An unexpected ring transformation of (*Z*)-3-benzyl-2-(nitromethylene)thiazolidine

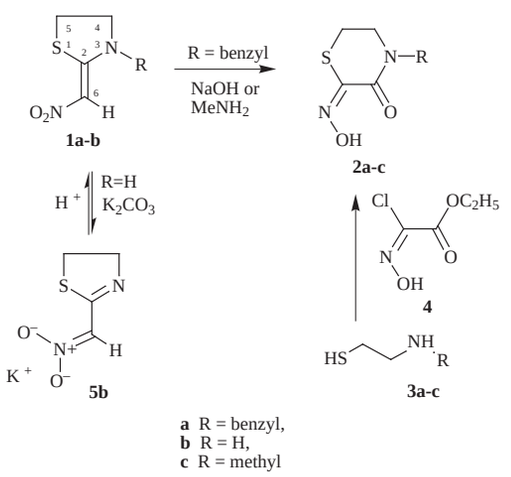
István Szabadkai,[a] Kálmán Harsányi,*[,a] Mária Bihari,†[,a] Márta Rényei[a] and György Rácz[b]

[a] *Chemical Works Gedeon Richter Ltd., PO Box 27, H-1475 Budapest, Hungary*
[b] *Technical University of Budapest, Department of Physical Chemistry, H-1521 Budapest, Hungary*

An unexpected ring enlargement, accompanied by oxidative–reductive transformation of the nitromethylene group, was brought about in almost quantitative yield by the reaction of (*Z*)-3-benzyl-2-(nitromethylene)thiazolidine (1a) and sodium hydroxide. The suggested mechanism is based on MS measurements involving isotope-labelled compounds.

Introduction

Among a series of thiazolidines,[1] (*Z*)-3-benzyl-2-(nitromethylene)thiazolidine[2] **1a** (RGH-5981)[3] was selected for preclinical studies as an antisecretory and gastrocytoprotective agent. When **1a** was refluxed with aqueous sodium hydroxide and the resulting solution acidified, the white crystals of compound **2a** separated in practically quantitative yield (Scheme 1).



Scheme 1 Rearrangement of **1a**

The same product (**2a**) had been obtained earlier, when **1a** was refluxed in aqueous methylamine, but in much lower yield (30%).

The structure of **2a**, mainly based on mass spectroscopy, was later verified synthetically by a method originally described for the preparation of **2b–c** using cysteamine **3b** or *N*-methylaminoethanethiol **3c** and ethyl chlorooximidoacetate **4** as starting materials.[4] When applied to **3a**, this procedure afforded compound **2a** in 82% yield.[5] The treatment of **1b** with benzyl chloride in the presence of K_2CO_3 afforded neither **1a** nor **2b**, but rather the nitronic acid salt **5b**, from which **1b** was recovered by acidification.

NMR Measurements showed that **2a**, assuming that the oxime (*E*)→(*Z*) isomeric transformation is a slow process, exists as the (*E*) isomer in DMSO solution. The same conclusion followed from the broad peak at 3450–2000 cm^{-1} in the IR spectrum which indicates a strong H-bridge between the OH and C=O oxygen groups.

Related reactions

The following more or less analogous reactions are known from the literature (see Scheme 2).

(a) The reaction of **1b** with methylamine affords **6** as the main product and a ring enlargement product **7** in very low yield (5%).[6]

(b) Some nitroolefins are transformed into α-oximino ketones photochemically[7] (**8**→**9**) or by a proton catalyzed rearrangement[8] (**10**→**11**). Surprisingly, the positions of the C=O and C=N–OH groups were transposed between the products of these two reactions. In the first case the reaction has been shown to proceed *via* a nitro–nitrite transformation, while in the second one an intramolecular redox reaction occurred involving either an intramolecular (oxygen from the nitro-group) or an external oxygen source.

(c) An α-oximino ketone from the benzothiazine series, **14**, was obtained in 74% yield by the reaction of 2-aminothiophenol **12** and nitroacetic acid ethyl ester **13**; this reaction involves an oxidative–reductive transformation of the nitromethyl group.[9]

(d) Cysteamine **3b** when heated with allenyl cyanides (*e.g.* **15**) gave thiazoline derivatives (*e.g.* **17**), but in the presence of sodium ethoxide a ring enlargement took place to yield dihydrothiazine derivatives (*e.g.* **18**). The common intermediate in these reactions is thiazolidine (*e.g.* **16**). In the latter reaction the role of sodium ethoxide was explained in terms of deprotonation of this intermediate.[10]

Results and discussion

Our observations concerning the mechanism of this rearrangement (**1a**→**2a**) are summarised below.

