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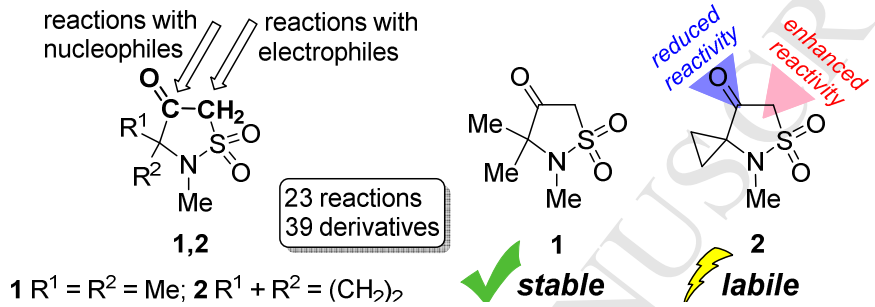

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ABSTRACT

Herein, we present a full account of our studies with respect to the reactivity of insufficiently explored 1λ^6-isothiazolidine-1,1,4-triones (so-called β-keto-γ-sultams). This heterocyclic system possesses two reaction centers: the EWG-activated methylene group and the carbonyl moiety which were investigated in the course of present study. 2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4-trione and 4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione were chosen as representatives of the given class of substances. The former is a classical spatially uncomplicated model substance, the latter bearing a spiranic cyclopropane substituent is interesting in terms of evaluation of strain cycle effects. Indeed, the data obtained convey information about the impact of the highly strained substituent on the reaction centers of the ketosultam core. Thus, in addition to less stability of the strained spiranic ketosultam, the reactivity of its carbonyl group is suppressed whereas the activity of the methylene group is enhanced being compared with the nonspiranic substrate. Apart from the difference in the chemical character of the given β-keto-γ-sultams we faced unprecedented products (1,1-dioxo-5-[2-(triphenylphosphonio)acetyl]-2,3-dihydro-1*H*-1λ^6-isothiazol-4-olates) formed during the course of the reaction with the Wittig reagent triphenylcarbethoxymethylenephosphorane.

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1. Introduction

The structural and therapeutic diversity, coupled with the commercial viability of small heterocyclic molecules has fascinated organic and medicinal chemists for a long period of time. Cyclic sulfonamides (sultams),[1] although not found in nature, are present in a number of biologically active compounds. Sulfonamides are generally stable under physiological conditions and only a few known enzymes are able to hydrolyze SO_2-N bond.[2] Therefore, substituted sulfonamides are frequently used in drug discovery projects as common starting or target materials. Among them is S-2474, a cytokine suppressive dual inhibitor of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO).[3] As well, 3*a*,4,5,6-tetrahydro-pyrrolo[1,2-*b*]-isothiazole-1,1-diones have been found to constitute a therapeutic approach to inflammation and autoimmune diseases. They were patented[4] by Novartis Pharma GmbH in 2007 as components for treating disorders which are mediated by interaction of LFA-1 with its ligands involved in cell adhesion, migration and activation (**Figure 1**).

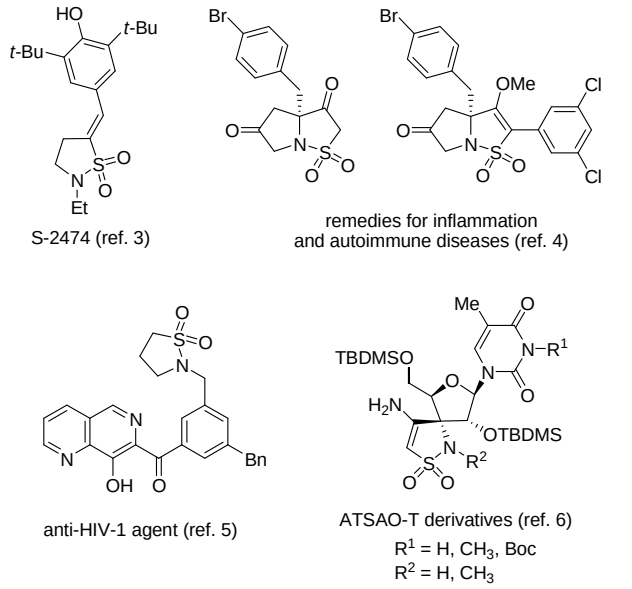

Figure 1. Synthetic biologically active sultams.

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At the same time, naphthyridine bearing a sultam substitution at the 3rd position of the central phenyl ring exhibits an excellent potency and a good pharmacokinetic profile as an HIV-1 integrase inhibitor.[5] Four families of ATSAO-T derivatives were also studied in the same manner and were found to be HIV-1(III_B)-specific and potent reverse transcriptase inhibitors[6] (**Figure 1**).

In medicinal chemistry and biochemistry, the sulfonamide group is known as a bioisosteric equivalent of the carboxamide group. Their similarity is based on the consideration of electronic and conformational aspects and it serves as a powerful tool in drug discovery. The most classic example is the family of sulfonamide antibiotics. At this point, β-keto-γ-sultams are the closest sulfur-containing bioisosters of tetramic acid (**Figure 2**).

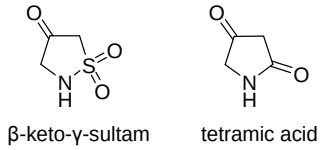


Figure 2. Tetramic acid and its sulfur-containing isoster.

Naturally occurring tetramic acids constitute a vast array of bioactive secondary metabolites among which are erythroskyrine[7] and PF 1052.[8] In general, tetramic acid-containing natural products display a wide range of biological activities, including antibiotic,[9] antiviral, cytotoxicity, and cytostatic activities.[10] A great deal of attention to synthetically occurring tetramic acids was focused by Bayer CropScience. Eventually, they patented a series of ingredients for fungicidal and herbicidal use[11] and in 2007 released a pesticide spirotetramat (brand name Movento®)[12] which is active against piercing-sucking insects (**Figure 3**).

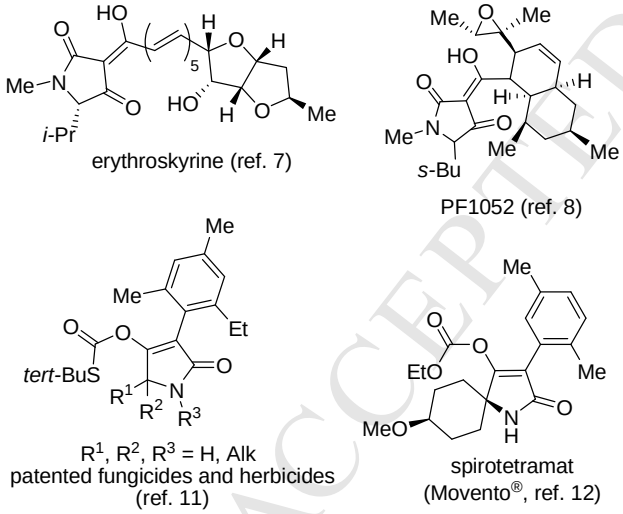


Figure 3. Naturally occurring and synthetic tetramic acid derivatives.

Although isothiazolidine-1,1,4-triones have been known since 1976[13a,b] they are not studied sufficiently and the reported transformations are mostly limited to condensation reactions.[13a,c] At the same time, the methylene and the carbonyl groups provide an opportunity for further modification giving access to intermediates that are of high value for pharmaceutical-directed organic synthesis. To this purpose, we aimed to investigate the reactivity of both centers and chose 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**) and 4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione (**2**) as model compounds for the chemical properties evaluation (**Figure 4**).

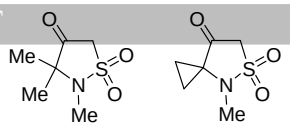


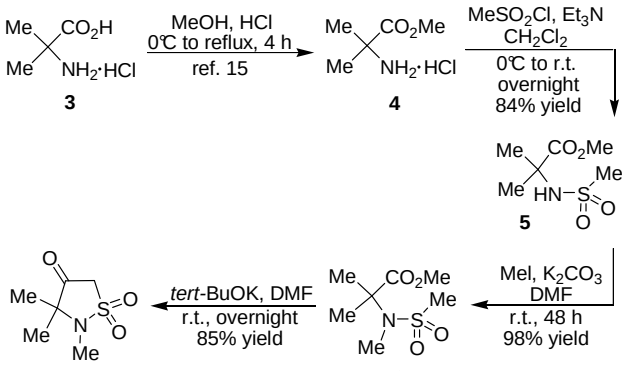
Figure 4. 1λ^6-Isothiazolidine-1,1,4-triones chosen for the chemical properties evaluation.

The strained spirocarbocyclic substituent at the 3rd position of the isothiazolidine-1,1,4-trione scaffold might influence the activity of the reaction centers. Due to this reason, the difference in the reactivity of the non-spiranic and strained spiranic substrates towards nucleophiles and electrophiles was expected.

2. Results and discussion

In conjunction with our interest in developing efficient syntheses of functionalized sultams[14] we have already described the preparation of 4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione (**2**).[14a] Albeit an approach to the construction of 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**) had been published,[13a,b] we envisioned an improved synthetic route wherein isobutyric amino acid **3** was found as an appropriate starting material.

Thus, amino isobutyric acid **3** was esterified with methanol following the methods described in the literature.[15] Subsequently, sulfonylation of the amino acid ester **4** with MsCl in CH_2Cl_2 in the presence of Et_3N as a base resulted in the corresponding methyl 1-methylsulfonamido carboxylate **5** in 84% yield. It was found to be advantageous to allow the reaction mixture standing at r.t. at least overnight to ensure the completion of the sulfonylation process. Subsequent alkylation of **5** with MeI in DMF afforded methylated sulfonamido carboxylate **6** in a nearly quantitative yield and this was followed by treatment with *tert*-BuOK in DMF to produce the target 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**) *via* sulfa-Dieckmann cyclization in 85% yield (**Scheme 1**).



Scheme 1. An improved synthesis of 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**).

As it will be shown below, the mother solutions remained after recrystallization of crude **1** as well as **2** were effectively used on the principle of non-waste production. Thus, they were processed with an excess of DMFDMA (dimethylformamide dimethyl acetal) to give the corresponding dimethylaminomethylene derivatives (refer to **Scheme 8**, products **38**,**39**).

We began our study of the chemical properties of ketosultams **1** and **2** with the examination of the carbonyl group reactivity. First, the possibility of the ketonic C=O bond reduction was explored.

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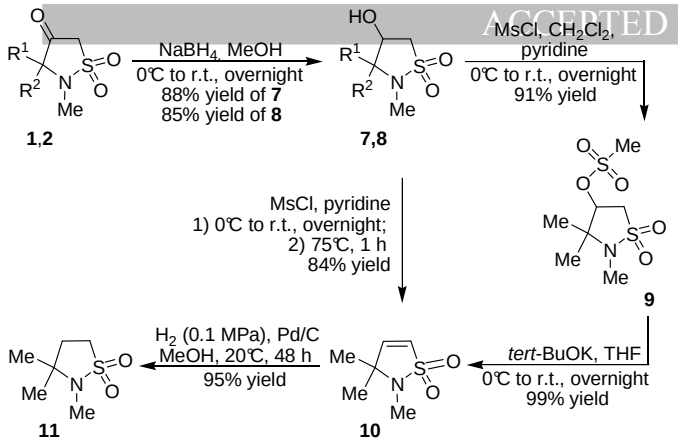


1, 7 $R^1 = R^2 = Me$; **2, 8** $R^1 + R^2 = (CH_2)_2$

Scheme 2. The reduction of ketosultams **1**,**2** and subsequent transformations of the alcohol **7**.

Thus, the interaction of ketosultams **1**,**2** with $NaBH_4$ in MeOH led to the corresponding alcohols **7**,**8** in 88 and 85% yields, respectively (**Scheme 2**).

The carbinol **7**, when reacted with MsCl, provided mesylate **9** which in turn was subjected to the action of *tert*-BuOK in THF. The elimination of a mesylate-anion proceeded smoothly and the corresponding alkene **10** was isolated in a nearly quantitative yield. It is important to note that alkene **10** can be prepared directly from the alcohol **7** by carrying out a mesylation reaction in a pyridine media followed by heating of the reaction mixture up to 75°C. Hydrogenation of alkene **10** catalyzed by palladium on charcoal in a methanol media gave the saturated 1,3-propanesultam **11** in 95% yield (**Scheme 2**).

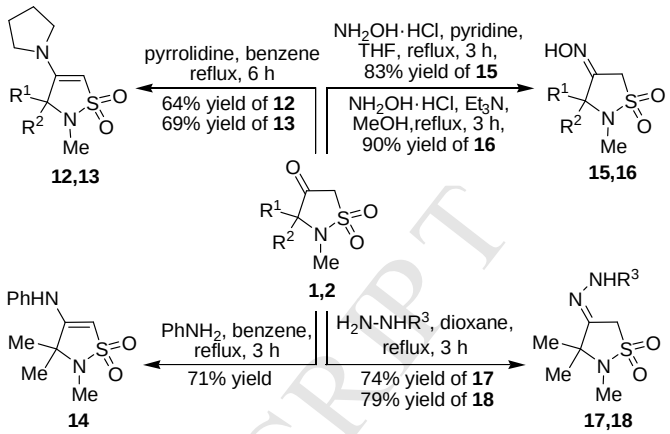
Unfortunately, the mesylation of carbinol **8** was not successful and did not allow obtaining any identifiable product.

Then we investigated classical reactions with *N*-nucleophiles. After refluxing the benzene solutions of **1**,**2** with excess pyrrolidine with a Dean-Stark attachment it was isolated the corresponding enamines **12**,**13** with a pyrrolidinyl-bearing substituent at the 4th position. The related enamine with an aromatic substituent at the amino group was obtained only from ketosultam **1**. The spiranic derivative **2** did not react with aniline (**Scheme 3**).

Refluxing the ketosultam **1** with $H_2NOH{\bullet}HCl$ and pyridine in THF led to ketoxime **15** in 83% yield. However, in the case of spiranic sultam **2**, the best result was obtained with Et_3N under reflux in a methanol media and the corresponding ketoxime **16** was isolated in 90% yield (**Scheme 3**). It is of note here that attempts at the reduction of oximes **15** and **16** into the corresponding amines were unsuccessful ($LiAlH_4$ and $NaBH_4$+$Et_2O{\bullet}BF_3$ were explored).

