COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Addition of malonyl radicals to glycals with C-1 acceptor groups: remarkable influence of the substituents on the product distribution†

Viktor Gyóllai,[a] Dirk Schanzenbach,[b] László Somsák*[a] and Torsten Linker*[b]

[a] *Department of Organic Chemistry, University of Debrecen, PO Box 20, H-4010 Debrecen, Hungary. E-mail: somsak@tigris.klte.hu; Fax: +36-52-453-836; Tel: +36-52-512-900/2348*

[b] *Department of Chemistry, University of Potsdam, Karl-Liebknecht-Str. 24-25, D-14476 Golm, Germany. E-mail: linker@chem.uni-potsdam.de; Fax: +49-331-977-5056; Tel: +49-331-977-5212*

Received (in Cambridge, UK) 22nd March 2002, Accepted 9th May 2002
First published as an Advance Article on the web 17th May 2002

The ceric(IV) ammonium nitrate (CAN)-mediated radical addition of dimethyl malonate to glycals 1 affords methyl glycosides 2 and ortho esters 3 as main products; the product distribution strongly depends on the substitution pattern at the 1-position, which can be rationalized in terms of the oxidation potentials of the intermediary anomeric radicals.

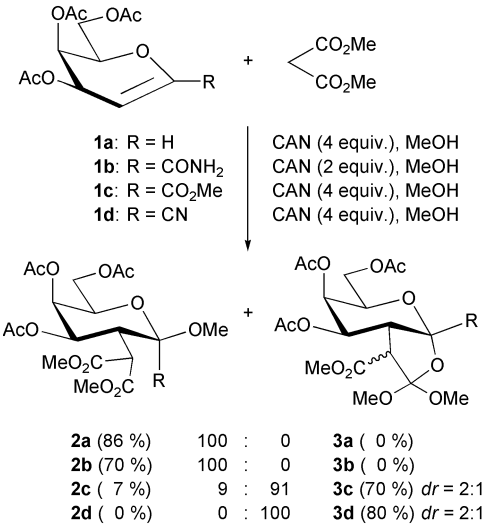
Glycals are versatile building blocks for carbohydrate chemistry and are readily available on a multigram scale.[1] During the last years we became interested in 1-acceptor substituted glycals **1b**–**d**, which can be synthesized from glycosyl cyanides in only a few steps.[2] Furthermore, we established the transformation of such compounds into various C-1-functionalized carbohydrates of biological interest.[3] However, the addition of radicals to the double bond of 1-acceptor substituted glycals was hitherto unknown. Herein we describe our preliminary results of such reactions, which exhibit a remarkable influence of the substituents R on the product distribution.

Transition-metal-mediated radical reactions have become a versatile tool for C–C-bond formations.[4] Very recently we applied this methodology for the first time in carbohydrate chemistry.[5] Dimethyl malonate in combination with ceric(IV) ammonium nitrate (CAN) was the method of choice to generate electrophilic malonyl radicals. Thus, we investigated the addition of such radicals to the acceptor-substituted galactals **1b**–**d**,‡ and compared it with the reaction of the unsubstituted derivative **1a** (Scheme 1).

It was of special interest to determine whether the radicals still attack the acceptor-substituted double bond. Indeed, the reactions proceed smoothly with moderate to good yields and excellent regioselectivity, to afford exclusively the 2-*C*-branched carbohydrates **2** and **3**. This result can be rationalized by the interaction of the SOMO of the electrophilic radical with the HOMO of the double bond.[6] Furthermore, due to the steric shielding of the *pseudo* axial *O*-acetyl-group, the radicals attack the double bond selectively from the α-face. Thus, *galacto*-isomers are formed as sole products, which is in accordance with our previous studies.[5]

Interestingly, the substituents R at the 1-position exhibit a remarkable influence on the product distribution. For the unsubstituted galactal **1a** and the carboxamide **1b** only the methyl glycosides **2a** and **2b** were obtained, whereas the nitrile **1d** affords exclusively the ortho esters **3d**. On the other hand, the ester **1c** gives a mixture of both products **2c** and **3c** (Scheme 1). This dramatic influence of the substituents R on the product distribution can only be rationalized by a change in the reaction mechanism (Scheme 2) and is of interest for transition-metal-mediated radical reactions.

