COMMUNICATIONS

Selective Light Supported Oxidation of Hexoses Using Air as Oxidant – Synthesis of Tetrahydroxyazepanes

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Abstract: Unprotected alkyl glycosides have been oxidized using air as oxidant and copper(I) chloride/TEMPO as the catalytic system. The primary hydroxy group in the 6 position is selectively transformed into an aldehyde equivalent. The process was optimized by irradiation with visible light. Without further purification and with high yields, the resulting lactols have been transformed into tetrahydroxyazepane.

Keywords: aerobic oxidation; biomimetic synthesis; azasugars; carbohydrates; photochemistry; TEMPO

Carbohydrates are valuable synthons for organic chemistry. As they possess numerous hydroxy groups, selective transformations often need a sophisticated strategy of using suitable protecting groups.[1] On the other hand, in living organisms, reactions of carbohydrates do not need protecting groups since they are catalyzed by enzymes. The enzymatic activity, however, is generally linked to a very restricted scope of substrates. As far as carbohydrates are concerned, their stereochemistry is often a key element of reactivity discrimination.

An artificial catalytic system possessing the same reactivity as an enzyme but applicable to a larger variety of substrates (biomimetic reactions[2]) may simplify or even make redundant a strategy of using protecting groups. In this way, syntheses involving carbohydrates as substrates would considerably be shortened and facilitated.

In this context, we became interested in the enzymatic activity of galactose oxidase. This enzyme catalyzes the oxidation of the primary alcohol function in the 6 position of galactose into an aldehyde function.[3,4] The presence of two aldehyde functions in the carbohydrate molecule increases its reactivity and enhances its scope of application to organic synthesis. In combination with catalase, this oxidation has been applied to the synthesis of polyhydroxyazepanes.[5] The galactose oxidase activity is. however. strictly related to the presence of a hydroxy function in position 4 possessing the configuration of hexoses belonging to the D-threose series.[5,6] For this reason, for instance, talose or galactose derivatives can be transformed while mannose or glucose derivatives cannot be oxidized.

In order to develop a more generally applicable method for this oxidation of carbohydrates, we became interested in the oxidation system of Semmelhack.[7] Hydroxy functions are oxidized by Cu(II) and TEMPO (Scheme 1).[4,8] TEMPO also reoxidizes Cu(I) to Cu(II). In both cases, TEMPOH is generated. The latter compound is reoxidized to TEMPO by air. The method is particularly attractive because air as a mild and environmentally friendly oxidant[9] is
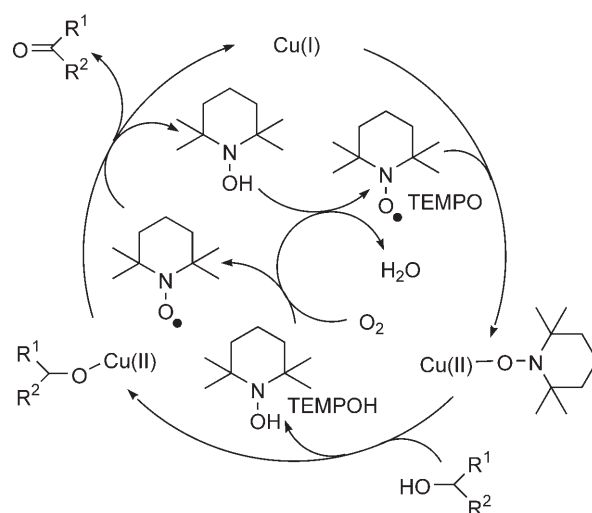
**Scheme 1.** Mechanism of oxidation using the Cu(I)/TEMPO system.[4,8]

Table 1. Selective oxidation of primary alcohols with air and the Cu(I)/TEMPO catalytic system and effect of irradiation with visible light.

