Synthesis A. V. Dobrydnev et al. Special Topic

Synthesis of the First Representatives of Spiro-1λ⁶-isothiazolidine-1,1,4-triones

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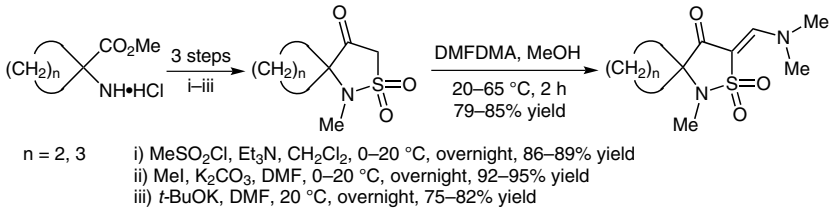


Received: 30.03.2015
Accepted after revision: 28.05.2015
Published online: 25.06.2015
DOI: 10.1055/s-0034-1380434; Art ID: ss-2015-t0209-st

Abstract A strategy for the construction of spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones through the sulfonylation of 1-aminocyclopropane- and 1-aminocyclobutanecarboxylates with methanesulfonyl chloride followed by alkylation with methyl iodide and subsequent cyclization in the presence of potassium *tert*-butoxide in *N*,*N*-dimethylformamide is reported. An efficient synthesis of starting 1-aminocyclopropane- and 1-aminocyclobutanecarboxylic acids was developed. The reaction of spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) gives 5′-[(*Z*)-(dimethylamino)methylene]spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones, the structure of which was confirmed by X-ray diffraction study.

Key words amino acids, sulfonamides, spiro compounds, cyclization, X-ray structure determination

Naturally occurring tetramic acids (PF 1052 and erythroskyrine)[1] constitute a rich family of bioactive secondary metabolites. All of them contain a pyrrolidine-2,4-dione moiety and display a wide range of biological activity, including antibiotic,[2–6] antiviral, cytotoxicity, and cytostatic activity.[7–9] Some synthetic analogues of certain tetramic acids have been the subject of clinical investigations as promising antibiotic substances. Additionally, in 2005 Bayer CropScience patented a series of substituted tetramic acids as ingredients for fungicidal and herbicidal use (Figure 1).[10]

The sulfonamide group is known as a bioisosteric equivalent of the carboxamide group. The similarity between these two groups, which is based on consideration of electronic and conformational aspects, is a powerful instrument in drug discovery (the most classic example is the family of sulfonamide antibiotics).

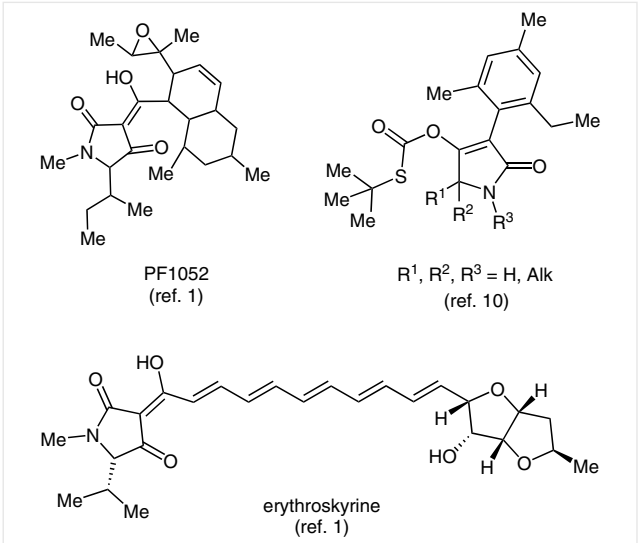


Figure 1 Naturally and synthetic occurring tetramic acids

Some approaches to the construction of the 2,3,3-trimethyl-1λ⁶-isothiazolidine-1,1,4-trione system **2** have been published.[11] However, strategies for the synthesis of spiro-substituted sulfur-containing isosters of tetramic acid **3a** and **3b** have not been previously investigated (Figure 2). Considering the importance of applying these compounds in medicinal chemistry and the absence of synthetic access to these key products, we have developed a synthetic route to **3a**,**b**.

