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Iodoacetoxylation of Glycals Using Cerium(IV) Ammonium Nitrate, Sodium Iodide, and Acetic Acid: Stereoselective Synthesis of 2-Deoxy-2-iodo-α-mannopyranosyl Acetates

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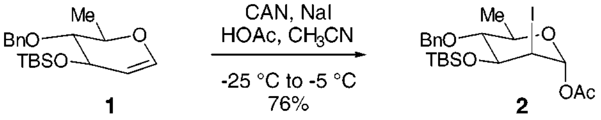
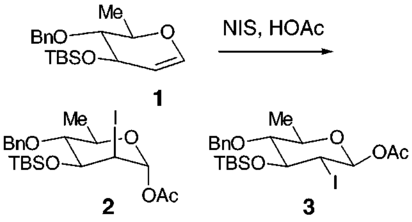
ABSTRACT



91 : 9 selectivity

The reactions of glycals with ceric(IV) ammonium nitrate and sodium iodide in the presence of acetic acid provides 2-deoxy-2-iodo-α-mannopyranosyl acetates with good stereoselectivity. In the majority of the cases examined, the selectivity was considerably better than that from reactions using *N*-iodosuccinimide and HOAc.

In connection with our studies on the synthesis of 2-deoxyglycosides from 2-deoxy-2-iodoglycosyl donors,[2−4] we were interested in developing improved methods for the synthesis of 2-deoxy-2-iodoglycosyl acetates of either the *manno* or *gluco* configuration. Prior to the initiation of these studies, we utilized the reaction of a glycal with *N*-iodosuccinimide and HOAc in a suitable solvent.[5,6] As summarized in Figure 1, this method provides the α-manno isomer (**2**) as the major product when the reactions are performed at ambient or subambient temperatures, with selectivity decreasing as the reaction temperature is raised.[3] In some cases, we have obtained up to 9:1 selectivity for the α-manno iodo acetate isomer in reactions performed at −78 °C;[2] however, in most cases selectivity for the α-manno isomer (cf., **2**) is no better than 3−4:1, as in the iodoacetoxylation of **1**. On the other



Conditions	**2** : **3**
23 °C, CH_2Cl_2, 73%	75 : 25
110 °C, toluene, 66%	55 : 45

Figure 1. Iodoacetoxylation of **1** using *N*-iodosuccinimide (NIS) and HOAc.

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hand, the amount of the β-gluco isomer (e.g., **3**) that can be obtained by this method reaches a maxium of approximately 50% when the reactions are performed in toluene at reflux (i.e., selectivity is no better than ca. 50:50 under these conditions).[3] Accordingly, it was desirable to develop more selective methods for synthesis of either iodo acetate stereoisomer.

Stimulated by the well-known azidonitration reaction,[7,8] which involves the addition of azide radical, generated from NaN_3 and ceric(IV) ammonium nitrate (CAN), to a glycal, we decided to explore the reactions of glycals with CAN and NaI. To our considerable delight, we found that this reaction constitutes a very useful method for synthesis of 2-deoxy-2-iodo-α-mannopyranosyl acetates (Figure 2). These reactions were typically performed by slow addition of 1.3 equiv of NaI to a solution of glycal, 2.6 equiv of CAN and 10 equiv of HOAc in CH_3CN. Total reaction times were generally 2−7 h. Products were isolated either by chromatography or by recrystallization. The reaction stereoselectivity was not highly temperature sensitive, although in most cases the best yields were obtained when the reactions were performed at temperatures ranging from −25 °C to ambient. As indicated by the examples presented in Figure 2, a range of standard carbohydrate protecting groups (e.g., acetate esters, silyl and benzyl ethers) are fully compatible with this new iodoacetoxylation reaction.