Entry	Substrate	Product	Condtions	Reaction time [h]	Yield [%]
1	1		Irradiation	14	72
2			Without irradiation	29	70
3	2	3	Irradiation	20	69
4			Without irradiation	30	60
5	4	5	Irradiation	140	51
6			Without irradiation	200	30–40
7	6	7	Irradiation	140	52
8	8	9	Irradiation	140	50

used. Primary alcohols are selectively oxidized to aldehydes. The reactivity of secondary hydroxy functions is significantly lower. It has been reported that the reactivity of simple primary aliphatic alcohols is also reduced[4,8] although later, some aerobic oxidations of these alcohols have been described which have been performed with Cu/TEMPO systems.[10]

When applied to the oxidation of carbohydrate derivatives, we observed that this oxidation system was not efficient. Using stronger oxidation reagents, the primary hydroxy group was oxidized most frequently to a carboxylic function leading to uronates.[11] Only recently have the corresponding aldehydes been obtained by oxidation with the TEMPO/TCC system (TCC: trichloroisocyanuric acid).[12] We wondered whether simultaneous irradiation with visible light could improve the results obtained with air as oxidant. Recently, similar effects of irradiation have been reported for other catalytic oxidations.[13]

In order to test this hypothesis, we started with the oxidation of 3-phenylpropanol **1** (Table 1, entry 1). When irradiated with visible light, the reaction time was significantly reduced. With several examples, we then checked whether under these modified reaction conditions, the oxidation is selective for primary alcohols (Figure 1). Indeed, none of the secondary alcohols in Figure 1 were oxidized. When the oxidation of the protected galactose derivative **2** to the aldehyde **3** was performed with irradiation, the yield was im-
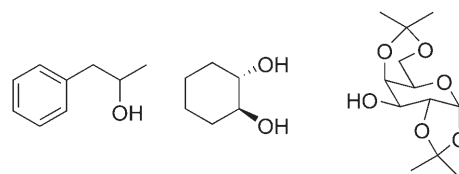
Figure 1. Secondary hydroxy functions were not oxidized under the discussed reaction conditions.

proved and the reaction time was reduced (Table 1, entries 3 and 4).

The reaction was then performed with the methyl glucoside **4** (entries 5 and 6). Once again, an improvement was observed when the transformation was performed under irradiation with visible light. No products resulting from the oxidation of secondary hydroxy functions have been detected. In this case, however, the lactol form **5** was isolated. For the case of corresponding galactose derivatives, the formation of lactol, hydrates and acetals has been previously described.[14] These structures proved to be more stable than the corresponding free aldehyde forms. This observation is in agreement with the fact that simple aldohexoses also prefer the lactol forms. Both constituents of the catalyst system are necessary. In the absence of TEMPO or CuCl, no reaction was observed. Under the same optimized reaction conditions, the benzyl glucoside **6** and the benzyl mannoside **8** were transformed into the corresponding lactols **7** and **9**
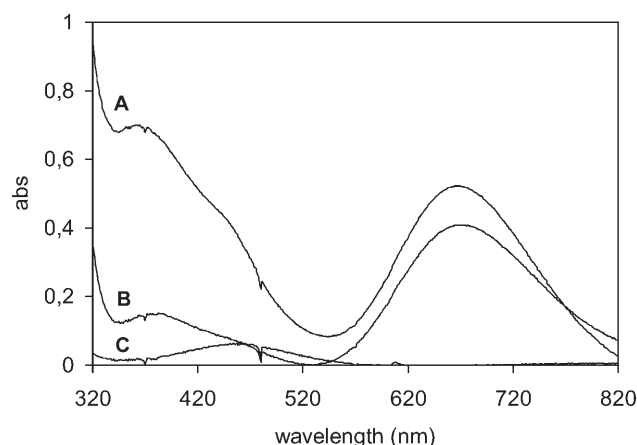
Figure 2. UV spectra obtained from solutions of TEMPO and Cu(I) acetate in acetonitrile. **A:** solution of TEMPO and Cu(I) acetate kept in the dark; **B:** solution of TEMPO and Cu(I) acetate irradiated with visible light; **C:** solution of TEMPO.

(entries 7 and 8). The products have been isolated and purified by flash chromatography using mixtures of CH_2Cl_2/MeOH containing 5% of triethylamine. When the purification was performed without the amine base, methyl half acetals have been isolated in low yields instead of the lactols.

In order to gain a first insight in the mechanism of the photo-promoted oxidation, and in analogy to previous experiments,[4] we prepared two solutions of Cu(I) acetate and TEMPO in acetonitrile possessing the same concentrations as the corresponding DMF solutions used for the transformations described in Table 1. One of them was kept in the dark, while the other was irradiated with visible light using the same conditions as for the transformation of the substrates. In the case of the irradiated sample, the intensity of the UV absorption at $\lambda = 362$ nm (Figure 2) ascribed to the Cu(II)-TEMPO intermediate[4] (Scheme 1) was significantly reduced with respect to the reference sample. This observation indicates that the transformation of this intermediate is photochemically accelerated, which may contribute to the higher efficiency under irradiation conditions. During this process, the concentration of Cu(II) ($\lambda = 666$ nm) does not significantly change with respect to the reference sample.

