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Oxidative cyclization of aryl-substituted (*Z*)-*N*-acetyl-α-dehydroalanines having a dialkylamino group, in the presence of dioxygen

Kohji Oshimi,[a] Kanji Kubo,[b] Atsushi Kawasaki,[a] Kei Maekawa,[a] Tetsutaro Igarashi[a] and Tadamitsu Sakurai[a,*]

[a]*Department of Applied Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686, Japan*
[b]*Institute of Advanced Material Study, 86, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816-8580, Japan*

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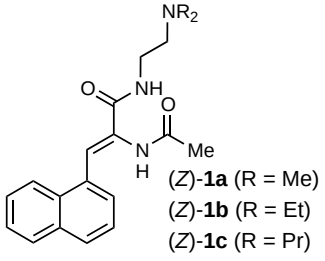
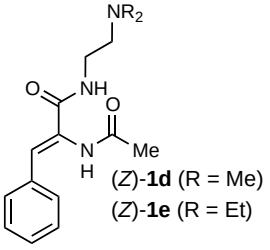
Abstract—It was found that the reactions of the title compounds (**1**) with dioxygen in methanol proceed according to the first-order kinetics to give (*Z*)-2-imidazolin-5-one derivatives and hydrogen peroxide in quantitative yields. Substituent and solvent effects on the rate constant for this oxidative cyclization reaction are consistent with the rate-determining electron transfer from the dialkylamino nitrogen in the starting **1** to dioxygen.

In recent years much attention has been devoted to the synthetic application of excited-state processes initiated by electron transfer, owing to the fact that many photoinduced electron-transfer reactions proceed in high chemical and quantum yields, thus enabling the construction of biologically active heterocyclic rings.[1,2] In the course of our systematic study toward the characterization of the excited-state reactivities of substituted α-dehydroamino acids, we discovered an interesting photocyclization of *N*-acyl-α-dehydrophenylalanine derivatives,[3] as well as photoinduced reductive cyclization of substituted *N*-acyl-α-dehydro(1-naphthyl)-alanines.[4] Since tertiary amines readily form charge-transfer complexes with dioxygen in nonpolar solvents,[5] it is possible that the presence of dioxygen in polar solvents thermally activates the tertiary amino nitrogen introduced into aryl-substituted α-dehydroalanines. In order to develop a new synthetic route to heterocyclic compounds and to clarify their formation mechanism, we designed aryl-substituted (*Z*)-*N*-acetyl-α-dehydroalanines [(*Z*)-**1a**–**e**] having a 2-(dialkylamino)ethyl group attached to the carboxamide nitrogen, and investigated the substituent and solvent effects on the reactivity of (*Z*)-**1** in the presence of dioxygen.

The starting (*Z*)-isomers were prepared by the ring-opening reactions of aryl-substituted oxazolones with



(*Z*)-**1a** (R = Me)
(*Z*)-**1b** (R = Et)
(*Z*)-**1c** (R = Pr)



(*Z*)-**1d** (R = Me)
(*Z*)-**1e** (R = Et)

2-(dialkylamino)ethylamine in good yields.[6,7] Each methanol solution of (*Z*)-**1a** (10 mL, 1.0×10^{-4} mol dm^{-3}) was purged with air for 10 min and then heated at 80°C in sealed tubes for a given period of time. As the reaction proceeds, the UV absorption of the starting **1a** at 312 nm decreases with appearance of the 378 nm absorption, while there are three isosbestic points at 252, 276 and 334 nm during the reaction (Fig. 1). Similar UV spectral changes were obtained also for the starting **1b**–**e**. In order to isolate the product and determine its structure, a dioxygen-saturated methanol solution of (*Z*)-**1a** (100 mL, 5.0×10^{-3} mol dm^{-3}; $[O_2]=1.02\times10^{-2}$ mol dm^{-3})[8] was heated at 80°C for 48 h in a sealed tube. The reaction mixture obtained was subjected to short column chromatography over silica gel (eluent: EtOAc–MeOH), which allowed us to isolate 1-[2-(dimethylamino)ethyl]-2-methyl-4-(1-naphthylmethylene)-2-imidazolin-5-one (**2a**) in a quantitative yield.[9] The reactions of **1b**–**e** with dioxygen under the same conditions gave the corresponding 2-imidazolin-5-

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* Corresponding author.

