Synthesis of Novel 2,3-Dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-Dioxides and Their Epoxidation Ability

Oksana Makota,[a]* Janine Wolf,[b] Yuriy Trach,[a] and Barbel Schulze[b]

[a]Institute of Chemistry and Chemical Technologies, Lviv Polytechnic National University, U-79013 Lviv, Ukraine
[b]Institute of Organic Chemistry, Leipzig University, Johannisallee 29, D-04103 Leipzig, Germany
*E-mail: makotaoksana@yahoo.com

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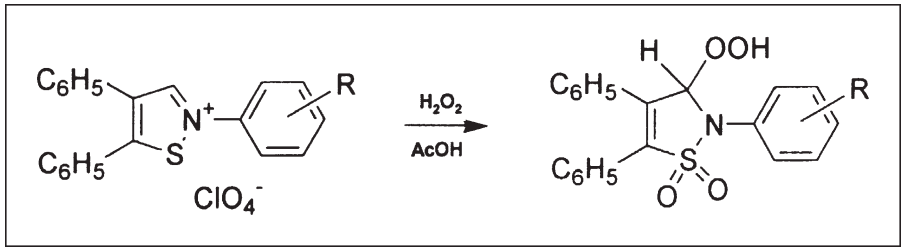

The novel hydroperoxy sultams, 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides, were synthesized by the oxidation of the 2-aryl-4,5-diphenyl substituted isothiazolium salts with H_2O_2. These hydroperoxy sultams were investigated as epoxidation agents in the epoxidation reaction of *cis*-cyclooctene catalyzed by MoB. 2-(2-Chlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide was found to have the highest epoxidation ability.

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INTRODUCTION

The cyclic sulfonamides (sultams) have been shown to be highly useful heterocycles for medicinal chemistry [1,2] as well as for chemical methodology [3,4]. They show biological activities such as antibacterial [5,6], anticonvulsant [7,8], sedative-hypnotic [9], and peptidomimetic [10,11]. Sultams have found application as chiral auxiliaries in several asymmetric processes such as Diels-Alder reactions [12,13], alkylation [14], and dihydroxylation [15] and are used in enantioselective catalysis [16]. Hydroperoxy sultams can also serve as oxidants in oxidation of heteroatoms (N, S, P) [17,18] and in epoxidation of double bonds [19].

We now report the synthesis of novel hydroperoxy sultams, 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides, and studies of their epoxidation ability in the epoxidation reaction of *cis*-cyclooctene catalyzed by molybdenum boride MoB.

RESULTS AND DISCUSSION

Our approach to hydroperoxy sultams started from isothiazolium salts (1) (Scheme 1) which were prepared for the first time by intramolecular cyclocondensation of β-thiocyanatovinyl aldehydes and the suitably substituted anilines in the presence of perchloric acid in acetic acid in moderate-to-good yields: 1a (61%), 1b (62%), and 1c (51%) according to already reported synthesis [20,21]. The oxidation of the 2-aryl-4,5-diphenyl substituted isothiazolium salts in glacial acetic acid with 30% H_2O_2 at r.t. gave stable 3-hydroperoxysultams (2) in good yields: 2-(2-chlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2a) (70%), 2-(2,6-dichlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2b) (70%) and 2-(2,6-dichloro-4-nitrophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2c) (72%) after 72, 72 and 96 h stirring, respectively.

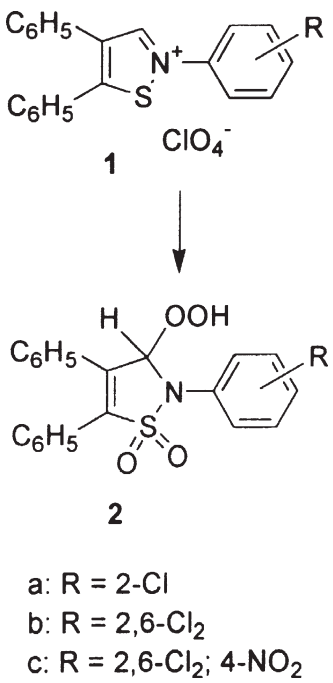
The structures of the 3-hydroperoxysultams 2a, 2b, and 2c were established by IR and NMR spectroscopy and composition was confirmed by mass spectrometry and elemental analysis.

