[2 + 2] Cycloaddition Reactions of Imines with Cyclic Ketenes: Synthesis of 1,3-Thiazolidine Derived Spiro-β-lactams and Their Transformations

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On the occasion of the 85th birthday of Professor *Rolf Huisgen*

Unsymmetric cyclic ketenes were generated from *N*-acyl-1,3-thiazolidine-2-carboxylic acids **1a** – **c** by means of *Mukaiyama*'s reagent, and then reacted with imines **2a** – **c** to the new, isomeric spiro-β-lactams **3** and **4** *via* [2 + 2] cycloaddition (*Staudinger* ketene – imine reaction; *Scheme 1*). The reactions were stereoselective (*Table 1*) and mainly afforded the spiro-β-lactams with a relative *trans* configuration. The spiro-β-lactams could be transformed into the corresponding monocyclic β-lactams by means of thiazolidine ring opening or into substituted thiazolidines *via* hydrolysis of the β-lactam ring.

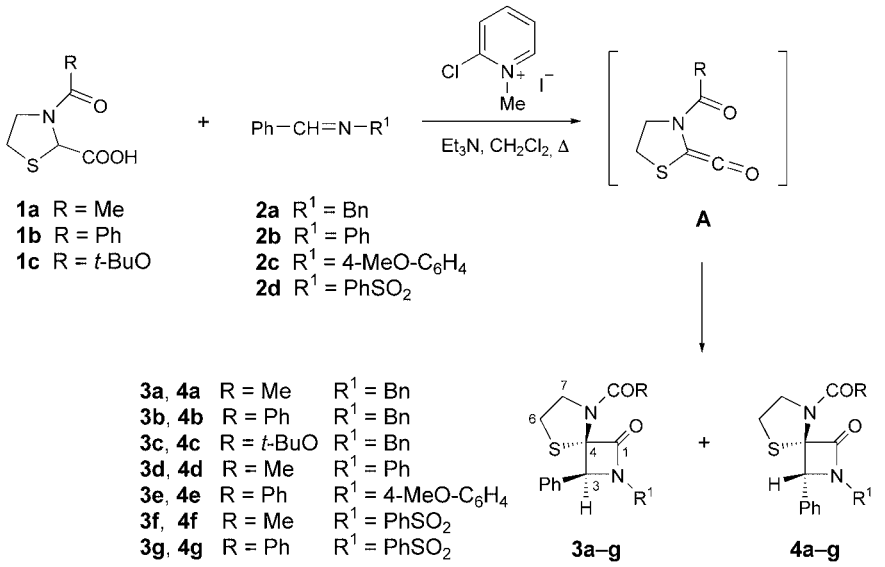
Introduction. – The reaction of ketenes with imines to 2-azetidinones, known as *Staudinger* ketene – imine cycloaddition [1], is one of the most-versatile and useful procedures for constructing β-lactam rings [2]. There is always great interest in these small heterocycles [3] because of their usefulness as synthetic intermediates in organic chemistry [4], and their antibacterial properties [5]. Recent discoveries have also shown that they are active as cholesterol absorption inhibitors [6], thrombin inhibitors [7], and anti-hyperglycemic agents [8].

Spiro-β-lactams are particularly interesting because their antiviral [9a] and antibacterial activities [9b], as well as their inhibition of cholesterol absorption [9c], make them potentially useful compounds for drug development. They can also act as β-turn mimetics [10] and, particularly the 4-spiro-β-lactams, are synthetic precursors for cyclic α,α-disubstituted β-amino acids and peptide derivatives [11]. The synthesis of conformationally constrained amino acids is of special interest because the peptides derived from these modified amino acids may have valuable biological properties. As a consequence, the synthesis of 4-spiro-β-lactams has recently received particular attention [12].

Further to our previous studies on the synthesis [13] and reactivity [14] of spiro-β-lactams, we now report the *Staudinger* ketene – imine reaction between unsymmetrical cyclic ketenes generated from *N*-acyl-1,3-thiazolidine-2-carboxylic acids **1** and imines **2** for the synthesis of the new 1,3-thiazolidine derived 4-spiro-β-lactams **3** and **4** (*Scheme 1*). Our interest in these compounds is based on the spiro-fused thiazolidine ring, which could be opened to obtain α-keto-β-lactams.

In our early work on cycloaddition reactions between mesoionic compounds (generated from cyclic *N*-acyl-α-amino acids *via* Ac_2O) and *N*-(phenylmethylidene)-benzenesulfonamide (**2d**) [13a,b], we obtained both the [3 + 2] and [2 + 2] adducts

Scheme 1



derived from the equilibrium between the two valence tautomer intermediates (ketene *vs.* mesoionic compound) already observed by *Huisgen* in his pioneering work on mesoionic compounds [15].

