DOI: 10.1002/ejoc.201000397

Synthesis of Sugar-Fused Isoxazoline *N*-Oxides from 2-Nitroglycals

Qingju Zhang,[a,b] Jiansong Sun,*[a] Fuyi Zhang,[b] and Biao Yu*[a]

Keywords: Synthetic methods / 2-Nitroglycal / Isoxazoline *N*-oxide / 1,3-Dipolar cycloaddition

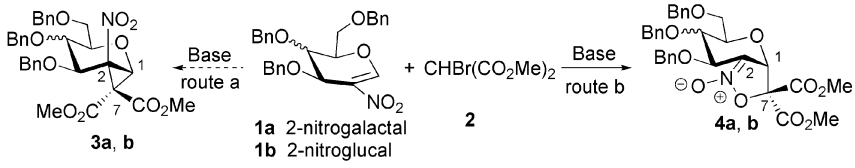
A new type of sugar-fused isoxazoline *N*-oxides was synthesized from 2-nitroglycals via [1+4] condensation with bromomalonate under the action of DBU. In addition, 1,3-dipolar cycloaddition of these isoxazoline *N*-oxides with alkene and alkyne dipolarophiles were also investigated.

Introduction

2-Nitroglucal and -galactal derivatives, firstly introduced by Lemieux et al. in 1968,[1] have been employed in the synthesis of 2-amino-2-deoxyglycosides by Schmidt and coworkers, in which the thermodynamically favored α-glycosidic products were predominantly formed in the presence of a strong inorganic base, such as KO*t*Bu.[2] Recently, we found that under the action of a weak Lewis base, i.e., DMAP [4-(dimethylamino)pyridine] or PPY [4-(1-pyrrolidino)pyridine], the addition of a nucleophile onto 2-nitroglycals led to β-glycosidic products.[3] Considering that nitro olefins are versatile reagents in organic synthesis[4] and the nitro olefin unit incorporated in a sugar scalffold may bring about new chemical properties, we continued our program to investigate new reactions of 2-nitroglycals.

Results and Discussion

It is well documented in the literature that the addition of chloro- or bromomalonate to α,β-unsaturated nitroalkenes can provide nitrocyclopropanes in good yields and excellent enantioselectivity.[5] We conjectured that 2-nitroglycals might also adopt a similar reaction pathway to afford 1,2-cyclopropanated sugar **3a** (Scheme 1, route a), which could be used as glycosyl donor to couple with nucleophiles.[6] Thus, 2-nitrogalactal **1a** was treated with bromomalonate **2** in the presence of DBU (1.2 equiv. based on 2-nitroglycal) in CH_2Cl_2 at room temperature. The reaction proceeded rapidly, and the putative adduct **3a** was obtained in excellent yield (91%). However, after scrutinizing carefully the ^1H and ^{13}C NMR spectra, we found that there were evident discrepancies between the spectra and those of the proposed structure. In



Scheme 1. Condensation of 2-nitroglycals and bromomalonate.

[a] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
Shanghai 200032, China
Fax: +86-21-64166128
E-mail: jssun@mail.sioc.ac.cn
byu@mail.sioc.ac.cn
[b] Chemistry Department, The Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Zhengzhou University,
Zhengzhou 450052, China
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000397.

the ^{13}C NMR spectrum, besides signals from the two ester carbonyl carbon atoms, there were another two signals from quaternary carbon atoms at δ = 109.56 and 84.21 ppm; these two signals should be assigned to C-2 and C-7 in compound **3a**; nevertheless, the chemical shift values of these two carbon atoms were in sharp difference to those of carbon atoms in known compounds with similar chemical environments. Regarding C-2 incorporated in a cyclopropane and substituted with NO_2, its chemical shift should be $\delta \approx 60$ ppm,[5b,7] and the signal of C-7 should appear at $\delta \approx 50$ ppm.[5b]

An alternative reaction pathway for the condensation of 2-nitroglycals and bromomalonate is route b, which would lead to isoxazoline *N*-oxide derivative **4a**. In fact, the structure of **4a** agrees with all the spectra quite well. The ^{13}C signals at δ = 109.6 and 84.2 ppm were therefore well assignable to C-2 and C-7.[8] A characteristic ^{1}H NMR singlet at δ = 5.78 ppm was assigned to the anomeric proton; HMBC correlations between this proton and the two ester carbonyl carbon atoms were observed. The configuration of the anomeric proton was determined to be β based on the strong NOE correlation with one proton on C-6 (Figure 1).

