Studies on the photochemical oxidation of $N,N$-diacyl-1, 4-dihydropyrazine derivatives

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ABSTRACT
The photochemical oxidation of $N,N$-diacyl-1,4-dihydropyrazines was investigated by irradiation from a medium-pressure mercury lamp. The main products of the photooxygenation were isolated and unambiguously confirmed by $^1$H NMR spectra, $^{13}$C NMR spectra, H-H, C-H correlation spectra, high-resolution mass spectrometry, and single-crystal x-ray diffraction analysis. The complicated NMR spectra of main products were studied by variable-temperature NMR experiments. The mechanism of the photooxygenation of $N,N$-diacyl-1,4-dihydropyrazines is suggested to be a $[2 + 2]$ cycloaddition of oxygen to the double bond.

GRAPHICAL ABSTRACT

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Introduction

1,4-Dihydropyrazines are widely used as intermediates in medicinal chemistry and for functional transformations.\textsuperscript{[1]} The 1,4-dihydropyrazine system, which is an interesting cyclic structure containing 8$\pi$-electron and an arrangement of two enamine structures, has attracted much interest and has led to detailed investigations of its chemical properties, including its antiaromatic character, its ability to donate electrons in conducting...
charge-transfer complexes, and its role as a redox-active biological molecule.\[2\] Although the chemical properties of 1,4-dihydropyrazines have been studied for many years, their photochemical properties have received little attention, except for the photochemical ring contraction of 1-aryl-1,4-dihydropyrazine to 1-aryl-1H-imidazole.\[3\] In this study, N,N-diacyl-1,4-dihydropyrazines (1) were synthesized by the reported method,\[4\] and their photochemical oxidation properties were investigated to continue our studies of the photochemical properties of heterocyclic compounds, such as photodimerization and photocycloaddition.\[5\] The photochemical reactions involving oxygen were found to result in oxygenation of nitrogen heterocycles.\[6\] The photochemical oxidation of N,N-diacyl-1,4-dihydropyrazines (1) was investigated by irradiation from a medium-pressure mercury lamp in an oxygen atmosphere.

Results and discussion

Photooxygenation of N,N-diacyl-1,4-dihydropyrazines (1)

The photooxygenation of N,N-diacyl-1,4-dihydropyrazines (1) was investigated by irradiation from a 450-W medium-pressure mercury lamp with Pyrex filter in the presence of oxygen. Considering the effects of the substituents, 1a (R=CH\(_3\)) and 1b (R=Ph) were selected as representative compounds. Compounds 1a and 1b were prepared from pyrazine in the presence of the corresponding anhydride with zinc reduced.\[4\] Acetone was chosen as the suitable solvent among the conventional solvents, such as tetrahydrofuran (THF), CH\(_3\)OH, CH\(_2\)Cl\(_2\), C\(_6\)H\(_6\), and CH\(_3\)CN. The acetone acted not only as a solvent to increase the solubility of 1,4-dihydropyrazines but also as a photoreactive reagent to enhance the rate of the reaction.\[7\] Compound 1 was dissolved in acetone (5 mmol in 200 mL) and poured into the photolysis unit in the presence of air. The reaction was monitored by thin-layer chromatography (TLC), and the reaction products were purified by chromatography on silica gel using a mixed solvent of petroleum ether and ethyl acetate (10:1 v/v) to provide its main products.

In the photochemical oxidation of 1a, one double bond was oxidized to give methylated diol 2a and diacetate 3a with yields of 31% and 23%, respectively (Scheme 1). The formation of 2a and 3a involved a [2 + 2] cycloaddition between the double bond of 1a and singlet oxygen, with subsequent homolysis of the peroxide bond, which was then attacked by H\(_2\)O and the products of the photolysis of acetone.

