HETEROCYCLES, Vol. 53, No12, 2000, pp. 2653 - 2660, Received, 13th July, 2000

STUDIES ON RING OPENING REACTIONS OF *N*-PHENYLSULFONYL SUBSTITUTED SPIRO-β-LACTAMS

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Abstract - Ring opening reactions of the spiro-β-lactam 5-benzoyl-3-phenyl-2-phenylsulfonyl-7-thia-2,5-diazaspiro[3.4]octan-1-one **(1a)** under hydrolytic, reductive and alkylating reaction conditions are reported. There is evidence for the influence of the spiro structure on azetidinone ring reactivity, which is also affected by the presence of the *N*-phenylsulfonyl group.

Introduction

The importance of β-lactams as antibiotics and useful synthons for the synthesis of natural products is well established.[1-3] In previous papers, we have reported the general[4,5] and stereoselective[6] synthesis of new *N*-phenylsulfonyl substituted spiro-β-lactams, which were obtained from the reaction between *N*-(phenylmethylene)benzenesulfonamide and the ketene valence tautomer of the bicyclic mesoionic compounds derived from cyclic *N*-acyl-α-amino acids in the presence of a dehydrating agent such as acetic anhydride.[5]

In all cases, the *trans*-spiro-β-lactam **(1)** was obtained as the predominant diastereoisomer. In addition to the β-lactams **(1**,**2)**, the 1,3-dipolar cycloaddition products **(3)** were obtained with yields depending on the nature of the X and R groups and the experimental conditions[4,5] (Scheme 1).

The presence of the phenylsulfonyl group increases the reactivity of the imine towards the 1,3-dipolar cycloaddition reaction, thus allowing the formation of the condensed imidazole derivatives **(3)**.[5] It also influences the thermal behavior of the spiro-β-lactams **(1**,**2)**[4] which, when heated to 100 °C or more, are transformed into the corresponding imidazo-condensed products **(3)**.

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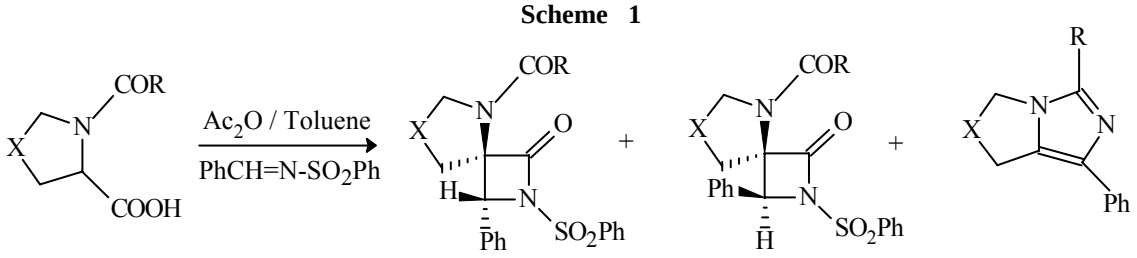
The electron-withdrawing character of the phenylsulfonyl group favors the nucleophilic attack of the *N*-acyl oxygen on the β-lactam carbonyl group, with the breaking of the N-CO bond and the formation of a tricyclic intermediary. The observed results can be explained by the possibility that the intermediary loses carbon dioxide and benzenesulfinic acid, leading to the aromatic product **(3)**.

Scheme 1



(1) **(2)** **(3)**

X = S, O, CH_2, $(CH_2)_2$ R = Me, Ph

Although various examples of β-lactams with a spiro structure deriving from penicillins or cephalosporins have been reported,[7] only a few simple spiro-β-lactams are known.[8-15] To the best of our knowledge, no systematic study of the reactivity of spiro-β-lactams has been carried out even though a large number of β-lactam reactions have been reported in the literature. Continuing our interest in the field of spiro-β-lactams, we planned a study of their reactivity towards some classes of reagents in order to investigate: a) the influence of the spiro structure on the reactivity of the azetidinone ring; and b) the possibility of obtaining monocyclic β-lactams functionalized with acylamino and methyl or mercaptomethyl groups.

