ELSEVIER

www.elsevier.com/locate/carres

Carbohydrate Research 336 (2001) 75–78

CARBOHYDRATE RESEARCH

Note

Facile nitroxide-mediated oxidations of D-glucose to D-glucaric acid

Nabyl Merbouh,[b] Jean Francois Thaburet,[a] Mathias Ibert,[a] Francis Marsais,[a] James M. Bobbitt[b,*]

[a]*IRCOF-INSA de Rouen, BP08, 76131 Mont Saint Aignan, France*
[b]*Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060, USA*

Received 7 June 2001; accepted 10 August 2001

Abstract

The oxidation of D-(+)-glucose to D-glucaric acid using the TEMPO-like nitroxide oxidation catalyst, 4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy (4-acetamido-TEMPO) was carried out using several oxidizing agents and co-catalyst. The pH and temperature of the reactions were closely monitored to decrease degradations during the oxidation, and several isolation methods were explored.

Keywords: Primary alcohol oxidation; Glucaric acid; Nitroxide; Bleach

1. Introduction

A number of preparations of D-glucaric acid from D-glucose or starch have been reported in the past.[1–4] In general, the methods involved such strong oxidants as nitric acid or NO_2, were expensive, and gave poor yields ($< 55\%$). In recent years, several nitroxide-mediated oxidations of alcohol groups have been carried out.[5,6] The reaction is particularly suitable for carbohydrates.[7–11] The various catalytic cycles are shown below (Fig. 1), based on our work and that of others.[5,8]

We recently described the nitroxide-catalyzed oxidation of D-glucose to D-glucaric acid in connection with more detailed work on the oxidation of polysaccharides.[12] Here, we present detailed experimental procedures for the oxidation of D-glucose using 4-acetamido-TEMPO,[13,14] rather than TEMPO. The acetamido derivative is more stable, much less volatile, and is commercially available. The catalyst was used in combination with two

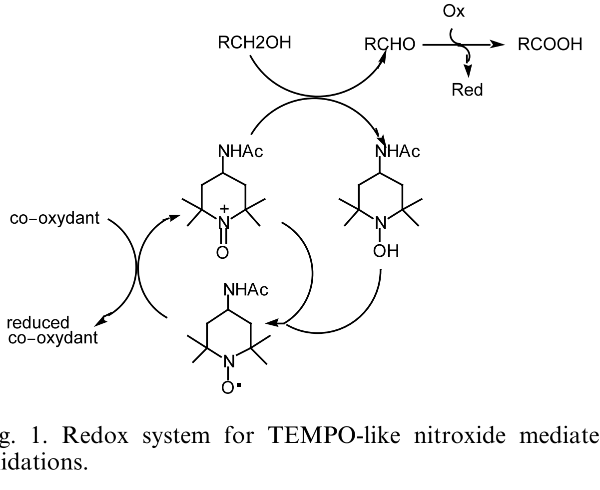

Fig. 1. Redox system for TEMPO-like nitroxide mediated oxidations.

---

* Corresponding author. Fax: + 1 860 486 2981.
E-mail address: bobbitt@nucleus.chem.uconn.edu (J.M. Bobbitt).

0008-6215/01/$ - see front matter
PII: S0008-6215(01)00231-2

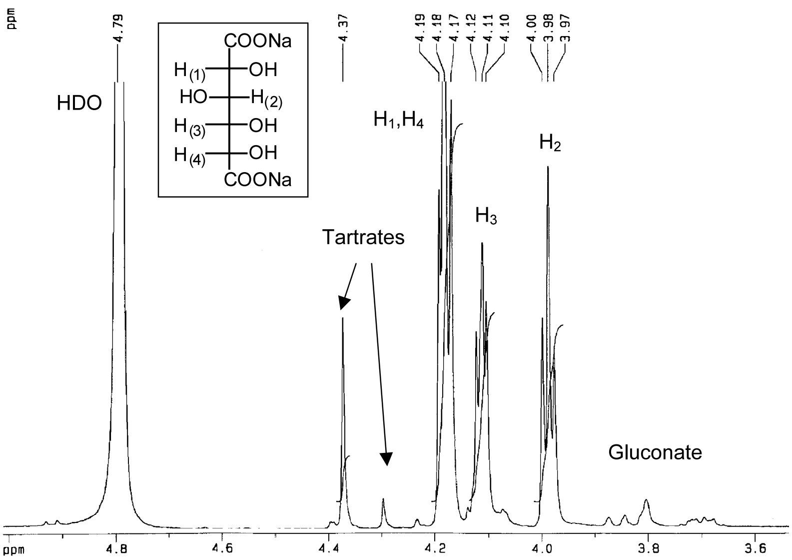

Fig. 2. ${}^{1}H$ Spectrum of the crude oxidation mixture.

different oxidants, sodium hypochlorite (bleach) and potassium hypochlorite. Sodium or potassium bromide was present as a co-catalyst. Other oxidants such as chlorine and bromine are under exploration.

