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Photooxygenation of 1,2-Diaryltetrahydrobenziimidazole and Crystal Structure of Its Product

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The reactions of 1-(4-methylsulfonylphenyl)-2-(2,5-chlorophenyl)tetrahydrobenziimidazole (**1**) with singlet oxygen has been investigated. Compound **1**, from a initially formed 2,5-endoperoxide and the subsequence instable zwitterion intermediate, generated a dioxetane. The formed dioxetane through ring-opening and interior-ring electrophilic reaction and finally converted into a more stable seven-membered ring product which has not been reported before. The structure of the photooxygenation product was elucidated by X-ray analysis, H NMR, MS and elemental analysis. The compound 1,2-diaryltetrahydrobenziimidazole crystallizes in monoclinic, space group P2(1)/c with a = 18.533(4) (Å), α = 90(°); b = 7.7658(16) (Å), β = 91.96(3)(°); c = 14.203(3) (Å), γ = 90(°); V = 2042.9(7) Å^3, Z = 4, F(000) = 948, D_c = 1.474 (g cm^{-3}), $C_{20}H_{18}N_2O_4SCl_2$, M_r = 453.39 and μ = 0.444 mm^{-1}.

Key Words: Diaryltetrahydrobenziimidazole, Photooxygenation, Crystal stucture.

INTRODUCTION

Oxygen is ubiquitous. It comprises nearly 50 % of the earth's crust and is an essential component in metabolic pathways in all higher organisms[1]. Singlet oxygen, as an electrophilic species, reacts readily with electron-rich heterocyclic compounds such as furan, oxazole, pyrrole and imidazole[2]. Among these substances, the reactions of imidazoles with singlet oxygen, called imidazole photooxygenation, are of great mechanistic interest because of their prevalence in nucleic acids and proteins[3-6]. The imidazole ring is the site of oxidative damage to guanosine[3]. It has also been postulated that enzyme deactivation by air and light was correlated with the destruction of histidine residues as result of the reaction of the imidazole portion of the molecule with singlet oxygen[7] and that N-benzoylhistidine could be photooxidated under physiological conditions to generate dimeric products[8]. The proposed mechanism provides an elegant explanation for the photosensitized crosslinking of proteins observed during the photodynamic therapy of tumors and other diseases[7] and during premature UV-induced skin aging[9].

In recent years, imidazole photooxygenation has been investigated from both theoretical and experimental perspectives and many investigations on imidazole photooxygenation and the reactive mechanism were reported, but the structure of the photoxidation product was limited to H NMR and IR spectra analysis and the photooxygenation of 1,2-diaryltetrahydrobenzimidazole has not been reported. In the studies described here, we report the photooxygenation and discuss the possible mechanism of 1-(4-methylsulfonylphenyl)-2-(2,5-chlorophenyl)tetrahydrobenzimidazole (**1**) at ambient room temperature. The structure of its ultimate photooxygenation product was elucidated by X-ray single crystal analysis, H NMR, MS and elemental analysis.

EXPERIMENTAL

Solvents were purified by standard procedures. Melting points were determined using a RY-1 apparatus and were uncorrected. NMR spectra were recorded on Varian UNITY INOVA 600 MHz and JNM-ECA-400 400 MHz instrument in the solvent indicated later. Chemical shift values are reported in parts per million (ppm) relative to that for tetramethylsilane used as an internal reference standard. Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; m, multiplet. Mass spectra were obtained using API3000 instruments. Elemental analysis was carried out at the CarloErba-1106.

All reactions were monitored by thin layer chromatography (TLC) on 25 × 75 mm glass sheets precoated with silica gel (GF254) to a thickness of 0.25 mm and viewed at 254 nm UV-light.