The proposed mechanism (Scheme 2) to explain the formation of photooxygenation products, which involves a [2 + 2] cycloaddition between 1a and singlet oxygen, is now
discussed. Compound 1a reacted with singlet oxygen by [2 + 2] cycloaddition and yielded dioxetane as referred to by Adam et al.[8] The singlet oxygen was probably produced upon irradiation of UV light (<320 nm).[9] The singlet oxygen acted as a critical intermediate, which was consistent with the control experiments. When air was continuously bubbled through the solution with an aerator, the formation of 2a was accelerated, whereas the formation of 2a was abated under a nitrogen atmosphere. The singlet oxygen-induced oxidation was further demonstrated by the addition of a quencher or photosensitizer that captured the singlet oxygen or converted the oxygen molecule to singlet oxygen. The formation of 2a was significantly suppressed by quencher 1,4-diazabicyclo[2.2.2]octane (yield 0%) and considerably accelerated by the photosensitizer rubrene (yield 37%). The formation of 2a and 3a from dioxetane was proposed to be an intramolecular electron-transfer mechanism by the cleavage of peroxides. Dioxetane was decomposed by homolysis of the peroxide bond to form a biradical intermediate, and the biradical intermediate reacted with H2O to form hydroxylated radical, which was methylated to give 2a by the methyl radical generated by the photolysis of acetone (Norrish type I).[10] Meanwhile, the recombination of this biradical intermediate with only acetoxyl radical yielded 3a.

In the photochemical oxidation of 1b, one double bond was oxidized to give diol 4b with a yield of 35% (Scheme 2). The formation of 4b was speculated that H2O in the system reacted with the dioxetane as that of 2a and the hydroxylated radical further reacted with H2O to yield 4b (Scheme 3).[10d]

The difference between the main products of 1 was impacted by the stability of the intermediate dioxetane. The substitution on the N atoms of 1,4-dihydropyrazines was the main factor. The dioxetane intermediates of 2a and 3a had little steric hindrance from the acetyl groups, and it reacted with H2O and the methyl radical together, giving 2a and 3a. While the dioxetane intermediate of 4b had a more prominent steric hindrance from the benzoyl groups than that of acetyl groups, it only reacted with H2O to give 4b.
Structural characterization of the main products

The structures of 2–4 were confirmed by $^1$H NMR spectra, $^{13}$C NMR spectra, high-resolution mass spectrometry (HRMS), and single-crystal x-ray diffraction analysis. In the $^1$H NMR spectra of 2a, there was a multiplet from the hydroxyl group at $\delta$ 6.45 ppm, a multiplet from the enamine group at $\delta$ 6.17 ppm, a multiplet from the two saturated protons on the ring at $\delta$ 5.59 ppm, a multiplet from the methoxy group at $\delta$ 3.24 ppm, and a multiplet from the two acetyl groups at $\delta$ 2.20 ppm. In the $^{13}$C NMR spectra of 2a, the three carbonyl carbons resided at $\delta$ 169.7, 169.6, 168.3, 168.1, 167.8, and 167.7 ppm; the signals of the double bond resided at $\delta$ 109.5, 108.0, 107.9, 107.0, 106.7, 105.6, and 104.5 ppm; the signals from the saturated carbons on the ring resided at $\delta$ 83.1, 82.9, 78.3, 78.0, 75.1, 74.7, 69.8, and 69.3 ppm; the signals from the saturated carbon of methoxy group resided at $\delta$ 55.5, 55.4, and 54.6 ppm; and the signals from the saturated carbon of acetyl groups resided at $\delta$ 21.9, 21.8, 21.7, 21.6, 21.3, 21.2, 21.1, and 21.0 ppm.

The complicated spectra resulted from the conformation isomerism of 2a because of the syn- and anti-orientations of the two acetyl groups on the ring (Scheme 4).[4] (The cis- and trans-configurations of the 2,3-positions in the structures of 2a also made the spectra complicated.) Therefore, variable-temperature experiments were used to further analyze the structure of 2a. With increasing temperature (323 K), the interconversion between these conformers shown in Scheme 4 should be accelerated, making the $^1$H NMR spectrum simplified, especially for the peaks at lower field (6.0–7.0 ppm) (Fig. 1). At the greatest temperature (353 K), the $^1$H NMR spectrum showed a simple peak shape, especially for the peaks at higher field (2.0–3.5 ppm), at which the protons of the methoxy group

Scheme 3. Proposed mechanism for the photooxygenation of 1.

