Properties and Reactions of Substituted 1,2-Thiazetidine 1,1-Dioxides: Methylation of β-Sultams

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Methylation of *N*-substituted 1,2-thiazetidine 1,1-dioxides in the presence of lithium diisopropylamide (LDA) yields 4,4-dimethyl derivatives. Monomethylation only occurs when one position at C-4 is blocked by a silyl group, which, afterwards, can be removed by treatment with tetrabutylammonium fluoride (TBAF). A silyl protecting group at the nitrogen is easily removed by cleavage with TBAF on silica gel under mild conditions.

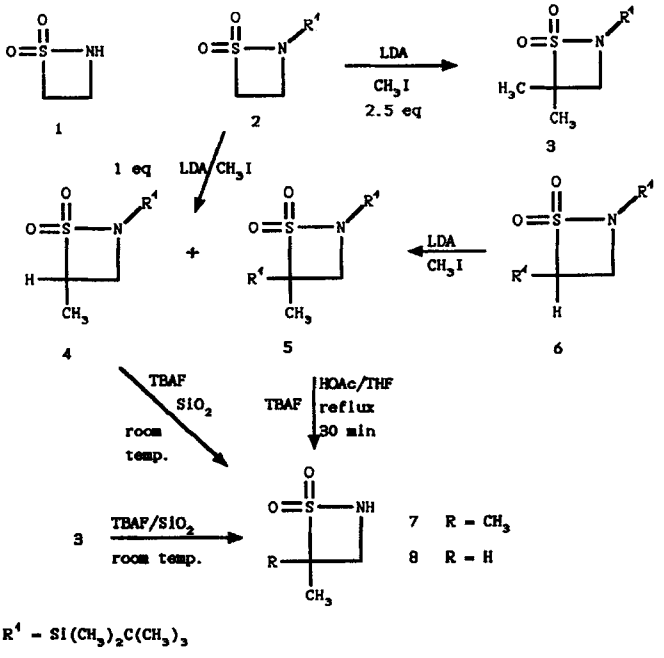
Eigenschaften und Reaktionen substituierter 1,2-Thiazetidin-1,1-Dioxide: Methylierung von β-Sultamen

Die Methylierung *N*-substituierter β-Sultame mit Methyliodid in Gegenwart von LDA ergibt 4,4-Dimethyl-Derivate. Eine Monomethylierung ist nur möglich, wenn eine Position an C-4 durch eine Silylgruppe blockiert ist. Letztere kann später durch TBAF abgespalten werden. Die Silyl-Schutzgruppe am Stickstoff ist mit TBAF auf Kieselgel unter milden Bedingungen entfernbar.

In a forthcoming paper we shall describe the reaction of silylated 1,2-thiazetidine 1,1-dioxides with ketones and aldehydes yielding hydroxyalkyl- or substituted methylene derivatives [1]. Here, we wish to report about the methylation of the unsubstituted β-sultam **1** and some of its substituted derivatives.

When **1** is treated at -78°C with an excess of base such as *n*-BuLi or LDA, a mixture of the mono- and the dianion is formed. Therefore, reaction with an electrophil results in a mixture of substitution products. Furthermore, with methyl iodide the overall yield is very poor. Therefore, we decided to study the methylation of *N*-substituted β-sultams, which can be easily prepared from **1**. The dianion of **2** is formed with 2.5 eq. of LDA and quenched by an excess of methyl iodide yielding the dimethylated β-sultam **3**. However, running the reaction with 1 eq. of LDA, and 1 eq. of methyl iodide, we did not obtain the monomethylated **4**, but a mixture of **4** (8%) and **5** (31%)[2], which was separated by CC. To establish the structure of **5**, the *N*,4-*bis*-silylated β-sultam [3] **6** was deprotonated with 1.5 eq. of LDA, and methylated with methyl iodide yielding the identical product **5**. The *N*-silylated compounds **3** and **4** were easily desilylated with TBAF on silica gel [4]. From **3**, the 4,4-dimethyl-β-sultam **7** (87%) was obtained, and from **4** resulted the monomethylated product **8** (83%). The identical product **8** is obtained from **5**, but only with 17% yield, and only when **5** is refluxed in a solution of TBAF in THF to which were added some drops of glacial acetic acid, thus demonstrating that *N*-desilylation is much faster and easier than *C*-desilylation from a tetrasubstituted carbon atom. Furthermore, the removal of a *tert*-butyldimethylsilyl group is more difficult than the removal of a trimethylsilyl group [3].

