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Stereoselective synthesis of *N*-phenylsulfonyl substituted spiro-β-lactams

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Abstract

A stereoselective synthesis of *N*-phenylsulfonyl substituted spiro-β-lactams obtained from the *N*-(phenylmethylene)benzenesulfonamide and the ketene valence tautomer of the bicyclic mesoionic compounds derived from 4-hydroxy substituted *N*-acyl-L-prolines in the presence of acetic anhydride as the dehydrating agent is presented. The reaction of (2*S*,4*R*)-4-acetyloxy or benzoyloxy-*N*-acyl-proline with the above imine afforded a mixture of two diastereoisomeric spiro-β-lactams with complete stereoselectivity for the spiro carbon.

1. Introduction

In previous communications, we have reported on the reactivity of cyclic *N*-acyl-α-aminoacids towards imines such as *N*-(phenylmethylene)aniline[1] and *N*-(phenylmethylene)benzenesulfonamide,[1,2] in the presence of a dehydrating agent such as *N*,*N*′-dicyclohexylcarbodiimide or acetic anhydride. The reaction of the *N*-acyl-α-aminoacids **1**–**4** with *N*-(phenylmethylene)benzenesulfonamide **5** in toluene solution at 80°C using 3 mols of acetic anhydride led to a mixture of diastereoisomeric *N*-phenylsulfonyl substituted spiro-β-lactams **6** and **7**, and/or bicyclic imidazole **8**, depending on the experimental conditions and the nature of the R and X groups[2] (Scheme 1).

The cyclodehydration of *N*-acyl-α-aminoacids **1**–**4** leads to the bicyclic mesoionic compound **9**, and this, or its ketene valence tautomer **10**, undergoes nucleophilic attack by the imine nitrogen onto the carbonyl carbon to give the zwitterionic intermediate **11** which, after ring closure, affords **6** and **7** (Scheme 2).

The phenyl group on the imine carbon can stabilize the positive charge so that the zwitterionic intermediate **11** can isomerize its double C=N bond to the *cis*-form, thus affording the thermodynamically

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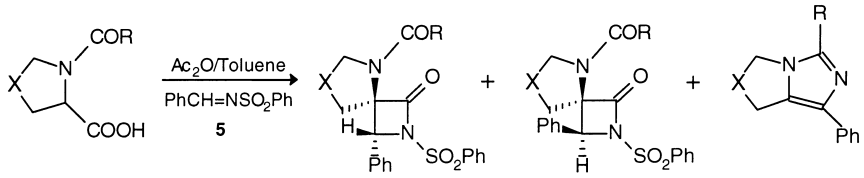
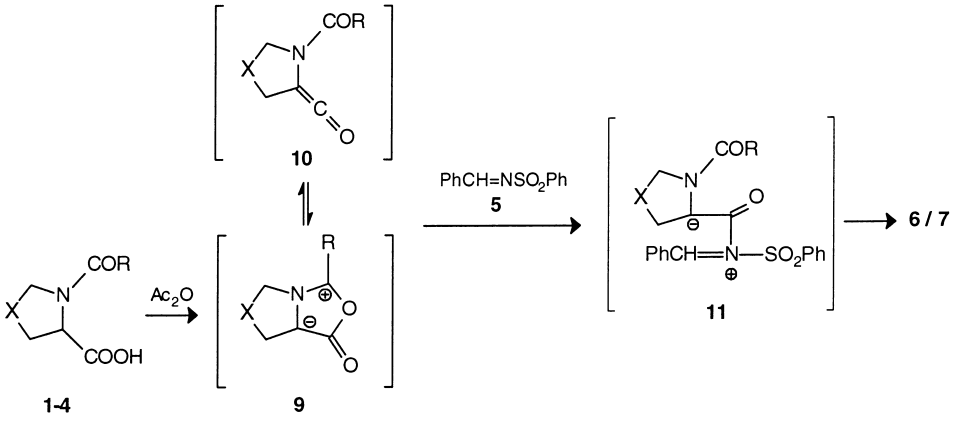


1-4 **6** **7** **8**

1 X = S R = Me,Ph ; **2** X = O R = Ph ; **3** X = CH_2 R = Me,Ph ; **4** X = $(CH_2)_2$ R = Me,Ph

Scheme 1.



