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Reactions of 2,3-Dihydro-1*H*-1,5-benzodiazepines and Chloroacetyl Chlorides: Synthesis of 2a,3,4,5-Tetrahydro-azeto [1,2-a][1,5] benzodiazepin-1(2*H*)-ones

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ABSTRACT: *2a,4-Disubstituted 5-benzoyl-2-chloro/2,2-dichloro-2a,3,4,5-tetrahydro-azeto[1,2-a] [1,5]benzodiazepin-1 (2H)-ones (***3a–h***) were synthesized by cycloaddition reactions of 2,4-disubstituted 1-benzoyl-2,3-dihydr o-1*H*-1,5-benzodiazepines (***2a–h***) and ketenes, generated from chloroacetyl chloride or dichloroacetyl chloride in the presence of triethylamine, in anhydrous benzene. In some cases, ring contraction of benzodiazepines has also been observed.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:636–640, 2001

INTRODUCTION

In recent years, numerous benzodiazepine tricyclic derivatives have been synthesized, and their stereostructures have been studied because of their biological and pharmaceutical importance [1–10]. Until now, only a few examples of the β-lactam derivatives of benzoxazepines, benzothiazepines, and benzodiazepines have been published [11–13]. Since some β-lactam derivatives, such as penicillin, show lifesaving antibacterial activity [11] and act as inhibitors of human leukocytase elastase [14], it is believed that the tricyclic benzodiazepine with a β-lactam moiety incorporated into the tricyclic ring system is highly possibly biologically active. For this reason and also as a continuation of our previous work in the study of benzodiazepine and benzothiazepine tricyclic derivatives [3–9], we here report in this paper the synthesis of new tricyclic benzodiazepine of β-lactam derivatives.

RESULTS AND DISCUSSION

The cycloaddition reaction of 2,4-disubstituted 1-benzoyl-2,3-dihydro-1*H*-1,5-benzodiazepines **2a–h** was conducted by treating **2a–h** with an appropriate acetyl chloride in the presence of triethylamine (Scheme 1).

Compounds **1a–h** were *N*-benzoylated to give **2a–h** [5]. Compounds **2a–f** were heated with monochloroketene, and generated in situ from chloroacetyl chloride and triethylamine in anhydrous benzene to yield **3a–f**. In a similar manner, compounds **3g–h** were prepared by the reaction of **2g–h** with dichloroketene in anhydrous benzene at room temperature.

The proposed structures for **3a–h** are based on ^{1}H NMR, IR, and mass spectral and elemental analysis data. In ^{1}H NMR spectra of **3a–f**, β-lactam benzodiazepine derivatives showed a characteristic singlet of the azetidinone ring proton at 4.94–5.07 ppm, and

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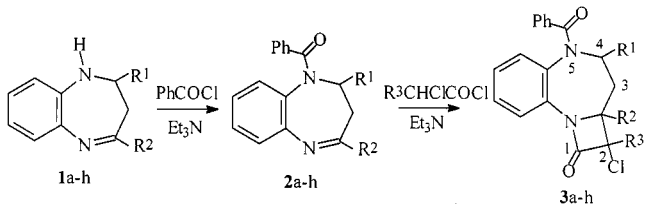
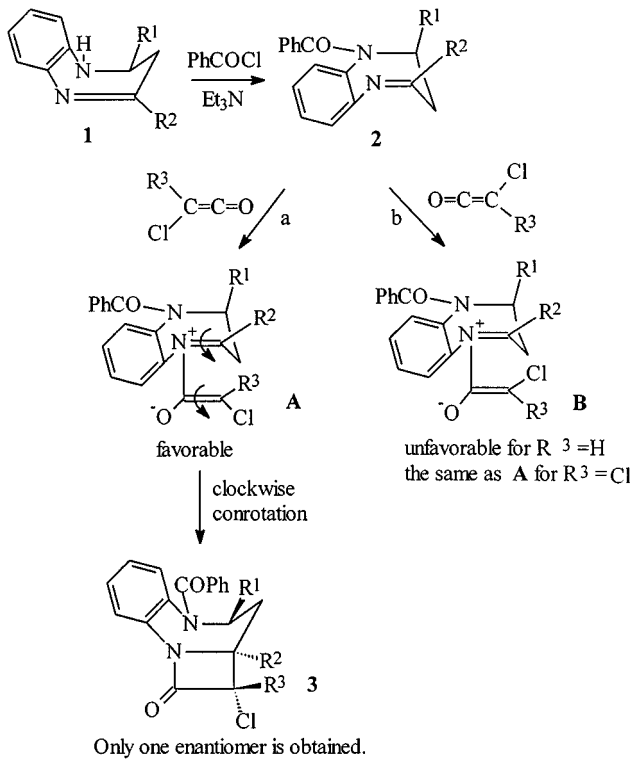


SCHEME 1 Synthesis of 2a,4-disubstituted 5-benzoyl-2-chloro/2,2-dichloro-2a,3,4,5-tetrahydro-azeto[1,2-a] [1,5]benzodiazepin-1(2*H*)-ones **3a – h**.