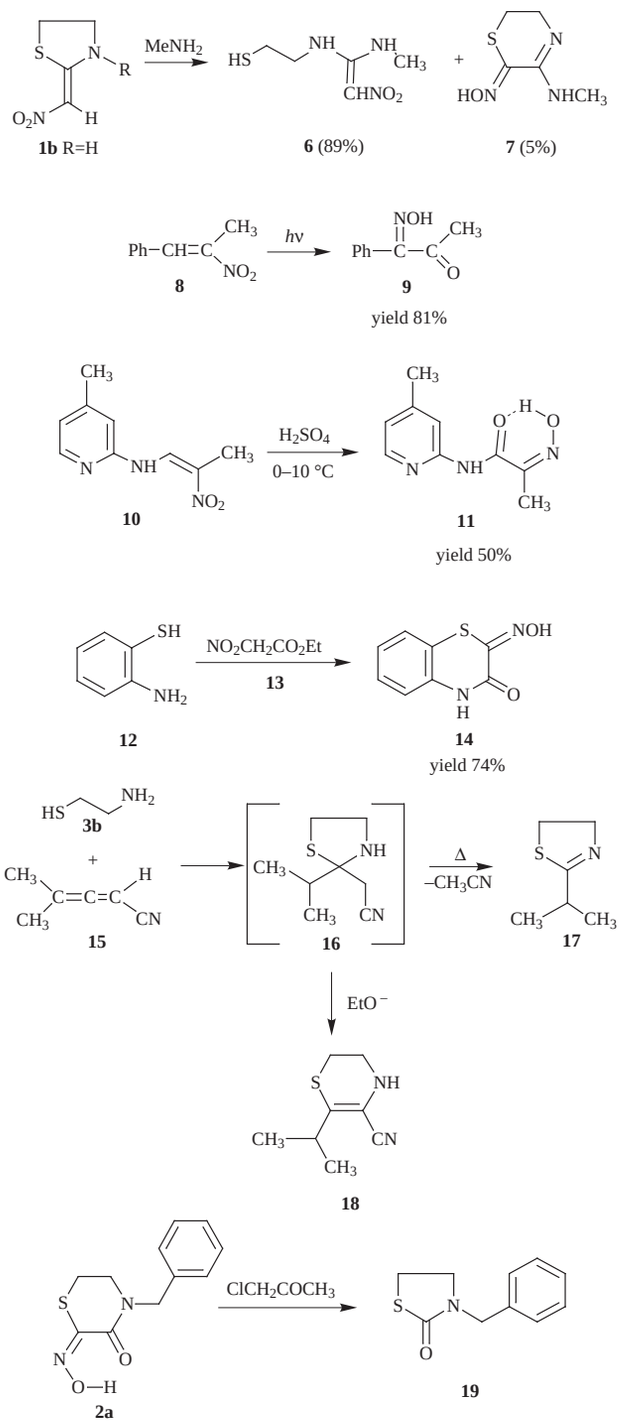
The role of the hydroxide ion

In order to determine whether the source of the amide oxygen in **2a** was an internal or external oxygen atom, the following reactions were carried out.

(a) When **1a** was refluxed in toluene in the presence of a proton-sponge, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), we did not observe any reaction. This indicated that the role of hydroxide ion was not the deprotonation of C(6)-H in **1a**.

(b) When **2a** ($M = 236$) was treated with $K^{16}OH$ in an $H_2{}^{16}O : H_2{}^{18}O$ mixture, oxygen exchange at the amide moiety

† *Present address*: Water Resources Research Centre Plc. (VITUKI Plc.), H-1095 Budapest, Kvassay Jenö út 1, Hungary.



