OZONOLYSIS OF 1-SUBSTITUTED IMIDAZOLES†

Choji Kashima,* Kaori Harada, and Akira Hosomi

Department of Chemistry, University of Tsukuba,
Tsukuba, Ibaraki 305, Japan

Abstract—1-Substituted imidazoles was ozonolyzed cleanly without any complicated procedures into the corresponding *N*-acylamides, which were regarded to be much useful derivatives of either amines or acyl compounds.

Previously, we have investigated the products and the mechanism of the ozonolysis of various five-membered heterocycles, such as pyrroles, pyrazoles, furans, isoxazoles, and oxazoles.[1] In the case of oxazoles, three types of ozonolysis reactions were observed, depending on the substituent groups.[2,3] 4-Substituted oxazoles gave directly *N*-acylamides and carbon dioxide, while 5-substituted oxazoles gave acid anhydrides and isocyanic acid. 4,5-Disubstituted oxazoles afforded carboxylic acids and *N*-acylisocyanates by the ozonolysis. From these facts, the consistent reaction mechanism was proposed for the ozonolysis of various oxazoles, where the key step was supposed to be the cleavage of C-H bond in the 1,2,4-dioxazoline intermediate.

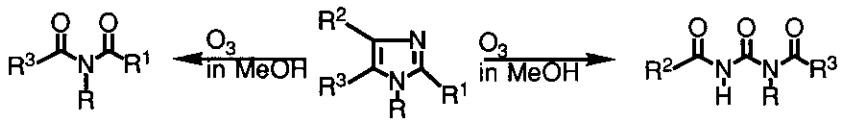
Since imidazole is isoelectronic with oxazole and exhibits the similar behaviors with those of oxazoles, the ozonolysis is expected to be the sufficient ring cleavage reaction of imidazoles affording the useful synthetic intermediate, and the research

† This paper is dedicated to Dr. Masatomo Hamana on the occasion of his 75th birthday for his brilliant achievement in the field of heterocyclic chemistry.

of ozonolysis of imidazoles seems to be very important to develop the new methodology for the synthesis of various organic compounds.

When 1-methylimidazole (**1a**) was treated with excess ozone-oxygen stream in methanol at -78°C, *N*-methyl-*N*-formylformamide (**7a**) was obtained in 80% yield instead of ordinary ozonide without any post-treatment such as oxidation and reduction. Also the formation of methyl *N*-methylcarbamate (**11**) was observed by ms and nmr spectroscopic analyses of the reaction residue. Similarly, various 1-

Scheme 1



7: R^1=R^3=H
8: R^1=Me, R^3=H
or R^1=H, R^3=Me
9: R^1=Ph, R^3=H
or R^1=H, R^3=Ph

1: R^1=R^2=R^3=H
2: R^1=Me, R^2=R^3=H
3: R^1=Ph, R^2=R^3=H
4: R^1=R^2=H, R^3=Me
5: R^1=R^2=H, R^3=Ph
6: R^1=R^3=H, R^2=Ph

10 R^2=Ph, R^3=H

R= **a**: Me, **b**: Et, **c**: Pr, **d**: Bu, **e**: i-Pr, **f**: Bn, **g**: PhCH(Me), **h**: $BnOCOCH_2$, **i**: MeCH(COOBn), **j**: $Me_2C(COOEt)$, **k**: $PhCH_2CH(COOMe)$, **m**: PhCOCH(Me), **n**: $BnOCOCH_2CH_2$, **p**: $BnOCOCH(Me)CH_2$, **q**: $EtOCOCH_2CH(COOEt)$

Table 1. Yields of *N*-Substituted *N*-Formylformamides (**7**)

	R	Yield (%)		R	Yield (%)
1a	Me	80	**1i**	MeCH(COOBn)	44
1b	Et	74	**1j**	$Me_2C(COOEt)$	69
1c	Pr	81	**1k**	$PhCH_2CH(COOMe)$	60
1d	Bu	52	**1m**	PhCOCH(Me)	59
1e	i-Pr	78	**1n**	$BnOCOCH_2CH_2$	81
1f	Bn	94	**1p**	$BnOCOCH(Me)CH_2$	90
1g	PhCH(Me)	95	**1q**	$EtOCOCH_2CH(COOEt)$	72
1h	$BnOCOCH_2$	71			