Synthesis of the dimethylated β-sultam **10** (51%) was successful, when **9** in THF was slowly added at -78°C to 3 eq. of LDA in THF, followed by methyl iodide. The *C*-4 monomethylated products **13** became available when **9** was first



FORMULA 1

silylated to **11** (70%). Reaction of **11** with 2 eq. of LDA and 2 eq. of methyl iodide gave **12** (60%) as a mixture of isomers. This mixture was refluxed with TBAF in THF/glacial acetic acid, and after usual work up was separated by CC. The (3R*,4R*)-isomer [5] of **13** was obtained as colorless crystals (34%) by kugelrohr distillation, and (3R*,4S*)-**13** was isolated as colorless crystals (47%) by recrystallisation from cyclohexane.

The ^{1}H NMR spectrum (80 MHz, $CDCl_3$) of **11** shows the doublets of 3-H at δ = 3.87 ppm (J = 8 Hz), and of 4-H at δ = 4.01 ppm (J = 8 Hz). Therefore, we assume that only one isomer with (3R*,4S*)-configuration[5] has been built. The resonance of 3-H is shifted to δ = 4.31 ppm (s) in the spectrum of **12**. This is enhanced by the vicinal methyl group[6], but must not involve another configuration. We interprete the singulet as a strong

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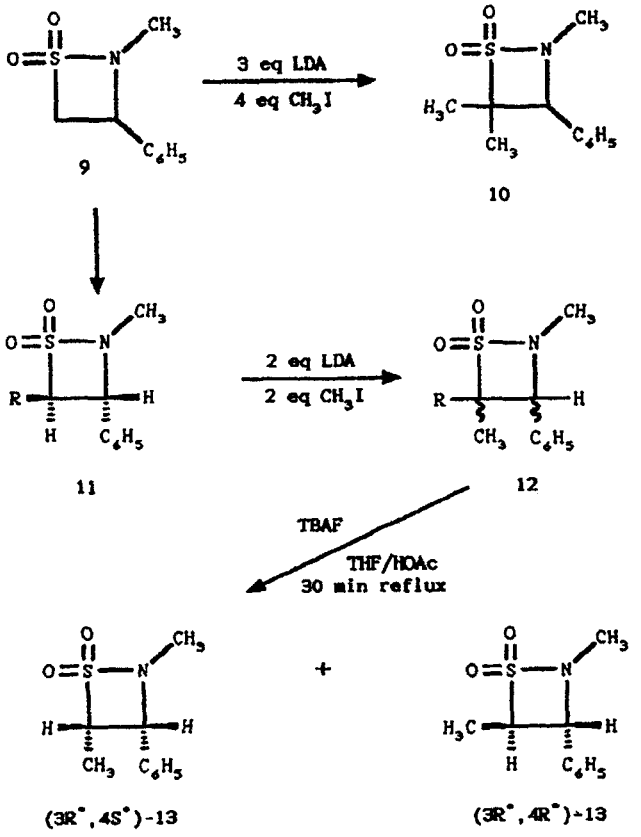
evidence for the existence of only one isomer being formed via a stabilized tetrahedral carbanion. Finally, desilylation of **12** yields 2 isomers, the (3R*,4S*)-isomer of **13** [3-H: δ = 4.40 ppm (d, J = 8 Hz); 4-H: δ = 4.55 ppm (dq, J = 8 and 7.5 Hz)], and the (3R*,4R*)-isomer of **13** [3-H: δ = 3.58 ppm (d, J = 6.5 Hz); 4-H: δ = 4.03 ppm (dq, J = 6.5 Hz)][6], which are formed by isomerisation under acidic conditions. This interpretation of the NMR spectra is established by NOE experiments with both isomers[7]. Thereby, it is verified, that the methyl group at C-4 is pseudoaxial, and the *N*-methyl- and phenyl-increments are pseudoequatorial orientated in the (3R*,4S*)-isomer. In the (3R*,4R*)-isomer, all substituents are in pseudoequatorial positions. *N*-methyl and *C*-methyl show negativ NOE's. That is possible only when *N*-methyl, 3-H, and *C*-methyl are linearly orientated, and 3-H has an equal distance to both the other groups[8].



