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Synthesis and Steric Structure of 1, 5-Benzothiazepine-Phenyl-β-Lactams

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Abstract: 1, 5-Benzothiazepines **1** react with phenylacetyl chloride to give the title compounds. The structures of these new compounds were confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR and MS spectroscopy, and their configuration (the mutual positions of the substituents relative to the β-lactam ring) and conformation of the compounds were determined by X-ray crystal analysis.

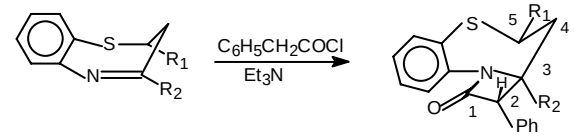
Keywords: 1, 5-benzothiazepine, β-lactam, stereospecific reaction.

1, 5-Benzothiazepines **1** possess potential biological activitives.[1-3] Cycloaddition reactions of the compounds with acid halides permit the construction of new cyclic system: β-lactam ring. The β-lactam moiety may modify the biological activity of 1, 5-benzothiazepines or may bring new effects. Therefore, the synthesis of the title compounds can be beneficial for pharmaceutical research.

We have previously studied the stereostructures of 1, 5-benzothiazepine-α-chloro-β-lactams and found that 2-chloro and 3-phenyl group are cis to the four-membered ring . In order to further investigate steric structure of this kind of compounds and elucidate the influence of the size of substituents at C-2 on the configuration of β-lactam moeity (Steric positon of the substituents at C-2 and C-3), our study was carried out with phenylacetyl chloride and 1, 5-benzothiazepines (**Scheme1**).

The synthesis of **2** is shown in **Scheme 1**: reactions of benzothiazepines (0.01 mol) with phenylacetyl chloride (0.01 mol) in the presence of Et_3N (0.01 mol) in refluxing benzene (30 ml) for 6 hr gave 1, 5-benzothiazepine-β-lactams. The triethylamine salt was removed by filtration, the benzene solution was evaporated and the residue was purified by column chromatography (ethyl acetate/petroleum ether=1/8) to produce **2**. The molecular structures of compounds **2** were confirmed by elemental analysis, MS, ^{1}H NMR and ^{13}C NMR spectra (**Table 1** and **2**).

Scheme 1.



1 2

a; R_1=C_6H_5, R_2=C_6H_5 b: R_1=p-$OCH_3C_6H_4$, R_2=C_6H_5
c: R_1=o-ClC_6H_5, R_2=C_6H_5 d: R_1=p-ClC_6H_5, R_2=C_6H_5

Table 1. The Elemental Analysis and Major MS of 2a-d

Compound	Analysis (calculated)%			MS
	C	H	N	
2a	80.27 (80.37)	5.30 (5.31)	3.01 (3.23)	433, 315, 211, 105
2b	77.60 (77.75)	5.16 (5.40)	3.02 (3.03)	463, 345, 211
2c	74.31 (74.44)	4.78 (4.71)	3.01 (2.99)	467, 349, 211, 108
2d	74.23 (74.44)	4.65 (4.71)	2.96 (2.99)	467, 349, 211, 108

Table 2. The Selected ^{13}C NMR and ^{1}H NMR Data on Compounds 2_{a-d}

Compound	^{13}C NMR					^{1}H NMR		
	C-1	C-2	C-3	C-4	C-5	H-2	Hax-4, Heq-4, H-5	OCH_3
2a	166.28	679.25	70.83	51.81	46.34	4.78 (s, 1H)	4.05-3.21 (m, 3H)	
2b	166.23	69.20	70.82	51.65	45.63	4.77 (s, 1H)	4.00-3.18 (m, 3H)	3.80 (s, 3H)
2c	166.26	69.21	70.81	51.72	45.52	4.78 (s, 1H)	4.00-3.32 (m, 3H)	
2d	166.23	69.23	70.82	51.72	45.56	4.78 (s, 1H)	3.98-3.57 (q, 2H)	
							3.33-3.27 (q, 1H)	

The ^{1}H NMR spectra of **2d** were obtained on a JNM-GX400 instrument, others on a FX-90Q instrument.

The cleavage patterns in mass spectrometry are common with the compounds, which are illustrated by **2d** shown in **Scheme 2**.