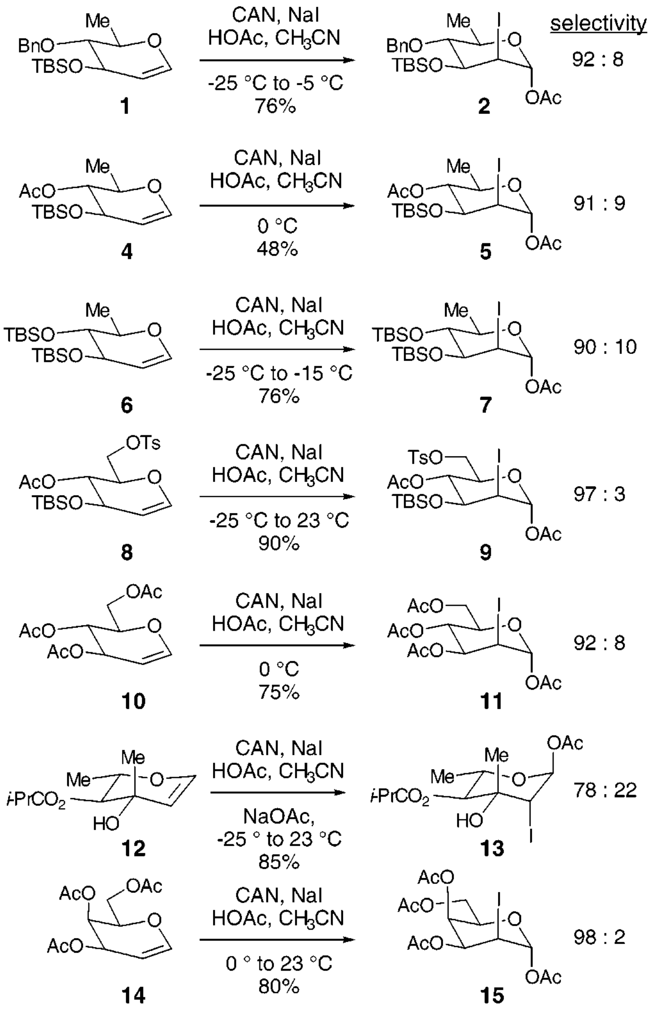
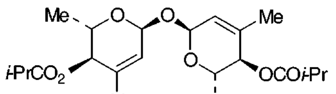


Figure 2. Iodoacetoxylation of glycals using NaI, HOAc, and ceric(IV) ammonium nitrate (CAN) in CH_3CN.

In the majority of cases that we have examined, the CAN−NaI−HOAc protocol has proven to be much more selective than the *N*-iodosuccinimide (NIS)−HOAc procedure summarized in Figure 1. Thus, for example, while the iodoacetoxylation of **1** using NIS and HOAc provides **2** with maximum selectivity of 75:25, use of the CAN−NaI−HOAc protocol provides **2** with 92:8 selectivity. In other comparative cases, **4** gave a 91:9 mixture of **5** and the β-gluco isomer using the CAN−NaI−HOAc method, while with NIS and HOAc the selectivity was 88:12 (61% yield). Similarly, **8** provided an 80:20 mixture (75%) of **7** and its β-gluco diastereomer using NIS and HOAc, while the selectivity was 97:3 using the CAN−NaI−HOAc procedure. The one exception is the iodoacetoxylation of **12**, which with CAN−NaI−HOAc provided a 78:22 mixture favoring **13**, while with NIS−HOAc at −78 °C a 90:10 mixture is obtained.[2] However, it should be noted that the CAN−NaI−HOAc reaction of **12** was performed in the presence of NaOAc in order to suppress acid-catalyzed decomposition reactions of this substrate. When this reaction was performed in the absence of NaOAc, using the standard conditions employed for all other substrates, **13** was obtained with 94:6 selectivity, but in only 18% yield. The major product obtained under these conditions was the 1,1′-disaccharide **16**, resulting from Ferrier elimination of the tertiary alcohol followed by acid-catalyzed dimerization. The new CAN−NaI−HOAc protocol also appears to be more selective than the recently introduced iodoacetoxylation method involving diacetoxyiodine(I) anions, based on the comparitive case provided by glycal **6** (the enantiomer of **6** provided a 73:27 mixture of *ent*-**7** and the gluco isomer using the diacetoxyiodine(I) anion procedure).[9]



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The mechanism of this new iodoacetoxylation process is unclear at present. It is conceivable that the reaction could proceed by addition of an iodine atom ($I^•$) to C(2) of the glycal, by analogy to the azidonitration reaction.[10] Carbon-based radicals are also known to add to glycals at the C(2) position, but radical addition trans to the C(3) substituent is generally favored,[7,8,11] unlike the iodoacetoxylation reactions summarized here. 2-Iodo-1α-nitrates are intermediates in the CAN−NaI reactions of glycals and are converted to the iodo acetates in a substitution step after the iodonitration. The reaction mixtures become colored during the course of the

