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Stereospecific Synthesis of 2-Phthalimido-2a,3,4,5-Tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones

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ABSTRACT: *2a,4-Disubstituted 2-phthalimido-2a,3,4,5-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones were synthesized by cycloaddition reactions of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and phthalimidoketene, generated from phthalimidoacetyl chloride, in the presence of triethylamine in anhydrous benzene. The stereochemistry was discussed for the cycloaddition reaction.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:276–279, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10029

INTRODUCTION

The β-lactam (2-azetidinone) skeleton is the key structural element of the most widely employed family of antimicrobial agents. Most of the important antibiotics possess the representative structure of an α-amino-β-lactam fused to a five- or six-membered heterocyclic ring containing nitrogen and sulfur atoms [1–3]. For instance, the effective antibiotics penicillin, penam, and penem have fused thiazolidine-β-lactam structures, and the effective antibiotics cephalosporin and cephem are fused dihydrothiazine-β-lactams [1–3]. The synthesis of bicyclic β-lactams became a desirable goal based on the discovery of penicillin and cephalosporin. Although most of the penicillin and cephalosporin-like compounds have been obtained by biosynthesis, by chemical modification of intermediates that are produced via biosynthesis, or by chemical synthesis [4,5], it seemed to be necessary to synthesize some novel compounds with a fused β-lactam-heterocyclic ring for bioassay of antibacterial activity because of the growing resistance of bacteria against penicillin and cephalosporin-like compounds and the need for medicines with a more specific antibacterial activity. Some β-lactam derivatives have also been recognized as inhibitors of human leukocytase elastase [6]. Up to now, some α-amino-β-lactam derivatives of thiazoline and dihydrothiazine, containing a five- and six-membered sulfur and nitrogen-containing heterocyclic ring, respectively, have been synthesized by various methods [7–9]. In recent years, our working group has synthesized numerous benzothiazepine tricyclic derivatives and studied their stereo-structures because of their potential biological and pharmaceutical importance [10–14]. The synthesis of a few examples of β-lactam derivatives of benzothiazepines have been published [15–18]. Herein, we report the synthesis of α-amino-β-lactam derivatives of dihydrobenzothiazepine, having a seven-membered sulfur and nitrogen-containing heterocyclic ring, for pharmaceutical research and we discuss the stereochemistry of the cycloaddition reaction.

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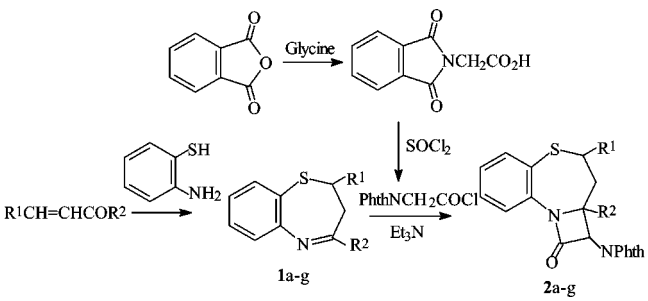
RESULTS AND DISCUSSION

The commonly applied routes for the direct construction of a β-lactam ring include the Staudinger cycloaddition of imines to ketenes, the enolate–imine condensations and subsequent ring-closure of β-amino esters, the ketene–imine cycloaddition using metallo-carbene intermediates, and the annelation of aziridines by use of transition-metal catalysts [4,5]. The Staudinger cycloaddition of imines to ketenes is probably the most important method among the above mentioned strategies.

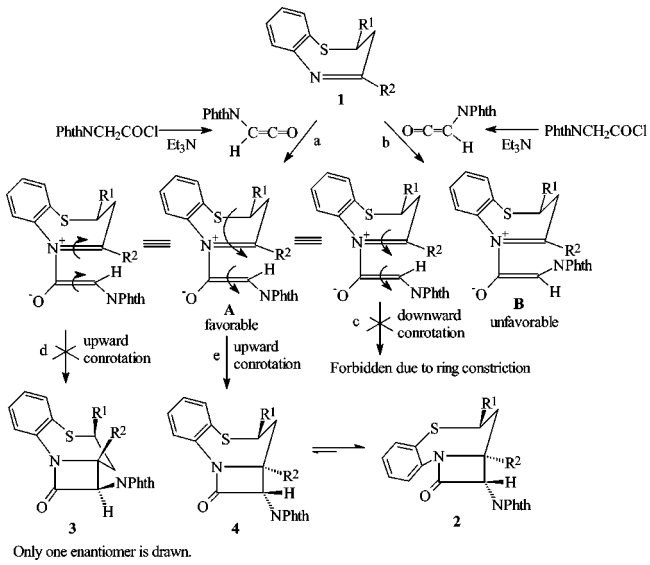
As a continuation of our work on the cycloadditions of 1,5-benzoheteroazepines, herein we report cycloadditions involving 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and phthalimidoacetyl chloride, and discuss the stereochemistry in the cycloaddition reaction (Scheme 1).

