Oxidation of 3,4-dialkyl substituted isothiazolium salts to 1,1-dioxides

Antje Noack, Janine Wolf and Bärbel Schulze*

Institute of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany
E-mail: bschulze@chemie.uni-leipzig.de

Dedicated to Professor Heinz Heimgartner on the occasion of his 70th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.615

Abstract

A new approach to 2-aryl-3-methylene-2,3-dihydroisothiazole 1,1-dioxides 11 from 3,4-dialkyl substituted N-phenyl-isothiazolium salts 6 via stable hydroperoxides 7 by reduction and elimination of water is introduced. Furthermore, 2-aryl-3-methylene-2,3-dihydroisothiazole 1,1-dioxides 11 are shown to be interesting synthons for the synthesis of 3-oxyfunctionalized sultams 8 and 9.

Keywords: Oxidations, hydroperoxides, sultams, methylene substituted isothiazoles

Introduction

Functionalized monocyclic sultams are known in the recent years to attract much attention due to their importance in biological and pharmaceutical research.¹ The first monocyclic 2,3-dihydroisothiazole 1,1-dioxide 1 (R¹ = NH₂) with anti-HIV-1 activity has recently been prepared.¹⁻³ The sultams 1 can be used as fungicides, herbicides and pesticides.⁴ The synthesis of such cyclic vinylsultams 2 by ring-closing metathesis (RCM) of vinylsulfonamide templates in the presence of Grubbs catalyst has been described.⁵

Sultams 3 react with cyclopentadiene in stereoselective Diels-Alder reactions to yield endo-norbornenyl sulfonamides as the major diastereomer. Ring-opening metathesis polymerization (ROMP) of these cycloadducts was applied to prepare oligomeric sulfonamides (Scheme 1).⁶,⁷
Scheme 1. Functionalized monocyclic sultams 1-3.

Recently we prepared a series of 3-hydroperoxy-, hydroxy- as well as alkoxyderivatives by oxyfunctionalization of monocyclic isothiazolium salts 4 (R$^1$ = CH$_3$) which are unsubstituted at the 3-position.$^{8,9}$ Here we report a new approach to introduce the oxy substituents at the methyl substituted 3-position of the isothiazole ring 6 with simultaneous oxidation of the sulfur to the sulfur dioxide in a one-step process. Furthermore we were able to compare now different pathways to prepare oxyfunctionalized 3-methyl-2,3-dihydroisothiazole 1,1-dioxides.

Results and Discussion

3-Methylisothiazolium salts 6, used as starting compounds for the following reactions, were synthesized by ring transformation of 3-unsubstituted isothiazolium salts 4 with anilines 5 by a known method (Scheme 2).$^{10}$

Scheme 2. Ring transformation of isothiazolium salts 4 to 6.

The oxidation of unsubstituted (R$^3$ = H) and donor substituted (R$^3$ = OCH$_3$, CH$_3$) salts 6a-c, f, g with hydrogen peroxide (30%) in acetic acid at 50°C gave after 8 hrs stable 3-hydroperoxysultams 7a-c,f,g in 19-81% yield (Scheme 3). Surprisingly, the
3-hydroperoxysultams with acceptor groups \( 7d, e \) \((R^3 = 4-Cl, 4-Br)\) could only be isolated as a mixture with methylenesultams \(11d,e\) (Scheme 3). That gave us reason to investigate the formation of these new compounds.

**Scheme 3.** Products 7-11 of the oxidation of isothazolium salts 6.

Here we present for the first time the synthesis of the stable, crystalline 2-aryl-3-methylene-2,3-dihydroisothiazole1,1-dioxides \(11a-c,g\) formed by reduction of the hydroperoxides \(7a-e,g\) with \(Na_2SO_3\cdot7H_2O\) at r.t. for 24 hrs. We interpret the formation of 3-methylenesultams \(11\) as a two-step process. The reduction of 3-hydroperoxysultams \(7\) takes place *in situ* to give non-isolable 3-hydroxy-3-methylsultams \(8\) under these reaction conditions, which directly react by elimination of water to \(11\) \(a-e, g\) with a yield range of 10-86% (poor to good yields). Acceptor substituted 3-methylenesultams \(11d, e\) \((R^3 = 4-Cl, 4-Br)\) could only be isolated in a mixture with
3-hydroperoxysultams 7d,e. Until now, only one example was known of a dihydro-2-methyl-3-methylenethieno[2,3-d]isothiazole 1,1-dioxide, prepared from 3-thioxothieno[2,3-d]isothiazole 1,1-dioxide and diazomethane. 11

Exomethylenesultams 11 are favorable building blocks for the oxyfunctionalization in the 3-position. For the first time we obtained 3-alkyl substituted 3-hydroxysultams 8a-c,f,g as stable colourless crystals by the addition of water to a solution of 11 resulting in good to very good yields in the range of 40-99% (method A). We also were able to synthesize 8a,b in the presence of DMSO from the 3-hydroperoxides 7a,b (method C). Finally, we investigated the oxidation of the salts 6 with MMPP6H2O in an ultrasonic bath at 50°C (3 hrs) as previously described for monocyclic 4,5-dimethylisothiazolium salts, 9 and obtained 3-hydroxy-3-methylsultam 8a with 57% yield (method B). In contrast to the oxidation-reduction method with Na2SO3 followed by elimination of water to produce 11a-e,g (method A), the method B starting from salts 6 was very convenient (Table 1). In the case of the 3-hydroxysultam 8c we observed the formation of 3-methylenesultam 11c from 8c by NMR-detection in DMSO-d6 at 120°C within 2 hrs.