2. Results and discussion

D-Glucose was oxidized with either sodium or potassium hypochlorite in the presence of catalytic amounts of 4-acetamido-TEMPO (0.078 molar%) and sodium or potassium bromide. Two solutions of sodium hypochlorite were used, commercial bleach (5.25% NaOCl) and Aldrich 'available chlorine, 10–13%' (11% NaOCl, by iodometric titration). Concentrated potassium hypochlorite, 1.25 M, was prepared by the method of Newman and Holmes.[15] We showed in previous work[12] that carbohydrate oxidations with the system ClO^-/Br^-/TEMPO were dependent on the pH and temperature, with optimum conversions (for monosaccharides) at pH 11.4–11.6 and at temperatures between 0 °C and 5 °C. Under these conditions, little chain degradation was detected by ${}^{13}C$ or ${}^{1}H$ NMR (about 90% of the product was D-glucaric acid salts, Fig. 2). The rest was a mixture of tartrate salts, gluconate salts, oxalate salts, carbonates, and halides.

The primary products in both reactions were the dipotassium or disodium salts of D-glucaric acid. For the sodium experiments, the disodium salt was precipitated with ethanol, (twice) to give a crude yield of 95%. Using ${}^{1}H$ NMR and gravimetric analysis for halides, the crude product was shown to contain about 90% disodium glucarate, 5% disodium tartrate, and less than 5% halide salts. Thus, the corrected yield of disodium glucarate was 85%.

Since the disodium salt is amorphous and does not seem to have been carefully characterized, this crude material was converted into the less soluble and crystalline monopotassium salt, which was isolated by precipitation. This was done by passing the aqueous disodium salt solution through an acid ion-exchange resin (Amberlite IR-120) to convert it into the free acid and then by half neutralization with potassium hydroxide to afford the monopotassium salt in about 70% yield. When the filtrates from the monopotassium salt were concentrated, the yields were raised to ~ 90%. The monopotassium D-glucaric acid was characterized by mp, ${}^{13}C$ NMR spectroscopy, and optical rotation.

For the potassium experiments, the salt was half neutralized with hydrochloric acid, and the slightly soluble monopotassium salt was collected by filtration. Although this reaction was very simple, the potassium hypochlorite had to be prepared from calcium hypochlorite and potassium carbonate.

3. Experimental

General methods.—Melting points were determined with a Kofler-block apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. The ^{13}C and ^{1}H NMR spectra were recorded in D_2O with a Bruker DRX-400 instrument. All chemicals were commercially available (Acros or Aldrich) and used as received.

Oxidation apparatus.—The reactions were carried out in an open beaker fitted with a pH-meter electrode, a thermometer and a 50 mL syringe pump controlled by the pH meter in such a manner as to keep the pH above any given value by the addition of sodium or potassium hydroxide solution. The beaker was cooled in ice. The hypochlorite solution was added through a burette.

Oxidation with commercial bleach.—D-(+)-Glucose (3.00 g, 16.6 mmol), 4-acetamido-TEMPO (0.04 g, 0.013 mmol), and NaBr (0.40 g, 3.36 mmol) in water (50 mL) were cooled in ice to 0–5 °C, and the pH was adjusted to 11.5 with 2 M NaOH solution. Bleach solution (a total of 77 mL of 5.25% NaOCl, 3.3 eq/mole of sugar) was then added slowly (2 mL every 2 min for the first 25 mL, then 5 mL every 20 min for the rest). Using the automatic syringe system, the pH was kept between 11.4 and 11.6 with 2 M NaOH solution.

The end of the reaction was detected by a negative KI–starch paper test and occurred about 1 h after the last bleach had been added. ^{1}H NMR spectra were measured in D_2O after removal of H_2O by freeze drying; ^{13}C NMR spectra were measured on freeze-dried samples or on the actual reaction mixtures after the addition of a small amount of D_2O for locking purposes. The data showed that 90% (quantitative ^{1}H and ^{13}C NMR) of the mixture was sodium D-glucarate, about 4% was sodium gluconate, about 4% were sodium tartrates (*meso*: $\delta = 4.30$ ppm and *dl*: $\delta = 4.37$ ppm), and 1% was sodium oxalate (not always observed).

The reaction mixture (about 150 mL) was concentrated under good vacuum (0.1 mm Hg) to ~30 mL, and 100 mL of 95% EtOH was added to precipitate a mixture of disodium D-glucarate and some inorganic salts. The supernatant liquid was decanted and the gummy precipitate was dissolved again in 30 mL of water and precipitated with 100 mL of EtOH. The resulting gum, after decantation, was washed with 4:1 EtOH–water to give 3.9 g of *crude* disodium D-glucarate (95% yield) after drying at 50 °C under reduced pressure.