Another interesting feature was the reactivity towards hydrazines. The interactions of ketosultam **1** with substituted hydrazines (namely, $PhNHNH_2$ and $BocNHNH_2$) resulted in the direct formation of the corresponding hydrazones **17** and **18** in moderate (74 and 79%) yields. Whereas an analogous treatment with $NH_2NH_2{\bullet}H_2O$ as well as reactions of **2** with all the mentioned hydrazines failed to give the desired hydrazones, instead, the mixtures of unidentifiable by-products were isolated.

After, we explored the reactions with *C*-nucleophiles. To a certain extent, predictable result was obtained during the course of the reaction of ketosulfonamides **1**,**2** with KCN and $(NH_4)_2CO_3$ in aqueous methanol. Thus, instead of hydantoins **19**,**20** formation according to the Bucherer–Bergs method we observed the *retro*-Claisen reaction and CO-CH_2 bond splitting that gave the corresponding acids **21** and **22** (**Scheme 4**).



1,12,15 $R^1 = R^2 = Me$; **2,13,16** $R^1 + R^2 = (CH_2)_2$; **17** $R^3 = Ph$; **18** $R^3 = Boc$

Scheme 3. The reactions of **1** and **2** with *N*-nucleophiles.

Quite unforeseen results were obtained during the course of the reaction of ketosultams **1**,**2** with a Wittig reagent the triphenylcarbethoxymethylenephosphorane ($Ph_3P{=}CHCO_2Et$). The reaction took place under mild conditions in refluxing toluene media using benzoic acid as a catalyst. We expected the oxygen atom of the ketone group to be replaced with $=CHCO_2Et$ moiety. However, the major product in the case of nonspiranic ketosultam **1** was 2,3,3-trimethyl-1,1-dioxo-5-[2-(triphenylphosphonio)acetyl]-2,3-dihydro-1*H*-1λ^6-isothiazol-4-olate (isolated as solvate **23**•PhMe in 61% yield). Noteworthy fact, the 'acylation' with $Ph_3P{=}CHCO_2Alk$[16] is unprecedented and had been hitherto unknown. The structure of this unusual compound was mainly established by X-ray structure determination of a single crystal (solvate **23**•DMF) obtained by slow evaporation of the solution of **23**•PhMe in DMF upon standing (**Figure 5**). According to XRD data, the thiazolidine cycle adopts an envelope conformation. The deviation of the N1 atom from the mean plane of the remaining atoms of this cycle is -0.43 Å. The N1 atom has the pyramidal configuration (the sum of the valence angles centered at the N1 atom is 349°). The methyl group at the atom N1 is located in an equatorial position to the plane of the thiazolidine cycle (the C2-C1-N1-C4 torsion angle is -170.7(4)°). The carbonyl group and the C8 atom of the substituent at the C3 atom are coplanar to the C2-C3 endocyclic bond (the C2-C3-C7-C8 torsion angle is 8.7(7)°). It is stabilized additionally by the C8-H…O1 intramolecular hydrogen bond (H…O 2.21 Å, C-H…O 138º). The triphenylphosphonio fragment is located in +*sc*-position relatively the carbonyl group (the O4-C7-C8-P1 torsion angle is 57.8(5)°).

The minor product (22% yield) was a nearly equimolar mixture of tautomeric sultamo esters with an exocyclic (**24**) and an endocyclic (**25**) double C=C bonds with some predominance of the latter (**Scheme 4**). At the same time, the treatment of **2** with this Wittig reagent at equal conditions resulted in the expected 2-([*E*]-4-methyl-5,5-dioxo-5λ^6-thia-4-azaspiro[2.4]hept-7-ylidene)acetate **26** as a sole isomer in 57% yield. The corresponding betaine derivative **27** was also formed, but only in trace amounts and it was identified according to LCMS and HRMS data.

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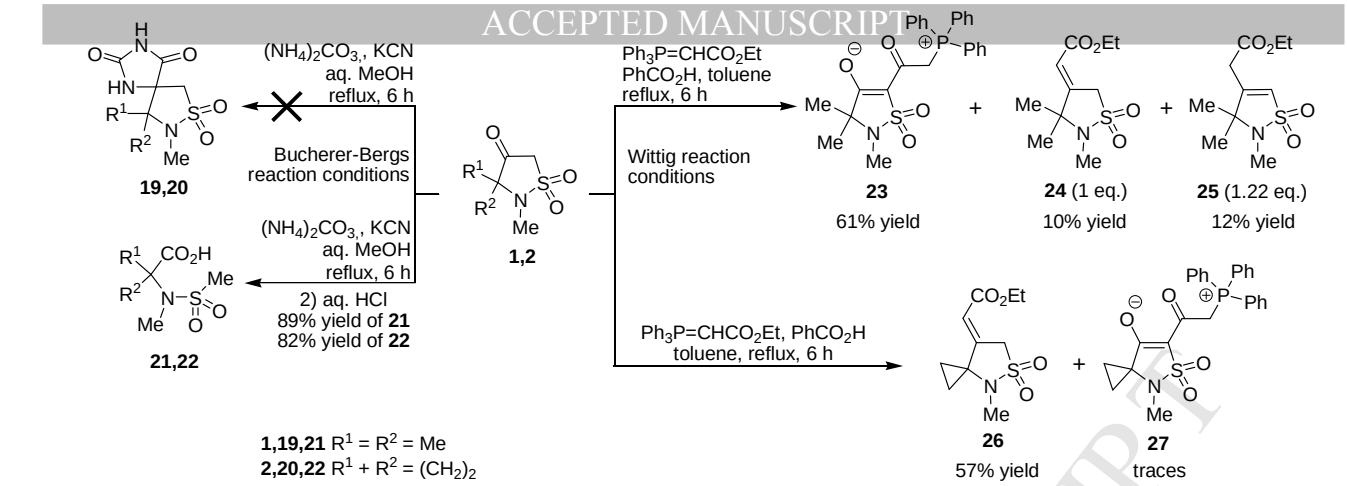
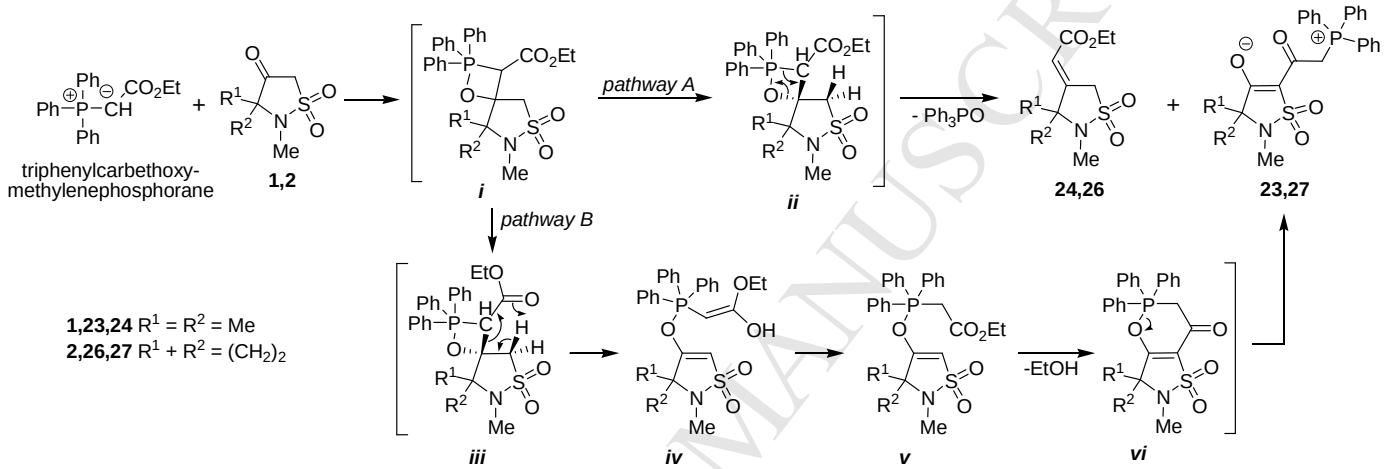


Scheme 4. The reactions of **1** and **2** with *C*-nucleophiles.



Scheme 5. A mechanism proposed for the formation of products **24,26** and betaines **25,27**.

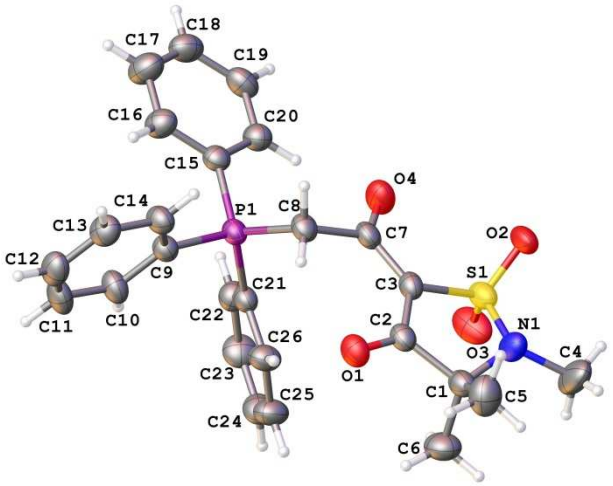


Figure 5. The molecular structure of compound **23** according to the results of an X-ray diffraction study. Thermal ellipsoids are shown at 50% probability level.

We propose, that the reaction proceeds *via* the nucleophilic addition of the zwitterionic phosphine ylide to the carbonyl moiety of ketosultam **1**,**2** to give the oxaphosphetane intermediate ***i***. In the classical course of the reaction (*pathway A*, **Scheme 5**) the intermediate conversion leads to products **24**,**26** that is accompanied by triphenylphosphine oxide release. However, the isomeric product **25** is more energetically favorable tautomer. It is formed upon heating and exists in thermodynamic equilibrium with **24**. Alternatively (*pathway B*, **Scheme 5**), the C–C bond of the oxaphosphetane ring splits, that is accompanied by a proton migration from the 5th position of the isothiazole cycle to an oxygen atom of the carbonyl moiety. Further tautomeric rearrangement of ethylenylphosphorane ***iv*** results in the formation of the intermediate ***v*** that cyclizes turning into oxaphosphinino[6,5-*d*]isothiazole ***vi***. The latter, due to steric hindrances, splits the P–O bond to form the betaines **23**,**27**.

In order to confirm the configuration of the ethyl acrylate fragment in product **26**, a single crystal of the product **26** was obtained by slow evaporation of a dilute solution in cyclohexane. The X-ray crystal structure determination decisively confirmed the proposed structure. **Figure 6** shows the molecular structure together with the atomic numbering scheme of **26**. According to XRD data, the thiazolidine cycle adopts an envelope conformation. The deviation of the N1 atom from the mean plane of the remaining atoms of this cycle is -0.59 Å. The N1 atom has the pyramidal configuration (the sum of valence angles centered at the N1 atom is 332°). The methyl group at the atom N1 is located in an axial position to the plane of the thiazolidine cycle (the C6-C3-N1-C2 torsion angle is 88.6(3)°). The C7-C8-(O3)-O4-C9 fragment of the ethyl acrylate substituent is coplanar to the C1-C6 endocyclic bond (the C1-C6-C7-C8 torsion angle is 5.9(4)°). The methyl group at the atom C9 is orthogonal to the plane of the planar fragment of this substituent (the C10-C9-O4-C8 torsion angle is 85.9(3)°).

The similarity in structures of compounds **24** and **26** permits the supposition that the former has the same configuration of the double C=C bond.

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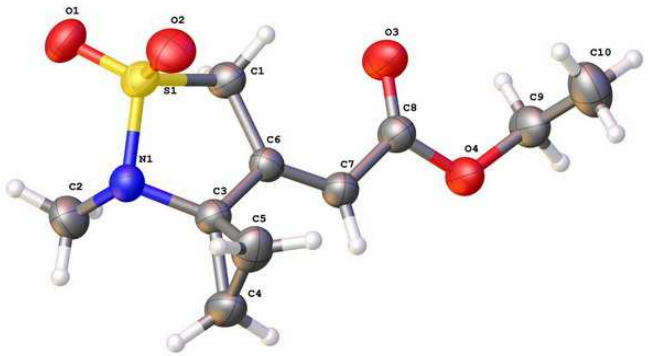
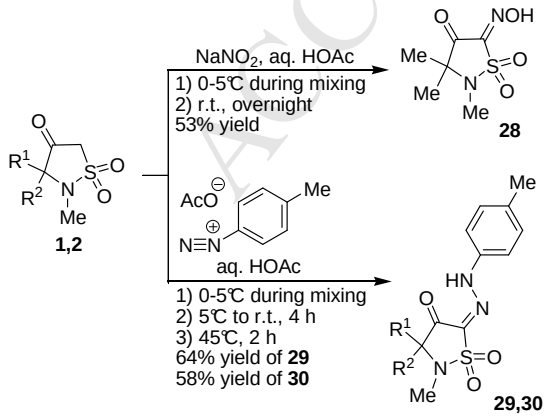


Figure 6. The molecular structure of compound **26** according to the results of an X-ray diffraction study. Thermal ellipsoids are shown at 50% probability level.

Finally, apart from the synthetic utility of the C=O group we should also mention the limitations associated with the carbonyl group activity. Thus, we did not find appropriate conditions for protecting group attachment: methanol, ethylene glycol, propanedithiol *et al.* in acidic conditions were tried but were not set. Then, attempts to employ Corey-Chaykovsky reagent (Me_3SO^+ I^-) for epoxidation of ketosultams **1** and **2** also failed, we obtained a complex mixture of ring-opening and other side products. The same situation was observed when **1** and **2** were involved in the Knoevenagel reaction: the condensation products with malononitrile, malonic acid as well as malonates were not detected. Besides, under the Grignard reaction conditions we did not obtain the corresponding tertiary carbinols; instead, the starting ketosultams were recovered that occurred due to enolization, induced by EWG-group (SO_2).

To further explore the synthetic utility of 1λ^6-isothiazolidine-1,1,4-triones **1**,**2** we next focused on reactions of the SO_2 and CO-activated methylene group to obtain the derivatives which would bear different substituents at the 5th position of the heterocyclic core. So, the following step in this direction was the study of interaction with electrophilic agents.

We first investigated classical reactions with *N*-electrophiles. When β-keto-γ-sultams **1**,**2** reacted with a nitrosation agent (sodium nitrite solution in aq. acetic acid) at 0-5°C only the non-spiranic ketoxime **28** was isolated in a moderate (53%) yield (**Scheme 6**). The suitable conditions for nitrosation of spiranic ketosultam **2** were not found. Variation of temperature, amount of the electrophile and isolation procedures, even so, resulted in the unidentified mixtures only.

