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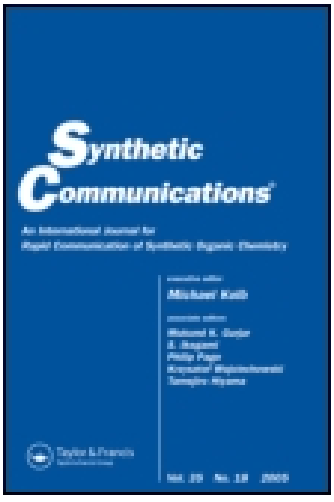

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Optimized Procedure for the Synthesis of 6-Azido-6-deoxy-galactopyranosides From 6-O-Tosyl-galactopyranosides

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Optimized Procedure for the Synthesis of 6-Azido-6-deoxy-galactopyranosides From 6-*O*-Tosyl-galactopyranosides

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Abstract: The reaction conditions for preparation of 6-azido-6-deoxy-glycoside remain elusive, although there are many successful cases in hand. After careful investigation of the reaction conditions, a practical procedure for the preparation of 6-azido-6-deoxy-galactopyranoside derivatives was demonstrated.

Keywords: Aqueous DMF, 6-azido-6-deoxy-galactoside, nucleophilic substitution

INTRODUCTION

Synthetic approaches to azidodeoxysugars have been widely described in the literature because since these compounds are precursors of aminoglycoside antibiotics. Several efficient methods for the introduction of an azido group at sugar *C*-6 have been developed: 1) The displacement reactions of *C*-6 halides[1] with sodium azide; 2) the displacement reactions of 6-*O*-tosylates,[1,2] mesylates,[3] and triflates,[4] of sugars with sodium azide; 3) the direct selective reactions of primary hydroxyl groups with $PPh_3/CBr_4/NaN_3$,[5] or a Mitsunobu procedure;[6] 4) The displacement reactions of sugar isoureas with NaN_3.[7]

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Among all these methods, the displacement of sulfonates with azido ions are by far the most common procedures, because the 6-*O*-sulfonates can be obtained readily by treatment of sugar with a sulfonyl chloride in the presence of pyridine or triethylamine.

It is well known that the rates of the bimolecular replacements involving anionic nucleophiles are enchanced in polar aprotic solvent. *N*,*N*-dimethyl formamide (DMF) is frequently used in preparation of carbohydrate azide because it has a lower boiling point than dimethyl sulfoxide (DMSO) or hexamethylphosphortriamide (HMPT). Most researchers employ the anhydrous solvents, whereas others add water.[2c,8]

The substitution of 6-*O*-sulfonate group by azide is widely used but not universally applicable, being subject to the following restrictions. The incoming nucleophile is hindered when the C_4-*O*-substituent is in an axial position[9] (i.e, 6-*O*-tosyl-galactosides), thus the rates and yields of the displacement of 6-*O*-tosyl-galactosides with sodium azide are always lower than those of 6-*O*-tosyl-glucosides or -mannosides; the nucleophilic substitution may also be frustrated by acyl migration or formation of 3,6-[1,10] or 4,6-anhydro derivatives[2b] under anhydrous conditions, where sodium azide acts as a weak Lewis base; the discrepant results from different groups may be due, at least in part, to the subtle factors controlled by the investigators.

Anderson reported that the addition of an amount of water to DMF increases the solubility of sodium azide enough to more than offset the intrinsic rate-depressing effect of the water.[8] In the present article, to overcome the unfavorable factors and seek for a reproducible procedure, the displacement reactions of several 6-*O*-tosyl-galactosides with sodium azide were studied under various conditions in detail. We found that the yields of the displacement reactions of 6-*O*-tosyl-galactosides with sodium azide in aqueous DMF are considerable better than those in anhydrous solvent.

RESULTS AND DISCUSSION

Because 6-*O*-tosylate and 6-azido-6-deoxy galactoside derivatives are both subject to elimination, decomposition, and even carbonization at high temperature, we found that a yellow to dark brown solution was obtained after 24 h if the reaction temperature is between 90 and 140 °C. All the reactions were carried out at 80 °C. We firstly choose 6-*O*-tosyl-1,2,3,4-di-*O*-isopropylidenegalactopyranoside[8,11] (Figure 1) as the substrate to optimize the reaction in various solvents. 1,2,3,4-di-O-isopropylidence-d-D In Table 1 it may be seen that the best yield (88%) of the nucleophilic displacement of 6-*O*-tosyl galactoside was obtained at 80 °C in DMF containing 10% water. 6-Azido-6-deoxy-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranoside can also be prepared in quantitive yield in DMSO at 160 °C.[12] It should be pointed out that the high-boiling-point solvent cannot be used universally; for example, the synthesis of methyl 6-azido-6-deoxy-α-D-galactopyranoside