We have recently reported [13d] a procedure for the exclusive synthesis of the ketene intermediate **A** by means of *Mukaiyama*'s reagent (=2-chloro-1-methylpyridinium iodide): the reaction of **1a**,**b** with **2d** afforded a mixture of the diastereoisomeric *N*-phenylsulphonyl-spiro-β-lactams **3f**,**g** and **4f**,**g** in good yields, with a ratio of 97:3 in favor of the cis-configured isomers **4** (*Scheme 1*). We would now like to optimize and extend this protocol to differently *N*-substituted imines and 1,3-thiazolidine-2-carboxylic acids, with the aim of obtaining spiro-β-lactams susceptible to further transformations. The hydrolytic opening of the thiazolidine ring of **3f**,**g** and **4f**,**g** showed that these compounds are more reactive at the β-lactam than at the thiazolidine ring because of the presence of the strong electron-withdrawing sulfonyl group.

Results and Discussion. – We first decided to substitute the phenylsulphonyl group (R^1) at the imine N-atom of **2** with a benzyl (Bn) group, which has an opposite electronic effect and, when necessary, could be easily eliminated. Subsequently, a *tert*-butoxycarbonyl (Boc) protecting group (R) was introduced on the thiazolidine-2-carboxylic acid **1** in order to be able to remove it more easily. We then investigated the reaction between the acetyl- (Ac), benzoyl- (Bz), and Boc-protected substrates **1a**–**c**, resp., and imine **2a** (*Scheme 1*). We found that our previous experimental conditions [13d] could be improved: an equimolar mixture of **1** and **2a**, *Mukaiyama*'s reagent, and Et_3N was heated at reflux in CH_2Cl_2 for 6–8 h, which afforded a mixture of the diastereoisomeric spiro-β-lactams **3a**–**c** and **4a**–**c** in good yields (*Table 1*, *Entries 1–3*).

The mixtures were separated by means of column chromatography, and the relative configurations at C(3) and C(4) of the azetidinone ring were established by means of ^{1}H-NMR spectra, and compared with those of previously obtained compounds [13a,d]. The chemical shift of H–C(3) changed from δ(H) 4.51 – 4.60 in **3a**–**c** to 5.01–5.22 in **4a**–**c**, thus showing a deshielding effect of the *N*-acyl group in compounds **4**.

Table 1. *Yields and Diastereoisomer Ratios* **3**/**4** *in the Reactions of* **1** *and* **2** (see *Scheme 1* and *Exper. Part*)

Entry	**3** and **4**	R	R^1	Total yield [%]	**3**/**4**
1	**a**	Me	Bn	72	68 : 32
2	**b**	Ph	Bn	87	75 : 25
3	**c**	*t*-BuO	Bn	91	93 : 7
4	**d**	Me	Ph	20	91 : 9
5	**e**	Ph	4-MeO-C$_6$H$_4$	39	88 : 12
6[a])	**f**	Me	PhSO$_2$	70	3 : 97
7[a])	**g**	Ph	PhSO$_2$	80	3 : 97

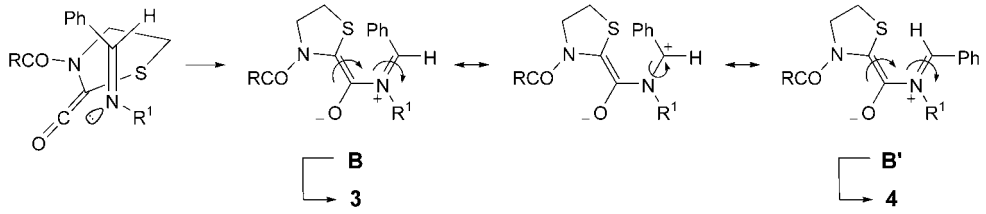
[a]) According to [13d].

When looking at the isomer distribution (*Table 1*), it should be noted that the observed *cis*/*trans* ratio (in favor of the *trans*-isomer) is inverted in comparison with that previously obtained in the reactions between **1a**,**b** and **2d**, in which, under the same experimental conditions, this ratio was in favor of the *cis*-isomer (*Entries 6* and *7*).

Two other imines, **2b** and **2c**, were also tested in the reaction with **1a** and **1b**, respectively, to determine the diastereoisomeric ratio for a different substituent at the imine N-atom. Under the same experimental conditions, **2b** was more reactive, but afforded **3d** and **4d** in modest total yields. Imine **2c** led to a better yield, and a favorable *trans*-selectivity was observed (*Entries 4* and *5*).