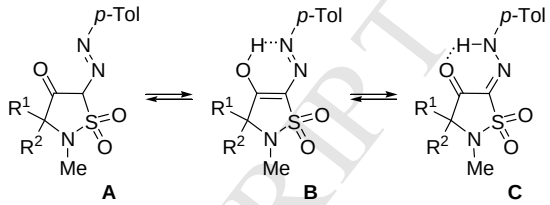


1,**29** $R^1 = R^2$ = Me; **2**,**30** $R^1 + R^2 = (CH_2)_2$

Scheme 6. The reactions of **1** and **2** with *N*- electrophiles.

At the same time, both ketosulfonamides **1** and **2** successfully underwent an azo coupling reaction with *p*-tolyl diazonium acetate and the corresponding azo compounds **29**,**30** were obtained in satisfactory (64 and 58%) yields (**Scheme 6**).

Three tautomers of azo compounds **29**,**30** are possible, two of which (**B** and **C**) feature the intramolecular hydrogen bond that contributes to the conformational stability (**Scheme 7**). Howbeit, both types of bondings (NH···O and OH···N) are strong[17] it should be considered the persistent tendency of azo compounds to tautomerize to hydrazones even when no through-conjugated structures can result.[18]



29 $R^1 = R^2$ = Me; **30** $R^1 + R^2 = (CH_2)_2$

Scheme 7. The azo-tautomers of **29** and **30**.

The structure of **29** was established on the basis of its spectral data. The ^{1}H NMR spectrum displayed a broad singlet at δ_H = 13.36 ppm, typical for intramolecular hydrogen bond, and the lack of downfield singlet, assignable to a 5-CH proton, that is contrary to structure **A**. Moreover, the ^{13}C NMR spectrum showed two downfield signals at δ_C = 188.5 and 139.4 ppm assigned to the ketone fragment and the imine moiety, respectively. These data are therefore consistent with structure **C** (**Scheme 7**). For the spiro derivative **30**, the same pattern was observed and the analogical structure was proposed.

Next, we turned our attention to reactions of β-keto-γ-sultams **1**,**2** with *C*-electrophiles. Among them acylating and alkylating agents, as well as reactants for condensation reactions, were chosen.

The behavior of the keto sultam system towards acylating agents was investigated in order to generate β-diketone derivatives, the widely applicable substances. However, the direct acylation with benzoyl chloride in benzene/pyridine media did not prove to be a regiosective method. For this reason, we examined the acylation with benzoic acid in the presence of a coupling agent EDC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride) and DMAP (4-dimethylaminopyridine) as a base. Indeed, after 96 h standing at 20°C and a standard work-up procedure the desired products **31** and **32** were obtained, but in low (38 and 44%) yields (**Scheme 8**). Interestingly, the spiranic derivative **32** was isolated as a mixture of enol and ketone tautomers in 3:1 ratio.

1λ^6-Isothiazolidine-1,1,4-triones **1**,**2** also readily react with phenyl isocyanate and phenyl isothiocyanate according to a known method.[19] As a result, the corresponding amides **33**,**34** and thioamides **35**,**36** were obtained (**Scheme 8**).

The condensation of sultam **1** with benzaldehyde in the presence of NaOAc in HOAc has been reported.[13a] Again, we decided to use an alternative method and base-mediated conditions that gave the corresponding conjugated ketone **37** in a better (84%) yield (**Scheme 8**). At once, the similar reaction between spiranic ketosultam **2** and benzaldehyde was not fruitful. The condensation under both acidic (NaOAc+HOAc) and basic (pyridine) conditions gave at the best scenario the partial recovery of the starting material and at the worst the total decomposition of ketosultam **2**.

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Dimethylaminomethylene derivative **37** was obtained in a similar manner to the previously described synthesis of spiranic product **38** (**Scheme 8**).[14a] It is worthwhile to note that a tangible amount of products **38**,**39** can be obtained from the combined filtrates and wash solutions remained after purification of ketosultams **1**,**2**. Thus, treatment of such a mixture with the abundance of DMFDMA gave another crop of pure crystalline material.

A single crystal of the product **39** was obtained by slow evaporation of the mother solution in methanol upon standing. X-ray crystal structure determination decisively confirmed the structure of **39** (**Figure 7**). According to XRD data, the thiazolidine cycle adopts an envelope conformation. The deviation of the N1 atom from the mean plane of the remaining cyclic atoms is -0.29 Å. The configuration of the N1 atom is slightly pyramidal (the sum of the valence angles centered at the N1 atom is 345°). The methyl group at the atom N1 has an equatorial orientation relatively to the plane of the thiazolidine cycle (the C1-N1-S1-C4 torsion angle is -162.1(1)°). The dimethylaminomethylene fragment lies in the plane of the planar part of the thiazolidine cycle (the torsion angle C3-C4-C6-N2 is 180.0(1)°).

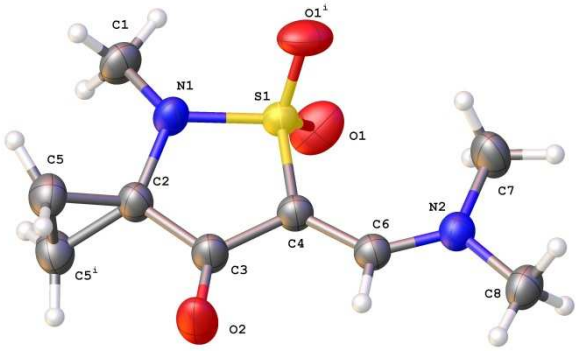


Figure 7. The molecular structure of compound **39** according to the results of an X-ray diffraction study. Thermal ellipsoids are shown at 50% probability level.

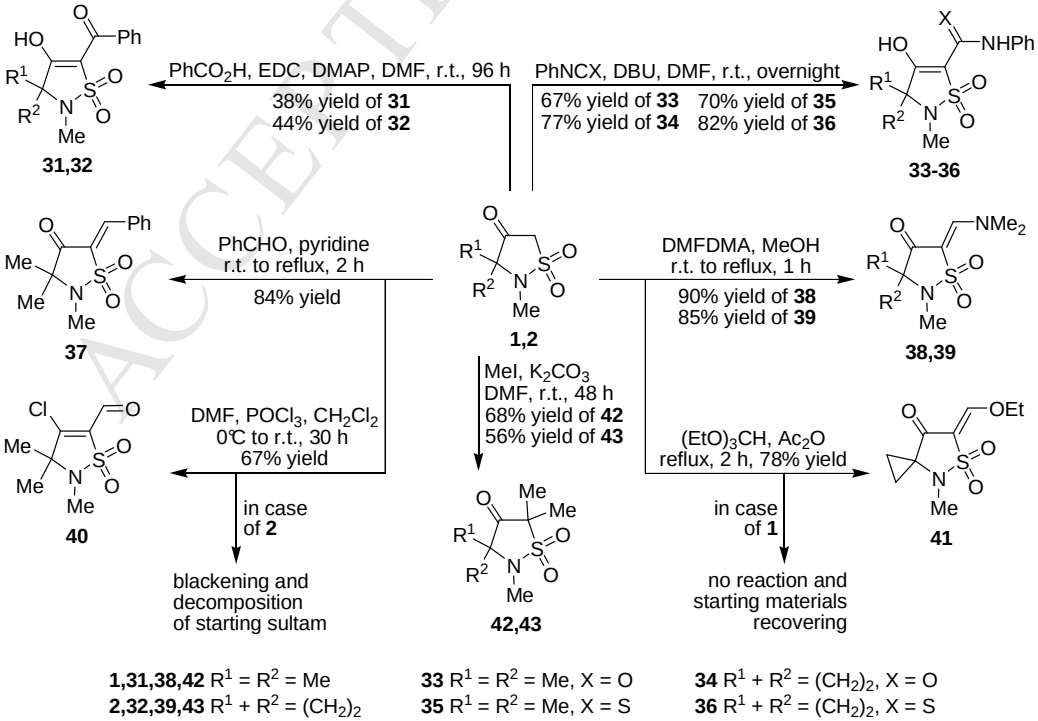
Another example of striking differences in the chemical behavior of **1** and **2** was found upon the Vilsmeier reaction conditions. Thus, the chloroformylation of **1** with the Vilsmeier reagent ($DMF/POCl_3$) successfully afforded β-chlorovinylaldehyde **40** in 67% yield according to the method described by Li Tian.[20] At the same time, when this procedure was applied to **2** a quite dissatisfactory result was obtained: complete decomposition of the starting material occurred (**Scheme 8**).

However, bearing in mind that β-chlorovinylaldehydes are related to β-ketoenols and could be frequently replaced with each other, we turned our attention to condensation of **1** and **2** with triethyl orthoformate. In this way, the spiranic derivative **41** was synthesized in a straightforward manner in 78% yield. Interestingly, when this methodology was tried out on **1**, after workup procedure starting materials were recovered.

Compounds **40** and **41** are expected to be useful intermediates, as on interaction with diverse amidines they may supply a range of fused heterocyclic systems. The successful application of this strategy will be described later.

Finally, we subjected **1** and **2** to the action of an alkylating agent. Despite the β-keto-γ-sultam ring has two reaction centers at C-5 and 4-keto, respectively, the reactions of **1**,**2** with an excess of MeI in the presence of K_2CO_3 in DMF media afforded exclusively the C-5 dimethylated derivatives **42**,**43** in moderate (68 and 56%) yields (**Scheme 8**). The monoalkylated products were not readily available using equimolar amounts of the reagents.

The dimethylaminomethylene derivatives **38** and **39** are particularly well functionalized since they contain a ketone moiety and a dimethylaminomethylene group which is considered as a hidden carbonyl group. The scope of a literature review demonstrates the importance of these functional groups in the synthesis of fused heterocycles.[21] From this point of view compounds **38** and **39** looked to be promising reagents. Therefore, interaction with *C*-, *N*-, and *O*-nucleophiles was next addressed in our substrates.



Scheme 8. The reactions of **1** and **2** with *C*-electrophiles.

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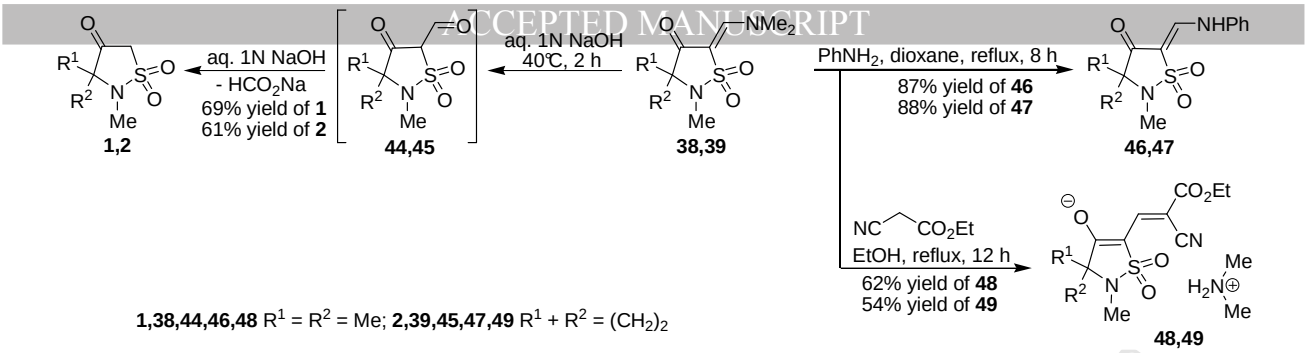

Scheme 9. The reactions of **38** and **39** with *C*-, *N*-, and *O*-nucleophiles.

The interaction of compounds **38**,**39** with 1N aq. NaOH resulted in the formation of ketosultams **1**,**2** instead of the desired aldehydes **44**,**45**. A possible mechanism of this reaction and the general method were described previously[22] (**Scheme 9**).

Having established the synthesis of **38**,**39** we turned our attention to the preparation of other aminomethylene derivatives by means of transamination reaction. Thus, the interaction with aniline gave the corresponding products **46**,**47** in good (87 and 88%) yields (**Scheme 9**). Theoretically, these compounds can exist as s-*cis*- and s-*trans*-conformers, thereby we observed a duplicate set of signals which can be explained by a high energy barrier of rotation of the conjugated =CH–NR^{1}R^2 bond. On the basis of the ^{1}H NMR spectra, we deduced that the s-*trans*-conformer is characterized by a *J*-coupling constant with a greater frequency value (approx. *J* = 15 Hz). The further evaluation of the integral intensities of the signals allowed proposing the predominance of the s-*cis*-conformers in the mixtures. The conformer ratio s-*cis*/s-*trans* in both cases were 2.6:1.

To our disappointment, all the attempts to involve the dimethylamino and ketonic groups of compounds **38**,**39** in interaction with hydrazines in order to obtain the corresponding fused heterocyclic systems failed. Instead, we obtained a set of contradicting and irreproducible results (atypical transamination, rearrangement, and condensation) that are a subject of further investigations. A suchlike result was obtained when hydroxylamine and amidines were explored. At mild conditions (Et_3N/*i*-PrOH, reflux) the starting materials were recovered whereas more stringent conditions (EtONa/EtOH, reflux) resulted in a complex mixture of side products. The only alternative interpretation of the observed data evident to the authors was that, perhaps, the lability of the single C–C bond between the ketonic moiety and the dimethylaminomethylene group. The interaction was assumed to proceed *via* the initial *retro*-Claisen reaction followed by other adverse reactions.

Continuing with the theme of the replacement of the easily leaving dimethylamino group we envisaged a similar approach for *C*-nucleophiles. This was implemented by carrying out the reaction of **38**,**39** with ethyl cyanoacetate. Consequently, the corresponding substitution products **48**,**49** were isolated as the anions with dimethylammonium counterion in satisfactory (62 and 54%) yields. X-ray crystal structure determination allowed us to confirm the structure of the product **48** (**Figure 8**). According to the XRD data, the organic salt **48** exists in the crystal phase as monohydrate. The protonation of the dimethylammonium is confirmed by the localization of two hydrogen atoms from electron density difference maps. The distribution of the electron density in the carboanion allows to presume the localization of the negative charge within the C3-C7-C8 fragment (the C3-C7 and C7-C8 bonds (1.394(3) Å and 1.366(3) Å) are longer than the mean value of the Csp^2=Csp^2 bond (1.326 Å) and shorter than the mean value of the Csp^2–Csp^2 bond (1.455 Å)).