<table>
<thead>
<tr>
<th>Table 1. Yield (%) of products 7-11</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>b</td>
</tr>
<tr>
<td>b</td>
</tr>
<tr>
<td>c</td>
</tr>
<tr>
<td>d</td>
</tr>
<tr>
<td>e</td>
</tr>
<tr>
<td>f</td>
</tr>
<tr>
<td>g</td>
</tr>
</tbody>
</table>

a 3:1 mixture with 11 d. b 1:2 mixture with 11e. c method A. d 57% by using method B / 48% by using method C. e 53% by using method C. f solution of 7d in DMSO-d6. g solution of 7f in DMSO-d6. h method E. i 23% by using method D. j 1:3 mixture with 7d. k 2:1 mixture with 7e.

Furthermore, when the salt 6a is reacted with MMPP6H2O in ethanol in an ultrasonic bath (method D), the 3-ethoxysultam 9a was synthesized after 3 hrs resulting in a yield of 23%. In contrast, refluxing of the exomethylenesultams 11a,c in ethanol produced 3-ethoxysultams 9a,c resulting in good yields in a range of 60-63% (method E).

Finally the oxidation of the salts 6b, d-g with hydrogen peroxide at 70 °C afforded the 3-oxosultams 10b,d-g as we have already described for 6a,c. 10 The mechanism of this reaction is explained by formation of 3-hydroperoxysultams 7, which are not isolated, but give stable 3-oxosultams 10 by elimination of water and methanol. The structure of these compounds was confirmed by X-ray structure analysis for derivative 10a in a former paper. 10
Conclusions

In summary, the oxidation of isothiazolium salts 6 with \( \text{H}_2\text{O}_2 \) gives new 3-hydroperoxysultams 7 and 3-oxosultams 10. A new efficient method is introduced for the synthesis of 3-hydroxy- and 3-alkoxyxultams 8 and 9 in a one-step reaction of isothiazolium salts 6 with MMPP6H2O, and also in a multi-step reaction via novel 3-methylene-functionalized sultams 11.

Experimental Section

General. Melting points were measured on a Boetius micro-melting-point apparatus and are corrected. \(^1\)H- and \(^13\)C-NMR spectra were recorded on a Varian Gemini-200MHz spectrometer using deuterochloroform or DMSO-d\(_6\) as solvent and with TMS as internal standard; \( \delta \) values are recorded in ppm. IR spectra were recorded on a Genesis FTIR Unicam Analytical System (ATI Mattson) as KBr-pellets; \( \nu_{\text{max}} \) are in cm\(^{-1}\). Mass spectra were performed on a Quadrupole-MS VG 12-250 operating at an ionization potential of 70eV, and elemental analyses were performed on a Heraeus CHNO Rapid Analyzer.

General procedure for the preparation of 4,5-dialkyl-2-aryl-isothiazolium perchlorates (4) and 3,4-dialkyl-2-aryl-isothiazolium perchlorates (6)

The isothiazolium salts 4 and 6 were prepared according to the procedure described.\(^{10,12,13}\)

General procedure for the preparation of 2-aryl-3-hydroperoxy-2,3-dihydroisothiazole 1,1-dioxides (7)

The new 3-hydroperoxysultams 7b, d-g were prepared according to the procedure described.\(^10\)

3-Hydroperoxy-3,4-dimethyl-2-(4-methylphenyl)-2,3-dihydroisothiazole 1,1-dioxide (7b).

Yield: 52%, 0.14g. colourless crystals. m.p. 87-91°C. IR (KBr-pellets, \( \nu_{\text{max}} \), cm\(^{-1}\)): 1168 (SO\(_2\)), 1276 (SO\(_2\)). \(^1\)H-NMR (200MHz, CDCl\(_3\)): \( \delta = 1.34 \) (s, 3H, CH\(_3\)); 2.08 (s, 3H, CH\(_3\)); 2.38 (s, 3H, p-CH\(_3\)); 6.60 (s(br), 1H, =CH-5); 7.23 (d, J\(_{AB} = 8.0\) Hz, 2H, arom. H)); 7.39 (d, J\(_{AB} = 8.0\) Hz, 2H, arom. H). \(^13\)C-NMR (50MHz, CDCl\(_3\)): \( \delta = 12.6\) (CH\(_3\)); 18.9 (CH\(_3\)); 27.6 (p-CH\(_3\)); 121.7 (CH-5); 124.7 (i-C); 130.9 (o-CH); 131.3 (m-CH); 139.9 (p-C); 149.6 (C-4). MS (EI 70eV): \( \text{m/z} \) (%) = 251.0 ([M\(^{+}\)-H\(_2\)O\(^{+}\)]\(^{+}\)). Anal. Calcd for C\(_{18}\)H\(_{19}\)NO\(_4\)S (269.3) C: 53.52, H 5.61, N 5.34, O 19.34. Found C 53.49, H 5.43, N 5.34, O 23.60%.