SCHEME 2 Stereospecificity in cycloaddition reaction.

signals of the diazepine =$CHCH_2$= protons, in most cases, were of the ABX coupling system and shifted upfield. In the case of **3g–h**, signals of the C_4-proton and the C_4-methyl protons were all shifted downfield. One of the C_3-methylene protons was shifted downfield and the other was shifted upfield.

According to their ^{1}H NMR spectra, only one pair of enantiomers was found in the cycloaddition reaction. The formation of the compound could be rationalized by the reaction mechanisms as depicted in Scheme 2 (only one enantiomer is drawn). It has been well known that 2,4-disubstituted 2,3-dihydro-1*H*-1,5-benzodiazepine adopts a boat-like conformation [15]. After it was benzolyated, *N*-benzoyl-2,3-dihydro-1*H*-1,5-benzodiazepine underwent a conformation transformation, in which it was inverted [16]. Based on the literature reports [17,18], the nitrogen atom of the C=N bond in benzodiazepines **2** attacks the carbonyl group of the ketene to yield a zwitterionic intermediate **A**. The attack should occur from the less hindered side of the ketene; for monochloroketene it is from the small H group (path a), and for dichloroketene, the approach from either side of the molecule (paths a or b) is virtually the same. The conrotatory ring closure can only occur *via* counterclockwise rotation of the bonds involved, as shown in **A**, viewed from the right side of the molecule. Since closure in the other direction would necessitate ring constriction in the diazepine ring, this was forbidden. Only one enantiomer was obtained as the product in the cycloaddition reaction. The result is well consistent with their sulfur analogues, 2a,4-disubstituted 2-chloro-2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5] benzothiazepin-1-ones [8].

Physical and spectral data are presented in Table 1, and elemental analysis data are presented in Table 2. The yields of most cycloadducts were moderate except for the preparations of **3b** and **3d**; these compounds were obtained in low yields, 6 and 16%, respectively. Low yields were ascribed to the formation of 1-phenyl-3-aryl-propenones, 20% in the case of **3b** and 60% in the case of **3d**, and to the formation of 2-phenylbenzimidazole [19]. It was reported that some 1,5-benzodiazepines could undergo the ring contraction rearrangement reaction to yield benzimidazole derivatives in the presence of acid [20,21] or by heating [20,22]. In order to avoid this ring contraction, reactions were carried out under basic conditions. Compounds **2b** and **2d** were refluxed separately in the presence of triethylamine hydrochloride in anhydrous benzene for 24 h, and, in both reactions, no change was observed.

The cycloadduct **3b** or **3d** was obtained and was increased slightly when chloroacetyl chloride was added dropwise to the solution of the 1,5-benzodiazepines(**2b**) or **2d** in the presence of triethylamine in anhydrous benzene. Unreacted starting materials **2b** and **2d** were recovered in both reactions. A ring contraction reaction also happened in the reaction of **2b**, in which 3-(2-chlorophenyl)-1-phenylpropanone was obtained in 25% yield.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and were 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