R = $Si(CH_3)_2C(CH_3)_3$

FORMULA 2

Support of this work by Fonds der Chemischen Industrie, Frankfurt/M., and Chemie Linz AG is gratefully acknowledged. We thank Dr. *D. Hunkler*, Chemisches Laboratorium der Universität Freiburg, for the 250-MHz NMR spectra.

Experimental Part

M.p. (uncorrected): Linström apparatus. - IR (KBr, cm^{-1}): Perkin-Elmer IR 1310, Beckman IR 4240. - ^{1}H-NMR: Varian T60, Bruker WP80, or Bruker WP250; δ (ppm), δ_{TMS} = 0.00; temp. of the probe 37°C; δ values from 80 MHz spectra, if not otherwise noted, solvent $CDCl_3$. - ^{13}C NMR: Bruker WP80 (20.15 MHz); δ (ppm), δ_{TMS} = 0.00, solvent $CDCl_3$. - MS: Finnigan GC MS 4000. - Elementary analyses: Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg. - Solvents were dried according to literature procedures. - Abbreviations: TBAF = Tetrabutylammonium fluoride; n-BuLi = n-Butyl lithium, 15% in hexane; LDA = Lithium diisopropylamide, freshly prepared by mixing equimolar amounts of n-BuLi and diisopropylamine; THF = Tetrahydrofuran.

Methylation of Silylated β-Sultams, General procedure

The solution of the β-sultam in 40 ml of THF is added to the solution of LDA in 10 ml of THF at -78°C. After 30 s, CH_3I is added, the mixture is stirred for 30 min at -78°C, hydrolized with saturated NaCl-solution, the org. layer is separated, dried with Na_2SO_4, and concentrated in vacuo. Work up as noted below.

2-(tert-Butyldimethylsilyl)-4,4-dimethyl-1,2-thiazetidine 1,1-dioxide (**3**)

From 12.5 mmol LDA, 1.1 g (5 mmol) **2**, and 0.8 ml (12.5 mmol) CH_3I; kugelrohr distillation; yield 925 mg (75%), colorless liquid, slowly crystalizing, b.p. 110°C/0.01 Torr. - IR (Film): 2960; 2940; 2900; 2860 (CH); 1470; 1395; 1365 (CH_3); 1295; 1170; 1130 (SO_2). - ^{1}H-NMR: δ = 0.26 (s, 6H, Si-CH_3), 0.97 [s, 9H, Si-C(CH_3)$_3$], 1.64 (s, 6H, CH_3), 3.08 (s, 2H, CH_2). - $C_{10}H_{23}NO_2SSi$ (249.4) Calcd. C 48.2 H 9.29 N 5.6 Found C 48.4 H 9.36 N 5.5.

2-(tert-Butyldimethylsilyl)-4-methyl-1,2-thiazetidine 1,1-dioxide (**4**)

From 5 mmol LDA, 1.1 g (5 mmol) **2**, and 0.62 ml (10 mmol) CH_3I. The residue is separated by CC (silica gel, cyclohexane/ethyl acetate 3:1). The fraction R_f = 0.55 contains **5**, the fraction R_f = 0.22 contains **4**; purification by kugelrohr distillation; yield 95 mg (8%), colorless liquid, b.p. 108°C/0.005 Torr. - IR (Film): 2960; 2940; 2900; 2870 (CH); 1475; 1470; 1370 (CH_3); 1310; 1150 (SO_2). - ^{1}H-NMR: δ = 0.32 (s, 6H, Si-CH_3), 0.98 [s, 9H, Si-C(CH_3)$_3$], 1.6 (d, J = 7.5 Hz, 3H, CH_3), 2.87 [t(dd), J = -5 Hz and 5 Hz, 1H, 3-H], 3.50 (dd, J = 8 Hz and -5 Hz, 1H, 3'-H), 4.55 (mc, J = 8 Hz, 7.5 Hz, and 5 Hz, 1H, 4-H). - $C_9H_{21}NO_2SSi$ (235.4) Calcd. C 45.9 H 8.99 N 6.0 Found C 45.9 H 8.97 N 5.9.

