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

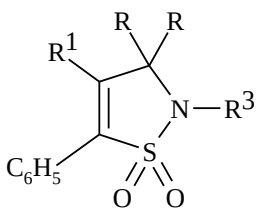
A new approach to 2-aryl-3-methylene-2,3-dihydroisothiazole 1,1-dioxides **11** from 3,4-dialkyl substituted *N*-phenyl-isothiazolium salts **6** via stable hydroperoxides **7** by reduction and elimination of water is introduced. Furthermore, 2-aryl-3-methylene-2,3-dihydroisothiazole 1,1-dioxides **11**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

Keywords: Oxidations, hydroperoxides, sultams, methylene substituted isothiazoles

Introduction

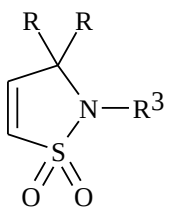
Functionalized monocyclic sultams are known in the recent years to attract much attention due to their importance in biological and pharmaceutical research.[1] The first monocyclic 2,3-dihydro-isothiazole 1,1-dioxide **1** ($R^1 = NH_2$) with anti-HIV-1 activity has recently been prepared.[1-3] The sultams **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]



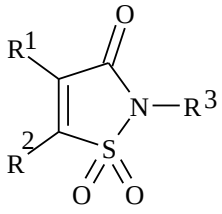
1

R = H, Me, t-Bu
R^1 = NH_2, OH
R^3 = H, Me, Bz



2

R = H, Me, t-Bu
R^3 = H, Me, Bz



3

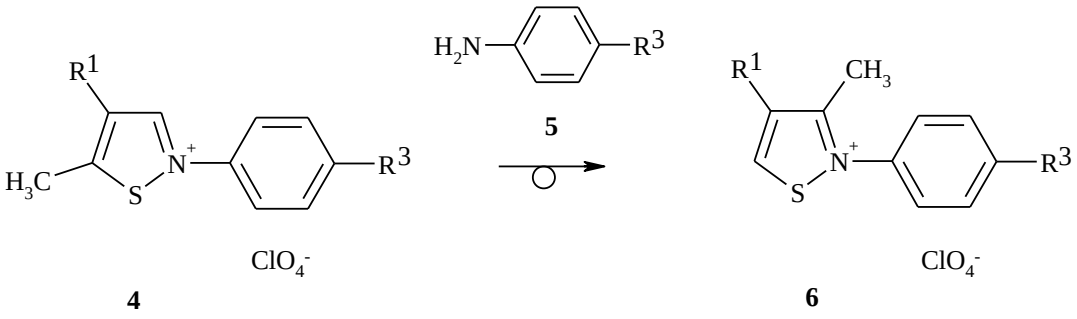
R^1 = R^2 = H, Me
R^3 = H, t-Bu, CH_2COOEt

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]