In view to further optimize the procedure and to prove its usefulness for organic synthesis, we decided to perform further ground state transformations with the crude product. It was previously reported that purification of such oxidation products of carbohydrates is difficult.[12] After concentration, the raw reaction mixture was subjected to reductive amination (Scheme 2). The overall yields of these two steps were increased to 76%. The resulting 6-aminopyranosides **10** and **11** were treated under hydrogenation conditions. In this way deprotection at the anomeric
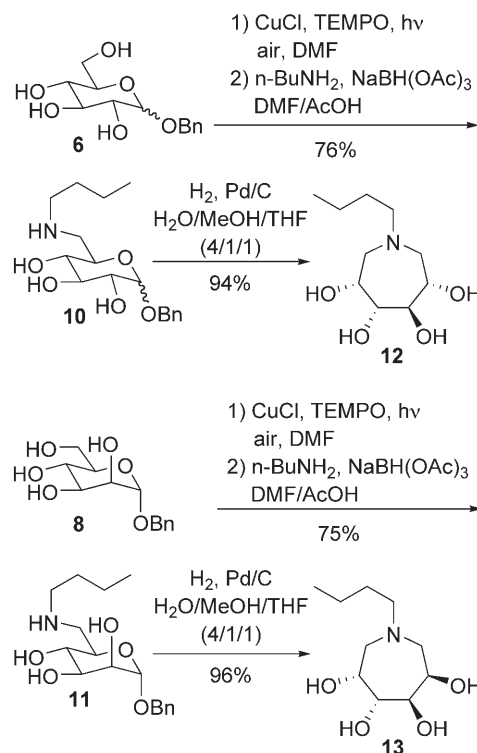
Scheme 2. Efficient transformation of benzyl glycosides into tetrahydroxyazepanes.

center and intramolecular reductive amination occurred. The resulting tetrahydroxyazepanes **12** and **13** have been obtained in high yields.

Attempts were made to perform debenzylation of the anomeric center, the first intermolecular and the second intramolecular reductive amination in one step using hydrogenation conditions. However, under these conditions, considerable amounts of products resulting from the addition of two butylamine molecules were observed. Tetrahydroxyazepanes belong to the family of azasugars possessing various biological activities such as the inhibition of glycosidases or glycosyltranferases.[15]

In conclusion, we have developed an efficient biomimetic oxidation method using the CuCl/TEMPO catalytic system and air as oxidant. The reactivity is enhanced when the reaction mixture was irradiated with visible light. Thus the activity of galactose oxidase was imitated. In contrast to the enzymatically catalyzed reaction, the presented method also enables the oxidation of hexoses of the D- or L-*erythro* series such as glucose or mannose derivatives. Only two additional steps led to tetrahydroxyazepane derivatives in high yields. At this stage, the oxidation should be considered as semi-catalytic since larger amounts (0.5 equivalents) of the catalytic system are necessary. Further investigations concerning the improvement of the catalytic process, the scope of the oxidation and mechanistic aspects in order to explain the enhanced

reactivity under light irradiation are currently underway.

Experimental Section

General Procedure for the Oxidation of Primary Alcohols

A stirred solution of the primary alcohol (1 or 2 mmol), CuCl (0.5 mol equivalents) and TEMPO (0.5 mol equivalents) in DMF (15 mL) was filled in a pyrex tube (length: 30 cm, diameter: 1 cm) and placed in a water bath in order to maintain the temperature at 25 °C. The reaction mixture was stirred and air was bubbled in while it was irradiated with a halogen lamp (500 W) at a distance of 1 m. After 140 h of irradiation, the solvent was evaporated and the residue chromatographed on silica gel (eluent: CH_2Cl_2/MeOH: 9/1).

3-Phenylpropionaldehyde: 0.136 g (1 mmol) of 3-phenylpropan-1-ol were transformed; yield: 0.096 g (72 %).

Compound 3:[16] 0.26 g (1 mmol) of compound **2** were transformed; yield: 0.18 g (69 %).

Compound 5: 0.388 g (2 mmol) of compound **4** were transformed; yield: 0.197 g (51 %).

Compound 7: 0.27 g (1 mmol) of compound **6** were transformed; yield: 0.14 g (52 %).

Compound 9: 0.20 g (0.74 mmol) of compound **8** were transformed; yield: 0.099 g (51 %).