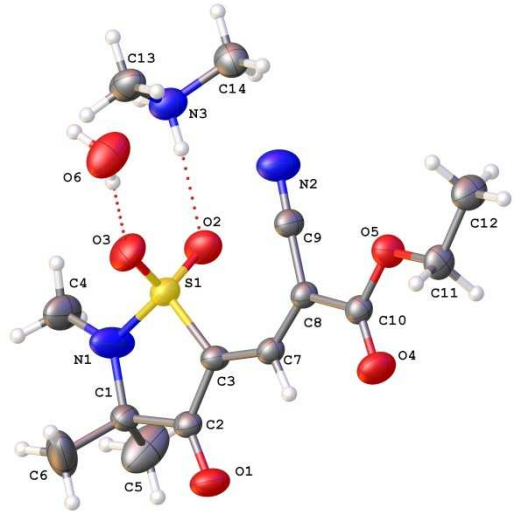

Figure 8. The molecular structure of compound **48** according to the results of an X-ray diffraction study. Thermal ellipsoids are shown at 50% probability level.

In contrast to structures **26** and **39**, the heterocycle in the carbanion is flat. The sum of the valence angles centered at the N1 atom is 359°). The ethyl cyanoacrylate fragment lies in the plane of the thiazolidine cycle (the torsion angle S1-C3-C7-C8 is -3.0(3)°).

3. Conclusion

As a part of a program launched into the development of novel methods for the preparation of synthetically occurring tetramic acid isosters, we introduced the behavior and comparative assessment of chemical properties of spatially uncomplicated 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**) and geometrically tensed 4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione (**2**) which is interesting in terms of strain cycle effects.

An exploration of the EWG-activated methylene group and the carbonyl function of the β-keto-γ-sultam system, on the one hand, disclosed their potential synthetic utility providing access to a range of derivatives, and on the other hand, revealed the influence of the sterical tension on the chemical activity. Though the range of investigated compounds is limited, the data presented suggest that the size of the substituent ring and the geometry of the resulting sultam framework have an impact on its chemical properties. In this way, the reactivity of the carbonyl group in 4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione towards *N*-nucleophiles is suppressed whereas the activity of the

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EWG-activated methylene group towards electrophiles is enhanced being compared with ones in 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione all arising from the steric and conformational effects caused by a strained spirocyclic substituent. Additionally, it should be noted that the geometric tension and rigidity of this structure cause less stability which is the reason for adverse reactions.

Toward the end of the present work, we would like to make the suppositions regarding the chemical behavior of spiranic β-keto-γ-sultams with unstrained angles and bond lengths. In general such compounds might react similarly to 2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**), as the spiranic feature of the system enhances the reactivity towards electrophiles while being more stable than **2**. Analogous conclusions on the activity of non-spiranic and spiranic substrates were drawn in respect to the β-amino-γ-sultone scaffold.[23] However, each individual case has some specific peculiarities, caused by the chemical nature of the substrates and the reagents.

These results pave the way for the more detailed study of β-keto-γ-sultams and other relative compounds, especially with the β-keto-sulfone fragment. With the reported syntheses we believe that sultam and sultone derivatives will find practical application in drug discovery projects, especially in those where tetramic acid is involved.

4. Experimental section

X-ray diffraction study of compounds 23, 26, 39, and 48

Intensities of reflections were measured on an automatic 'Xcalibur 3' diffractometer (graphite monochromated MoKα radiation, CCD-detector ω scanning). All structures were solved by the direct method using the SHELXTL package.[24] Positions of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with U_{iso} = nU_{eq} of carrier non-hydrogen atom (n = 1.5 for methyl groups and water molecule and n = 1.2 for other hydrogen atoms). Structures were refined by full-matrix least-squares method against F^2 in anisotropic approximation for non-hydrogen atoms. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). CCDC deposition numbers for structures **23**, **26**, **39** and **48** are 1876821, 1838623, 1838624 and 1838625, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.

General

Reactions requiring anhydrous conditions were performed with the usual precautions for the rigorous exclusion of air and moisture. *N*,*N*-Dimethylformamide was dried by distillation from phosphorus pentoxide. The other chemicals were purchased from Aldrich or Fluka and, when necessary, chemicals were purified according to the reported procedures.[25] ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained on a Varian Mercury 400 spectrometer at 400.45 MHz, 100.61 MHz, 161.97 MHz, respectively, and Bruker Avance 500 instrument at 500.13 MHz, 125.76 MHz, 202.46 MHz, respectively, using DMSO-d_6 or $CDCl_3$ as solvents and Me_4Si (^{1}H, ^{13}C) or H_3PO_4 (^{31}P) as an internal standards. IR spectra were recorded on a Perkin Elmer BX II spectrometer in KBr pellets and are reported in cm^{-1}. LCMS spectra were recorded on Agilent 1100 Series with an Agilent LC/MSD SL detector by chemical ionization (CI) and GCMS spectra were recorded with Agilent 7890 using electron impact ionization at 1176 V. LC-HRMS analysis was performed with an LTQ Orbitrap MS system, consisting of a Surveyor autosampler model Plus, a Surveyor quaternary gradient LC-pump, and LTQ-Orbitrap mass-spectrometer (Thermo Electron GmbH, Bremen, Germany). Separation was achieved using a C18 column (50×4.6 mm; Polaris Varian) in isocratic mode at a constant flow rate of 0.35 mL/min (70/30 methanol:water). Analyzes were carried out in positive mode with ESI, using an ion spray voltage of 4000 V and the capillary temperature 350 °C. Accurate masses (50 to 650 Da) were obtained at high resolution (60,000 FWHM), AGC=1.6 and processed using Xcalibur v.2.0. software. Elemental analysis was performed on a CHNOS elementary Vario MICRO Cube analyzer. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected.

*Methyl 2-methyl-2-[(methylsulfonyl)amino]propanoate (**5**)*

Methyl 2-amino-2-methylpropanoate hydrochloride **4** (30.72 g, 0.2 mol) was added to a stirred solution of Et_3N (60.72 g, 84.30 mL, 0.6 mol) in CH_2Cl_2 (950 mL). As soon as the solid phase was dissolved (approximately 30 min. required) the mixture was cooled with an ice water bath. Then the solution of CH_3SO_2Cl (27.5 g, 18.51 mL, 0.24 mol) in CH_2Cl_2 (150 mL) was added dropwise, maintaining the temperature below 5°C. The ice water bath was allowed to melt, and the mixture was stirred at room temperature overnight. The excess CH_2Cl_2 and Et_3N were evaporated at reduced pressure, the residue was diluted with water (300 mL) and acidified with 2N HCl to pH = 3. The crystal precipitate formation occurred, the mixture was allowed to stand for 1 h. and then it was filtered, resulting in 13.45 g of pure methyl 2-methyl-2-[(methylsulfonyl)amino]propanoate (**5**). The mother solution was extracted with EtOAc (6×60 mL). The combined extracts were dried over Na_2SO_4 and evaporated at reduced pressure yielding additionally 19.20 g of spectrally pure *title compound* **5**. Yield 32.65 g (0.17 mol), 84%; m.p. = 86-87°C (can be recryst. from cyclohexane/EtOAc 2:1); [Found: C, 36.97; H, 6.45; N, 7.47; S, 16.14. $C_6H_{13}NO_4S$ requires C, 36.91; H, 6.71; N, 7.17; S, 16.42%]; n_{max} (KBr) 3271, 2990, 1747, 1315, 1127, 982, 521 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.41 (s, 6H, 2×CH_3), 2.90 (s, 3H, SO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 7.46 (s, 1H, NH); d_C (100 MHz, DMSO-d_6) 26.53, 43.88, 52.15, 58.40, 174.46; *m/z* 194.0 $[M-H]^-$.

*Methyl 2-methyl-2-[methyl(methylsulfonyl)amino]propanoate (**6**)*

Methyl 2-methyl-2-[(methylsulfonyl)amino]propanoate **5** (20.8 g, 0.11 mol) was dissolved in dry DMF (250 mL). K_2CO_3 (35.6 g, 0.165 mol) and MeI (23.43 g, 10.28 mL, 0.165 mol) were added to the stirred solution in consecutive order at ambient temperature. 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 room temperature and left for 48 h. with stirring. The precipitate was filtered and twice washed with DMF (20 mL). The excess DMF was evaporated at reduced pressure, the residue was diluted with water (150 mL) and the crystal precipitate formation occurred. The mixture was allowed to stand for 1 h. and then it was filtered, resulting in 14.88 g of pure methyl 2-methyl-2-[methyl(methylsulfonyl)amino]propanoate (**6**). The mother solution was extracted with CH_2Cl_2 (5×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated at reduced pressure yielding the crude product, which was twice washed with *i*-PrOH (5 mL), obtaining additional 7.80 g of spectrally pure *title compound* **6**. Yield 22.68 g (0.108 mol), 98%; m.p. = 84-86°C (can be recryst. from cyclohexane/EtOAc 3:1); [Found: C, 40.51; H, 7.09; N, 7.02; S, 15.62. $C_7H_{15}NO_4S$ requires C, 40.18; H, 7.22; N, 6.69; S,

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15.32%]; n_{max} (KBr) 3012, 2957, 1736, 1309, 1137, 960, 534 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.43 (s, 6H, 2×CH_3) , 2.79 (s, 3H, NCH_3), 2.90 (s, 3H, SO_2CH_3), 3.66 (s, 3H, CO_2CH_3); d_C (100 MHz, DMSO-d_6) 25.36, 30.93, 40.41, 52.53, 63.00, 174.45; *m/z* 210.2 $[M+H]^+$.

*2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4-trione (**1**)*

Methyl 2-methyl-2-[methyl(methylsulfonyl)amino]propanoate **6** (20.93 g, 0.10 mol) was dissolved in dry DMF (75 mL) and the resulting solution was added dropwise to a stirred solution of *t*-BuOK (23.56 g, 0.21 mol) in DMF (250 mL). A slight exotherm occurred. The mixture was allowed to equilibrate to room temperature and left overnight with stirring. HOAc (33.50 mL) was added dropwise then the mixture was evaporated to dryness *in vacuo* at the temperature not higher than 60°C. The residue was triturated with water (100 mL) and extracted with CH_2Cl_2 (6×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* yielding the light-brown product. The pure *title product*, the colorless crystals, was obtained by vacuum sublimation (at 0.3 mbar and 70°C in an oil bath). Yield 15.06 g (85.0 mmol), 85%; m.p. = 79-80°C (lit.[13a,b] m.p. = 76°C, from EtOH); [Found: C, 41.00; H, 6.05; N, 8.3; S, 17.92. $C_6H_{11}NO_3S$ requires C, 40.66; H, 6.26; N, 7.90; S, 18.09%]; n_{max} (KBr) 3006, 2942, 1758, 1308, 1233, 1108, 960 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.33 (s, 6H, 2×CH_3), 2.69 (s, 3H, NCH_3), 4.28 (s, 2H, CH_2); d_C (125 MHz, $CDCl_3$) 21.08, 22.23, 53.22, 69.48, 200.71; *m/z* 178.2 $[M+H]^+$.

*4-Hydroxy-2,3,3-trimethyl-1λ^6-isothiazolidine-1,1-dione (**7**)*

2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4-trione **1** (0.2 g, 1.13 mmol) was dissolved in 10 mL of MeOH and cooled with an ice water bath. $NaBH_4$ (0.15 g, 4 mmol) was added portion-wise with vigorous stirring during 2 h, maintaining the reaction temperature below 10°C. The mixture was allowed to equilibrate to room temperature and left overnight without stirring. The solvent was evaporated *in vacuo*, the residue was triturated with water (4 mL), acidified to pH 5-6 with 2N HCl and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was sublimated *in vacuo* (0.1 Torr and 100-110°C in an oil bath) giving the *title compound* **7** as white crystals. Yield 0.18 g (1.0 mmol), 88%; m.p. = 64-65°C; [Found: C, 40.24; H, 7.57; N, 7.50; S, 18.17. $C_6H_{13}NO_3S$ requires C, 40.21; H, 7.31; N, 7.81; S, 17.89%]; n_{max} (KBr) 3457, 2981, 2947, 1291, 1130, 962, 569 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.08 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.47 (s, 3H, NCH_3), 2.98 (dd, *J* 13.4, 8.2 Hz, 1H, CH_2), 3.47 (dd, *J* 13.1, 7.6 Hz, 1H, CH_2), 4.08 (dt, *J* 7.6, 5.5 Hz, 1H, C<u>H</u>-OH), 5.71 (d, *J* 5.2 Hz, 1H, OH); d_C (100 MHz, DMSO-d_6) 16.96, 23.17, 24.07, 52.09, 63.78, 71.58; *m/z* 180.1 $[M+H]^+$.

*7-Hydroxy-4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5-dione (**8**)*

4-Methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione **2** (0.2 g, 1.14 mmol) was dissolved in 10 mL of MeOH and cooled with an ice water bath. $NaBH_4$ (0.15 g, 4 mmol) was added portion-wise with vigorous stirring during 2 h, maintaining the reaction temperature below 10°C. The mixture was allowed to equilibrate to room temperature and left overnight without stirring. The solvent was evaporated *in vacuo*, the residue was triturated with water (7 mL), acidified to pH 5-6 with 2N HCl and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was heated in vacuum (50°C in an oil bath and 0.1 Torr) for 30 min to give the *title compound* **8** as a light yellow oil that solidified upon standing. Yield 0.17 g (0.96 mmol), 85%; m.p. = 66-67°C; [Found: C, 41.05; H, 6.25; N, 7.50; S, 18.07. $C_6H_{11}NO_3S$ requires C, 40.66; H, 6.26; N, 7.90; S, 18.09%]; n_{max} (KBr) 3497, 3028, 2942, 1466, 1295, 1131, 789 cm^{-1}; d_H (400 MHz, DMSO-d_6) 0.69-0.77 (m, 1H, cyclopropyl), 0.83-1.01 (m, 3H, cyclopropyl), 2.58 (s, 3H, NCH_3), 3.09 (d, *J* 12.4 Hz, 1H, CH_2), 3.63 (dd, *J* 14.0, 7.2 Hz, 1H, CH_2), 4.19 (m, 1H, C<u>H</u>-OH), 5.56 (br. s, 1H, OH); d_C (100 MHz, DMSO-d_6) 4.77, 9.08, 31.35, 48.87, 56.52, 71.64; *m/z* 178.2 $[M+H]^+$.