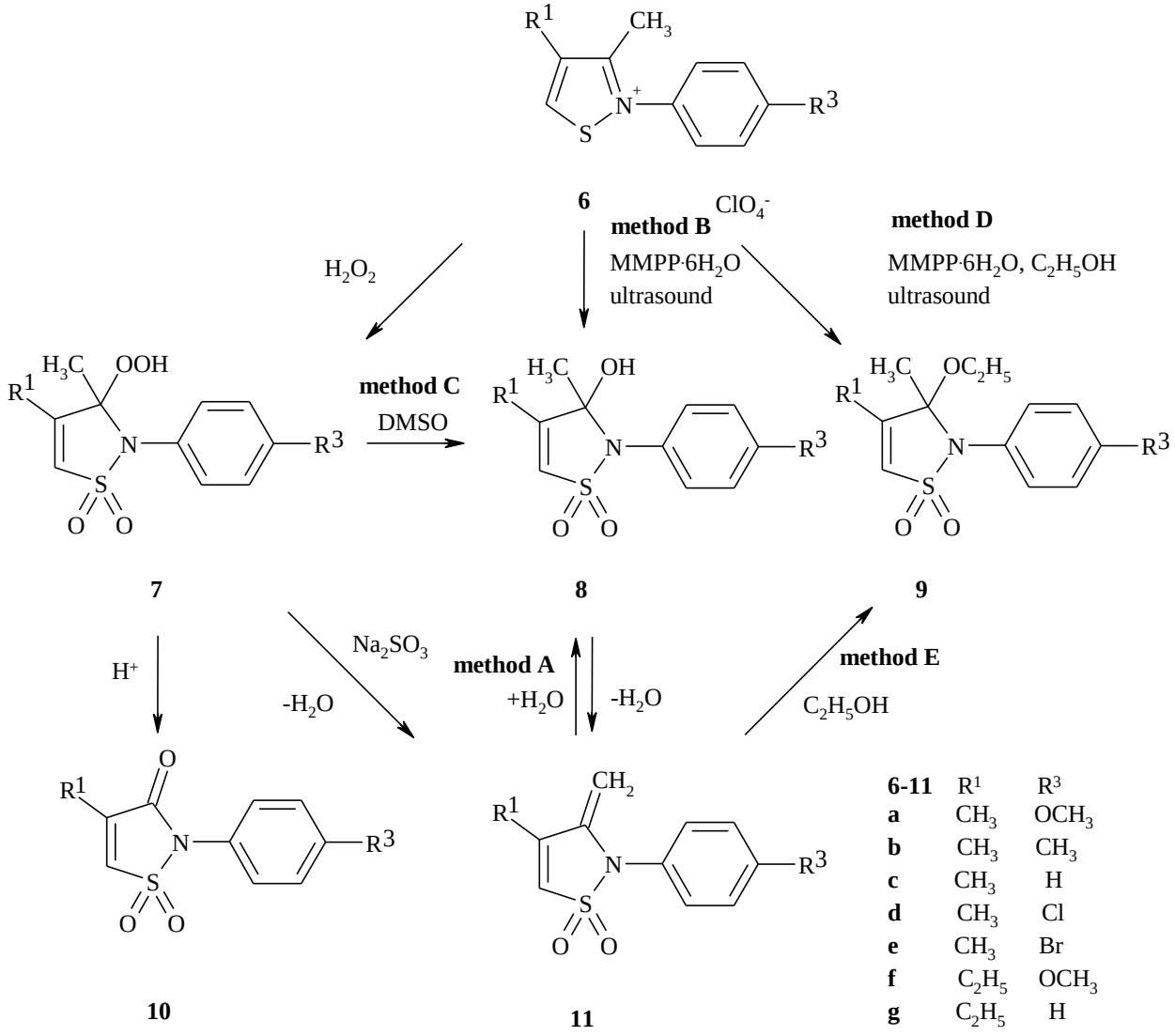


4 **5** **6**

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 $Na_2SO_3 \cdot 7H_2O$ 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-methylenthieno[2,3-*d*]isothiazole 1,1-dioxide, prepared from 3-thioxothieno[2,3-*d*]isothiazole 1,1-dioxide and diazomethane.[11]

Exomethylenesultams **11** are favourable 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 MMPP·$6H_2O$ 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 Na_2SO_3 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-d_6 at 120°C within 2 hrs.

Table 1. Yield (%) of products **7-11**

	R^1	R^3	**7**	**8**[c]	**9**[h]	**10**	**11**
b	Me	4-MeO	81[10]	70[d]	60[i]	36[10]	44
b	Me	4-Me	52	63[e]		33	63
c	Me	H	67[10]	81	66	47[10]	55
d	Me	4-Cl	27[a]	99[f]		10	10[j]
e	Me	4-Br	6[b]			16	12[k]
f	Et	4-MeO	33	99[g]		9	
g	Et	H	19	40		21	86

[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-d_6. [g] solution of **7f** in DMSO-d_6. [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 MMPP·$6H_2O$ 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 H_2O_2 gives new 3-hydroperoxysultams **7** and 3-oxosultams **10**. A new efficient method is introduced for the synthesis of 3-hydroxy- and 3-alkoxysultams **8** and **9** in a one-step reaction of isothiazolium salts **6** with MMPP·$6H_2O$, 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; δ values are recorded in ppm. IR spectra were recorded on a Genesis FTIR Unicam Analytical System (ATI Mattson) as KBr-pellets; ν_{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, ν_{max}, cm^{-1}): 1168 (SO_2), 1276 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 13.7 (CH_3); 19.8 (CH_3); 21.9 (*p*-CH_3); 98.3 (C-3); 124.7 (CH-5); 128.4 (*i*-C); 130.9 (*o*-CH); 131.3 (*m*-CH); 139.9 (*p*-C); 149.6 (C-4). MS (EI 70eV): *m/z* (%) = 251.0 ([M^+-H_2O]$^+$). Anal. Calcd for $C_{11}H_{13}NO_4S$ (269.3) C: 53.52, H 5.61, N 5.20; O 23.76; 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, ν_{max}, cm^{-1}): 1171 (SO_2), 1276 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 13.3 (CH_3); 19.5 (CH_3); 98.1 (C-3); 125.4 (CH-