Scheme 4. Several conformations of 2a in solution.
(-OCH₃) showed only a single peak and the protons of two acetyl groups (-2COCH₃) showed only two close peaks (Fig. 2). The complicated nature of the spectra resulted from the conformational isomerism of 2a because of the two acetyl groups on the ring. Different conformational isomers resulted in a different chemical environment of protons and then

![Figure 1](image-url)

**Figure 1.** Expansion of low-field of variable-temperature ^1^H NMR spectrum of 2a in DMSO-d₆.

![Figure 2](image-url)

**Figure 2.** Expansion of high-field of variable-temperature ^1^H NMR spectrum of 2a in DMSO-d₆.
Figure 3. ORTEP diagrams of the crystal structure of 2a.

Figure 4. Expansion of aromatic region of H-H COSY spectrum of 3a in DMSO-$d_6$. 
different shift values, giving complex NMR spectra of 2a. Single-crystal x-ray diffraction of 2a (deposition number CCDC-995230) further confirmed that the photooxygenation product was 1,1′-(2-hydroxy-3-methoxy-2,3-dihydropyrazine-1,4-diyl)diethanone (Fig. 3).

In the $^1$H NMR spectra of 3a, there was a multiplet from the enamine group at $\delta$ 7.00 ppm, a multiplet from the two saturated protons on the ring at $\delta$ 6.38 ppm, a multiplet from the two methoxycarbonyl groups at $\delta$ 2.31 ppm, and a multiplet from the two acetyl groups at $\delta$ 2.08 ppm. In the $^{13}$C NMR spectra of 3a, the three carbonyl carbons resided at $\delta$ 169.4, 169.1, 169.0, 168.0 and 167.7 ppm; the signals of the double bond appeared at $\delta$ 108.2, 107.2, 106.6, and 105.6 ppm; the signals from the saturated carbons on the ring were found at $\delta$ 73.9 and 73.3 ppm; the signals from the saturated carbon of methoxy group were found at $\delta$ 70.3 and 69.6 ppm; and the signals from the saturated carbon of acetyl groups were found at $\delta$ 21.2, 20.8, 20.7, and 20.6 ppm.

The 2D-NMR spectra further proved that the structure of 3a was 1,4-diacetyl-1,2,3,4-tetrahydropyrazine-2,3-diyl diacetate. The H-H COSY spectrum showed that only two groups of protons had correlations (Fig. 4): the NMR proton signal at 6.18 ppm had correlation with the NMR proton signal at 6.68 ppm (group A) and the NMR proton signal at 6.72 ppm had correlation with the NMR proton signal at 7.04 ppm (group B). According to the C-H COSY spectrum of 3a in dimethylsulfoxide (DMSO-$d_6$, Fig. 5), there was a correlation between the NMR proton signal at 6.18 and 6.68 ppm and the NMR $^{13}$C signal at 108.3 and 105.6 ppm respectively (group A). There was a correlation between the NMR proton signal at 6.72 and 7.04 ppm and the $^{13}$C NMR signal at 73.3 and 70.3 ppm.

![Figure 5](image-url)  
**Figure 5.** Expansion of aromatic region of C-H COSY spectrum of 3a in DMSO-$d_6$. 
respectively (group B). It was obvious that the protons of group A were protons of unsaturated carbon atoms (=CH) and that the protons of group B were protons of saturated carbon atoms (-CH). The H-H and C-H COSY spectra of 3a in DMSO-\textit{d}_6 further confirmed its structure.