*2,3,3-Trimethyl-1,1-dioxo-1λ^6-isothiazolidin-4-yl methanesulfonate (**9**)*

4-Hydroxy-2,3,3-trimethyl-1λ^6-isothiazolidine-1,1-dione **7** (1.00 g, 5.58 mmol) was added to a stirred solution of pyridine (0.57 g, 0.59 mL, 7.25 mmol) in CH_2Cl_2 (50 mL). As soon as the solid phase was dissolved the mixture was cooled with an ice water bath. Then the solution of CH_3SO_2Cl (0.77 g, 0.52 mL, 6.70 mmol) in CH_2Cl_2 (5 mL) was added dropwise, maintaining the temperature below 5°C. The ice water bath was allowed to melt, and the mixture was stirred at room temperature overnight. The excess CH_2Cl_2 and pyridine were evaporated at reduced pressure and temperature below 40°C, the residue was diluted with water (10 mL) acidified with 2N HCl to pH = 3 and extracted with CH_2Cl_2 (6×6 mL). The combined extracts were dried over Na_2SO_4 evaporated at reduced pressure at the temperature below 40°C and the residue was recrystallized from *i*-PrOH yielding spectrally pure *title compound* **9**. Yield 1.30 g (5.05 mmol), 91 %; m.p. = 99-100°C; [Found: C, 32.34; H, 5.70; N, 5.29; S, 24.88. $C_7H_{15}NO_5S_2$ requires C, 32.67; H, 5.88; N, 5.44; S, 24.92%]; n_{max} (KBr) 3023, 2972, 1352, 1301, 1174, 1139, 960, 528 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.52 (s, 3H, NCH_3), 3.23 (s, 3H, OSO_2CH_3), 3.53 (dd, *J* 14.3, 4.3 Hz, 1H, CH_2), 3.87 (dd, *J* 14.3, 7.0 Hz, 1H, CH_2), 5.11 (dt, *J* 2.4, 4.3 Hz, 1H, C<u>H</u>-OMs); d_C (100 MHz, DMSO-d_6) 19.95, 22.60, 23.54, 38.43, 51.39, 63.32, 79.17; *m/z* 258.0 $[M+H]^+$.

*2,3,3-Trimethyl-2,3-dihydro-1H-1λ^6-isothiazole-1,1-dione (**10**)*

Method A. 2,3,3-Trimethyl-1,1-dioxo-1λ^6-isothiazolidin-4-yl methanesulfonate **9** (0.50 g, 1.94 mmol) was added portion-wise to cold (0°C) solution of *tert*-BuOK (0.26 g, 2.33 mmol) in dry THF (10 mL). The resulting clear solution gradually became cloudy and precipitate formation occurred. The mixture was allowed to equilibrate to room temperature and left overnight with stirring. The solvent was evaporated *in vacuo*, the residue was triturated with water (7 mL) and extracted with CH_2Cl_2 (5×7 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo* affording the pure *title compound* **10** as white crystals. Yield 0.31 g (1.92 mmol), 99 %.

Method B. 4-Hydroxy-2,3,3-trimethyl-1λ^6-isothiazolidine-1,1-dione **7** (1.00 g, 5.58 mmol) was dissolved in pyridine (10 mL) and the resulting solution was cooled with an ice water bath. Then the solution of CH_3SO_2Cl (0.77 g, 0.52 mL, 6.70 mmol) in CH_2Cl_2 (5 mL) was added dropwise, maintaining the temperature below 5°C. The ice water bath was allowed to melt, and the mixture was stirred at room temperature overnight. Then solution was heated at 75°C with stirring during 1 h. The volatiles were evaporated at reduced pressure, the residue was triturated with water (10 mL) and extracted with EtOAc (5×10 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo* affording pure *title compound* **10** as white crystals. Yield 0.75 g (4.69 mmol), 84%; m.p. = 90-91°C; [Found: C, 44.55; H, 6.54; N, 8.33; S, 19.65. $C_6H_{11}NO_2S$ requires C, 44.70; H, 6.88; N, 8.69; S, 19.89%]; n_{max} (KBr) 3084, 2981, 1464, 1277, 1127, 762, 566 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.27 (s, 6H, 2×CH_3), 2.59 (s, 3H, NCH_3), 6.91 (d, *J* 7.0 Hz, 1H, H-5),

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7.02 (d, *J* 7.0 Hz, 1H, H-4); d_C (100 MHz, DMSO-d_6) 23.03, 24.00, 63.28, 125.39, 146.25; *m/z* 162.0 $[M+H]^+$.

*2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1-dione (**11**)*

2,3,3-Trimethyl-2,3-dihydro-1*H*-1λ⁶-isothiazole-1,1-dione **10** (0.16 g, 1 mmol), Pd/C (10 wt. % loading, 0.05 g) and MeOH (5 mL) were placed in a dried Schlenk tube. The mixture was septa-sealed, evacuated to exclude the presence of air and then hydrogenated at 0.1 MPa for 48 h at r.t. Then the resulting mixture was filtered through Celite and washed with MeOH (10 mL). Concentration of the filtrate *in vacuo* afforded pure *title compound* **11** as yellowish oil. Yield 0.15 g (0.95 mmol), 95%; [Found: C, 43.95; H, 7.82; N, 8.62; S, 19.87. $C_6H_{13}NO_2S$ requires C, 44.15; H, 8.03; N, 8.58; S, 19.64%]; n_{max} (KBr) 2974, 1295, 1192, 1129, 919, 796, 503 cm^{-1}; d_H (400 MHz, $CDCl_3$) 1.59 (s, 6H, 2×CH_3), 2.19 (t, *J* 7.5 Hz, 2H, $SO_2CH_2C\underline{H}_2$), 2.54 (s, 3H, NCH_3), 3.08 (t, *J* 7.5 Hz, 2H, $SO_2C\underline{H}_2CH_2$); d_C (100 MHz, $CDCl_3$) 23.54, 25.69, 34.33, 45.26, 58.23; *m/z* 164.2 $[M+H]^+$.

*2,3,3-Trimethyl-4-(1-pyrrolidinyl)-2,3-dihydro-1H-1λ⁶-isothiazole-1,1-dione (**12**)*

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.20 g, 1.13 mmol) and pyrrolidine (0.40 g, 5.62 mmol) were dissolved in benzene (7 mL). The mixture was refluxed with Dean-Stark trap for 6 hours and then it was evaporated to dryness. The recrystallization of crude product from *i*-PrOH gave the *title compound* **12** as cream-colored crystals. Yield 0.17 g (0.72 mmol), 64%; m.p. = 225-226°C; [Found: C, 52.47; H, 7.63; N, 12.56; S, 13.72. $C_{10}H_{18}N_2O_2S$ requires C, 52.15; H, 7.88; N, 12.16; S, 13.92%]; n_{max} (KBr) 3099, 2974, 1579, 1250, 1109, 883, 576 cm^{-1}; d_H (400 MHz, $CDCl_3$) 1.46 (s, 6H, 2×CH_3), 1.95 (m, 4H, 2×$NCH_2C\underline{H}_2$), 2.65 (s, 3H, NCH_3), 3.31 (m, 4H, 2×$NC\underline{H}_2CH_2$), 4.94 (s, 1H, CH); d_C (100 MHz, DMSO-d_6) 22.26, 22.43, 25.14, 49.66, 62.97, 88.34, 158.03; *m/z* 231.3 $[M+H]^+$.

*4-Methyl-7-(1-pyrrolidinyl)-5λ⁶-thia-4-azaspiro[2.4]hept-6-ene-5,5-dione (**13**)*

4-Methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione **2** (0.10 g, 0.57 mmol) and pyrrolidine (0.20 g, 2.82 mmol) were dissolved in benzene (5 mL). The mixture was refluxed with Dean-Stark trap for 6 hours and then it was evaporated to dryness. The recrystallization of crude product from dioxane-cyclohexane (3:1) gave the *title compound* **13** as cream-colored crystals. Yield 0.09 g (0.39 mmol), 69%; m.p. = 203-205°C; [Found: C, 52.36; H, 7.00; N, 12.22; S, 14.42. $C_{10}H_{16}N_2O_2S$ requires C, 52.61; H, 7.06; N, 12.27; S, 14.04%]; n_{max} (KBr) 3110, 2974, 1570, 1249, 1103, 833, 594 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.30 (m, 2H, cyclopropyl), 1.48 (m, 2H, cyclopropyl), 1.90 (m, 4H, 2×$NCH_2C\underline{H}_2$), 2.46 (s, 3H, NCH_3), 3.19 (m, 4H, 2×$NC\underline{H}_2CH_2$), 5.19 (s, 1H, CH); d_C (100 MHz, DMSO-d_6) 9.99, 25.16, 31.36, 47.03, 49.43, 90.75, 156.05; *m/z* 229.2 $[M+H]^+$.

*4-Anilino-2,3,3-trimethyl-2,3-dihydro-1H-1λ⁶-isothiazole-1,1-dione (**14**)*

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.20 g, 1.13 mmol) and aniline (0.21 g, 0.21 mL, 2.26 mmol) were dissolved in dry benzene (5 mL). The mixture was refluxed with Dean-Stark trap for 6 hours and then it was evaporated to dryness. The recrystallization of crude product from *i*-PrOH gave the *title compound* **14** as cream-colored crystals. Yield 0.20 g (0.80 mmol), 71%; m.p. = 203-204°C; [Found: C, 57.46; H, 6.49; N, 11.35; S, 12.63. $C_{12}H_{16}N_2O_2S$ requires C, 57.12; H, 6.39; N, 11.10; S, 12.71%]; n_{max} (KBr) 3280, 2979, 1617, 1595, 1536, 1238, 1098, 757 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.46 (s, 6H, 2×CH_3), 2.59 (s, 3H, NCH_3), 5.67 (s, 1H, CH), 7.06 (t, *J* 7.0 Hz, 1H, H-4'), 7.22 (d, *J* 7.9 Hz, 2H, H-2' and H-6'), 7.33 (t, *J* 7.6 Hz, 2H, H-3' and H-5'), 8.36 (s, 1H, NH); d_C (100 MHz, DMSO-d_6) 23.32, 63.52, 89.97, 121.86, 124.18, 129.56, 140.97, 156.12; *m/z* 253.2 $[M+H]^+$.

*2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione 4-oxime (**15**)*

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.2 g, 1.13 mmol) was dissolved in a mixture of THF (3 mL) and pyridine (3 mL) then $NH_2OH{\cdot}HCl$ (0.1 g, 1.32 mmol) was added. The resulting solution was refluxed with stirring for 3 hours. The volatiles were evaporated *in vacuo* and the residue was triturated with water (3 mL). After a while the bottom viscous phase crystallized. The resulting white crystals were filtered and washed consequently with minimal amount of aq. 2N HCl and water affording pure *title compound* **15**. Yield 0.18 g (0.94 mmol), 83%; m.p. = 136-137°C; [Found: C, 37.29; H, 6.62; N, 14.53; S, 16.69. $C_6H_{12}N_2O_3S$ requires C, 37.49; H, 6.29; N, 14.57; S, 16.68%]; n_{max} (KBr) 3438, 3360, 2980, 1440, 1287, 1121, 962, 865 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.44 (s, 6H, 2×CH_3), 2.62 (s, 3H, NCH_3), 3.99 (s, 2H, CH_2), 11.35 (s, 1H, NOH); d_C (100 MHz, DMSO-d_6) 22.62, 24.78, 46.73, 62.81, 151.85; *m/z* 193.2 $[M+H]^+$.

*4-Methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione 7-oxime (**16**)*

4-Methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione **2** (0.2 g, 1.14 mmol) was dissolved in MeOH (10 mL) then $NH_2OH{\cdot}HCl$ (0.1 g, 1.32 mmol) and Et_3N (0,5 mL, 3.5 mmol) were added consequently. The resulting solution was refluxed with stirring for 3 hours. MeOH was evaporated *in vacuo*; the residue was triturated with saturated aqueous $NaHCO_3$ (7 mL) and extracted into CH_2Cl_2 (4×5 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was heated in vacuum (at 50°C and 0.3 Torr) for 30 min to give the *title compound* **16** as colorless crystals. Yield 0.20 g (1.0 mmol), 90%; m.p. = 95-96°C; [Found: C, 37.55; H, 5.04; N, 14.46; S, 17.06. $C_6H_{10}N_2O_3S$ requires C, 37.88; H, 5.30; N, 14.73; S, 16.86%]; n_{max} (KBr) 3390, 2980, 2929, 1458, 1307, 1129, 951 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.19 (m, 2H, cyclopropyl), 1.30 (m, 2H, cyclopropyl), 2.61 (s, 3H, NCH_3), 4.07 (s, 2H, CH_2), 11.20 (s, 1H, NOH); d_C (100 MHz, DMSO-d_6) 13.50, 32.72, 46.40, 47.08, 150.59; *m/z* 189.2 $[M-H]^-$.

*General method for the preparation of hydrazones **17** and **18***

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.20 g, 1.13 mmol) was dissolved in dioxane (4 mL) then substituted hydrazine was added. The resulting solution was refluxed with stirring for 3 hours. The volatiles were evaporated *in vacuo* and the residue was recrystallized from the corresponding solvent, affording the title compounds **17,18.** as colorless crystals.

*2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione 4-(N-phenylhydrazone) (**17**)*

Using **2** (0.20 g, 1.14 mmol) and PhNH-NH_2 (0.18 g, 0.17 mL, 1.70 mmol). Yield 0.22 g (0.84 mmol), 74%; m.p. = 173-174°C (*i*-PrOH); [Found: C, 53.90; H, 6.58; N, 15.68; S, 12.02. $C_{12}H_{17}N_3O_2S$ requires C, 53.91; H, 6.41; N, 15.72; S, 11.99%]; n_{max} (KBr) 3334, 2973, 1604, 1310, 1123, 961, 749 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.47 (s, 6H, 2×CH_3), 2.65 (s, 3H, NCH_3), 4.15 (s, 2H, CH_2), 6.74 (t, *J* 7.0 Hz, 1H, H-4'), 7.02 (d, *J* 7.6 Hz, 2H, H-2' and H-6'), 7.16 (t, *J* 7.6 Hz, 2H, H-3' and H-5'), 9.09 (s, 1H, NH); d_C (100 MHz, DMSO-d_6) 22.52, 24.69, 46.96, 64.12, 112.81, 119.44, 128.80, 138.55, 145.60; *m/z* 268.0 $[M+H]^+$.

