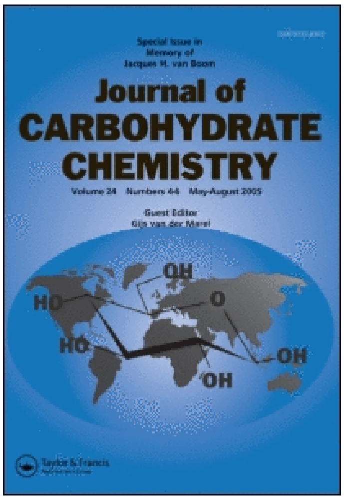

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Lincoln Noecker[a]; Robert M. Giuliano[a]; Michael Cooney[a]; Walter Boyko[a]; Walter W. Zajac Jr[a]
[a] Department of Chemistry, Villanova University, Villanova, PA, U.S.A.

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OZONE/OXONE-MEDIATED OXIDATIONS OF AMINO AND *O*-BENZYLHYDROXYLAMINO SUGARS

Lincoln Noecker, Robert M. Giuliano,* Michael Cooney,
Walter Boyko, and Walter W. Zajac Jr.

Department of Chemistry, Villanova University, Villanova, PA 19085, USA

ABSTRACT

A method for the preparation of *C*-methyl branched nitro sugars from the corresponding amino sugars by oxidation with mixed oxidants is described. Ozonolysis of the amino sugars in the presence of OXONE (potassium monopersulfate) and acetone (Bashir-Hashemi's procedure) gave nitro sugars in good yields. Oxidation of an *O*-benzylhydroxylamino sugar by this method resulted in deprotection and oxidation in a single step, giving the nitro sugar directly. The mixed oxidant method is experimentally simpler and more convenient to use than DMDO, which had been previously reported for the oxidation of amino sugars.

INTRODUCTION

Nitro sugars are found in several antibiotics.[1] An example is the anthracycline antibiotic cororubicin, which contains the 3-methyl-branched nitro sugar decilonitrose.[2] The synthesis of nitro sugars is usually carried out by oxidation of the corresponding amino sugars with *m*-chloroperoxybenzoic acid. The generation of carboxylate by this method can be problematic for the labile glycosidic linkages in 2-deoxy sugars, resulting in lower-than-expected yields of nitro sugar. We previously reported that the oxidation of the amino group to nitro in methyl-branched amino sugars can be carried out by treatment of the amino sugar with excess dimethyldioxirane

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*Corresponding author.

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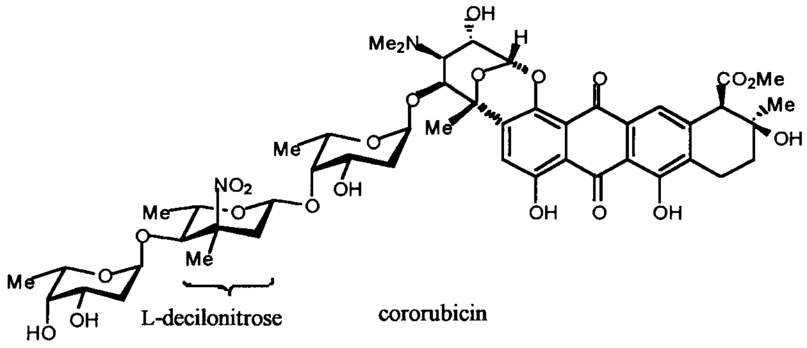
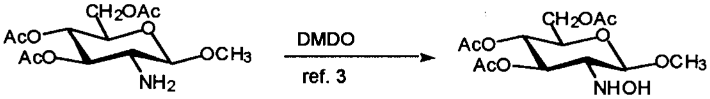
(DMDO).[3] Oxidation with ozone/silica gel was also used in the synthesis of the methyl-branched nitro sugar kijanose in a previous report from this laboratory.[4]