The m/z 467 peak is the molecular ion of **2d**, and the m/z 349 fragment is due to expulsing a neutral molecule (Ph=C=O) from the molecular ion. The base peak is at m/z 211, and there is a peak at m/z 108, corresponding to loss of PhCN. Parts of the ^{13}C NMR and ^{1}H NMR data on compounds 2a-d are shown in **Table 2**. Taking **2d** as an example, the resonances at 166.23, 69.23, 70.82, 51.72, 45.56ppm in the ^{13}C NMR. correspond to carbonyl carbon and four saturated carbons. Resonances at 125.8-140.4 ppm belong to benzene ring carbons. In the ^{1}H NMR spectrum of **2d**, signal of H-2 is at 4.78ppm, H-4 and H-5 give eight peaks.

The stereostructure of the compounds was determined by X-ray diffraction method[4]. A colourless crystal ($0.38\times0.42\times0.46$mm) of **2d** was chosen for the measurement. Diffraction data were obtained with an ENRAF-NONIUS CAD-4 four-circle diffractometer with graphite-monochromated MoKα radiation (λ =0.71073) using ω-2θ scan mode. A total of 3235 reflections were collected within the range of $2.0°\leqslant\theta\leqslant25°$, of which 1557 are observed reflections ($I\geqslant3\sigma(I)$). The structure was solved by direct method using SHELXS-86 program.

Scheme 2.

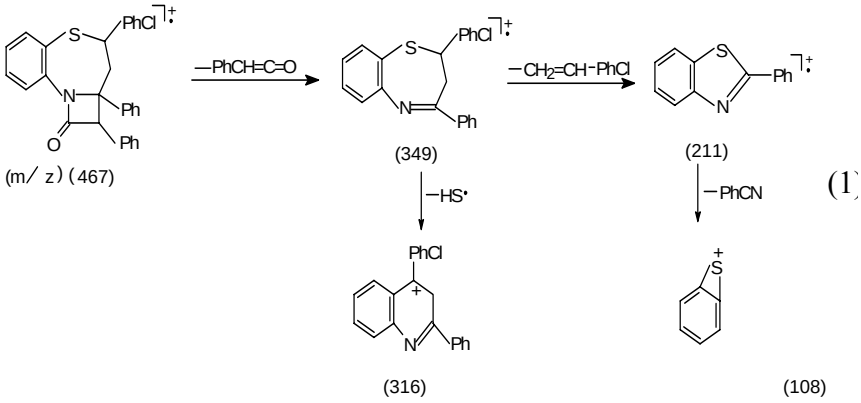
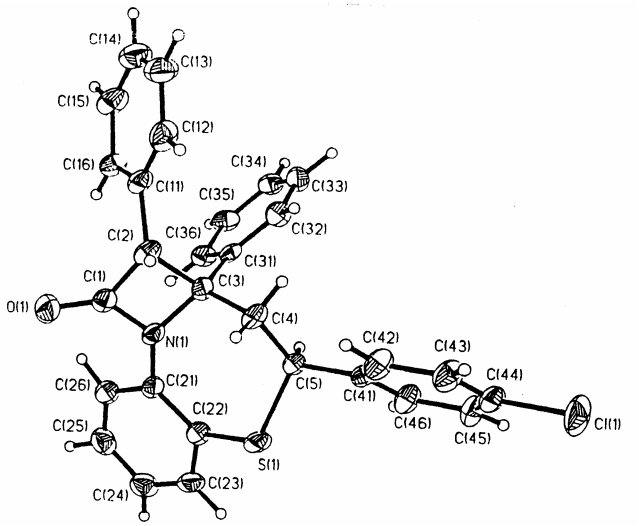


Figure 1. X-ray crystal structure of 2d



The X-ray analysis reveals that conformation and configuration of the title compounds are similar to those found in 1, 5-benzothiazepine-α-chloro-β-lactams. β-Lactam ring of **2d** is planar, conformation of seven-membered ring is also chair-like. As expected, the configuration of β-lactam moiety is the same as before, two vicinal phenyl groups attached to C-2 and C-3 are *cis* to the four-membered ring.The X-ray data also show that dihedral angle between the two phenyl rings is 42.6° . The two planes do not lie parallel to each other, indicating that the two phenyls on the same side are not very crowded, so they do not make the molecule distorted and unstable. All the β-lactam derivatives prepared in this work are stereohomogeneous according to spectroscopic evidence (**Table 1** and **2**), hence, the cyclizations to β-lactam are stereospecific.

References

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4. Crystallographic parameters have been deposited in the editorial office of CCL.

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