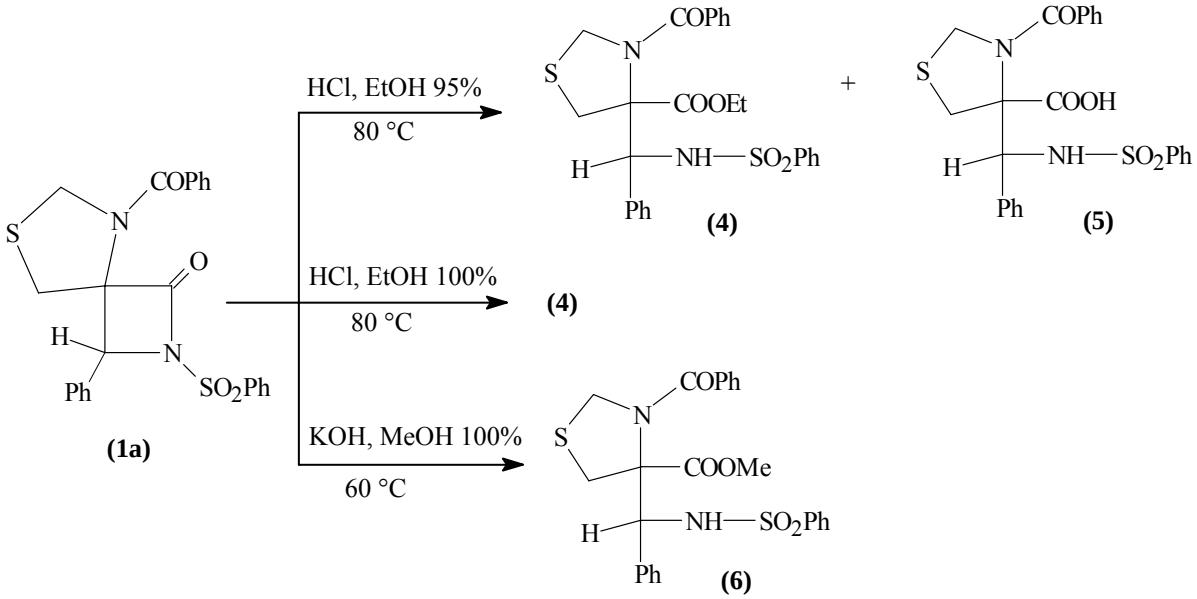
Results and discussion

There were two main reasons for selecting (±)-*trans*-5-benzoyl-3-phenyl-2-phenylsulfonyl-7-thia-2,5-diazaspiro[3.4]octan-1-one **(1a)** (X=S, R=Ph) as the model substrate for our studies: its good yield and the possibility of opening the thiazolidine ring offered by the presence of the sulfur atom.

The studied reactions were acid or basic hydrolysis, hydrogenolysis, desulfurization with Raney nickel, alkylation on the sulfide moiety, and the detachment of the phenylsulfonyl group to obtain *N*-unsubstituted β-lactam.

With 10% hydrochloric acid in tetrahydrofuran or dioxane as co-solvent, the substrate **(1a)** reacted to afford a complex mixture of non-separable products when heated to 60°C. The presence of water made this substrate extremely unstable: when **1a** was treated with gaseous hydrochloric acid in 95% ethyl alcohol, the two products **(4)** and **(5)** were isolated but with low yield; when gaseous hydrochloric acid in dry ethyl alcohol was used, only product **(4)** was obtained in 88% yield (Scheme 2). The structures of products **(4)** and **(5)**, were assigned on the basis of analytical and spectroscopic data.