Scheme 2.

more stable β-lactam **6**;[3] in fact the ratio of products **6**:**7** is always in favor of the β-lactam **6**, which has the *C*-phenyl and the *N*-acyl groups *trans* to each other (ratio **6**:**7**=3:1).

These results prompted us to plan a stereoselective synthesis of the spiro-β-lactams **6** and **7** starting from one of the two reagents (α-aminoacid or imine) containing a stereocenter in a suitable position. Given the growing interest in the stereoselective synthesis of β-lactam antibiotics or natural products having β-lactams as chiral starting materials, the asymmetric synthesis of β-lactams has received much attention over recent years,[4] in particular, the asymmetric Staudinger reaction (a [2+2] cycloaddition between a ketene and an imine) has been extensively and successfully studied.[5–7] However, to the best of our knowledge, no study regarding the stereoselective synthesis of β-lactams through the Staudinger reaction of imines and ketenes derived from bicyclic mesoionic compounds 1,3-oxazolium-5-one has ever been published.

2. Results and discussion

Asymmetric induction in the Staudinger reaction can be achieved by introducing a chiral auxiliary in the precursor of the ketene (normally an acid chloride) or in the *C*- or *N*-substituent of imine.[5–7] In our case, we could have placed it on the *C*- or *N*-substituent of the imine, on the α-aminoacid ring or on the *N*-acyl residue (Fig. 1).

It is worth noting that, although the α-aminoacids **1**–**4** contain a stereocenter in position 2, this is lost during the formation of the mesoionic compound and is therefore irrelevant to the stereochemical course of the reaction. We excluded possibilities (B) and (D) because the stereocenter would have been too far from the newly forming C_3–C_4 bond in the zwitterionic intermediate; between (A) and (C), we

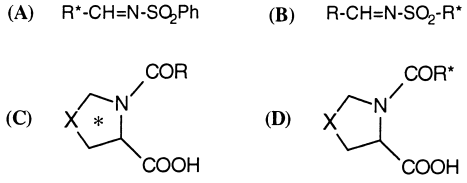


Figure 1.

chose the latter on the basis of synthetic considerations and the commercial availability of the reagent precursors. *N*-Benzoyl-L-proline was chosen as the cyclic α-aminoacid on the basis of our previous results.[1,2] Position 3 of the ring proved to be the most promising as it is nearest to the reaction centers of the intermediate, but the commercial availability of the inexpensive (2*S*,4*R*)-4-hydroxy-proline initially prompted us to evaluate the effect of the stereocenter in position 4 on the stereochemical course of the reaction. The presence of an acidic hydrogen (such as that of a hydroxyl group) might interfere with mesoionic formation, and so we decided to acylate the hydroxyl group and also evaluate the influence of the acylating group size. Therefore we studied the stereochemical course of the reactions between the imine **5** and the prolines **12** and **13** shown in Fig. 2.

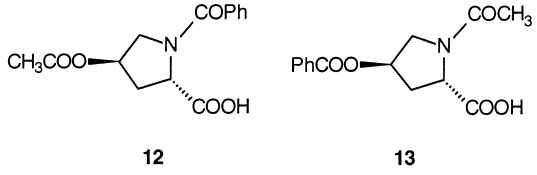
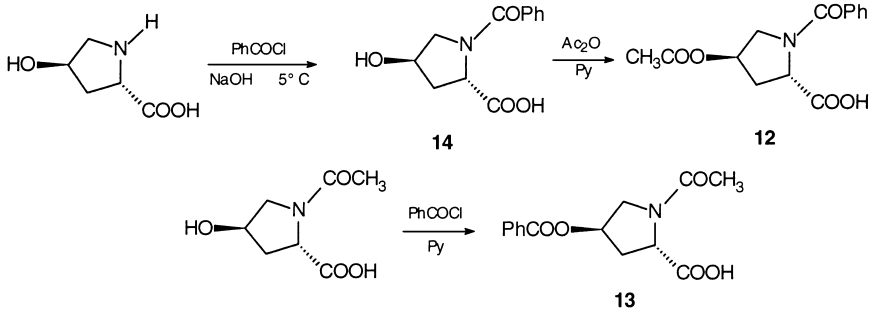


Figure 2.