In the first step, the intermediary radicals **4** are formed after the addition of the malonyl radicals to the double bond. For the unsubstituted galactal **1a** and the carboxamide **1b** this radical is obviously oxidized to the cation **5** by the strong oxidant ceric(IV) ammonium nitrate (CAN) (E^0 = +1.37 V *vs*. SCE)

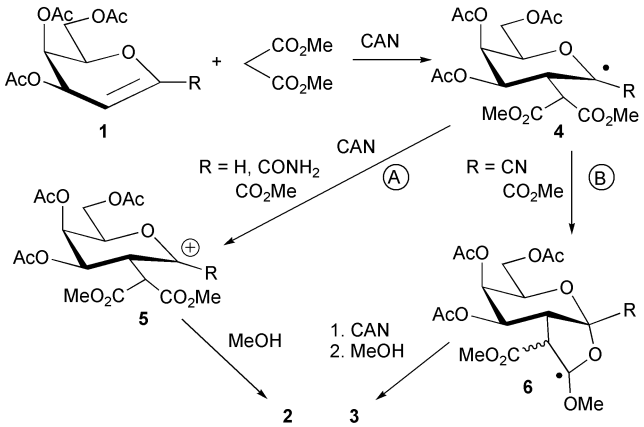


Scheme 1

(pathway A). Finally, trapping by the solvent methanol affords the products **2a** and **2b**. The exclusive formation of the β-methyl glycosides can be explained by a neighboring group participation of the adjacent malonyl substituent, and is in accordance with our previous studies.[5]

On the other hand, due to the nitrile substituent the oxidation potential of the intermediary radical **4d** is remarkably increased, and the oxidation by CAN is suppressed. Furthermore, the captodative substitution pattern[7] at the anomeric center stabilizes the radical **4d**, and an intramolecular attack of the carbonyl group can compete (pathway B). Due to the two alkoxy substituents, the resulting radical **6** is now easily oxidized by ceric(IV) ammonium nitrate (CAN) to afford the ortho esters **3d** after trapping with the solvent methanol.

Finally, for the ester **1c** both products, the methyl glycoside **2c** and the ortho esters **3c** were obtained. Obviously, the



Scheme 2

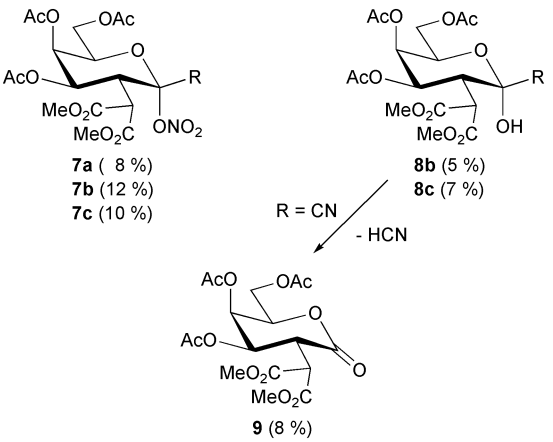
† Electronic supplementary information (ESI) available: NMR data for C-2 branched sugar derivatives. See http://www.rsc.org/suppdata/cc/b2/b202898k/

DOI: 10.1039/b202898k

oxidation potential of the intermediary radical **4c** is in between the values for **4b** and **4d** so that both pathways A and B can compete with each other. Thus, the product distribution directly correlates with the oxidation potential of the anomeric radicals. From the mechanistic point of view, the addition of radicals to substituted glycals provides qualitative oxidation potentials of captodative substituted radicals, which is an interesting alternative to quantitative measurements by photomodulated voltammetry.[8]

In addition to the main products **2** and **3**, minor side products were formed in all reactions (Scheme 3). Thus, the nitrates **7** and hemiacetals **8** were found, which may result from the trapping of the intermediates **4** and **5** by CAN through ligand transfer,[5] traces of oxygen, or traces of water, respectively. Interestingly, the hemiacetal **8d** directly affords the lactone **9** under the reaction conditions, due to its cyanohydrin structure.