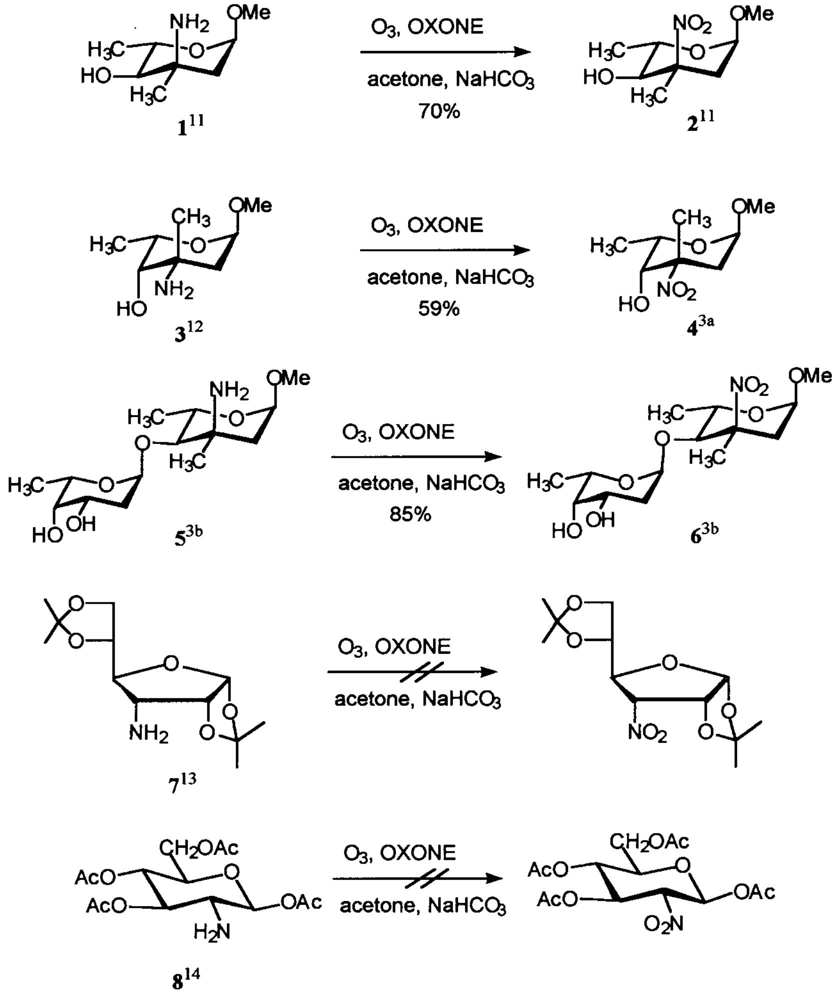


Other methods for the oxidation of amino groups in carbohydrate as well as non-carbohydrate substrates have been described. The oxidation of primary amines with DMDO was reported to give mainly nitroso compounds by Crandall, with nitro compounds being obtained when a large excess of DMDO was used.[5] Murray prepared several nitro compounds by oxidation of primary amines with excess DMDO.[6] Danishefsky described the synthesis of hydroxylamino sugars by oxidation of the amines with DMDO;[7] however, the amino group was attached to a secondary carbon in all cases. In nitro sugars that occur in antibiotics this carbon (C3) is tertiary.



Bashir-Hashemi has recently described a procedure for the preparation of nitro compounds through the use of mixed oxidizing agents ozone and monopersulfate.[8] Examples of nitro compounds prepared by this method included nitro adamantane and nitro cubane, both of which were prepared by ozonation of the corresponding amine in a solution of acetone–water in the presence of potassium monopersulfate (OXONE).[9] The attempted oxidation of 2-aminoadamantane and 1,2-diaminocyclohexane using Bashir's procedure gave intractable mixtures of products, presumably because the primary amino group is attached to a secondary carbon atom in these substrates.[10] Since the amino group in these substrates is attached to a tertiary carbon, we became interested in the potential application of this procedure to the synthesis of nitro sugars such as decilonitrose. Experimentally, the ozone/OXONE method is much simpler to carry out than DMDO oxidations. In this paper, we describe the oxidation of amino and *O*-benzylhydroxylamino sugars to nitro sugars using the ozone/OXONE mixed oxidant system.

