

## [2 + 2] Cycloaddition Reactions of Imines with Cyclic Ketenes: Synthesis of 1,3-Thiazolidine Derived Spiro- $\beta$ -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- $\beta$ -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- $\beta$ -lactams with a relative *trans* configuration. The spiro- $\beta$ -lactams could be transformed into the corresponding monocyclic  $\beta$ -lactams by means of thiazolidine ring opening or into substituted thiazolidines via hydrolysis of the  $\beta$ -lactam ring.

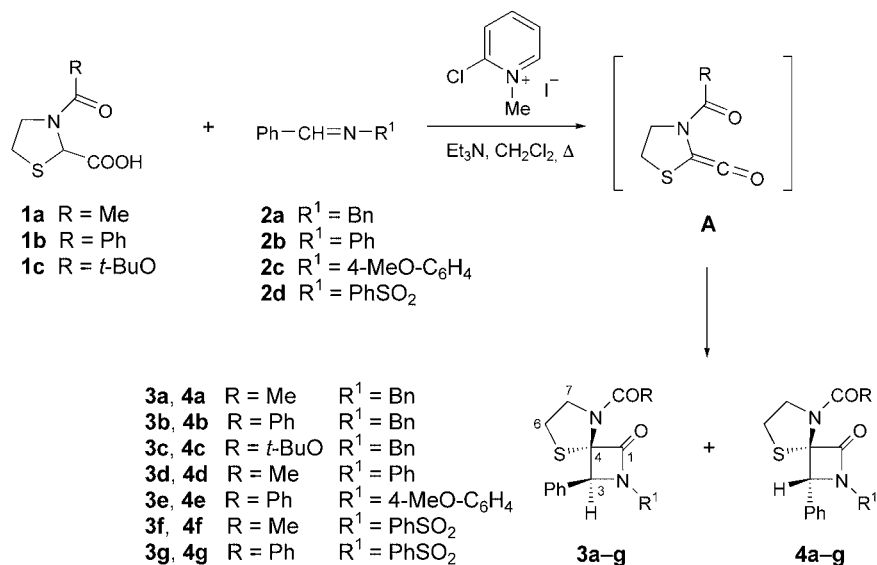
**Introduction.** – The reaction of ketenes with imines to 2-azetidinones, known as *Staudinger* ketene–imine cycloaddition [1], is one of the most-versatile and useful procedures for constructing  $\beta$ -lactam rings [2]. There is always great interest in these small heterocycles [3] because of their 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- $\beta$ -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  $\beta$ -turn mimetics [10] and, particularly the 4-spiro- $\beta$ -lactams, are synthetic precursors for cyclic  $\alpha,\alpha$ -disubstituted  $\beta$ -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- $\beta$ -lactams has recently received particular attention [12].

Further to our previous studies on the synthesis [13] and reactivity [14] of spiro- $\beta$ -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- $\beta$ -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  $\alpha$ -keto- $\beta$ -lactams.

In our early work on cycloaddition reactions between mesoionic compounds (generated from cyclic *N*-acyl- $\alpha$ -amino acids via  $\text{Ac}_2\text{O}$ ) 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*-phenylsulfonyl-spiro- $\beta$ -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- $\beta$ -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  $\beta$ -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 phenylsulfonyl group (R<sup>1</sup>) 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<sub>3</sub>N was heated at reflux in CH<sub>2</sub>Cl<sub>2</sub> for 6–8 h, which afforded a mixture of the diastereoisomeric spiro- $\beta$ -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  $^1\text{H}$ -NMR spectra, and compared with those of previously obtained compounds [13a,d]. The chemical shift of H–C(3) changed from  $\delta(\text{H})$  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            | <b>3</b> and <b>4</b> | R             | R <sup>1</sup>                      | Total yield [%] | <b>3/4</b> |
|------------------|-----------------------|---------------|-------------------------------------|-----------------|------------|
| 1                | <b>a</b>              | Me            | Bn                                  | 72              | 68 : 32    |
| 2                | <b>b</b>              | Ph            | Bn                                  | 87              | 75 : 25    |
| 3                | <b>c</b>              | <i>t</i> -BuO | Bn                                  | 91              | 93 : 7     |
| 4                | <b>d</b>              | Me            | Ph                                  | 20              | 91 : 9     |
| 5                | <b>e</b>              | Ph            | 4-MeO-C <sub>6</sub> H <sub>4</sub> | 39              | 88 : 12    |
| 6 <sup>a</sup> ) | <b>f</b>              | Me            | PhSO <sub>2</sub>                   | 70              | 3 : 97     |
| 7 <sup>a</sup> ) | <b>g</b>              | Ph            | PhSO <sub>2</sub>                   | 80              | 3 : 97     |

