The 1,3-Dipolar Cycloaddition Reaction of 7,14-Dioxa-1-azadispiro[4.2.5.2]pentadec-1-ene 1-Oxide Derivatives with *N*-Phenylmaleimide. An Attempt to Synthesize Azasugar Analogues of *Showdomycine*

J. Chem. Research (S), 1998, 298–299
J. Chem. Research (M), 1998, 1356–1365

Mariola Koszytkowska-Stawińska and Wojciech Sas*

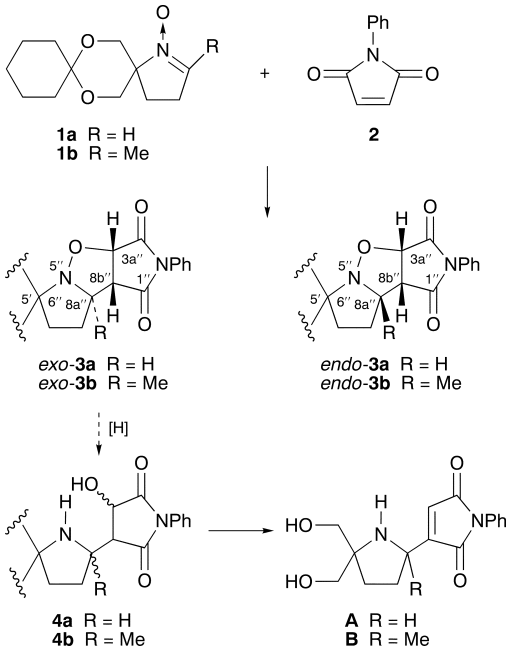
Faculty of Chemistry, Warsaw University of Technology, ul. Noakowskiego 3, 00-664 Warszawa, Poland

7,14-Dioxa-1-azadispiro[4.2.5.2]pentadec-1-ene 1-oxide derivatives (**1**) undergo 1,3-dipolar cycloaddition reaction with *N*-phenylmaleimide (**2**) giving the corresponding isoxazolidines (**3**); attempts to convert **3** into the showdomycine azasugar analogues **A** and **B** failed.

The 1,3-dipolar cycloaddition reaction of nitrones to alkenes is widely used for the synthesis of various nitrogen-containing organic compounds *via* preparation of intermediate isoxazolidine derivatives followed by their conversion into required products.[1,2] We envisaged that this approach might be used to prepare azasugar analogues[3] of the popular C-nucleoside *showdomycine* [3-(β-D-ribofuranosyl)-1*H*-pyrrole-2,5-dione], in which the maleimide residue played the role of the base. To examine this concept we set out to synthesize compounds **A** and **B**, which might be considered as 2′,3′-dideoxy branched-chain azasugar derivatives of *showdomycine*, from the title 1-pyrroline 1-oxide derivatives **1**[4] and inexpensive *N*-phenylmaleimide, **2**. Our synthetic plan assumed the preparation of the isoxazolidine derivatives **3**, one isomer if possible, followed by reductive opening the isoxazolidine ring, dehydration of the intermediate **4** and final deprotection of the hydroxy groups (Scheme 1).

Both nitrones **1a** and **1b** reacted with *N*-phenylmaleimide **2** readily, although **1b** did so with more difficulty than **1a**, giving the corresponding isoxazolidines **3a** or **3b** with yields depending upon the reaction conditions (Table 1). When the reaction of **1a** was carried out at or below 70 °C both the *endo* and *exo* isomers were formed (Table 1, entries 1–3). However, at 110 °C this reaction afforded only the *exo* isomer (Table 1, entries 4–6). The ketonitrone **1b** yielded a single isomer only under solvent-less conditions (Table 1, entry 12). In each case the minor isomer was isolated by column chromatography from the corresponding reaction mixture obtained at 70 °C.