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experiments, indicating that some I_2 is generated. However, treatment of glycal **8** with I_2 and HOAc in CH_3CN led to none of the desired glycosyl iodoacetate. In addition, complex mixtures (containing none of **11**) were obtained when **10** was treated with CAN, I_2, and HOAc in CH_3CN.[12,13] Use of CAN and I_2 in alcohol solvent has been reported to be a useful method for alkoxyiodination and iodonitration of olefins.[12,13] However, our results indicate that I_2 is not an intermediate in the CAN−NaI−HOAc iodoacetoxylation procedure. One additional and relevant piece of information is that complex product mixtures, again containing none of the desired iodoacetate **11**, were obtained in attempts to perform the iodoacetoxylation of triacetyl-D-glucal (**10**) using ceric(IV) sulfate in place of ceric(IV) ammonium nitrate. This experiment indicates that the nitrate ligand on Ce(IV) plays an important role in the reaction.

This information prompts us to consider the possiblity that iodonium nitrate (INO_3) could be an intermediate in the CAN−NaI reaction.[14,15] When cyclohexene was used as the substrate, *trans*-1-iodo-2-nitratocyclohexane (**17**) was obtained in 71% isolated yield (Figure 3). Products of alkene iodination were not obtained when ceric(IV) sulfate was used in place of CAN in the cyclohexene experiment summarized in Figure 3, once again pointing to the key role of the nitrate ligands in these experiments.

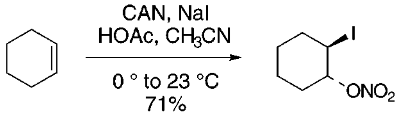

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Figure 3. Iodonitration of Cyclohexene using CAN−NaI−HOAc.

In summary, we have demonstrated that the reactions of glycals with NaI and ceric(IV)ammonium nitrate in the presence of acetic acid consititutes an efficient, stereoselective method for synthesis of 2-deoxy-2-iodomannopyranosyl acetates. In most cases the selectivity of this new method is superior to that obtained by using NIS and HOAc or diacetoxyiodine(I) anions.[9] Applications of the glycosyl iodoacetates in the synthesis of 2-deoxy-α-glycosides are reported in the accompanying Letter.[16]

Acknowledgment. We thank the NIH (GM 38907) for support of this research.

Supporting Information Available: Tabulated spectroscopic data for iodo acetates **2**, **5**, **7**, **9**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Kirschning, A.; Plumeier, C.; Rose, L. *Chem. Commun.* **1998**, 33. **Representative Experimental Procedure:** To a stirred slurry of glycal **1** (0.985 g, 2.94 mmol), CAN (4.19 g, 7.64 mmol), and acetic acid (1.7 mL, 29.4 mmol) in 20 mL of acetonitrile at −25 °C was added NaI (0.573 g, 3.82 mmol) in 10 mL of acetonitrile over 45 min. The reaction mixture was maintained at −25 °C for 2 h and then was allowed to warm to −5 °C. At the end of 3 h, the mixture was quenched by adding 0.1 M $Na_2S_2O_3$ (until color disappeared) and saturated $NaHCO_3$ (until solution was weakly basic). The aqueous solution was extracted with EtOAc (3 × 100 mL), and the organic extract was washed with brine, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using 10% EtOAc in hexanes as the eluent to obtain a white solid (1.17 g, 76%), consisting of iodoacetates **2** and **3** in a 92:8 ratio. The mixture was crystallized from diethyl ether to obtain a mixture enriched in **2** (96:4). Further separation of the diastereomers was effected by HPLC (41 mm column) with 7.5% EtOAc in hexanes as the mobile phase.

(10) For a brief discussion of possible mechanisms for the synthesis of α-azido-*β*-nitratoalkanes from olefins, NaN_3, and ceric(IV) ammonium nitrate, see: Trahanovsky, W. S.; Robbins, M. D. *J. Am. Chem. Soc.* **1971**, *93*, 5256.

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