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One-Pot Azidochlorination of Glycals

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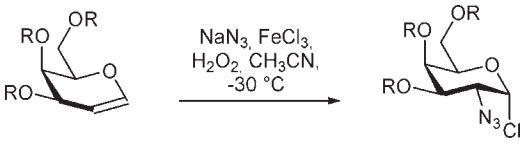
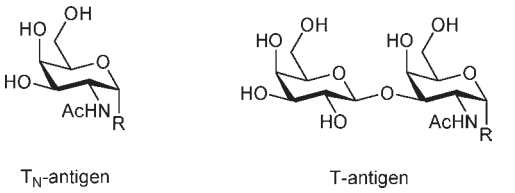
ABSTRACT



A simple one-pot azidochlorination for the preparation of nitrogen-containing Koenigs−Knorr glycosyl donors proceeds upon reaction of protected glycals with sodium azide, ferric chloride, and hydrogen peroxide. Different mono- and disaccharide galactals and glucals are converted in a highly α-selective manner to the 2-azido glycosyl chlorides. Starting from disaccharide galactals, building blocks for the synthesis of the T-antigen are obtained in a straightforward manner. The simplicity of the reaction conditions allows for an efficient and scalable α-selective synthesis of 2-azido substituted glycosyl chlorides.

2-*N*-Acetamido-2-deoxygalactosides, among other 2-acetamido-2-deoxysugars, are key components of naturally occurring glycoconjugates and oligosaccharides.[1,2] They are present in glycoproteins on the cell surface playing major roles in biological recognition processes, such as cell adhesion, cell differentiation, and immuno-recognition.[3] The aminosugars serve as receptor ligands for enzymes,[4] antibodies,[5] and lectins;[6] are the key moiety of tumor-associated antigens (T_N-antigen and T-antigen, Figure 1);[7] and are present in antifreeze glycoproteins.[8]

Hence, an efficient preparation of 2-acetamido galactoside precursors and, in a more general way, for 2-acetamido functionalized glycosyl donors is of high importance for oligosaccharide and glycopeptide syntheses. There are various methods for the preparation, starting from protected glycals as reagents. The azidonitration,[9] the nitration of glycals,[10,11] and the azidophenylselenation reaction[12,13] have to be mentioned in this context. A one-pot azidochlorination resulting directly in 2-azido substituted



T_N-antigen T-antigen

Figure 1. Structures of the T_N- and the T-antigen.

(1) Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495–4537.
(2) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720.
(3) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579–602.
(4) Sperandio, M.; Gleissner, C. A.; Ley, K. *Immunol. Rev.* **2009**, *230*, 97–113.
(5) Yuriev, E.; Agostino, M.; Farrugia, W.; Christiansen, D.; Sandrin, M. S.; Ramsland, P. A. *Expert. Opin. Biol. Ther.* **2009**, *9*, 1017–1029.
(6) Gabius, H.-J.; Siebert, H.-C.; André, S.; Jiménez-Barbero, J.; Rüdiger, H. *ChemBioChem* **2004**, *5*, 740–764.
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(8) Harding, M. M.; Anderberg, P. I.; Haymet, A. D. *Eur. J. Biochem.* **2003**, *270*, 1381–1392.
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(10) Lemieux, R. U.; Nagabhushan, T. L.; Werner, S. W. *Can. J. Chem.* **1968**, *46*, 405–411.
(11) Das, J.; Schmidt, R. R. *Eur . J. Org. Chem.* **1998**, 1609–1613.
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(13) Santoyo-Gonzalez, F.; Calvo-Flores, F. G.; Garcia-Mendoza, P.; Hernandez-Mateo, F.; Isac-Garcia, J.; Robles-Diaz, R. *J. Org. Chem.* **1993**, *58*, 6122–6125.