5); 130.2 (*o*-CH); 131.5 (*i*-C); 132.2 (*m*-CH); 135.6 (*p*-C); 149.7 (C-4). MS (EI 70eV): *m/z* (%) = 271.0 ($[M^+-H_2O]^+$). $C_{11}H_{12}ClNO_4S$ (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, ν_{max}, cm^{-1}): 1171 (SO_2), 1277 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.37 (s, 3H, CH_3); 2.10 (s, 3H, CH_3); 6.63 (s(br), 1H, =CH-5); 7.44 (d, J_{AB} = 8.6 Hz, 2H, arom. H); 7.54 (d, J_{AB} = 8.6 Hz, 2H, arom. H) MS (EI 70eV): *m/z* (%) = 316.0 ($[M^+-H_2O]^+$). $C_{11}H_{12}BrNO_4S$ (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, ν_{max}, cm^{-1}): 1165 (SO_2), 1249 (OCH_3), 1284 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.27 (t, ^3J=7.2 Hz, 3H, CH_3); 1.34 (s, 3H, CH_3); 2.32-2.36 (m, 1H, CH_2^a); 2.46-2.50 (m, 1H, CH_2^b); 3.83 (s, 3H, OCH_3); 6.61 (s(br), 1H, =CH-5); 6.96 (d, J_{AB} = 8.8 Hz, 2H, arom. H); 7.41 (d, J = 8.8 Hz, 2H, arom. H); 8.39 (s, 1H, OOH); ^{13}C-NMR (50MHz, $CDCl_3$): δ = 11.3 (CH_3); 20.0 (CH_3); 20.6 (CH_2); 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*-C). MS (EI 70eV): *m/z* (%) = 265.0 ($[M^+-H_2O, -CH_3]^+$). Anal. Calcd for $C_{13}H_{17}NO_5S$ (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-phenyl-2,3-dihydroisothiazole 1,1-dioxide (7g). Yield: 19%, 0.05g. colourless crystals. m.p. 109-111°C. IR (KBr-pellets, ν_{max}, cm^{-1}): 1164 (SO_2), 1287 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.3 Hz, 3H, CH_3); 1.35 (s, 3H, CH_3); 2.26-2.36 (m, 1H, CH_2^a); 2.43-2.57 (m, 1H, CH_2^b); 6.57 (s(br), 1H, =CH-5); 7.40-7.45 (m, 3H, arom. H); 7.52-7.55 (m, 2H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 12.3 (CH_3); 20.0 (CH_3); 20.9 (CH_2); 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 (M^+). Anal. Calcd for $C_{12}H_{15}NO_4S$ (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·$6H_2O$ is added and the mixture is stirred for 3 hrs at 50°C in an ultrasonic bath. To the mixture is given sat. $NaHCO_3$ solution and extracted with diethylether (3x). The combined organic layers are dried over anhydrous $MgSO_4$. 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-hydroxysultams **8** were filtered off and are 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

needles. m.p. 150-153°C. IR (KBr-pellets, ν_{max}, cm^{-1}): 1140 (SO_2), 1221 (OCH_3), 1278 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.42 (s, 3H, CH_3); 2.11 (s, 3H, CH_3); 3.32 (s, 1H, OH); 3.83 (s, 3H, OCH_3); 6.53 (s(br), 1H, =CH-5); 6.69 (d, J_{AB} = 8.9 Hz, 2H, arom.H); 7.40 (d, J_{AB} = 8.9 Hz, 2H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.7 (CH_3); 23.5 (CH_3); 56.1 (OCH_3); 90.1 (C-3); 115.3 (*m*-CH); 122.8 (CH-5); 123.2 (*i*-C); 134.1 (*o*-CH); 161.0 (C-4); 164.1 (*p*-C). MS (EI 70eV): *m/z* (%) = 269.0 (M^+). Anal. Calcd for $C_{12}H_{15}NO_4S$ (269.3) C: 53.52, H 5.61, N 5.20; O 23.76; found C 53.47, H 5.87, N 5.52, O 23.70%.