The IR spectra of compounds 2 show two absorption bands at 1302–1316 and 1146–1160 cm^{-1} for the SO_2 groups which are characteristic for the antisymmetric and symmetric vibrations of the 1,1-dioxides, respectively. The two absorption bands for the NO_2 group are observed at 1335 and 1537 cm^{-1} in the spectrum of compound 2c.

In ^1H NMR spectra of 3-hydroperoxysultams 2, the typical absorption of the 3-H atom appears at 6.49–6.60 ppm. The ^{13}C NMR signals for C-3 at 92.5–95.0 ppm are characteristic for compounds 2.

The 2 were investigated as epoxidation agents in the epoxidation reaction of cyclooctene in the presence of molybdenum boride. The kinetic curves of 2 consumption and 1,2-epoxycyclooctane accumulation in the

Scheme 1



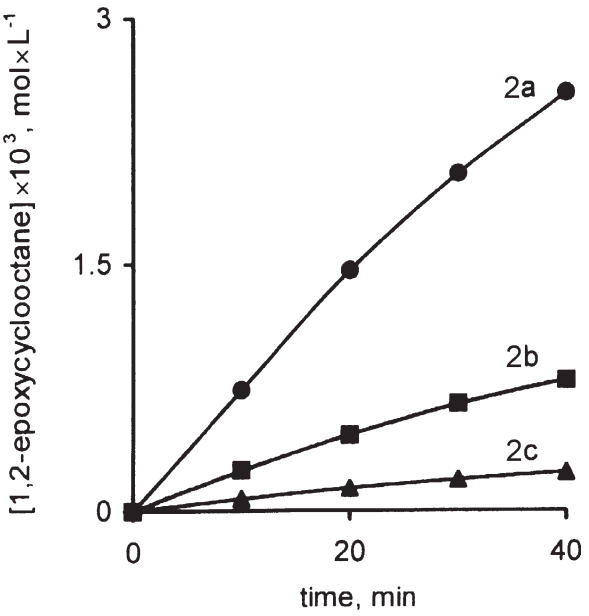


Figure 2. The kinetic curves of the 1,2-epoxycyclooctane accumulation in the catalytic epoxidation reaction of cyclooctene by **2**.

epoxidation process are presented in Figures 1 and 2, respectively. It is evident that epoxidation ability of investigated 2 is different and is defined by the nature of the substituents on the aromatic ring connected at nitrogen atom of hydroperoxide molecule.

The highest value of hydroperoxy sultam consumption in the catalytic epoxidation process was observed for 2a containing only one *ortho*-chlorine atom and conversion of this hydroperoxide was equal to 73% after 40 min of reaction. In the case of 2b with two chlorine atoms in ortho-position to bond of nitrogen with aromatic ring, the hydroperoxide consumption was the lowest and hydroperoxide conversion was 41%. The value of hydroperoxide conversion for 2c which contains three substituents—two chlorine atoms and one NO_2 group—is 47% so it is between 2a and 2b.

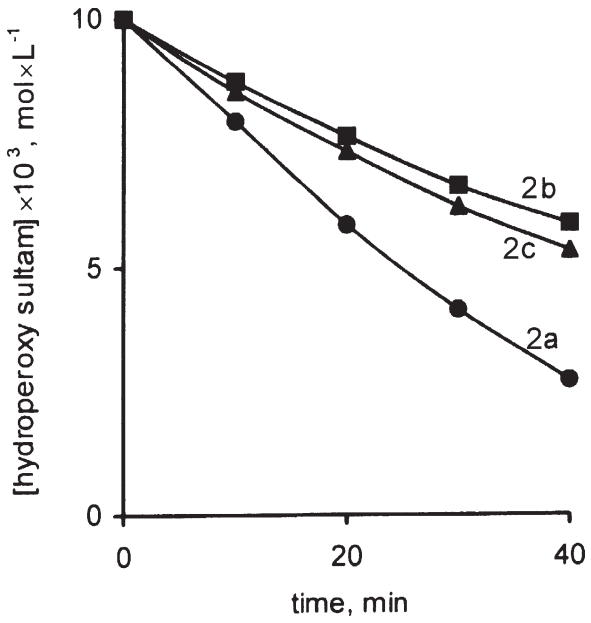


Figure 1. The kinetic curves of the consumption of **2** in the catalytic epoxidation reaction of cyclooctene.