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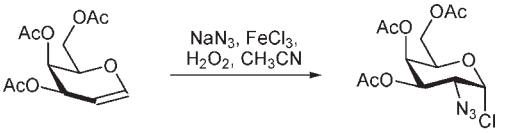
Koenigs–Knorr donors has been claimed in a patent.[14] According to this procedure, a mixture of ferric chloride, ferrous sulfate, ammonium peroxodisulfate, hydrogen peroxide, and sodium azide is used for the conversion of galactals to 2-azido galactosyl chlorides. All these procedures suffer from specific problems such as low yields, the requirement of a large reagent excess, and hazardous reaction conditions.

We have developed a one-pot azidochlorination procedure that uses few, nontoxic, and simple reagents in practically stoichiometric amounts. The synthesis uses protected glycals like, e.g., 3,4,6-tri-*O*-acetyl-D-galactal **1a** as the starting material and ferric chloride hexahydrate (0.8 equiv), sodium azide (1.1 equiv), and hydrogen peroxide (1.1 equiv) (Table 1) as reagents. The reaction is easily reproduced on different reaction scales and provides high yields (up to 78%).

Table 1. Azidochlorination of 3,4,6-Tri-*O*-acetyl-D-galactal **1a**



1a **2a**

molar ratio $FeCl_3 \cdot H_2O/NaN_3/H_2O_2$	conditions	yield[a]
3.0/2.0/2.0	CH_3CN, −30 °C, 3 h	78%
1.1/1.1/1.5	CH_3CN, −30 °C, 3 h	71%
0.8/1.2/1.5	CH_3CN, −30 °C, 7 h	74%
0.8/1.1/1.1	CH_3CN, −20 °C, 7 h	70%
0.8/1.2/1.5	CH_3CN, 0 °C, 6 h	62%
0.8/1.2/1.5	CH_3CN, rt, 16 h	–

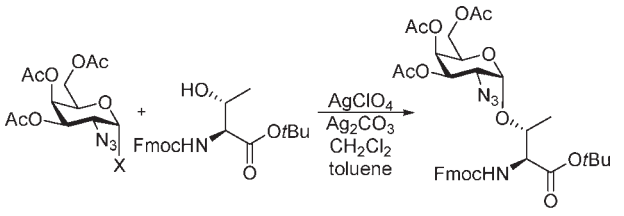
[a] Unpurified product. Yield determined by ^1H NMR after complete conversion of starting material.

Variation of the reaction conditions revealed that larger amounts of the reagents do not distinctly influence the reaction time and the yield. Strikingly, no reaction occurred at room temperature, while the reaction proceeded smoothly at 0 °C with a slightly reduced yield compared to the reaction at −30 °C. Acetonitrile is the solvent of choice, as all reagents are dissolved at the chosen concentration. Stirring and subsequent workup of the homogeneous reaction is clearly facilitated compared to working with a suspension. No conversion was observed in THF, dioxane, and methylene chloride. Moreover, the yields are not improved under strictly anhydrous reaction conditions. Large amounts of inorganic salts are employed in the literature procedures of azidonitration and azidochlorination and have to be removed in the workup.[9,14] In contrast, our protocol only employs stoichiometric amounts or a slight excess of the inorganic components which can be easily removed by aqueous workup.

(14) Naicker, S.; Noujaim, A. Patent US4935503, 1990.

The method was repeatedly applied up to 15.0 g of the starting material giving reproducibly good yields of about 70% of the protected 2-azido galactosyl chloride **2a**. The crude mixture consisted of the α-anomer as the major product (85–90%) and different byproducts in low amounts. Minute amounts of the β-anomer could only be detected in the samples after purification by SiO_2 column chromatography. However, chromatographic purification is detrimental as it results in a considerable loss of material due to hydrolysis and/or decomposition.