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, ν_{max}, cm^{-1}): 1145 (SO_2), 1274 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.40 (s, 3H, CH_3); 2.07 (s, 3H, CH_3); 2.39 (s, 3H, *p*-CH_3); 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). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.7 (CH_3); 21.6 (*p*-CH_3); 23.5 (CH_3); 90.3 (C-3); 115.3 (*m*-CH); 122.6 (CH-5); 128.5 (*i*-C); 131.8 (*o*-CH); 139.6 (*p*-C); 152.6 (C-4). MS (EI 70eV): *m/z* (%) = 253.0 (M^+). Anal. Calcd for $C_{12}H_{15}NO_3S$ (253.3) 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. mp 128-131 °C. IR (KBr-pellets, ν_{max}, cm^{-1}): 1139 (SO_2), 1284 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.44 (s, 3H, CH_3); 2.12 (s, 3H, CH_3); 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). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.6 (CH_3); 23.5 (CH_3); 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. Calcd for $C_{11}H_{13}NO_3S$ (239.3) C: 55.21, H 5.48, N 5.85; O 20.06; found C 54.77, H 5.59, N 5.82, O 20.80%.

2-(4-Chlorphenyl)-3-hydroxy-3,4-dimethyl-2,3-dihydroisothiazole 1,1-dioxide (8d). Yield: 99% (solution from **7d** in DMSO-d_6). ^{1}H-NMR (200MHz, DMSO-d_6): δ = 1.32 (s, 3H, CH_3); 2.04 (s, 3H, CH_3); 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). ^{13}C-NMR (50MHz, DMSO-d_6): δ = 12.6 (CH_3); 23.8 (CH_3); 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). $C_{11}H_{12}ClNO_3S$ (273.7)

4-Ethyl-3-hydroxy-2-(4-methoxylphenyl)-3-methyl-2,3-dihydroisothiazole 1,1-dioxide (8f). Yield: 99% (solution from **7d** in DMSO-d_6). ^{1}H-NMR (200MHz, DMSO-d_6): δ = 1.15 (t, ^3J = 7.3 Hz, 3H, CH_3); 1.25 (s, 3H, CH_3); 2.39 (m , 2H, CH_2); 3.78 (s, 3H, OCH_3); 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). ^{13}C-NMR (50MHz, DMSO-d_6): δ = 10.8 (CH_3); 19.4 (CH_2); 24.0 (CH_3); 55.3 (OCH_3); 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). $C_{13}H_{17}NO_4S$ (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, ν_{max}, cm^{-1}): 1128 (SO_2), 1265 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.3 Hz, 3H, CH_3); 1.43 (s, 3H, CH_3);