First, the building blocks for construction of the 1λ⁶-isothiazolidine-1,1,4-trione system, 1-aminocyclopropanecarboxylic acid (**4**) and 1-aminocyclobutanecarboxylic acid (**5**), were obtained. The starting cyclic α-amino acids were prepared according to the reaction sequences shown in Schemes 1 and 2.

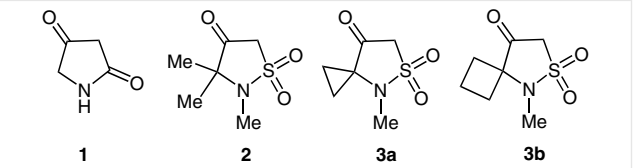


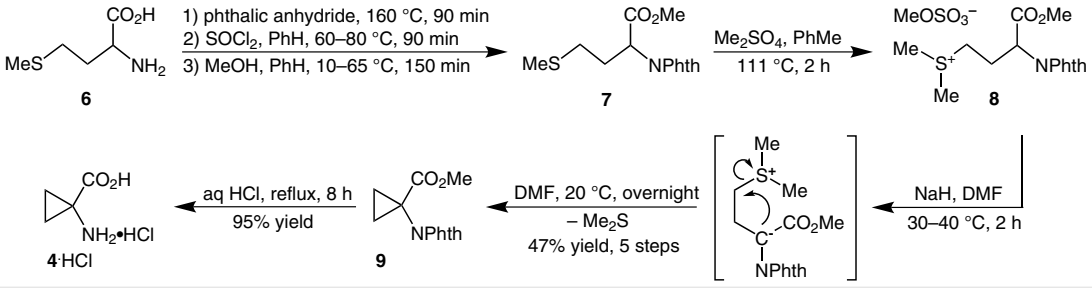
Figure 2 The tetramic acid **1** and its sulfur-containing isosteres **2**, **3a**,**b**

1-Aminocyclopropanecarboxylic acid (**4**) was synthesized starting from commercially available D,L-methionine (**6**). This synthetic pathway included introduction of the phthalimide protecting group, esterification, and alkylation of **7** with dimethyl sulfate resulting in formation of the methylsulfonium salt **8**. The isolated intermediate underwent a cyclization reaction to methyl 1-phthalimidocyclopropanecarboxylate **9** through an intramolecular alkylation. The hydrolysis of **9** upon treatment with aqueous 20% hydrochloric acid under reflux led to the hydrochloric salt of the acid **4**·HCl in 95% yield (Scheme 1).

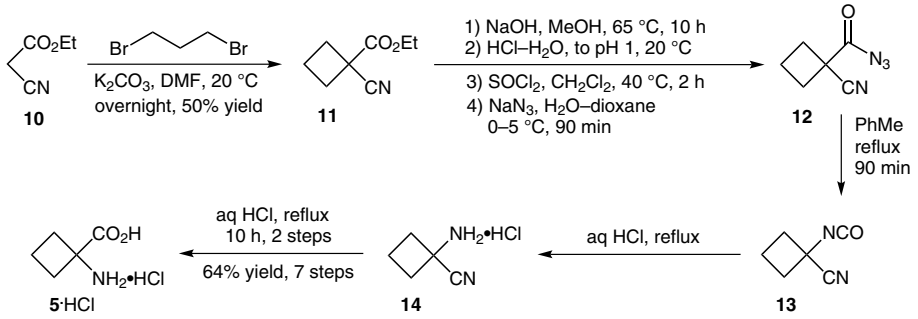
The amino acid **5** was prepared by an eight-step procedure starting from commercially available ethyl cyanoacetate (**10**) (Scheme 2). First, ester **10** was alkylated with 1,3-dibromopropane. The hydrolysis of the cyano ester **11**, followed by preparation of corresponding acid chloride and Curtius rearrangement of the azide **12** with subsequent hydrolysis of both functional groups in the isocyanate **13** yielded crude amino acid **5**, which was further purified using ion-exchange resin Amberlite IR-120 Plus. The cyclic amino acids **4** and **5** were esterified with methanol following the methods described in the literature.[12,13] Subsequently, sulfonylation of the amino acid esters **15a**,**b** with methanesulfonyl chloride in dry dichloromethane in the presence of triethylamine as base resulted in corresponding methyl 1-(methylsulfonamido)cycloalkanecarboxylates **16a**,**b** in 86–89% yield (Scheme 3). It was found to be advantageous to allow the reaction mixture to stand at room temperature at least overnight to ensure completion of the sulfonylation process. Subsequent alkylation of **16a**,**b** with methyl iodide in *N*,*N*-dimethylformamide afforded methyl 1-(*N*-methylmethylsulfonamido)cycloalkanecarboxylates **17a**,**b** and was followed by their treatment with potassium *tert*-butoxide in dry *N*,*N*-dimethylformamide to produce the target spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones **3a**,**b** in 75 and 82% yields, respectively.