Scheme 2



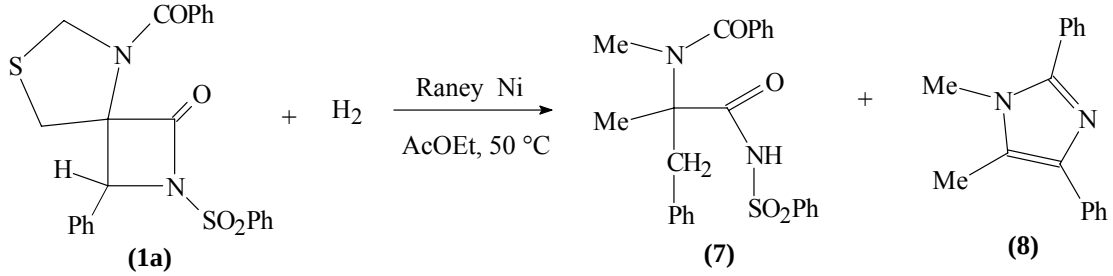
Only the azetidinone amidic bond was broken probably because the presence of the phenylsulfonyl group makes this bond weaker.

Interestingly, compound **(4)** is simultaneously an α– and β–amino acid derivatives. It is also worth noting that, although it could be the result of the alkylation of the enolate of the ethyl *N*-benzoyl-4-thiazolidinecarboxylate with *N*-(phenylmethylene)benzenesulfonamide, the reaction between the two products with LDA in THF at –78 °C was completely unsuccessful.[5]

The reaction of **1a** with potassium hydroxide was also affected by the water content: if anhydrous methanol was used, the methyl ester **(6)** was obtained in 72% yield (Scheme 2).

In the catalytic hydrogenation of **1a**, the nature of the catalyst was critical. No reaction took place in various solvents (AcOH, AcOEt, EtOH) when 10% Pd/C was used at temperatures ranging from 25 to 60 °C but, when Raney nickel was used as the hydrogenation catalyst, the reaction carried out in ethyl acetate at 50 °C and under atmospheric pressure led to a mixture of the two products **(7)** and **(8)** in the same yield (42%) (Scheme 3).

Scheme 3



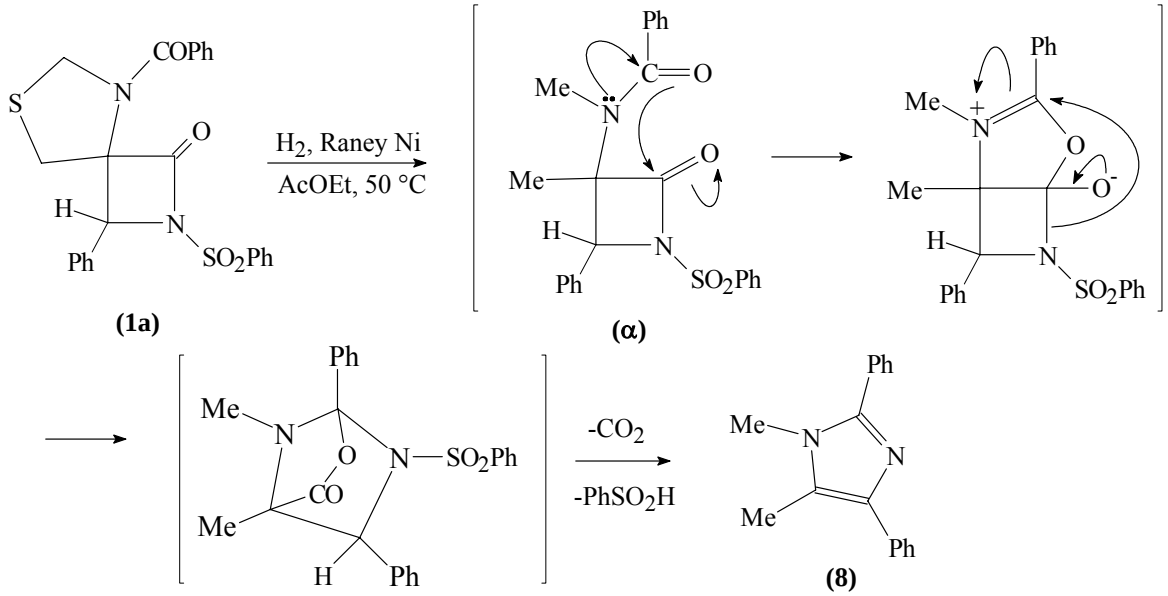
The structure of compound **(7)** is due to the expected hydrogenolysis of the β-lactam C4-N bond and thiazolidine ring desulfurization. It is an *N*-phenylsulfonylamide of an α,*N*-disubstituted phenylalanine, and thus confirms the usefulness of β-lactam systems as precursors of amino acids.

