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Stereospecific Synthesis of Azeto[2,1-*d*]-[1,5]benzothiazepin/diazepin-1-ones

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ABSTRACT: *2a,4-Disubstituted 2-phenoxy-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones and 5-benzoyl-2-phenoxy-2a,3,4,5-tetrahydro-azeto[1,2-a][1,5]benzodiazepin-1(2H)-ones were synthesized in moderate to good yields by stereospecific Staudinger cycloaddition reactions of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and 1-benzoyl-2,3-dihydro-1H-1,5-benzodiazepines, respectively, with phenoxy acetyl chloride in the presence of triethylamine in anhydrous benzene.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:564–569, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10196

INTRODUCTION

The β-lactam (2-azetidinone) skeleton has gained significant interest among synthetic as well as medicinal chemists over the years, mainly because it represents the key structural element of synthetic and natural antibiotics. Most of the important antibiotics possess the representative structure of a 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 a lot of the penicillin- and cephalosporin-like compounds have been obtained by biosynthesis or 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 requirement for medicines with a more specific antibacterial activity. Some β-lactam derivatives have also been recognized as inhibitors of human leukocytase elastase [6] and serine protease [7,8]. Till now, numerous 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 [9–11]. In recent years, our working group has paid much attention to the synthesis and stereostructure investigation of tricyclic derivatives of benzothiazepines and benzodiazepines because of their potential biological and pharmaceutical importance [12–16]. Herein we report the synthesis of β-lactam derivatives of 2,3-dihydro-1,5-benzothiazepine, having a seven-membered sulfur- and nitrogen-containing heterocyclic ring, and 2,3-dihydro-1,5-benzodiazepine, with a seven-membered two nitrogen-containing heterocyclic ring, for pharmaceutical research.

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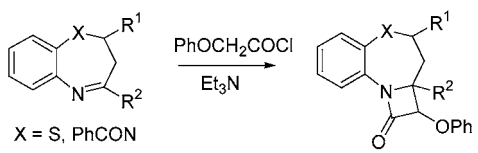
RESULTS AND DISCUSSION

The most popular methods for the preparation of the β-lactam ring involves 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.

Till now, a few examples of β-lactam derivatives of benzothiazepines and benzodiazepines have been prepared by us and others [17–23]. As a continuation of our efforts into the preparation of structurally diverse β-lactam derivatives of 1,5-benzoheteroazepines, herein we report synthesis of 2-phenoxy 1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones and azeto[1,2-*a*][1,5]benzodiazepin-1(2*H*)-ones.

2a,4-Disubstituted 2-chloro- and 2,2-dichloro-2, 2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5] benzothiazepin-1-ones and 2a,4-disubstituted 5-benzoyl-2-phthalimido-2a,3,4,5-tetrahydro-azeto[1,2-*a*][1,5] benzodiazepin-1(2*H*)-ones were prepared previously by us. To build up a structurally devise β-lactam derivative library of 1,5-benzoheteroazepine, 2-phenoxy β-lactam derivatives of 1,5-benzothiazepine, and 1*H*-1,5-benzodiazepines, 2a,4-disubstituted 2-phenoxy 2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones **2a–h** and 5-benzoyl-2a,3,4,5-tetrahydro-azeto[1,2-*a*][1,5]benzodiazepin-1(2*H*)-ones **2i–p** were prepared from phenoxyacetyl chloride with 1,5-benzothiazepine **1a–h** and 1*H*-1,5-benzodiazepines **1i–p**, respectively, in the presence of triethylamine in anhydrous benzene in moderate to good yields (Scheme 1, Table 1).

The structures of all products 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 δ-5.21–5.40 ppm. According to their ^{1}H NMR spectra, only one pair of enantiomers was found in each of the cycloaddition reactions. This indicates that



1 **2**

SCHEME 1 Synthesis of 2a,4-disubstituted 2-phenoxy-tetrahydro-1*H*-azeto[1,2-*a*][1,5]benzothiazepin-1-ones and azeto[1,2-*a*][1,5]benzodiazepin-1(2*H*)-ones.