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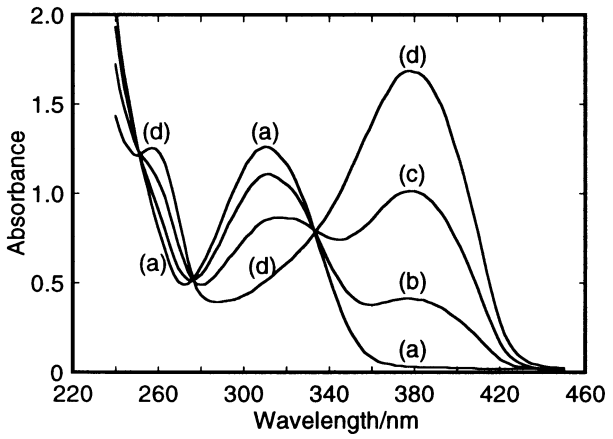


Figure 1. UV absorption spectra of air-saturated methanol solutions of (*Z*)-**1a** (1.0×10^{-4} mol dm^{-3}) heated for 0 h (curve a), 0.6 h (curve b), 1.8 h (curve c), and 24 h (curve d) at 80°C.

one derivative **2** in quantitative yields. The structure of these products was determined based on their spectroscopic and physical properties including ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY and HMBC spectra. An X-ray structural analysis of a single crystal derived from **2d** revealed that **2** has the (*Z*)-configuration (Fig. 2).[10] On the other hand, (as a dioxygen-derived product) hydrogen peroxide was found to be formed in a yield comparable to that of **2** by voltammetry of the same reaction mixture in 50:50 water:methanol containing 0.1 mol dm^{-3} KCl.[11]

The findings that no reaction occurs in an atmosphere of argon and also without the dialkylamino group even in dioxygen-saturated methanol suggest the participation of electron transfer from the tertiary amino nitrogen to dioxygen in the reaction, as already suggested. Thus, taking into account that this electron transfer is a not so thermodynamically favorable process in the ground state, we are led to propose Scheme 1 in which reverse electron transfer (from superoxide) affording the starting **1** and dioxygen should proceed preferentially.

It is likely that the presence of the oxidized dialkylamino group ($-N^{+\bullet}R_2$) and the amide carbonyl having strong electron-withdrawing ability in the **1**-derived radical cation enables a basic superoxide to abstract the amide proton affording hydroperoxyl and amidyl radicals.[12] The final product (*Z*)-**2** may be obtained by dehydration of the amino alcohol formed via cyclization of the amidyl radical and subsequent hydrogen abstraction from methanol.

Fortunately, the reaction of (*Z*)-**1a** (1.0×10^{-4} mol dm^{-3}) in air-saturated methanol ($[O_2]=2.1\times10^{-3}$ mol dm^{-3})[8] at 80°C proceeded according to the first-order kinetics in **1**, so that we scrutinized the substituent and solvent effects on the rate constant for the reaction of **1a** (Table 1). An inspection of the substituent effects on the reaction confirms that the rate constant is not much different among **1a–c** and also between **1d** and **1e**. Additionally, the replacement of the 1-naphthyl group by a phenyl exerts only a small effect on the rate constant for the reaction. Interestingly, the change in the polarity of protic solvents affects the reaction rate

Table 1. Rate constant (k) for the reaction of (*Z*)-**1** (1.0×10^{-4} mol dm^{-3}) with dioxygen at 80°C

Compound	Solvent (ε)[a]	$[O_2]$[b]/10^{-3} mol dm^{-3}	$k/10^{-4}$ s^{-1}
1a	MeOH (32.66)	2.1	1.3
1b	MeOH	2.1	1.5
1c	MeOH	2.1	0.94
1d	MeOH	2.1	1.1
1e	MeOH	2.1	2.3
1a	EtOH (24.55)	2.1	0.12
1a	*i*-PrOH (19.92)	2.1	0.035
1a	MeCN (35.94)	1.9	0.069

[a] Relative permittivity at 25°C.
[b] See Ref. 8.

