A Novel Conversion of 2,4-Diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines into 2,4-Diaryl-3*H*-1,5-benzodiazepines

ZHANG, Qi-Han(张奇涵) XU, Jia-Xi*(许家喜)

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

A novel conversion of 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepins into 2,4-diaryl-3*H*-1,5-benzodiazepines by the reaction with *m*-chloroperbenzoic acid (MCPBA) was reported.

Keywords 1*H*-1,5-Benzodiazepine, 3*H*-1,5-benzodiazepine, *m*-chloroperbenzoic acid, conversion

Introduction

In recent three decades many new pharmaceuticals synthesized have structures containing heterocyclic rings, especially benzodiazepine. Benzodiazepine derivatives are one of the most important classes of bioavailible therapeutic agents having widespread biological activities including anxiolytic, anticonvulsant, and antihypnotic activities.[1] They also act as selective cholecystokinin (CCK) receptor subtype A and B antagonists,[2] platelet-activating factor antagonists, human immunodeficiency virus *trans*-activator Tat/Tar antagonists,[3] and as farnesyltransferase inhibitors.[4] During recent years, our research group has focused on studies of the synthesis and stereo-structure of novel 1,5-benzothiazepine and 1,5-benzodiazepine derivatives in order to develop new pharmaceuticals.[5-9] The present work deals with the conversion of 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepins into 2,4-diaryl-3*H*-1,5-benzodiazepines by reaction with *m*-chloroperbenzoic acid (MCPBA).

Results and Discussion

2,4-Disubstituted 3*H*-1,5-benzodiazepine derivatives, such as clozapine, chlorpromazine, *etc*., showed potential neuroleptic activity.[10] Synthesis of 2,4-disubstituted 3*H*-1,5-benzodiazepines has been previously reported.[11-14] The two most common methods are Micheal additions of *o*-diaminobenzene derivatives with α-carbonyl alkynes followed by intramolecular condensation reactions of amines and ketones[11,12] or condensation of *o*-diaminobenzene derivatives and 1,3-diketones.[13,14]

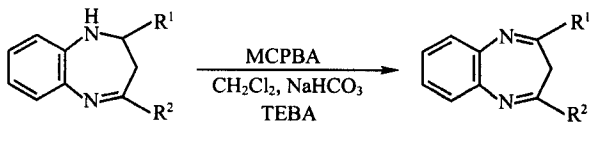
We herein report a novel method to convert 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepins into 2,4-diaryl-3*H*-1,5-benzodiazepines by oxidation of *m*-chloroperbenzoic acid and dehydrolysis in a one-pot reaction.

m-Chloroperoxybenzoic acid (MCPBA) is a useful peroxy-acid. It has been widely used to synthesize epoxy compounds and oxaziridine derivatives by oxidation of olefins and imines,[15,16] respectively. However, the use of a buffered aqueous medium seems to be especially suitable for oxidation of somewhat acid-sensitive starting materials or products.[17] We carried out our experiments by a basic biphasic oxidation procedure in a mixture of dichloromethane and saturated aqueous sodium bicarbonate by applying a phase transfer catalyst benzyltriethylammonium chloride (TEBA) because the imine group in 1,5-benzodiazepine is acid-sensitive. 2,4-Diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines **1** can react readily with MCPBA to yield 2,4-diaryl-3*H*-1,5-benzodiazepines **2** in moderate yields. This is a new method for synthesis of 3*H*-1,5-benzodiazepine derivatives and is also a novel conversion of a secondary amine into an imine derivative.

* E-mail: jiaxu99@yahoo.com

Received August 14, 2000; revised November 15, 2000; accepted December 11, 2000.

Project supported by the National Natural Science Foundation of China (No. 29772002).



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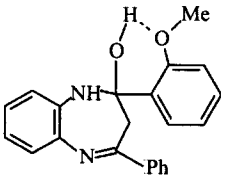

3d

Table 1 Conversion of 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines **1** into 2,4-diaryl-3*H*-1,5-benzodiazepines **2**

Entry	R^1	R^2	Yield of **2** (%)	m.p. of **2** (℃)/(Lit)
a	Ph	Ph	63	140—141(139—140[12])
b	3-ClPh	Ph	68	170—171(171[13])
c	4-ClPh	Ph	72	176—177(176—177[12])
d	2-MeOPh	Ph	54	102—103[a](102—103[18])
e	4-MeOPh	Ph	58	153—154(153—154[12])
f	2-BrPh	Ph	45	172—174
g	3-BrPh	Ph	60	154—155 (154[13])
h	Ph	4-MeOPh	52	153—154(153—154[12])

[a]In the same reaction conditions, **1d** was converted into 2,3-dihydo-2-hydroxy-2-(2-methoxylphenyl)-4-phenyl-1*H*-1,5-benzodiazepine **3d**, which was further refluxed in benzene in the presence of *m*-chlorobenzoic acid to yield **2d** in 54% combined yield. Aminohydrins are a kind of unstable compounds. Compound **3d** is a stable aminohydrin probably due to its intramolecular hydrogen-bonding.