*tert-Butyl 2-(2,3,3-trimethyl-1,1-dioxo-1λ⁶-isothiazolidin-4-ylidene)-1-hydrazine-carboxylate (**18**)*

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Using **2** (0.20 g, 1.14 mmol) and BocNH-NH_2 (0.15 g, 1.13 mmol). Yield 0.26 g (0.89 mmol), 79%; m.p. = 245-246°C (water) with decomposition; [Found: C, 45.47; H, 7.23; N, 14.20; S, 11.04. $C_{11}H_{21}N_3O_4S$ requires C, 45.34; H, 7.26; N, 14.42; S, 11.01%]; n_{max} (KBr) 3191, 2980, 1698, 1560, 1314, 1130, 886 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.40 (s, 6H, 2×CH_3), 1.48 (s, 9H, *tert*-Bu), 2.61 (s, 3H, NCH_3), 4.08 (s, 2H, CH_2), 9.87 (s, 1H, NH); d_C (100 MHz, DMSO-d_6) 22.50, 24.23, 28.36, 47.34, 64.27, 79.81, 152.51; *m/z* 290.2 $[M-H]^-$.

*General method for the preparation of acids **21** and **22** (The unsuccessful synthesis of hydantoins **19** and **20**)*

The mixture of ketosultam **1**,**2** (0.20 g), KCN (0.15 g, 2.3 mmol) and $(NH_4)_2CO_3$ (0.5 g, 5.2 mmol) in aqueous methanol (1:1) (6 mL) was refluxed for 6 h. The solvent was evaporated *in vacuo*, the residue was diluted with water (4 mL), acidified with 2N HCl to pH = 1 and extracted into CH_2Cl_2 (6×5 mL). The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* yielding the light brown precipitate. The recrystallization of the crude product from toluene gave the *title compound* **21**,**22** as colorless crystals.

*N,2-Dimethyl-N-(methylsulfonyl)alanine (**21**)*

Using **1** (0.20 g, 1.13 mmol). Yield 0.20 g (1.01 mmol), 89%; m.p. = 167-169°C; [Found: C, 37.13; H, 6.67; N, 7.24; S, 16.70. $C_6H_{13}NO_4S$ requires C, 36.91; H, 6.71; N, 7.17; S, 16.42%]; n_{max} (KBr) 3416, 2999, 2671, 1710, 1321, 1137, 960, 818 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.45 (s, 6H, 2×CH_3), 2.81 (s, 3H, NCH_3), 2.92 (s, 3H, SO_2CH_3), 12.47 (broad singlet, 1H, CO_2H); d_C (100 MHz, DMSO-d_6) 25.32, 30.86, 40.04, 62.69, 175.27; *m/z* 194.2 $[M-H]^-$.

*1-[Methyl(methylsulfonyl)amino]cyclopropanecarboxylic acid (**22**)*

Using **2** (0.20 g, 1.14 mmol). Yield 0.18 g (0.93 mmol), 82%; m.p. = 134-135°C; [Found: C, 37.50; H, 5.83; N, 7.46; S, 16.24. $C_6H_{11}NO_4S$ requires C, 37.30; H, 5.74; N, 7.25; S, 16.60%]; n_{max} (KBr) 3450, 3037, 2613, 1709, 1328, 1150, 965 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.25-1.65 (broad singlet, 4H, cyclopropyl), 2.93 (s, 3H, NCH_3), 2.98 (s, 3H, SO_2CH_3); d_C (100 MHz, DMSO-d_6) 17-22 (broad singlet), 35.86, 39.43, 42.28, 174.02; *m/z* 192.0 $[M-H]^-$.

*2,3,3-Trimethyl-1,1-dioxo-5-[2-(triphenylphosphonio)acetyl]-2,3-dihydro-1H-1λ^6-isothiazol-4-olate toluene monosolvate (**23**•PhMe)*

2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4-trione **1** (1.0 g, 5.64 mmol) and triphenylcarbethoxymethylenephosphorane (2.95 g, 7.61 mmol) were dissolved in dry toluene (75 mL). Then benzoic acid (5 mg) was added. The resulting mixture was refluxed for 6 h and then it was cooled. The precipitate was filtered and washed with toluene (2×4 mL) affording the *title compound* **23**•PhMe as colorless crystals. Yield 1.97 g (3.44 mmol), 61%; dec. = 267-268°C; n_{max} (KBr) 2960, 1593, 1406, 1256, 1102, 741, 690 cm^{-1}; d_H (500 MHz, DMSO-d_6) 1.02 (s, 6H, 2×CH_3), 2.30 (s, 3H, CH_3 [toluene]), 2.42 (s, 3H, NCH_3), 5.33 (d, *J* 14.2 Hz, 2H, CH_2P), 7.14 (t, *J* 7.0 Hz, 1H, H-4 [toluene]), 7.17 (d, *J* 7.2 Hz, 2H, H-2 and H-6 [toluene]), 7.25 (t, *J* 7.0 Hz, 2H, H-3 and H-5 [toluene]), 7.67-7.76 (m, 12H, 3×(H-2', H-3', H-5', H-6')), 7.84 (t, *J* 6.6 Hz, 3H, 3×H-4'); d_C (126 MHz, DMSO-d_6) 21.05, 21.67, 22.26, 33.28 (d, *J* 52.4 Hz), 64.24, 105.34 (d, *J* 4.5 Hz), 119.18, 119.88, 125.31, 128.65 (d, *J* 87.3 Hz), 129.77 (d, *J* 12.5 Hz), 133.78 (d, *J* 10.5 Hz), 134.44 (d, *J* 2.5 Hz), 137.34, 175.78 (d, *J* 6.0 Hz), 187.26; d_P (202 MHz, DMSO-d_6) 23.08; *m/z* 480.0 $[M+H]^+$; HRMS (ESI): $M+H^+$, found 480.1391. $C_{26}H_{27}NO_4PS$ requires 480.1393.

*A mixture of ethyl 2-(2,3,3-trimethyl-1,1-dioxo-1λ^6-isothiazolidin-4-ylidene)acetate (**24**) and ethyl 2-(2,3,3-trimethyl-1,1-dioxo-2,3-dihydro-1H-1λ^6-isothiazol-4-yl)acetate (**25**)*

The mother and washing solutions remained after isolation of **23** were combined and evaporated *in vacuo*. The crude residue was directly subjected to silica gel column chromatography using MTBE-hexane (1:1) as the eluting solvent. Evaporation of the eluate *in vacuo* afforded the sum of *title compounds* **24** and **25** (1:1.22 ratio) as yellowish oil. Yield 0.31 g (1.24 mmol), 22%; [Found: C, 48.30; H, 7.12; N, 5.29; S, 13.34. $C_{10}H_{17}NO_4S$ requires C, 48.56; H, 6.93; N, 5.66; S, 12.97%]; n_{max} (KBr) 2979, 2937, 1734, 1713, 1463, 1285, 1022 cm^{-1}; ***24*** d_H (500 MHz, $CDCl_3$) 1.27 (m, 3H, $CH_2C\underline{H}_3$), 1.43 (s, 6H, 2×CH_3), 2.67 (s, 3H, NCH_3), 4.19 (m, 2H, $C\underline{H}_2CH_3$), 4.40 (s, 2H, CH_2SO_2), 6.04 (s, 1H, CH); ***25*** d_H (500 MHz, $CDCl_3$) 1.27 (m, 3H, $CH_2C\underline{H}_3$), 1.30 (s, 6H, 2×CH_3), 2.72 (s, 3H, NCH_3), 3.25 (s, 2H, CH_2CO_2Et), 4.19 (m, 2H, $C\underline{H}_2CH_3$), 6.72 (s, 1H, CH); ***24*** d_C (125 MHz, $CDCl_3$) 14.15, 22.75, 25.72, 50.63, 60.87, 63.76, 117.09, 154.22, 165.27; ***25*** d_C (125 MHz, $CDCl_3$) 14.07, 22.64, 23.05, 32.86, 61.76, 65.13, 122.75, 150.74, 168.07; *m/z* 248.2 $[M+H]^+$.

*Ethyl 2-([E]-4-methyl-5,5-dioxo-5λ^6-thia-4-azaspiro[2.4]hept-7-ylidene)acetate (**26**)*

4-Methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione **2** (0.10 g, 0.57 mmol) and triphenylcarbethoxymethylenephospho-rane (0.20 g, 0.57 mmol) were dissolved in dry toluene (10 mL) and a pair of crystals of benzoic acid (approx. 0.75 mg) were added. The resulting mixture was refluxed for 6 h and then it was evaporated to dryness. The crude residue was directly subjected to silica gel column chromatography using MTBE-hexane (1:1) as the eluting solvent. Evaporation of the eluate *in vacuo* afforded the *title compound* **26** as colorless crystals. Yield 0.08 g (0.33 mmol), 57%; m.p. = 117-118°C; [Found: C, 48.77; H, 6.25; N, 6.08; S, 13.34. $C_{10}H_{15}NO_4S$ requires C, 48.96; H, 6.16; N, 5.71; S, 13.07%]; n_{max} (KBr) 3016, 2939, 1702, 1654, 1335, 1195, 1145, 760 cm^{-1}; d_H (400 MHz, $CDCl_3$) 0.96 (m, 2H, cyclopropyl), 1.05 (t, *J* 7.0 Hz, 3H, $CH_2C\underline{H}_3$), 1.28 (m, 2H, cyclopropyl), 2.42 (s, 3H, NCH_3), 3.95 (q, *J* 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 4.19 (s, 2H, CH_2SO_2), 5.27 (s, 1H, CH); d_C (100 MHz, $CDCl_3$) 13.81, 16.67, 32.78, 48.24, 51.36, 60.37, 110.58, 154.22, 164.80; *m/z* 245.0 $[M]^+$.

*2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4,5-tetrone 5-oxime (**28**)*

2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4-trione **1** (0.2 g, 1.13 mmol) was dissolved in aq. 95% HOAc (4 mL) and the resulting solution was cooled with an ice water bath. Then the solution of $NaNO_2$ (0.09 g, 1.36 mmol) in water (2 mL) was added dropwise upon stirring maintaining the temperature below 5°C. The resulting mixture was septa-sealed, allowed to equilibrate to r.t. and left to react overnight with stirring. Then it was diluted with water (6 mL) and extracted with CH_2Cl_2 (5×5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in *i*-PrOH (3 mL), filtered and evaporated *in vacuo* affording the *title compound* **28** as yellow crystals. Yield 0.12 g (0.60 mmol), 53%; m.p. = 123-125°C; [Found: C, 34.68; H, 4.93; N, 13.28; S, 15.20. $C_6H_{10}N_2O_4S$ requires C, 34.95; H, 4.89; N, 13.58; S, 15.55%]; n_{max} (KBr) 3580, 3473, 2807, 1751, 1499, 1292, 1152, 929 cm^{-1}; d_H (500 MHz, $CDCl_3$) 1.45 (s, 6H, 2×CH_3), 2.81 (s, 3H, NCH_3); d_C (125 MHz, $CDCl_3$) 21.21, 21.94, 68.04, 141.39, 189.98; *m/z* 207.0 $[M+H]^+$.

*General method for the azo coupling of keto sultams **1** and **2***

$NaNO_2$ (0.08 g, 1.12 mmol) was dissolved in water (5 mL) and then it was added dropwise to stirred cold (0°C) solution of

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p-toluidine (0.12 g, 1.12 mmol) in 95% aqueous acetic acid (5 mL) maintaining the temperature below 5°C. After the addition was completed the mixture was allowed to stir for 30 min. Thus obtained solution of diazonium salt was added dropwise to stirred cold (0°C) solution of keto sultam **1**,**2** (0.2 g) in aq. 95% HOAc (7 mL) maintaining the temperature below 5°C. The resulting solution was allowed to stir at room temperature for 4 h and then at 45°C for 2h. The precipitate that formed upon cooling to r.t. was filtered and washed with water. The recrystallization of crude product from *i*-PrOH gave the *title compound* **29**,**30** as dark red prisms.

*2,3,3-Trimethyl-1λ^6-isothiazolidine-1,1,4,5-tetrone 5-[N-(4-methylphenyl)hydrazone] (**29**)*

Using **1** (0.20 g, 1.13 mmol). Yield 0.21 g (0.73 mmol), 64%; m.p. = 183-185°C; [Found: C, 53.09; H, 5.90; N, 14.13; S, 11.15. $C_{13}H_{17}N_3O_3S$ requires C, 52.86; H, 5.80; N, 14.23; S, 10.86%]; n_{max} (KBr) 3452, 2990, 1657, 1542, 1458, 1292, 1098, 820 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.37 (s, 6H, 2×CH_3), 2.35 (s, 3H, CH_3), 2.71 (s, 3H, NCH_3), 7.20 (d, *J* 7.3 Hz, 2H, H-3' and H-5'), 7.52 (d, *J* 7.9 Hz, 2H, H-2' and H-6'), 13.36 (broad s, 1H, NH); d_C (100 MHz, DMSO-d_6) 21.38, 21.59, 22.87, 65.43, 117.57, 127.61, 130.40, 136.81, 139.43, 188.47; *m/z* 296.2 $[M+H]^+$.

*4-Methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,6,7-tetrone 6-[N-(4-methylphenyl)hydrazone] (**30**)*

Using **2** (0.20 g, 1.14 mmol). Yield 0.19 g (0.65 mmol), 58%; m.p. = 191-192°C; [Found: C, 52.98; H, 5.41; N, 14.29; S, 11.11. $C_{13}H_{15}N_3O_3S$ requires C, 53.23; H, 5.15; N, 14.32; S, 10.93%]; n_{max} (KBr) 3435, 3154, 1676, 1534, 1444, 1289, 1110, 592 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.39 (s, 2H, cyclopropyl), 1.52 (s, 2H, cyclopropyl), 2.35 (s, 3H, CH_3), 2.69 (s, 3H, NCH_3), 7.20 (d, *J* 5.2 Hz, 2H, H-3' and H-5'), 7.51 (d, *J* 6.0 Hz, 2H, H-2' and H-6'), 13.17 (broad s, 1 H, NH); d_C (100 MHz, DMSO-d_6) 13.70, 20.74, 31.88, 50.82, 116.63, 128.93, 129.76, 135.80, 138.93, 187.31; *m/z* 294.2 $[M+H]^+$.