Scheme 2 Related reactions

Table 1 Examination of the amide oxygen source in **2a** by isotope labelling

	^{18}O : ^{16}O Ratio	
Reactions with KOH	In the solution	In the product
Treatment of unlabelled **2a**	42 : 58	14 : 86
Rearrangement of unlabelled **1a**	44 : 56	42 : 58

was observed. The isolated product contained 14% of ^{18}O by mass spectroscopy ($M = 238$). When the rearrangement of unlabelled **1a** was carried out under the same conditions, product **2a** was found by MS to contain almost the same ratio of ^{18}O in the amide oxygen as in the reaction mixture [$H_2{}^{18}O$: ($H_2{}^{16}O$ + $K^{16}OH$)] (Table 1).

These results indicate that the rearrangement of **1a** is faster than the subsequent oxygen exchange in **2a**, and that the oxygen atom of the amide group originates from an external source and is introduced during the rearrangement of the starting material.

UV Studies

During the rearrangement the yellow starting material changes into a colourless solution of the oximate. To gain further insight into the reaction route the reaction was followed by UV. To this end, dilute ethanolic–aqueous solutions were used in which the starting material dissolved promptly and completely at 25 °C; the reaction was then initiated by adding a large excess of aqueous sodium hydroxide (initial concentrations were 1.6×10^{-4} mol dm^{-3} for **1a** and 1.25×10^{-1} mol dm^{-3} for sodium hydroxide). The progress of the rearrangement was monitored by taking samples after 0, 5, 10, 20, 40, 60 minutes; subsequently the UV spectra were taken (λ_{max} **1a** = 354 nm, λ_{max} **2a** oximate = 298 nm).

In connection with the UV results the following should be noted.

(a) No other peak than those of the starting material and the end product was observed.

(b) The concentration of the starting material (**1a**) and the reaction rate constants could be directly derived by monitoring the decrease of the UV maximum of the starting material, since at this point the UV absorption of the product is negligible.

(c) Using a large excess of sodium hydroxide the reaction was found to be pseudo first-order (k_1), but k_1 proved to be proportional to the sodium hydroxide concentrations b_0 ($k_1 = k_2 b_0$) and hence the reaction proved to be second-order.

(d) The rate constant of the reaction was found to be (at 25 °C):[11] $k_2 = 1.86 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}.

(e) The thermodynamic parameters of the reactions are (at 25 °C): $\Delta H = 52\,200$ J mol^{-1}; $\Delta S = -122$ J mol^{-1} K^{-1}.

(f) The rate-limiting step of the overall reaction is the reaction of the hydroxide ion and **1a**.

Suggested mechanism

A plausible mechanism that accounts for the ring enlargement may be envisaged as shown in Scheme 3.

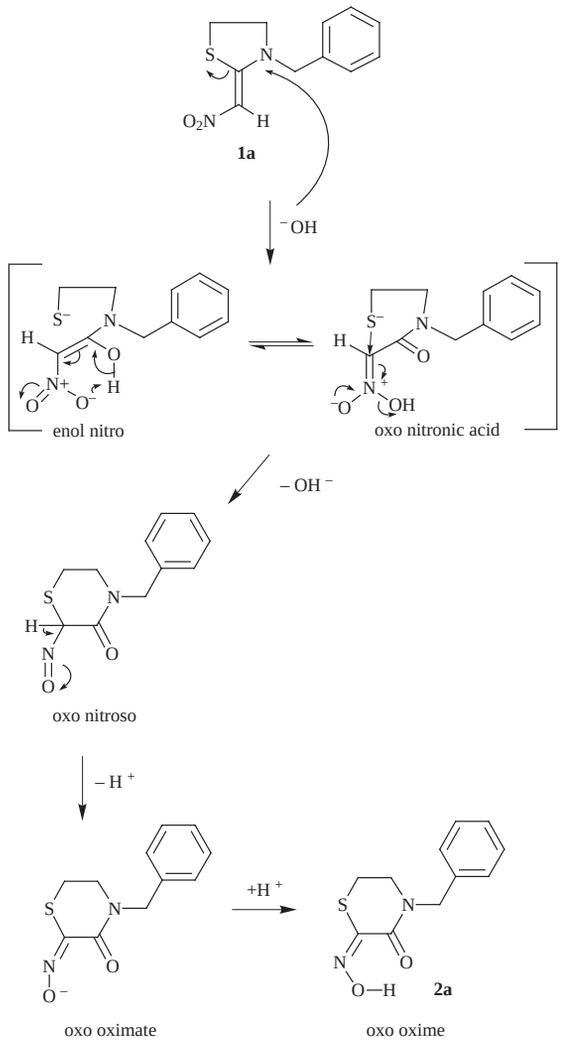
Nucleophilic attack on C(2) by the hydroxide ion at **1a** is assumed to be accompanied by simultaneous cleavage of the C(2)–S bond leading to the enol nitro state. During a cyclic proton transfer process the oxo nitronic acid intermediate was formed which is then attacked by the anionic sulfur. This attack is very fast since no disulfide side-product could be detected. Ring closure is accompanied by the loss of a hydroxide ion resulting in the reduction of the nitro group followed by proton loss from the original nitromethylene group. During this rearrangement the nitro group is reduced and the carbon atom directly joined to the nitro group is oxidised.