In order to extend the application of this reaction, we also carried out the oxidation of several secondary amines, such as $PhCH_2NHPh$, $PhCH_2NHPhOMe$-*p*, $(PhCH_2)_2NH$, *etc*. However, no expected products have been isolated in these reaction conditions. For $PhCH_2NHPh$ and $PhCH_2NHPhOMe$-*p*, only nitrone derivatives PhCH = N(→O)Ph and PhCH = N(→O)PhOMe-*p* were obtained.[19] But $(PhCH_2)_2NH$ was converted into hydroxyamine derivative, $(PhCH_2)_2NOH$.

All products were characterized by ^1H NMR spectra and the melting points compared with those in the literatures.[12,13,18,19] The unknown products **2f** and **3d** were also characterized by IR and MS spectrometries and elemental analysis. In summary, a novel conversion of 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepins into 2,4-diaryl-3*H*-1,5-benzodiazepines by oxidation of *m*-chloroperbenzoic acid (MCPBA) in moderate yields was reported.

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 ^1H NMR spectra were recorded on a Varian Mercury 200 spectrometer in $CDCl_3$ with TMS as the internal standard. 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℃)/ethyl acetate (5:1), and the plates were visualized with UV light and/or iodine vapor.

2, 4-Diaryl-2, 3-dihydro-1*H*-1, 5-benzodiazepines were synthesized according to the literature method.[5-7,20]

Conversion of 2, 4-diaryl-2, 3-dihydro-1H-1, 5-benzodiazepins into 2, 4-diaryl-3H-1, 5-benzodiazepines

In a 50 mL three-necked flask equipped with a magnetic stirrer and a dropping funnel were placed 1.0 mmol of the aqpropriate 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepine **1** in 7 mL of CH_2Cl_2, 20 mL of saturated aqueous $NaHCO_3$ and 0.05 g (0.25 mmol) of TEBA (benzyltriethylammonium chloride). The solution was cooled to 0—5℃ with an ice bath and 2.0—3.0 mmol of MCPBA (*m*-chloroperbenzoic acid) in 9 mL of CH_2Cl_2 was added dropwise with rapid stirring over 1 h. After the addition was complete, the solution was stirred

for additional 4—10 h at room temperature, and the CH_2Cl_2 solution was washed subsequently with water (25 mL), 10% Na_2SO_3 (3 × 25 mL), 10% $NaHCO_3$ (3 × 25 mL) and water (25 mL). After the solution was dried over anhydrous K_2CO_3, the solvent was removed on the rotatory evaporator to give a brown residue. After crystallizing from a mixture of benzene and methanol or separating on a silica gel column with petroleum ether (30—60℃) /ethyl acetate (5:1) as an eluent, the respective products were obtained.

In the same reaction conditions, **1d** was converted into 2, 3-dihydo-2-hydroxy-2-(2-methoxylphenyl)-4-phenyl-1*H*-1,5-benzodiazepine **3d** in 60% yield, which was further refluxed in benzene in the presence of *m*-chlorobenzoic acid to give **2d** in 90% yield.

2-(2-Bromophenyl)-4-phenyl-3H-1,5-benzodiazepine (**2f**) Yield: 45%; m.p. 172—174℃; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.27 (s, br, 2H, CH_2), 6.02—7.98 (m, 13H, ArH); IR (KBr) ν: 1595 cm^{-1}; EI-MS (70 eV) *m/z*: 374 (M^+), 376 ($M+2)^+$; Anal. calcd for $C_{21}H_{15}N_2Br$: C 67.21, H 4.03, N 7.46; found C 66.99, H 4.29, N 7.24.

2,3-Dihydo-2-hydroxy-2-(2-methoxylphenyl)-4-phenyl-1H-1,5-benzodiazepine (**3d**) Yield: 60%; m.p. 134—135℃; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.47 (s, 3H, MeO), 3.96 (s, 2H, CH_2), 6.04 (s, 1H, NH), 6.32—7.97 (m, 13H, Aromatic), 12.73 (s, 1H, OH, forming H-bond with ArOMe); IR (KBr) ν: 3450, 3370, 3061, 1633, 1595 cm^{-1}; EI-MS (70 eV) *m/z*: 344 (M^+), 326 (M^+-18); Anal. calcd for $C_{22}H_{20}N_2O_2$: C 76.24, H 4.57, N 8.47; found C 76.11, H 4.87, N 8.20.

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(E200008155 LI, L.T.; LING, J.)