Pergamon

Tetrahedron Letters 42 (2001) 4239–4241

TETRAHEDRON
LETTERS

Unusual cyclization of 1-thianaphthenone-3-dioxide-1,1 to a 1,5-diazabicyclo[3.3.1]nonane—a heterocyclic analogue of a Tröger's base

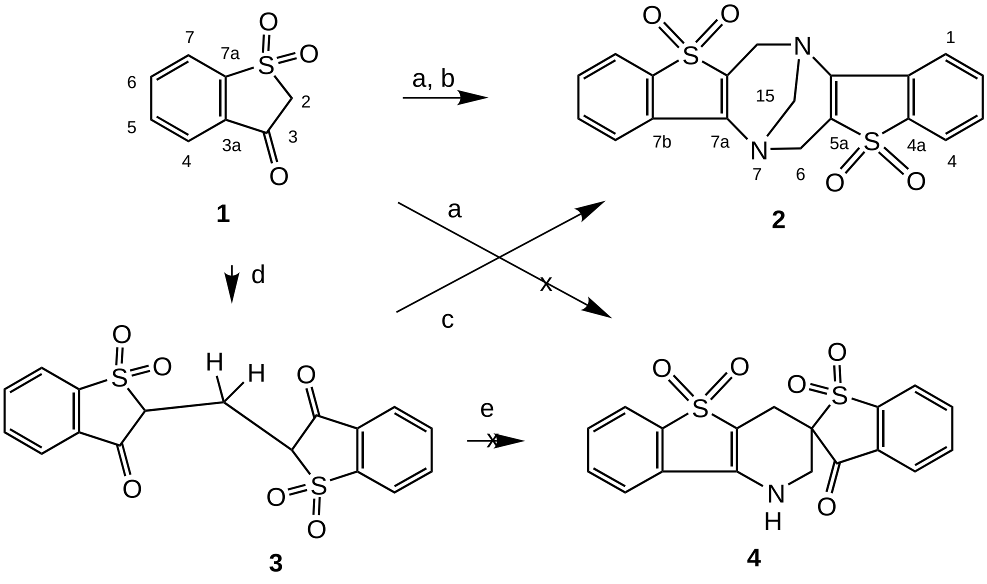
Brigita Čekavičus,* Edvards Liepinsh, Brigita Vīgante, Arkadijs Sobolevs, Jānis Ozols and Gunārs Duburs

Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga LV 1006, Latvia

Received 12 January 2001; accepted 19 April 2001

Abstract—The synthesis of a novel heterocyclic system, bisbenzthieno[2,3-*c*:2′,3′-*g*]-1,5-diazabicyclo[3.3.1]nonane-5,12-dioxide, is described. The structure of the product was confirmed by high resolution NMR techniques. © 2001 Elsevier Science Ltd. All rights reserved.

The cyclic β-diketone, 1,3-indandione, readily forms 2-spirocyclic 1,3-diones with formaldehyde and primary amines.[1] On the other hand, 3-aminocyclohex-2-enones with formaldehyde also give spirocyclic compounds and these reactions have been investigated in detail.[2,3] The *gem*-dimethyl groups of the dimedone derivative direct the reaction to give exclusively the spiran formed by an internal Mannich reaction, but the unsubstituted cyclo-



a) $(CH_2)_6N_4$, CH_3COONH_4, CH_3COOH or CF_3COOH;
b) $(CH_2O)_n$, CH_3COONH_4, CH_3COOH, $C_6H_5CH_3$;
c) $(CH_2)_6N_4$, CH_3COONH_4, CH_3COOH;
d) $(CH_2O)n$, EtOH, rt;
e) $(CH_2)_6N_4$, CH_3COOH/CF_3COOH

Scheme 1.

Keywords: 1-thianaphthenone-3-dioxide; bisbenzthieno-1,5-diazabyclo[3.3.1]nonane; Mannich reaction; cyclization.

* Corresponding author. E-mail: arkady@osi.lv

PII: S0040-4039(01)00658-X

hexanedione enaminone gives mixtures of spiro- and acridinedione derivatives.

