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Spectral and Mechanistic Studies of the Reactions of Substituted 1,5-Benzothiazepine with Dichloroacetyl Chloride and Triethylamine

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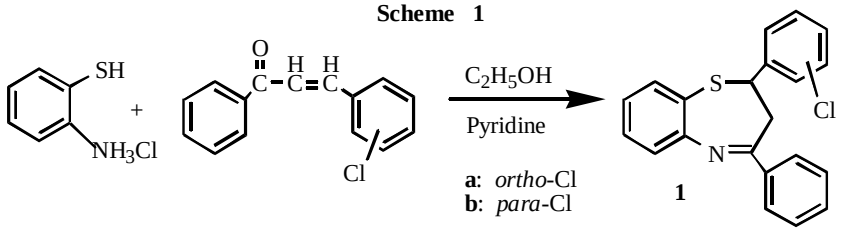
Abstract: A [2+2] cycloaddition adduct **2** and a novel ring-opening product **3** were obtained from the reactions of 2,3-benzothiazepines **1** with dichloroacetyl chloride and triethylamine. The relative ratios of **2** and **3** were affected by the addition order of reactants and reaction temperature. The structures were determined by spectral data and the reaction mechanisms for the formation of **2** and **3** were elucidated.

Keywords: Benzothiazepine, dichloroacetyl chloride, cycloaddition adduct, ring-opening product.

A lot of attentions have been paid to the synthesis of benzothiazepines and derivatives[1,2] due to their significant physiological activities. It has been reported that β-lactam, a major part of the antibiotic skeleton, can be introduced to a molecule by reaction of an imine moiety with ketene[3,4]. We introduced a β-lactam skeleton to benzothiazepine and hoped the new compounds may possess certain biological activities.

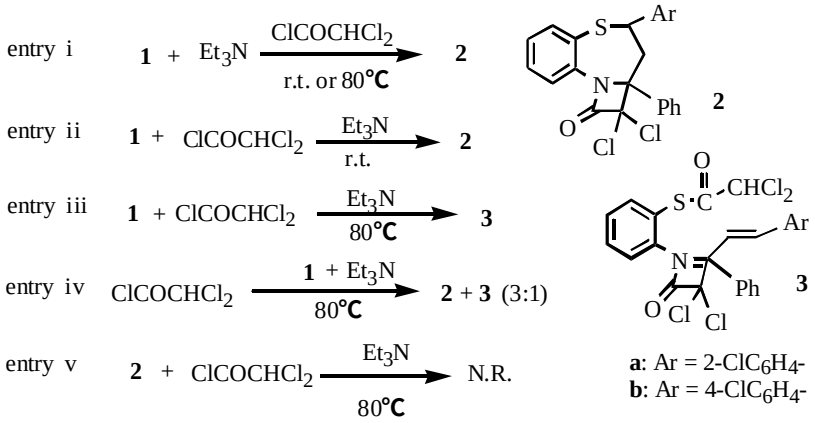
Scheme 1



2,3-Dihydro-2-chlorophenyl-4-phenyl-1, 5-benzothiazepine **1** was used as the starting materials and which was prepared from the reaction[5] of aminothiophenol and phenyl vinyl ketone (**Scheme 1**). The reaction of **1** with dichloroacetyl chloride and triethylamine gave the products, which were identified as **2** and **3**, and the ratios of **2** and **3** were noted to be dependent upon the experimental conditions (**Scheme 2**). When dichloroacetyl chloride was added dropwise to the mixture of **1** and triethylamine at room temperature or 80°C, **2** was the main product (yield and mp were 83%, 215-217°C and 81%, 216-127°C for **2a** and **2b**, respectively); no **3** was detected (entry i). In a modified addition mode that triethylamine was added into the mixture of **1** and dichloroacetyl

chloride at room temperature, **2** was the main product (entry ii); while at 80°C, **3** was the main product (yield and mp were 63%, 170-171°C and 56 %, 169-171°C for **3a** and **3b**, respectively) (entry iii). In a reverse addition mode that mixture of **1** and triethylamine was added dropwise to the hot solution of dichloroacetyl chloride and benzene, the product mixture of **2** and **3** was obtained with the ratio 3:1 which was analyzed by ^{1}H NMR spectra (entry iv). The reaction of **2** with dichloroacetyl chloride and triethylamine gave no ring-opening product **3** either by regular or reverse addition mode (entry v).