2-(4-Chlorophenyl)-3-hydroperoxy-3,4-dimethyl-2,3-dihydroisothiazole 1,1-dioxide (7d).

Yield: 27%, 0.07g (3:1 mixture with 11d). colourless crystals. m.p. 94-98°C. IR (KBr-pellets, \( \nu_{\text{max}} \), cm\(^{-1}\)): 1171 (SO\(_2\)), 1276 (SO\(_2\)). \(^1\)H-NMR (200MHz, CDCl\(_3\)): \( \delta = 1.32 \) (s, 3H, CH\(_3\)); 2.06 (s, 3H, CH\(_3\)); 6.60 (s(br), 1H, =CH-5); 7.38 (d, J\(_{AB} = 9.20\) Hz, 2H, arom. H); 7.48 (d, J\(_{AB} = 9.21\) Hz, 2H, arom. H). \(^13\)C-NMR (50MHz, CDCl\(_3\)): \( \delta = 13.3\) (CH\(_3\)); 19.5 (CH\(_3\)); 98.1 (C-3); 125.4 (CH-
5); 130.2 (o-CH); 131.5 (i-CH); 132.2 (m-CH); 135.6 (p-CH); 149.7 (C-4). MS (EI 70eV): m/z (%) = 271.0 ([M+H₂O]+). C₁₁H₂ClNO₄S (289.7).

2-(4-Bromophenyl)-3-hydroperoxy-3,4-dimethyl-2,3-dihydroisothiazole 1,1-dioxide (7e). Yield: 6%, 0.02g (2:1 mixture with 11e). colourless crystals. m.p. 102-105 °C. IR (KBr-pellets, νmax. cm⁻¹): 1171 (SO₂), 1277 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 1.37 (s, 3H, CH₃); 2.10 (s, 3H, CH₃); 6.63 (s(br), 1H, =CH-5); 7.44 (d, JAB = 8.6 Hz, 2H, arom. H); 7.54 (d, JAB = 8.6 Hz, 2H, arom. H) MS (EI 70eV): m/z (%) = 316.0 ([M+H₂O]+). C₁₁H₁₂BrNO₄S (334.2).

4-Ethyl-3-hydroperoxy-2-(4-methoxyphenyl)-3-methyl-2,3-dihydroisothiazole 1,1-dioxide (7f). Yield: 33%, 0.09g. colourless crystals. m.p. 115-118°C. IR (KBr-pellets, νmax. cm⁻¹): 1165 (SO₂), 1249 (OCH₃), 1284 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 1.27 (t, ³J = 7.2 Hz, 3H, CH₃); 1.34 (s, 3H, CH₃); 2.32-2.36 (m, 1H, CH₂); 2.46-2.50 (m, 1H, CH₂); 3.83 (s, 3H, OCH₃); 6.61 (s(br), 1H, =CH-5); 6.96 (d, JAB = 8.8 Hz, 2H, arom. H); 7.41 (d, J = 8.8 Hz, 2H, arom. H); 8.39 (s, 1H, OOH); ¹³C-NMR (50MHz, CDCl₃): δ = 11.3 (CH₃); 20.0 (CH₂); 20.6 (CH₂); 98.4 (C-3); 115.4 (m-CH); 122.9 (i-C); 123.4 (CH-5); 133.5 (o-CH); 155.6 (C-4); 160.9 (p-CH). MS (EI 70eV): m/z (%) = 265.0 ([M+H₂O], -CH₃). Anal. Calcd for C₁₃H₁₇NO₅S (299.3) C: 52.16, H 5.72, N 4.68; O 26.72; found C 52.46, H 5.63, N 4.81, O 26.76%.

4-Ethyl-3-hydroperoxy-3-methyl-2,3-dihydroisothiazole 1,1-dioxide (7g). Yield: 19%, 0.05g. colourless crystals. m.p. 109-111°C. IR (KBr-pellets, νmax. cm⁻¹): 1164 (SO₂), 1287 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 1.24 (t, ³J = 7.3 Hz, 3H, CH₃); 1.35 (s, 3H, CH₃); 2.26-2.36 (m, 1H, CH₂); 2.43-2.57 (m, 1H, CH₂); 6.57 (s(br), 1H, =CH-5); 7.40-7.45 (m, 3H, arom. H); 7.52-7.55 (m, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 12.3 (CH₃); 20.0 (CH₂); 20.9 (CH₂); 98.6 (C-3); 123.5 (CH-5); 129.6 (p-CH); 130.2 (o-CH); 131.1 (m-CH); 131.4 (i-C); 155.7 (C-4). MS (EI 70eV): m/z (%) = 269.0 (Mᵢ). Anal. Calcd for C₁₂H₁₅NO₃S (269.3) C: 53.52, H 5.61, N 5.20; O 23.76; found C 52.83, H 5.47, N 5.29, O 23.60%.