TABLE 1 Synthesis of 2a,4-Disubstituted 2-Phenoxy-tetrahydro-1*H*-azeto[1,2-*a*][1,5]benzothiazepin-1-ones **2a–h** and Azeto[1,2-*a*][1,5]benzodiazepin-1(2*H*)-ones **2i–p**

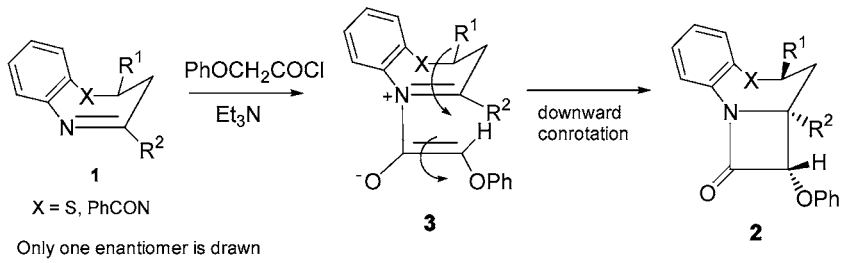
	X	*R*^{1}	*R*^{2}	*Yield (%)*	*mp (°C)*
2a	S	Me	Ph	90	179–180
2b	S	Me	4-MePh	80	165–166
2c	S	Me	4-MeOPh	75	155–156
2d	S	Ph	Ph	93	190–191
2e	S	2-ClPh	Ph	29	179–180
2f	S	4-ClPh	Ph	87	220–222
2g	S	4-BrPh	Ph	64	239–240
2h	S	Ph	4-ClPh	40	195–196
2i	PhCON	Me	4-MePh	88	248–249
2j	PhCON	Me	4-MeOPh	57	183–184
2k	PhCON	Ph	Ph	95	226–227
2l	PhCON	3-ClPh	Ph	81	209–210
2m	PhCON	4-ClPh	Ph	92	235–236
2m	PhCON	3-BrPh	Ph	83	191–192
2o	PhCON	4-MeOPh	Ph	51	183–184
2p	PhCON	Ph	4-ClPh	33	249–250

the cycloaddition reaction is stereospecific as those in the reactions of 1,5-benzoheteroazepines with chloroacetyl chloride and phthalimidoacetyl chloride, which were discussed in our previous papers [22,23]. The process of the stereospecific cycloaddition is depicted in Scheme 2. 2,4-Disubstituted 2,3-dihydro-1,5-benzoheteroazepines **1** adopt a boat-like conformation [24]. They react with phenoxyketene, generated from phenoxyacetyl chloride with triethylamine, to form zwitterionic intermediates **3** from the less hindered side of the ketene over the small group H [25,26]. The intermediates **3** then undergo a conrotatory ring closure in the downward direction, in which the whole azepine ring rotates downwards, to yield a β-lactam ring from the outside of the azepine ring. Thus, only one pair of diastereomers of each cycloadduct, with shown stereoconfiguration, was obtained in the cycloaddition reaction.

In summary, 2a,4-disubstituted 2-phenoxy-2, 2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones and 5-benzoyl-2-phenoxy-2a,3,4,5-tetrahydro-azeto[1,2-*a*][1,5]benzodiazepin-1(2*H*)-ones were synthesized in moderate to good yields by Staudinger cycloaddition reactions of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and 1-benzoyl-2,3-dihydro-1*H*-1,5-benzodiazepines, respectively, with phenoxy acetyl chloride in the presence of triethylamine in anhydrous benzene. The cycloaddition reaction is stereospecific.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario



SCHEME 2 Stereospecificity in the cycloaddition reaction.

EL elemental analyzer. The ^{1}H NMR spectra were recorded on a Varian Mercury 300 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 with petroleum ether (60–90°C)/ethyl acetate (5:1), and the plates were visualized with UV light.

Synthesis of 2a,4-disubstituted 2-phenoxy-2,2a,3,4-tetrahydro-1H-azeto[2,1-d]-[1,5]benzothiazepin-1-ones **2a–h** *and 2a,4-disubstituted 5-benzoyl-2-phenoxy-2a,3,4,5-tetrahydro-azeto[2,1-d]-[1,5]benzodiazepin-1(2H)-ones* **2i–p**

General Procedure. To a solution of 1,5-benzothiazepine (or 1-benzoyl-1,5-benzodiazepine) **1** (1 mmol) and phenoxyacetyl chloride (0.268 g, 2 mmol) in anhydrous benzene (20 ml) was added dropwise dried triethylamine (0.222 g, 2.2 mmol) in anhydrous benzene (10 ml) under stirring at room temperature over a period of 20 min. After having been stirred for 4 h at room temperature, for 1-benzoyl-1,5-benzodiazepine **1i–p**, at refluxing, 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, and then dried over Na_2SO_4. After removal of the solvent, the resulting residue was recrystallized from ethanol to yield colorless crystals **2** except for **2h, 2o**, and **2p**, which were obtained through a silica gel column with petroleum ether (60–90°C)/ethyl acetate (5:1) as an eluent.