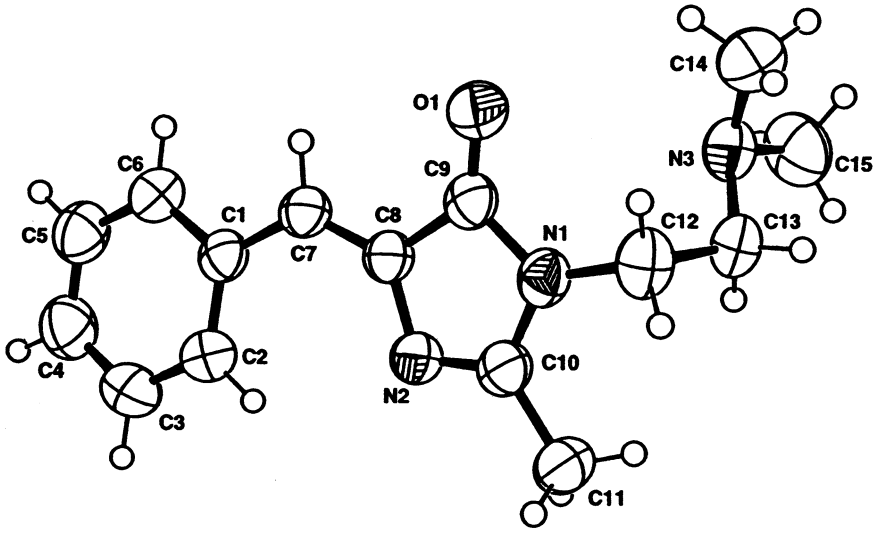
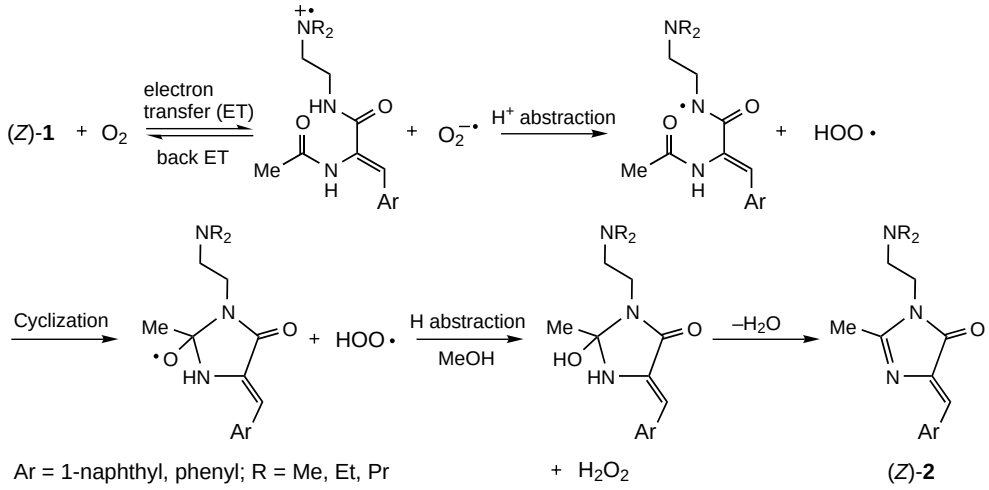


Figure 2. ORTEP drawing of (*Z*)-**2d**.