1-Thianaphthenone-3-dioxide-1,1 **1** is the sulfonyl group containing an analogue of 1,3-indandione.[4] Previously, we have found that 1-thianaphthenone-3-dioxide-1,1 **1** like 1,3-indandione undergoes cyclization to 1,4-dihydrobenzthieno[3,2-*b*]pyridine-5,5-dioxides.[5] We now report our attempts to generate the 2-spiro-derivatives **4** of 1-thianaphthenone-3-dioxide-1,1 **1** using hexamethylenetetramine in acidic medium in the presence of ammonium acetate which led to an unexpected macrocyclization reaction product, bisbenzthieno[2,3-*c*:2′,3′-*g*]-1,5-diazabicyclo[3.3.1]nonane-5,12-dioxide **2**, a heterocyclic analogue of Tröger's base.[6] A similar reaction occurred when 1-thianaphthenone-1,1 **1** was heated with paraformaldehyde in the presence of ammonium acetate (toluene–acetic acid). 2,2′-Methylenebisthianaphthenone-3-dioxide-1,1 **3** also afforded, with hexamethylenetetramine, the unexpected 1,5-diazabicyclo[3.3.1] nonane-5,12-dioxide **2** (Scheme 1).

The ^{1}H NMR spectrum of **2** (δ, ppm): 2.70 (s, 2H, 15-CH_2), 4.02 and 4.59 (d, and d, $J=19.1$ Hz, 2H and 2H, 2×6-CH_2), 7.995 (d, $J=8.4$ Hz, 2H, H_4), 7.990 (d, $J=8.4$ Hz, 2H, H_1), 7.80 (t, $J=8.4$ Hz, 2H, H_3), 7.78 (t, $J=8.4$ Hz, 2H, H_2).

The ^{13}C NMR spectrum of **2** (δ, ppm): 20.9 (C_{15}), 55.9 (C_6), 159.1 (C_{7a}), 59.7 (C_{5a}), 141.4 (C_{7b}), 124.5 (C_4), 133.6 (C_3), 134.6 (C_2), 121.9 (C_1), 133.0 (C_{4a}).

The novel heterocyclic system, the 1,5-diazabicyclo[3.3.1]nonane-5,12-dioxide **2**, might reasonably arise from an intramolecular Mannich reaction of 1-thianaphthenone-3-dioxide-1,1 **1** due to the steric hindrance of the sulfonyl group in comparison with the carbonyl group of 1,3-indandione, where the internal Mannich reaction leads to 2-spirocyclic 1,3-diones (Scheme 2).

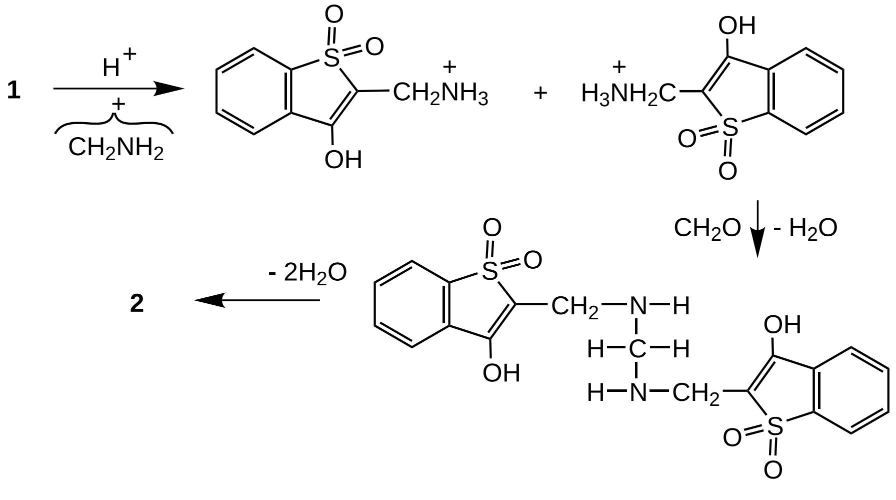
The structural elucidation of the 1,5-diazabicyclo-[3.3.1]nonane-5,12-dioxide **2** was mainly based on NMR spectra.[7] Besides the conventional ^{1}H and ^{13}C 1D spectra and the two-dimensional NOESY, ROESY[8,9] and ^{13}C–^{1}H HMBC[10] unambiguously confirmed the structure of compound **2**.

The assignment of the relative spatial orientation of protons in the ring positions 15 and 6 was carried out by analysing NOESY/ROESY connectivities as well as ^{13}C–^{1}H HMBC long range correlation intensities. For the *trans*-position of the vicinal $^{13}C_{15}$ and high field ^{1}H doublet at C_6, the correlation gave strong HMBC cross-peaks, but for *gauche*-orientations between a low field ^{1}H nucleus at carbon C_6 such peaks were very weak. In agreement, the NOE between the 15-CH_2-singlet in the NOESY/ROESY spectra was strong with the low field proton doublet at C_6, but very weak for the high field ^{1}H doublet. These results indicate that the high field proton at C_6 is pointing away from the NCH_2N bridge. The high absolute value of the geminal coupling $^{2}J_{HH}=$ 19.1 Hz for the protons attached to C_6 is very unusual, in comparison to the NMR spectra of the other Tröger bases.[11] As was pointed out by X-ray analysis,[10] the diazocine framework in Tröger bases usually has some mobility.[11] One can propose that the mobility of the heterocyclic ring in **2** is greatly reduced by steric or electronic interactions with the neighboring S–O bonds so the geminal coupling constant approaches its maximal possible value, determined by the stereoorientation of both the double bond 5a–7a, and the nitrogen lone pair relative to the C_6 geminal protons. The use of the HMBC spectrum also allowed the undoubted ^{1}H and ^{13}C assignments of the signals corresponding to the dioxobenzo[*b*]thiophene moiety.