Preparation of 1-(4-methylsulfonylphenyl)-2-(2,5-chlorophenyl)tetrahydrobenziimidazole (1): Under nitrogen atmosphere, to the 4 mL of DMSO solution of 0.27 g

2-(2,5-chlorophenyl)tetrahydrobenziimidazole (1 mmol, prepared as the literature method[10]), 10 % weight equivalent 18-crown-6, one weight equivalent 37 % potassium fluoride absorbed onto basic alumina and 0.17 g 4-methylsulfonyl-fluorobenze (1 mmol) in 4 mL DMSO were added successively. The mixture was stirred and heated to 120 ºC until the reaction was completed, for *ca.* 8 h. The reaction progress was monitored by TLC. Then, the mixture was filtrated. The filtrate was poured into ice and stirred. The resulting precipitate was filtrated off and washed by water. The crude reaction mixture was purified by silica gel column chromatography using 1:1.4:0.1 petroleum ether/ethyl acetate/ethylenediamine (v/v/v) as elute to give 0.22 g compounds **1** as white solid. R_f = 0.30. Yield: 52 %. m.p. 191-193 ºC. ^{1}H NMR ($CDCl_3$) δ: 7.92 (2 H, d, *J* = 8.68 Hz, ArH), 7.56 (1 H, d, *J* = 2.52 Hz, ArH), 7.26-7.30 (3 H, m, ArH), 7.19 (1 H, d, *J* = 8.68 Hz, ArH), 3.08 (3 H, s, SO_2CH_3), 2.76 (2 H, t, *J* = 5.76 Hz, CH_2), 2.49 (2 H, t, *J* = 5.76 Hz, CH_2), 1.86-1.92 (4 H, m, CH_2). ESI-MS: 421.2 (M+1). Anal. calcd. for $C_{20}H_{18}N_2O_2SCl_2$ (420.05): C 57.01, H 4.31, N 6.65; found: C 57.00, H 4.54, N 6.48.

Photooxygenation of 1 and the single crystal culture of the photooxygenation product: Compound **1** (0.05 g, 0.11 mmol) was dissolved in 20 mL $CHCl_3$ and placed at room ambient. Colourless single crystals suitable for X-ray structure determination of the photooxygenation product **6** were obtained by slow evaporation of the solvent through capillaries after two weeks. ^{1}H NMR($CDCl_3$) (δ): 7.92 (2 H, d, *J* = 8.4 Hz, ArH), 7.79 (1 H, s, ArH), 7.36-7.40 (2 H, m, ArH), 7.03 (2 H, d, *J* = 8.4 Hz, ArH), 3.06 (3 H, s, SO_2CH_3), 1.24-2.64 (8 H, m, CH_2). ESI-MS: 454.3 (M+1). Anal. calcd. for $C_{20}H_{18}N_2O_4SCl_2$ (453.34) : C 52.99, H 4.00, N 6.18; found: C 53.20, H 4.24, N 6.28.

X-ray crystal structure analysis of photooxygenation product: A colourless single crystal of the title compound with dimensions of 0.65 mm × 0.61 mm × 0.45 mm was selected for crystal structure determination. X-ray diffraction was performed at T = 293(2) K on a Bruker Smart Apex II equipped with a CCD area detector using a graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). A total of 15935 reflections were collected in the range of 3.04≤θ≤25.50º by using a φ and ω scan mode, among which 3753 (R_{int} = 0.0332) were unique. The structure was solved by direct methods using SHELXS-97 program and expanded with Fourier technique. The final refinement was carried out by full matrix least-squares methods with anisotropic thermal parameters for nonhydrogen atoms on F^2. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were determined by theoretical calculations and refined isotropically. Further details of the structure analysis are given in Table-1, where $w=1/[\sigma^2(F_o^2) + (0.1413P)^2 + 0.0000P]$, S = 1.027, $P = (F_o^2 + 2F_c^2)/3$.

RESULTS AND DISCUSSION

Crystal structure analysis of the photooxygenation product molecular structure and packing diagram of the photooxygenation product of 1-(4-methylsulfonylphenyl)-2-(2,5-chlorophenyl)tetrahydrobenziimidazole (**1**) are revealed in Figs. 1 and 2, respectively. Selected bond lengths and bond angles are shown in Table-2. Seen from Fig. 1, it was known that the structure was totally different from that of compound **1**. The tetrahydrobenziimidazole ring was decomposed into a 7-numbered ring as adipimide and the large π-π conjugated system of 1,2-diarylimdazole was cleaved. The bond between N(2) and C(7) is a double bond and the bond length, 1.253, is much shorter than other bonds between atoms C and N. The bond length of N(1)-C(5), N(1)-C(6), N(1)-C(7) and N(2)-C(14) is 1.391, 1.407, 1.449 and 1.430, respectively. The