General procedure for the preparation of 2-aryl-3-hydroxy-2,3-dihydroisothiazole 1,1-dioxides (8)

Method A. 0.5 mmol 3-methylene-2,3-dihydroisothiazole 1,1-dioxide 11 is dissolved in 10 mL of a 1:1 mixture of ethanol and distilled water and refluxed for 5-10 minutes. By slow removal of a little solvent, crystals of 8 are obtained, filtered off and dried.

Method B. 0.25 mmol isothiazolium salt 6 is dissolved in 4 mL of a 3:1 mixture of acetonitrile and water. Then 1.5 mmol MMPP 6H₂O is added and the mixture is stirred for 3 hrs at 50°C in an ultrasonic bath. To the mixture is given sat. NaHCO₃ solution and extracted with diethylether (3x). The combined organic layers are dried over anhydrous MgSO₄. The solvent is evaporated and 8 is purified by recrystallization from ethanol.

Method C. 0.5 mmol 3-hydroperoxysultam 7 are dissolved in 2 mL DMSO. After 2 hrs standing at room temperature the solution of 8 was lyophilized and the precipitated 3-hydroxyisultams were filtered off and purified by recrystallization from acetone.

3-Hydroxy-2-(4-methoxyphenyl)-3,4-dimethyl-2,3-dihydroisothiazole 1,1-dioxide (8a). Yield: 70%, 0.09 g (method A) / 57%, 0.04 g (method B) / 48%, 0.06 g (method C). Colourless
3-Hydroxy-3,4-dimethyl-2-(4-methylphenyl)-2,3-dihydroisothiazole 1,1-dioxide (8b). Yield: 63%, 0.08g (method A) / 53%, 0.07g (method C). Colourless needles. m.p. 122-124°C. IR (KBr-pellets, v_max, cm⁻¹): 1145 (SO₂), 1274 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 1.40 (s, 3H, CH₃); 2.07 (s, 3H, CH₃); 2.39 (s, 3H, p-CH₃); 3.64 (s, 1H, OH); 6.51 (s(br), 1H, =CH-5); 7.18 (d, J_AB = 8.2 Hz, 2H, arom. H); 7.37 (d, J_AB = 8.2 Hz, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 13.7 (CH₃); 21.6 (p-CH₃); 23.5 (CH₃); 90.3 (C-3); 115.3 (m-CH); 122.8 (CH-5); 132.3 (i-C); 134.1 (o-CH); 161.0 (C-4); 164.1 (p-C). MS (EI 70eV): m/z (%) = 253.0 (M⁺). Anal. Calcld for C₁₂H₁₃NO₃S (239.3) C: 56.90, H 5.97, N 5.53; O 18.95; found C 56.59, H 5.72, N 5.43, O 19.20%. 

3-Hydroxy-3,4-dimethyl-2-phenyl-2,3-dihydroisothiazole 1,1-dioxide (8c). Yield: 81%, 0.09g (method A). Colourless needles. m.p 128-131 °C. IR (KBr-pellets, v_max, cm⁻¹): 1139 (SO₂), 1284 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 1.44 (s, 3H, CH₃); 2.12 (s, 3H, CH₃); 3.23 (s, 1H, OH); 6.53 (s(br), 1H, =CH-5); 7.44-7.47 (m, 3H, arom. H); 7.51-7.53 (m, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 13.6 (CH₃); 23.5 (CH₃); 90.5 (C-3); 123.0 (CH-5); 129.7 (p-C); 130.1 (o-CH); 131.6 (i-C); 132.0 (m-CH); 152.5 (C-4). MS (EI 70eV): m/z (%) = 239.0 (M⁺). Anal. Calcld for C₁₁H₁₂NO₃S (239.3) C: 52.21, H 5.48, N 5.85; O 20.06; found C 54.77, H 5.59, N 5.82, O 20.80%. 

2-(4-Chlorophenyl)-3-hydroxy-3,4-dimethyl-2,3-dihydroisothiazole 1,1-dioxide (8d). Yield: 99% (solution from 7d in DMSO-d₆). ¹H-NMR (200MHz, DMSO-d₆): δ = 1.32 (s, 3H, CH₃); 2.04 (s, 3H, CH₃); 7.13 (s(br), 1H, =CH-5); 7.50 (d, J_AB = 9.0 Hz, 2H, arom.H); 7.57 (d, J_AB = 9.0 Hz, 2H, arom.H). ¹³C-NMR (50MHz, DMSO-d₆): δ = 12.6 (CH₃); 23.8 (CH₃); 90.3 (C-3); 122.0 (CH-5); 129.4 (o-CH); 131.8 (m-CH); 132.8 (i-C); 141.3 (p-C); 152.8 (C-4). C₁₁H₁₂ClNO₃S (273.7) 

