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Anodic Oxidation of Amides and Lactams Using *N*-Hydroxyphthalimide as a Mediator

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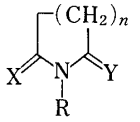
Indirect electrochemical oxidation of amides and *N*-alkyllactams was performed using *N*-hydroxyphthalimide as a mediator. A carbonyl group was introduced in good yield at the α-carbon to the nitrogen of the compounds.

Keywords——anodic oxidation; mediator; amide; *N*-alkyllactam; *N*-hydroxyphthalimide; imide; *N*-acyllactam; glassy-carbon electrode

Electrochemical methoxylation, cyanation and acetoxylation at the carbon α to nitrogen of amides and carbamates have been widely studied.[1] The introduction of a carbonyl group at the carbon adjacent to nitrogen by direct anodic oxidation has also been reported in the oxidation of *N*-alkyllactams, but α-hydroxylated lactams were the major products and the corresponding imides or *N*-acyllactams were minor products.[2]

In the previous preliminary report we described an indirect anodic oxidation of various types of compounds having benzylic or allylic carbons and hetero atoms using *N*-hydroxyphthalimide (NHPI) as a mediator, resulting in the introduction of a carbonyl group into these compounds.[3a] As a continuation of the above work, we report in the present paper the anodic oxidation of amides and *N*-alkyllactams in detail. The yields of the carbonyl compounds are superior to those obtained by direct anodic oxidation or photocatalytic oxidation.[4] In the case of *N*-alkylpyrrolidinone, our oxidation takes place predominantly at the *endo*-cyclic carbon α to nitrogen except in the *N*-benzyl derivative. Compounds **1**—**6**, *N*-ethylacetamide and *N*,*N*-diethylacetamide were examined.



	n	R	X	Y		*n*	R	X	Y
1	1	COMe	H_2	H_2	**7**	1	Me	O	O
2	1	COPh	H_2	H_2	**8**	1	Et	O	O
3	2	COPh	H_2	H_2	**9**	1	CH_2Ph	O	O
4	1	Me	O	H_2	**10**	1	CHO	O	H_2
5	1	Et	O	H_2	**11**	1	COMe	O	H_2
6	1	CH_2Ph	O	H_2	**12**	1	COPh	O	H_2
	MeCONHEt,		MeCO	NEt_2	**13**	2	COPh	O	H_2

Results and Discussion

The results of cyclic voltammetry carried out in acetonitrile containing 0.1 M $NaClO_4$ at a glassy-carbon electrode are summarized in Table I. The oxidation potentials of the first wave

TABLE I. Cyclic Voltammetric Data on Amides and Lactams (5 mM) in Acetonitrile Containing 0.1 M $NaClO_4$

Compd.	E_{pl}[a]	Compd.	E_{pl}[a]
MeCONHEt	2.06	**3**	1.79
$MeCONEt_2$	1.86	**4**	1.83
1	1.78	**5**	1.84
2	1.71	**6**	1.80

a) V *vs.* SCE.

TABLE II. Products of Electrochemical Oxidation of Amides (20 mM) Using NHPI (5 mM) as an Electron Carrier

Compd.	F/mol[a]	Product	Yield (%)[b]	NHPI recovery (%)
MeCONHEt	2.0	$(MeCO)_2NH$	69	34
$MeCONEt_2$	1.9[c]	$(MeCO)_2NEt$	54	20
1	2.0	**11**	80	66
2	2.0	**12**	79	53
3	1.3[c]	**13**	9[d]	[e]

a) Electricity passed per mole of the amides. *b*) Based on the amides. *c*) Electrolysis did not proceed further. *d*) 44% of **3** was recovered. *e*) Not determined.

TABLE III. Products from Electrochemical Oxidation of *N*-Alkylpyrrolidinone (20 mM) Using NHPI as an Electron Carrier

Compd.	F/mol[a]	Product	Yield (%)[b]	NHPI recovery (%)
4	2.0	**7**	81	45
		10	—[c]	
5	2.0	**8**	73	46
		11	11	
6	2.0	**9**	47	36
		12	34	

a) Electricity passed per mole of *N*-alkyllactams. *b*) Based on *N*-alkyllactams. *c*) Not detected.

are within the range of 1.80—2.06 V *vs.* SCE. These values are much higher than the applied potential (0.85 V *vs.* SCE) used in the NHPI-mediated method.