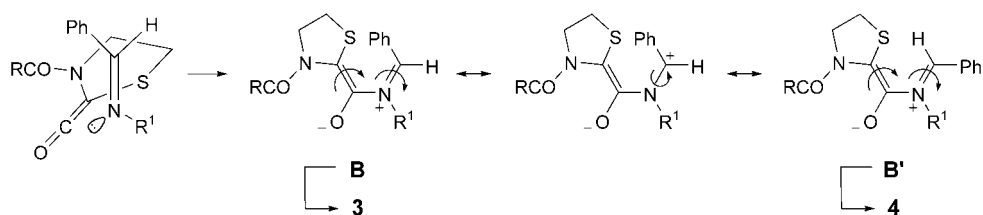
<sup>a</sup>) According to [13d].

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  $\beta$ -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

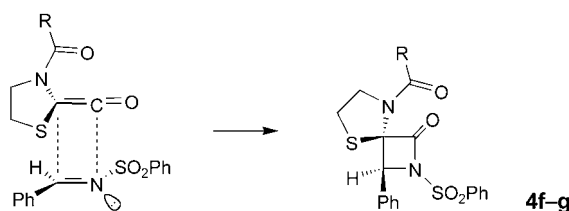
Scheme 2



the positive charge by the phenyl group on the imine C-atom [16f,g], thus leading to the thermodynamically more-stable  $\beta$ -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*- $\beta$ -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



In an attempt to support the anticipated change in mechanism when passing from imines **2a,c** to **2d**, solvent effects on the ratio of diastereoisomers 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                         | <b>3b/4b</b> | <b>3g/4g</b> |
|---------------------------------|--------------|--------------|
| 1,4-Dioxane                     | 80 : 20      | 7 : 93       |
| Toluene                         | 79 : 21      | 5 : 95       |
| CH <sub>2</sub> Cl <sub>2</sub> | 75 : 25      | 7 : 93       |
| DMF                             | 66 : 33      | 7 : 93       |
| DMI <sup>a)</sup>               | 58 : 42      | 4 : 96       |

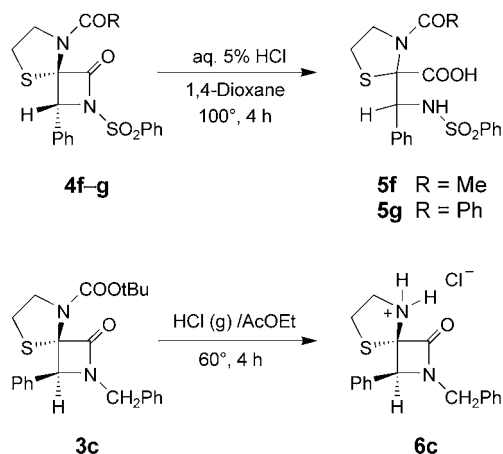
<sup>a)</sup> 1,3-Dimethylimidazolidin-2-one

Next, we studied the hydrogenolysis, acid hydrolysis, and desulfurization of spiro- $\beta$ -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*-(phenylsulfonyl) substituted spiro- $\beta$ -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- $\beta$ -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  $\alpha,\beta$ -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- $\beta$ -lactam **6c**, but was decomposed when heated with aq. HCl (*Scheme 4*).