TABLE-1
CRYSTAL DATA OF THE PHOTOOXYGENATION PRODUCT

Empirical formula	$C_{20}H_{18}N_2O_4SCl_2$
Formula weight	453.39
Crystal system	Monoclinic
Space group	P2(1)/c
a(Å), α (º)	18.533(4), 90
b(Å), β (º)	7.7658(16), 91.96(3)
c(Å), γ (º)	14.203(3), 90
V(Å^3)	2042.9(7)
Z,$D_{calc.}$ (g cm^{-3})	4, 1.474
μ (mm^{-1})	0.444
Reflect. collected/Unique reflect.	15935 /3753
R(int)	0.0332
F(000)	948
Crystal size	0.65 × 0.61 × 0.45
Index ranges	-20≤h≤22, -9≤k≤9, -17≤l≤17
Max./min. transmission	0.8255/0.7602
Data/restraints/params.	3753/1/262
Goodness of fit on F^2	1.027
Final R indices [(I>2σ(I)]	R1 = 0.0574, wR2 = 0.1776
R indices (all data)	R1 = 0.0639, wR2 = 0.1857
Largest diff. peak and hole	1.029/-0.549 e Å^{-3}

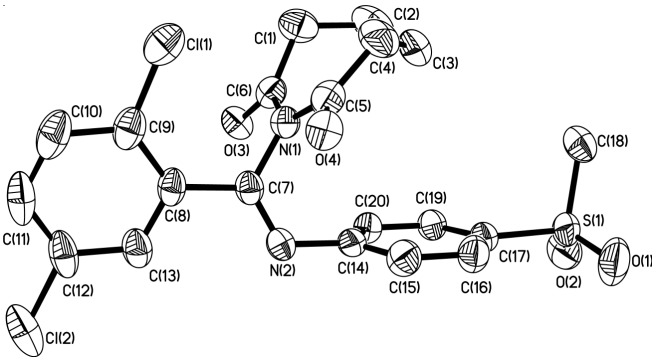


Fig. 1. Crystal structure of the photooxygenation product

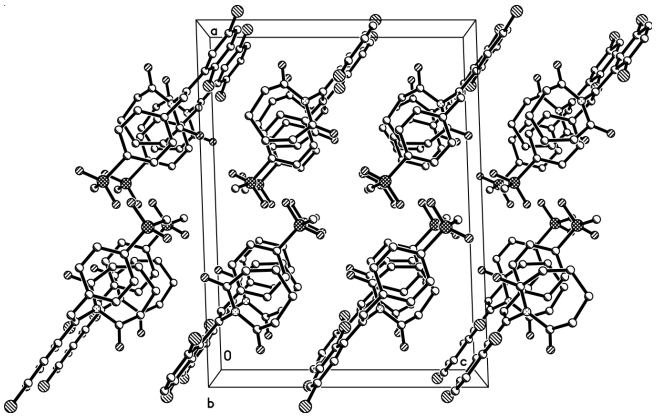
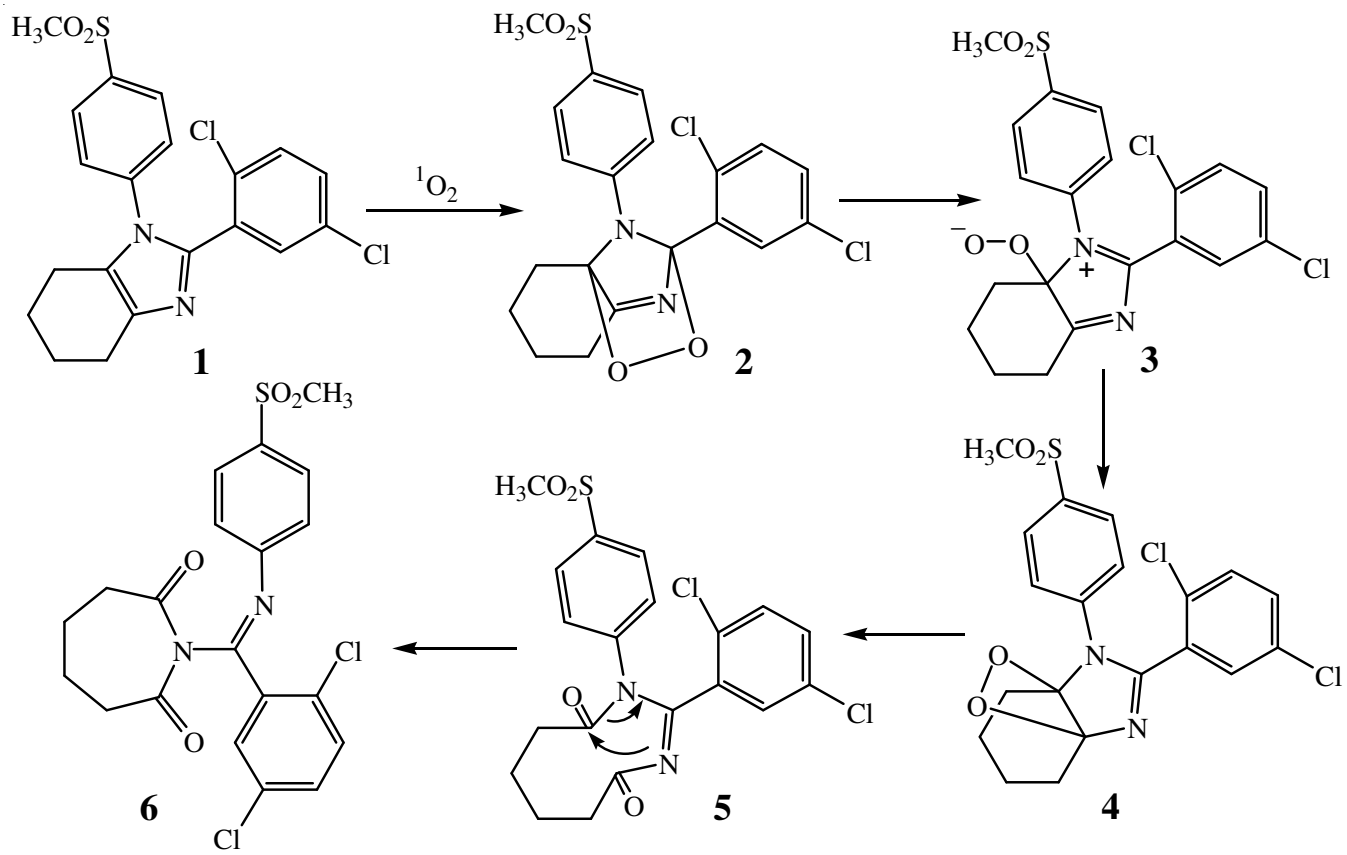