*4-Methyl-2-phenoxy-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2a***)*

Colorless crystal, yield 90%, mp 179–180°C. R_f 0.40 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–6.73 (m, 14H, ArH), 5.31 (s, 1H, CH), 3.35 (dd, J = 1.2, 14.4 Hz, 1H, H in CH_2), 2.99 (ddq, J = 1.2, 10.8, 7.2 Hz, 1H, CH), 2.63 (dd, J = 10.8, 14.4 Hz, 1H, H in CH_2), 1.43 (d, J = 7.2 Hz, 3H, CH_3); IR (KBr): ν1763 (C=O) cm^{-1}; EI-MS (*m/z*): 387 (M^+, 25), 294 (M—PhO, 21), 293 (M—PhOH, 34), 253 (M—PhOCHCO, 83), 211 (100); Anal. Calcd for $C_{24}H_{21}NO_2S$ (387.49): C, 74.39; H, 5.46; N, 3.61. Found: C, 74.22; H, 5.57; N, 3.75.

*4-Methyl-2a-(4-methylphenyl)-2-phenoxy-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2b***)*

Colorless crystal, yield 80%, mp 165–166°C. R_f 0.40 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96–6.75 (m, 13H, ArH), 5.27 (s, 1H, CH), 3.32 (d, J = 14.1 Hz, 1H, H in CH_2), 3.00 (dq, J = 10.8, 6.8 Hz, 1H, CH), 2.60 (dd, J = 10.8, 14.1 Hz, 1H, H in CH_2), 2.24 (s, 3H, CH_3), 1.43 (d, J = 6.8 Hz, 3H, CH_3); IR (KBr): ν1763 (C=O) cm^{-1}; EI-MS (*m/z*): 401 (M^+, 2.9), 308 (M—PhO, 3.5), 307 (M—PhOH, 5.8), 267 (M—PhOCHCO, 8.7), 225 (10); Anal. Calcd for $C_{25}H_{23}NO_2S$ (401.52): C, 74.78; H, 5.77; N, 3.49. Found: C, 74.50; H, 5.88; N, 3.50.

*4-Methyl-2a-(4-methoxylphenyl)-2-phenoxy-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2c***)*

Colorless crystal, yield 75%, mp 155–156°C. R_f 0.40 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94–6.73 (m, 13H, ArH), 5.27 (s, 1H, CH), 3.69 (s, 3H, CH_3O), 3.30 (d, J = 14.1 Hz, 1H, H in CH_2), 3.01 (dq, J = 10.5, 6.9 Hz, 1H, CH), 2.60 (dd, J = 10.5, 14.1 Hz, 1H, H in CH_2), 1.43 (d, J = 6.9 Hz, 3H, CH_3); IR (KBr): ν 1761 (C=O) cm^{-1}; EI-MS (*m/z*): 417 (M^+, 15), 324 (M—PhO, 12), 323 (M—PhOH, 23), 283 (M—PhOCHCO, 64), 241 (63); Anal. Calcd for $C_{25}H_{23}NO_3S$ (417.52): C, 71.92; H, 5.55; N, 3.35. Found: C, 72.08; H, 5.60; N, 3.49.

*2-Phenoxy-2a,4-diphenyl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-one (***2d***)*

Colorless crystal, yield 93%, mp 190–191°C. R_f 0.40 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04–6.68 (m, 19H, ArH), 5.39 (s, 1H, CH), 4.02 (d, J = 11.0 Hz, 1H, H in CH_2), 3.67 (d, J = 14.0 Hz, 1H, CH), 3.22 (dd, J = 11.0, 14.0 Hz, 1H, H in CH_2); IR (KBr): ν1765 (C=O) cm^{-1}; EI-MS (*m/z*): 449 (M^+, 16), 356 (M—PhO, 7.1), 355 (M—PhOH, 16), 315 (M—PhOCHCO, 2.9), 211 (100); Anal. Calcd for $C_{29}H_{23}NO_2S$ (449.56): C, 77.48; H, 5.16; N, 3.12. Found: C, 77.47; H, 5.09; N, 3.20.