The mechanism of the *Staudinger* ketene–imine cycloaddition is still a subject of discussion [12a][16]. According to experimental and theoretical studies, this [2+2] cycloaddition is a two-step reaction, with the formation of a solvent-stabilized zwitterionic intermediate. In our case, it would involve the attack of the imine lone pair from the least-hindered side of the ketene opposite to the *N*-acyl group to provide the zwitterionic intermediate **B** (*Scheme 2*). Conrotatory ring-closure of the latter then leads to β-lactams **3**, with a relative *trans*-configuration. Assuming that the (*E*)-configuration of the starting imines (confirmed by NMR spectra) does not change during the course of the reaction, the *cis*-diastereoisomers **4** could derive from double-bond isomerization of **B** to **B′**, a process that should be favored by the stabilization of

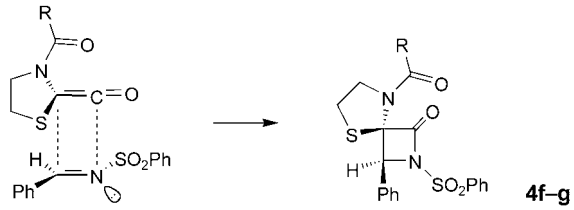
Scheme 2



the positive charge by the phenyl group on the imine C-atom [16f,g], thus leading to the thermodynamically more-stable β-lactams **4**, with the more-encumbering *N*-acyl and 3-Ph groups on opposite sides. Note that the *cis*-isomers **4a**–**e** are not due to a secondary isomerization, because no *cis*-isomers were found when the *trans*-β-lactams **3a**–**e** were subjected to the reaction conditions for 8 h.

In order to rationalize the reversed diastereoselectivity of the reaction with imine **2d**, it is worth considering a possible change in reaction mechanism from a stepwise process (involving a zwitterionic intermediate) to a concerted process. An asynchronous concerted reaction pathway cannot be excluded for ketene–imine cycloaddition reactions in which the imine N-atom is substituted with an electron-withdrawing group [16b,d]. The reduced nucleophilicity of **2d** may cause the reaction to follow a concerted [2 + 2] cycloaddition rather than a two-step mechanism affording the *cis*-isomer: in this case, the preferred approach between the ketene and the imine is that in which the *N*-acyl and the C–Ph groups are on opposite sides (*Scheme 3*).

Scheme 3



4f–g

In an attempt to support the anticipated change in mechanism when passing from imines **2a**,**c** to **2d**, solvent effects on the ratio of diasteroisomers were investigated. The reactions between **1b** and **2a**,**d** were performed in solvents with different polarities, and the results are summarized in *Table 2*. The **3g**/**4g** ratio remained almost the same in the case of **2d**, but a change in **3b**/**4b** was observed with **2a**: in this case, the *trans*/*cis* ratio decreased, when passing from a less polar (1,4-dioxane) to a very polar solvent (1,3-dimethylimidazolidin-2-one; DMI). This clearly illustrates the influence of the solvent on the zwitterionic intermediate and, therefore, on the products ratio.

Table 2. *Solvent-Dependent Product Ratios* **3**/**4** *in the Reaction of* **1b** *with* either **2a** or **2d** (see *Scheme 1*)

Solvent	**3b**/**4b**	**3g**/**4g**
1,4-Dioxane	80 : 20	7 : 93
Toluene	79 : 21	5 : 95
CH_2Cl_2	75 : 25	7 : 93
DMF	66 : 33	7 : 93
DMI[a])	58 : 42	4 : 96

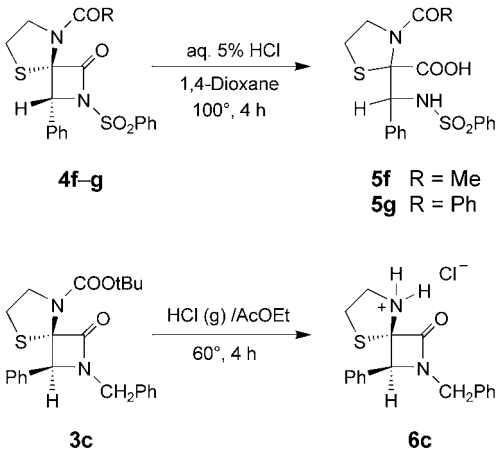
[a]) 1,3-Dimethylimidazolidin-2-one

Next, we studied the hydrogenolysis, acid hydrolysis, and desulfurization of spiro-β-lactams **3** and **4**. Compounds of type **a**, **b**, **f**, and **g** were hydrogenated in the presence of different catalysts (Pd, Pt, *Raney*-Ni) and solvents (AcOEt, EtOH, AcOH), at

temperatures ranging from room temperature to 100°, and pressures from 1 to 30 atm. These compounds turned out to be highly resistant at room temperature and atmospheric pressure (no reaction), but were degraded when the temperature and/or pressure was increased. The results were different from those of our previous experiments obtained with *N*-(phenylsulphonyl) substituted spiro-β-lactams derived from 1,3-thiazolidine-4-carboxylic acids, where the S-atom was not adjacent to the spiro-C-atom [14]. In the latter case, the thiazolidine ring was desulfurized with *Raney*-Ni as catalyst, and the azetidinone ring was opened at the C(3)–N bond. One possible explanation for the different behaviors of the new compounds **3** or **4** could be that, in this case, the S-atom is more-encumbered, thus preventing the attack.