*General method for the preparation of 5-benzoyl-4-hydroxy-2-methyl-2,3-dihydro-1H-1λ^6-isothiazole-1,1-dione **31** and **32***

Ketosultam **1**,**2** (0.18 g, 1.00 mmol), $PhCO_2H$ (0.12 g, 1.00 mmol), EDC (0.20 g, 1.00 mmol) and DMAP (0.12 g, 1.00 mmol) in the indicated order were dissolved in DMF (3 mL) and the resulting mixture was left to react upon stirring at r.t. for 96 h. Then it was evaporated *in vacuo* at the temperature not higher than 60°C and the residue was triturated with water (5 mL). The resulting precipitate was filtered and successively washed with aq. 1M HCl (1 mL) and water (3×1 mL) affording the *title compound* **31**,**32** as white powder.

*5-Benzoyl-4-hydroxy-2,3,3-trimethyl-2,3-dihydro-1H-1λ^6-isothiazole-1,1-dione (**31**)*

Using **1** (0.18 g, 1.00 mmol). Yield 0.11 g (0.38 mmol), 38%; m.p. = 141-142°C; [Found: C, 55.21; H, 5.01; N, 4.87; S, 11.28. $C_{13}H_{15}NO_4S$ requires C, 55.50; H, 5.37; N, 4.98; S, 11.40%]; n_{max} (KBr) 3451, 2983, 1602, 1568, 1288, 1151, 698 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.22 (s, 6H, 2×CH_3), 2.55 (s, 3H, NCH_3), 7.42 (t, *J* = 6.5 Hz, 2H, H-3' and H-5'), 7.50 (t, *J* = 6.5 Hz, 1H, H-4'), 7.65 (d, *J* = 6.5 Hz, 2H, H-2' and H-6'), 7.84 (br s, 1H, OH); d_C (125 MHz, DMSO-d_6) 22.03, 23.03, 63.80, 128.11, 129.03, 131.79, 138.46, 184.06; *m/z* 282.2 $[M+H]^+$.

*6-Benzoyl-7-hydroxy-4-methyl-5λ^6-thia-4-azaspiro[2.4]hept-6-ene-5,5-dione (**32**)*

Using **2** (0.18 g, 1.00 mmol). Yield 0.12 g (0.44 mmol), 44%; m.p. = 98-100°C; [Found: C, 55.90; H, 4.41; N, 4.72; S, 11.09. $C_{13}H_{13}NO_4S$ requires C, 55.90; H, 4.69; N, 5.01; S, 11.48%]; n_{max} (KBr) 3429, 2919, 1742, 1603, 1334, 1158, 1097, 741 cm^{-1}; enol/ketone ratio 3:1; enolic tautomer d_H (400 MHz, DMSO-d_6) 1.13 (s, 2H, cyclopropyl), 1.28 (s, 2H, cyclopropyl), 2.55 (s, 3H, NCH_3), 7.45 (m, 2H, H-3' and H-5'), 7.55 (m, 1H, H-4'), 7.67 (m, 2H, H-2' and H-6'), 10.19 (br s, 1H, OH) ; ketonic tautomer (rotamers are present) d_H (400 MHz, DMSO-d_6) 1.36 (m, 2H, cyclopropyl), 1.52 (m, 1H, cyclopropyl), 1.82 (m, 1H, cyclopropyl), 2.85 (s, 3H, NCH_3), 4.58 (m, 1H, CH), 7.45 (m, 2H, H-3' and H-5'), 7.55 (m, 1H, H-4'), 7.67 (m, 2H, H-2' and H-6'); enolic tautomer d_C (125 MHz, DMSO-d_6) 11.88, 14.63, 32.03, 50.32, 128.39, 129.22, 132.33, 136.53, 181.51; ketonic tautomer (rotamers are present) d_C (125 MHz, DMSO-d_6) 20.16+20.53, 21.64+21.98, 34.13+34.42, 54.19, 59.57+59.88, 128.39, 129.22, 132.33, 136.53, 203.71+204.05; *m/z* 280.0 $[M+H]^+$.

*General method for the preparation of 4-hydroxy-2-methyl-1,1-dioxo-N-phenyl-2,3-dihydro-1H-1λ^6-isothiazole-5-carboxamides **33**,**34** and 4-hydroxy-2-methyl-1,1-dioxo-N-phenyl-2,3-dihydro-1H-1λ^6-isothiazole-5-carbothioamides **35**,**36***

The solution of ketosultam **1**,**2** (1.38 mmol) and PhNCO or PhNCS (1.38 mmol) in dry DMF (2 mL) was added to the stirred solution of DBU (0.21 g, 1.38 mmol) in dry DMF (2 mL). The resulting mixture was stirred overnight at r.t. and then poured onto aq. 4M HCl (12 mL). The resulting precipitate was filtered and washed with water (3×1 mL) affording the *title compound* **33**-**36**. The product thus obtained was pure. If necessary, it can be recrystallized from *n*-BuOH.

*4-Hydroxy-2,3,3-trimethyl-1,1-dioxo-N-phenyl-2,3-dihydro-1H-1λ^6-isothiazole-5-carboxamide (**33**)*

Using **1** (0.24 g, 1.38 mmol) and PhNCO (0.19 g, 1.38 mmol). Yield 0.27 g (0.92 mmol), 67%; m.p. = 179-180°C; [Found: C, 52.76; H, 5.54; N, 9.30; S, 10.65. $C_{13}H_{16}N_2O_4S$ requires C, 52.69; H, 5.44; N, 9.45; S, 10.82%]; n_{max} (KBr) 3485, 3295, 2981, 1646, 1527, 1276, 1146, 1089 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.31 (s, 6H, 2×CH_3), 2.58 (s, 3H, NCH_3), 7.01 (t, *J* = 7.3 Hz, 1H, H-4'), 7.27 (t, *J* = 7.6 Hz, 2H, H-3' and H-5'), 7.56 (d, *J* = 7.9 Hz, 2H, H-2', and H-6'), 9.75 (br. s, 1H, NH) , 9.95 (br. s, 1H, OH); d_C (100 MHz, DMSO-d_6) 22.33, 23.16, 63.59, 120.36, 123.61, 129.10, 139.22, 160.16; *m/z* 297.2 $[M+H]^+$.

*7-Hydroxy-4-methyl-5,5-dioxo-N-phenyl-5λ^6-thia-4-azaspiro[2.4]hept-6-ene-6-carboxamide (**34**)*

Using **2** (0.08 g, 0.46 mmol) and PhNCO (0.06 g, 0.46 mmol). Yield 0.10 g (0.35 mmol), 77%; m.p. = 188-189°C; [Found: C, 52.76; H, 4.54; N, 9.67; S, 11.15. $C_{13}H_{14}N_2O_4S$ requires C, 53.05; H, 4.79; N, 9.52; S, 10.89%]; n_{max} (KBr) 3333, 3092, 1642, 1536, 1446, 1259, 761 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.38 (s, 4H, cyclopropyl), 2.71 (s, 3H, NCH_3), 7.03 (t, *J* = 6.1 Hz, 1H, H-4'), 7.28 (t, *J* = 7.0 Hz, 2H, H-3' and H-5'), 7.55 (d, *J* = 7.0 Hz, 2H, H-2', and H-6'), 10.46 (br. s, 1H, NH); d_C (100 MHz, DMSO-d_6) 7.75, 28.07, 48.76, 96.73, 118.79, 121.56, 128.61, 140.30, 161.65, 180.67; *m/z* 295.0 $[M+H]^+$.

*4-Hydroxy-2,3,3-trimethyl-1,1-dioxo-N-phenyl-2,3-dihydro-1H-1λ^6-isothiazole-5-carbothioamide (**35**)*

Using **1** (0.24 g, 1.38 mmol) and PhNCS (0.19 g, 1.38 mmol). Yield 0.30 g (0.97 mmol), 70%; m.p. > 300°C; [Found: C, 49.63; H, 4.96; N, 9.15; S, 20.36. $C_{13}H_{16}N_2O_3S_2$ requires C, 49.98; H, 5.16; N, 8.97; S, 20.53%]; n_{max} (KBr) 3440, 2969, 1608, 1536, 1396, 1211, 1133, 766 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.20 (s, 6H, 2×CH_3), 2.54 (s, 3H, NCH_3), 7.04 (t, *J* = 6.4 Hz, 1H, H-4'), 7.27 (t, *J* = 7.2 Hz, 2H, H-3' and H-5'), 7.81 (d, *J* = 6.4 Hz, 2H, H-2', and H-6'), 12.97 (s, 1H, NH); d_C (100 MHz, DMSO-d_6)

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22.28, 22.97, 62.16, 106.68, 122.76, 123.69, 128.10, 140.53, 182.75, 183.03; *m/z* 313.2 $[M+H]^+$.

*7-Hydroxy-4-methyl-5,5-dioxo-N-phenyl-5λ⁶-thia-4-azaspiro[2.4]hept-6-ene-6-carbothioamide (**36**)*

Using **2** (0.10 g, 0.57 mmol) and PhNCS (0.08 g, 0.57 mmol). Yield 0.14 g (0.46 mmol), 81%; m.p. > 300°C; [Found: C, 50.12; H, 4.59; N, 8.93; S, 20.86. $C_{13}H_{14}N_2O_3S_2$ requires C, 50.31; H, 4.55; N, 9.03; S, 20.66%]; n_{max} (KBr) 3451, 3048, 1631, 1541, 1413, 1242, 1105, 912 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.03 (m, 4H, cyclopropyl), 2.41 (s, 3H, NCH_3), 7.04 (t, *J* = 7.3 Hz, 1H, H-4'), 7.27 (t, *J* = 7.27 Hz, 2H, H-3' and H-5'), 7.80 (d, *J* = 7.6 Hz, 2H, H-2', and H-6'), 12.80 (s, 1H, NH); d_C (100 MHz, DMSO-d_6) 8.49, 29.32, 47.47, 109.19, 122.67, 123.57, 128.06, 140.61, 179.89, 182.24; *m/z* 309.0 $[M-H]^-$.

*2,3,3-Trimethyl-5-[(Z)-phenylmethylidene]-1λ⁶-isothiazolidine-1,1,4-trione (**37**)*

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.2 g, 1.13 mmol) was dissolved in pyridine (5 mL) then PhCHO (0.3 g, 0.29 mL, 2.83 mmol) was added to the stirred solution in one portion. The mixture was refluxed for 2 h and then it was evaporated to dryness. The solid remainder was recrystallized from *i*-PrOH affording the *title compound* **37** as colorless crystals. Yield 0.25 g (0.95 mmol), 84%; m.p. = 93-94°C (lit.[13a] m.p. = 92°C, from EtOH); [Found: C, 58.66; H, 5.91; N, 5.37; S, 11.92. $C_{13}H_{15}NO_3S$ requires C, 58.85; H, 5.70; N, 5.28; S, 12.09%]; n_{max} (KBr) 2979, 1729, 1609, 1296, 1142, 1109, 773 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.41 (s, 6H, 2×CH_3), 2.80 (s, 3H, NCH_3), 7.57 (t, *J* 7.3 Hz, 2H, H-3' and H-5'), 7.64 (t, *J* 7.0 Hz, 1H, H-4'), 7.97 (s, 1H, C<u>H</u>Ph), 8.09 (d, *J* 7.0 Hz, 2H, H-2' and H-6'); d_C (100 MHz, DMSO-d_6) 21.68, 22.76, 68.00, 126.86, 129.60, 130.82, 134.09, 134.24, 145.57, 192.97; *m/z* 266.1 $[M+H]^+$.

*5-[(Z)-(Dimethylamino)methylidene]-2,3,3-trimethyl- 1λ⁶-isothiazolidine-1,1,4-trione (**38**)*

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (1.77 g, 10 mmol) was dissolved in warm anhydrous MeOH (15 mL) then DMFDMA (1.79 g, 1.99 mL, 15 mmol) was added to the stirred solution in one portion. The crystal precipitate formation was occurred and the mixture was allowed to stir for 30 min. After, the reaction mixture was refluxed for 1 h and then it was evaporated to dryness. The solid remainder was recrystallized from *i*-PrOH affording the *title compound* **38** as colorless crystals. Yield 2.09 g (9.0 mmol), 90%; m.p. = 164-165°C (lit.[13a] m.p. = 162°C, from EtOH); [Found: C, 46.56; H, 7.27; N, 12.28; S, 13.73. $C_9H_{16}N_2O_3S$ requires C, 46.53; H, 6.94; N, 12.06; S, 13.80%]; n_{max} (KBr) 2976, 1679, 1618, 1257, 1103, 946, 602 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.24 (s, 6H, 2×CH_3), 2.62 (s, 3H, NCH_3), 3.42 (s, 3H, $N(CH_3)_2$), 3.44 (s, 3H, $N(CH_3)_2$), 7.59 (s, 1H, CH); d_C (100 MHz, DMSO-d_6) 21.78, 22.61, 41.56, 47.94, 66.29, 98.96, 151.99, 190.54; *m/z* 233.2 $[M+H]^+$.

*General procedure for the recycling of mother solutions after keto sultams **1** and **2**. Another crop of dimethylaminomethylene derivative **38**,**39**.*

The combined mother solution remained after recrystallization and washing of keto sultam **1**,**2** was treated with DMFDMA (the quantity was calculated from the ratio of 0.75 eq. of DMFDMA to 1 eq. of isolated keto sultam **1**,**2**), the resulting mixture was allowed to stand overnight then filtered and washed with minimal amount of *i*-PrOH. The product thus obtained was spectrally pure and can be used without further purification. In this way, from 0.05 to 0.12 eq. (based on amount of isolated keto sultam **1**,**2**) of the *title compound* **38**,**39** can be obtained.