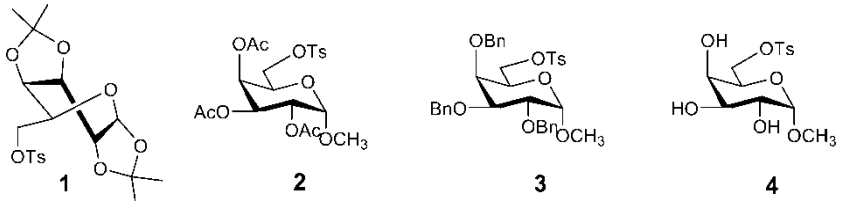

Figure 1.

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was frustrated by working up and formation of anhydro sugar. The additive, tetrabutylammonium iodide (TBAI), does not seem to improve the yield of this reaction. The yield was decreased in DMF containing more or less water than 10%. In DMF containing some other protic solvent, such as ethanol, the yield was lower than that in the solvent of DMF containing water. The reactions did not work at all in protic solvent, such as ethanol or aqueous ethanol under reflux.

To further extend the scope of the substrates, other three 6-*O*-tosyl-galactosides (**2**,[10a] **3**,[3b] and **4**,[10a] Figure 1) derivatives were prepared and tried under selected conditions (Table 2). The yields of the displacement reactions in DMF containing 10% water improved more obviously than those in anhydrous solvent, especially substrate **4**.

The typical S_N2 reaction may be transformed into a pseudo-first-order process in aqueous DMF. The reaction rate increased after the solubility of nucleophile increased.[8] The solubility of sodium azide increased in DMF containing more than 10% water, but the solubility of the substrates decreased. At the same time, the hydrolysis rate heightened dramatically. As a compromise,

Table 1.

Entry	Solvent (additive)	NaN_3 (eqiv)	Temp (°C)	Time (h)	Isolated yield (%)
1	Dry DMF	1.0	80	24.0	48
2	Dry DMF	2.0	80	24.0	56
3	Dry DMF	3.0	80	24.0	58
4	DMF (5% H_2O)	3.0	80	24.0	76
5	DMF (10% H_2O)	3.0	80	24.0	88
6	DMF (15% H_2O)	3.0	80	24.0	71
7	DMF (20% H_2O)	3.0	80	24.0	65
8	DMF (10% ethanol)	3.0	80	24.0	65
9	95% ethanol	3.0	Reflux	24.0	0
10	Ethanol (10% H_2O)	3.0	Reflux	24.0	0
11	DMF/(TBAI)	3.0	80	24.0	69
12	DMF/(10% H_2O + 5% mol TBAI)	3.0	80	24.0	85

Table 2.

Entry	Substrate	Solvent (additive)	Temp (°C)	Time (h)	Isolated yield (%)
1	**2**	Dry DMF	80	30	65
2	**2**	DMF (10% H_2O)	80	30	88
3	**3**	Dry DMF	80	30	57
4	**3**	DMF (10% H_2O)	80	30	85
5	**4**	Dry DMF	80	30	35
6	**4**	DMF (10% H_2O)	80	30	78
7	**4**	DMF (TBAI)	80	30	46
8	**4**	DMF (10% H_2O + 5% mol TBAI)	80	30	78

the reaction yield and rate is better in DMF containing 10% water than in any other conditions. The unfavorable reactions (acyl migration and formation of anhydro sugar) catalyzed by the weak Lewis base, NaN_3, under anhydrous conditions, were also avoided in the aqueous solution.

All the reactions (listed in Tables 1 and 2) were carried out in parallel in a 100-mg scale. Grams-scale of 6-deoxy-6-deoxy galactosides can be prepared under the optimized condition and give consistent and satisfied isolated yields.

In conclusion, we have found a practical procedure for the preparation of 6-azido-6-deoxy-galactopyranoside derivatives under simple conditions. The optimized procedure is reproducible, does not need the anhydrous DMF, and gives the desired products in good yields.

EXPERIMENTAL

General Methods

^1H and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer with Me_4Si as the internal standard and $CDCl_3$ or Me_2SO-d_6 as solvent. Optical rotations were measured at 25 °C with an Optical Activity AA-10R polarimeter. The progress of reactions was monitored by TLC on silica-gel GF_{254} plates. Detection was performed by examination under UV light and by charring with 5% phosphomolybdic acid hydrate in EtOH or 15% concd. H_2SO_4 in EtOH. Preparative TLC was performed on silica-gel GF_{254} plates and column chromatography on silica-gel H. Only the desired product was isolated, and the by-products were omitted.