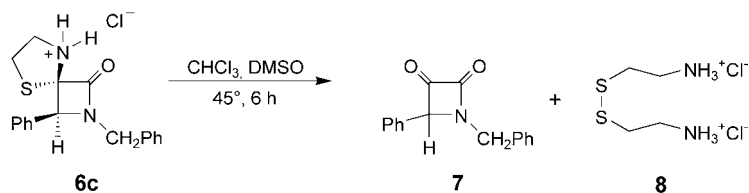
Scheme 4



In addition to hydrolysis and hydrogenolysis, other procedures for opening the thiazolidine ring were tested (with the aim of obtaining  $\alpha$ -keto- $\beta$ -lactams), namely *a*) oxidative cleavage with ‘metachloroperbenzoic acid’ (MCPBA) [17], H<sub>2</sub>O, or KIO<sub>4</sub> [18]; and *b*) metal-catalyzed hydrolysis with HgCl<sub>2</sub> [19] or CuO/CuCl<sub>2</sub> [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<sub>3</sub>/DMSO 9:1 solution of **6c** to 45° for 6 h (*Scheme 5*). Under these conditions, the  $\alpha$ -keto- $\beta$ -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 ( $\text{Me}_2\text{S}$ ) was identified by means of  $^1\text{H}$ -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  $\text{cm}^{-1}$ .  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Spectra were recorded in  $\text{CDCl}_3$  (unless specified otherwise) on a Bruker AC-300 spectrometer; chemical shifts  $\delta$  in ppm rel. to  $\text{Me}_4\text{Si}$ , 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),  $(\text{Boc})_2\text{O}$  (6.55 g, 30 mmol), and  $\text{Et}_3\text{N}$  (4.2 ml, 30 mmol) in MeOH (36 ml) was heated at  $50^\circ$  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 ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated under reduced pressure. The product was treated with hexane, and filtered to afford **1c** (6.14 g, 88%). Colorless solid. M.p.  $96-97^\circ$  (hexane). IR (nujol): 1677, 1721.  $^1\text{H}$ -NMR: 1.39 (s,  $\text{Me}_3\text{C}$ ); 2.94 (m, 1 H of  $\text{CH}_2(5)$ ); 3.19 (m, 1 H of  $\text{CH}_2(5)$ ); 3.77 (m, 1 H of  $\text{CH}_2(4)$ ); 3.91 (m, 1 H of  $\text{CH}_2(4)$ ); 5.09 (s, H-C(2)).  $^{13}\text{C}$ -NMR: 28.2 ( $\text{Me}_3\text{C}$ ); 29.6 (C(5)); 49.8 (C(4)); 55.9 (C(2)); 81.7 ( $\text{Me}_3\text{C}$ ); 168.0 (CO); 177.0 (C=O). EI-MS: 188 ( $[\text{M} - \text{COOH}]^+$ ), 132, 88. Anal. calc. for  $\text{C}_9\text{H}_{13}\text{NO}_4\text{S}$  (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*-methylpyridinium iodide (1.16 mmol), and  $\text{Et}_3\text{N}$  (3.0 mmol) in anhyd.  $\text{CH}_2\text{Cl}_2$  (15 ml) was heated at reflux for 6–8 h under an  $\text{N}_2$  atmosphere. After cooling, the soln. was washed with  $\text{H}_2\text{O}$ , 5% aq. HCl soln., and  $\text{H}_2\text{O}$ . The combined org. layers were dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was removed under reduced pressure to afford the crude products **3** and **4**, which were purified by column chromatography (CC) ( $\text{SiO}_2$ ; 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.  $165-166^\circ$  (toluene). IR (nujol): 1664, 1763.  $^1\text{H}$ -NMR: 1.70 (s, Me); 3.06 (m,  $\text{CH}_2\text{S}$ ); 3.22 (m, 1 H of  $\text{CH}_2\text{N}$ ); 3.70 (m, 1 H

of  $\text{CH}_2\text{N}$ ); 4.15 ( $d$ ,  $J = 15.0$ , 1 H of  $\text{PhCH}_2$ ); 4.53 ( $s$ , CH); 5.10 ( $d$ ,  $J = 15.0$ , 1 H of  $\text{PhCH}_2$ ); 7.12–7.24 ( $m$ , 10 arom. H).  $^{13}\text{C}$ -NMR: 23.2 (Me); 29.9 (C(6)); 45.1 ( $\text{PhCH}_2$ ); 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  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$  (352.12): C 68.16, H 5.72, N 7.95; found C 68.09, H 5.79, N 7.87.