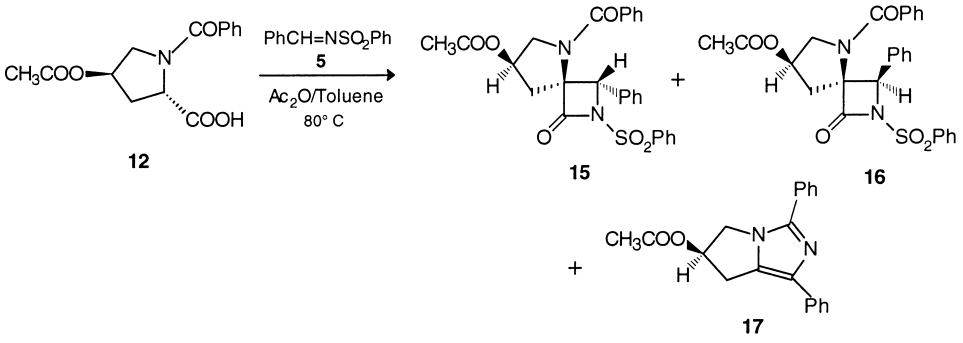
Product **12** was previously unknown. As shown in Scheme 3, the best experimental conditions under which to introduce the benzoyl on the N- and acetyl groups on the O-atoms of the commercial (2*S*,4*R*)-4-hydroxy-proline were: (1) benzoyl chloride and sodium hydroxide at 5°C, and (2) acetic anhydride in pyridine at room temperature. In this way the (2*S*,4*R*)-4-acetyloxy-*N*-benzoyl-proline **12** was obtained with a total yield of 81%. Similarly, the commercially available *N*-acetyl-4-hydroxy-L-proline was benzoylated with benzoyl chloride in pyridine and afforded the (2*S*,4*R*)-*N*-acetyl-4-benzoyloxy-proline **13** with a yield of 75% (Scheme 3).



Scheme 3.

The reactions of **12** and **13** with imine **5** were performed in toluene solution at 80°C using 3 mols of acetic anhydride as the dehydrating agent. The crude reaction mixtures were analyzed by means of ^{1}H NMR in order to identify all the obtained stereoisomers. The product mixtures were separated by means of column chromatography and further purified by crystallization.

The reaction between **12** and **5** gave a mixture of three products (Scheme 4), similar to those observed in the reaction of *N*-benzoyl-L-proline and **5**.[2]

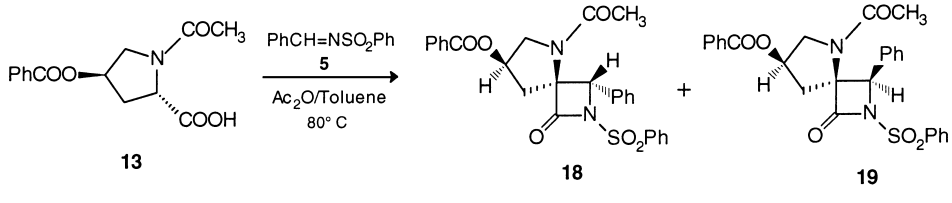


Scheme 4.