A reverse 1,4-thiazine→thiazolidine ring contraction has been found to take place on treating compound **2a** with α-halo ketones in the presence of potassium carbonate to yield 3-benzylthiazolidin-2-one **19**[12] (see Scheme 2).

Conclusion

Carrying out the reaction of 3-benzyl-2-(nitromethylene)-thiazolidine **1a** in aqueous sodium hydroxide containing $H_2{}^{18}O$ has allowed us to determine the initial step of this rearrangement, which is nucleophilic attack on C(2) by the hydroxide ion at **1a**. Beyond that the kinetical data derived by UV measurement determined this step as the rate-limiting one of the overall reaction. Then the elimination of water may occur simultaneously or in two steps (as illustrated).

This work complements our earlier studies concerning the inclination of *N*-benzylcysteamine derivatives for different ring closure and rearrangements.[2,12]



Scheme 3 Suggested mechanism

Experimental

General

Melting points (uncorrected) were taken on a Büchi 510 instrument. IR Spectra were obtained on a Nicolet 205 FT-IR spectrophotometer using KBr pellets. NMR Measurements were carried out on a Varian VXR-300 instrument (^{1}H: 300 MHz, ^{13}C: 75 MHz). Chemical shifts are given relative to $\delta_{TMS} = 0.00$. Mass spectra were recorded on a VG-TRIO-2 mass spectrometer using direct insertion. The ionisation energy was 70 eV, the source temperature was 250 °C. UV Spectra were recorded on a Varian DMS-100s instrument.

4-Benzyl-2-hydroxyimino-3,4,5,6-tetrahydro-2*H*-1,4-thiazin-3-one 2a

Method a. 3-Benzyl-2-(nitromethylene)thiazolidine **1a** (2.36 g, 0.01 mol) was refluxed in 50 ml of 1M (0.05 mol) aqueous sodium hydroxide until the disappearance of the starting material as measured on TLC in a sample taken from the reaction mixture (~1 hour). Subsequently the pure solution was cooled and acidified to a pH value of 1 by adding hydrochloric acid diluted to 1:1 with water; the precipitated product was filtered off, washed with water and dried to give the title compound in a yield of 2.31 g (98%), mp 225–227 °C. The purity of this product was 99.7% as measured by titration with sodium hydroxide in pyridine, in the presence of silver nitrate; ν_{max}/cm^{-1} 3450–2000 (OH), 1628 (C=O); δ_H(DMSO-d_6): 3.00 (m, 2H, H_2-5), 3.67 (m, 2H, H_2-4), 4.67 (s, 2H, H_2-7), 7.26–7.41 (m, 5H, ArH), 12.43 (br s, 1H, OH); δ_C(DMSO-d_6) 24.9 (C-5), 48.3 (C-4), 50.8 (C-7), 127.3, 127.5, 128.5 (ArCH), 137.0 (ArC), 143.9 (C-6), 157.2 (C-2); *m*/*z* 236 (2.1%); 219 (25), 192 (8.0), 164 (18), 132 (4.0), 104 (8.0), 91 (100); λ_{max}(96% EtOH)/nm 254 (ε 7940; oxime) 298 (ε 12 200; oximate).

Method b. *N*-Benzylcysteamine **3a** (6.68 g, 0.04 mol) was dissolved in 30 ml of ethanol, then NaOH (1.6 g, 0.04 mol) in 50 ml of ethanol was added. After 1 hour ethyl chlorooximidoacetate **4** (5.46 g, 0.04 mol) in 25 ml of ethanol was added dropwise between 25–30 °C within 30 minutes. The reaction mixture was stirred over 72 hours, then diluted with water; the precipitated product was filtered off, washed with water and dried to give 7.74 g of the title compound (yield 82%), mp 224–226 °C. The purity of this product was 98% by titration.

