Heteroatom Chemistry
Volume 11, Number 2, 2000

Synthesis of Oxazirino[2,3-*a*][1,5]benzodiazepines by Oxidation of 1*H*-1,5-Benzodiazepines with *m*-Chloroperbenzoic Acid (MCPBA)

Jiaxi Xu and Liangbi Chen

College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

Received 25 August 1999; revised 4 November 1999

ABSTRACT: *2,4-Disubstituted 1-benzoyl-2,3-dihydro-1H-1,5-benzodiazepines were oxidized by m-chloroperbenzoic acid (MCPBA) to produce 1a,3-disubstituted 4-benzoyl-1a,2,3,4-tetrahydro-oxazirino[2,3-a][1,5]benzodiazepines, a novel tricyclic heterocyclic system. However, 2,4-disubstituted 2,3-dihydro-1H-1,5-benzodiazepines were oxidized by MCPBA under the same conditions to give a 2,4-disubstituted 2,3-dihydro-2-hydroxy-1H-1,5-benzodiazepine or a 2,4-disubstituted 3H-1,5-benzodiazepine, respectively. We propose a hydroxylation mechanism of peracid oxidation.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:158–162, 2000

INTRODUCTION

Benzothiazepine and benzodiazepine derivatives are two of the most important classes of bioavailable therapeutic agents, having widespread biological activities including anxiolytic, anticonvulsant, and antihypnotic activities [1]. They also function as selective cholecystokinin (CCK) receptor subtype A and B antagonists [2], opioid-receptor ligands [3], platelet-activating factor antagonists [4], human immunodeficiency virus transactivator Tat/Tar antagonists [5], reverse-transcriptase inhibitors [6], and as farnesyltransferase inhibitors [7]. During recent years, our research group has focused on studies of the synthesis and stereo-structure of novel tricyclic 1,5-benzothiazepine and 1,5-benzodiazepine derivatives because most benzodiazepine derivatives with well-documented clinical value are in the form of their tricyclic derivatives [8–12]. The present work deals with the syntheses of some novel 1a,2,3,4-tetrahydro-oxazirino[2,3-*a*][1,5]benzodiazepine derivatives by oxidation of the respective benzodiazepines with *m*-chloroperbenzoic acid (MCPBA).

Correspondence to: Jiaxi Xu.

RESULTS AND DISCUSSION

It is a general method to synthesize oxaziridine ring derivatives by oxidation of imines with peroxy-acids. In the realm of peroxy-acids, MCPBA is most often used to oxidize olefins, the reactions being carried out in organic solvents, such as dichloromethane or chloroform [13]. However, the use of a buffered aqueous medium seems to be especially suitable for oxidation of somewhat acid-sensitive starting materials or products [14–16]. The imine group in 1,5-benzodiazepine is acid-sensitive. Thus, we performed our experiments by a basic biphasic oxidation procedure in a mixture of dichloromethane and saturated aqueous sodium bicarbonate by applying as a phase transfer catalyst benzyltriethylammonium chloride (TEBA). 2,4-Disubstituted 1-benzoyl-2,3-dihydro-1*H*-1,5-benzodiazepines **1** can react readily with MCPBA to yield 1a,3-disubstituted 4-benzoyl-1a,2,3,4-tetrahydro-oxazirino [2,3-*a*][1,5]benzodiazepines **2** in satisfactory yields by the aforementioned basic biphastic oxidation procedure.

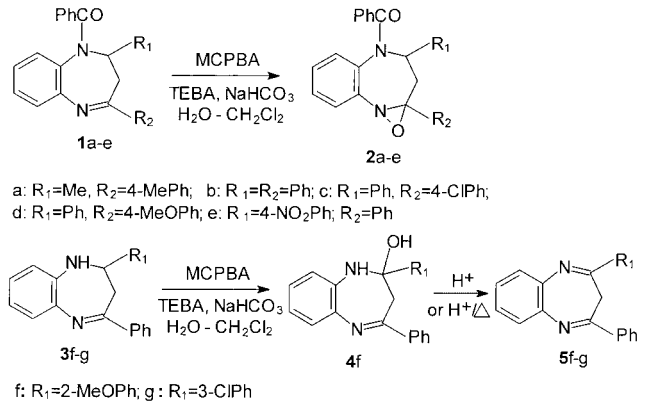
The epoxidation mechanism of an alkene with a

peroxycarboxylic acid is essentially an electrophilic-addition reaction. Electron-deficient and sterically hindered C = C double bonds usually undergo epoxidation reactions only with difficulty [17]. A similar phenomenon was also observed in the oxaziridation of imines with MCPBA. For example, 1-benzoyl-4-(4-nitrophenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine **1** (with R_1 = Ph, R_2 = 4-NO_2Ph) is very difficult to oxidize under these conditions. It is presumed that the imine group in the molecule is electron-deficient due to the presence of the electron-withdrawing NO_2 group in the para-position of R_2 (See Scheme 1).