A different behavior was observed when the benzyl (**3a**,**b**) or phenylsulfonyl substituted spiro-β-lactams (**4f**,**g**) were subjected to acid hydrolysis. The derivatives **4f**,**g** were selectively hydrolyzed at the azetidinone ring, and afforded the 2-substituted 1,3-thiazolidine-2-carboxylic acids **5f**,**g**, *i.e.*, cyclic α,β-diamino acids (*Scheme 4*). In contrast, the corresponding *N*-benzyl derivatives **3a**,**b** were stable in 10% aq. HCl at room temperature, but completely decomposed when heated. A better result was obtained with the *N*-Boc derivative **3c**. In this case, the compound was deprotected at the thiazolidine N-atom under anhydrous conditions, and afforded the spiro-β-lactam **6c**, but was decomposed when heated with aq. HCl (*Scheme 4*).

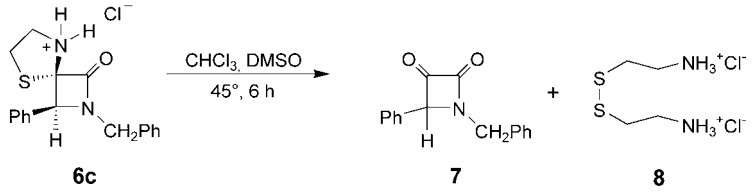
Scheme 4



In addition to hydrolysis and hydrogenolysis, other procedures for opening the thiazolidine ring were tested (with the aim of obtaining α-keto-β-lactams), namely *a*) oxidative cleavage with 'metachloroperbenzoic acid' (MCPBA) [17], H_2O, or KIO_4 [18]; and *b*) metal-catalyzed hydrolysis with $HgCl_2$ [19] or $CuO/CuCl_2$ [20]. Unfortunately, none of these experiments were fruitful. However, finally, we managed to cleave the thiazolidine ring under very mild conditions by simply heating a $CHCl_3$/DMSO 9:1 solution of **6c** to 45° for 6 h (*Scheme 5*). Under these conditions, the α-keto-β-lactam **7** was obtained in a yield of 72%, together with a 71% yield of the cystamine bis(hydrochloride) **8**. DMSO is a well-known oxidant [21], which, in our

case, might attack the electrophilic spiro-C-atom, which carries a good leaving group. Such a mechanism is supported by the observation that the reaction does take place neither when the free base (and not an ammonium salt) is reacted, nor if DMF is used as a co-solvent instead of DMSO. Nevertheless, the mechanism of this reaction has not been completely understood, even though the oxidation product **8** was isolated, and the corresponding reduction product (Me_2S) was identified by means of ^{1}H-NMR analysis.

Scheme 5



Conclusions. – The results of this study confirm the generality of the reported 1,3-thiazolidine-derived spiro-β-lactam synthesis. Opposite *trans* or *cis* diastereoselectivity can be obtained using different imines with electron-donating or electron-withdrawing substituents at the N-atom. Finally, simple and mild chemical transformations of the differently substituted compounds **3** and **4** made it possible to obtain thiazolidine derivatives or α-keto-β-lactams. This new approach to α-keto-β-lactams will be a subject of future development.

Experimental Part

General. Compounds **1a**,**b** [22], **2b** [23], and **2c** [24] were prepared according to reported methods. Imines **2a**,**d** and 2-chloro-1-methylpyridinium iodide (*Mukaiyama*'s reagent) were obtained from commercial sources. Melting points (m.p.) were measured on a *Büchi* apparatus, and are uncorrected. IR Spectra were determined on a *Perkin-Elmer 1725X FT-IR* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra were recorded in $CDCl_3$ (unless specified otherwise) on a *Bruker AC-300* spectrometer; chemical shifts δ in ppm rel. to Me_4Si, coupling constants *J* in Hz. Mass spectra were determined on a *VG Analytical 7070 EQ* mass spectrometer, with an attached *VG analytical 11/250* data system.