To confirm the structure of the synthesized compounds, formylation of the sulfonamides **3a**,**b** was performed by reaction with *N*,*N*-dimethylformamide dimethyl acetal to afford the crystalline derivative **18a**,**b** (Scheme 4). Single crystals of product **18b** were obtained by slow evaporation of a dilute solution in methanol. X-ray diffraction analysis of enamine **18b** revealed the *Z* configuration of the (dimethylamino)methylene group relative to the SO_2 fragment at the C4–C3 bond (Figure 3).

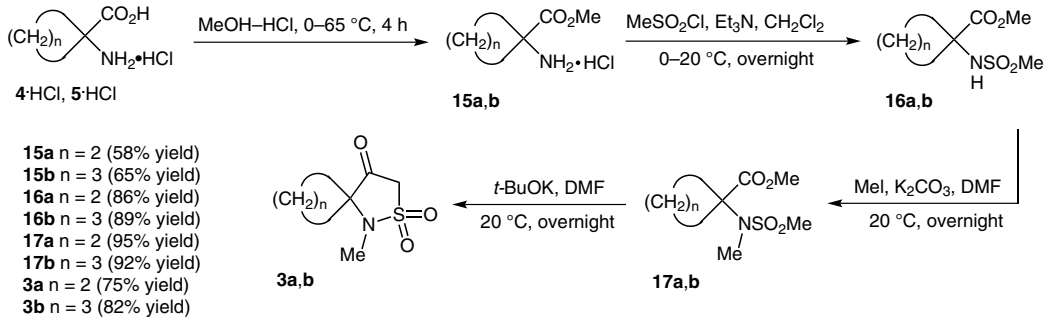
In summary, spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones **3a**,**b** were designed as isosteric analogues of pharmacologically relevant tetramic acid. The synthesis of both compounds was performed in four steps from 1-aminocyclopropane- and 1-aminocyclobutanecar-



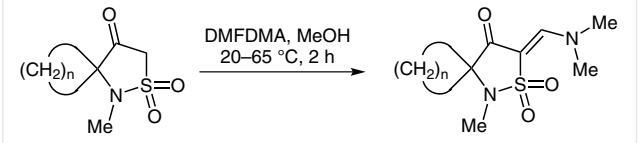
Scheme 1 The synthesis of 1-aminocyclopropanecarboxylic acid (**4**)



Scheme 2 The synthesis of 1-aminocyclobutanecarboxylic acid (**5**)



Scheme 3 The synthesis of spiro[cycloalkane-1,3′-1λ⁶-isothiazolidine]-1′,1′,4′-triones **3a**,**b**



Scheme 4 The reaction of spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones **3a**,**b** with *N*,*N*-dimethylformamide dimethyl acetal

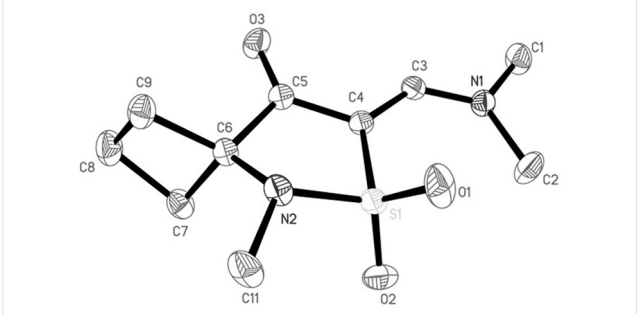


Figure 3 Molecular structure of compound **18b** according to results of X-ray diffraction study

boxylic acids. New methods for the syntheses of cyclic amino acids were developed, employing inexpensive commercially available reagents. With the reported rapid synthesis we believe that spiro[cycloalkane-1,3′-1′λ⁶-isothiazolidine]-1′,1′,4′-triones **3a**,**b** will find practical application in drug discovery projects, especially in those where tetramic acid is involved.