Further verification of the oxaziridine structure in oxazirino[2,3-*a*][1,5]benzodiazepines **2** has been achieved by reaction of the randomly selected compound **2d** with triphenylphosphine and with HI. When the compound **2d** was stirred in benzene with an equivalent amount of triphenylphosphine overnight, triphenylphosphine oxide and the starting material 1*H*-1,5-benzodiazepine **1d** were produced in good yield. This and related products were identified by comparison of their properties with those of authentic samples on silica gel TLC plates [19]. With aqueous potassium iodide in acetic acid, **2d** liberated iodine [19]. Both these reactions are characteristic of oxaziridines [20].

In order to extend the application of these reactions, we also carried out the oxidation of 2,4-disubstituted 2,3-dihydro-1*H*-1,5-benzodiazepines **3**. They did not yield oxaziridation products. According to the spectral data and elemental analyses, the 1*H*-1,5-benzodiazepine **3f** underwent a tertiary C-H oxidation to produce a 2,3-dihydro-2-hydroxy-2-(2-methoxylphenyl)-4-phenyl-1*H*-1,5-benzodiazepine **4f**. In its ^{1}H NMR spectrum, an ABX spinning system $CHCH_2$ disappeared and two singlet peaks for CH_2 and OH appeared. It is very surprising that the structure of the compound **4f** is the equivalent of the adduct of an amine to a ketone. It should be unstable. However, the compound **4f** survives the reaction procedure and is somewhat stable at room temperature, even in refluxing benzene. However, the benzodiazepine **3g**, with only a different substituent in the 2-phenyl group, yielded directly 2-(3-chlorophenyl)-4-phenyl-3*H*-1,5-benzodiazepine **5g** [18], a dehydrated product of the C-H oxidized product of the compound **3g**. Although the compound **4f** is stable in refluxing benzene, it could undergo a dehydration reaction to yield 2-(2-methoxyphenyl)-4-phenyl-3*H*-1,5-benzodiazepine **5f** in refluxing benzene in the presence of *m*-chloroperbenzoic acid as an acidic catalyst. Up to now, we can't explain why hydroxylation products of benzodiazepines **3f** and **3g** showed different stabilities. It is very interesting that the oxidation of a 2,4-disubstituted 2,3-dihydro-1*H*-1,5-benzodiazepine with MCPBA provides a conversion method from a 2,3-dihydro-1*H*-1,5-benzodiazepine to a 3*H*-1,5-benzodiazepine. It is also a novel method for the synthesis of a 3*H*-1,5-benzodiazepine, which is usually prepared by reaction of *o*-phenylenediamine with a *β*-diketone or an *a*-carbonyl alkyne [18,21].

Based on the results published in the literature [22,23] and our experimental results, a possible mechanism of 1*H*-1,5-benzodiazepine hydroxylation could be presumed to be a radical procedure (Scheme 2). At first, the peracid MCPBA decomposes to yield a carboxy radical and a hydroxy radical. The carboxy radical can further decompose to form an aryl radical and a carbon dioxide molecule. The aryl radical reacts with benzodiazepines **3** to produce benzodiazepine radicals. They further react with MCPBA to yield the corresponding hydroxylation products **4**. The unstable aminohydrin, for example, **4g**, could undergo a dehydration reaction to produce a 3*H*-1,5-benzodiazepine **5g** in the oxidation procedure. However, the stable aminohydrin, for example, **4f**, does not dehydrate under the same conditions. It could dehydrate in refluxing benzene in the presence of acid as a catalyst. In an attempt to verify our proposed mechanism and establish whether the aminohydrin **4f** was obtained by the hydroxylation of the 1,5-benzodiazepine **2f** or by water addition to 3*H*-1,5-benzodiazepine **5f** (which could be generated as the 3*H*-1,5-benzodiazepine **5g** under the same oxidation conditions), we performed the addition reaction of 3*H*-1,5-benzodiazepine **5f**, which was obtained from **4f** by a dehydration reaction, with water under neutral or acidic conditions. No adduct has been found under these addition conditions. These