TABLE 1 Physical and Spectral Data

Compound	R^1	R^2	R^3	*Yield (%)*	*m.p. (°C)*	*^{1}H NMR ($CDCl_3$/TMS) δ (ppm), J (Hz)*	*IR(KBr) ν(cm^{-1})*	*MS m/z (M^+)*
3a	Me	*p*-Meph	H	67	224–225	1.24 (3H, d, $J=6.4$, Me), 2.22 (1H, dd, $J=10.8$, 14.8), 2.23 (3H, s, MeAr), 2.24 (1H, dd, $J=7.6$, 14.8), 4.94 (1H, s, CHCl), 5.25 (1H, dd, $J=6.4$, 7.6, 10.8), 6.40 (1H, d, $J=7.8$, aromatic), 6.72 (1H, t, $J=7.6$, aromatic), 7.04–7.26 (9H, m, aromatic), 7.80 (1H, m, aromatic), 8.42 (1H, d, $J=8.2$, aromatic)	1780.9 1644.5	430
3b	*o*-ClPh	Ph	H	6 18[a]	210–211	2.64 (1H, dd, $J=6.8$, 14.9), 3.48 (1H, dd, $J=11.9$, 14.9), 5.01 (1H, s, CHCl), 6.39 (1H, dd, $J=6.8$, 11.9), 6.55 (1H, d, $J=7.6$, aromatic), 6.76 (1H, t, $J=7.8$, aromatic),7.02–7.56 (14H, m, aromatic), 7.79 (1H, m, aromatic), 8.53 (1H, d, $J=8.2$, aromatic)	1755.9 1664.5	512
3c	*m*-ClPh	Ph	H	40	235–236	2.87 (1H, dd, $J=7.8$, 15.1), 3.41 (1H, dd, $J=11.8$, 15.1), 5.07 (1H, s, CHCl), 6.18 (1H, dd, $J=7.8$, 11.8), 6.11 (1H, d, $J=8.2$, aromatic), 6.67 (1H, t, $J=7.8$, aromatic),7.02–7.54 (14H, m, aromatic), 7.81 (1H, m, aromatic), 8.49 (1H, d, $J=9.6$, aromatic)	1776.4 1642.7	512
3d	*p*-ClPh	Ph	H	16 32[a]	237–238	2.87 (1H, dd, $J=7.8$, 14.8), 3.39 (1H, dd, $J=11.8$, 14.8), 5.06 (1H, s, CHCl), 6.20 (1H, dd, $J=7.8$, 11.8), 6.04, (1H, d, $J=7.8$, aromatic), 6.65 (1H, t, $J=7.6$, aromatic), 7.01–7.48 (14H, m, aromatic), 7.80 (1H, m, aromatic), 8.48 (1H, d, $J=8.2$, aromatic)	1776.5 1639.0	512
3e	*m*-BrPh	Ph	H	53	227–239	2.86 (1H, dd, $J=7.6$, 14.8), 3.41 (1H, dd, $J=11.8$, 14.8), 5.07 (1H, s, CHCl), 6.17 (1H, dd, $J=7.6$, 11.8), 6.12 (1H, d, $J=8.2$, aromatic), 6.68 (1H, t, $J=7.6$, aromatic), 7.02–7.54 (14H, m, aromatic), 7.82 (1H, d, $J=4.2$, aromatic), 8.50 (1H, d, $J=8.2$, aromatic)	1777.8 1647.2	556
3f	Ph	*p*-ClPh	H	30	251–252	2.93 (1H, dd, $J=7.6$, 15.0), 3.37 (1H, dd, $J=11.8$, 15.0), 5.05 (1H, s, CHCl), 6.20 (1H, dd, $J=7.6$, 11.8), 6.08 (1H, d, $J=8.2$, aromatic), 6.47 (1H, d, $J=2.6$, aromatic), 6.97–7.52 (14H, m, aromatic), 7.78 (1H, d, $J=0.8$, aromatic), 8.46 (1H, d, $J=8.2$, aromatic)	1771.9 1631.6	512
3g	Me	Ph	Cl	65	185–187	1.25 (3H, d, $J=6.0$, Me), 2.35 (1H, dd, $J=11.0$, 15.4), 3.25 (1H, dd, $J=7.6$, 15.4), 5.10 (1H, ddq, $J=6.0$, 7.6, 11.0), 6.43 (1H, d, $J=7.4$, aromatic), 6.79 (1H, t, $J=7.6$, aromatic), 7.06–7.46 (10H, m, aromatic), 7.74 (1H, d, $J=7.6$, aromatic), 8.47 (1H, d, $J=8.4$, aromatic)	1775.8 1638.2	450

(Continued)

TABLE 1 Continued

Compound	R^1	R^2	R^3	*Yield (%)*	*m.p. (°C)*	*^{1}H NMR ($CDCl_3$/TMS) δ (ppm), J (Hz)*	*IR(KBr) ν(cm^{-1})*	*MS m/z (M^+)*
3h	Me	*p*-MeOPh	Cl	71	201–202	1.27 (3H, d, $J=6.2$, Me), 2.34 (1H, dd, $J=11.4, 15.2$), 3.21 (1H, dd, $J=7.4, 15.2$), 3.69 (3H, s, MeO), 5.12 (1H, ddq, $J=6.2, 7.4, 11.4$), 6.43 (1H, d, $J=8.0$, aromatic), 6.68–6.81 (2H, m, aromatic), 6.99–7.36 (8H, m, aromatic), 7.63 (1H, d, $J=8.4$, aromatic), 8.45 (1H d, $J=8.2$, aromatic)	1775.5 1639.5	480

[a]Yield based on the converted 1,5-benzodiazepine in method B.