Reactions requiring anhydrous conditions were performed with the usual precautions for the rigorous exclusion of air and moisture. DMF was dried by distillation from P_2O_5. The other chemicals were purchased from Aldrich or Fluka and, when necessary, chemicals were purified according to the reported procedure.[14] ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer at 400.45 MHz and 100.61 MHz respectively using DMSO-d_6 or $CDCl_3$ as solvents and TMS as an internal standard. IR spectra were obtained on a Perkin Elmer BX II spectrophotometer in KBr pellets. Mass spectra were recorded on an Agilent 1100 Series with an Agilent LC/MSD SL detector by chemical ionization (CI). All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected.

Methyl 1-(1,3-Dioxo-2,3-dihydro-1*H*-isoindol-2-yl)cyclopropanecarboxylate (9); One-Pot General Procedure

A mixture of D,L-methionine (**6**, 100 g, 0.67 mol) and phthalic anhydride (101 g, 0.68 mol) was ground to a powder and placed in a 1-L round-bottomed flask that was then heated in an oil bath previously heated to 160 °C. The mixture fused and vigorous emission of water vapor occurred; heating was continued for a further 90 min and then the mixture was cooled to r.t. The resulting crude phthalylmethionine was blended (in the same flask) with benzene (400 mL) and few drops of DMF were added followed by the dropwise addition of $SOCl_2$ (98 mL, 161 g, 1.36 mol) at 60 °C. When all the $SOCl_2$ had been added, the mixture was refluxed for 1 h and then cooled to r.t. Benzene and excess $SOCl_2$ were evaporated under reduced pressure and the residue was heated under vacuum (60–80 °C/0.4 mbar) for 90 min. The acid chloride was dissolved in benzene (200 mL) (in the same flask), cooled in a cold (10–15 °C) water bath then MeOH (55 mL, 43.6 g, 1.36 mol) was added dropwise to the stirred solution; the first 25 mL of MeOH should be added with caution! When the addition of MeOH was complete, the mixture was refluxed for 2 h. Benzene and excess MeOH were evaporated under reduced pressure and the residue was heated under vacuum (60–80 °C/0.4 mbar) for 90 min. Toluene (200 mL) was added to crude phthalylmethionine methyl ester **7** and the mixture was heated (80–100 °C) with stirring for 15 min. The clear hot solution was separated and the procedure was repeated using toluene (2 × 100 mL). The combined toluene extracts were poured into a 1-L round flask followed by addition of fresh distilled Me_2SO_4 (70 mL, 93 g, 0.74 mol); the resulting solution was refluxed with stirring for 2 h. After approx. 30 min from the time heating began, a dark heavy oil formed. The two-phase mixture was cooled to r.t. and the toluene phase (top layer) was decanted. The dark viscous residue (bottom phase) was heated under vacuum (60–80 °C/0.4 mbar) for 90 min. The methylsulfonium salt of phthalylmethionine methyl ester **8** thus obtained was pure and no further purification was required.

A 60% suspension of NaH in oil (40 g, 1 mol) was weighed into a 2-L two-necked flask equipped with a thermometer and a dropping funnel and covered with anhyd DMF (250 mL). A solution of methylsulfonium salt **8** in anhyd DMF (500 mL) was added dropwise with vigorous stirring, maintaining the temperature at 30–40 °C. The mixture became orange and gas evolution (Me_2S) occurred. When the addition of methylsulfonium salt was complete, the mixture was allowed to stir at r.t. overnight. The orange-brown suspension was quenched

with AcOH (86 mL, 90 g, 1.5 mol) (*Caution!* Exotherm and foaming occurred.) DMF and excess AcOH were evaporated under reduced pressure and the residue was heated under vacuum (60–80 °C/0.4 mbar) for 90 min. The resulting brown viscous mass was triturated with water (700 mL) and the resulting precipitate was filtered, sequentially washed with water (3 × 50 mL) and hexane (3 × 50 mL) then recrystallized (50% aq *i*-PrOH) to give pale yellow crystals; yield: 77.2 g (0.31 mol, 47%); mp 140–141 °C (*i*-PrOH–H_2O, 1:1) [Lit.[15] mp 139–141 °C (Et_2O–hexane)].

