Conversion of *N*-Arylglycolohydroxamic Acids to 1,2,3-Oxathiazolidin-4-one 2,2-Dioxides*

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*Dedicated to Professor Dr. Gerwalt Zinner on the occasion of his 70th birthday.

N-Arylglycolohydroxamic acids **1A** are converted by *in situ* prepared 2,2'-dipyridyl sulfite to 1,2,3-oxathiazolidin-4-one 2,2-dioxides **5**, the formation of which can be rationalized *via* a radical pair mechanism. The alkylating potential of the heterocyclic system **5** is demonstrated by the alkaline ethanolysis giving rise to the open chained 2-ethoxypropionanilide **6**.

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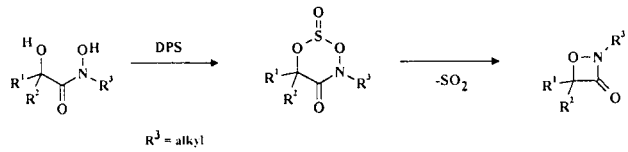
N-Substituted glycolohydroxamic **1** acids have been demonstrated as versatile building blocks for a variety of heterocyclic systems [1-6]. Among the reported ring-forming reactions the efficient transformation of *N*-alkylated **1** into 1,2-oxazetidin-3-ones **3** by 2,2'-dipyridyl sulfite *via* the intermediate cyclic sulfites **2** deserves particular interest because it offers an easy access to the four-membered system **3** [7].

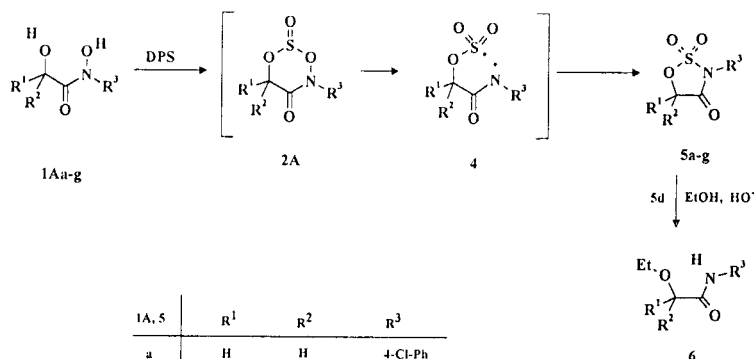
Scheme 1



In order to investigate the scope and synthetic utility of this ring contracting process we now turned our attention to the *N*-arylglycolohydroxamic acids **1A** which at first glance should behave in a similar manner by forming the corresponding 1,2-oxazetidin-3-one. However, as pointed out below, **1A** underwent an unexpected transformation to the five-membered system **5** under the same conditions.

According to the literature procedure [7] the hydroxamic acids **1Aa-g** were allowed to react with freshly prepared 2,2'-dipyridyl sulfite at low temperature until no starting material could be detected by the ferric chloride spot test. Extracting the reaction mixture with dilute hydrochloric acid, followed by sodium hydrogencarbonate solution and filtration upon silica gel furnished crystalline, sulfur containing compounds exhibiting a strong carbonyl stretching band in the ir-spectra at 1740-1770 cm^{-1} but lacking any absorption in the region 1790-1800 cm^{-1} which is typical for the 1,2-oxazetidin-3-one **3**. On the basis of elemental analysis and spectroscopic data (ir, ^1H-nmr and ^{13}C-nmr, see Experimental) the isolated compounds could be identified as 1,2,3-oxathiazolidin-4-one 2,2-dioxides **5a-g**. In all cases the crude product was obtained in yields of 40-50% and the yields given in the Experimental of recrystallized, analytically pure material reflect losses during chromatographic separation.