Procedure for the Preparation of 10 and 11

Compound **6** (0.360 g, 1.33 mmol) or compound **8** (0.254 g, 0.94 mmol) was oxidized according to the general procedure. The reaction mixture was concentrated to about 2 mL. *n*-Butylamine (5 mL) and acetic acid (0.19 mL, 3.26 mmol) were added. The resulting mixture was stirred at 80 °C for 1 h and at room temperate for 72 h. The mixture was then concentrated and the residue was chromatographed on silica gel (eluent: CH_2Cl_2/MeOH: 9/1).

Compound 10: Yield: 0.328 g (76 %).
Compound 11: Yield: 0.228 g (75 %).

Procedure for the Preparation of 12 and 13

A mixture of compound **10** (0.238 g, 0.73 mmol) or compound **11** (0.200 g, 0.615 mmol), Pd/C (5 %, catalytic amounts), MeOH (1 mL), THF (1 mL) and H_2O (4 mL) was filled in an autoclave and kept under H_2 pressure (20 bar) at 80 °C. After 72 h, the mixture was filtered over celit and concentrated.

Compound 12: Yield: 0.150 g (95 %).
Compound 13: Yield: 0.129 g (96 %).

Supporting Information

Characterization of 3-phenylpropionaldehyde, compounds **3**, **5**, **7**, **9**, **10**, **11**, **12** and **13**.

References

[1] P. J. Kocienski, *Protecting Groups*, 3rd edn., Thieme Verlag, Stuttgart, **2005**.

[2] *Artificial Enzymes*, (Ed.: R. Breslow), Wiley-VCH, Weinheim, **2005**; H. Dugas, *Bioorganic Chemistry*, 3rd edn., Springer-Verlag, New York, **1996**; M. C. de La Torre, M. A. Sierra, *Angew. Chem. Int. Ed.* **2004**, *43*, 160–181.

[3] N. Ito, S. E. V. Phillips, C. Stevens, Z. B. Ogel, M. J. McPhersonn J. N. Keen, K. D. S. Yadav, P. F. Knowles, *Nature* **1991**, *350*, 87–90; J.-L. Pierre, *Chem. Soc. Rev.* **2000**, *29*, 251–257; P. Chaudhuri, M. Hess, K. Hildenbrand, E. Bill, T. Weyhermüller, K. Wieghardt *J. Am. Chem. Soc.* **1999**, *121*, 9599–9610; E. A. Lewis, W. B. Tolman, *Chem. Rev.* **2004**, *104*, 1047–1076; L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013–1045; A. Berkessel, M. Dousset, S. Bulat, K. Glaubitz, *Biol. Chem.* **2005**, *386*, 1035–1041.

[4] A. Dijksman, I. W. C. E. Arends, R. A. Sheldon, *Org. Biomol. Chem.* **2003**, *1*, 3232–3237.

[5] P. R. Andreana, T. Sanders, A. Janczuk, J. I. Warrick, P. G. Wang, *Tetrahedron Lett.* **2002**, *43*, 6525–6528.

[6] R. L. Root, J. R. Durrwachter, C.-H. Wong, *J. Am. Chem. Soc.* **1985**, *107*, 2997–2999;.

[7] M. F. Semmelhack, C. R. Schmid, D. A. Cortés, C. S. Chou, *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376.

[8] R. A. Sheldon, I. W. C. E. Arends, *J. Mol. Catal. A: Chem.* **2006**, *251*, 200–214.

[9] J. Muzart, *Tetrahedron* **2003**, *59*, 5789–5816; D. Lenoir, *Angew. Chem. Int. Ed.* **2006**, *45*, 3206–3210; B.-Z. Zhan, A. Thompson, *Tetrahedron* **2004**, *60*, 2917–2935; M. J. Schultz, M. S. Sigman, *Tetrahedron* **2006**, *62*, 8227–8241; T. Mallat, A. Baiker, *Chem. Rev.* **2004**, *104*, 3037–3058; I. E. Markó, P. R. Giles, M. Tsukazaki, S. M. Brown, C. J. Urch, in: *Transition Metals for Organic Synthesis*, Vol. 2, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp 350–360; *Modern Oxidation Methods*, (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, **2004**; R. Liu, C. Dong, X. Liang, X. Wang, X. Hu, *J. Org. Chem.* **2005**, *70*, 729–731; D. I. Enache, J. K. Edwards, P. Landon, B. Solsona-Espriu, A. F. Carley, A. A. Herzing, M. Watanabe, C. J. Kiely, D. W. Knight, G. J. Hutchings, *Science* **2006**, *311*, 362–365.