*3-(*tert*-Butoxycarbonyl)-1,3-thiazolidine-2-carboxylic Acid* (**1c**). A mixture of 1,3-thiazolidine-2-carboxylic acid [22] (2.0 g, 15.0 mmol), $(Boc)_2O$ (6.55g, 30 mmol), and Et_3N (4.2 ml, 30 mmol) in MeOH (36 ml) was heated at 50° for 6 h. After evaporation of the solvent, the residue was treated with cold 5% aq. HCl soln. (50 ml), and extracted with toluene. The org. layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The product was treated with hexane, and filtered to afford **1c** (6.14g, 88%). Colorless solid. M.p. 96–97° (hexane). IR (nujol): 1677, 1721. ^{1}H-NMR: 1.39 (*s*, Me_3C); 2.94 (*m*, 1 H of CH_2(5)); 3.19 (*m*, 1 H of CH_2(5)); 3.77 (*m*, 1 H of CH_2(4)); 3.91 (*m*, 1 H of CH_2(4)); 5.09 (*s*, H–C(2)). ^{13}C-NMR: 28.2 (*Me*$_3$C); 29.6 (C(5)); 49.8 (C(4)); 55.9 (C(2)); 81.7 (Me_3*C*); 168.0 (CO); 177.0 (C=O). EI-MS: 188 ([*M* – COOH]$^+$), 132, 88. Anal. calc. for $C_9H_{15}NO_4S$ (233.07): C 46.34, H 6.48, N 6.00; found C 46.27, H 6.53, N 5.86.

General Procedure for the Reactions of **1a–c** *with* **2a–c**. A mixture of **1** (1.0 mmol), **2** (1.0 mmol), 2-chloro-*N*-methylpyridium iodide (1.16 mmol), and Et_3N (3.0 mmol) in anh. CH_2Cl_2 (15 ml) was heated at reflux for 6–8 h under an N_2 atmosphere. After cooling, the soln. was washed with H_2O, 5% aq. HCl soln., and H_2O. The combined org. layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford the crude products **3** and **4**, which were purified by column chromatography (CC) (SiO_2; toluene/AcOEt) and recrystallization. For rel. yields, see *Table 1*.

*(3*S**,4*S**)-8-Acetyl-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**3a**). M.p. 165–166° (toluene). IR (nujol): 1664, 1763. ^{1}H-NMR: 1.70 (*s*, Me); 3.06 (*m*, CH_2S); 3.22 (*m*, 1 H of CH_2N); 3.70 (*m*, 1 H

of CH_2N); 4.15 (*d*, *J* = 15.0, 1 H of PhCH_2); 4.53 (*s*, CH); 5.10 (*d*, *J* = 15.0, 1 H of PhCH_2); 7.12–7.24 (*m*, 10 arom. H). ^{13}C-NMR: 23.2 (Me); 29.9 (C(6)); 45.1 (Ph*C*H$_2$); 51.6 (C(7)); 75.0 (C(3)); 83.2 (C(4)); 127.9–129.3 (Ph); 134.3 (Ph); 136.2 (Ph); 165.0 (C=O); 167.5 (C=O). EI-MS: 352 (M^+), 309, 219, 157. Anal. calc. for $C_{20}H_{20}N_2O_2S$ (352.12): C 68.16, H 5.72, N 7.95; found C 68.09, H 5.79, N 7.87.

*(3*R*,4*S*)-8-Acetyl-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**4a**). M.p. 200–201° (i-PrOH). IR (nujol): 1655, 1767. ^{1}H-NMR: 2.14 (*s*, Me); 2.52 (*m*, 1 H of CH_2S); 2.88 (*m*, 1 H of CH_2S); 3.63 (*m*, 1 H of CH_2N); 3.83 (*m*, 1 H of CH_2N); 4.12 (*d*, *J* = 14.8, 1 H of PhCH_2); 4.72 (*d*, *J* = 14.8, 1 H of PhCH_2); 5.08 (*s*, CH); 7.02 (*m*, 2 arom. H); 7.14–7.27 (*m*, 8 arom. H). ^{13}C-NMR: 24.3 (Me); 29.2 (C(6)); 45.6 (Ph*C*H$_2$); 52.4 (C(7)); 66.4 (C(3)); 85.0 (C(4)); 127.6–129.2 (Ph); 134.4 (Ph); 134.7 (Ph); 167.7 (C=O); 168.7 (C=O). EI-MS: 352 (M^+), 309, 219, 157. Anal. calc. for $C_{20}H_{20}N_2O_2S$ (352.12): C 68.16, H 5.72, N 7.95; found C 68.06, H 5.68, N 7.83.