(3R\*,4S\*)-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.  $^1\text{H}$ -NMR: 2.14 ( $s$ , Me); 2.52 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 2.88 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.63 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.83 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 4.12 ( $d$ ,  $J = 14.8$ , 1 H of  $\text{PhCH}_2$ ); 4.72 ( $d$ ,  $J = 14.8$ , 1 H of  $\text{PhCH}_2$ ); 5.08 ( $s$ , CH); 7.02 ( $m$ , 2 arom. H); 7.14–7.27 ( $m$ , 8 arom. H).  $^{13}\text{C}$ -NMR: 24.3 (Me); 29.2 (C(6)); 45.6 ( $\text{PhCH}_2$ ); 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  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$  (352.12): C 68.16, H 5.72, N 7.95; found C 68.06, H 5.68, N 7.83.

(3S\*,4S\*)-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.  $^1\text{H}$ -NMR: 2.83 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.00 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.19 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.61 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 4.14 ( $d$ ,  $J = 15.0$ , 1 H of  $\text{PhCH}_2$ ); 4.60 ( $s$ , CH); 5.04 ( $d$ ,  $J = 15.0$ , 1 H of  $\text{PhCH}_2$ ); 6.70 ( $dd$ , 2 arom. H); 7.14–7.29 ( $m$ , 13 arom. H).  $^{13}\text{C}$ -NMR (( $\text{D}_6$ )DMSO): 30.7 (C(6)); 45.4 ( $\text{PhCH}_2$ ); 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  $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$  (414.14): C 72.44, H 5.35, N 6.76; found C 71.83, H 5.22, N 6.53.

(3R\*,4S\*)-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.  $^1\text{H}$ -NMR: 2.52 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.00 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.63 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.84 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 4.21 ( $d$ ,  $J = 14.8$ , 1 H of  $\text{PhCH}_2$ ); 4.75 ( $d$ ,  $J = 14.8$ , 1 H of  $\text{PhCH}_2$ ); 5.22 ( $s$ , CH); 7.06–7.54 ( $m$ , 15 arom. H).  $^{13}\text{C}$ -NMR (( $\text{D}_6$ )DMSO): 30.1 (C(6)); 45.2 ( $\text{PhCH}_2$ ); 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  $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$  (414.14): C 72.44, H 5.35, N 6.76; found C 72.23, H 5.48, N 6.60.

(3S\*,4S\*)-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.  $^1\text{H}$ -NMR: 1.27 ( $s$ ,  $\text{Me}_3\text{C}$ ); 2.90–3.13 ( $m$ ,  $\text{NCH}_2\text{CH}_2\text{S}$ ); 4.02 ( $d$ ,  $J = 15.3$ , 1 H of  $\text{PhCH}_2$ ); 4.51 ( $s$ , CH); 5.04 ( $d$ ,  $J = 15.6$ , 1 H of  $\text{PhCH}_2$ ); 7.11–7.25 ( $m$ , 10 arom. H).  $^{13}\text{C}$ -NMR: 27.9 ( $\text{Me}_3\text{C}$ ); 29.9 (C(6)); 45.2 ( $\text{PhCH}_2$ ); 50.7 (C(7)); 74.1 (C(3)); 80.2 ( $\text{Me}_3\text{C}$ ); 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  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$  (410.17): C 67.29, H 6.38, N 6.82; found C 67.17, H 6.22, N 6.65.

(3R\*,4S\*)-8-(tert-Butoxycarbonyl)-3-phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one (**4c**). Oil. IR (nujol): 1662, 1767.  $^1\text{H}$ -NMR: 1.42 ( $s$ ,  $\text{Me}_3\text{C}$ ); 2.43 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 2.79 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.51 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.87 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 4.25 ( $br. s$ ,  $\text{PhCH}_2$ ); 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  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$  (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.  $^1\text{H}$ -NMR: 1.67 ( $s$ , Me); 3.16 ( $m$ ,  $\text{CH}_2\text{S}$ ); 3.36 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.79 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 5.18 ( $s$ , CH); 7.17–7.33 ( $m$ , 10 arom. H).  $^{13}\text{C}$ -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  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$  (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.  $^1\text{H}$ -NMR: 1.19 ( $s$ , Me); 2.65 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 2.98 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.73 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.91 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 5.66 ( $s$ , CH); 7.12–7.32 ( $m$ , 10 arom. H). Anal. calc. for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$  (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.  $^1\text{H}$ -NMR: 2.92 ( $ddd$ ,  $J = 2.4, 5.6, 10.7$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.09 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.33 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.70 ( $ddd$ ,  $J = 2.3, 5.9, 11.0$ , 1 H of  $\text{CH}_2\text{N}$ ); 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).  $^{13}\text{C}$ -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  $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$  (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.  $^1\text{H}$ -NMR: 2.63 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.09 ( $m$ , 1 H of  $\text{CH}_2\text{S}$ ); 3.67 ( $s$ , MeO); 3.75 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 3.81 ( $m$ , 1 H of  $\text{CH}_2\text{N}$ ); 5.75 ( $s$ , CH); 6.73 ( $d$ , 2 arom. H); 7.34–7.54 ( $m$ , 12 arom. H).  $^{13}\text{C}$ -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- $\beta$ -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.  $^1H$ -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  $\delta(H)$  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.  $^1H$ -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,  $J = 9.11$ , CH); 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  $\delta(H)$  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.