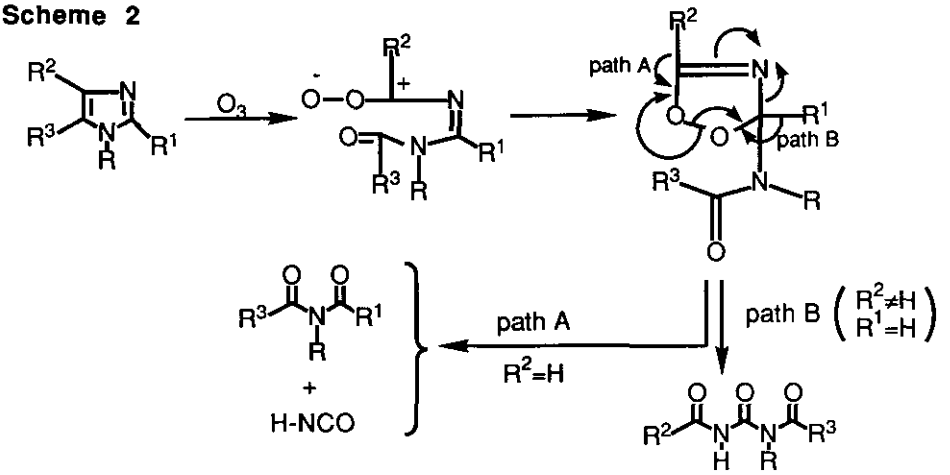
monosubstituted imidazoles (**1**) were ozonolyzed to give the corresponding *N*-substituted *N*-formylformamides (**7**) as summarized in Table 1.

When 2-substituted 1-methylimidazoles (**2a** and **3a**) were treated with excess ozone in dry methanol, the corresponding *N*-acyl-*N*-methylformamides (**8a** and **9a**) were obtained. Similarly, 2,5-disubstituted imidazoles (**4** and **5**) gave **8** and **9** in high yields respectively. In contrast, 4-phenyl-1-methylimidazoles (**6a**) showed the different behavior to ozone, and the corresponding *N*'-benzoyl-*N*-methyl-*N*-formylurea (**10a**) was formed. From these results, the ozonolysis of 1-substituted imidazoles (**1**, **2**, **3**, **4**, **5** and **6**) was classified to two types based on the presence or absence of substituent group at C-4 on the imidazole ring. *N*-Substituted *N*-acylamides (**7**, **8**, and **9**) were formed from 1-substituted imidazoles having no substituent group at C-4, while 1,4-disubstituted imidazole (**6**) afforded *N*-substituted *N*,*N*'-diacylurea (**10**). This reaction profile was supposed to be analogous to that of oxazoles,[3] and was consistently explained by the reaction mechanism through 1,2,4-dioxazoline intermediate summarized in the Scheme 2. After all, the ozonolysis was the quite useful ring-opening reaction of imidazole ring, because of the clean reaction under the mild conditions without any complicated procedures. Moreover, the utility of this reaction should be displayed

Table 2. Yields of Ozonolysis Product of Disubstituted Imidazoles

	Substrate				Product	
	R^1	R^2	R^3	R		Yield (%)
2a	Me	H	H	Me	**8a**	100
3a	Ph	H	H	Me	**9a**	91
4a	H	H	Me	Me	**8a**	85
4f	H	H	Me	Bn	**8f**	89
5a	H	H	Ph	Me	**9a**	94
6a	H	Ph	H	Me	**10a**	73

Scheme 2



by the formation of *N*-acylamides, which were regarded to be much reactive derivatives of either amines[4] or acyl compounds.[5]

EXPERIMENTAL

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus, and uncorrected. Ir spectra were measured on a Shimadzu IR-460 spectrophotometers. ^{1}H-Nmr and ^{13}C-nmr spectra were recorded using JEOL JNM-PMX 60SI (60 MHz) and JEOL FX 100 (100 MHz) spectrometers using tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu QP-2000 spectrometer. Elemental analyses were performed by Perkin-Elmer Model 240 elemental-analyzer.

Ozonolysis of 1-substituted imidazoles

Into the solution of 1-substituted imidazole (3 mmol) in dry methanol (15 ml), ozone-oxygen stream was bubbled at -78°C. When the reaction mixture became pale blue, the bubbling of ozone-oxygen was stopped, the excess ozone in the solution was purged out by bubbling of argon gas. After the solution was allowed to warm to room temperature, the resulting reaction mixture was evaporated. The crude product was purified by distillation under reduced pressure or by chromatography on silica gel with benzene-ethyl acetate mixture.

***N*-(1-Phenyl-1-ethyl)-*N*-formylformamide (7g)**

95 % yield; bp 150 °C/5 mmHg; ir ($CHCl_3$): 3400-2900, 1719, 1674, 1298, 1219 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.73(2H, s), 7.23(5H, s), 5.60(1H, q, J=8 Hz), 1.77(3H, d, J=8 Hz); ms (m/z): 177(M^+, 35), 148(75), 120(42), and 42(100). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.71; H, 6.26; N, 7.75.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-formylformamide (7h)**

71 % yield; mp 123-126 °C (from benzene-hexane mixture); ir (KBr): 2890, 1716, 1690, 1351, 1226 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.70(2H, s), 7.30(5H, s), 5.13(2H, s), 4.67(2H, s). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.59; H, 4.81; N, 6.48.