*4-(2-Chlorophenyl)-2-phenoxy-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2e***)*

Colorless crystal, yield 29%, mp 179–180°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–6.65 (m, 18H, ArH), 5.40 (s, 1H, CH), 4.54 (dd, J = 0.9, 10.6 Hz, 1H, H in CH_2), 3.58 (dd, J = 0.9, 14.1 Hz, 1H, CH), 3.22 (dd, J = 10.6, 14.1 Hz, 1H, H in CH_2); IR (KBr): ν 1764 (C=O) cm^{-1}; EI-MS (*m/z*): 483 (M^+, 8.8), 390 (M—PhO, 5.9), 389 (M—PhOH, 13), 349 (M—PhOCHCO, 5.5), 211 (100); Anal. Calcd for $C_{29}H_{22}ClNO_2S$ (484.01): C, 71.96; H, 4.58; N, 2.89. Found: C, 72.11; H, 4.77; N, 3.00.

*4-(4-Chlorophenyl)-2-phenoxy-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2f***)*

Colorless crystal, yield 87%, mp 220–222°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04–6.69 (m, 18H, ArH), 5.39 (s, 1H, CH), 3.98 (d, J = 11.0 Hz, 1H, H in CH_2), 3.62 (d, J = 14.1 Hz, 1H, CH), 3.17 (dd, J = 11.0, 14.1 Hz, 1H, H in CH_2); IR (KBr): ν 1764 (C=O) cm^{-1}; EI-MS (*m/z*): 483 (M+, 6.5), 390 (M—PhO, 4.9), 389 (M—PhOH, 9.1), 349 (M—PhOCHCO, 1.0), 211 (100); Anal. Calcd for $C_{29}H_{22}ClNO_2S$ (484.01): C, 71.96; H, 4.58; N, 2.89. Found: C, 71.95; H, 4.66; N, 2.99.

*4-(4-Bromophenyl)-2-phenoxy-2a-phenyl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2g***)*

Colorless crystal, yield 64%, mp 239–240°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04–6.69 (m, 18H, ArH), 5.39 (s, 1H, CH), 3.96 (d, J = 10.8 Hz, 1H, H in CH_2), 3.61 (d, J = 14.0 Hz, 1H, CH), 3.17 (dd, J = 10.8, 14.0 Hz, 1H, H in CH_2); IR (KBr): ν 1765 (C=O) cm^{-1}; EI-MS (*m/z*): 527 (M^+, 4.0), 434 (M—PhO, 3.1), 433 (M—PhOH, 6.5), 393 (M—PhOCHCO, 0.6), 211 (100); Anal. Calcd for $C_{29}H_{22}BrNO_2S$ (528.46): C, 65.91; H, 4.20; N, 2.65. Found: C, 65.99; H, 4.29; N, 2.58.

*2a-(4-Chlorophenyl)-2-phenoxy-4-phenyl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]-benzothiazepin-1-one (***2h***)*

Colorless crystal, yield 40%, mp 195–196°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–6.71 (m, 18H, ArH), 5.39 (s, 1H, CH), 3.95 (d, J = 11.0 Hz, 1H, H in CH_2), 3.60 (d, J = 14.2 Hz, 1H, CH), 3.22 (dd, J = 11.0, 14.2 Hz, 1H, H in CH_2); IR (KBr): ν 1766 (C=O) cm^{-1}; EI-MS (*m/z*): 483 (M^+, 6.9), 390 (M—PhO, 3.1), 389 (M—PhOH, 6.9), 349 (M—PhOCHCO, 2.4), 245 (59); Anal. Calcd for $C_{29}H_{22}ClNO_2S$ (484.01): C, 71.96; H, 4.58; N, 2.89. Found: C, 72.18; H, 4.50; N, 2.78.