Fig. 2. Crystal packing of the photooxygenation product along the b axis

TABLE-2
BOND LENGTHS AND ANGLES FOR THE PHOTOOXYGENATION PRODUCT

Bond	Distance (Å)	Bond	Distance (Å)	Bond	Distance (Å)	Bond	Distance (Å)
S(1)–O(1)	1.430(3)	N(1)–C(7)	1.449(3)	C(4)–C(5)	1.483(5)	C(12)–C(13)	1.388(4)
S(1)–O(2)	1.432(3)	N(2)–C(14)	1.430(3)	C(5)–O(4)	1.238(4)	C(14)–C(15)	1.380(4)
S(1)–C(18)	1.755(3)	O(3)–C(6)	1.212(4)	C(7)–C(8)	1.492(3)	C(14)–C(20)	1.385(4)
S(1)–C(17)	1.771(3)	N(2)–C(7)	1.253(4)	C(8)–C(13)	1.385(4)	C(15)–C(16)	1.389(4)
Cl(1)–C(9)	1.729(4)	C(1)–C(6)	1.494(4)	C(8)–C(9)	1.415(4)	C(16)–C(17)	1.384(4)
Cl(2)–C(12)	1.735(4)	C(1)–C(2)	1.526(5)	C(9)–C(10)	1.386(5)	C(17)–C(19)	1.388(4)
N(1)–C(5)	1.391(3)	C(2)–C(3)	1.534(6)	C(10)–C(11)	1.387(6)	C(19)–C(20)	1.387(4)
N(1)–C(6)	1.407(3)	C(3)–C(4)	1.511(6)	C(11)–C(12)	1.363(5)	–	–
Angle	(°)	Angle	(°)	Angle	(°)		
O(1)–S(1)–O(2)	118.57(18)	O(4)–C(5)–C(4)	122.7(3)	C(12)–C(11)–C(10)	119.5(3)		
O(1)–S(1)–C(18)	108.73(17)	N(1)–C(5)–C(4)	120.7(3)	C(11)–C(12)–C(13)	120.6(3)		
O(2)–S(1)–C(17)	108.50(16)	O(3)–C(6)–N(1)	117.2(2)	C(11)–C(12)–Cl(2)	120.1(2)		
O(1)–S(1)–C(17)	107.77(15)	O(3)–C(6)–C(1)	123.4(2)	C(13)–C(12)–Cl(2)	119.3(3)		
O(2)–S(1)–C(17)	108.90(14)	N(1)–C(6)–C(1)	119.4(2)	C(8)–C(13)–C(12)	121.4(3)		
C(18)–S(1)–C(17)	103.31(14)	N(2)–C(7)–N(1)	121.2(2)	C(15)–C(14)–C(20)	120.9(3)		
C(5)–N(1)–C(6)	129.6(2)	N(2)–C(7)–C(8)	120.2(2)	C(15)–C(14)–N(3)	118.8(3)		
C(5)–N(1)–C(7)	115.8(2)	N(1)–C(7)–C(8)	118.6(2)	C(20)–C(14)–N(3)	120.3(2)		
C(6)–N(1)–C(7)	114.5(2)	C(13)–C(8)–C(9)	117.6(3)	C(14)–C(15)–C(16)	119.7(3)		
C(7)–N(2)–C(14)	118.8(2)	C(13)–C(8)–C(7)	115.4(2)	C(17)–C(16)–C(15)	119.2(3)		
C(6)–C(1)–C(2)	113.9(3)	C(9)–C(8)–C(7)	126.9(3)	C(16)–C(17)–C(19)	121.4(3)		
C(1)–C(2)–C(3)	114.4(3)	C(10)–C(9)–C(8)	120.1(3)	C(16)–C(17)–S(1)	119.1(2)		
C(4)–C(3)–C(2)	113.5(3)	C(10)–C(9)–Cl(1)	115.7(3)	C(19)–C(17)–S(1)	119.5(2)		
C(5)–C(4)–C(3)	113.7(3)	C(8)–C(9)–Cl(1)	124.3(2)	C(20)–C(19)–C(17)	119.0(3)		
O(4)–C(5)–N(1)	116.5(3)	C(11)–C(10)–C(9)	120.7(3)	C(14)–C(20)–C(19	119.8(3)		

Symmetry transformation used to generate the equivalent atoms: i: –x, –y+1, –z+1



Scheme-I: Mechanism of photooxygenation of compound **1**

4-methylsulfonylphenyl group and the 7-numbered ring exist on the same side of C=N, but the 2,5-chlorophenyl group does on the other. The conformation of 7-numbered ring is chair form and the atoms C(3) and N(1) exist on the opposite sides. This conformation minimizes the intermolecular stretching force. From the cell packing figure, it is known that there exists no hydrogen bond and the molecules pack closely with a couple as a unit.

The ene, [2+2] and [4+2] reactions represent powerful protocols for the addition of molecular oxygen to organic substrates[2]. The [4+2] cycloaddition is the fundamental reaction model and could generate various endoperoxides as versatile intermediates to be transformed into many different oxygenated products. Wasserman *et al.*[5] extensively investigated the photooxygenation s of a wide range of alkyl and aryl substituted imidazoles. The endoperoxide is the key intermediate formed in these reactions and can be directly observed by low temperature NMR[11]. The decomposition of the endoperoxide is a sensitive function of the substitution pattern. When the hydrogen on the N position of imidazole is substituted by other group, the endoperoxide would decomposited into dioxetanes, otherwise, into hydroperoxides.

In view of the above, it was speculated that the observed reaction products might be derived from subsequent decomposition of the peroxidic species. CCl_3 might function as a photosensitizer. The possible mechanism is shown in **Scheme-I**. 1,2-Diaryltetrahydrabenzimidazole **1** underwent reaction to form the cleavage product **5**, which further converted into a more stable product **6** through interior-ring electrophilic reaction. Product **5** most probably arose from the dioxetane **4**, formed by the sequence shown in **Scheme-I**. The generation of **4** from initially formed 2,5-endoperoxide **2** is consistent with the findings of Foote *et al.*[1,10] on low temperature photooxygenations of imidazoles and may involve the zwitterionic product **3** as a non-isolable intermediate.

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