The very small amount of nitroxide remained in the water was ignored. Gravimetric halide analysis and NMR studies showed that the crude material contained less than 4% halide (measured as sodium chloride), about 4–5% tartrate salts and very little gluconate salts. The crude disodium D-glucarate was a fine white, non-crystalline powder, and no further decolorization was required.[1]

Oxidation with concentrated sodium hypochlorite.—The procedure just described was carried out with concentrated sodium hypochlorite (11%, 1.37 M). The reaction mixture (about 105 mL) was processed in the same manner to give 3.9 g of crude sodium D-glucarate (the only advantage of this reaction was an appreciable reduction in the amount of water to be removed at the end).

Isolation of potassium D-glucarate from sodium D-glucarate.—A solution of the crude sodium D-glucarate (1.5 g in 10 mL) was passed slowly over a column (2 cm × 15 cm) of Amberlite IR-120 that had previously been washed with water. The eluant was treated with a KOH (2 M) solution to a final pH of 3.8. The solution was concentrated to ~20 mL and, after several min, the monopotassium D-glucarate crystallized. The solid was collected by filtration and dried to yield 1.2 g (80%) of potassium D-glucarate, m.p. 188–190 °C, $[\alpha]^{20} + 5°$ (c1, H_2O). Commercial samples (Aldrich) melted at 188 °C, with $[\alpha]^{21} + 5°$ (c1, H_2O), and ^{13}C NMR (D_2O): $\delta = 71.9$, 72.8, 73.0, 73.8 (C-2,3,4,5), 177.4, 177.5 (C-1,6). The NMR spectrum was identical to that of a commercial sample.

Attempts to isolate the potassium salt directly from the sodium salt by partial neutralization and the addition of excess KCl gave poor yields of the potassium salt.

Oxidation with potassium hypochlorite.—The oxidation was carried out in the same manner as just described except that the pH was controlled with KOH, and potassium hypochlorite[15] (1.075 M) was the oxidant, with KBr as co-oxidant. At the end of the reaction, the mixture (~ 130 mL) was partially acidified with one equivalent of concd HCl to give a final pH of 3.8. The precipitated product, after drying under vacuum at 40 °C was identical to the one obtained above and amounted to 2.4 g (55%). The filtrate was concentrated; the pH was adjusted to 3.8 and a small amount of KCl was added. An additional 1.00 g of product precipitated (total yield was 85%).

The resulting material was a white crystalline compound with properties identical to those already cited.

4. Conclusion

At pH values between 11.4 and 11.6, and at temperatures below 5 °C, the nitroxide mediated oxidation of D-glucose yields glucaric acid salts with high selectivity and good yields (more than 85%, isolated as the monopotassium salt). This would appear to be an excellent method for oxidation of unprotected glucose.

The use of 4-acetamido-TEMPO instead of TEMPO as catalyst reduces the price and allows more freedom for oxidation conditions due to its greater stability and much lower volatility.

Acknowledgements

The authors thank Professors Steven Suib and Christian Brückner of this Department for help and support and Mr. Charles Gallo of the University of Connecticut Technical Services for designing and building the pH control device.

References

1. Mehltretter, C.L. *Methods Carbohydr. Chem.* **1963**, *II*, 46–48.
2. Mehltretter, C. L. *Adv. Carbohydr. Chem.* **1953**, *8*, 231–249.
3. Mehltretter, C. L.; Rist, C. E. *J. Agr. Food Chem.* **1953**, *1*, 779–783.
4. Kiliani, H. *Chem. Ber.* **1925**, *58*, 2344–2362.
5. Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509–533.
6. de Nooy, A.E.J.; Besemer, A.C.; van Bekkum H. *Synthesis* **1996**, 1153–1174.
7. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 165–166.
8. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Carbohydr. Res.* **1995**, *269*, 89–98.
9. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Tetrahedron* **1995**, *29*, 8023–8032.
10. de Nooy, A.E.J.; Besemer A.C., Patent, WO 95 07,303 (16 March 1995).
11. Davis, N. J.; Flitsh, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181–1184.
12. Thaburet, J. F.; Merbouh, N.; Ibert, M.; Marsais, F.; Queguiner, G. *Carbohydr. Res.* **2001**, *330*, 21–29.
13. Bobbitt, J. M. *J. Org. Chem.* **1998**, *25*, 9367–9374.
14. Bragd, P. L.; Besemer, A. C.; van Bekkum, H. *J. Mol. Catal. A.* **2001**, *170*, 3542.
15. Newman, M.S.; Holmes, H.L. *Org. Syn. Coll.* **1966**, *II*, 428–430.