Scheme 1.

to a much greater extent, as compared to that in the substituent R: the rate constant decreases markedly with decreasing polarity of the solvents. Furthermore, the use of acetonitrile (having almost the same polarity as methanol) as a solvent also greatly lowered the reaction rate. The former observation is consistent with the fact that an increase in solvent polarity accelerates electron transfer reaction, and the latter observation reveals that the solvation of $-N^{+\bullet}R_2$ by the hydroxy oxygen of methanol plays a critical role in determining the reaction rate. The considerations described above, therefore, allow us to propose that electron transfer from the dialkylamino nitrogen to dioxygen is the rate-determining step in the reaction sequence.

Although many synthetic routes to 2-imidazolin-5-one derivatives are known,[13] there is no synthetic method (of these derivatives) which employs the cyclization of aryl-substituted *N*-acetyl-α-dehydroalanines **1** activated by electron transfer to dioxygen. The procedure for preparing the starting **1** is simple and easily applicable to its related compounds. In addition, the oxidative cyclization of **1** proceeds quantitatively to afford the corresponding 2-imidazolin-5-one derivative **2** and, hence, provides a novel route to **2**. The finding that the reaction can be monitored accurately by UV absorption spectroscopy enables us to elucidate the mechanism of these intriguing cyclization reactions of **1** in detail.

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7. Data for (*Z*)-**1a**. Mp 157.5–158.5°C. IR (KBr): 3298, 3196, 1620 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.84 (3H, s), 2.18 (6H, s), 2.37 (2H, t, $J=6.7$ Hz), 3.27 (dt, 2H, $J=6.7$, 6.7 Hz), 7.51 (1H, s), 7.52–7.58 (4H, m), 7.91 (1H, d, $J=7.9$ Hz), 7.95–7.97 (2H, m), 7.98 (1H, t, $J=6.7$ Hz), 9.28 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 22.6, 37.3, 45.2 (2C), 58.0, 124.1, 124.2, 125.5, 126.0, 126.2, 126.3, 128.35, 128.42, 131.0, 131.3, 132.5, 133.2, 164.6, 169.4. Anal. calcd (found) for $C_{19}H_{23}N_3O_2$: C, 70.13 (70.35); H, 7.12 (7.06); N, 12.91 (12.85%).
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9. Data for (*Z*)-**2a**. Mp 88.0–89.0°C. IR (KBr): 1719, 1635 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.19 (6H, s), 2.42 (3H, s), 2.43 (2H, t, $J=6.7$ Hz), 3.68 (2H, t, $J=6.7$ Hz), 7.58 (1H, dd, $J=7.3$, 7.9 Hz), 7.62 (1H, dd, $J=7.3$, 7.9 Hz), 7.64 (1H, dd, $J=7.3$, 7.3 Hz), 7.71 (1H, s), 7.98 (1H, d, $J=7.3$ Hz), 8.00 (1H, d, $J=7.3$ Hz), 8.29 (1H, d,

$J=7.9$ Hz), 8.86 (1H, d, $J=7.3$ Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.3, 38.1, 45.3 (2C), 57.5, 119.5, 122.8, 125.6, 126.1, 127.3, 128.9, 129.5, 130.4, 130.9, 131.7, 133.3, 139.6, 165.2, 169.8. Anal. calcd (found) for $C_{19}H_{21}N_3O$: C, 74.24 (74.05); H, 6.89 (6.91); N, 13.67 (13.68%). HR EI-MS m/z calcd for $C_{19}H_{21}N_3O$: 307.1685. Found: 307.1685.

10. Crystal data for (*Z*)-**2d**: $C_{15}H_{19}N_3O$, $f_w=257.33$; pale yellow prism, 0.38×0.35×0.25 mm, triclinic, space group $P\bar{1}$; $a=9.1992(14)$, $b=13.727(3)$, $c=6.2009(10)$ Å, $\alpha=98.194(8)$, $\beta=96.347(5)$, $\gamma=108.254(6)°$, $V=726.0(2)$ Å^3; $Z=2$; $D_{calcd}=1.177$ g cm^{-3}; $R=0.0840$, $wR(F^2)=0.2428$.
11. The concentration of hydrogen peroxide produced was determined based on oxidation current-potential curves for **1a**-derived sample and for authentic hydrogen peroxide and **2a**.
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