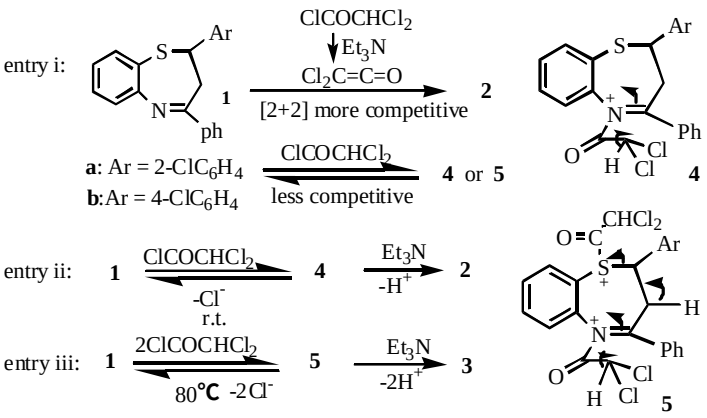
Scheme 2



The structures of **2** and **3** were identified by spectral analysis[6]. The mechanisms for the formation of **2** and **3** are rationalized and illustrated in **Scheme 3**. It is known that acyl halide and ketene can react with imine to form β-lactam[7] and that ketene is more reactive than acetyl chloride[8]. When dichloroacetyl chloride was added into the mixture of **1** and triethylamine, the following competition reactions might occur (entry i). Dichloroacetyl chloride might react with triethylamine to form dichloroketene which reacted with **1** to give **2** *via* [2+2] cycloaddition process. Meanwhile, dichloroacetyl chloride might react with **1** directly to form intermediate **4** which cyclized to give lactam **2** in the presence of triethylamine base. From the result we supposed that dichloroketene was generated *in-situ* earlier than dichloroacetyl chloride could have reacted with **1** since no **3** was detected under this condition.

When dichloroacetyl chloride was treated with **1** at room temperature, intermediate **4** was supposed to be formed which led to lactam **2** when triethylamine was added (entry ii). Since no **3** was observed, the activation energy for the reaction of dichloroacetyl chloride and sulfur was assumed relatively large. The nitrogen, or the imine part, of benzothiazepine **1** had great tendency than the sulfur atom toward reaction with dichloroacetyl chloride or dichloroketene. The low reactivity of sulfur in comparison with nitrogen in benzothiazepine was supported by MNDO calculation where data showed that electron density is significantly greater at nitrogen than at sulfur[9]. When dichloroacetyl chloride was treated with **1** at 80°C (entry iii), both nitrogen and sulfur of **1** reacted with dichloroacetyl chloride which generated intermediate **5** and the cleavage of S-C2 bond of **5** by triethylamine afforded **3**.

Scheme 3



When mixture of **1** and triethylamine was added to the hot solution of dichloroacetyl chloride in benzene by reverse addition mode, dichloroketene was generated when dichloroacetyl chloride encountered triethylamine and then reacted with **1** to give **2**. Meanwhile the excess dichloroacetyl chloride during the initial reaction stage might react with both the nitrogen and sulfur atoms of **1** to form intermediate **5** at 80°C, which led to ring-opening product **3**. Product **3** appeared as the minor product (**2**:**3**=3/1) since the formation of dichloroketene was more quickly than that of intermediate **5** which is necessary to led to product **3**. It was interesting to note that **3** was not obtained by treating lactam **2** with excess dichloroacetyl chloride and triethylamine by regular or inverse addition mode at 80°C. The electronic or steric effect induced by the structure of lactam **2** might play an important role for decreasing the reactivity of sulfur atom.