In the \textsuperscript{1}H NMR spectra of 4b, there was a multiplet from the two phenyl groups at $\delta$ 7.59 ppm, a multiplet from the two hydroxyl groups at $\delta$ 6.74 ppm, a multiplet from the enamine group at $\delta$ 6.27 ppm, and a multiplet from the two saturated protons on the ring at $\delta$ 5.45 ppm. In the \textsuperscript{13}C NMR spectra of 4b, the carbonyl carbons resided at $\delta$ 168.3 ppm; the signals of the phenyl groups resided at $\delta$ 134.6, 131.1, 128.8, and 128.3 ppm; the signals of the double bond resided at $\delta$ 110.9, 108.0, and 105.3 ppm; and the signals from the saturated carbons on the ring resided at $\delta$ 77.3 and 72.4 ppm. Single-crystal x-ray diffraction of 4b (deposition number CCDC-995229) further confirmed that the photooxygenation product was (2,3-dihydroxy-2,3-dihydropyrazine-1,4-diyl)bis(phenylmethanone) (Fig. 6).

**Conclusions**

The photochemical oxidation of N,N-diacyl-1,4-dihydropyrazines is an oxidation of the double bond on the ring of pyrazine. It involves a [2 + 2] cycloaddition between the double bond and singlet oxygen, with subsequent homolysis of the peroxide bond, which is attacked by H$_2$O and the products of the photolysis of acetone. The main products of the photooxygenation of N,N-diacyl-1,4-dihydropyrazines were isolated, and their structures were determined by \textsuperscript{1}H NMR spectra, \textsuperscript{13}C NMR spectra, H-H, C-H correlation,
(COSY) spectra, HRMS, and single-crystal x-ray diffraction analysis. The complicated NMR spectra of the main products result from the structure’s asymmetry and conformational isomerism, which have been demonstrated by variable-temperature NMR experiments.

**Experimental**

All chemicals were purchased from commercial sources and used without further purification. Thin-layer chromatography (TLC) was conducted on silica-gel 60 F254 plates (Merck KGaA). Melting points were determined on a XT-5A digital melting-point apparatus and are uncorrected. $^1$H NMR spectra and $^{13}$C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz using CDCl$_3$ or DMSO-d$_6$ as the solvent and tetramethylsilane (TMS) as the internal standard. High-resolution mass spectral (HRMS) analyses were carried out using a VG 70SE mass spectrometer from Manchester, UK, which was operated in electron impact or electrospray ionization mode. Irradiation for the photochemical reactions was conducted using an Osram HBO 450 W medium-pressure mercury lamp. The samples were irradiated while in quartz cuvettes.

**General procedure for the photooxygenation of N,N-diacyl-1,4-dihydropyrazines (1)**

An amount of 5 mmol of 1 was dissolved in 200 mL of acetone and poured into the photolysis unit. Photoirradiations were performed using a 450-W medium-pressure mercury lamp and monitored by TLC. After completion, the solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel using a mixed solvent of petroleum ether and ethyl acetate (10:1 v/v) to provide the main products (2–4).

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.44–6.63 (m, 1H, -OH), 6.08–6.42 (m, 2H, -CH=CH), 5.26–5.87 (m, 2H, -CH), 3.16–3.27 (m, 3H, -OCH$_3$), 2.14–2.22 (m, 6H, -COCH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 169.7, 169.6, 168.3, 168.1, 167.8, 167.7, 167.5, 109.5, 108.0, 107.9, 107.0, 106.7, 105.6, 104.5, 83.1, 82.9, 78.3, 78.0, 75.1, 74.7, 69.8, 69.3, 55.5, 55.4, 54.6, 21.9, 21.8, 21.7, 21.6, 21.3, 21.2, 21.1, 21.0; HRMS (ESI) calculated for C$_9$H$_{14}$N$_2$O$_4$ (M + Na$^+$): 237.08513, found 237.08357. Single-crystal x-ray diffraction of 2a is filed under deposition number CCDC-995230.

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