Spiro-β-lactams **15** and **16** were obtained with a total yield of 61% and a ratio of 60:40, respectively. The bicyclic imidazole **17** (deriving from the 1,3-dipolar cycloaddition between **5** and the mesoionic intermediate **9**) was obtained with a yield of 20%. The spiro-β-lactams are diastereoisomers: their ^{1}H NMR spectra show some differences in the chemical shifts (from 0.05 to 0.5 ppm) and, sometimes, in the multiplicity of the main signals. Unlike previous examples,[1,2] their ^{1}H NMR spectra did not allow them to be assigned the *cis*- or *trans*-relative configuration because the difference between the chemical shift values (5.55 and 5.60 δ) of the two benzylic protons was too small to determine what hydrogen is in the deshielding cone of the *N*-benzoyl carbonyl group. Consequently, a single crystal X-ray analysis was performed to assign the absolute configuration to the new stereocenters C_3 and C_4.[8] The relative *trans*-configuration was assigned to the more abundant product and *cis* to the other, with the absolute configurations of, respectively, 3*S*,4*S*,7*R* and 3*R*,4*S*,7*R*. The two spiro-β-lactams thus had the same absolute configuration *S* to the spiranic carbon C_4 and differed in that of the benzylic carbon C_3.

The formation of the same configuration for C_4 is the result of the stereochemical induction of the stereocenter on the proline ring during the course of the reaction. This induction takes place at the level of the ring closure of the zwitterionic intermediate to β-lactam: the presence of the acetyloxy group favors this closure from the less hindered opposite side of the proline ring and leads to the *S*-configuration of C_4. Such a high degree of induction was not observed for the stereocenter C_3: the formation of both diastereoisomers **15** and **16** with a ratio of 1.5:1 derives from the *trans–cis* isomerization of the C=N double bond of the imine in the zwitterionic intermediate;[3] the presence of the stereocenter in the proline ring seems to be irrelevant to this isomerization. On the contrary, the energy difference between the two products **15** and **16** seems to decrease as their ratio tends to one.

We subsequently verified the effect on stereocenter formation of a more bulky acyl group on the hydroxyl of the 4-hydroxy-L-proline: product **13** was reacted with imine **5** in the presence of acetic anhydride at 80°C (Scheme 5).



Scheme 5.

This reaction afforded a mixture of spiro-β-lactams **18** and **19**, which were obtained with a total yield of 65% and a ratio of 63:37. As in the case of *N*-acetyl-L-proline,[2] no 1,3-dipolar cycloaddition product was formed. The difference between the chemical shift values of the benzylic protons of β-lactams **18** and

19 (5.51 and 5.58 δ) was too small to assign their relative configuration. Assuming that the reaction was totally stereoselective for the spiranic carbon C_4, and therefore obtained with the same *S*-configuration in both products, we analyzed the more abundant β-lactam by means of homonuclear NOE difference spectra in order to evaluate the spatial proximity between the *ortho*-protons of C_3-phenyl and C_8-protons (β-lactam **18**) or between the C_3-H and C_8-protons (β-lactam **19**).

The NOE experiment allowed structure **18** to be assigned to the predominant spiro-β-lactam and structure **19** to the other. The obtained products therefore have the same 3*S*,4*S*,7*R* and 3*R*,4*S*,7*R* absolute configurations even with a more bulky acyl group on the stereocenter of the proline ring. It is worth noting that the size of the acyl group does not have any appreciable effect on the stereoselectivity of the benzylic carbon C_3: the two β-lactams were obtained with almost the same ratio regardless of whether the acetyl or benzoyl group was used.

3. Conclusion

The present paper describes the first example of a stereoselective synthesis of spiro-β-lactams by means of a reaction between imines and chiral ketenes deriving from bicyclic mesoionic compounds. The presence of a stereocenter in position 4 of the cyclic aminoacid is sufficient to ensure complete stereoselectivity on the spiranic carbon C_4, but is almost irrelevant to C_3. The possibility of obtaining this new class of enantiomerically pure diastereoisomeric spiro-β-lactams, with the desired absolute configuration of C_4 and in good yields, makes this reaction worthy of the further studies that are currently ongoing.

4. Experimental

Melting points were determined using a Büchi apparatus and are uncorrected. All the ^{1}H NMR spectra were recorded in $CDCl_3$ solution 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. Optical rotations were measured using a Perkin–Elmer 241 spectropolarimeter. The X-ray crystallographic analyzes[8] were carried out on single crystals obtained by precipitation from ethyl acetate **15** and acetone **16**. Compounds **5**[9] and **14** were prepared according to the method of Jennings[10] and Portoghese,[11] respectively.