Preparation of 6-*O*-Tosyl-galactopyranoside: 1, 2, 3, and 4

6-*O*-Tosyl-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranoside (**1**) was prepared according to Ref. 8. Methyl 6-*O*-tosyl-α-D-galactopyranoside (**4**)

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and methyl 6-*O*-tosyl-2,3,4-tri-*O*-acetyl-α-D-galactopyranoside (**2**) were prepared following the known procedure.[10a] Methyl 6-*O*-tosyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (**3**) was prepared from methyl α-D-galactopyranoside via four steps.[3b] Data for compound **3:** $[\alpha]_D^{25}$ +51.4° (*c* 0.70 $CHCl_3$). ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 2.39$ (s, 3H, $PhC\underline{H}_3$), 3.43 (s, 3H, H_3CO-), 3.44–4.90 (m, 12H, H-2~6, 3 × $PhC\underline{H}_2$), 4.92 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 7.13–7.33 (m, 15H, 3 × Ph), 7.38 (d, 2H, *J* 8.1 Hz), 7.84 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.67 (CH_3Ph), 55.42 (CH_3O), 69.17, 73.13, 73.38, 75.23, 76.04 (sugar C-2~6), 80.16, 80.17, 80.17 (3 × $\underline{C}H_2Ph$), 98.34 (C-1), 127.34, 127.51, 127.92, 128.18, 128.32, 128.47, 128.50, 128.62, 128.80, 129.57, 129.72, 133.42, 137.35, 137.57, 138.11, 144.84 (Ph); ESI-TOF MS m/z: 636.24 ($M + NH_4$). Calcd. for $C_{35}H_{38}O_8S$: 618.23.

General Procedure for 6-Azido-6-deoxy-1,2,3,4-di-*O*-Isopropylidene-α-D-galacto-pyranoside

A suspension of 6-*O*-tosyl-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranoside (**1**, 100 mg, 0.32 mmol) and sodium azide in various solvents (2 mL, listed in Table 1) was heated for 24 h at 80 °C. The cooled solution was poured into ice water (10 mL) and extracted with chloroform (10 mL × 3). The combined extracts was washed with water, dried ($MgSO_4$), and evaporated to leave a syrup. The pure product was obtained as a colorless oil after separation on a preparative TLC (petroleum ether–ethyl acetate 4 : 1). The spectral data was the same as reported.[8]

General Procedure for Methyl 6-Azido-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-galacto-pyranoside

A suspension of methyl 6-*O*-tosyl-2,3,4-tri-*O*-acetyl-α-D-galactopyranoside (100 mg, 0.21 mmol) and sodium azide (42 mg, 0.64 mmol) in the solvent (2 mL, listed in Table 2, entries 1 and 2) was heated for 30 h at 80 °C. The cooled solution was poured into ice water (10 mL) and extracted with ethyl ether (10 mL × 3). The combined extracts was washed with brine, dried ($MgSO_4$), and evaporated to give the crude product, which was purified on a preparative TLC (petroleum ether–ethyl acetate, 2 : 1) to give a white solid. The spectral data was the same as reported.[10a]

General Procedure for Methyl 6-Azido-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-galactopyrano-side

A suspension of methyl 6-*O*-tosyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (100 mg, 0.16 mmol) and sodium azide (32 mg, 0.48 mmol) in the solvent (2 mL, listed in Table 2, entries 3 and 4) was heated for 30 h at 80 °C. The

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cooled solution was poured into ice water (10 mL) and extracted with ethyl ether (10 mL × 3). The extract was washed with brine, dried ($MgSO_4$), and evaporated to give the crude product, which was purified on a preparative TLC (petroleum ether–ethyl acetate, 4 : 1) to give a colorless syrup. The spectral data was the same as reported.[3b]

General Procedure for Methyl 6-Azido-6-deoxy-α-D-galactopyranoside

A suspension of methyl-6-tosyl-6-deoxy-α-D-galactopyranoside (100 mg, 0.29 mmol) and sodium azide (57 mg, 0.87 mmol) in the solvent (2.0 mL, listed in Table 2, entries 5–8; in entries 7 and 8, 6 mg of TBAI was added) was heated for 30 h at 80 °C. The reaction mixture was evaporated in vacuum. The residue was purified on PTLC ($CHCl_3$–CH_3OH, 8 : 1) and the desired product was obtained as a colorless syrup. The spectral data was the same as reported.[10a]

Scaled-Up Reactions

A suspension of **1** (**2, 3,** or **4**) (5–10 mmol) and sodium azide (3 eq) in DMF–H_2O (9 : 1, enough to dissolve the tosylate) was heated for 24 h (30 h) at 80 °C. The reaction solutions were worked up conventionally, and the crude products were purified on flash column chromatography to give the desired products in 75–90% yields.