4-Ethyl-3-hydroxy-2-(4-methoxyphenyl)-3-methyl-2,3-dihydroisothiazole 1,1-dioxide (8f). Yield: 99% (solution from 7d in DMSO-d₆). ¹H-NMR (200MHz, DMSO-d₆): δ = 1.15 (t, 3J = 7.3 Hz, 3H, CH₃); 1.25 (s, 3H, CH₃); 2.39 (m, 2H, CH₂); 3.78 (s, 3H, OCH₃); 7.04 (s(br), 1H, CH-5); 7.02 (d, J_AB = 8.9 Hz, 2H, arom.H); 7.31 (d, J_AB = 8.9 Hz, 2H, arom.H). ¹³C-NMR (50MHz, DMSO-d₆): δ = 10.8 (CH₃); 19.4 (CH₂); 24.0 (CH₃); 55.3 (OCH₃); 89.4 (C-3); 114.2 (m-CH); 120.5 (CH-5); 123.4 (i-C); 133.3 (o-CH); 158.3 (p-C); 159.4 (C-4). C₁₃H₁₇NO₄S (283.3) 

4-Ethyl-3-hydroxy-3-methyl-2-phenyl-2,3-dihydroisothiazole 1,1-dioxide (8g). Yield: 40%, 0.05g (method A). Colourless needles. m.p. 93-98°C. IR (KBr-pellets, v_max, cm⁻¹): 1128 (SO₂), 1265 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 1.26 (t, 3J = 7.3 Hz, 3H, CH₃); 1.43 (s, 3H, CH₃);
2.30 (m, 1H, CH2); 2.41 (m, 1H, CH2); 3.46 (s, 1H, OH); 6.50 (s(br), 1H, =CH-5); 7.43-7.45 (m, 3H arom. H); 7.47-7.53 (m, 2H arom. H). 13C-NMR (50MHz, CDCl3): δ = 11.5 (CH3); 20.6 (CH2); 23.7 (CH3); 90.7 (C-3); 121.3 (CH5); 129.6 (o-CH); 131.6 (i-C); 132.0 (m-CH); 158.8 (C-4). MS (EI 70eV): m/z (%) = 253.0 (M+). Anal. Calcd for C12H15NO3S (253.3) C: 56.90, H 5.97, N 5.53; O 18.95; found C 57.38, H 6.09, N 5.55, O 19.15%.

General procedure for the preparation of 2-aryl-3-ethoxy-2,3-dihydroisothiazole 1,1-dioxides (9)
Method D: 0.25 mmol isothiazolium salt 6 is dissolved with 4 mL ethanol. Then 1.5 mmol MMPP6H2O is added and stirred for 3hrs at 50°C in ultrasonic bath. To the mixture is given sat. NaHCO3-solution and the mixture is extracted with diethylether (3x). The combined organic layers are dried over MgSO4. The solvent is evaporated and 9 is purified by recrystallization from ethanol.
Method E: 0.5 mmol 3-methylene-2,3-dihydroisothiazole 1,1-dioxide 11 is refluxed with ethanol. After 10 min a small volume of the solvent is evaporated. Crystals of 9 are obtained, filtered off and dried.

3-Ethoxy-2-(4-methoxyphenyl)-3,4-dimethyl-2,3-dihydroisothiazole 1,1-dioxide (9a). Yield: 23%, 0.02g (method D) / 60% 0.09g (method E). colourless powder. m.p. 108-110°C. IR (KBr-pellets, νmax, cm⁻¹): 1179 (SO2), 1247 (OCH3), 1287 (SO2). 1H-NMR (200MHz, CDCl3): δ = 1.24 (t, J = 7.2 Hz, 3H, CH3); 1.39 (s, 3H, CH3); 2.01 (d, J = 1.8 Hz, 3H, CH3); 3.21 (dq, J = 12.8 Hz, J = 7.2 Hz, 1H, OCH2); 3.82 (dq, J = 12.8 Hz, J = 7.2 Hz, 1H, OCH3); 6.60 (q, J = 1.8 Hz, 1H, =CH-5); 6.95 (d, J = 9.0 Hz, 2H, arom. H ); 7.31 (d, J = 9.0 Hz, 2H, arom.H). 13C-NMR (50MHz, CDCl3): δ = 13.8 (CH3); 19.1 (CH3); 19.1 (CH3); 23.8 (CH3); 56.1 (OCH3); 94.4 (C-3); 115.3 (m-CH); 123.8 (i-C); 124.9 (CH5); 123.9 (o-CH); 150.1 (C-4); 160.5 (p-C). MS (EI 70eV): m/z (%) = 297.0 (M+). Anal. Calcd for C14H19NO3S (297.3) C: 56.55, H 6.44, N 4.71; O 21.52; found C 56.80, H 6.56, N 4.72, O 21.70%.