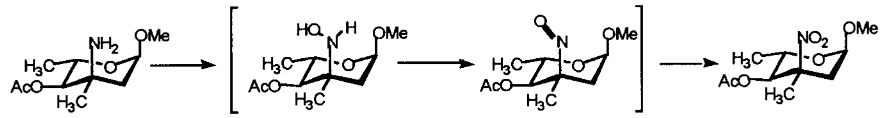
Oxidations of methyl-branched amino sugars using ozone/OXONE are shown in Scheme 1. Oxidation of methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranoside (**1**) gave the corresponding nitro sugar **2** (methyl α-L-decilonitroside) in 70% yield. The diastereomeric amino sugar **3** (methyl α-L-vancosaminide) gave nitro sugar **4** in similar yield. In neither case was the presence of isomerized nitro alcohols observed



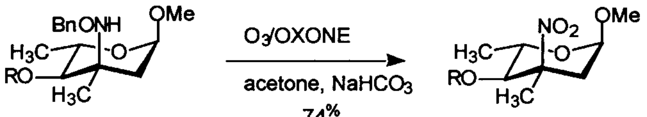
Scheme 1. Ozone/OXONE oxidations of amino sugars.

in the NMR spectra of the reaction products, which might be expected under the mildly basic conditions of the oxidation. Epimerization of the enantiomer of **2** in the presence of sodium methoxide in methanol was previously shown to give a mixture of three diastereomers, presumably by retro-aldol reaction and ring closure.[3a]

Extension of the oxidation method to disaccharides was also successful, as demonstrated by the oxidation of **5** to nitro disaccharide **6**. However, the procedure was not applicable to amino sugars with a secondary carbon; for example, acetonide **7** or glucosamine derivative **8**, neither of which gave clean oxidation products. The oxidation of amino to nitro is assumed to proceed through hydroxylamino and nitroso intermediates. The presence of an α-hydrogen at C-3 in **7** and C-2 in **8** might be expected to lead to tautomerization of the nitroso intermediate, or other side reactions such as dimerization. These processes have been well documented for the oxidation of primary aliphatic amines with peroxyacetic acid,[15] but were not observed in the oxidation of **8** with MCPBA.[14] The nitro compound obtained from **8** was found, however, to be unstable to silica gel chromatography.[14]



It was also of interest to attempt the oxidative cleavage of an *O*-benzylhydroxylamine ether using the ozone/OXONE procedure.[16] In our synthesis of the corubicin trisaccharide, this transformation was carried out with DMDO on an acetylated trisaccharide with a hydroxylamino function protected as its benzyl ether.[17] Deprotection and oxidation of the amino group to nitro occurred with DMDO.[18] Oxidation of **9a** with ozone/OXONE gave disappointing results, with incomplete oxidation and epimerization in some cases. However, oxidation of acetate **9b** for a longer period at 0°C gave the crystalline nitro sugar **10** in 74% yield. This novel deprotection of the amino group and oxidation to nitro in a single step may be useful in other synthetic problems in which nitro sugars are involved. Further applications of the mixed oxidant method for the oxidation of amino sugars and *O*-benzylhydroxylamino sugars are in progress.



9a R=H
9b R=Ac

10 R=Ac

EXPERIMENTAL

Typical procedure. To a stirring suspension of potassium monopersulfate (OXONE, 2.75 g) and $NaHCO_3$ (1.75 g) in water (100 mL) at 0°C was added acetone (25 mL) followed by a solution of amino sugar (0.083 g, 0.27 mmol) in acetone (25 mL) dropwise while ozone was bubbled into the reaction mixture for 30 min (gas dispersion tube). After stirring for another 2 h at 0°C, the mixture was concentrated on a rotary evaporator, removing the acetone and some water. The residue was extracted with ethyl acetate (3 × 25 mL) and the combined extracts were washed with saturated NaCl solution, dried (sodium sulfate) and concentrated to give nitro sugar products, which were identified by their ^{1}H NMR spectra. See references in Scheme 1.