IR (KBr): 3100, 2954, 1731, 1409, 1314, 1142, 720 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.51 (m, 2 H, cyclopropyl), 1.67 (m, 2 H, cyclopropyl), 3.61 (s, 3 H, OCH_3), 7.90 (m, 4 H, Phth).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.4, 31.4, 53.2, 123.7, 131.5, 135.2, 167.9, 171.3.

MS (APCI): *m*/*z* = 246.2 $[M + H]^+$.

1-Aminocyclopropanecarboxylic Acid Hydrochloride (4·HCl)

Phthalimidocyclopropanecarboxylate **9** (30.0 g, 122.3 mmol) was covered with 20% aq HCl (400 mL) and the mixture was refluxed with stirring for 8 h. The solid phase gradually dissolved and a clear solution formed. The mixture was allowed to equilibrate to r.t. and left overnight without stirring. The precipitate was filtered off and the filtrate was extracted with CH_2Cl_2 (5 × 60 mL). The aqueous phase was evaporated to dryness, the residue was heated under vacuum (60 °C/0.4 mbar) for 90 min, triturated (*i*-PrOH, 20 mL) and filtered to give pure product as white crystals that required no further purification; yield: 18.1 g (116.2 mmol, 95%); mp 221–222 °C (dec.) [Lit.[13,15] mp 220–222 °C (H_2O–acetone)].

IR (KBr): 3402, 2980, 2923, 1733, 1531, 1189, 834, 551 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.27 (s, 2 H, cyclopropyl), 1.37 (s, 2 H, cyclopropyl), 8.90 (br s, 3 H, NH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.1, 33.7, 171.5.

MS (APCI): *m*/*z* = 102.0 $[M + H]^+$.

1-Aminocyclobutanecarboxylic Acid Hydrochloride (5·HCl)

Ethyl 1-cyanocyclobutanecarboxylate[16] (**11**, 4.60 g, 30 mmol) was added to solution of NaOH (1.32 g, 33 mmol) in MeOH (40 mL) and the resulting mixture was refluxed for 10 h. The excess MeOH was evaporated under reduced pressure, and the residue was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The aqueous phase was acidified with HCl to pH 1 and extracted into CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and poured into a round-bottom flask (100 mL). A few drops of DMF were added to the magnetically stirred solution followed by addition of fresh distilled $SOCl_2$ (4.35 mL, 7.14 g, 60 mmol). When the addition of $SOCl_2$ was complete, the mixture was refluxed for 2 h, and then the volatiles were removed under vacuum at a temperature no higher than 60 °C. The residue was dissolved in dry dioxane (20 mL) and added dropwise to a stirred solution of NaN_3 (7.8 g, 120 mmol) in water (50 mL), maintaining the temperature at 0–5 °C. Stirring was continued for an additional 75 min, the mixture was diluted with water (50 mL), and the acid azide **12** was extracted with toluene (5 × 25 mL). The combined toluene phases were dried (Na_2SO_4), filtered, and additionally dried ($CaCl_2$) overnight. The filtered clear solution was carefully heated and refluxed for 90 min; gas evolution (N_2) occurred. Then 20% aq HCl (150 mL) was added to the hot toluene solution and the two-phase mixture was refluxed with vigorous stirring for a further 10 h. The aqueous phase was separated and evaporated to dryness. The residue was dissolved in water (50 mL) and alkalized with 1 M NaOH to pH 7. The solution was passed through a Amberlite IR-120 Plus column (5% aq NH_3). The residue obtained on evaporation of the eluate was dried under vacuum (80 °C/0.4 mbar) for 90 min. The product thus obtained was pure and no further purification was required to give the product as white crystals; yield: 2.21 g (19.2 mmol, 64%); mp >300 °C (Lit.[12] >300 °C).