2.30 (m, 1H, CH_2); 2.41 (m , 1H, CH_2); 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). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 11.5 (CH_3); 20.6 (CH_2); 23.7 (CH_3); 90.7 (C-3); 121.3 (CH-5); 129.6 (*p*-C); 130.0 (*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 $C_{12}H_{15}NO_3S$ (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 MMPP·$6H_2O$ is added and stirred for 3hrs at 50°C in ultrasonic bath. To the mixture is given sat. $NaHCO_3$-solution and the mixture is extracted with diethylether (3x). The combined organic layers are dried over $MgSO_4$. 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, ν_{max}, cm^{-1}): 1179 (SO_2), 1247 (OCH_3), 1287 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.2 Hz, 3H, CH_3); 1.39 (s, 3H, CH_3); 2.01 (d, ^4J = 1.8 Hz, 3H, CH_3); 3.21 (dq, ^2J = 12.8 Hz, ^3J = 7.2 Hz, 1H, OCH_2^a); 3.82 (dq, ^2J = 12.8 Hz, ^3J = 7.2 Hz, 1H, OCH_2^b); 3.83 (s, 3H, OCH_3); 6.60 (q, ^4J = 1.8 Hz, 1H, =CH-5); 6.95 (d, ^3J = 9.0 Hz, 2H, arom. H); 7.31 (d, ^3J = 9.0 Hz, 2H, arom.H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.8 (CH_3); 19.1 (CH_3); 19.1 (CH_3); 23.8 (CH_3); 56.1 (OCH_3); 59.5 (CH_2); 94.4 (C-3); 115.3 (*m*-CH); 123.8 (*i*-C); 124.9 (CH-5); 132.9 (*o*-CH); 150.1 (C-4); 160.5 (*p*-C). MS (EI 70eV): *m/z* (%) = 297.0 (M^+). Anal. Calcd for $C_{14}H_{19}NO_4S$ (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, ν_{max}, cm^{-1}): 1179 (SO_2), 1286 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.3 Hz, 3H, CH_3); 1.44 (s, 3H, CH_3); 2.01 (d, ^4J =1.7 Hz, 3H, CH_3); 3.25 (dq, ^2J =13.0 Hz, ^3J =7.3 Hz, 1H, OCH_2^a); 3.75 (dq, ^2J = 13.0 Hz, ^3J = 7.3 Hz, 1H, OCH_{2b}); 6.60 (q, ^4J =1.7 Hz, 1H, =CH-5); 7.38-7.49 (m, 5H arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.3 (CH_3); 23.4 (CH_3); 58.8 (CH_2); 94.6 (C-3); 124.6 (CH-5); 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 $C_{13}H_{17}NO_3S$ (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, ν_{max}, cm^{-1}): 1188 (SO_2), 1329 (SO_2), 1743 (C=O). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.22 (d, ^4J = 1.5 Hz, 3H, CH_3); 2.41 (s, 3H, *p*-CH_3); 7.16 (q, ^4J = 1.5 Hz, 1H, =CH-5); 7.38-7.39 (m, 4H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 12.5 (CH_3); 21.9 (*p*-CH_3); 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 $C_{11}H_{11}NO_3S$ (237.3) C: 55.68, H 4.67, N 5.90; O 20.23; 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, ν_{max}, cm^{-1}): 1187 (SO_2), 1331 (SO_2), 1743 (C=O). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.23 (d, ^4J = 1.5 Hz, 3H, CH_3); 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).^{13}C-NMR (50MHz, $CDCl_3$): δ = 12.5 (CH_3); 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 $C_{10}H_8ClNO_3S$ (257.7) C: 46.61, H 3.13, N 5.44; O 18.63; 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, ν_{max}, cm^{-1}): 1187 (SO_2), 1332 (SO_2), 1743 (C=O). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.22 (d, ^4J = 1.7 Hz, 3H, CH_3); 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). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 12.3 (CH_3); 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 $C_{10}H_8BrNO_3S$ (302.1) C: 39.75, H 2.67, N 4.64; O 15.89; 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, ν_{max}, cm^{-1}): 1180 (SO_2), 1256 (OCH_3), 1324 (SO_2), 1738 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.6 Hz, 3H, CH_3); 2.61 (dq, ^3J = 7.6 Hz, J = 1.8 Hz, 2H, CH_2); 3.84 (s, 3H, OCH_3); 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); ^{13}C-NMR (50MHz, $CDCl_3$): δ = 11.6 (CH_3); 20.2 (CH_2); 56.2 (OCH_3); 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 $C_{12}H_{13}NO_4S$ (267.3) C: 53.92, H 4.90, N 5.24; O 23.94; 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, ν_{max}, cm^{-1}): 1182 (SO_2), 1322 (SO_2), 1739 (C=O). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 7.2 Hz, 3H, CH_3); 2.61 (dq, ^3J = 7.2 Hz, ^4J = 2.0 Hz, 2H, CH_2); 7.1 (t, ^4J = 2,0 Hz, 1H, =CH-5); 7.43-7.54 (m, 5H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 11.5 (CH_3); 20.2 (CH_2); 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 $C_{11}H_{11}NO_3S$ (237.3) C: 55.68, H 4.67, N 5.90; O 20.23; 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 $Na_2SO_3 \cdot 7H_2O$ is added. After 24 hrs stirring at room temperature 3 mL water are added to the mixture and extracted with 20 mL diethylether. The organic layers are washed with sat. NaCl-solution and water and dried over anhydrous Na_2SO_4. After evaporation of the solvent crystals of **11** are filtered off and dried.