Methyl 4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-3-(*O*-benzylhydroxylamino)-α-L-*ribo*-hexopyranoside (9b). A solution of **9a** (120 mg, 0.427 mmol), acetic anhydride (0.2 mL), and pyridine (0.3 mL) was stirred at room temperature for 8 h. The reaction was poured into satd aqueous sodium bicarbonate and the mixture was extracted with ether. The combined ether extracts were dried (sodium sulfate) and concentrated to an oil (123 mg) that was purified by flash chromatography using 20% ethyl acetate/

hexanes as eluate; yield 110 mg (79%): $[\alpha]_D^{23} - 13.2$ (*c* 1.2, $CHCl_3$), R_f 0.33 (20% ethyl acetate/hexanes), ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H, Ph-H), 4.80–4.67 (m, 2H, H-1, H4), 4.02 (m, 1H, H-5), 3.38 (s, 3H, OCH_3), 2.30 (dd, 1H, $J_{2e,2a} = 15.0$ Hz, H-2e), 2.10 (s, 3H, CH_3CO), 1.64 (dd, 1H, $J_{1,2a} = 6.0$ Hz, H-2a), 1.60 (bs. 1H, NH), 1.17 (s, 3H, 3–CH_3), 1.13 (d, 3H, H-6); ^{13}C NMR ($CDCl_3$) δ 169.4 (CO), 137.8, 128.0, 127.6, 127.1, 98.0 (C-1), 77.9, 77.0, 62.4, 58.3, 55.3, 37.7, 24.0, 21.4, 18.3.

HRMS (CI) Calcd for $C_{17}H_{25}NO_5$ (M + 1): 323.1732. Found: 323.1723.

Methyl 4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-3-nitro-α-L-*ribo*-hexopyranoside (10). A solution of *O*-benzylhydroxylamino sugar **9b** (123 mg, 0.38 mmol) in acetone (10 mL) was added to a stirred suspension of OXONE (2.75 g) and $NaHCO_3$ (1.75 g) in water (50 mL)—acetone (10 mL) at 0°C while ozone was bubbled through the mixture. Ozonation was carried out for 2 h, after which the reaction was stirred for another 2 h at 0°C. Processing as described above gave crystalline nitro ester **10** (70 mg, 74 %): mp 70–71°C, $[\alpha]_D^{23} - 15.9$ (*c* 0.62, $CHCl_3$), R_f 0.35 (20% ethyl acetate/hexanes), ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, 1H, $J_{4,5} = 9.7$ Hz, H-4), 4.67 (dd, 1H, $J_{1,2a} = 4.1$Hz, $J_{1,2e} = 1.6$ Hz, H-1), 4.45 (m, 1H, $J_{5,6} = 6.3$ Hz, H-5), 3.27 (s, 3H, OCH_3), 2.78 (dd, 1H, $J_{2e,2a} = 14.9$ Hz, H-2e), 2.15 (s, 3H, CH_3CO), 2.07 (dd, 1H, H-2a), 1.55 (s, 3H, 3–CH_3), 1.20 (d, 3H, H-6); ^{13}C NMR ($CDCl_3$) δ 170.1 (CO), 96.1 (C-1), 84.7 (C-3), 74.7, 63.8, 54.8, 40.7, 25.6, 20.9, 17.9.

HRMS (CI) Calcd for $C_{10}H_{16}NO_6$ (M-1): 246.0971. Found: 246.0977.