3-Ethoxy-3,4-dimethyl-2-phenyl-2,3-dihydroisothiazole 1,1-dioxide (9c). Yield: 66%, 0.09g (method E). colourless powder. m.p. 88-90°C. IR (KBr-pellets, νmax, cm⁻¹): 1179 (SO2), 1286 (SO2). 1H-NMR (200MHz, CDCl3): δ = 1.22 (t, J = 7.3 Hz, 3H, CH3); 1.44 (s, 3H, CH3); 2.01 (d, J = 1.7 Hz, 3H, CH3); 3.25 (dq, J = 13.0 Hz, J = 7.3 Hz, 1H, OCH2); 3.75 (dq, J = 13.0 Hz, J = 7.3 Hz, 1H, OCH2); 6.60 (q, J = 1.7 Hz, 1H, =CH-5); 7.38-7.49 (m, 5H arom. H). 13C-NMR (50MHz, CDCl3): δ = 13.3 (CH3); 23.4 (CH3); 58.8 (CH2); 94.6 (C-3); 124.6 (CH5); 128.3 (p-C); 129.0 (o-CH); 129.9 (m-CH); 132.6 (i-C); 149.8 (C-4). MS (EI 70eV): m/z (%) = 267.0 (M+). Anal. Calcd for C13H17NO3S (267.3) C: 58.40, H 6.41, N 5.24; O 17.95; found C 58.82, H 6.45, N 5.49, O 18.00%.

General synthetic procedure for the preparation of 2-arylisothiazol-3(2H)-one 1,1-dioxides (10). The new sultams 10b, d-g are prepared according to the procedure described.10
4-Methyl-2-(4-methylphenyl)-isothiazol-3(2H)-one 1,1-dioxide (10b). Yield: 33%, 0.07g. colourless needles. m.p. 200-202°C. IR (KBr-pellets, cm⁻¹): 1188 (SO₂), 1329 (SO₂), 1743 (C=O). ¹H-NMR (200MHz, CDCl₃): δ = 2.22 (d, ⁴J = 1.5 Hz, 3H, CH₃); 2.41 (s, 3H, p-CH₃); 7.16 (q, ⁴J = 1.5 Hz, 1H, =CH-5); 7.38-7.39 (m, 4H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 12.5 (CH₃); 21.9 (p-CH₃); 126.5 (i-C); 128.7 (o-CH); 131.2 (m-CH); 132.1 (CH-5); 141.0 (C-4); 141.4 (p-C); 160.8 (C=O). MS (EI 70eV): m/z (%) = 237.0 (M⁺). Anal. Calcd for C₁₁H₁₁NO₃S (237.3) C: 55.68, H 4.67, N 5.90; found C 55.04, H 4.88, N 6.16, O 20.40%.

2-(4-Chlorophenyl)-4-methyl-isothiazol-3(2H)-one 1,1-dioxide (10d). Yield: 10%, 0.02g. colourless powder. m.p. 161-163°C. IR (KBr-pellets, cm⁻¹): 1187 (SO₂), 1331 (SO₂), 1743 (C=O). ¹H-NMR (200MHz, CDCl₃): δ = 2.23 (d, ⁴J = 1.5 Hz, 3H, CH₃); 7.18 (q, ⁴J = 1.5 Hz, 1H, =CH-5); 7.40 (d, J_AB = 9.0 Hz, 2H, arom. H); 7.50 (d, J = 9.0 Hz, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 12.5 (CH₃); 128.0 (i-C); 129.8 (o-CH); 130.9 (m-CH); 132.3 (CH-5); 136.7 (p-C); 141.4 (C-4); 160.5 (C=O). MS (EI 70eV): m/z (%) = 257.0/259.0 (M⁺). Anal. Calcd for C₁₀H₉ClNO₃S (257.7) C: 46.61, H 3.13, N 5.44; found C 46.28, H 3.07, N 5.48, O 18.70%.

2-(4-Bromophenyl)-4-methyl-isothiazol-3(2H)-one 1,1-dioxide (10e). Yield: 16%, 0.04g. colourless crystals. m.p. 121-123°C. IR (KBr-pellets, cm⁻¹): 1187 (SO₂), 1332 (SO₂), 1743 (C=O). ¹H-NMR (200MHz, CDCl₃): δ = 2.22 (d, ⁴J = 1.7 Hz, 3H, CH₃); 7.18 (q, ⁴J = 1.7 Hz, 1H, =CH-5); 7.34, (d, J_AB = 8.7 Hz, 2H, arom. H); 7.64 (d, J = 8.7 Hz, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 12.3 (CH₃); 124.6 (p-C); 128.4 (i-C); 129.8 (o-CH); 132.0 (CH-5); 133.6 (m-CH); 141.2 (C-4); 160.3 (C=O). MS (EI 70eV): m/z (%) = 301.0/303.0 (M⁺). Anal. Calcd for C₁₀H₈BrNO₃S (302.1) C: 39.75, H 2.67, N 4.64; found C 39.56, H 2.44, N 4.42, O 16.00%.