*(3*S*,4*S*)-8-Benzoyl-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**3b**). M.p. 204–206° (toluene). IR (nujol): 1657, 1767. ^{1}H-NMR: 2.83 (*m*, 1 H of CH_2S); 3.00 (*m*, 1 H of CH_2S); 3.19 (*m*, 1 H of CH_2N); 3.61 (*m*, 1 H of CH_2N); 4.14 (*d*, *J* = 15.0, 1 H of PhCH_2); 4.60 (*s*, CH); 5.04 (*d*, *J* = 15.0, 1 H of PhCH_2); 6.70 (*dd*, 2 arom. H); 7.14–7.29 (*m*, 13 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 30.7 (C(6)); 45.4 (Ph*C*H$_2$); 53.8 (C(7)); 73.9 (C(3)); 82.6 (C(4)); 126.3–129.7 (Ph); 134.0 (Ph); 136.0 (Ph); 136.8 (Ph); 165.7 (C=O); 167.9 (C=O). EI-MS: 414 (M^+), 354, 323, 309, 281, 219, 105. Anal. calc. for $C_{25}H_{22}N_2O_2S$ (414.14): C 72.44, H 5.35, N 6.76; found C 71.83, H 5.22, N 6.53.

*(3*R*,4*S*)-8-Benzoyl-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**4b**). M.p. 194–195° (toluene). IR (nujol): 1634, 1765. ^{1}H-NMR: 2.52 (*m*, 1 H of CH_2S); 3.00 (*m*, 1 H of CH_2S); 3.63 (*m*, 1 H of CH_2N); 3.84 (*m*, 1 H of CH_2N); 4.21 (*d*, *J* = 14.8, 1 H of PhCH_2); 4.75 (*d*, *J* = 14.8, 1 H of PhCH_2); 5.22 (*s*, CH); 7.06–7.54 (*m*, 15 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 30.1 (C(6)); 45.2 (Ph*C*H$_2$); 54.7 (C(7)); 65.8 (C(3)); 84.9 (C(4)); 127.6–129.0 (Ph); 130.9 (Ph); 135.5 (Ph); 136.8 (Ph); 167.9 (C=O); 168.7 (C=O). EI-MS: 414 (M^+), 309, 281, 219, 105. Anal. calc. for $C_{25}H_{22}N_2O_2S$ (414.14): C 72.44, H 5.35, N 6.76; found C 72.23, H 5.48, N 6.60.

*(3*S*,4*S*)-8-(*tert-*Butoxycarbonyl)-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**3c**). M.p. 136–137° (i-PrOH). IR (nujol): 1673, 1769. ^{1}H-NMR: 1.27 (*s*, Me$_3$C); 2.90–3.13 (*m*, NCH_2CH_2S); 4.02 (*d*, *J* = 15.3, 1 H of PhCH_2); 4.51 (*s*, CH); 5.04 (d, *J* = 15.6, 1 H of PhCH_2); 7.11–7.25 (*m*, 10 arom. H). ^{13}C-NMR: 27.9 (*Me*$_3$C); 29.9 (C(6)); 45.2 (Ph*C*H$_2$); 50.7 (C(7)); 74.1 (C(3)); 80.2 (Me$_3$*C*); 82.3 (C(4)); 127.2–128.8 (Ph); 133.7 (Ph); 134.8 (Ph); 151.6 (C=O); 165.9 (C=O). EI-MS: 410 (M^+), 309, 277, 177, 132. Anal. calc. for $C_{23}H_{26}N_2O_3S$ (410.17): C 67.29, H 6.38, N 6.82; found C 67.17, H 6.22, N 6.65.

*(3*R*,4*S*)-8-(*tert-*Butoxycarbonyl)-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**4c**). Oil. IR (nujol): 1662, 1767. ^{1}H-NMR: 1.42 (*s*, Me$_3$C); 2.43 (*m*, 1 H of CH_2S); 2.79 (*m*, 1 H of CH_2S); 3.51 (*m*, 1 H of CH_2N); 3.87 (*m*, 1 H of CH_2N); 4.25 (br. *s*, PhCH_2); 5.01 (*s*, CH); 6.98 (*m*, 2 arom. H); 7.15–7.23 (*m*, 8 arom. H). EI-MS: 410 (M^+), 309, 277, 177, 132. Anal. calc. for $C_{23}H_{26}N_2O_3S$ (410.17): C 67.29, H 6.38, N 6.82; found C 67.19, H 6.25, N 6.71.