*4.1. (2*S*,4*R*)-4-Acetyloxy*-N*-benzoyl-proline **12***

A mixture of (2*S*,4*R*)-*N*-benzoyl-4-hydroxy-proline **14** (1 g, 4.25 mmol), acetic anhydride (3 ml) and pyridine (0.04 ml, 0.487 mmol) was stirred at room temperature for 24 h. After evaporation of the solvent, the residue was taken up in dichloromethane and the solution was washed with water. The organic phase was dried (Na_2SO_4) and the solvent evaporated off. The residue was purified by column chromatography over silica gel (EtOH) affording **12** as colorless solid (1.06 g, 90% yield); mp 172–173°C; $[\alpha]_D^{20}$ −41.1 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (mixture of two conformers) δ 1.98, 2.05 (3H, s, CH_3), 2.48 (2H, m, H_3), 3.63 (1H, AB syst. J=10.4, H_5), 3.85 (1H, AB syst. J=10.4 and 2.2, H_5), 4.85, 4.91 (1H, t, H_2), 5.2, 5.3 (1H, m, H_4), 7.3–7.6 (5H, m, Ar), 7.8 (1H, broad, COOH). Anal. calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.42; N, 5.05. Found: C, 60.38; H, 5.12; N, 5.00.

4.2. (2S,4R)-N-Acetyl-4-benzoyloxy-proline **13**

A mixture of *N*-acetyl-4-hydroxy-L-proline (0.5 g, 2.89 mmol), pyridine (2 ml) and benzoyl chloride (0.37 ml, 3.17 mmol) was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was taken up in dichloromethane and the solution was washed with water. The organic phase was dried (Na_2SO_4) and the solvent evaporated off. Recrystallization from H_2O:EtOH gave **13** as a colorless solid (0.6 g, 75% yield); mp 180–181°C (lit.[12] 185–186°C); $[\alpha]_D^{20}$ −28.8 (*c* 1, H_2O); ^{1}H NMR (D_2O) (mixture of two conformers) δ 2.08, 2.13 (3H, s, CH_3), 2.30, 2.40 (1H, m, H_3), 2.67, 2.80 (1H, m, H_3), 3.75 (1H, AB syst. J=15.7 and 3.1, H_5), 4.03 (1H, AB syst. J=15.7, H_5), 4.49, 4.60 (1H, t, H_2), 5.58, 5.65 (1H, m, H_4), 7.55 (2H, t, Ar), 7.70 (1H, t, Ar), 8.05 (2H, d, Ar).

4.3. General procedure for reactions of **12** and **13** with **5**

Acetic anhydride (30 mmol) was added dropwise, under nitrogen, to a stirred solution of **12** and **13** (10 mmol) in toluene (20 ml). The mixture was heated at 80°C for 1 h, and then a solution of **5** (10 mmol) in toluene (10 ml) was added dropwise and the heating continued for 24–30 h. After evaporation of the solvent, the residue was taken up in dichloromethane (50 ml) and the solution was washed with 10% sodium bicarbonate and water. The organic phase was dried (Na_2SO_4) and the solvent evaporated off. The crude mixture was separated by means of column chromatography (silica gel, toluene:ethyl acetate, 90:10). The products were recrystallized and identified by means of analytical and spectroscopic data.

4.4. (3S,4S,7R)-7-Acetyloxy-5-benzoyl-3-phenyl-2-(phenylsulfonyl)-2,5-diazaspiro[3.4]octan-1-one **15**

Mp 165–167°C (*i*PrOH); $[\alpha]_D^{20}$ −51.46 (*c* 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.65 (1H, AB syst. J=15.8 and 6.3, H_8), 2.02 (3H, s, CH_3), 2.25 (1H, AB syst. J=15.8 and 2.1, H_8), 3.58 (1H, AB syst. J=13.2, H_6), 3.71 (1H, AB syst. J=13.2 and 5.3, H_6), 4.87 (1H, m, H_7), 5.55 (1H, s, H_3), 7.1–7.7 (13H, m, Ar), 8.05 (2H, d, Ar). Anal. calcd for $C_{27}H_{24}N_2O_6S$: C, 64.28; H, 4.76; N, 5.55. Found: C, 63.96; H, 4.55; N, 5.25.