The epoxide is formed in the presence of all investigated hydroperoxy sultams. This fact indicates on possibility of their application as epoxidation agents in the catalytic reaction with cyclooctene. The highest epoxidation ability exhibits 2a, the selectivity of epoxide formation (calculated as ratio of formed epoxide quantity to consumed hydroperoxide quantity) in its presence is 35%. The lowest epoxidation ability demonstrates 2c in the case of which the selectivity of epoxide formation is only 5%. 2b shows intermediate selectivity 19%.

From the obtained results, one can conclude that the most effective oxidant in the catalytic epoxidation reaction of cyclooctene is 2a, which molecule contains only one substituent—chlorine atom in α-position to bond of nitrogen with aromatic ring. Introduction of another one chlorine atom and especially NO_2 group leads to decrease of the parameters of the epoxidation reaction. It is probably caused by dominant influence of a steric factor. The increase in quantity of substituents complicates possibility of the simultaneous coordination of hydroperoxy sultam and cyclooctene on catalyst and formation of intermediate triple complex which is

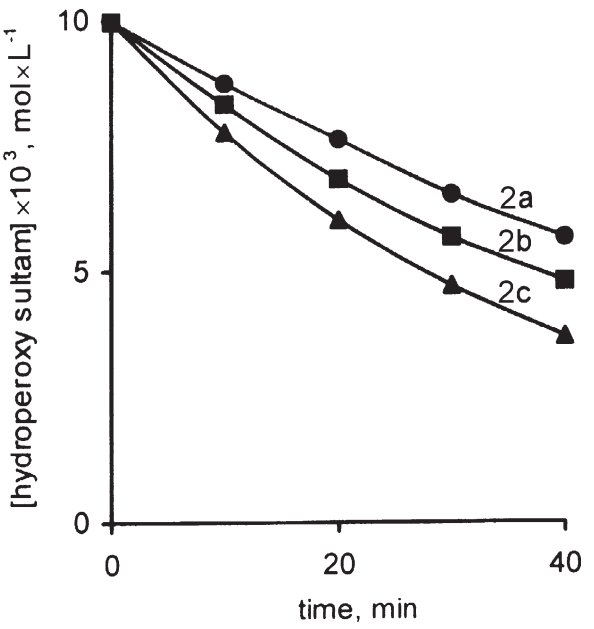


Figure 3. The kinetic curves of the consumption of **2** in the catalytic decomposition reaction.

responsible for epoxide formation [22–24]. Accordingly, the efficiency of the epoxidation reaction decreases.

Taking into account the significant contribution of unproductive 2 consumption into overall process of the cyclooctene epoxidation, it is reasonable to study the decomposition process of investigated hydroperoxy sultams catalyzed by MoB at the same reaction conditions in the absence of cyclooctene in the reaction system. Figure 3 shows the kinetic curves of 3-hydroperoxysultams consumption in the process of catalytic decomposition. One can see that the decomposition process most actively occurs in the case of 2c with hydroperoxide conversion 63%. One may suggest that presence of NO_2 group in a para-position to bond of nitrogen with aromatic ring favors the proceeding of the catalytic decomposition process. The values of conversions of 2b and 2a are smaller and are equal to 52% and 43%, correspondingly.

Comparing the data of the decomposition process with the data of the epoxidation process, it is possible to conclude that the highest epoxidation ability in the epoxidation process has 2a which is the least active in the decomposition reaction. At the same time, the 2c, which is the most actively consumed in the decomposition process, has the lowest epoxidation ability in the reaction with cyclooctene.

In summary, we have described the synthesis of novel 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides by oxidation of the 2-aryl-4,5-diphenyl substituted isothiazolium salts with H_2O_2. We have shown that these hydroperoxy sultams can act as epoxidation agent in the epoxidation reaction of cyclooctene catalyzed by MoB.