Scheme 2



1A, 5	R^1	R^2	R^3
a	H	H	4-Cl-Ph
b	CH_3	Ph	Ph
c	CH_3	Ph	2-Cl-Ph
d	CH_3	Ph	4-Cl-Ph
e	CH_3	4-Cl-Ph	Ph
f	CH_3	4-Cl-Ph	2-Cl-Ph
g	CH_3	4-Cl-Ph	4-Cl-Ph

The alkaline ethanolysis of **5d** which gave rise to the open chained 2-ethoxy-2-phenylpropionanilide **6** not only confirms the structure of **5** but also mirrors the alkylating potential of the cyclic sulfuric ester amide moiety which resembles the well established reactivity of cyclic sulfates [8]. In accordance with literature reports concerning the rearrangement of *O*-sulphinylated hydroxamic acids to sulphonamides [9,10] the conversion of **1A** to the 1,2,3-oxathiazolidin-4-one 2,2-dioxides **5** can be rationalized *via* a radical pair **4** arising from homolysis of the N-O bond of the intermediate cyclic sulfite **2A** (Scheme 2).

Experiments to verify this mechanism which differs markedly from the above mentioned sulfur dioxide extruding ring contraction of **1** to the corresponding 1,2-oxazetidin-4-ones **3**, which obviously involves heterolytic fission of the C6-O bond of **2** [11], are now in progress as well as a close examination toward further ring opening reactions of the heterocyclic system **5** that has been reported only once [12] by a doubtful route.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The ir-spectra were recorded on a Philips Unicam SP 3 200. The ^{1}H- and ^{13}C-nmr-spectra were recorded on a Bruker AC 250 P spectrometer with TMS as the internal reference. Chromatographic separation were performed on ICN Silica 100-200, active, 60 Å, 5 x 2 cm ϕ. The hydroxamic acids **1Aa-g** were prepared according to literature [13,14].

General Procedure for the Conversion of **1A** to the 1,2,3-Oxathiazolidin-4-one 2,2-Dioxides **5**.

To a stirred solution of 1.90 g (20 mmoles) of 2-pyridone and 2.02 g (20 mmoles) of triethylamine in 40 ml of anhydrous dichloromethane was added dropwise at 0° a solution of 1.19 g (10 mmoles) of thionyl chloride. After stirring for 5 minutes at ambient temperature the corresponding glycolohydroxamic acid **1A** was added and the reaction mixture stirred until no **1A** could be detected by ferric chloride (5-10 minutes). *n*-Hexane (50 ml) and 20 ml of diethyl ether were added and the mixture extracted twice with 10 ml of 3*N* hydrochloric acid, followed by 10 ml of saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, evaporated and the remaining crude products were separated by column chromatography. Elution with 150 ml of dichloromethane, evaporation and recrystallization from the given solvents afforded analytically pure **5a-g**.

3-(4-Chlorophenyl)-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5a**).

This compound was obtained from **1Aa** [13] in 43% yield (1.07 g), mp 144° (*n*-hexane-dichloromethane); ir (potassium bromide): 1740 (C=O), 1350, 1200 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 5.19 (s, 2H), 7.40-7.59 (m, 4H, aromatic protons); ^{13}C-nmr (deuteriochloroform): δ 71.7 (t, CH_2), 128.4, 130.5, 127.2, 137.0 (aromatic carbons), 161.6 (C=O).

Anal. Calcd. for $C_8H_6ClNO_4S$: C, 38.80; H, 2.44; N, 5.66; Cl, 14.32; S, 12.94. Found: C, 38.91; H, 2.56; N, 5.62; Cl, 14.47; S, 12.76.

3,5-Diphenyl-5-methyl-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5b**).

Compound **5b** was obtained from **1Ab** [14] in 31% yield (0.94 g), mp 74° (*n*-hexane-dichloromethane); ir (potassium bromide): 1770 (C=O), 1360, 1190 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.20 (s, CH_3), 7.45-7.73 (m, 10 aromatic protons); ^{13}C-nmr (deuteriochloroform): δ 25.9 (q, CH_3), 94.8 (s, C-5), 125.0, 127.5, 129.1, 129.3, 129.8, 130.1, 130.5, 135.4 (aromatic carbons), 166.4 (C=O).

