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Synthesis and Stereostructure of New β-Lactam Derivatives of 1,5-Benzothiazepines

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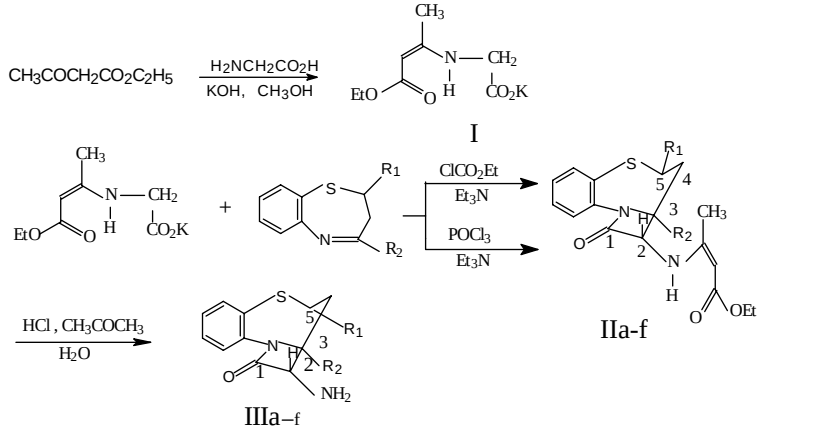
Abstract: Reaction of 1,5-benzothiazepine with N-protected glycine gives new α-amino-β-lactam derivatives of 1,5-benzothiazepine. The configuration and conformation of the products were confirmed by x-ray diffraction. The result further reveals that the reaction of 1,5-benzothiazepines with derivatives of carboxylic acid is stereospecific.

Keywords: 1,5-Benzothiazepine, β-lactam; stereospecific reaction.

Because of the importance of benzothiazepine derivatives, which exhibit versatile biological activities, the chemistry of benzothiazepine has aroused interest for a long time[1-4]. In our previous papers, we have reported the synthesis and elucidation of the stereostructure of two kinds of 1,5-benzothiazepine-β-lactams[5-6]. In order to elucidate the influence of the size of the substituent at C-2 on the configuration of β-lactam moiety and further study the stereochemistry of the cycloaddition reaction, we prepared a series of new β -lactam derivatives of 1,5-benzothiazepine and studied their steric structure.

Scheme 1



a. R_1=C_6H_5, R_2=C_6H_5 c. R_1=p-ClC_6H_4, R_2=C_6H_5 e. R_1=C_6H_5, R_2=p-$CH_3C_6H_4$
b. R_1=p-$CH_3OC_6H_4$, R_2=C_6H_5 d. R_1=o-ClC_6H_4, R_2=C_6H_5 f. R_1=C_6H_5, R_2=p-$CH_3CH_2C_6H_4$

Compound **I** reacted with N-protected glycine in the presence of ethyl chloroformate or phosphorous oxychloride and triethylamine. After the reaction, the products were purified by column chromatography to obtain Ⅱ. Hydrolysis of compounds Ⅱ in acidic solution obtain 1,5-benzothiazepine-α-β-lactams. The yields and simple physical constants are summarized in **Table 1**

Table 1 The yields and melting points of compounds **Ⅲa-f**

Compd.	Activating reagent	Yield (%)	Activating reagent	Yield (%)	M.P (℃)
Ⅲa	$ClCO_2C_2H_5$	32	$POCl_3$	30	103
Ⅲb	$ClCO_2C_2H_5$	37	$POCl_3$	32	87
Ⅲc	$ClCO_2C_2H_5$	25	$POCl_3$	26	100
Ⅲd	$ClCO_2C_2H_5$	23	$POCl_3$	23	95
Ⅲe	$ClCO_2C_2H_5$	27	$POCl_3$	20	93
Ⅲf	$ClCO_2C_2H_5$	25	$POCl_3$	26	78

All of the new compounds **Ⅲa-f** were identified by elemental analysis, MS, ^{1}HNMR and IR. The MS spectra and ^{1}HNMR spectra are very similar to those previously reported of other β-lactam derivatives of 1,5-benzothiazepine[5-6]. In the MS Spectra, there is fragment peak, corresponding to M^+- $H_2NCH=C=O$, and the base peak at *m/z* 211 for all the compounds. In the ^{1}HNMR spectra of the seven-membered heterocycle, three protons on C-4 and C-5 are observed as eight peaks.

We also studied the steric structure of the β-lactam derivatives by x-ray diffraction. The conformation of seven-membered ring is also chair-like. The β-lactam ring resulting from the reaction shown in **scheme 1** is planar, two groups attached to C-2 and C-3 are *cis* to the four-membered ring. From the above results we can conclude that the reaction of 1,5-benzothiazepines with derivatives of carboxylic acid is stereospecific .

References

1. L. Fodor, J. Szabo, *Tetrahedron*, **1981**, *37*(5), 963.
2. Aron Szollosy, George Kotovgch, *Can. J. Chem.*, **1988**, *66*, 279.
3. P. Sohar, L. Fodor, J. Szabo, *et al., Tetrahedron*, **1984**, *40*(21), 4387.
4. R. X. Lan, S. Jin, Z. M. Li, *Chinese Chemical Letters*, **1992**, *3*(1), 9.
5. Q. Y. Xing, Y. Li, C. Y. Du, *et al., Chinese Chemical Letters*, **1998**, *9*(10), 919.
6. Y. Li, J. D. Shi, Y. J. Zhang, *et al., Chinese Chemical Letters*, **1999,** *1*(1).

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