We have previously obtained imidazole **(8)**[16] from the 1,3-dipolar cycloaddition reaction of the *N*-(phenylmethylene)benzenesulfonamide with the mesoionic 3,4-dimethyl-2-phenyl-1,3-oxazolium-5-olate. In the present case, its formation (Scheme 4) could be explained as the desulfurization of the starting thiazolidine **(1a)** to the intermediary monocyclic β-lactam **(α)**, followed by a thermal transformation similar to that observed in the transformation of **1,2** into **3** at 100-120 °C.[4,5]

As this temperature is necessary to accomplish this thermal transformation, we can exclude the possibility that **1a** first changes into the corresponding bicyclic imidazole **(3)**, which then desulfurizes to **8**.

Moreover, since the reduced product **(7)** is not able to transform into the imidazole **(8)**, **7** and **8** are formed *via* two distinct pathways.

Scheme 4



(1a) (α) (8)

With the aim of obtaining only the product derived from thiazolidine ring desulfurization **(α)**, we treated **1a** with Raney nickel and without hydrogen, under various experimental conditions. All attempts to isolate the monocyclic β-lactam **(α)** were unsuccessful. In acetic acid or ethyl alcohol at 80 °C, complex mixtures of products were obtained including small amounts of **7** and **8**. In methyl alcohol, which better solubilizes the substrate, only **8** was obtained in quantitative yield at 60 °C.

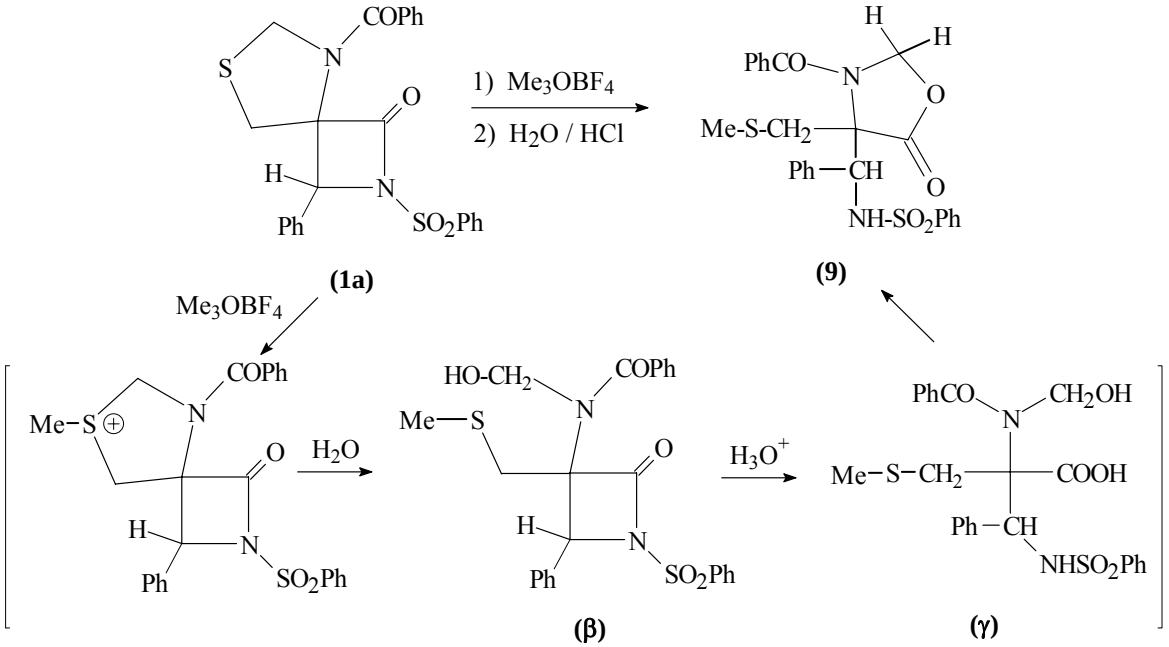
The reaction temperature was further reduced using acetone as solvent, which completely solubilizes **1a** at room temperature and makes the desulfurization reaction milder, thus reducing the β-lactam ring cleavage.[17] However compound **(1a)** was recovered unchanged after 74 h at 40 °C and 80% of **8** was obtained after 100 h at 60 °C: the transformation of the intermediary monocyclic β-lactam **(α)** into **8** might therefore be much faster than its formation from **1a**.