*(3S\*,4S\*)-3-Phenyl-2-(phenylmethyl)-5-thia-2,8-diazaspiro[3.4]octan-1-one Hydrochloride (6c).* A soln. of **3c** (0.7 g, 1.7 mmol) 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.  $^1H$ -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 ( $PhCH_2$ ); 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  $C_{18}H_{18}ClN_2OS$  (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%)<sup>1)</sup>. 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) $_2O$ ; lit. oil [26]). IR (nujol): 1743, 1825.  $^1H$ -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 ( $PhCH_2$ ); 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.

## REFERENCES

- [1] M. Staudinger, *Liebigs Ann. Chem.* **1907**, 356, 51.
- [2] N. S. Isaacs, *Chem. Soc. Rev.* **1976**, 5, 181; L. Ghosez, S. Marchand-Brynaert, in 'Comprehensive Organic Synthesis', Eds. B. Trost, I. Fleming, Pergamon Press, Oxford, 1991, Vol. 5, p. 85; G. I. Georg, V. T. Ravikumar, in 'The Organic Chemistry of  $\beta$ -Lactams', Eds. G. I. Georg, Wiley-VCH, Weinheim, New York, 1993, p. 295–381; N. DeKimpe, in 'Comprehensive Heterocyclic Chemistry II', Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriven, A. Padwa, Pergamon Press, Oxford, 1996, Vol. 1B, p. 507.
- [3] Special issue: 'Recent Aspects of the Chemistry of  $\beta$ -Lactams-II', Ed. M. J. Miller, *Tetrahedron* **2000**, 56, 5553–5742.
- [4] A. Pommier, J. M. Pons, *Synthesis* **1995**, 729; I. Ojima, *Acc. Chem. Res.* **1995**, 28, 383.
- [5] a) 'Chemistry and Biology of  $\beta$ -Lactam Antibiotics', Eds. R. B. Morin, M. Gorman, Academic Press, New York, 1982, Vols. 1–3; 'The Chemistry of  $\beta$ -Lactams', Ed. M. I. Page, Blackie, Glasgow, 1992; S. Coulton, E. Hunt, in 'Recent Progress in The Chemical Synthesis of Antibiotics and Related Microbial Products', Ed. G. Lukacs, Springer, Berlin, 1993, Vol. 2, p. 621.
- [6] W. D. Vaccaro, H. R. Davis Jr., *Bioorg. Med. Chem. Lett.* **1998**, 8, 313; W. D. Vaccaro, R. Sher, H. R. Davis Jr., *Bioorg. Med. Chem. Lett.* **1998**, 8, 35; D. A. Burnett, M. A. Caplen, H. R. Davis Jr., R. E. Burrier, J. W. Clader, *J. Med. Chem.* **1994**, 37, 1733.

<sup>1)</sup> M.p. 220–221° (lit. 220° [25]).