Isotope labelling

Rearrangement of 1a. A mixture of $H_2{}^{18}O$ (0.92 g, 0.046 mol), $H_2{}^{16}O$ (1.01 g, 0.063 mol), $K^{16}OH$ (0.19 g, 0.003 mol) and **1a** (0.30 g, 0.001 27 mol) was boiled for 1 hour in an oil bath (temperature 110 °C), then cooled to 10 °C over a period of 30 minutes, then acidified by adding 2 ml of 1:1 diluted hydrochloric acid. The precipitated product was filtered off, washed with 2 × 2 ml $H_2{}^{16}O$ and dried to give the title compound in a yield of 0.25 g (83%) **2a**, mp 209–214 °C. The purity of this product was 99.4% by titration by taking the molecular weight to be 236. The ^{18}O:^{16}O ratio in the isolated product (according to the 194:192 peak of the mass spectrum) is 42:58.

Displacement of the amide oxygen in 2a. A mixture of $H_2{}^{18}O$ (0.89 g, 0.0445 mol), $H_2{}^{16}O$ (1.05 g, 0.0583 mol), $K^{16}OH$ (0.19 g, 0.0034 mol) and **2a** (0.30 g, 0.00127 mol) (3-one=^{16}O) was stirred over the same oil bath and for the same time and was handled as the rearrangement reaction above. We obtained 0.25 g of **2a** (83%) mp 209–214 °C. The purity of this product is 98.5% by titration (considered molecular weight: 236). The ^{18}O:^{16}O ratio in the isolated product is 14:86 (according to the 194:192 peak of the mass spectrum).

Acknowledgements

The authors wish to thank Dr B. Hegedüs for IR spectra, Dr Cs. Szántay Jr. for NMR spectra, Dr F. Trischler for the titration measurements.

References

1 E. Ezer, L. Szporny, P. Tétényi, J. Matúz, K. Pallagi, Gy. Domány, K. Harsányi, B. Hegedüs and I. Szabadkai, *US Patent* 4 616 025 [1986], *Chem. Abstr.*, 1985, **102**, 78 864.
2 Cs. Szántay Jr., I. Szabadkai, K. Harsányi and F. Trischler, *Heterocycles*, 1997, **45**, 1081.
3 *Drugs of the Future*, 1986, **11**, 389; 1987, **12**, 509.
4 R. F. Bellina, *US Patent* 3 790 566 [1971], *Chem. Abstr.*, 1974, **80**, 83 010d.
5 I. Szabadkai, *Hungarian Patent* 199 812 [1987], *Chem. Abstr.*, 1990, **113**, 6358w.
6 J. Kosáry and K. Pólos, *Pharmazie*, 1993, **48**, 143.
7 (*a*) O. L. Chapman, P. G. Cleveland and E. D. Hoganson, *J. Chem. Soc., Chem. Commun.*, 1966, 101; (*b*) I. Saito, M. Takami and T. Matsuura, *Tetrahedron Lett.*, 1975, 3155; (*c*) J. S. Cridland, P. J. Moles, S. T. Reid and K. T. Taylor, *Tetrahedron Lett.*, 1976, 4497.
8 A. Krówscynski and L. Kozerski, *Heterocycles*, 1986, **24**, 1209.
9 A. I. Kiprianov and T. M. Verbovskaya, *Zh. Obshch. Khim.*, 1961, **31**, 531 (*cf.* Houben-Weyl-Müller *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, 1968, **X/4**, 172).
10 Z. T. Fomum and J. T. Mbafor, *Heterocycles*, 1982, **19**, 465.
11 In the kinetic experiments the concentrations of **1a** were 1×10^{-4}, 4×10^{-4} and 2×10^{-3} mol dm^{-3} while those of NaOH were 1.25×10^{-1}, 2.5×10^{-1} and 5×10^{-1} mol dm^{-3} respectively. The solvent was a 1:1 v/v mixture of H_2O and EtOH. The temperature was varied between 20 and 40 °C.
12 I. Szabadkai, K. Harsányi and Cs. Szántay Jr., *Acta Chim. Hung.*, 1994, **131**, 529.

Paper 8/03823F
Received 20*th May* 1998
Accepted 6*th July* 1998