2,4-Disubstituted 2,3-dihydro-1,5-benzothiazepines **1a–g** were synthesized from *o*-aminothiophenol and α,β-unsaturated ketones in excellent yields [10,14]. Phthalimidoacetyl chloride was prepared from phthalic anhydride and glycine, followed by chlorination with thionyl chloride [19]. 1,5-Benzothiazepines **1a–g** reacted with phthalimidoketene, generated by use of phthalimidoacetyl chloride in the presence of triethylamine in refluxing anhydrous benzene, to give new 2a,4-disubstituted 2-phthalimido-2a,3,4,5-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones **2a–g**. Their structures were confirmed by ^{1}H NMR, IR, MS, and elemental analyses. In their ^{1}H NMR spectra, β-lactam derivatives show a characteristic singlet of the azetidinone ring proton at 5.34–5.48 ppm. The NOESY spectrum of the compound **2b** shows that R^2 and PhthN are cis and R^1 is trans to them (Table 1 and 2).

According to their ^{1}H NMR spectra, only one pair of enantiomers was found in each of the cycloaddition reactions. This could be rationalized as follows (Scheme 2). It is well-known that 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepine



SCHEME 1 Synthesis of 2a,4-disubstituted 2-phthalimido-2a,3,4,5-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones **2**.



SCHEME 2 Stereospecificity and stereochemistry in cycloaddition reaction.

adopts a boat-like conformation [20]. Based on literature results [21,22], the nitrogen atom of the C=N bond in each benzothiazepine (**1**) attacks the carbonyl group of the ketene, generated from acyl chloride and triethylamine, to yield a zwitterionic intermediate **A**. The attack should occur from the less hindered side of the ketene (path a, over the small group H). Since closure in the downward direction of the N=C bond in the thiazepine ring (path c) would necessitate ring constriction of the thiazepine ring, it cannot happen. Although the conrotatary ring closure could occur in the upward direction of the N=C bond (path d), it would form product **3** with cis R^1, R^2, and PhthN substituents. It is still a forbidden process because R^1 and R^2 substituentes occupy the sterically hindered 1,3-quasi-axial positions of the thiazepine ring. The conrotatory ring closure can occur only with the sense shown (downward, path e), in which the whole thiazepine ring rotates downwards, to yield a boat-like product **4** through forming a β-lactam ring from the outside of the thiazepine ring. It then undergoes conformational transfer to produce finally the predominant chair-like product **2**, based on the results of stereostructures from the nuclear magnetic resonance and X-ray diffraction analyses [15,23]. Thus, only one pair of diastereomers of each cycloadduct was obtained in this cycloaddition reaction. The result is consistent with synthetic results of their 2-chloro and 2-phenyl analogues, 2a,4-disubstituted 2-chloro or 2-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*]-[1,5]-benzothiazepin-1-ones [15,23]. However, it is somewhat different to the reaction of 1-benzoyl