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REFERENCES

1. Maunier, V.; Boullanger, P.; Lafont, D.; Chevalier, Y. Synthesis and surface-active properties of amphiphilic 6-aminocarbonyl derivatives of D-glucose. *Carbohydr. Res.* **1997**, *299*, 49–57.
2. (a) Kieburg, C.; Sadalapure, K.; Lindhorst, T. K. Glucose-based AB_2-building blocks for the construction of branched glycopeptidomimetics. *Eur. J. Org. Chem.* **2000**, 2035–2040; (b) Hansen, H. C.; Magnusson, G. Synthesis of selected aminodeoxy analogues of galabiose and globotriose. *Carbohydr. Res.* **1999**, *322*, 166–180; (c) Szarek, W. A.; Jones, J. K. N. Carbohydrates containing nitrogen in a five-membered ring and an attempted synthesis of a carbohydrate with nitrogen in a seven-membered ring. *Can. J. Chem.* **1965**, *43*, 2345–2356.

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3. (a) Bullock, C.; Hough, L.; Richardson, A. C. A novel route to 1,4-anhydro derivatives of β-D-galactopyranose. *Carbohydr. Res.* **1990**, *197*, 131–138; (b) Yoshimura, J.; Asano, K.; Umemura, K.; Horito, S.; Hashimoto, H. Synthesis of methyl 2,3-*O*-D-glycopyranosylidene-α-D-mannopyranosides having various substituents. *Carbohydr. Res.* **1983**, *121*, 187–204.
4. Hui, Y.; Chang, C. T. Convenient divergent synthesis of a library of trehalosamine analogues. *Org. Lett.* **2002**, *4* (13), 2245–2248.
5. Blanco, J. L. J.; Fernandez, J. M. G.; Gadelle, A.; Defaye, J. A mild one-step selective conversion of primary hydroxyl groups into azides in mono- and oligosaccharides. *Carbohydr. Res.* **1997**, *303*, 367–372.
6. (a) Moris-Varas, F.; Qian, X. H.; Wong, C. H. Enzymatic/chemical synthesis and biological evaluation of seven-membered iminocyclitols. *J. Am. Chem. Soc.* **1996**, *118*, 7647–7652; (b) Lafont, D.; Boullanger, P. Preparation of primary and secondary azidosugars from diols using the dioxaphosphorane methodology. *J. Carbohydr. Chem.* **1999**, *18*, 675–688; (c) Kobayashi, Y.; Shiozaki, M. Syntheses of trehazolin derivatives and evaluation as glycosides inhibitors. *J. Org. Chem.* **1995**, *60*, 2570–2580.
7. Christian, S.; Ralf, M.; Helmut, R. Non-anomeric sugar isoureas. *J. Carbohydr. Chem.* **2002**, *21*, 293–304.
8. Wu, M.; Anderson, L.; Slife, C. W.; Jenson, L. J. Effect of solvent, temperature, and nature of sulfonate group on the azide displacement reaction of sugar sulfonates. *J. Org. Chem.* **1974**, *39 (20)*, 3014–3019.
9. Sugihara, J. M.; Teerlink, W. J.; MacLeod, R.; Dorrence, S. M.; Springer, C. Direct syntheses of some cyano and nitro derivatives of carbohydrates by nucleophilic displacement. *J. Org. Chem.* **1963**, *28*, 2079–2082.
10. (a) Carmen, L.; Romero, Z.; Oscar, V. Synthesis of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acide, a key precursor of a steroregular polyamide. *J. Carbohydr. Chem.* **2001**, *20*, 689–701; (b) Patel, A.; Lindhorst, T. K. Synthesis of "mixed type" oligosaccharide mimetics based on a carbohydrate scaffold. *Eur. J. Org. Chem.* **2002**, 79–86.
11. 1,2,3, 4-di-*O*-isopropylidene-α-D-galactopyranoside adopted a skew-boat conformation. See Roslund, M. U.; Klika, K. D.; Lehtilä, R. L.; Tähtinen, P.; Sillanpää, R.; Leino, R. Conformation of the galactose ring adopted in solution and in crystalline form as determined by experimental and DFT ^{1}H NMR and single-crystal X-ray analysis. *J. Org. Chem.* **2004**, *69*, 18–25.
12. Joosten, J. A. F.; Evers, B.; van Summeren, R. P.; Kamerling, J. P.; Vliegenthart, J. F. G. Synthesis of β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → 2)-α-D-Man*p*-(1 → *O*)-$(CH_2)_7CH_3$ mimics to explore the substrate specificity of sialyltransferases and *trans*-sialidases. *Eur. J. Org. Chem.* **2003** (18), 3569–3586.

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