2,4-Bis(tert-butyldimethylsilyl)-4-methyl-1,2-thiazetidine 1,1-dioxide (**5**)

a) From the preparation of **4**, see above. b) From 7.5 mmol LDA, 1.69 g (5 mmol) 2,4-bis(tert-butyldimethylsilyl)-1,2-thiazetidine 1,1-dioxide (**6**), and 0.93 ml (15 mmol) CH_3I. Some drops of pentane are added to the residue, the crystals are separated; yield a) 270 mg (31%), b) 1.14 g (66%), colorless crystals, m.p. 49°C (pentane). - IR: 2960; 2930; 2885; 2860 (CH); 1470; 1395; 1365 (CH_3); 1290; 1150 (SO_2). - ^{1}H-NMR: δ = 0.25 (s, 12H, Si-CH_3), 0.95 [s, 9H, Si-C(CH_3)$_3$], 0.98 [s, 9H, Si-C(CH_3)$_3$], 1.72 (s, 3H, C-CH_3), 2.80 (d, J = -5 Hz, 1H, 3'-H), 3.32 (d, J = -5 Hz, 1H, 3-H). - $C_{15}H_{35}NO_2SSi_2$ (349.7) Calcd. C 51.5 H 10.09 N 4.0 S 9.2 Found C 51.4 H 10.01 N 4.1 S 9.3.

Desilylation with TBAF on silica gel, General procedure

The β-sultam is solved in 10 ml of absol. ethanol, TBAF on silica gel[4] is added, the mixture is stirred for 14 h under N_2, diluted with 20 ml of absol. ethanol, dried with Na_2SO_4, and concentrated in vacuo. The residue is recrystalized or distilled bulb-to-bulb.

4,4-Dimethyl-1,2-thiazetidine 1,1-dioxide (**7**)

From 499 mg (2 mmol) **3** and 50 mg TBAF on silica gel; yield 235 mg (87%), colorless crystals, m.p. 39°C (chloroform). - IR: 3330 (NH); 2980; 2940; 2910 (CH); 1465 (CH_3); 1300; 1155; 1130 (SO_2). - ^{1}H-NMR (60 MHz): δ = 1.65 (s, 6H, CH_3), 3.16 (d, J = 2.5 Hz, 2H, 3-H, and 3'-H), 5.63 (bs, 1H, NH). - $C_4H_9NO_2S$ (135.2) Calcd. C 35.5 H 6.71 N 10.4 S 23.7 Found C 35.3 H 6.60 N 10.2 S 23.9.

4-Methyl-1,2-thiazetidine 1,1-dioxide (**8**)

a) 1.75 (5 mmol) of **5** are dissolved in 20 ml of THF, 1.52 g (20 mmol) glacial acetic acid and 12.5 ml of TBAF solution[9] are added, and the mixture is refluxed for 30 min. After hydrolysis with saturated $NaHCO_3$-solution the org. layer is separated, the aquous layer is extracted with 20 ml of THF, the combined org. layers are dried with Na_2SO_4, and concentrated in vacuo; purification by CC, silica gel, CH_2Cl_2, the fraction R_f = 0.07 contains the product, which is distilled by kugelrohr. b) From 117 mg (0.05 mmol) **4** and 22 mg TBAF on silica gel [4]; yield a) 105 mg (18%), b) 50 mg (83%), colorless liquid, b.p. 115°C/0.01 Torr. - IR (Film): 3300 (NH); 2980; 2940; 2910 (CH); 1450; 1385 (CH_3); 1300; 1150 (SO_2). - ^{1}H-NMR: δ = 1.59 (d, J = 7.5 Hz, 3H, CH_3), 2.90 (mc, J = 6 Hz, -6 Hz, and 4.5 Hz, 1H, 3-H), 3.50 (mc, J = 8 Hz, -6 Hz, and 3 Hz, 1H, 3'-H), 4.57 (mc, J = 8 Hz, 7.5 Hz, and -1 Hz, 1H, 4-H), 5.32 (bs, 1H, NH). - $C_3H_7NO_2S$ (121.2) Calcd. C 29.7 H 5.83 N 11.6 Found C 29.9 H 5.89 N 11.7.

2,4,4-Trimethyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (**10**)

986 mg (5 mmol) of 2-methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide [10] are dissolved in 40 ml of THF, cooled to -78°C, and 15 mmol of LDA, and - after 10 min - 1.25 ml (20 mmol) of CH_3I are added. The mixture is stirred at -78°C for 30 min, hydrolyzed with saturated NaCl-solution, the org. layer is separated, dried with Na_2SO_4, and concentrated in vacuo. The residue is dissolved in a few drops of cyclohexane, and cooled to 0°C; yield 565 mg (51%), colorless crystals, m.p. 118°C (cyclohexane). - IR: 3025; 2985; 2960; 2915 (CH); 1490; 1450 (arC-C); 1460; 1390; 1360 (CH_3); 1305; 1180; 1145 (SO_2). - ^{1}H-NMR: δ = 1.26 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.74 (s, 3H, N-CH_3), 3.92 (s, 1H, 3-H), 7.26-7.55 (m, 5H, arom.H). - $C_{11}H_{15}NO_2S$ (225.3) Calcd. C 58.6 H 6.71 N 6.2 S 14.2 Found C 58.9 H 6.85 N 6.0 S 14.0.