4-Ethyl-2-(4-methoxylphenyl)-isothiazol-3(2H)-one 1,1-dioxide (10f). Yield: 9%, 0.02g. colourless needles. m.p. 133-134°C. IR (KBr-pellets, cm⁻¹): 1180 (SO₂), 1256 (OCH₃), 1324 (SO₂), 1738 (C=O). ¹H-NMR (200 MHz, CDCl₃): δ = 1.22 (t, ³J = 7.6 Hz, 3H, CH₃); 2.61 (dq, ³J = 7.6 Hz, J = 1.8 Hz, 2H, CH₂); 3.84 (s, 3H, OCH₃); 7.01 (d, J = 8.9 Hz, 2H, arom. H); 7.09 (d, ³J = 1.8 Hz, 1H, =CH-5); 7.34 (d, J_AB = 8.9 Hz, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 11.6 (CH₃); 20.2 (CH₂); 56.2 (OCH₃); 115.9 (m-CH); 121.2 (i-C); 130.6 (o-CH); 130.8 (CH-5); 147.3 (C-4); 160.6 (p-C); 160.8 (C=O). MS (EI 70eV): m/z (%) = 267.0 (M⁺). Anal. Calcd for C₁₂H₁₃NO₄S (267.3) C: 53.92, H 4.90, N 5.24; found C 54.10, H 4.85, N 5.32, O 23.50%.

4-Ethyl-2-phenyl-isothiazol-3(2H)-one 1,1-dioxide (10g). Yield: 21%, 0.05g. colourless needles. m.p. 135-137°C. IR (KBr-pellets, cm⁻¹): 1182 (SO₂), 1322 (SO₂), 1739 (C=O). ¹H-NMR (200MHz, CDCl₃): δ = 1.27 (t, ³J = 7.2 Hz, 3H, CH₃); 2.61 (dq, ³J = 7.2 Hz, ⁴J = 2.0 Hz, 2H, CH₂); 7.1 (t, ⁴J = 2.0 Hz, 1H, =CH-5); 7.43-7.54 (m, 5H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 11.5 (CH₃); 20.2 (CH₂); 128.7 (o-CH); 129.4 (p-CH); 130.5 (m-CH); 130.8 (CH-5); 147.2 (C-4); 160.4 (C=O). MS (EI 70eV): m/z (%) = 237.0 (M⁺). Anal. Calcd for C₁₁H₁₁NO₃S (237.3) C: 55.68, H 4.67, N 5.90; found C 55.53, H 4.57, N 5.92, O 20.70%.
General procedure for the preparation of 2-aryl-3-methylene-2,3-dihydroisothiazole 1,1-dioxides (11). 1.0 mmol 2-aryl-3-hydroperoxy-2,3-dihydroisothiazole 1,1-dioxide 7 is suspended in 3 mL distilled water and 1.0 mmol Na₂SO₃·7H₂O is added. After 24 hrs stirring at room temperature 3 mL water are added to the mixture and extracted with 20 mL diethyl ether. The organic layers are washed with sat. NaCl-solution and water and dried over anhydrous Na₂SO₄. After evaporation of the solvent crystals of 11 are filtered off and dried.

2-(4-Methoxyphenyl)-4-methyl-3-methylene-2,3-dihydroisothiazole 1,1-dioxide (11a). Yield: 44%, 0.11g. colourless crystals. m.p. 108-110°C. IR (KBr-pellets, νmax, cm⁻¹): 1139 (SO₂), 1252 (OCH₃), 1267 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 2.17 (d, 4J = 1.4 Hz, 3H, CH₃); 3.84 (s, 3H, OCH₃); 4.26 (m, 1H, =CH₂); 4.63 (m, 1H, =CH₂); 6.51 (s(br), 1H, =CH-5); 6.99 (d, J = 8.9 Hz, 2H, arom. H); 7.35 (d, J = 8.9 Hz, 2H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 14.6 (CH₃); 57.0 (OCH₃); 92.2 (CH₂); 116.8 (m-CH); 122.2 (CH-5); 125.4 (i-C); 133.2 (o-CH); 142.3 (C-4); 145.3 (C-3); 161.9 (p-C). MS (EI 70eV): m/z (%) = 251.0 (M⁺). Anal. Calcd for C₁₂H₁₃NO₃S (251.3) C: 57.35, H 5.21, N 5.57; O 19.10; found C 56.86, H 5.42, N 5.51, O 19.00%.

2-(4-Methylphenyl)-4-methyl-3-methylene-2,3-dihydroisothiazole 1,1-dioxide (11b). Yield: 63%, 0.15g. colourless crystals. m.p. 116-118°C. IR (KBr-pellets, νmax, cm⁻¹): 1145 (SO₂), 1275 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 2.20 (d, 4J = 1.3 Hz, 3H, CH₃); 2.40 (s, 3H, p-CH₃); 4.31 (m, 1H, =CH₂); 4.65 (m, 1H, CH₃); 6.51 (s(br), 1H, =CH-5); 7.30-7.31 (m, 4H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 13.4 (CH₃); 21.7 (p-CH₃); 91.3 (CH₂); 121.2 (CH-5); 128.5 (o-CH); 130.0 (i-C); 131.1 (m-CH); 140.0 (C-4); 140.8 (p-C); 143.8 (C-3). MS (EI 70eV): m/z (%) = 235.0 (M⁺). Anal. Calcd for C₁₂H₁₄NO₂S (235.3) C: 61.25, H 5.57, N 5.95; O 13.60; found C 61.60, H 5.63, N 5.86, O 13.69%.