***N*-[1-(Benzyloxycarbonyl)ethyl]-*N*-formylformamide (7i)**

44 % yield; bp 160 °C/5 mmHg; ^{1}H-nmr (δ, $CDCl_3$): 8.70(2H, s), 7.27(5H, s), 5.03(1H, s), 4.63(2H, s), 2.07(3H, s); ms (m/z): 235(M^+, 4) 129(50), 91(100), 72(84), 44(100). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.25; H, 5.56; N, 5.95. Found: C, 61.41; H, 5.72; N, 6.28.

***N*-[2-Methyl-2-(ethoxycarbonyl)propyl]-*N*-formylformamide (7j)**

69 % yield; bp 130 °C/5 mmHg; ^{1}H-nmr (δ, $CDCl_3$): 8.93(2H, s), 4.12(2H, q, J=7 Hz), 1.70(6H, s), 1.27(3H, t, J=7 Hz). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33, H, 7.00; N,7.48. Found: C, 51.09; H, 6.99; N, 7.51.

***N*-[2-Phenyl-1-(methoxycarbonyl)ethyl]-*N*-formylformamide (7k)**

60 % yield; bp 160 °C/1 mmHg; mp 72 °C; ir (KBr): 2920, 1729, 1671, 1331, 1250 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.60(2H, s), 7.13(5H, s), 3.77(2H, s), 3.50-3.23(1H, m) and 1.57(3H, s); ms (m/z): 235(M^+, 3), 162(100), 131(52), 91(84). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.12; H, 5.78; N, 5.92.

***N*-[2-(1-Phenyl-1-oxo)ethyl]-*N*-formylformamide (7m)**

59 % yield; oil; ir ($CHCl_3$): 3385-3005, 1665, 1492, 1212 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.80(2H, s), 7.50(5H, s), 5.80(1H, q, J=8 Hz), and 1.58(3H, d, J=7 Hz); ms (m/z): 205(M^+, 3), 105(100), 77(430), 51(18). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.17; H, 5.63; N, 6.77.

***N*-[2-(Benzyloxycarbonyl)ethyl]-*N*-formylformamide (7n)**

81 % yield; oil; ir ($CHCl_3$): 3400-3000, 1772, 1322, 1216 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.80(2H, s), 7.30(5H, s), 5.07(2H, s), 3.95(2H, t, J=7 Hz), 2.67(2H, t, J=7 Hz); ms (m/z): 235(M^+, 4), 128(38), 91(100), 55(91). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.06; H, 5.72; N, 5.78.

***N*-[2-Methyl-2-(benzyloxycarbonyl)ethyl]-*N*-formylformamide (7p)**

90 % yield; bp 190°C/5 mmHg; ir ($CHCl_3$): 3400-2950, 1719, 1677, 1216, 1183 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.70(2H, s), 7.30(5H, s), 5.03(2H, s), 3.97-3.83(2H, m), 2.92(1H, q, J=7 Hz), 1.18(3H, d, J=7 Hz); ms (m/z): 249(M^+, 1), 142(33), 107(42), 91(100), 69(39). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.62; H, 6.38; N, 5.41.

***N*-[1,2-Di(ethoxycarbonyl)ethyl]-*N*-formylformamide (7q)**

72 % yield; oil; ir ($CHCl_3$): 3400-2700, 1726, 1219, 1192 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 8.77(2H, s), 5.46-5.14(1H, m), 4.30-3.90(4H, m), 3.20(1H, d, J=6 Hz), 3.00(1H, d, J=8 Hz), 1.30(6H, t, J=7 Hz). Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 49.07; H, 6.33; N, 5.36.

***N'*-Benzoyl-*N*-methyl-*N*-formylurea (10a)**

73 % yield; mp 147-148°C (from benzene); ir ($CHCl_3$): 3190, 1760, 1680, 1330, 1200 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 3.31(3H, s), 7.30(1H, s), 7.30-7.70(3H, m), 7.90-8.00(2H, m), 8.66(1H, s), 12.2(1H, broad s, D-exchangable); ^{13}C-nmr (δ, $CDCl_3$): 32.4(q), 127.8 (s), 129.0 (d), 132.7(s), 133.3(d), 148.8(s), 164.5(s), 166.0(d). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.57. Found: C, 57.73; H, 4.91; N, 13.41.

REFERENCES

1) C. Kashima, S. Hibi, T. Maruyama, K. Harada, and Y. Omote, *J. Heterocycl. Chem.*, 1987, **24**, 637.

2) C. Kashima, S. Hibi, K. Harada, and Y. Omote, *J. Chem. Soc., Perkin. Trans. I*, **1988**, 529.

3) C. Kashima, H. Arao, and S. Hibi, *J. Chem. Res. (S)*, **1991**, 34.

4) Y. Han and H. Hu, *Synthesis*, **1990**, 122.

5) K. Tomioka, T. Suenaga, and K. Koga, *Tetrahedron Lett.*, 1986, **27**, 369.

Received, 5th November, 1991