Acknowledgment

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References and Notes

1. T. Patonay, W. Adam, J. Jeko, K. E. Kover, A. Levai, M. Nemeth, K. Peters, *Heterocycles*, 1999, *51*, 85.
2. A. K. Bose, W. A. Hoffman III, M. S. Manhas, *J. Chem. Soc. Perkin Trans*, 1976, 2343.
3. A. Szollosy, G. Kotovych, G. Toth, A. Levai, *Can. J. Chem.*, 1988, 279.
4. H. Arai, Y. Matsushima, T. Eguchi, K. Shindo, K. Kakihuma, *Tetrahedron Lett.*, 1998, *39*, 3181.
5. R. X. Lan, S. Jin, *Chin. Chem. Lett.*, 1992, *3* (1), 9.
6. Spectral data of compound 2a: IR (KBr, cm^{-1}): 1779; MS (*m/z*): 459 (M^+), 423, 321, 285, 211 (100), 108, 77; ^1H NMR (400 MHz, $CDCl_3$, δppm): 3.36 (dd, 1H, J=14.1 Hz, 0.42 Hz,CH_2), 3.45 (dd, 1H, J=14.1 Hz, 0.40 Hz, CH_2), 4.43 (dd, 1H, J=10.6 Hz, 0.40 Hz, CHS), 7.22-7.94 (m, 13H, aromatic H); Elemental analysis: $C_{23}H_{16}OSNCl_3$, 460.5, calculated: C %: 59.93; N %:3.04; H %: 3.47, found: C %: 60.06; N%: 2.80; H%: 3.54. Spectral data of compound 2b: IR (KBr, cm^{-1}): 1783; MS (*m/z*): 459 (M^+), 423, 321, 211 (100); ^1H NMR (400 MHz, $CDCl_3$,

δppm): 3.42 (dd, 1H, J=14.2 Hz, 0.42 Hz, CH_2), 3.43 (dd, 1H, J=14.2 Hz, 0.40 Hz, CH_2), 3.86 (dd, 1H, J=10.8 Hz, 0.40 Hz, CHS), 7.21-7.94 (m, 13H, aromatic H); Elemental analysis: $C_{23}H_{16}OSNCl_3$, 460.5, calculated: C%: 59.93, N%, 3.04; H%: 3.47, found: C %: 59.88; N%: 2.77; H%: 3.64. Spectral data of compound 3a: IR (KBr, cm^{-1}): 1789, 1640; MS (*m/z*): 569 (M^+), 535, 423, 201 (100); ^1H NMR (400 MHz, $CDCl_3$, δppm): 6.00 (s, 1H, $CHCl_2$), 6.85 (s, 2H, vinyl H), 7.16-7.59 (m, 13H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, δppm): 69.59, 81.69, 90.00, 123.27, 124.10, 127.23, 127.43, 128.01, 128.42, 128.99, 129.05, 129.88, 130.01, 130.39, 131.73, 133.76, 133.90, 134.98, 135.02, 137.28, 139.03, 160.03 (C=O), 188.68 (C=O); DEPT, CH_3 carbons: none; CH_2 carbons: none; CH carbons: (14 peaks) 69.59, 124.10, 127.23, 127.43, 128.01, 128.42, 128.99, 129.05, 129.88, 130.01, 130.39, 131.73, 135.02, 139.03; Elemental analysis: $C_{25}H_{16}O_2SNCl_5$, 571.5, calculated: C%: 52.49; N%: 2.45; H%: 2.80, found: C%: 52.40; N%: 2.46; H%: 3.05. Spectral data of compound 3b: IR (KBr, cm^{-1}): 1780, 1640; MS (*m/z*): 569 (M^+), 535, 423, 151 (100); ^1H NMR (400 MHz, $CDCl_3$, δppm): 6.05 (s, 1H, $CHCl_2$), 6.38 (d, 1H, J=16.4 Hz, vinyl H), 6.93 (d, 1H, J=16.4 Hz, vinyl H), 7.12-7.62 (m, 13H, aromatic H); Elemental analysis: $C_{25}H_{16}O_2SNCl_5$, 571.5, calculated: C% 52.49; N%: 2.45; H%: 2.80, found: C%: 52.59; N%: 2.89; H%: 2.57.

7. L. Fodor, J. Szabo, P. Sohar, *Tetrahedron*, 1981, *37*, 963.
8. C. D. Gutsche, D. J. Pasto, *Fundamentals of Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1975.
9. Y. C. Lu, P. Liu, S. Jin, Q. Y. Xing, *Science in China, B*, 1987, 339.

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