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REFERENCES

1. Wade, P.A.; Giuliano, R.M. The Role of the Nitro Group in Carbohydrate Chemistry. In *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Feuer, H., Nielsen, A.T., Eds.; VCH: New York, 1993; 137–266.
2. Ishii, K.; Nishimura, Y.; Kondo, S.; Umezawa, H. Decilonitrose and 4-*O*-succinyl-L-diginose, sugar components of decilorubicin. J. Antibiot. **1983**, *36*, 454–456.
3. (a) Ye, H.; Noecker, L.; Boyko, W.; Giuliano, R.M.; Yap, G.P.A.; Rheingold, A.L. Studies of the synthesis of rubranitrose and crystal structure of methyl 2,3,6-trideoxy-3-*C*-methyl-3-nitro-α-D-*ribo*-hexopyranoside. J. Carbohydr. Chem. **1997**, *16*, 373–383.; (b) Noecker, L.; Duarte, F.; Giuliano, R.M. Synthetic studies of the cororubicin oligosaccharide: Glycosylation of branched amino and nitro sugars. J. Carbohydr. Chem. **1998**, *17*, 39–48.
4. Giuliano, R.M.; Deisenroth, T.W. Synthesis of methyl α-D-kijanoside. J. Carbohydr. Chem. **1987**, *6*, 295–299.
5. Crandall, J.K.; Reix, T. Dimethyldioxirane oxidation of primary amines. J. Org. Chem. **1992**, *57*, 6754–6759.

6. Murray, R.W.; Jeyaraman, R.; Mohan, L. A new synthesis of nitro compounds using dimethyldioxirane. Tetrahedron Lett. **1986**, *27*, 2335–2336.
7. Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. On the conversion of biologically interesting amines to hydroxylamines. J. Org. Chem. **1990**, *55*, 1981–1983.
8. Bashir-Hashemi, A. Preparations of Organic Nitro Compounds Through Mixed Oxidizing Agents. U.S. Patent 5,998,661, December 7, 1999.
9. A recent paper describes the synthesis of hydroxylamines from amines by oxidation with OXONE in the presence of silica gel or alumina: Fields, J.D.; Kropp, P.J. Surface-mediated reactions 9. Selective oxidation of primary and secondary amines to hydroxylamines. J. Org. Chem. **2000**, *65*, 5937–5941.
10. Cooney, M.A. M.S. Thesis; Villanova University, 2000.
11. (a) Giuliano, R.M.; Deisenroth, T.W. Synthesis of methyl α-L-decilonitroside. Carbohydr. Res. **1986**, *158*, 249–252.; (b) Greven, R.; Jutten, P.; Scharf, H.-D. A new stereoselective route to branched-chain nitro and amino sugars: Synthesis of both enantiomers of decilonitrose and avidinosamine. J. Org. Chem. **1993**, *58*, 3742–3747.
12. Smith, G.R.; Giuliano, R.M. Synthesis of methyl α-L-vancosaminide. Carbohydr. Res. **2000**, *323*, 208–212.
13. Tanaka, S. Daunosamine from D-glucose. Jpn. Kokai Tokyo Koho **1979**, 33–35. Tanaka, S. Daunosamine from D-glucose. Chem. Abstr. **1979**, *91*, 5437m. Lemieux, R.; Chu, P. 1,2;5,6-di-*O*-isopropylidene-3-deoxy-amino-α-D-allose. J. Am. Chem. Soc. **1958**, *80*, 4745.
14. Vega-Perez, J.M.; Candela, J.I.; Iglesias-Guerra, F. A facile synthesis of saturated 2-nitrosugar derivatives. J. Org. Chem. **1997**, *62*, 6608–6611.
15. Zajac, W.W., Jr.; Walters, T.R.; Woods, J.M. Oxidation of primary aliphatic amines to *C*-nitroso dimers. Synthesis **1988**, 808–810.
16. Oxidative debenzylation of *N,N*-dibenzylamines with CAN or DDQ has been reported: Hungerhoff, B.; Subhendu, S.S.; Roels, J.; Metz, P. Chemoselective oxidative debenzylation of *N,N*-dibenzylamines. Synlett **2000**, 77–79.
17. Noecker, L.; Duarte, F.; Bolton, S.A.; McMahon, W.G.; Diaz, M.T.; Giuliano, R.M. Glycosylation of branched amino and nitro sugars. Part II. Synthesis of the cororubicin trisaccharide. J. Org. Chem. **1999**, *64*, 6275–6282.
18. For previous studies of benzyl ether cleavage with DMDO, see: Csuk, R.; Dorr, P. Convenient oxidative debenzylation using dimethyldioxirane. Tetrahedron **1994**, *50*, 9983–9988.

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