(3S,4S*)-8-Acetyl-2,3-diphenyl-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**3d**). M.p. 216–217° (i-PrOH). IR (nujol): 1667, 1763. ^{1}H-NMR: 1.67 (*s*, Me); 3.16 (*m*, CH_2S); 3.36 (*m*, 1 H of CH_2N); 3.79 (*m*, 1 H of CH_2N); 5.18 (*s*, CH); 7.17–7.33 (*m*, 10 arom. H). ^{13}C-NMR: 23.4 (Me); 31.0 (C(6)); 52.1 (C(7)); 75.2 (C(3)); 82.3 (C(4)); 118.0–129.5 (Ph); 133.0 (Ph); 138.0 (Ph); 163.0 (C=O); 168.0 (C=O). Anal. calc. for $C_{19}H_{18}N_2O_2S$ (338.11): C 67.43, H 5.36, N 8.28; found: C 67.22, H 5.33, N 8.08.

(3R,4S*)-8-Acetyl-2,3-diphenyl-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**4d**). M.p. 210–211° (i-PrOH). IR (nujol): 1646, 1762. ^{1}H-NMR: 1.19 (*s*, Me); 2.65 (*m*, 1 H of CH_2S); 2.98 (*m*, 1 H of CH_2S); 3.73 (*m*, 1 H of CH_2N); 3.91 (*m*, 1 H of CH_2N); 5.66 (*s*, CH); 7.12–7.32 (*m*, 10 arom. H). Anal. calc. for $C_{19}H_{18}N_2O_2S$ (338.11): C 67.43, H 5.36, N 8.28; found: C 67.23, H 5.16, N 8.08.

(3S,4S*)-8-Benzoyl-2-(4-methoxyphenyl)-3-phenyl-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**3e**). M.p. 188–189° (toluene). IR (nujol): 1636, 1753. ^{1}H-NMR: 2.92 (*ddd*, *J* = 2.4, 5.6, 10.7, 1 H of CH_2S); 3.09 (*m*, 1 H of CH_2S); 3.33 (*m*, 1 H of CH_2N); 3.70 (*ddd*, *J* = 2.3, 5.9, 11.0, 1 H of CH_2N); 3.71 (*s*, MeO); 5.21 (*s*, CH); 6.71 (*d*, 2 arom. H); 6.78 (*d*, 2 arom. H); 7.12–7.37 (*m*, 10 arom. H). ^{13}C-NMR: 31.8 (C(6)); 54.5 (C(7)); 55.9 (MeO); 74.1 (C(3)); 81.9 (C(4)); 114.8 (Ph); 119.3 (Ph); 126.9–130.6 (Ph); 131.6 (Ph); 132.8 (Ph); 136.6 (Ph); 156.7 (C=O); 163.2 (C=O); 169.2 (C=O). EI-MS: 430 (M^+), 325, 281, 219. Anal. calc. for $C_{25}H_{22}N_2O_3S$ (430.14): C 69.75, H 5.15, N 6.51; found: C 69.60, H 5.04, N 6.24.

(3R,4S*)-8-Benzoyl-2-(4-methoxyphenyl)-3-phenyl-5-thia-2,8-diazaspiro[3.4]octan-1-one* (**4e**). M.p. 178–180° (toluene). IR (nujol): 1636, 1755. ^{1}H-NMR: 2.63 (*m*, 1 H of CH_2S); 3.09 (*m*, 1 H of CH_2S), 3.67 (*s*, MeO); 3.75 (*m*, 1 H of CH_2N); 3.81 (*m*, 1 H of CH_2N); 5.75 (s, CH); 6.73 (*d*, 2 arom. H); 7.34–7.54 (*m*, 12 arom. H). ^{13}C-NMR: 30.4 (C(6)); 54.9 (C(7)); 55.4 (MeO); 65.5 (C(3)); 84.8 (C(4)); 114.3 (Ph), 119.2 (Ph),

127.3–131.0 (Ph), 131.6 (Ph), 134.9 (Ph), 135.9 (Ph), 154.3 (C=O), 165.3 (C=O), 169.6 (C=O). EI-MS: 430 (M^+), 325, 281, 219. Anal. calc. for $C_{25}H_{22}N_2O_3S$ (430.14): C 69.75, H 5.15, N 6.51; found: C 69.62, H 5.01, N 6.28.

General Procedure for the Hydrolysis of Compounds **4f** and **4g**. A suspension of the spiro-β-lactam (0.25 mmol) in a mixture of 1,4-dioxane (10 ml) and 5% aq. HCl soln. (10 ml) was heated at reflux for 3 h. After evaporation of the dioxane and cooling, the products were collected by filtration.