4.5. (3R,4S,7R)-7-Acetyloxy-5-benzoyl-3-phenyl-2-(phenylsulfonyl)-2,5-diazaspiro[3.4]octan-1-one **16**

Mp 186–187°C (*i*PrOH); $[\alpha]_D^{20}$ −4.67 (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.72 (3H, s, CH_3), 2.07 (1H, AB syst. J=15.8 and 5.2, H_8), 2.4 (1H, AB syst. J=15.8 and 7.3, H_8), 3.5 (1H, AB syst. J=14.2 and 4.2, H_6), 3.78 (1H, AB syst. J=14.2 and 6.8, H_6), 5.03 (1H, m, H_7), 5.60 (1H, s, H_3), 7.3–7.7 (13H, m, Ar), 7.98 (2H, d, Ar). Anal. calcd for $C_{27}H_{24}N_2O_6S$: C, 64.28; H, 4.76; N, 5.55. Found: C, 64.10; H, 4.65; N, 5.35.

4.6. (6R)-6-Acetyloxy-1,3-diphenyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole **17**

Mp 183–184°C (*i*PrOH); $[\alpha]_D^{20}$ +9.38 (*c* 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.1 (3H, s, CH_3), 3.22 (1H, AB syst. J=11.0, H_7), 3.54 (1H, AB syst. J=11.0 and 5.9, H_7), 4.23 (1H, AB syst. J=9.2, H_5), 4.58 (1H, AB syst. J=9.2 and 3.7, H_5), 5.9 (1H, m, H_6), 7.2–7.6 (6H, m, Ar), 7.78 (2H, d, Ar), 7.87 (2H, d, Ar). Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.66; N, 8.81. Found: C, 75.21; H, 5.55; N, 8.78.

*4.7. (3*S*,4*S*,7*R*)-5-Acetyl-7-benzoyloxy-3-phenyl-2-(phenylsulfonyl)-2,5-diazaspiro[3.4]octan-1-one* ***18***

Mp 164–165°C (*i*PrOH); $[\alpha]_D^{20}$ +2.09 (*c* 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.1 (3H, s, CH_3), 2.49 (2H, d, J=3.57, H_8), 3.72 (1H, AB syst. J=11.73, H_6), 3.92 (1H, AB syst. J=11.73 and 6.1, H_6), 5.26 (1H, m, H_7), 5.51 (1H, s, H_3), 7.0–7.7 (13H, m, Ar), 7.98 (2H, d, Ar). Anal. calcd for $C_{27}H_{24}N_2O_6S$: C, 64.28; H, 4.76; N, 5.55. Found: C, 64.08; H, 4.73, N, 5.48.

*4.8. (3*R*,4*S*,7*R*)-5-Acetyl-7-benzoyloxy-3-phenyl-2-(phenylsulfonyl)-2,5-diazaspiro[3.4]octan-1-one* ***19***

Mp 205–207°C (*i*PrOH); $[\alpha]_D^{20}$ +88.98 (*c* .59, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.84 (1H, AB syst. J=14.73 and 5.13, H_8), 2.04 (3H, s, CH_3), 2.34 (1H, AB syst. J=14.73 and 3.2, H_8), 3.69 (1H, AB syst. J=11.5 and 1.87, H_6), 3.79 (1H, AB syst. J=11.5 and 4.5, H_6), 5.18 (1H, m, H_7), 5.58 (1H, s, H_3), 7.3–7.7 (11H, m, Ar), 8.08 (2H, d, Ar), 8.13 (2H, d, Ar). Anal. calcd for $C_{27}H_{24}N_2O_6S$: C, 64.28; H, 4.76; N, 5.55. Found: C, 64.15; H, 4.68, N, 5.50.

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