We then tried opening the thiazolidine ring using the sulfur functionality. The idea was to alkylate the sulfur atom in the presence of a base in order to obtain a sulfonium salt which, after the nucleophilic attack of water on the C2 of the thiazolidine ring and the loss of formaldehyde, would give a β-lactam

functionalized with an alkylthiomethyl and a benzoylamino group in position 3 of the ring. We used benzyl bromide as the alkylating agent and various experimental conditions [changing the solvent (THF, THF/H_2O, 2-butanone, DMF), base (K_2CO_3, TEA), and temperature (from 25 to 80°C)], but all attempts were unsuccessful.

With the more reactive alkylating agent trimethyloxonium tetrafluoroborate and aqueous hydrochloric acid, the substrate **(1a)** reacted giving the *N*-benzoylazalactone **(9)**. As shown in Scheme 5, it might be derived from *S*-methylation followed by the nucleophilic attack of water in order to give the intermediary **(**β**)**, which then more easily undergoes hydrolysis to form γ and finally cyclizes to give **9**.

Scheme 5



The observed results suggest that the reactivity of **1a** is influenced by the presence of both the spiro structure and the *N*-phenylsulfonyl group. The presence of the spiro-condensated thiazolidine ring sterically encumbers the β-lactam ring. When the thiazolidine ring is opened, the β-lactam carbonyl group is more easily attacked by the *N*-acyl oxygen (see Scheme 4) or the water (see Scheme 5). These nucleophilic attacks are promoted by the presence of the electron-withdrawing *N*-phenylsulfonyl group.

With the aim of reducing the reactivity of the monocyclic β-lactams **(**α**)** and **(**β**)**, we finally tried to eliminate the phenylsulfonyl group using Bu_3SnH[18] in refluxing toluene, *tert*-BuOK[19] in THF at -10 to 25 °C, or sodium naphthalide[20] in DME at –78 °C but, in all cases, only very complex mixtures were obtained.

In conclusion, the reactivity of our spiro-β-lactam seems to be influenced by the presence of the phenylsulfonyl group and the spiro structure; the presence of the sulfur atom in the thiazolidine ring is not helpful for opening the ring if the nitrogen is substituted with a phenylsulfonyl group.

EXPERIMENTAL

General Methods. Melting points were measured using a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded by means of a Bruker AC 300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS; all coupling constants (J) are in Hertz. IR spectroscopy was performed using a Perkin-Elmer 1725X FT-IR spectrophotometer. Compound **(1a)**[4] was prepared according to the reported method.