3-Acetyl-2-{phenyl[(phenylsulfonyl)amino]methyl}-1,3-thiazolidine-2-carboxylic acid (**5f**). Yield: 56%. M.p. 212–214° (dec.; H_2O). IR (nujol): 1628, 1704, 3257. ^{1}H-NMR ((D_6)acetone): 1.70 (*s*, Me); 2.50 (*m*, 1 H of CH_2S); 2.68 (*ddd*, J = 2.3, 5.2, 10.9, 1 H of CH_2S); 2.99 (*m*, 1 H of CH_2N); 3.83 (*ddd*, J = 2.3, 5.2, 10.9, 1 H of CH_2N); 5.45 (br. *s*, CH); 6.60 (br. *s*, NH); 7.00–7.50 (*m*, 10 arom. H); with D_2O, the signal at δ(H) 6.60 disappeared, and that at 5.45 became a *singlet*. Anal. calc. for $C_{19}H_{20}N_2O_5S_2$ (420.08): C 54.27, H 4.79, N 6.66, found: C 54.39, H 4.72, N 6.35.

3-Benzoyl-2-{phenyl[(phenylsulfonyl)amino]methyl}-1,3-thiazolidine-2-carboxylic Acid (**5g**). Yield: 84%. M.p. 235–237° (dec.; H_2O). IR (nujol): 1629, 1712, 3261. ^{1}H-NMR ((D_6)DMSO): 2.80 (*m*, CH_2S); 3.00 (*m*, 1 H of CH_2N); 3.54 (*m*, 1 H of CH_2N); 5.62 (*d*, J = 9.11, *C*H); 6.70 (*d*, 2 arom. H); 7.11–7.57 (*m*, 11 arom. H); 7.59 (*d*, 2 arom. H); 7.85 (*d*, J = 9.11, NH); 12.30 (br. *s*, COOH); with D_2O, the signals at δ(H) 7.85 and 12.30 disappeared, and that at 5.62 became a *singlet*. Anal. calc. for $C_{24}H_{22}N_2O_5S_2$ (482.10): C 59.73, H 4.60, N 5.81; found: C 59.52, H 4.55, N 5.70.

*(3*S*,4S*)-3-Phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one Hydrochloride* (**6c**). A soln. of **3c** (0.7 g, 1.7mmol) in 1M HCl in AcOEt (10 ml) was heated at 60° for 3 h. After cooling, the product was collected by filtration, and recrystallized (i-PrOH). Yield: 0.47 g (80%). M.p. 180–181° (i-PrOH). IR (nujol): 1773, 1749, 3271. ^{1}H-NMR: 2.98 (*m*, 1 H of CH_2S); 3.18 (*m*, 1 H of CH_2S); 3.48 (*m*, 1 H of CH_2N); 3.66 (*m*, 1 H of CH_2N); 4.18 (*d*, J = 14.8, 1 H of PhCH_2); 4.70 (*d*, J = 14.8, 1 H of PhCH_2); 5.36 (*s*, CH); 7.13–7.32 (*m*, 10 arom. H). ^{13}C-NMR ((D_6)DMSO): 30.9 (C(6)); 44.5 (Ph*C*H$_2$); 48.7 (C(7)); 63.8 (C(3)); 90.3 (C(4)); 127.4–128.9 (Ph); 134.0 (Ph); 134.3 (Ph); 165.7 (C=O); 177.8 (C=O). EI-MS: 310 ([M – HCl]$^+$), 219, 195, 177. Anal. calc. for $C_{18}H_{19}ClN_2OS$ (346.09): C 62.33, H 5.52, N 8.08; found: C 62.14, H 5.22, N 7.92.

4-Phenyl-1-(phenylmethyl)azetidine-2,3-dione (**7**). A soln. of **3c** (50 mg, 0.14 mmol) in $CHCl_3$ (4 ml) and DMSO (0.4 ml) was heated at 45° for 6 h. The resulting solid was filtered off to afford **8** (23 mg, 71%)[1]). The filtrate was evaporated to dryness, and the residue was purified by flash chromatography (SiO_2; hexane/AcOEt 3:1) to afford **7** (52 mg, 72%). M.p. 80–81° ((i-Pr)$_2$O; lit. oil [26]). IR (nujol): 1743, 1825. ^{1}H-NMR: 4.11 (*d*, J = 14.6, 1 H of PhCH_2); 4.83 (*s*, H–C(4)); 5.13 (*d*, J = 14.6, 1 H of PhCH_2); 7.10–7.34 (*m*, 10 arom. H). ^{13}C-NMR: 45.9 (Ph*C*H$_2$); 73.9 (CH); 126.4–131.0 (Ph); 131.9 (Ph); 133.5(Ph); 164.0 (C=O); 202.0 (C=O). FAB-MS: 252 ([M + H]$^+$), 194, 91. Anal. calc. for $C_{16}H_{13}NO_2$ (251.09): C 76.48, H 5.21, N 5.57; found: C 76.36, H 5.04, N 5.45.

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