In conclusion, the addition of radicals to glycals exhibits a strong influence of the substituents at the 1-position on the product distribution. The C-1 carboxamido- and unsubstituted glycals afford exclusively methyl glycosides whereas nitrile and ester groups yield ortho esters as the predominant products. Such a strong influence of substituents on the reaction pathway of radical reactions was hitherto unknown and could be applied for further synthetic applications. From the mechanistic point of view, the product distribution directly reflects the oxidation potentials of the intermediary anomeric radicals, and provides information on the stability of captodative substituted radicals. Further studies will focus on such mechanistic details and expand the scope of radical additions to glycals for synthetic applications.



Scheme 3

This paper is dedicated to Professor Waldemar Adam on the occasion of his 65th birthday. The work was supported by a scientific technologic collaboration (WTZ) between Germany and Hungary (D-12/98.), the Hungarian Scientific Research Fund (OTKA T32124) and the Deutsche Forschungsgemeinschaft (SFB 347, Li 556/7-1).

Notes and references

‡ *Typical procedure*. A solution of CAN (2–4 equiv., Scheme 1) in methanol (20–40 ml) was added to a solution of the glycal (2.0 mmol) and dimethyl malonate (2.64 g, 20 mmol) in methanol (5 ml) at 0 °C. After TLC showed complete conversion (2–5 h) an ice-cold diluted solution of sodium thiosulfate (100 ml) was added, and the mixture was extracted with dichloromethane (4 × 40 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the excess of dimethyl malonate was removed at 0.01 mbar. The residue was purified by column chromatography (hexane–ethyl acetate) and all products were characterized by NMR and X-ray measurements.

1 M. Bols, *Carbohydrate Building Blocks*, Wiley, New York, 1996, pp. 49–53; L. Somsák and I. Németh, *J. Carbohydr. Chem.*, 1993, **12**, 679; L. Somsák, *Chem. Rev.*, 2001, **101**, 81.
2 L. Somsák, I. Bajza and G. Batta, *Liebigs Ann. Chem.*, 1990, 1265.
3 A. Banaszek, *Tetrahedron*, 1995, **51**, 4231; L. Somsák, *Carbohydr. Res.*, 1996, **286**, 167; L. Kiss and L. Somsák, *Carbohydr. Res.*, 1996, **291**, 43.
4 Reviews: P. I. Dalko, *Tetrahedron*, 1995, **51**, 7579; B. B. Snider, *Chem. Rev.*, 1996, **96**, 339; G. G. Melikyan, *Org. React.*, 1996, **49**, 427; T. Linker, in *Radicals in Organic Synthesis*, Ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, Volume 1, pp. 219–228.
5 T. Linker, K. Hartmann, T. Sommermann, D. Scheutzow and E. Ruckdeschel, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1730; T. Linker, T. Sommermann and F. Kahlenberg, *J. Am. Chem. Soc.*, 1997, **119**, 9377.
6 B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 753; B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 553.
7 R. Sustmann and H.-G. Korth, *Adv. Phys. Org. Chem.*, 1990, **26**, 131; F. M. Welle, S. P. Verevkin, H.-D. Beckhaus and C. Rüchardt, *Liebigs Ann. Chem.*, 1997, 155; F. M. Welle, H.-D. Beckhaus and C. Rüchardt, *J. Org. Chem.*, 1997, **62**, 552; H.-G. Korth, J.-P. Praly, L. Somsák and R. Sustmann, *Chem. Ber.*, 1990, **123**, 1155.
8 D. D. M. Wayner and A. Houmam, *Acta Chem. Scand.*, 1998, **52**, 377; T. Lund, D. D. M. Wayner, M. Jonsson, A. G. Larsen and K. Daasbjerg, *J. Am. Chem. Soc.*, 2001, **123**, 12590.