Reaction of 1a with HCl in EtOH 95%. To a suspension of **1a** (94 mg, 0.2 mmol) in 10 mL of 95% ethyl alcohol, 0.2 mL (0.4 mmol) of a 2 M solution of gaseous HCl in 95% ethyl alcohol was added. The mixture was heated at reflux for 24 h. After evaporation of the solvent the residue was recrystallized from isopropyl alcohol giving 4-(benzenesulfonylaminophenylmethyl)-3-benzoylthiazolidine-4-carboxylic acid **(5)**: 9 mg (9%); mp 217-220 °C; ^{1}H-NMR (DMSO-d_6): δ 3.3, 3.8 (two d, AB syst., J=13.5, 2H, S-CH_2-C); 3.5, 4.2 (two d, AB syst., J=9.7, 2H, S-CH_2-N); 5.5 (d, J=8.5, 1H, CH); 6.9-7.6 (m, 15H, H_{arom}); 8.1 (br s, 1H, NH exchangeable); 12.7 (s, 1H, COOH exchangeable); IR (nujol): cm^{-1} 1632 (COPh); 1708 (COOH); 3265 (NH); Anal. Calcd for $C_{24}H_{22}N_2O_5S_2$: C, 59.75; H, 4.56; N, 5.81. Found: C, 59.85; H, 4.49; N, 5.70. The column chromatography of the crystallization solvent (silica gel, toluene/ethyl acetate : 90/10) afforded 4-(benzenesulfonylaminophenylmethyl)-3-benzoylthiazolidine-4-carboxylic acid ethyl ester **(4)**: 16 mg (16%); mp 190-192 °C (EtOH); ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, J=7.1, 3H, CH_3); 3.3, 3.7 (two d, AB syst., J=12.7, 2H, S-CH_2-C); 3.9, 4.4 (two d, AB syst., J=9.4, 2H, S-CH_2-N); 4.25 (q, J=7.1, 2H, $COOCH_2$); 5.2 (d, J=4.6, 1H, CH); 6.55 (d, J=4.6, 1H, NH exchangeable); 7.15-7.7 (m, 15H, H_{arom}); ^{13}C NMR (DMSO-d_6): δ 15 (q, CH_3); 37 (t, S-$\underline{C}H_2$-C); 54 (t, S-CH_2-N); 59 (d, CH); 61 (t, O-$\underline{C}H_2$-C); 73 (s, C_{spir}); 125-142 (C_{arom}); 168,170 (2s, 2CO); IR (nujol): cm^{-1} 1632 (COPh); 1736 (COOEt); 3274 (NH); Anal. Calcd for $C_{26}H_{26}N_2O_5S_2$: C, 61.18; H, 5.10; N, 5.49. Found: C, 61.02; H, 4.95; N, 5.35.

Reaction of 1a with HCl in EtOH 100%. A mixture of **1a** (230 mg, 0.5 mmol) in dry ethyl alcohol (50 mL) and 0.17 mL (0.51 mmol) of a 3 M solution of gaseous HCl in the same solvent was heated at reflux for 48 h. After evaporation of the solvent product **(4)** was obtained in 88% yield.

Reaction of 1a with KOH in MeOH 100%. A mixture of **1a** (200 mg, 0.43 mmol) in 30 mL of MeOH and 32 mL (1.28 mmol) of a 0.04 M solution of KOH in the same solvent was heated at reflux for 1 h. After evaporation of the solvent the residue was taken up in water obtaining 4-(benzenesulfonylamino-phenylmethyl)-3-benzoylthiazolidine-4-carboxylic acid methyl ester **(6)**: 154 mg (72%); mp 183-184 °C (MeOH); ^{1}H-NMR ($CDCl_3$): δ 3.25, 3.6 (two d, AB syst., J=12.7, 2H, S-CH_2-C); 3.7 (s, 3H, $COOCH_3$);

3.9, 4.3 (two d, AB syst., J=9.4, 2H, S-CH_2-N); 5.25 (d, J=4.5, 1H, CH); 6.5 (d, J=4.5, 1H, NH exchangeable); 7.0-7.7 (m, 15H, H_{arom}); ^{13}C NMR (DMSO-d_6): δ 38 (t, S-$\underline{C}H_2$-C); 52 (q, O-CH_3); 54 (t, S-CH_2-N); 61 (d, CH); 75 (s, C_{spir}); 125-145 (C_{arom}); 168,172 (2s, 2CO); IR (nujol): cm^{-1} 1630 (COPh); 1753 (COOMe); 3527 (NH); Anal. Calcd for $C_{25}H_{24}N_2O_5S_2$: C, 60.48; H, 4.84; N, 5.65. Found: C, 60.35; H, 4.52; N, 5.44.