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.40; H, 4.32; N, 4.62; S, 10.57. Found: C, 59.44; H, 4.38; N, 4.60; S, 10.56.

3-(2-Chlorophenyl)-5-methyl-5-phenyl-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5c**).

Compound **5c** was obtained from **1Ac** [14] in 36% yield (1.22 g), mp 104° (*n*-hexane-diethyl ether); ir (potassium bromide): 1770 (C=O), 1375, 1210 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.22 (s, CH_3), 7.35-7.76 (m, 9 aromatic protons); ^{13}C-nmr (deuteriochloroform): δ 26.11 (q, CH_3), 95.64 (s, C-5), 125.18,2, 128.3, 129.1, 129.8, 130.9, 131.2, 132.4, 120.4, 134.4, 135.2 (aromatic carbons), 166.3 (C=O).

Anal. Calcd. for $C_{15}H_{12}ClNO_4S$: C, 53.34; H, 3.58; N, 4.15; Cl, 10.50; S, 9.49. Found: C, 53.30; H, 3.73; N, 4.49; Cl, 10.56; S, 9.51.

3-(4-Chlorophenyl)-5-methyl-5-phenyl-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5d**).

Compound **5d** was obtained in 30% yield (1.00 g) from **1Ad** [14], mp 98° (*n*-hexane-dichloromethane); ir (potassium bromide): 1760 (C=O), 1375, 1210 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.20 (s, CH_3), 7.39-7.69 (m, 9 aromatic protons); ^{13}C-nmr (deuteriochloroform): δ 25.9 (q, CH_3), 95.1 (s, C-5), 125.0, 128.7, 129.2, 129.9, 130.4, 127.7, 135.2, 136.8 (aromatic carbons), 166.3 (C=O).

Anal. Calcd. for $C_{15}H_{12}ClNO_4S$: C, 53.34; H, 3.58; N, 4.15; Cl, 10.50; S, 9.49. Found: C, 53.43; H, 3.62; N, 4.09; Cl, 10.64; S, 9.59.

5-(4-Chlorophenyl)-5-methyl-3-phenyl-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5e**).

Compound **5e** was obtained in 35% yield (1.17 g), from **1Ae** [14] mp 103° (*n*-hexane-diethyl ether); ir (potassium bromide): 1740 (C=O), 1365, 1205 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.20 (s, CH_3), 7.39-7.68 (m, 9 aromatic protons); ^{13}C-nmr (deuteriochloroform): δ 26.1 (q, CH_3), 94.7 (s, C-5), 126.5, 127.5, 129.1, 129.4, 130.1, 130.6, 134.0, 136.1 (aromatic carbons), 166.1 (C=O).

Anal. Calcd. for $C_{15}H_{12}ClNO_4S$: C, 53.34; H, 3.58; N, 4.15; Cl, 10.50; S, 9.49. Found: C, 53.27; H, 3.65; N, 4.43; Cl, 10.63; S, 8.98.

5-(4-Chlorophenyl)-3-(2-chlorophenyl)-5-methyl-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5f**).

Compound **5f** was obtained in 31% yield (1.16 g) from **1Af** [14], mp 65° (*n*-hexane-diethyl ether); ir (potassium bromide): 1765 (C=O), 1360, 1205 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.21 (s, CH_3), 7.38-7.69 (m, 9 aromatic protons); ^{13}H-nmr (deuteriochloroform): δ 21.5 (q, CH_3), 94.8 (s, C-5), 126.6, 128.4, 129.3, 130.8, 131.2, 132.5, 133.8, 134.3, 136.6 (aromatic carbons), 165.1 (C=O).

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_4S$: C, 48.40; H, 2.98; N, 3.76; Cl, 19.05; S, 8.61. Found: C, 48.25; H, 3.08; N, 3.88; Cl, 18.93;

S, 8.64.