SCHEME 1 Oxidation reactions of 2,3-dihydro-1*H*-1,5-benzodiazepines with *m*-chloroperoxybenzoic acid (MCPBA)

TABLE 1 Physical and Spectral Data

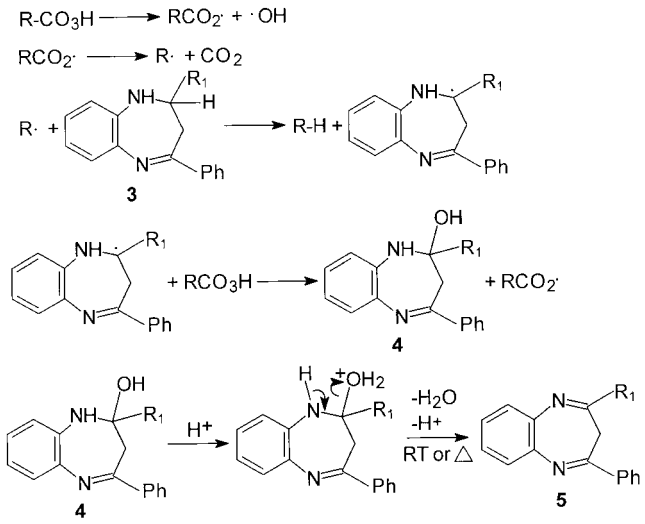
Compound	Yield (%)	m.p. (°C)	^{1}HNMR ($CDCl_3$/TMS) δ (ppm), J(Hz)	IR(KBr) ν(cm^{-1})	MS/EI (m/z)
2a	62	150–151	1.22(3H, d, J = 6.6, Me), 1.62(1H, dd, J = 13.0, 14.4), 2.35 (3H, s, ArMe), 2.99(1H, dd, J = 4.8, 14.4), 4.79(1H, ddq, J = 4.8, 6.6, 13.0), 6.56–7.96(13H, m, Aromatic)	3031, 2968, 1641	370(M^+), 354, 265, 249
2b	72	190–192	2.24(1H, dd, J = 13.6, 14.8), 3.21(1H, dd, J = 4.6, 14.4), 5.70(1H, dd, J = 4.6, 13.6), 6.48(1H, d, J = 8.4, Aromatic), 6.90–8.13(18H, m, Aromatic)	3061, 1643	418(M^+), 402, 313, 297
2c	64	163–164	2.33(1H, dd, J = 13.8, 14.8), 3.18(1H, dd, J = 4.6, 14.8), 5.70(1H, dd, J = 4.6, 13.8), 6.46(1H, d, J = 8.4, Aromatic), 6.88–8.07(17H, m, Aromatic)	3060, 1643	452(M^+), 436, 347, 331
2d	54	200–201	3.12(1H, dd, J = 13.6, 13.8), 3.31(1H, dd, J = 4.8, 13.6), 3.90(3H, s, MeO), 6.19(1H, dd, J = 4.8, 13.8), 6.62–7.45(16H, m, Aromatic), 8.07(2H, d, J = 8.4, Aromatic)	3060, 1642, 1595	448(M^+), 432, 343, 327
2e	76	188–189	3.18(1H, dd, J = 13.6, 3.6), 3.29(1H, dd, J = 4.6, 13.6), 5.72(1H, dd, J = 4.6, 13.6), 6.46(1H, d, J = 8, Aromatic), 6.87–8.30(17H, m, Aromatic)	3061, 1642, 1594	463(M^+), 447, 358, 342
4f	24	134–135	3.47(3H, s, MeO), 3.96(2H, s, CH_2), 6.04(1H, s, OH), 6.32–7.97(13H, m, Aromatic), 12.73(1H, s, NH, forming H-bond with OH)	3450, 3370, 3061, 1633, 1595	344(M^+), 326, 267
5f	95	102–103	3.47(2H, s, CH_2), 3.71(3H, s, MeO), 6.89–7.84(13H, m, Aromatic)	3054, 1594, 1568	326(M^+)
5g	21	170–171 (lit [18] 171)	3.48(2H, s, CH_2), 7.32–8.00(13H, m, Aromatic)	3056, 1592, 1566	330(M^+)