TABLE 2 Elemental Analysis Data

Compound	*Molecular Formula*	*Molecular Weight*	*Cacd.*			*Found*		
			C	*H*	*N*	*C*	*H*	*N*
3a	$C_{26}H_{23}N_2ClO_2$	430.93	72.47	5.38	6.50	72.06	5.49	6.47
3b	$C_{30}H_{22}N_2Cl_2O_2$	513.42	70.18	4.32	5.46	70.00	4.54	5.22
3c	$C_{30}H_{22}N_2Cl_2O_2$	513.42	70.18	4.32	5.46	69.97	4.31	5.70
3d	$C_{30}H_{22}N_2Cl_2O_2$	513.42	70.18	4.32	5.46	70.31	4.31	5.67
3e	$C_{30}H_{22}N_2BrClO_2$	557.87	64.59	3.97	5.02	64.83	4.05	4.99
3f	$C_{30}H_{22}N_2Cl_2O_2$	513.42	70.18	4.32	5.46	70.29	4.41	5.70
3g	$C_{25}H_{20}N_2Cl_2O_2$	451.35	66.53	4.47	6.21	66.61	4.50	6.10
3h	$C_{26}H_{22}N_2Cl_2O_3$	481.38	64.87	4.61	5.82	64.62	4.50	5.99

tetramethylsilane (TMS) as an internal standard in $CDCl_3$. 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. Thin-layer chromatography (TLC) separations were performed on silica gel G plates with petroleum ether (60–90°C)/ethyl acetate (5:1), and the plates were visualized with UV light and/or iodine vapor.

*Synthesis of 2*a*, 4-Disubstituted-5-benzoyl-2-chloro/-2,2-di-chloro-2a,3,4,5-tetrahydro-azeto[1,2-*a*][1,5] benzodiazepin-1 (2H)-ones(***3a–h***)*

General Procedure: Method A. 1,5-Benzodiazepine (**2**) (1 mmol) and the appropriate chloroacetyl chloride (2 mmol) were gently refluxed in anhydrous benzene (20 ml). Dried triethylamine (0.202 g, 2 mmol) in anhydrous benzene (10 ml) was added dropwise into the refluxing solution over a period of 20 min, and the mixture was stirred (for dichloracetyl chloride in the preparation of **3g–h**, refluxing was not required, and it was conducted at room temperature). After the addition was completed, the mixture was refluxed for a further 2 h and cooled (for **3g–h**, it was stirred at room temperature for 4 h). The crystalline triethylamine hydrochloride formed was removed by filtration. The benzene solution was washed with water, saturated aqueous $NaHCO_3$, and then brine. The separated benzene layer was dried over Na_2SO_4. The benzene was removed, and the residue collected was crystallized from ethanol to yield the product as colorless crystals (**3a, 3c, 3e, 3g**, and **3h**). For **3f**, the residue obtained was separated on a silica gel column with petroleum ether (60–90°C)/ethyl acetate (5:1) as the eluent and afforded **3f** as colorless crystals.

In the preparation of **3b** and **3d**, after the removal of benzene, the residue remaining was then crystallized from ethanol to yield yellowish crystals of 2- or 4-chloro-chalcone: 20% yield (m.p. 49–51°C) in the **3b** preparation and 60% (114–116°C) in the **3d** case. Both of them have a molecular ion peak at *m/z* of 242 (electron ionization–mass spectrometry [EI-MS]). The mother liquid was concentrated, and the residue was separated on a silica gel column with petroleum ether (60–90°C)/ethyl acetate (5:1) as the eluent to give colorless crystals of the product (**3b** or **3d**).

General Procedure: Method B. A mixture of the appropriate 1,5-benzodiazepine (**2b**) or **2d**, (0.437 g, 1 mmol) and dried triethylamine (0.202 g, 2 mmol) was gently refluxed in anhydrous benzene (20 ml).

Chloroacetyl chloride (0.226 g, 2 mmol) in anhydrous benzene (10 ml) was added dropwise into the aforementioned refluxing solution over a period of 20 min with stirring. After addition was completed, the mixture was refluxed for a further 2 h and then cooled. The crystalline triethylamine hydrochloride formed was removed by filtration. The benzene solution was washed with water, saturated aqueous $NaHCO_3$, and then brine. The separated benzene layer was dried over Na_2SO_4. The benzene was removed, and the residue collected was separated on a silica gel column with petroleum ether (60–90°C)/ethyl acetate (5:1) as the eluent. The product, as colorless crystals (**3b** and **3d**), and a small amount of unreacted starting material (**2b** or **2d**) was also recovered. In addition, in the reaction of **2b**, 3-(2-chlorophenyl)-1-phenylpropanone was also obtained in 25% yield.

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