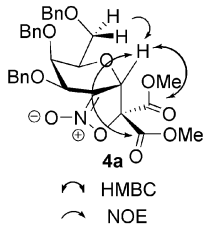
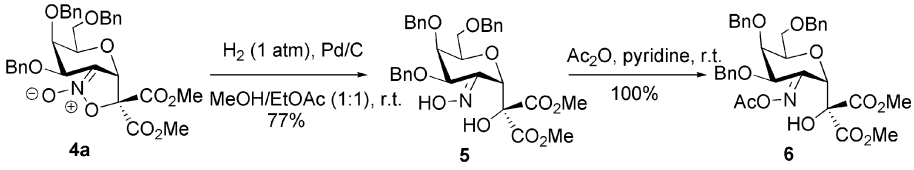


Figure 1. Key correlations observed by 2D NMR spectroscopy.

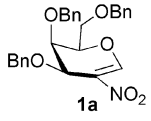
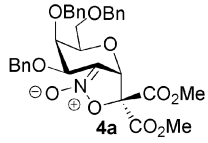
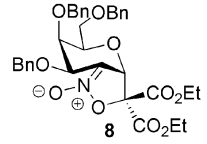
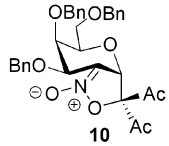
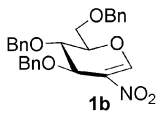
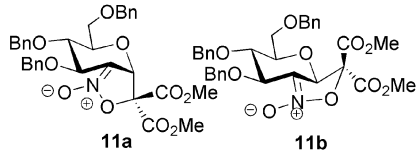
To further corroborate the proposed structure of **4a**, chemical derivatizations were undertaken subsequently (Scheme 2). It is well documented that isoxazoline *N*-oxides can be easily reduced to ketone oxime derivatives by hydrogenolysis.[9] Thus, compound **4a** was subjected to hydrogenolysis (H_2, 1 atm) in the presence of Pd/C. A new compound, which was assigned to ketone oxime **5**, was obtained in good yield (77%), while all the benzyl groups remained intact. The structure of **5** correlated well with the ^{1}H and ^{13}C NMR spectra; to this end, two deuterable proton signals corresponding to ketone oxime proton and hydroxy proton were found at δ = 8.31 and 4.10 ppm, and the nascent ketone oxime carbon signal appeared at δ = 150.1 ppm. Subsequent acetylation of **5** (Ac_2O, pyridine, room temp.) led to *N*-OAc derivative **6** quantitatively. Incorporation of the Ac group on the ketone oxime resulted in a downfield shift of the ketone oxime carbonyl carbon signal from δ = 150.1 ppm to δ = 158.4 ppm and disappearance of the proton signal at δ = 8.31 ppm.

Isoxazoline *N*-oxide derivatives are frequently used as intermediates in the synthesis of natural products and biologically active compounds.[10] The preparation methods of



Scheme 2. Derivatization of compound **4a**.

Table 1. [4+1] cycloaddition of 2-nitroglycals and 2-bromo-1,3-dicarbonyl compounds.

Entry	2-Nitroglycal	2-Bromo-1,3-dicarbonyl compounds	Products	Yield[a]
1	 **1a**	$CHBr(CO_2Me)_2$ **2**	 **4a**	91%
2	**1a**	$CHBr(CO_2Et)_2$ **7**	 **8**	98%
3	**1a**	 **9**	 **10**	54%[b]
4	 **1b**	**2**	 **11a** **11b**	61% (3.6:1)

[a] Isolated yields. [b] 2 equiv. of **9** and DBU were used.

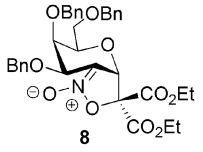
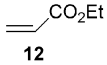
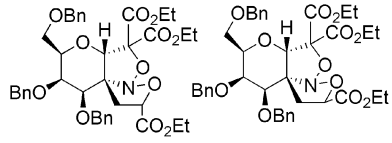
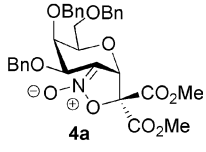
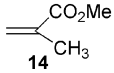
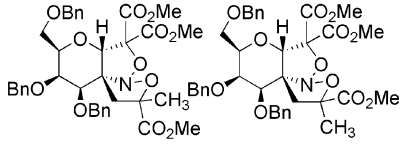
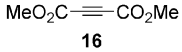
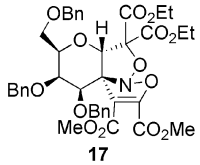
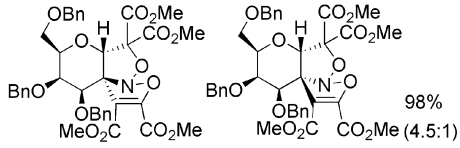
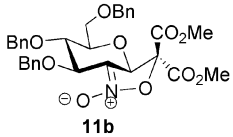
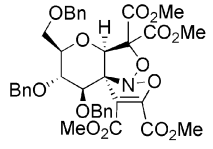
isoxazoline *N*-oxides can be divided into three categories: (1) intramolecuar *O*-alkylation of aliphatic nitro compounds;[11] (2) [3+2] cycloaddition;[12] (3) [4+1] cycloaddition.[13] Nevertheless, compared to the former two methods, the [4+1] cycloaddition strategy was less explored and reported only once, in which a Michael addition was involved, and the Michael donor was attached to cinconidine to secure a high enantioselectivity.[13] The present synthesis of **4a** belongs to this [4+1] strategy as well, but the high stereoselectivity was realized through the chiral Michael acceptor.