- [7] W. T. Han, A. K. Trehan, J. J. K. Wright, M. E. Federici, S. M. Seiler, N. A. Meanwell, *Bioorg. Med. Chem.* **1995**, *3*, 1123.
- [8] R. K. Goel, M. P. Mahajan, S. K. Kulkarni, *J. Pharm. Pharmaceut. Sci.* **2004**, *7*, 80.
- [9] a) J. W. Skiles, D. McNeil, *Tetrahedron Lett.* **1990**, *31*, 7277; b) J. C. Sheehan, E. Chacko, Y. S. Lo, D. R. Ponzi, E. Sato, *J. Org. Chem.* **1978**, *43*, 4856; c) G. Wu, W. Tormos, *J. Org. Chem.* **1997**, *62*, 6412, and refs. cit. therein.
- [10] E. Alonso, F. López-Ortiz, C. del Pozo, E. Peralta, A. Macías, J. González, *J. Org. Chem.* **2001**, *66*, 6333, and refs. cit. therein.
- [11] E. Alonso, C. del Pozo, J. González, *Synlett* **2002**, 69.
- [12] a) A. B. Khasanov, M. M. Ramirez-Weinhouse, T. R. Webb, M. Thiruvazhi, *J. Org. Chem.* **2004**, *69*, 5766; b) A. Macías, E. Alonso, C. del Pozo, A. Venturini, J. Gonzáles, *J. Org. Chem.* **2004**, *69*, 7004.
- [13] a) P. Dalla Croce, R. Ferraccioli, C. La Rosa, *Tetrahedron* **1995**, *51*, 9385; b) P. Dalla Croce, R. Ferraccioli, C. La Rosa, *Tetrahedron* **1999**, *55*, 201; c) P. Dalla Croce, C. La Rosa, *Tetrahedron: Asymmetry* **1999**, *10*, 1193; d) G. Cremonesi, P. Dalla Croce, C. La Rosa, *Tetrahedron* **2004**, *60*, 93.
- [14] P. Dalla Croce, C. La Rosa, *Heterocycles* **2000**, *53*, 2653.
- [15] R. Huisgen, E. Funke, F. C. Schaefer, R. Knorr, *Angew. Chem., Int. Ed.* **1967**, *6*, 367; R. Huisgen, E. Funke, *Chem. Ber.* **1971**, *104*, 3222.
- [16] a) A. Venturini, J. González, *J. Org. Chem.* **2002**, *67*, 9089; b) E. Alonso, C. del Pozo, J. González, *J. Chem. Soc., Perkin Trans. 1* **2002**, 571; c) A. Arrieta, B. Lecea, F. P. Cossío, *J. Org. Chem.* **1998**, *63*, 5869; d) F. P. Cossío, J. M. Ugalde, X. Lopez, B. Lecea, C. Palomo, *J. Am. Chem. Soc.* **1993**, *115*, 995; e) R. López, T. L. Sordo, J. A. Sordo, J. González, *J. Org. Chem.* **1993**, *58*, 7036; f) L. S. Hegedus, J. Montgomery, Y. Narukawa, D. C. Snustad, *J. Am. Chem. Soc.* **1991**, *113*, 5784; g) W. T. Brady, Y. Q. Gu, *J. Org. Chem.* **1989**, *54*, 2838.
- [17] K. Ogura, N. Katoh, I. Yoshimura, G. Tsuchihashi, *Tetrahedron Lett.* **1978**, 375.
- [18] A. H. Cook, I. M. Heilbron, in 'The Chemistry of Penicillin'; Eds. H. T. Clarke, J. R. Johnson, R. Robinson, Princeton University Press, Princeton, New Jersey, 1949.
- [19] H. E. Applegate, C. M. Cimarusti, W. A. Slusarchyk, *Tetrahedron Lett.* **1979**, 1637.
- [20] A. Dondoni, A. Marra, D. Perrone, *J. Org. Chem.* **1993**, *58*, 275.
- [21] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165; C. N. Yiannios, J. V. Karabinos, *J. Org. Chem.* **1963**, *28*, 3246.
- [22] I. Lalezari, E. L. Schwartz, *J. Med. Chem.* **1988**, *31*, 1427.
- [23] L. A. Bigelow, H. Eatough, *Org. Synth., Coll. Vol. 1* **1946**, 80.
- [24] J. H. Hartley, M. D. Phillips, T. D. James, *New J. Chem.* **2002**, *26*, 1228.
- [25] E. Brzezinska, A. L. Ternay Jr., *J. Org. Chem.* **1994**, *59*, 8239.
- [26] M. D. Mihovilovic, A. Feicht, M. M. Kayser, *J. Prakt. Chem.* **2000**, *342*, 585.

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