*5-Benzoyl-4-methyl-2a-(4-methylphenyl)-2-phenoxy-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (***2i***)*

Colorless crystal, yield 88%, mp 248–249°C. R_f 0.40 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50–6.39 (m, 18H, ArH), 5.33 (ddq, J = 7.5, 10.5, 6.6 Hz, 1H, CH), 5.21 (s, 1H, CH), 3.30 (dd, J=7.5, 14.5 Hz, 1H, H in CH_2), 2.25 (dd, J=10.5, 14.5 Hz, 1H, H in CH_2), 2.15 (s, 3H, CH_3), 1.24 (d, J = 6.6 Hz, 3H, CH_3); IR (KBr): ν 1762, 1644 (C=O) cm^{-1}; EI-MS (*m/z*): 488 (M^+, 0.4), 395 (M—PhO, 8.6), 394 (M—PhOH, 6.6), 354 (M—PhOCHCO, 2.5); Anal. Calcd for $C_{32}H_{28}N_2O_3$ (488.58): C, 78.67; H, 5.78; N, 5.73. Found: C, 78.82; H, 5.91; N, 5.94.

*5-Benzoyl-4-methyl-2a-(4-methoxylphenyl)-2-phenoxy-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (***2j***)*

Colorless crystal, yield 57%, mp 183–184°C. R_f 0.30 (petroleum ether AcOEt = 3:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50–6.39 (m, 18H, ArH), 5.35 (ddq, J = 8.4, 9.9, 6.6 Hz, 1H, CH), 5.21 (s, 1H, CH), 3.62 (s, 3H, CH_3), 3.30 (dd, J = 8.4, 15.0 Hz, 1H, H in CH_2), 2.26 (dd, J=9.9, 15.0 Hz, 1H, H in CH_2), 1.25 (d, J = 6.6 Hz, 3H, CH_3); IR (KBr): ν 1761, 1644 (C=O) cm^{-1}; EI-MS (*m/z*): 504 (M^+, 0.6), 411 (M—PhO, 20), 410 (M—PhOH, 16), 370 (M—PhOCHCO, 23); Anal. Calcd for $C_{32}H_{28}N_2O_4$ (504.58): C, 76.17; H, 5.59; N, 5.55. Found: C, 76.44; H, 5.66; N, 5.69.

*5-Benzoyl-2-phenoxy-2a,4-diphenyl-2a,3,4,5-tetrahydro-azeto[1,2-a][1,5]-benzodiazepin-1(2H)-one (**2k**)*

Colorless crystal, yield 95%, mp 226–227°C. R_f 0.50 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57–6.27 (m, 24H, ArH), 6.07 (d, $J = 7.8$ Hz, 1H, CH), 5.37 (s, 1H, CH), 3.48 (dd, $J = 7.8$, 15.0 Hz, 1H, H in CH_2), 2.96 (dd, $J = 12.0$, 15.0 Hz, 1H, H in CH_2); IR (KBr): ν 1763, 1647 (C=O) cm^{-1}; EI-MS (*m*/*z*): 536 (M^+, 1.6), 443 (M—PhO, 11), 442 (M—PhOH, 7.3), 402 (M—PhOCHCO, 1.8); Anal. Calcd for $C_{36}H_{28}N_2O_3$ (536.62): C, 80.58; H, 5.26; N, 5.22. Found: C, 80.39; H, 5.09; N, 5.41.

*5-Benzoyl-4-(3-chlorophenyl)-2-phenoxy-2a-phenyl-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (**2l**)*

Colorless crystal, yield 81%, mp 209–210°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58–6.10 (m, 23H, ArH), 6.23 (dd, $J = 11.8$, 7.8 Hz, 1H, CH), 5.37 (s, 1H, CH), 3.47 (dd, $J = 7.0$, 14.8 Hz, 1H, H in CH_2), 2.91 (dd, $J = 11.8$, 14.8 Hz, 1H, H in CH_2); IR (KBr): ν 1763, 1645 (C=O) cm^{-1}; EI-MS (*m*/*z*): 570 (M^+, 0.6), 477 (M—PhO, 3.0), 476 (M—PhOH, 2.3), 436 (M—PhOCHCO, 2.7); Anal. Calcd for $C_{36}H_{27}ClN_2O_3$ (571.06): C, 75.72; H, 4.77; N, 4.91. Found: C, 75.70; H, 5.01; N, 4.80.