IR (KBr): 3433, 3020, 2800, 1728, 1492, 1213, 1158, 865 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.09–2.30 (m, 2 H, cyclobutyl), 2.43–2.51 (m, 2 H, cyclobutyl), 2.67–2.74 (m, 2 H, cyclobutyl).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 29.3, 56.3, 172.3.

MS (APCI): *m*/*z* = 116.0 $[M + H]^+$.

Methyl 1-(Methylsulfonamido)cycloalkanecarboxylates 16a,b; General Procedure

Methyl 1-aminocycloalkanecarboxylate hydrochloride **15a**,**b** (50 mmol) was added to a magnetically stirred solution of Et_3N (15.2 g, 20.9 mL, 150 mmol) in CH_2Cl_2 (250 mL). As soon as the solid phase dissolved (approx. 30 min required), the mixture was cooled with an ice-water bath. Then the solution of $MeSO_2Cl$ (6.8 g, 60 mmol) in CH_2Cl_2 (50 mL) was added dropwise, maintaining the temperature below 5 °C. The ice-water bath was allowed to melt, and the mixture was stirred at r.t. overnight. Excess CH_2Cl_2 and Et_3N were evaporated under reduced pressure, the residue was diluted with water (150 mL), acidified with HCl to pH 3, and extracted with EtOAc (5 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude oily product. The pure product, a colorless oil, was obtained by vacuum distillation.

Methyl 1-(Methylsulfonamido)cyclopropanecarboxylate (16a)

Using **15a** (9.00 g, 60 mmol); yield: 9.81 g (51 mmol, 86%); bp 115–119 °C/0.4 mbar).

IR (KBr): 3280, 3028, 2957, 1733, 1318, 1148, 522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.62 (s, 2 H, cyclopropyl), 1.64 (s, 2 H, cyclopropyl), 3.15 (s, 3 H, SO_2CH_3), 3.88 (s, 3 H, CO_2CH_3), 6.27 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 36.3, 42.5, 52.6, 173.1.

MS (APCI): *m*/*z* = 194.2 $[M + H]^+$.

Anal. Calcd for $C_6H_{11}NO_4S$: C, 37.30; H, 5.74; N, 7.25. Found: C, 37.49; H, 5.68; N, 7.14.

Methyl 1-(Methylsulfonamido)cyclobutanecarboxylate (16b)

Using **15b** (1.75 g, 11 mmol); yield 2.09 g (9.4 mmol, 89%); bp 120–125 °C/0.4 mbar.

IR (KBr): 3281, 3006, 2958, 1732, 1304, 1142, 979, 524 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.99–2.10 (m, 2 H, cyclobutyl), 2.36–2.44 (m, 2 H, cyclobutyl), 2.56–2.63 (m, 2 H, cyclobutyl), 3.02 (s, 3 H, SO_2CH_3), 3.81 (s, 3 H, CO_2CH_3), 6.03 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 32.4, 43.4, 52.5, 60.5, 173.4.

MS (APCI): *m*/*z* = 206.1 $[M - H]^-$.

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.57; H, 6.32; N 6.76. Found: C, 40.61; H, 6.28; N 6.66.

Methyl 1-(*N*-Methylmethylsulfonamido)cycloalkanecarboxylates 17a,b; General Procedure

Methyl 1-(methylsulfonamido)cycloalkanecarboxylate **16a**,**b** (10 mmol) was dissolved in dry DMF (35 mL). K_2CO_3 (2.76 g, 20 mmol) and MeI (2.84 g, 1.25 mL, 20 mmol) were added to the magnetically

stirred solution consecutively at r.t. The flask was equipped with a Dimroth condenser and sealed with a rubber balloon; a slight exotherm occurred. The mixture was allowed to equilibrate to r.t. and stirred overnight. The precipitate was filtered and washed with DMF (2 × 5 mL). Excess DMF was evaporated under reduced pressure and the residue was diluted with water (15 mL) and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure yielding crude oily product. The pure product, a light yellow oil, was obtained by vacuum distillation.

Methyl 1-(*N*-Methylmethylsulfonamido)cyclopropanecarboxylate (17a)

From **16a** (9.5 g, 49 mmol); yield: 9.8 g (47 mmol, 95%); bp 98–103 °C/0.4 mbar.