Then the scope of this reaction was briefly examined (Table 1). Under the above-mentioned conditions (1.2 equiv. of bromomalonate, 1.2 equiv. of DBU, CH_2Cl_2, room temp.), the condensation of 2-nitroglycal **1a** with ethyl bromomalonate **7** gave isoxazoline *N*-oxide **8** in excellent yield (98%), and only the α-isomer was obtained (Table 1, Entry 2). With 3-bromo-2,4-pentanedione **9** as the Michael donor, the desired product was obtained in 54% yield. Nevertheless, the stereoselectivity was maintained (Entry 3). The reaction of 2-nitroglucal **1b** with **2** also proceeded along the [4+1] pathway to yield **11**; however, inferior yields and stereoselectivity (**11a**/**11b** = 3.6:1) were registered because of the lower reactivity of **1b**. These results were in accordance with our previous finding on the nucleophlic addition to 2-nitroglucal.[3]

With these sugar-fused isoxazoline *N*-oxides in hand, we tested their synthetic utility in the 1,3-dipolar cycloaddition to form nitroso acetals with three fused rings. Nitronates, both in cyclic and acyclic form, have been proved to be versatile 1,3-dipoles that undergo reactions with neutral, electron-rich or -poor dipolarophiles.[4b,9] In addition, the regiochemical course of the dipolarophile approach is such that the carbon atom bearing the substituent always becomes attached to the oxygen atom of the dipole.[4b]

Indeed, when isoxazoline *N*-oxide **8** was treated with ethyl acrylate **12** (as co-solvent with dichloroethane in a 1:1 ratio) at room temperature, two diastereoisomers **13a** and **13b** were obtained in good yield (57%, **13a**/**13b** = 1.2:1) (Table 2, Entry 1), indicating that **12** approached **8** with a high facial selectivity (from the β-face exclusively) and a low *endo*/*exo* (*exo* product **13a** was weakly favored) dis-

Table 2. [3+2] cycloaddition of isoxazoline *N*-oxides with dipolarophiles.

Entry	Isoxazoline *N*-oxides	Dipolarophiles	Products	Yield[a]
1	 **8**	 **12**	 **13a** **13b**	57% (1.2:1)
2	 **4a**	 **14**	 **15a** **15b**	88% (1.8:1)
3	**8**	 **16**	 **17**	91%
4	**4a**	**16**	 **18a** **18b**	98% (4.5:1)
5	 **11b**	**16**	 **19**	78%

[a] Isolated yields.

crimination manner. Similar results were obtained when **4a** was treated with methyl methacrylate **14**, but the yield and *exo* selectivity were enhanced (88%, **15a/15b** = 1.8:1) (Table 2, Entry 2). Next, dimethyl acetylenedicarboxylate (**16**) was examined as dipolarophile. Notably, **8** reacted with **16** facial-selectively to form **17** in an excellent 91% yield (Entry 3). Although the facial discrimination decreased when **16** reacted with **4a** (**18a/18b** = 4.5:1), the yield was still excellent (98%, Entry 4). Glucosylisoxazoline *N*-oxide **11b** was also a good substrate for the cycloaddition with **16**; a good yield (78%) and an excellent facial selectivity were obtained (Entry 5). It is worthy to note that the facial discrimination of olefins **12/14** and acetylene **16** (compare Entries 1, 2 with Entries 3, 4, 5) is opposite. In addition, to the best our knowledge, this is the first report that an alkyne is used as dipolarophile in the 1,3-dipolar cycloaddition with isoxazoline *N*-oxides. All these compounds were characterized spectroscopically. X-ray diffraction analysis of a single crystal of **19**[14] further confirmed the proposed structure (Figure 2).