TABLE 2 Elemental Analysis Data

Compound	Molecular Formula	Molecular Weight	Cald. C	Cald. H	Cald. N	Found C	Found H	Found N
2a	$C_{24}H_{22}N_2O_2$	370.45	77.81	5.99	7.56	78.05	5.79	7.88
2b	$C_{28}H_{22}N_2O_2$	418.50	80.36	5.30	6.69	80.02	5.20	6.78
2c	$C_{28}H_{21}ClN_2O_2$	452.94	74.25	4.67	6.18	74.16	4.38	5.92
2d	$C_{29}H_{24}N_2O_3$	448.52	77.66	5.39	6.25	77.97	5.46	6.03
2e	$C_{28}H_{21}N_3O_4$	463.49	72.56	4.57	9.07	72.31	4.86	9.20
4f	$C_{22}H_{20}N_2O_2$	344.41	76.24	4.57	8.47	76.11	4.87	8.20
5f	$C_{22}H_{18}N_2O$	326.40	80.96	5.56	8.58	80.70	5.81	8.73
5g	$C_{21}H_{15}ClN_2$	330.82	76.72	5.85	8.13	76.33	5.72	7.88

results support the concept that the aminohydrin is formed by the radical hydroxylation of the 1*H*-1,5-benzodiazepine **3**.

In summary, 1a,3-disubstituted 4-benzoyl-1a,2,3,4-tetrahydro-oxazirino[2,3-*a*][1,5]benzodiazepines were synthesized by oxidation of 2,4-disubstituted 1-benzoyl-2,3-dihydro-1*H*-1,5-benzodiazepines with MCPBA in a basic biphastic oxidation procedure with a phase-transfer catalyst, benzyltriethylammonium chloride (TEBA). However, 2,4-disubstituted 2,3-dihydro-1*H*-1,5-benzodiazepines were oxidized by MCPBA under the same conditions to give a 2,4-disubstituted 2,3-dihydro-2-hydroxy-1*H*-1,5-benzodiazepine or a 2,4-disubstituted 3*H*-1,5-benzodiazepine, respectively. The former possibly offers a new method for the preparation of an aminohydrin from an amine. The latter provides a novel method for conversion of a 2,3-dihydro-1*H*-



SCHEME 2 A possible hydroxylation and dehydrating reaction mechanism of 2,3-dihydro-1*H*-1,5-benzodiazepines with *m*-chloroperoxybenzoic acid (MCPBA)

1,5-benzodiazepine to a 3*H*-1,5-benzodiazepine. It is also a new method for the synthesis of a 3*H*-1,5-benzodiazepine.

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}HNMR spectra were recorded on a Varian Mercury 200 spectrometer with 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. TLC separations were performed on silica gel G plates with petroleum ether (30–60°C)/ethyl acetate (5:1), and the plates were visualized with UV light and/or iodine vapor.

Oxidation of 2,3-Dihydro-1H-1,5-benzodiazepine Derivatives

General Procedure. In a 100 mL three-necked flask equipped with magnetic stirrer and dropping funnel 1.0 mmol of the appropriate 1,5-benzodiazepine derivative, **1** or **3,** in 7 mL of CH_2Cl_2, 20 mL of saturated aqueous $NaHCO_3$, and 0.1 g (0.5 mmol) of TEBA were placed. The solution was cooled to 0–5°C in an ice bath and, with rapid stirring, 2.0 mmol of MCPBA in 9 mL of CH_2Cl_2 was added dropwise over 1 hour. After the addition was complete, the solution was stirred for an additional 4 hours at room temperature, and the CH_2Cl_2 solution was washed with water (50 mL), 10% Na_2SO_3 (3 × 50 mL), 10% $NaHCO_3$ (3 × 50 mL), and water (50 mL). After the solution was dried over anhydrous K_2CO_3, the solvent was removed on the rotatory evaporator, the bath temperature being maintained below 35°C, to give a brown residue. After crystallizing from a mixture of benzene and methanol, the respective products were obtained.

Reaction of 4-Benzoyl-1a-(4-methoxyphenyl)-3-phenyl-1a,2,3,4-tetrahydro-oxazirino[2,3-a][1,5]benzodiazepine **2d** *with Triphenylphosphine*

Into a 25 mL flask equipped with a magnetic stir bar and a reflux condenser and with a nitrogen inlet were placed 179 mg (0.4 mmol) of oxazirino[2,3-*a*][1,5]benzodiazepine **2d** and 105 mg (0.4 mmol) of triphenylphosphine in 5 mL of benzene. After the solution was stirred for 24 hours under a nitrogen atmosphere at room temperature, the reaction mixture was subjected to silica gel TLC analyses using mixtures of benzene-ether or petroleum ether-ethyl acetate as eluents. The corresponding 1*H*-1,5-benzodiazepine **1d** and triphenylphosphine oxide were identified by comparison of their properties with those of authentic samples on silica gel TLC plates.