*4-Chloro-2,3,3-trimethyl-1,1-dioxo-2,3-dihydro-1H-1λ⁶-isothiazole-5-carbaldehyde (**40**)*

To a cold (0°C) solution of $POCl_3$ (1.04 g, 0.63 mL, 6.78 mol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DMF (0.51 g, 0.54 mL, 7.0 mmol) in CH_2Cl_2 (3 mL) maintaining the temperature below 5°C. The ice water bath was removed and the mixture was allowed to stirr at r.t. for 0.5 h. Then it was cooled (0°C) again and the solution of 2,3,3-trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.2 g, 1.13 mmol) in CH_2Cl_2 (4 mL) was added dropwise at 0-5°C. The ice water bath was allowed to melt and the resulting mixture was stirred at room temperature overnight. Then it was poured on the crushed ice (10 g) in water (20 mL), stirred for 1 h and divided. The water phase was extracted with CH_2Cl_2 (5×7 mL), the combined organic layers were dried over Na_2SO_4 and evaporated at reduced pressure. The solid remainder was recrystallized from EtOAc affording the *title compound* **40** as colorless crystals. Yield 0.17 g (0.76 mmol), 67%; m.p. = 184-185°C; [Found: C, 37.40; H, 4.52; N, 6.40; S, 14.26. $C_7H_{10}ClNO_3S$ requires C, 37.59; H, 4.51; N, 6.26; S, 14.34%]; n_{max} (KBr) 2900, 1692, 1618, 1287, 1144, 882, 551 cm^{-1}; d_H (400 MHz, $CDCl_3$) 1.47 (s, 6H, 2×CH_3), 2.77 (s, 3H, NCH_3), 9.88 (s, 1H, CHO); d_C (125 MHz, $CDCl_3$) 22.74, 23.54, 65.47, 131.67, 161.40, 179.96; *m/z* 223.0 $[M]^+$.

*6-[(Z)-Ethoxymethylidene]-4-methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione (**41**)*

4-Methyl-5λ⁶-thia-4-azaspiro[2.4]heptane-5,5,7-trione **2** (0.2 g, 1.14 mmol) was dissolved in Ac_2O (4 mL) then $HC(OEt)_3$ (0.84 g, 0.95 mL, 5.70 mmol) was added in one portion. The resulting solution was refluxed for 3 h. The volatiles were evaporated *in vacuo* and the solid remainder was sublimated in vacuum (0.1 Torr and 100-110°C in an oil bath) giving the *title compound* **41** as white powder (*Note:* This compound is quite sensitive to moisture! Being left in air it decomposes in a few hours!). Yield 0.21 g (0.89 mmol), 78%; m.p. = 121-122°C; [Found: C, 46.98; H, 5.67; N, 5.70; S, 14.02. $C_9H_{13}NO_4S$ requires C, 46.74; H, 5.67; N, 6.06; S, 13.87%]; n_{max} (KBr) 3104, 2980, 1712, 1614, 1326, 1010, 730 cm^{-1}; d_H (400 MHz, $CDCl_3$) 1.36 (m, 2H, cyclopropyl), 1.47 (m, 2H, cyclopropyl), 1.51 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 2.71 (s, 3H, NCH_3), 4.45 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 7.74 (s, 1H, CH); d_C (125 MHz, $CDCl_3$) 14.81, 15.24, 33.85, 53.24, 75.10, 112.46, 162.52, 193.21; *m/z* 202.2 $[M-Et]^-$.

*2,3,3,5,5-Pentamethyl-1λ⁶-isothiazolidine-1,1,4-trione (**42**)*

2,3,3-Trimethyl-1λ⁶-isothiazolidine-1,1,4-trione **1** (0.20 g, 1.13 mmol) was dissolved in DMF (5 mL) then K_2CO_3 (0.47 g, 3.39 mmol) and MeI (0.48 g, 0.21 mL, 3.39 mmol) were added consequently. The resulting mixture was stirred at room temperature for 48 h, after the precipitate was filtered and twice washed with DMF (1 mL). The combined DMF layer was evaporated *in vacuo*, the residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (5×4 mL). The combined extracts were dried over Na_2SO_4, evaporated at reduced pressure and sublimated in vacuum (0.1 Torr and 50°C in an oil bath) giving the *title compound* **42** as white crystals which had been washed with mixture cyclohexane/*i*-PrOH (9:1) before scraping from cold finger. Yield 0.16 g (0.77 mmol), 68%; m.p. = 71-72°C; [Found: C, 47.14; H, 7.44; N, 6.78; S, 15.69. $C_8H_{15}NO_3S$ requires C, 46.81; H, 7.37; N, 6.82; S, 15.62%]; n_{max} (KBr) 2992, 2941, 1754, 1466, 1301, 1116, 1035 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.35 (s, 6H, 2×CH_3-3), 1.44 (s, 6H, 2×CH_3-5), 2.75 (s, 3H, NCH_3); d_C (100 MHz, DMSO-d_6) 19.95, 22.49, 22.88, 61.04, 67.60, 208.75; *m/z* 206.2 $[M+H]^+$.

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4,6,6-Trimethyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione ***(43)***

4-Methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione **2** (0.2 g, 1.14 mmol) was dissolved in DMF (5 mL) then K_2CO_3 (0.48 g, 3.39 mmol) and MeI (0.47 g, 0.21 mL, 3.39 mmol) were added consequentially and the resulting mixture was stirred at room temperature for 48 h. The precipitate was filtered and twice washed with DMF (1 mL). The combined DMF layer was evaporated *in vacuo*, the residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (5×4 mL). The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was distilled *in vacuo* giving the *title compound* **43** as colorless oil. Yield 0.13 g (0.64 mmol), 56%; b.p. = 70-75°C (0.1 Torr); [Found: C, 47.63; H, 6.45; N, 7.09; S, 16.16. $C_8H_{13}NO_3S$ requires C, 47.27; H, 6.45; N, 6.89; S, 15.78%]; n_{max} (KBr) 2987, 1745, 1462, 1333, 1194, 1126, 731 cm^{-1}; d_H (500 MHz, $CDCl_3$) 1.41 (m, 2H, cyclopropyl), 1.43 (m, 2H, cyclopropyl), 1.51 (s, 6H, 2×CH_3), 2.72 (s, 3H, NCH_3); d_C (125 MHz, $CDCl_3$) 14.18, 19.29, 28.79, 51.30, 62.94, 206.46; *m/z* 204.0 $[M+H]^+$.

General method for the preparation of 5-[(Z)-anilinomethylidene]-2-methyl-1λ^6-isothiazolidine-1,1,4-triones ***46*** *and* ***47***

Dimethylaminomethylideneketosultam **38**,**39** (0.23 g, 1.0 mmol) was dissolved in dioxane (6 mL) then $PhNH_2$ (0.37 g, 0.37 mL, 4 mmol) was added and the resulting mixture was refluxed for 8 h. The volatiles were evaporated *in vacuo* and the residue was recrystallized from *i*-PrOH affording the *title compound* **46**,**47** as colorless crystals.

5-[(Z)-Anilinomethylidene]-2,3,3-trimethyl-1λ^6-isothiazolidine-1,1,4-trione ***(46)***

Using **38** (0.23 g, 1.0 mmol). Yield 0.24 g (0.87 mmol), 87%; m.p. = 176-178°C; [Found: C, 56.00; H, 5.66; N, 10.36; S, 11.70. $C_{13}H_{16}N_2O_3S$ requires C, 55.70; H, 5.77; N, 9.99; S, 11.44%]; n_{max} (KBr) 3255, 3148, 3075, 2980, 1655, 1624, 1432, 1314, 1271, 1148, 754 cm^{-1}; s-*cis*/s-*trans* ratio 2.6:1; s-*cis* conformer d_H (400 MHz, DMSO-d_6) 1.33 (s, 6H, 2×CH_3), 2.65 (s, 3H, NCH_3), 7.21 (t, *J* 7.0 Hz, 1H, H-4'), 7.39 (t, *J* 7.6 Hz, 2H, H-3' and H-5'), 7.54 (d, *J* 7.6 Hz, 2H, H-2' and H-6'), 8.62 (d, *J* 9.8 Hz, 1H, C<u>H</u>-NH), 11.48 (d, *J* 8.5 Hz, 1H, NH); s-*trans* conformer d_H (400 MHz, DMSO-d_6) 1.30 (s, 6H, 2×CH_3), 2.67 (s, 3H, NCH_3), 7.21 (t, *J* 7.0 Hz, 1H, H-4'), 7.36 (t, *J* 7.9 Hz, 2H, H-3' and H-5'), 7.49 (d, *J* 7.9 Hz, 2H, H-2' and H-6'), 7.94 (br s, 1H, C<u>H</u>-NH), 11.14 (br s, 1H, NH); s-*cis* conformer d_C (100 MHz, DMSO-d_6) 21.86, 23.08, 66.52, 104.33, 118.92, 126.47, 130.01, 138.90, 146.03, 193.25; s-*trans* conformer d_C (100 MHz, DMSO-d_6) 21.97, 22.78, 67.43, 102.65, 119.58, 126.11, 129.83, 140.52, 143.04, 191.04; *m/z* 281.2 $[M+H]^+$.

6-[(Z)-Anilinomethylidene]-4-methyl-5λ^6-thia-4-azaspiro[2.4]heptane-5,5,7-trione ***(47)***

Using **39** (0.23 g, 1.0 mmol). Yield 0.24 g (0.88 mmol), 88%; m.p. = 209-210°C; [Found: C, 56.13; H, 5.34; N, 10.04; S, 11.91. $C_{13}H_{14}N_2O_3S$ requires C, 56.10; H, 5.07; N, 10.06; S, 11.52%]; n_{max} (KBr) 3053, 2992, 1650, 1586, 1435, 1312, 1275, 1150 cm^{-1}; s-*cis*/s-*trans* ratio 2.6:1; s-*cis* conformer d_H (400 MHz, DMSO-d_6) 1.28 (s, 4H, cyclopropyl), 2.58 (s, 3H, NCH_3), 7.19 (t, *J* 6.7 Hz, 1H, H-4'), 7.38 (t, *J* 6.7 Hz, 2H, H-2' and H-6'), 7.52 (d, *J* 7.3 Hz, 2H, H-3' and H-5'), 8.54 (d, *J* 13.4 Hz, 1H, C<u>H</u>-NH), 11.27 (d, *J* 12.8 Hz, 1H, CH-N<u>H</u>); s-*trans* conformer d_H (400 MHz, DMSO-d_6) 1.34 (s, 4H, cyclopropyl), 2.62 (s, 3H, NCH_3), 7.19 (t, *J* 6.7 Hz, 1H, H-4'), 7.38 (t, *J* 6.7 Hz, 2H, H-2' and H-6'), 7.47 (d, *J* 8.2 Hz, 2H, H-3' and H-5'), 7.98 (d, *J* 14.6 Hz, 1H, C<u>H</u>-NH), 11.03 (d, *J* 15.0 Hz, 1H, CH-N<u>H</u>); s-*cis* conformer d_C (100 MHz, DMSO-d_6) 11.71, 31.25, 51.13, 105.52, 118.10, 125.61, 129.36, 138.42, 144.33, 191.05; s-*trans* conformer d_C (100 MHz, DMSO-d_6) 12.48, 33.12, 52.06, 104.09, 118.67, 125.23, 129.21, 139.87, 141.70, 189.89; *m/z* 279.1 $[M+H]^+$.

General method for the preparation of dimethylammonium salt of ethyl (E)-2-cyano-3-(4-hydroxy-2-methyl-1,1-dioxo-2,3-dihydro-1H-1λ^6-isothiazol-5-yl)-2-propenoates ***48*** *and* ***49***

Dimethylaminomethylideneketosultam **38**,**39** (0.25 g, 1.07 mmol) was dissolved in EtOH (5 mL), ethyl 2-cyanoacetate (0.15 g, 0.14 mL, 1.28 mmol) was added and the resulting mixture was refluxed for 10 h. Then the mixture was cooled to r.t. and filtered. The mother solution was evaporated *in vacuo* and the residue was recrystallized from EtOAc affording the *title compound* **48**•H_2O, **49** as colorless crystals.

*Dimethylammonium salt of ethyl (E)-2-cyano-3-(4-hydroxy-2,3,3-trimethyl-1,1-dioxo-2,3-dihydro-1H-1λ^6-isothiazol-5-yl)-2-propenoate monohydrate (****48****•H_2O)*

Using **38** (0.25 g, 1.07 mmol). Yield 0.24 g (0.66 mmol), 62%; m.p. = 88-89°C; [Found: C, 46.04; H, 7.21; N, 11.27; S, 8.87. $C_{14}H_{25}N_3O_6S$ requires C, 46.27; H, 6.93; N, 11.56; S, 8.82%]; n_{max} (KBr) 3532, 3076, 2200, 1700, 1634, 1534, 1226, 1119 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.17 (s, 6H, 2×CH_3), 1.27 (t, *J* 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 2.62 (s, 3H, NCH_3), 2.59 (s, 6H, $H_2N^+(C\underline{H}_3)_2$), 4.15 (q, *J* 6.7 Hz, 2H, $C\underline{H}_2CH_3$), 7.72 (s, 1 H, CH), 8.10 (broad s, 2H, $\underline{H}_2N^+(CH_3)_2$); d_C (100 MHz, DMSO-d_6) 14.73, 22.04, 22.59, 34.80, 59.86, 65.47, 101.78, 118.11, 141.07, 166.33; *m/z* 244.1 $[M-C_2H_5\text{-}HCN]^-$.

Dimethylammonium salt of ethyl (E)-2-cyano-3-(7-hydroxy-4-methyl-5,5-dioxo-5λ^6-thia-4-azaspiro[2.4]hept-6-en-6-yl)-2-propenoate ***(49)***

Using **39** (0.25 g, 1.07 mmol). Yield 0.17 g (0.58 mmol), 54%. m.p. = 140-141°C; [Found: C, 49.17; H, 6.48; N, 12.02; S, 9.18. $C_{14}H_{21}N_3O_5S$ requires C, 48.97; H, 6.16; N, 12.24; S, 9.34%]; n_{max} (KBr) 3218, 2986, 2201, 1686, 1620, 1554, 1254, 1113 cm^{-1}; d_H (400 MHz, DMSO-d_6) 1.06 (s, 4H, cyclopropyl), 1.28 (t, *J* 7.0 Hz, 3H, $CH_2C\underline{H}_3$), 2.46 (s, 3H, NCH_3), 2.58 (s, 6H, $H_2N^+(C\underline{H}_3)_2$), 4.15 (q, *J* 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 7.74 (s, 1 H, CH); d_C (125 MHz, $CDCl_3$) 10.57, 14,97, 27.31, 31.12, 34.87, 51.24, 60.34, 76.37, 104.82, 118.24, 140.69, 166.85; *m/z* 297.0 $[M-H]^-$.

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