The structures of compounds **3** were assigned by their NMR spectra. By analogy to literature data[5] we ascribed an *exo* structure to the major isomer **3a**, which shows a coupling constant between H-8a″ and H-8b″ of $^3J_{8a''-8b''} \approx 0$. For the minor product, *endo*-**3a**, the value of $^3J_{8a''-8b''}$ could not be measured owing to overlap of the multiplets of the protons H-8a″ and H-8b″. The structural assignment of the isoxazolidines **3b** was made on the basis of both the ^{1}H and ^{13}C (DEPT) chemical shifts of the methyl group. Thus we assigned the *exo* configuration to the major isomer, *exo*-**3b** having its methyl resonance at 1.32 ppm, and *endo*-**3b** to the minor isomer, which shows the signal of this group at 1.56 ppm. In the *exo* structure the methyl group is *cis* to the imide moiety and is shielded by the C-1″ carbonyl group; therefore, this methyl group appears at higher field than that of *endo* isomer. The same is also valid for ^{13}C signals; *exo*-**3b** and *endo*-**3b** show ^{13}C signals of the methyl group at 22.93 and 28.38 ppm, respectively. A similar dependence was observed for *exo*- and *endo*-isoxazolidines obtained from 2-methyl-1-pyrroline 1-oxide and dimethyl maleate.[6]



Scheme 1

The stereochemistry of the cycloaddition of **1a** to **2** is very similar to the stereochemistry of the reaction of **2** with 5,5-dimethyl-1-pyrroline 1-oxide.[5] Thus the *endo*-transition state (*endo*-TS) as well as the final cycloadduct *endo*-**3a** are much less favoured (owing to steric destabilization) than the corresponding *exo* species that results in the formation of *exo*-**3a** as the major isomer under kinetic control (Table 1, entries 1–3), and under thermodynamic control *endo*-**3a** could not be detected by ^{1}H NMR at all (Table 1, entries 4 and 5). Based on literature data on the 1,3-dipolar cycloaddition reaction of 2-mono-[6] and 2,5-di-substituted derivatives of 1-pyrroline 1-oxide[7] we anticipated that the *exo*/*endo* ratio for **3b** would be lower than that for **3a**. Indeed this was observed under both kinetic (Table 1, entries 7–9) and thermodynamic conditions (Table 1, entries 10 and 11). The kinetic *exo*-**3b**/*endo*-**3b** ratio is the result of two contrary effects: destabilization of the *exo*-TS by steric interaction of the 2-methyl group with the approaching dipolarophile[6] and destabilization of the *endo*-TS by steric repulsion between the substituent at position 5 of the nitrone[5,6] and the alkene. The former effect causes the kinetic *exo*-**3b**/*endo*-**3b** ratio to be lower than the *exo*-**3a**/*endo*-**3a** ratio. The latter effect is responsible for the formation of *exo*-**3b** as the major isomer. In contrast the reaction of 2-mono- and 2,5-di-substituted derivatives of 1-pyrroline 1-oxide with alkenes gives the *exo* derivative

*To receive any correspondence (*e-mail:* sas@ch.pw.edu.pl).

Table 1 Conditions, yield and *exo*/*endo* ratio for the reaction of **1** with **2**

Entry	R	Solvent	Temp. (T/°C)	Time (t/h)	Yield (%)[a]	*exo*/*endo*[a]
1	H	Toluene	Room	120	74	84:16
2		Benzene	70	5	74	86:14
3		Neat	70	5	86	87:13
4		Toluene	110	1	95	≥95[b]
5		Toluene	110	5	95	≥95[b]
6		Neat	110	1	95	≥95[b]
7	Me	Toluene	Room	288	59	57:43
8		Benzene	70	5	70	64:36
9		Neat	70	5	80	68:32
10		Toluene	110	1	50	61:39
11		Toluene	110	5	60	63:37
12		Neat	110	1	86	≥95[b]

[a]The yield and *exo*/*endo* ratio were calculated from ^{1}H NMR spectra. [b]The *endo* isomer was not detected by ^{1}H NMR spectra.

as the minor product.[6,7] Similar considerations may be applied to the thermodynamic ratio; steric hindrances of the 2-methyl group destabilizes, mainly, the *exo*-**3b** isomer, causing the energy difference between *exo* and *endo* isomers to be lower for **3b** than for **3a**, and consequently *endo*-**3b** is also formed in solvents under thermodynamic conditions (Table 1, entries 10 and 11).