3,5-Bis(4-chlorophenyl)-5-methyl-1,2,3-oxathiazolidin-4-one 2,2-Dioxide (**5g**).

Compound **5g** was obtained in 31% yield (1.17 g) from **1Ag** [14], mp 105° (*n*-hexane-dichloromethane); ir: 1740 (C=O), 1365, 1200 (SO_2) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.19 (s, CH_3), 7.38-7.63 (m, 8 aromatic protons; ^{13}C-nmr (deuteriochloroform): δ 26.1 (q, CH_3), 94.2 (s C-5), 126.4, 127.5, 128.6, 129.4, 130.4, 133.7, 136.2, 136.9 (aromatic carbons), 165.9 (C=O).

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_4S$: C, 48.40; H, 2.98; N, 3.76; Cl, 19.05; S, 8.61. Found: C, 48.68; H, 3.12; N, 3.90; Cl, 19.13; S, 8.49.

Ethanolysis of **5d**.

A solution of 300 mg (1 mmole) of **5d** in 10 ml of ethanol and 1 ml of 3*N* sodium hydroxide was refluxed for 30 minutes. The solvent was evaporated, the residue dissolved in 50 ml of diethyl ether and extracted with 5 ml of water. The organic layer was dried (anhydrous magnesium sulfate), evaporated and the crude product separated by column chromatography. Elution with 50 ml of dichloromethane afforded *N*-(4-chlorophenyl)-2-ethoxy-2-phenylpropionamide **6** in 36% yield (119 mg), mp 87° (*n*-hexane-dichloromethane); ir (potassium bromide): 3370 (NH), 1680 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.31 (m, CH_3), 1.85 (s, CH_3), 3.40-3.60 (m, OCH_2), 7.19-7.59 (m, 9 aromatic protons), 8.82 (s, NH); ^{13}C-nmr (deuteriochloroform): δ 15.8 (q, CH_3), 21.1 (q, CH_3), 59.4 (t, OCH_2), 81.9 (s, C-3), 120.8, 126.0, 128.1, 128.5, 128.9, 129.1, 136.2, 140.8 (aromatic carbons), 171.8 (C=O).

Anal. Calcd. for $C_{17}H_{18}ClNO_2$: C, 67.12; H, 5.97; N, 4.61; Cl, 11.67. Found: C, 66.94; H, 6.07; N, 4.76; Cl, 12.02.

REFERENCES AND NOTES

[1] D. Geffken, *Synthesis*, 38 (1981).

[2] D. Geffken, *Arch. Pharm. (Weinheim)*, **315**, 802 (1982).

[3] D. Geffken, *Z. Naturforsch.*, **38b**, 1008 (1983).

[4] D. Geffken, *Heterocycles*, **12**, 519 (1979).

[5] T. Lauterbach and D. Geffken, *Liebigs Ann. Chem.*, 1478 (1986).

[6] T. Lauterbach and D. Geffken, *Z. Naturforsch.*, **41b**, 1186 (1986).

[7] A. Burchardt and D. Geffken, *Arch. Pharm. (Weinheim)*, **323**, 967 (1990); for an excellent review on the chemistry of 1,2-oxazetidin-3-ones see: D. Moderhack, *J. Heterocyclic Chem.*, **30**, 579 (1993).

[8] B. B. Lohray, *Synthesis*, 1035 (1992) and references cited therein.

[9] A. Heesing, W. K. Homann and W. Müllers, *Chem. Ber.*, **113**, 152 (1980).

[10] M. R. Banks and R. F. Hudson, *J. Chem. Soc., Perkin Trans. II*, 1211 (1986).

[11] D. Geffken, *Chem.-Ztg.*, **106**, 442 (1982).

[12] H. Steinbeisser, R. Mews and O. Glemser, *Z. Anorg. Allg. Chem.*, **406**, 299 (1974).

[13] M. D. Corbett and B. R. Chipko, *Experientia*, **34**, 1126 (1978).

[14] D. Geffken and S. Geisel, *Pharmazie*, **49**, in press.