IR (KBr): 3019, 2956, 1732, 1335, 1147, 522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.76 (br s, 4 H, cyclopropyl), 3.02 (s, 3 H, NCH_3), 3.04 (s, 3 H, SO_2CH_3), 3.78 (s, 3 H, CO_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17–23 (br s), 35.7, 39.0, 42.4, 52.3, 172.4.

MS (APCI): *m*/*z* = 208.2 $[M + H]^+$.

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.57; H, 6.32; N 6.76. Found: C, 40.45; H, 6.24; N, 6.81.

Methyl 1-(*N*-Methylmethylsulfonamido)cyclobutanecarboxylate (17b)

From **16b** (1.47 g, 7.1 mmol); yield: 1.47 g (6.7 mmol, 92%); bp 100–105 °C/0.4 mbar.

IR (KBr): 3008, 2958, 1731, 1337, 962, 768, 526 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.88 (m, 1 H, cyclobutyl), 2.02–2.14 (m, 1 H, cyclobutyl), 2.43–2.58 (m, 4 H, cyclobutyl), 2.79 (s, 3 H, NCH_3), 2.84 (s, 3 H, SO_2CH_3), 3.79 (s, 3 H, CO_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 31.6, 32.4, 39.0, 52.0, 64.6, 173.4.

MS (APCI): *m*/*z* = 222.0 $[M + H]^+$.

Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.43; H, 6.83; N, 6.33. Found: C, 43.32; H, 6.79; N, 6.27.

4-Methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione (3a)

A solution of **17a** (9 g, 43.4 mmol) in DMF (40 mL) was added dropwise to a magnetically stirred solution of *t*-BuOK (10.7 g, 95.6 mmol) in DMF (200 mL); a slight exotherm occurred. The mixture was allowed to equilibrate to r.t. and stirred overnight. AcOH (15 mL) was added dropwise then the mixture was evaporated to dryness under reduced pressure and at a temperature no higher than 60 °C. The residue was triturated with water (80 mL) and extracted with CH_2Cl_2 (5 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure yielding a dark oily product. The pure product was obtained by hot extraction into cyclohexane and subsequent recrystallization (*i*-PrOH) to give colorless crystals; yield: 5.7 g (32.5 mmol, 75%); mp 78–79 °C (cyclohexane–*i*-PrOH).

IR (KBr): 3022, 2957, 1735, 1332, 1211, 1102, 832 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.43 (s, 2 H, cyclopropyl), 1.50 (s, 2 H, cyclopropyl), 2.76 (s, 3 H, NCH_3), 4.24 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.2, 34.4, 54.2, 55.3, 202.6.

MS (APCI): *m*/*z* = 174.0 $[M - H]^-$.

Anal. Calcd for $C_6H_9NO_3S$: C, 41.13; H, 5.18; N, 7.99. Found: C, 40.99; H, 5.07; N, 7.83.

5-Methyl-6λ⁶-thia-5-azaspiro[3.4]octane-6,6,8-trione (3b)

A solution of **17b** (1.0 g, 4.5 mmol) in DMF (5 mL) was added dropwise to a magnetically stirred solution of *t*-BuOK (1.1 g, 9.6 mmol) in DMF (20 mL); a slight exotherm occurred. The mixture was allowed to equilibrate to r.t. and left overnight with stirring. AcOH (1.5 mL) was added dropwise then mixture was evaporated to dryness under reduced pressure and at a temperature no higher than 60 °C. The residue was triturated with water (10 mL) and extracted into CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure yielding a light-brown oily product. The pure product was obtained by hot extraction into cyclohexane and subsequent vacuum sublimation to give colorless crystals; yield: 0.70 g (3.7 mmol, 82%); bp 98–103 °C/0.4 mbar; mp 50–51 °C.

IR (KBr): 2998, 2948, 1756, 1317, 1222, 1135, 1057 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.84–1.94 (m, 1 H, cyclobutyl), 2.04–2.16 (m, 1 H, cyclobutyl), 2.41–2.53 (m, 4 H, cyclobutyl), 2.91 (s, 3 H, NCH_3), 3.72 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 24.2, 28.9, 54.6, 71.8, 202.5.