Reaction of 4-Benzoyl-1a-(4-methoxyphenyl)-3-phenyl-1a,2,3,4-tetrahydro-oxazirino[2,3-a][1,5]benzodiazepine **2d** *with Hydrogen Iodide*

In a 50 mL flask equipped with a magnetic stir bar was dissolved 179 mg (0.4 mmol) of oxazirino[2,3-*a*][1,5]benzodiazepine **2d** in 10 mL of glacial acetic acid. Approximately 2.0 mL of a 5% potassium iodide solution was added, and the resulting iodine was titrated with a standard 0.1 N sodium thiosulfate solution until clear.

Dehydration Reaction of 2,3-Dihydro-2-hydroxy-2-(2-methoxyphenyl)-4-phenyl-1H-1,5-benzodiazepine **4f**

In a 25 mL flask equipped with a magnetic stir bar and a reflux condenser were placed 275 mg (0.8 mmol) of 2,3-dihydro-2-hydroxy-2-(2-methoxyphenyl)-4-phenyl-1*H*-1,5-benzodiazepine **4f** and a catalytic amount of MCPBA in 10 mL of benzene. The reaction mixture was refluxed for 1 hour and cooled to room temperature. After washing with 10% $NaHCO_3$ and drying over anhydrous Na_2SO_4, removal of solvent gave an oily solid, which was crystallized from methanol to yield yellow crystallines **5f.**

REFERENCES

[1] Sternbach, L. H. J Med Chem 1979, 22, 1.
[2] Bock, M. G.; Dipardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. J Med Chem 1989, 32, 13.
[3] Romer, D.; Buscher, H. H.; Hill, R. C.; Maurer, R.; Petcher, T. J.; Zeugner, H.; Benson, W.; Finner, E.; Milkowski, W.; Thies, P. W. Nature (London) 1982, 298, 759.
[4] Kornecki, E.; Ehrlich, Y. H.; Lenox, R. H. Science 1984, 226, 1454.
[5] Hsu, M.-C.; Schutt, A. D.; Hooly, M.; Slice, L. W.; Sherman, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. Science 1991, 254, 1799.
[6] Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaechers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A. C.; Clercq, E. D.; Janssen, P. A. J. Nature (London) 1990, 343, 470.
[7] James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, C. W.; Lucas, B. K.; Levinson, A. D.; Marsters, J. C., Jr. Science 1993, 260, 1937.
[8] Xu, J. X.; Jin, S.; Xing, Q. Y. Phosphur Sulfur Silicon Relat Elem 1998, 141, 57.
[9] Xu, J. X.; Wu, H. T.; Jin, S. Chin J Chem 1999, 17, 84.
[10] Xu, J. X.; Jin, S. Heteroat Chem 1999, 10, 35.
[11] Zhang, X. Y.; Xu, J. X.; Jin, S. Chin J Chem 1999, 17, 404.
[12] Xu, J. X.; Lan, R. X.; Jin, S. Chem J Chin University 1998, 20, 1774.
[13] Rao, A. S.; Paknikar, S. K.; Kirtan, J. G. Tetrahedron 1989, 39, 232.
[14] Rao, C. P.; Srimannarayana, G. Syn Commun 1987, 17, 1507.
[15] Fringuelli, F.; Germani, R.; Pizzo, F.; Savvelli, G. Tetrahedron Lett 1989, 30, 1427.
[16] Davis, F. A.; Stringer, O. D. J Org Chem 1982, 47, 1774.
[17] Xu, J. X.; Liang, B.; Jin, S. Phosphur Sulfur Silicon Relat Elem 1999, 152, 1.
[18] Kulkarni, S. U.; Thakar, K. A. J Indian Chem Soc 1975, 52, 849.
[19] Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M.; J Am Chem Soc 1980, 102, 2000.
[20] Emmons, W. D. J Am Chem Soc 1957, 79, 2184.
[21] Finar, I. L. J Chem Soc 1958, 4094.
[22] Schneider, H.-J.; Muller, W. J Org Chem 1985, 50, 4609.
[23] Higuchi, T.; Shimada, K.; Maruyam, N.; Hirobe, M. J Am Chem Soc 1993, 115, 7551.