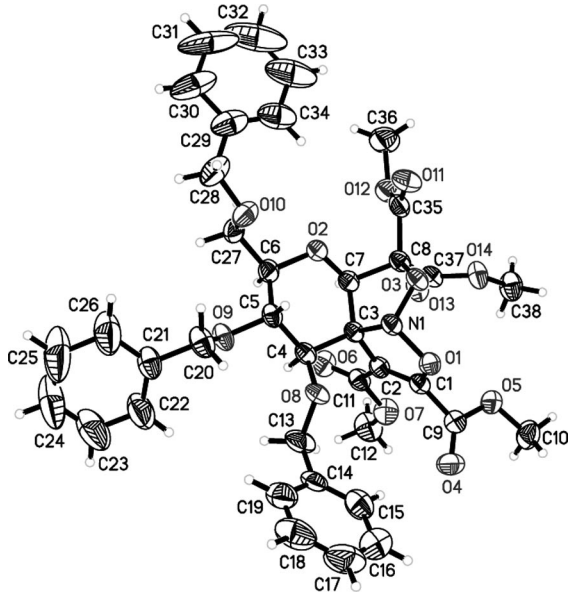


Figure 2. ORTEP drawing of compound **19**.

Conclusions

A new type of sugar-fused isoxazoline *N*-oxides was synthesized from 2-nitroglycals by [4+1] condensation with bromomalonate in the presence of DBU. 1,3-Dipolar cycloaddition of these isoxazoline *N*-oxides with alkenes and alkyne dipolarophiles led to nitroso acetals with three fused rings in good yields.

Supporting Information (see footnote on the first page of this article): Experimental details and reproductions of the NMR spectra for all new compounds and X-ray diffraction data for compound **19**.

Acknowledgments

This work was financially supported by the National Basic Research Program of China (2010CB833202) and the National Natural Science Foundation of China (20932009 and 20902097).

[1] R. U. Lemieux, T. L. Nagabhusha, I. K. O'Neil, *Can. J. Chem.* **1968**, *46*, 413–418.
[2] a) B. G. Reddy, R. R. Schmidt, *Nat. Protoc.* **2008**, *3*, 114–121; b) R. R. Schmidt, Y. D. Vankar, *Acc. Chem. Res.* **2008**, *41*, 1059–1073.
[3] W. Xue, J. Sun, B. Yu, *J. Org. Chem.* **2009**, *74*, 5079–5082.
[4] a) A. G. M. Barrett, G. G. Graboski, *Chem. Rev.* **1986**, *86*, 751–762; b) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137–165.
[5] a) S. H. McCooey, T. McCabe, S. J. Connon, *J. Org. Chem.* **2006**, *71*, 7494–7497; b) Y. Xuan, S. Nie, L. Dong, J. Zhang, M. Yan, *Org. Lett.* **2009**, *11*, 1583–1586.
[6] H. Shao, S. Ekthawatchai, C. Chen, S. Wu, W. Zou, *J. Org. Chem.* **2005**, *70*, 4726–4734 and references cited therein.
[7] V. Bagutski, A. de Meijere, *Adv. Synth. Catal.* **2007**, *349*, 1247–1255.
[8] E. Marotta, L. M. Micheloni, N. Scardovi, P. Righi, *Org. Lett.* **2001**, *3*, 727–729.
[9] *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis* (Ed.: H. Feuer), Wiely, Hoboken, **2008**.
[10] a) P. Righi, E. Marotta, A. Landuzzi, G. Rosini, *J. Am. Chem. Soc.* **1996**, *118*, 9446–9447; b) M. Frederickson, *Tetrahedron* **1997**, *53*, 403–425; c) B. M. Trost, L. S. Chupak, T. Lübbers, *J. Am. Chem. Soc.* **1998**, *120*, 1732–1740.
[11] a) M. V. Gil, E. Roman, J. A. Serrano, *Tetrahedron Lett.* **2000**, *41*, 3221–3224; b) N. Scardovi, A. Casalini, F. Peri, P. Righi, *Org. Lett.* **2002**, *4*, 965–968; c) P. M. Khan, R. Wu, K. S. Bisht, *Tetrahedron* **2007**, *63*, 1116–1126.
[12] a) I. E. Chlenov, M. V. Kashutina, S. L. Ioffe, S. S. Novikov, V. A. Tartakovsky, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Trans.)* **1969**, *18*, 1948; b) R. A. Kunetsky, A. D. Dilman, S. L. Loffe, M. I. Struchkova, Y. A. Strelenko, V. A. Tartakovsky, *Org. Lett.* **2003**, *5*, 4907–4909; c) H. Duang, X. Sun, W. Liao, J. L. Petersen, X. Shi, *Org. Lett.* **2008**, *10*, 4113–4116.
[13] C. Zhu, X. Deng, X. Sun, J. Zhang, Y. Tang, *Chem. Commun.* **2008**, 738–740.
[14] CCDC-773360 (for **19**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: March 24, 2010
Published Online: May 21, 2010