Experimental procedure for the preparation of compound 2

(a) 1-Thianaphthenone-3-dioxide-1,1 **1** (0.91 g, 5 mmol), hexamethylenetetramine (1.4 g, 7.5 mmol) and ammonium acetate (0.95 g, 12 mmol) were dissolved in 20 ml acetic acid or 20 ml acetic acid/5 ml trifluoroacetic acid. The mixture was heated to reflux for 1 h.

(b) 1-Thianaphthenone-3-dioxide-1,1 **1** (0.76 g, 4.2



Scheme 2.

mmol), paraformaldehyde (0.08 g, 2.5 mmol) and ammonium acetate (0.7 g, 9 mmol) were dissolved in 30 ml toluene/5 ml acetic acid. The mixture was heated to reflux with water removal for 3 h.

(c) 2,2′-Methylenebisthianaphthenone-3-dioxide-1,1 **3** (0.68 g, 2 mmol), hexamethylenetetramine (0.78 g, 4 mmol) and ammonium acetate (0.42 g, 6 mmol) were dissolved in 15 ml acetic acid. The mixture was heated to reflux for 1 h.

In all cases the white precipitate was filtered off after cooling and was crystallized from acetic acid, giving nonane **2** with mp 269–270°C. Yield % (a, b, c): 60, 60, 69.

Acknowledgements

Financial support provided by a Grant from the Latvian Council of Science N 718 is gratefully acknowledged.

References

1. Morhle, H.; Dornbrack, S.; Novak, H. I. *Monatsh. Chem.* **1981**, *112*, 1417–1423.
2. Greenhill, J. V. *J. Chem. Soc. (C)* **1971**, 2699–2703.
3. Chaavan, I. C.; Greenhill, J. V.; Akhtar, P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1593–1596.
4. Mackanova, M.; Vanags, G. *Dokl. Akad. Nauk. SSSR* **1960**, *132*, 615–618.
5. Dubure, R.; Vigante, B.; Ozols, J.; Duburs, G. *Chem. Heterocycl. Comp.* **1986**, *22*, 1267–1271.
6. Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225.
7. NMR experiments: NMR spectra were recorded with 8–10 mg samples in $CDCl_3$ solutions at 25°C on a Bruker DMX 600 NMR spectrometer. Besides the conventional ^1H and ^{13}C 1D spectra, the two-dimensional NOESY, ROESY[8,9] and ^{13}C HMBC spectra with a purge pulse to suppress one-bond ^{13}C–^1H correlations[10] were recorded. Pulsed field gradients were used for ^{13}C correlation spectra. The ^{13}C HMBC spectrum was recorded with coupling evolution delay for the generation of multiple bond correlations set to 45.2 ms, recording time 4 h. The NOESY spectrum with mixing time 1 s and the ROESY spectrum with mixing time 300 ms were recorded with $t_{1\max} = 104$ ms and $t_{2\max} = 208$ ms, whereas the ^{13}C–^1H correlation spectrum was recorded with $t_{1\max} = 25.6$ ms and $t_{2\max} = 208$ ms. ^{13}C–^1H HMBC data were multiplied by an unshifted sine-bell window function in the t_2 dimension prior to FT transformation and the magnitude spectrum was calculated. Chemical shifts were referenced to internal tetramethylsilane.
8. Ernst, R. R.; Bodenhausen, G.; Wokaun, A. *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*; Clarendon: Oxford, 1987.
9. Cavanagh, J.; Fairbrother, W. J.; Palmer, A. G.; Skelton, N. *Protein NMR Spectroscopy*, *Principles and Practice*; Academic Press: San Diego, CA, 1996.
10. Gresiek, S.; Bax, A. *J. Biomol. NMR* **1995**, *6*, 335–339.
11. Cudero, J.; Pardo, C.; Ramos, M.; Gutierrez-Puebla, E.; Monge, A.; Elguero, J. *Tetrahedron* **1987**, *53*, 2233–2240.