*5-Benzoyl-4-(4-chlorophenyl)-2-phenoxy-2a-phenyl-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (**2m**)*

Colorless crystal, yield 92%, mp 235–236°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 M Hz, $CDCl_3$) δ 8.58–6.03 (m, 23H, ArH), 6.23 (dd, $J = 7.8$, 11.6 Hz, 1H, CH), 5.37 (s, 1H, CH), 3.44 (dd, $J = 7.8$, 14.9 Hz, 1H, H in CH_2), 2.90 (dd, $J = 11.6$, 14.9 Hz, 1H, H in CH_2); IR (KBr): ν 1763, 1643 (C=O) cm^{-1}; EI-MS (*m*/*z*): 570 (M^+, 3.5), 477 (M—PhO, 28), 476 (M—PhOH, 19), 436 (M—PhOCHCO, 3.0); Anal. Calcd for $C_{36}H_{27}ClN_2O_3$ (571.06): C, 75.72; H, 4.77; N, 4.91. Found: C, 75.51; H, 4.49; N, 5.08.

*5-Benzoyl-4-(3-bromophenyl)-2-phenoxy-2a-phenyl-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (**2n**)*

Colorless crystal, yield 83%, mp 191–192°C. R_f 0.40 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57–6.10 (m, 23H, ArH), 6.22 (dd, $J = 7.8$, 12.0 Hz, 1H, CH), 5.37 (s, 1H, CH), 3.46 (dd, $J = 7.8$, 15.0 Hz, 1H, H in CH_2), 2.90 (dd, $J = 12.0$, 15.0 Hz, 1H, H in CH_2); IR (KBr): ν 1763, 1645 (C=O) cm^{-1}; EI-MS (*m*/*z*): 614 (M^+, 1.8), 521 (M—PhO, 14), 520 (M—PhOH, 9.6), 480 (M—PhOCHCO, 2.1); Anal. Calcd for $C_{36}H_{27}BrN_2O_3$ (615.52): C, 70.25; H, 4.42; N, 4.55. Found: C, 70.01; H, 4.54; N, 4.69.

*5-Benzoyl-4-(4-methoxylphenyl)-2-phenoxy-2a-phenyl-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (**2o**)*

Colorless crystal, yield 51%, mp 183–184°C. R_f 0.20 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56–6.03 (m, 23H, ArH), 6.27 (dd, $J = 7.8$, 12.0 Hz, 1H, CH), 5.36 (s, 1H, CH), 3.76 (s, 3H, CH_3O), 3.44 (dd, $J = 7.8$, 15.0 Hz, 1H, H in CH_2), 2.93 (dd, $J = 12.0$, 15.0 Hz, 1H, H in CH_2); IR (KBr): ν 1762, 1646 (C=O) cm^{-1}; EI-MS (*m*/*z*): 566 (M^+, 2.6), 473 (M—PhO, 11), 472 (M—PhOH, 6.0), 432 (M—PhOCHCO, 3.4); Anal. Calcd for $C_{37}H_{30}N_2O_4$ (566.65): C, 78.43; H, 5.34; N, 4.94. Found: C, 78.21; H, 5.30; N, 5.12.

*5-Benzoyl-2a-(4-chlorophenyl)-2-phenoxy-4-phenyl-2a,3,4,5-tetrahydro-azeto[1,2-a]-[1,5]benzodiazepin-1(2H)-one (**2p**)*

Colorless crystal, yield 33%, mp 249–250°C. R_f 0.30 (petroleum ether AcOEt = 5:1, silica gel plate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55–6.07 (m, 23H, ArH), 6.25 (dd, $J = 7.8$, 11.2 Hz, 1H, CH), 5.36 (s, 1H, CH), 3.43 (dd, $J = 7.8$, 14.7 Hz, 1H, H in CH_2), 2.97 (dd, $J = 11.2$, 14.7 Hz, 1H, H in CH_2); IR (KBr): ν 1765, 1642 (C=O) cm^{-1}; EI-MS (*m*/*z*): 570 (M^+, 2.6), 477 (M—PhO, 14), 476 (M—PhOH, 21), 436 (M—PhOCHCO, 3.8); Anal. Calcd for $C_{36}H_{27}ClN_2O_3$ (571.06): C, 75.72; H, 4.77; N, 4.91. Found: C, 75.91; H, 4.57; N, 5.14.

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