[10] I. A. Imtiaz, R. Gree, *Org. Lett.* **2002**, *4*, 1507–1509; G. Ragagnin, B. Betzemeier, S. Quici, P. Knochel, *Tetrahedron* **2002**, *58*, 3985–3991; P. Gamez, I. W. C. E. Arends, J. Reedijk, R. A. Sheldon, *Chem. Commun.* **2003**, 2414–2415; I. E. Markó, A. Gautier, R. Dumeunier, K. Doda, F. Philippart, S. M. Brown, C. J. Urch, *Angew. Chem. Int. Ed.* **2004**, *43*, 1588–1591.

[11] W. Adam, C. R. Saha-Möller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499–3548; P. L. Bragad, H. van Bekkum, A. C. Besemer, *Top. Catal.* **2004**, *27*, 49–66; Z. Györgydeák, J. Thiem, *Carbohydr. Res.* **1995**, *268*, 85–92; A. Megyes, E. Farkas, A. Lipták, V. Pozsgay, *Tetra-*

hedron **1997**, *53*, 4158–4178; A. Heeres, H. A. van Do-ren, K. F. Gotlieb, I. P. Bleeker, *Carbohydr. Res.* **1997**, *299*, 221–227; S. Trombotto, E. Violet-Courtens, L. Cottier, Y. Queneau, *Top. Catal.* **2004**, *27*, 31–37; K. Kloth, M. Brünjes, E. Kunst, T. Jörge, F. Gallier, A. Adibekian, A. Kirschning, *Adv. Synth. Catal.* **2005**, *347*, 1423–1434.

[12] M. Angelin, M. Hermansson, H. Dong, O. Ramström, *Eur. J. Org. Chem.* **2006**, 4323–4326.

[13] H. Egami, S. Onitsuka, T. Katsuki, *Tetrahedron Lett.* **2005**, *46*, 6049–6052; H. Shimizu, S. Onitsuka, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2005**, *127*, 5396–5413; G. Knör, *ChemBioChem.* **2001**, 593–596; K. Ohkubo, K. Suga, S. Fukuzumi, *Chem. Commun.* **2006**, 2018–2020; Y. Shiraishi, Y. Teshima, T. Hirai, *Chem. Commun.* **2005**, 4569–4571; S. Hirashima, A. Itoh, *Chem. Pharm. Bull.* **2006**, *54*, 1457–1458.

[14] A. Maradufu, A. S. Perlin, *Carbohydr. Res.* **1974**, *32*, 127–136; R. Schoevaart, T. Kieboom, *Carbohydr. Res.* **2001**, *334*, 1–6; R. Schoevaart, T. Kieboom, *Tetrahe-dron Lett.* **2002**, *43*, 3399–3400; V. Bonnet, R. Duval, C. Rabiller, *J. Mol. Catal. B: Enzym.* **2003**, *24–25*, 9–16.

[15] O. R. Martin, in: *Carbohydrate Mimics*, (Ed.: Y. Chap-leur), Wiley-VCH, Weinheim, **1998**, pp 259–282; J.-C. Depezay, in: *Carbohydrate Mimics*, (Ed.: Y. Chapleur), Wiley-VCH, Weinheim, **1998**, pp 307–326; V. H. Lille-lund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553; H. Paulsen, K. Todt, *Chem. Ber.* **1967**, *100*, 512–520; F. Moris-Varas, X.-H. Qian, C. H. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7645–7652; Y. Le Merrer, L. Poitout, J.-C. Depezay, I. Dosbaa, S. Geoff-roy, M.-J. Foglietti, *Bioorg. Med. Chem.* **1997**, *5*, 519–533; H. Li, C. Schütz, S. Favre, Y. Zhang, P. Vogel, P. Sinaÿ, Y. Blériot, *Org. Biomol. Chem.* **2006**, *4*, 1653–1662; L. Gireaud, L. Chaveriat, I. Stasik, A. Wadoua-chi, D. Beaupère, *Tetrahedron* **2006**, *62*, 7455–7458.

[16] K. Kloth, M. Brünjes, E. Kunst, T. Jöge, F. Gallier, A. Adibekian, A. Kirschning *Adv. Synth. Catal.* **2005**, *347*, 1423–1434.