4-Methyl-3-methylene-2-phenyl-2,3-dihydroisothiazole 1,1-dioxide (11c). Yield: 55%, 0.12g. colourless crystals. m.p. 138-140°C. IR (KBr-pellets, νmax, cm⁻¹): 1140 (SO₂), 1269 (SO₂). ¹H-NMR (200MHz, CDCl₃): δ = 2.18 (d, 4J = 1.3 Hz, 3H, CH₃); 4.33 (m, 1H, =CH₂); 4.68 (m, 1H, CH₃); 6.52 (s(br), 1H, =CH-5); 7.44-7.50 (m, 5H, arom. H). ¹³C-NMR (50MHz, CDCl₃): δ = 13.8 (CH₃); 91.7 (CH₂); 121.3 (CH-5); 130.0 (o-CH); 130.4 (m-CH); 130.6 (p-CH); 132.6 (i-C); 141.5 (C-4); 143.8 (C-3). MS (EI 70eV): m/z (%) = 221.0 (M⁺). Anal. Calcd for C₁₁H₁₁NO₂S (221.3) C: 59.71, H 5.01, N 6.33; O 14.46; found C 60.06, H 5.11, N 6.41, O 14.36%.

2-(4-Chlorophenyl)-4-methyl-3-methylene-2,3-dihydroisothiazole 1,1-dioxide (11d). Yield: 10%, 0.02g (1:3 mixture with 7d). colourless crystals. ¹H-NMR (200MHz, CDCl₃): δ = 2.21 (d, 4J = 1.4 Hz, 3H, CH₃); 4.36 (m, 1H, =CH₂); 4.66 (d, 1H, =CH₂); 6.50 (s(br), 1H, =CH-5); 7.51, 8.17 (d, 4H, JAB = 9.2Hz). ¹³C-NMR (50MHz, CDCl₃): δ = 13.5 (CH₃); 91.9 (CH₂); 121.0 (CH-5); 124.5 (o-CH); 130.6 (m-CH); 130.8 (p-C); 135.7 (i-C); 141.3 (C-4); 143.4 (C-3). MS (EI 70eV): m/z (%) = 255.0/257.0 (M⁺). C₁₁H₁₀ClNO₂S (255.7).

2-(4-Bromophenyl)-4-methyl-3-methylene-2,3-dihydroisothiazole 1,1-dioxide (11e). Yield: 12%, 0.03g (2:1 mixture with 7e). colourless crystals. ¹H-NMR (200MHz, CDCl₃): δ = 2.18 (d, 4J = 1.2 Hz, 3H, CH₃); 4.34 (m, 1H, =CH₂); 4.70 (m, 1H, CH₂); 6.52 (s(br), 1H, =CH-5);
7.32-7.62 (d, 4H, \( J_{AB} = 8.6 \) Hz). \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \( \delta = 13.8 \) (CH\(_3\)); 92.0 (CH\(_2\)); 121.3 (CH-5); 129.9 (i-C); 131.9 (o-CH); 133.7 (p-C); 133.9 (m-CH); 142.8 (C-4); 143.6 (C-3). MS (EI 70eV): \( m/z \) (%) = 299.0/301.0 (M\(^+\)'). C\(_{11}\)H\(_9\)BrNO\(_2\)S (300.2).

4-Ethyl-3-methylene-2-phenyl-2,3-dihydroisothiazole 1,1-dioxide (11g). Yield: 86%, 0.20g. colourless needles. m.p. 112-115°C. IR (KBr-pellets, \( \nu_{max} \), cm\(^{-1}\)): 1130 (SO\(_2\)), 1279 (SO\(_2\)).

\(^1\)H-NMR (200MHz, CDCl\(_3\)): \( \delta = 1.28 \) (t, \( ^3J = 7.4 \) Hz, 3H, CH\(_3\)); 2.54 (dq, \( ^3J = 7.4 \) Hz, \( ^4J = 1.4 \) Hz, 2H, CH\(_2\)); 4.31 (t, 1H, \( =CH_2a \)); 4.69 (d, 1H, \( =CH_2b \)); 6.50 (s(br), 1H, CH-5); 7.42-7.53 (m, 5H, arom. H). \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \( \delta = 11.6 \) (CH\(_3\)); 20.6 (CH\(_2\)); 91.2 (CH\(_2\)); 121.3 (CH-5); 130.4 (o-CH); 130.6 (m-CH); 132.0 (p-CH); 132.5 (i-C); 143.3 (C-4); 147.4 (C-3). MS (EI 70eV): \( m/z \) (%) = 235.0 (M\(^+\)'). Anal. Calcd for C\(_{12}\)H\(_{13}\)NO\(_2\)S (235.3) C: 61.25, H 5.57, N 5.95; O 13.60; found C 61.50, H 5.61, N 5.84, O 13.66%.

References