Reaction of 1a with H_2 and Raney nickel. To a solution of **1a** (100 mg, 0.215 mmol) in AcOEt (25 mL), 100 mg of Raney nickel was added. The mixture was heated at 50 °C under hydrogen atmosphere for 10 h. After filtration of the catalyst and evaporation of the solvent the residue was purified by column chromatography (silica gel, toluene/ethyl acetate : 90/10 to 0/100) affording 1,5-dimethyl-2,4-diphenyl-imidazole **(8)** (22 mg (42%), (R_f=0.4, toluene/ethyl acetate : 75/25)) which was identified by reported[16] spectroscopic data, and *N*-(2-benzenesulfonylamino-1-benzyl-1-methyl-2-oxoethyl)-*N*-methylbenzamide **(7)**: 39 mg (42%); (R_f=0.1, toluene/ethyl acetate : 75/25); mp 206-208 °C (MeOH); ^{1}H-NMR (DMSO-d_6): δ 1.25 (s, 3H, CH_3-C); 2.25 (s, 3H, CH_3-N); 2.85, 3.85 (two d, AB syst., J=12.6, 2H, CH_2-Ph); 7.2-7.8 (m, 15H, H_{arom}). Anal. Calcd for $C_{24}H_{24}N_2O_4S_2$: C, 66.05; H, 5.50; N, 6.42. Found: C, 65.85; H, 5.10; N, 6.20.

Reaction of 1a with trimethyloxonium tetrafluoroborate. To a solution of **1a** (232 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (20 mL) 250 mg (1.7 mmol) of trimethyloxonium tetrafluoroborate was added. The mixture was stirred, under nitrogen, at rt for 40 h. The colorless insoluble product formed was filtered and treated with 10% aqueous HCl (20 mL) for 24 h. The reaction mixture was extracted with CH_2Cl_2 (3x10 mL), the organic phase was separated and dried over Na_2SO_4, the solvent evaporated *in vacuo* and the residue was recrystallized from ethyl alcohol to afford *N*-[(3-benzoyl-4-methylsulfanylmethyl-5-oxo-oxazolidin-4-yl)phenylmethyl]benzenesulfonamide **(9)**: 154 mg (62%); mp 213-215 °C (EtOH); ^{1}H-NMR ($CDCl_3$): δ 1.5 (s, 1H, NH exchangeable); 2.15 (s, 3H, CH_3-S); 2.85, 4.05 (two d, AB syst., J=14.1, 2H, S-$\underline{C}H_2$-C); 4.15, 4.90 (two d, AB syst., J=3.5, 2H, N-CH_2-O); 5.2 (d, J=9.8, 1H, CH); 6.95-7.65 (m, 15H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 17 (q, CH_3-S); 36.7 (t, S-$\underline{C}H_2$-C); 62.1 (d, CH); 72.5 (s, C_{spir}); 78.8 (t, N-CH_2-O); 125-140 (C_{arom}); 170,171.5 (2s, 2CO); IR (nujol) cm^{-1} 1642 (COPh); 1798 (lactone); 3229 (NH); Anal. Calcd for $C_{25}H_{24}N_2O_5S_2$: C, 60.48; H, 4.84; N, 5.65. Found: C, 60.39; H, 4.62; N, 5.55. MS: m/e 496.

ACKNOWLEDGEMENTS

The authors thank Dr. Elena La Porta for her helpful technical assistance.

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