept at 80 °C for additional 1.5 h. The yield of **6a** was 78% (HPLC, see above). The product was isolated by silica-gel column chromatography (silica gel, 10 g; $CHCl_3$–MeOH 15:1) and recrystallized from EtOAc–hexane. It was identified with an authentic sample of **6a** by means of TLC, HPLC and ^{1}H-NMR.

b) With Hydrogen Sulfide: Hydrogen sulfide was bubbled through a solution of **6b** (21.0 mg, 36.2 mmol) in a mixture of pyridine–H_2O (2:1) (4 ml) at room temperature for 2 h. The mixture was then kept in a stoppered bottle at room temperature for 2 d. After the solvent had been removed in vacuo, EtOH was added to the residue and insoluble materials were filtered off. The filtrate was heated under reflux for 2 h. The yield of **6a** was 95% (HPLC, see above). The isolated product was identified with **6a** as above.

2-Acetamido-4-*O*-(4-azidobutyryl)-3,6-di-*O*-benzoyl-2-deoxy-D-glucose (7b). Compound **6b** (300 mg, 0.517 mmol) and $Ir(COD)[PCH_3(C_6H_5)_2]_2PF_6$[8] (15 mg) was dissolved in degassed THF (5 ml). The catalyst was activated as described in the literature.[8] The solution was then stirred at 50 °C for 1.5 h. After cooling, H_2O and I_2 (260 mg, 1.00 mmol) were added and the mixture was stirred at room temperature for 30 min. A 5% aqueous solution of $NaHSO_3$ was added to the mixture until the color of I_2 disappeared. The mixture was extracted with $CHCl_3$, the organic layer washed successively with aqueous $NaHSO_3$ solution and water. The product was purified with a silica-gel column (10 g, $CHCl_3$–acetone 5:1) and recrystallized from EtOAc–hexane; yield 230 mg (86%); mp 148—150 °C; IR (nujol) 2100 cm^{-1} (N_3); $[\alpha]_D^{24}$ +45.9° (*c* 1.00, $CHCl_3$). Found: C, 57.87; H, 5.27; N, 10.17%. Calcd for $C_{26}H_{28}N_4O_9$: C, 57.77; H, 5.22; N, 10.37%.

References

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2) E. Keschmann and E. Zbiral, *Justus Liebigs, Ann. Chem.*, **1973**, 1455. These authors described a preparation of ethyl 4-azidobutyrate (**3**) via different route.

3) This chloride could be kept in a refrigerator for several months without detectable decomposition.

4) Several protecting groups were proposed which can be removed by catalytic hydrogenation of aromatic nitro function followed by similar intramolecular cyclization reaction. For example; R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **74**, 3069 (1952); I. D. Entwistle, *Tetrahedron Lett.*, **1979**, 555.

5) H. Paulsen and H. Bottcher, *Chem. Ber.*, **112**, 3864 (1979).

6) Heating the reduction product in ethanol always gave a mixture of desired **6a** and the corresponding propyl glycoside.

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9) M. A. Nashed and L. Anderson, *J. Chem. Soc., Chem. Commun.*, **1982**, 1274.

10) M. Imoto, H. Yoshimura, H. Yamamoto, T. Shimamoto, S. Kusumoto, and T. Shiba, *Tetrahedron Lett.*, **25**, 2667 (1984).

11) Though disappearance of the starting azidobutyrate was confirmed by TLC after this period, the mixture was further heated to assure the cleavage of the aminobutyrate.