However, when the reaction of **1b** with **2** was conducted in the absence of solvent at 110 °C *exo*-**3b** was the sole product (Table 1, entry 12). In light of the results presented in Table 1 this outcome might be explained as follows: at 110 °C both reagents **1b** and **2** and both products *exo*-**3b** and *endo*-**3b** are in equilibrium in the liquid state, from which the more stable *exo* isomer crystallizes, shifting the equilibrium toward *exo*-**3b**. At 70 °C under solvent-less conditions the cycloreversion reacion is slow and both cycloadducts crystallize as they are formed (Table 1, entry 9). To support this rationalization additional experiments were performed. Heating of the 64:36 mixture of *exo*-**3b** and *endo*-**3b** at 110 °C without solvent for 1 h raised the *exo*/*endo* ratio to 85/15 despite the fact that at this temperature only a small part of the sample melted. This means that only a fraction of the *endo*-**3b** underwent cycloreversion and then conversion into *exo*-**3b**. Therefore, the *exo*/*endo* ratio was smaller than that obtained from the reaction of **1b** and **2** under the same conditions (Table 1, entry 9). *Exo*-**3b** was stable at 80 °C (this temperature was used since some reagents for reductive opening of the isoxazolidine ring act at *ca.* 80 °C, *e.g.* molybdenum hexacarbonyl reacts in a refluxing mixture of acetonitrile–water[8]) and after 5 h heating in toluene the cycloreversion reaction was not evident from ^{1}H NMR spectra. However, traces of the **1b** and **2**, detected by TLC, indicated that the cycloreversion had commenced. The cycloreversion was rapid at 110 °C (toluene) and after 0.5 h 42% of *exo*-**3b** was transformed into **1b** and **2**, and also *ca.* 7% of the *endo* isomer appeared. Maintaining *exo*-**3b** at this temperature for 5 h gave a mixture of *exo*/*endo* in the ratio 65:35. *Endo*-**3b** was less stable than the *exo* isomer and at 80 °C in toluene 68% of it underwent cycloreversion after 5 h.

In contrast to *exo*-**3b**, *exo*-**3a** was formed as sole isomer under both solvent and solvent-less conditions at 110 °C (Table 1, entries 4–6). We did not examine its stability, but all data seem to indicate that *exo*-**3a** should be at least as stable as *exo*-**3b**.

The next step of the proposed synthesis of **A** and **B** was the preparation of the intermediates **4a** and **4b** (Scheme 1, dashed arrows). Thus *exo*-**3a** and *exo*-**3b**, respectively, were treated with various reducing reagents described in literature:[1] zinc–acetic acid system, tin(II) chloride, hydrogen (under *ca.* 3 MPa) in the presence of 10% palladium–charcoal and finally molybdenum hexacarbonyl.[8] Unfortunately all these methods failed and most of the starting material was recovered. Probably owing to steric congestion, the N–O bond can not be broken by any of the reducing reagents and all attempts at preparing **4** and, subsequently, the azasugar analogues of showdomycine **A** and **B** failed.

Techniques used: ^{1}H and ^{13}C NMR, IR, TLC, MS

References: 8

Schemes: 1

Tables: 1

Received, 1st September 1997; Accepted, 30th December 1997
Paper E/7/06366K

References cited in this synopsis

1 J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 2, pp. 135–161.
2 K. B. G. Torsell, in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis-Novel Strategies in Synthesis*, VCH, Weinheim, 1988, ch. 3 and 5.
3 For the synthesis of the azasugar analogue of showdomycine see G. Just and G. P. Donnini, *Can. J. Chem.*, 1977, **55**, 2998.
4 M. Koszytkowska-Stawińska, W. Sas and A. Sowińska, *J. Chem. Res.* (*S*), 1996, 162.
5 M. Burdisso, R. Gandolfi, P. Grünanger and A. Rastelli, *J. Org. Chem.*, 1990, **55**, 3427.
6 H. G. Aurich, G. Frenzen and M. G. Rohr, *Tetrahedron*, 1994, **50**, 7417.
7 R. Grigg, M. Hadjisoteriou, P. Kennewell, J. Markandu and M. Thornton-Pett, *J. Chem. Soc., Chem. Commun.*, 1993, 1340.
8 S. Cicchi, A. Goti, A. Brandi, A. Guarna and F. De Sarlo, *Tetrahedron Lett.*, 1990, **31**, 3351.