2-(4-Methoxylphenyl)-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, ν_{max}, cm^{-1}): 1139 (SO_2), 1252 (OCH_3), 1267 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.17 (d, ^4J = 1.4 Hz, 3H, CH_3); 3.84 (s, 3H, OCH_3); 4.26 (m, 1H, $=CH_2^a$); 4.63 (m, 1H, $=CH_2^b$); 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). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 14.6 (CH_3); 57.0 (OCH_3); 92.2 (CH_2); 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 $C_{12}H_{13}NO_3S$ (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, ν_{max}, cm^{-1}): 1145 (SO_2), 1275 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.20 (d, ^4J = 1.3 Hz, 3H, CH_3); 2.40 (s, 3H, *p*-CH_3); 4.31 (m, 1H, $=CH_2^a$); 4.65 (m, 1H, CH_2^b); 6.51 (s(br), 1H, =CH-5); 7.30-7.31 (m, 4H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.4 (CH_3); 21.7 (*p*-CH_3); 91.3 (CH_2); 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 $C_{12}H_{13}NO_2S$ (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, ν_{max}, cm^{-1}): 1140 (SO_2), 1269 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.18 (d, ^4J = 1.3 Hz, 3H, CH_3) ; 4.33 (m, 1H, $=CH_2^a$); 4.68 (m, 1H, CH_2^b); 6.52 (s(br), 1H, =CH-5); 7.44-7.50 (m, 5H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ= 13.8 (CH_3); 91.7 (CH_2); 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 $C_{11}H_{11}NO_2S$ (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. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.21 (d, ^4J = 1.4 Hz, 3H, CH_3); 4.36 (m, 1H, $=CH_2^a$); 4.66 (d, 1H, $=CH_2^b$); 6.50 (s(br), 1H, = CH-5); 7.51, 8.17 (d, 4H, J_{AB} = 9.2Hz). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 13.5 (CH_3); 91.9 (CH_2); 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^+). $C_{11}H_{10}ClNO_2S$ (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. ^{1}H-NMR (200MHz, $CDCl_3$): δ = 2.18 (d, ^4J = 1.2 Hz, 3H, CH_3); 4.34 (m, 1H, $=CH_2^a$); 4.70 (m, 1H, CH_2^b); 6.52 (s(br), 1H, =CH-5);

7.32-7.62 (d, 4H, J_{AB} = 8.6 Hz). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 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^+). $C_{11}H_{10}BrNO_2S$ (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, ν_{max}, cm^{-1}): 1130 (SO_2), 1279 (SO_2). ^{1}H-NMR (200MHz, $CDCl_3$): δ = 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_2^a); 4.69 (d, 1H, CH_2^b); 6.50 (s(br), 1H, =CH-5); 7.42-7.53 (m, 5H, arom. H). ^{13}C-NMR (50MHz, $CDCl_3$): δ = 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 $C_{12}H_{13}NO_2S$ (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

1. (a) Marco, J. L.; Ingate, S. T. *Tetrahedron Lett*. **1997**, *38*, 4835. (b) Ingate, S. T.; Marco, J. L.; Witvrouw, M.; Pannecouque, C.; DeClerq, E. *Tetrahedron* **1997**, *53*, 17795.
2. (a) Marco, J. L.; Ingate, S. T. *Tetrahedron Lett*. **1998**, *39*, 4123. (b) Marco, J. L.; Ingate, S. T.; Chinon, P. M. *Tetrahedron* **1999**, *55*, 7625.
3. Marco, J. L.; Ingate, S. T.; Jaime, C.; Bea, J. *Tetrahedron* **2000**, *56*, 23.
4. Fischer, R.; Kretschik, O.; Schenke, T.; Schenkel, R.; Wiedemann, J.; Erdelen, C.; Loesel, P.; Drewes, M. W.; Feucht, D; Andersch, W. W. Ger. Offen. DE 1 999 244 668, 1999; *Chem. Abstr.* **2001**, *134*, 4932.
5. Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yan, M. *Tetrahedron Lett*. **1999,** *40*, 4761.
6. Ho, K. F.; Fung, D. C. W.; Wong, W. Y.; Chan, W. H.; Lee, A. W. *Tetrahedron Lett*. **2001**, *42*, 3121.
7. Wanner, J.; Harmed A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett*. **2002**, *43*, 917.
8. Taubert, K.; Sieler, J.; Hennig, L.; Findeisen, M.; Schulze, B. *Helv. Chim. Acta* **2002**, *85*, 183.
9. Taubert, K.; Siegemund, A.; Eilfeld, A.; Baumann, S.; Sieler, J.; Schulze, B. *Synthesis* **2003**, *14*, 2265.
10. Noack, A.; Jelonek, S.; Somoza Jr., F. B.; Schulze, B. *J. Prakt. Chem.* **1998**, *340*, 361.
11. Unterhalt, B.; Moghaddon, S. *Pharm.* **1994**, *49*, 317.
12. Schulze, B.; Obst, U.; Zahn, G.; Friedrich, B.; Cimiraglia, R.; Hofmann H.-J. *J. Prakt. Chem.* **1995**, *337*, 175.
13. Schulze, B.; Rosenbaum, K.; Hilbig, J.; Weber, L. *J. Prakt. Chem.* **1992**, *334*, 25.