(3R,4S*)-4-(tert-Butyldimethylsilyl)-2-methyl-3-phenyl-1,2-thiazetidine 1,1-dioxide* (**11**)

see ref.[3].

(3R,4S*)-4-(tert-Butyldimethylsilyl)-2,4-dimethyl-3-phenyl-1,2-thiazetidine 1,1-dioxide* (**12**)

From 1.56 g (5 mmol) **11**, 10 mmol LDA, and 0.62 ml (10 mmol) CH_3I as described for **10**. The residue is recrystalized from methanol; yield 965 mg (60%), colorless crystals, m.p. 140°C. - IR: 2950; 2920; 2880; 2850 (CH); 1490; 1455 (arC-C); 1465; 1390; 1365 (CH_3); 1285; 1145 (SO_2). - ^{1}H-NMR: δ = 0.20 (s, 3H, Si-CH_3), 0.42 (s, 3H, Si-CH_3), 1.02 [s, 9H, Si-C(CH_3)$_3$], 1.28 (s, 3H, C-CH_3), 2.67 (s, 3H, N-CH_3), 4.31 (s, 1H, 3-H), 7.43 (s, 5H, arom.H). - $C_{16}H_{27}NO_2SSi$ (325.5) Calcd. C 59.0 H 8.36 N 4.3 S 9.9 Found C 59.0 H 8.39 N 4.4 S 10.0.

2,4-Dimethyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (**13**)

3 ml (3 mmol) of TBAF solution [9], and 439 mg (6 mmol) of glacial acetic acid are added to 977 mg (3 mmol) of **12** in 15 ml of THF. The mixture is refluxed for 30 min, cooled to room temp., hydrolyzed with saturated $NaHCO_3$-solution, the org. layer is separated, the aquous layer is washed with 20 ml of CH_2Cl_2, the combined org. layers are dried with Na_2SO_4 and concentrated in vacuo. The residue is separated by CC, silica gel, cyclohexane/ethyl acetate 6:1.

(3R,4S*)*-**13**: R_f = 0.13; yield 298 mg (47%), colorless crystals, m.p. 88°C (cyclohexane). - IR: 3050; 2970; 2925; 2900 (CH); 1600; 1490; 1450 (arC-C); 1445; 1360 (CH_3); 1295; 1150; 1130 (SO_2). - ^{1}H-NMR (250 MHz): δ = 1.09 (d, J = 7.5 Hz, 3H, C-CH_3), 2.76 (s, 3H, N-CH_3), 4.40 (d, J = 8 Hz, 1H, 3-H), 4.55 ("quint", J = 8 Hz and 7.5 Hz, 1H, 4-H), 7.30-7.48 (m, 5H, arom.H). - $C_{10}H_{13}NO_2S$ (211.3) Calcd. C 56.9 H 6.20 N 6.6 S 15.2 Found C 56.8 H 6.11 N 6.7 S 15.3.

(3R,4R*)*-**13**: R_f = 0.18; kugelrohr distillation b.p. 126°C/0.01 Torr; yield 215 mg (34%), colorless crystals, m.p. 53°C. - IR: 3040; 2975; 2930; 2900; 2880 (CH); 1600; 1490; 1455 (arC-C); 1370 (CH_3); 1305; 1140 (SO_2). - ^{1}H-NMR: δ = 1.57 (d, J = 6.5 Hz, 3H, C-CH_3), 2.67 (s, 3H, N-CH_3), 3.58 (d, J = 6.5 Hz, 1H, 3-H), 4.03 ("quint", J = 6.5 Hz, 1H, 4-H), 7.27-7.50 (s, 5H, arom.H). - $C_{10}H_{13}NO_2S$ (211.3) Calcd. C 56.9 H 6.20 N 6.6 S 15.2 Found C 57.1 H 6.30 N 6.7 S 15.0.

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