Scheme 1. Synthesis of a T_N-Antigen Building Block



X = Cl **2a** 78% α:β = 7:3

X = Br **3** 74% α:β = 8:2

4

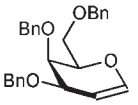
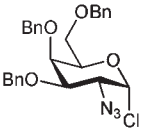
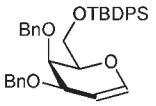
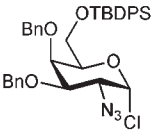
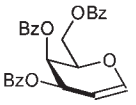
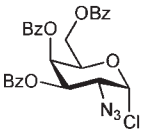
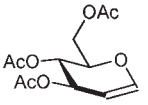
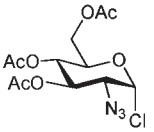
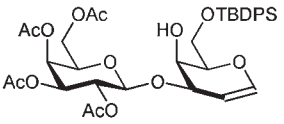
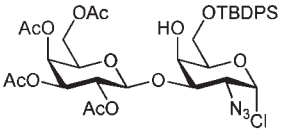
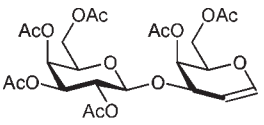
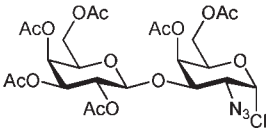
The crude azido chlorides can be used under typical Koenigs–Knorr activation conditions to prepare glycosylated amino acid building blocks or glyco conjugates (Scheme 1).[15] The azido derivative **2a** was used to prepare the glycosylated threonine building block **4**. The yields and diastereoselectivities of the threonine glycosylation are comparable to those reported for the corresponding bromide **3** obtained from an azidonitration reaction followed by bromination.[9,18]

We have furthermore subjected a series of differently protected galactals and other glycals to the reaction conditions to explore the scope of method. Generally, other protecting groups of the benzyl, benzoyl, and silyl type are also tolerated in glycals (Table 2). However, it must be stated that incomplete conversion occurred in the case of glucal derivative **5** and the galactal **1d**. Adding larger amounts of reagents did not improve the results. Instead, larger amounts of byproduct were formed.

In particular, the high yields in the case of the protected disaccharide glycals **7** have to be stressed as they represent precursors of the T-antigen moiety.[7] The protected galactal **7a** was completely converted to a yield of 69% of the corresponding 2-azido galactal **8a** without significant amounts of byproduct. Notably, one hydroxyl group was unprotected. Likewise, the peracetylated galactal **7b** gave 78% of crude chloride **8b**. As for the azido chloride **2a**, the crude material could be used in subsequent reactions without purification.

(15) Paulsen, H.; Adermann, K. *Liebigs Ann. Chem.* **1989**, 751–769.
(16) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823–3824.
(17) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1995**, *6*, 857–858.
(18) Broddefalk, J.; Nilsson, U.; Kihlberg, J. *J. Carbohydr. Chem.* **1994**, *13*, 129–132.

Table 2. Azidochlorination of Different Glycals[a]

substrate		product		conversion[b]	yield[b,c]
	**1b**		**2b**	100%	78%
	**1c**		**2c**	100%	37%
	**1d**		**2d**	54%	47%
	**5**		**6**	50%	50%
	**7a**		**8a**	100%	69%
	**7b**		**8b**	100%	78%

[a] Reaction conditions: 0.8 equiv of $FeCl_3 \cdot H_2O$, 1.1 equiv of NaN_3, 1.1 equiv of H_2O_2 in CH_3CN, −35 °C, 4−8 h. [b] Determined by ^1H NMR. [c] Unpurified product.

In conclusion, the one-pot azidochlorination described here clearly improves and simplifies the preparation of 2-azido glycosyl donors. For many interesting substrates, the reaction gives reproducibly good yields between 60 and 90% and can be easily upscaled to multigram reactions. Not only the acetyl protected monosaccharide glycals but also disaccharide glycals can be used as substrates leading mainly to the α-configured products. A relatively broad variety of starting glycals is accepted, though incomplete conversion occurs occasionally. This efficient and convenient method is an attractive alternative for the preparation of T- and T_N-antigen precursors compared to the methods employed so far.

Acknowledgment. We thank Deutsche Forschungsgemeinschaft (SFB 613) for financial support.

Supporting Information Available. A general experimental procedure and full spectroscopic data for compounds **2a**−**d**, **4**, **6**, **8a**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.