MS (APCI): *m*/*z* = 190.1 $[M + H]^+$.

Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.40. Found: C, 44.28; H, 5.83; N, 7.27.

(Dimethylamino)methylidene-Substituted Thiaazaspiroalkanetriones 18a,b; General Procedure

Cyclic sulfonamide **3a**,**b** (1 mmol) was dissolved in warm anhyd MeOH (5 mL) at r.t. DMFDMA (0.24 g, 0.27 mL, 2 mmol) was added to the stirred solution in one portion; a crystalline precipitate formed and the mixture was stirred for 30 min. The mixture was refluxed for 90 min to ensure completion of the reaction and then it was evaporated to dryness. Recrystallization (*i*-PrOH) afforded the pure product as white crystals.

6-[(*Z*)-(Dimethylamino)methylidene]-4-methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione (18a)

Using **3a** (0.20 g, 1.14 mmol); yield: 0.22 g (0.96 mmol, 85%); mp 203–204 °C.

IR (KBr): 3092, 2949, 1680, 1614, 1361, 1259, 957 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.18 (s, 2 H, cyclopropyl), 1.20 (s, 2 H, cyclopropyl), 2.56 (s, 3 H, NMe), 3.41 (s, 6 H, NMe_2), 7.62 (s, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.8, 32.9, 41.3, 47.4, 51.3, 155.4, 189.3.

MS (APCI): *m*/*z* = 231.2 $[M + H]^+$.

Anal. Calcd for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16. Found: C, 46.77; H, 6.00; N, 12.11.

7-[(*Z*)-(Dimethylamino)methylidene]-5-methyl-6λ⁶-thia-5-azaspiro[3.4]octane-6,6,8-trione (18b)

Using 3b (0.20 g, 1.05 mmol); yield 0.20 g (0.83 mmol, 79%); mp 167–168 °C.

IR (KBr): 2995, 2951, 1678, 1610, 1359, 1281, 955 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.71 (m, 1 H, cyclobutyl), 1.94 (sextet, *J* = 9.2 Hz, 1 H, cyclobutyl), 2.19 (m, 2 H, cyclobutyl), 2.40 (q, *J* = 8.8 Hz, 2 H, cyclobutyl), 2.74 (s, 3 H, NMe), 3.41 (s, 6 H, NMe_2), 7.60 (s, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.7, 23.6, 28.1, 41.3, 47.7, 68.0, 151.3, 189.6.

MS (APCI): m/z = 245.2 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.47. Found: C, 48.97; H, 6.51; N, 11.53.

Collection of Crystallographic Data and Structure Determination for 18b

The data were collected at low temperature (193 K) on a Bruker-AXS APEX II QUAZAR diffractometer equipped with a 30-W air-cooled microfocus source, using MoKα radiation (λ = 0.71073 Å). Phi and omega scans were used. The data were integrated with SAINT,[17] and an empirical absorption correction with SADABS was applied.[18] The structure was solved by direct methods (SHELXS-97)[19] and refined using the least-squares method on F^2 (SHELXL-97).[19] All non-H atoms were refined with anisotropic displacement parameters. The H atoms were refined isotropically at calculated positions using a riding model.

CCDC-1051098 (**18b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Selected data for **18b**: $C_{10}H_{16}N_2O_3S$, M = 244.31, monoclinic, space group $P2_1/c$, a = 12.8541(4) Å, b = 16.1078(6) Å, c = 11.2684(4) Å, α = γ = 90°, β = 95.7363(13)°, V = 2321.45(14) Å^3, Z = 8, crystal size 0.220 × 0.200 × 0.200 mm^3, 34181 reflections collected (5285 independent, R_{int} = 0.0273), 295 parameters, $R1$ [I >2σ(I)] = 0.0331, $wR2$ [all data] = 0.0965, largest diff. peak and hole: 0.393 and –0.354 e Å^{-3}.

Acknowledgment

Alexey Dobrydnev acknowledges Patricia Dobrydneva for a fellowship and technical support.

Primary Data

Primary data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084 and can be cited using the following DOI: 10.4125/pd0069th.

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