EXPERIMENTAL

Melting points were determined on Boetius micro-melting-point apparatus and are corrected. IR spectra are expressed in cm^{-1} and were recorded on Genisis FTIR Unicam Analytical System (ATI Mattson) using KBr pellets. ^1H NMR spectra were recorded on 200- (Varian Gemini-200) and 300-MHz (Varian Gemini-300). Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were received on the named spectrometers. Electron impact mass spectra (EI-MS) were recorded on a Quadrupol-MS VG 12-250 at an ionizing voltage of 70 eV. Elemental analysis was determined on Heraeus CHNO Rapid Analyzer.

Synthesis of 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides (2). H_2O_2 (0.7 mL, 30%) was added to a stirred suspension of **1** (0.26 mmol) in AcOH (0.7 mL) at room temperature. After dissolution of salts **1**, colorless precipitates of **2** were obtained after 72–96 h and isolated. The crude products were washed with water.

2-(2-Chlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2a). Mp 197–201°C; IR (KBr) 1157, 1302 (SO_2) cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 6.60 (s, 1H, 3–H), 7.37–7.96 (m, 14H, ArH), 11.38 (s, 1H, OOH); ^{13}C NMR (50 MHz, acetone-d_6) δ = 92.5, 128.1, 128.9, 129.5, 129.9, 130.0, 130.4, 130.7, 130.9, 131.6, 131.7, 131.8, 135.0, 135.6, 139.1; EI-MS m/z 413.0 ($M^{+\bullet}$). Anal. Calcd. for $C_{21}H_{16}ClNO_4S$: C, 60.94; H, 3.90; N, 3.38; O, 15.46. Found: C, 60.60; H, 4.01; N, 3.55; O, 15.80.

2-(2,6-Dichlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2b). Mp 124–127°C; IR (KBr) 1160, 1313 (SO_2) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 6.49 (s, 1H, 3–H), 7.25–7.64 (m, 13H, ArH), 11.23 (s, 1H, OOH); ^{13}C NMR (50 MHz, acetone-d_6) δ 95.0, 130.1, 130.3, 130.6, 130.7, 130.9, 131.0, 131.1, 131.3, 131.5, 131.7, 132.4, 132.9, 138.2, 139.4, 140.8; EI-MS m/z 447.0 (M^{+-}). Anal. Calcd. for $C_{21}H_{15}Cl_2NO_4S$: C, 56.26; H, 3.37; N, 3.12; O, 14.27. Found: C, 55.40; H, 3.56; N, 3.13; O, 14.00.

2-(2,6-Dichloro-4-nitrophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2c). Mp 148–151°C; IR (KBr) 1146, 1316 (SO_2), 1335, 1537 (NO_2) cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 6.58 (s, 1H, 3–H), 7.38–7.50 (m, 10H, ArH), 8.14 (s, 1H, ArH), 8.45 (s, 1H, ArH), 11.55 (s, 1H, OOH); ^{13}C NMR (50 MHz, acetone-d_6) δ 94.8, 125.6, 125.7, 126.1, 128.2, 130.1, 130.2, 130.4, 130.5, 130.6, 130.8, 131.0, 131.2, 131.7, 131.9, 139.4; EI-MS m/z 474.0 $(M-H_2O)^{+\bullet}$. Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O_6S$: C, 51.13; H, 2.86; N, 5.68; O, 19.46. Found: C, 50.83; H, 2.89; N, 5.72; O, 19.20.

General experimental procedure for the catalytic epoxidation of cyclooctene by 2. The epoxidation process was carried out in a thermostated glass reactor fitted with a reflux condenser and a magnetic stirrer under an argon atmosphere at temperature 23°C. The reactor was loaded with 0.01 g of MoB (Alfa Aesar) as a heterogeneous catalyst, 0.3 mL of *cis*-cyclooctene (Acros Organics), 3.5 mL chloroform as solvent, and 0.01 mol L^{-1} of **2**. It is established that **2** does not decompose in the absence of catalyst in the reaction system and 1,2-epoxycyclooctane is not formed under the reaction conditions. The concentration of **2** was determined by iodometric titration [25]. The reaction mixtures were analyzed by using a Hewlett Packard HP 6890 N chromatograph, a capillary column DB-1 (60 m × 0.32 mm × 0.5 μm) packed with dimethylsiloxane. The

column temperature was changed from 50 up to 250°C with rate of 10° in 1 min.

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