TABLE 1 Physical and Spectral Data

Compound	*R^1*	*R^2*	*Yield (%)*	*m. p. (°C)*	*^{1}H NMR ($CDCl_3$/TMS) [δ (ppm), J (Hz)]*	*IR (KBr) [ν (cm^{-1})]*	*MS [m/z(M^+)]*
2a	Me	Ph	79	251–252	1.32 (3H, d, $J = 6.8$, Me), 2.67 (1H, dd, $J = 10.6$, 13.4), 2.84 (1H, dq, $J = 10.6$, 6.8), 3.13 (1H, d, $J = 13.4$), 5.39 (1H, s), 7.04–8.12 (13H, m, aromatic)	1761.6 1719.4 1640.5	440
2b	Me	*p*-MePh	30 60[a]	253–254	1.32 (3H, d, $J = 6.8$, Me), 2.09 (3H, s, MePh), 2.69 (1H, dd, $J = 10.9$, 13.3), 2.84 (1H, dq, $J = 10.9$, 6.8), 3.10 (1H, d, $J = 13.3$), 5.37 (1H, s), 6.87–8.10 (12H, m, aromatic)	1710.3 1722.9 1642.5	454
2c	Me	*p*-MeOPh	29 39[a]	232–233	1.33 (3H, d, $J = 7.0$, Me), 2.68 (1H, dd, $J = 10.3$, 13.7), 2.84 (1H, dq, $J = 10.3$, 7.0), 3.10 (1H, d, $J = 13.7$), 3.60 (3H, s, MeO), 5.34 (1H, s), 6.57–6.81 (12H, m, aromatic)	1759.8 1722.1 1642.4	470
2d	Ph	*p*-MeOPh	16 76[a]	191–192	3.23 (1H, dd, $J = 10.4$, 14.1), 3.43 (1H, d, $J = 14.1$), 3.61 (3H, s, MeO), 3.86 (1H, d, $J = 10.4$), 5.42 (1H, s), 6.58–8.17 (17H, m, aromatic)	1768.4 1715.8 1641.9	532
2e	*p*-MeOPh	Ph	38 96[a]	224–225	3.26 (1H, dd, $J = 10.9$, 14.1), 3.45 (1H, d, $J = 14.1$), 3.80 (3H, s, MeO), 3.84 (1H, d, $J = 10.9$), 5.47 (1H, s), 6.84–8.18 (17H, m, aromatic)	1763.1 1716.3 1642.2	532
2f	*p*-ClPh	Ph	35	216–217	3.23 (1H, dd, $J = 10.4$, 14.0), 3.43 (1H, d, $J = 14.0$), 3.82 (1H, d, $J = 10.4$), 5.47 (1H, s), 7.06–8.19 (17H, m, aromatic)	1765.8 1718.5 1641.3	536
2g	*m*-ClPh	Ph	35 43[a]	244–245	3.24 (1H, dd, $J = 10.6$, 14.0), 3.44 (1H, d, $J = 14.0$), 3.80 (1H, d, $J = 10.6$), 5.48 (1H, s), 7.07–8.20 (17H, m, aromatic)	1771 1640	536

[a]Based on the converted starting materials (benzothiazepines).

2,3-dihydro-1,5-benzodiazepines with ketene, generated by use of acyl chloride in the presence of triethylamine [24].

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario EL elemental analyzer. The ^{1}H NMR spectra were recorded on a Varian Mercury 200 spectrometer with TMS as an internal standard in the $CDCl_3$ solution. The IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. TLC separations were performed on silica gel G plates

TABLE 2 Elemental Analysis Data

			Cald.			*Found*		
Compound	*Molecular Formula*	*Molecular Weight*	*C*	*H*	*N*	*C*	*H*	*N*
2a	$C_{26}H_{20}N_2O_3S$	440.51	70.89	4.58	6.36	70.76	4.26	6.13
2b	$C_{27}H_{22}N_2O_3S$	454.54	71.34	4.88	6.16	70.98	4.73	6.08
2c	$C_{27}H_{22}N_2O_4S$	470.54	68.92	4.71	5.95	68.64	4.70	5.75
2d	$C_{32}H_{24}N_2O_4S$	532.61	72.16	4.54	5.26	71.79	4.88	4.93
2e	$C_{32}H_{24}N_2O_4S$	532.61	72.16	4.54	5.26	72.35	4.56	5.10
2f	$C_{31}H_{21}ClN_2O_3S$	537.03	69.33	3.94	5.22	68.98	3.63	5.12
2g	$C_{26}H_{22}ClN_2O_3S$	537.03	69.33	3.94	5.22	69.33	3.79	4.93

with petroleum ether (60–90°C)/ethyl acetate (5:1), and the plates were visualized with UV light and/or iodine vapor.

Synthesis of 2a,4-Disubstituted 2-Phthalimido-2a,3,4,5-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-ones: General Procedure

1,5-Benzothiazepine (**1**) (1 mmol) and phthalimidoacetyl chloride (0.447 g, 2 mmol) were dissolved in anhydrous benzene (20 ml), and dried triethylamine (0.222 g, 2.2 mmol) in anhydrous benzene (10 ml) was added dropwise into the solution over a period of 20 min. After having been stirred 4 h to overnight, the crystalline triethylamine hydrochloride that had formed was removed by filtration, and the benzene solution was washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over Na_2SO_4. After removal of the solvent, the resulting residue was recrystallized from ethanol to yield colorless crystals **2a** and **2f**, or else the residue was passed through a silica gel column with petroleum ether (60–90°C)/ethyl acetate (5:1) as an eluent to give colorless crystals **2b–e** and **2g**.

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