Controlled Potential Electrolysis

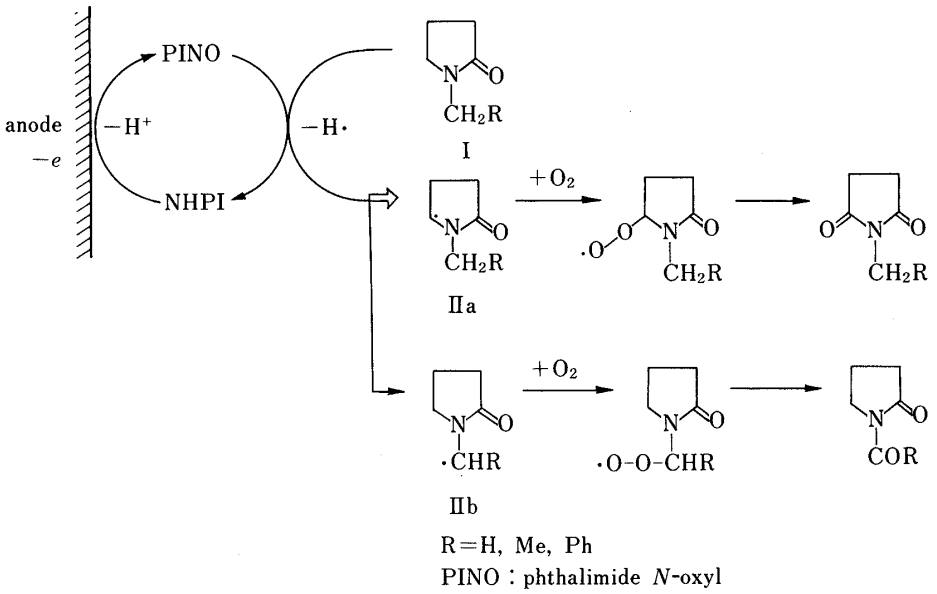
Controlled potential electrolysis of the starting compounds (20 mM) was performed in acetonitrile containing 0.1 M $NaClO_4$, NHPI (5 mM) and pyridine (53 mM) at 0.85 V *vs.* SCE using a glassy-carbon anode in an H-type divided cell under an oxygen atmosphere. The results are summarized in Tables II and III.

The oxidation occurred at the carbon α to the nitrogen to provide the imides in good yield except for **3** (Table II). *N*-Alkylpyrrolidinones gave the corresponding imides as the major products. This indicates that the *endo*-cyclic carbon α to the nitrogen in the pyrrolidinone ring is more susceptible to oxidation in the present system than the *exo*-cyclic one. The degree of oxidation of the *exo*-cyclic α-methylene was dependent on the *N*-alkyl group (R), and increased in the order, $Me < Et \ll CH_2Ph$. The susceptibility to oxidation of the

benzylic carbon is rather comparable with that of *endo*-cyclic carbon in the pyrrolidinone ring, even if it exists at the *exo*-cyclic position. The susceptibility to oxidation of a five-membered ring is much higher than that of a six-membered ring (compare **1**, **2**, and **3**).

The magnitude of C–H bond energy, which is in the order of Me > Et > PhCH,[5] and the difference in ring distortion between five- and six-membered rings, which is similar to that observed in carbonium ion formation,[6] may be among the factors influencing the ease of formation and the relative amounts of the reaction products. However, on the other hand, the relative rates of reaction of the compounds oxidized with phthalimide *N*-oxyl (PINO) are not always parallel to the yield of the oxidation products.[3c] The results presented above thus appear to reflect the combination of many factors, including the above ones and others not yet identified, and there seems to be no simple relation between structure and reactivity.

The oxidation process can be depicted as follows.



R=H, Me, Ph
PINO : phthalimide *N*-oxyl

Since the applied potential in the electrolysis (0.85 V *vs.* SCE) is much lower than the oxidation potentials of amides and lactams, it is apparent that the compounds are oxidized by homogeneous reaction with electrogenerated phthalimide *N*-oxyl. A hydrogen atom on either α-carbon will be abstracted by PINO to give a radical (IIa or IIb) in a manner similar to that occurring in the oxidation of olefins.[3b] The advantages of the present method are as follows. i) The oxidation is simple and easy to carry out under very mild conditions without the use of any expensive or pollutant reagent. ii) The method gives fairly good yields of imides or lactams except in six-membered rings.

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-20 or R-60 spectrometer with Me_4Si as an internal standard. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. Gas liquid chromatographic (GLC) analyses were performed on a JEOL JGC-20K instrument. High-performance liquid chromatography (HPLC) was done on a Waters M-600 A instrument equipped with a Shimadzu SPD-2A spectrophotometric detector. Thin layer chromatography (TLC) was performed on Merck aluminum plates (0.2 mm layer of silica gel). Column chromatographies were done on Wakogel C-200 (Wako Pure Chemicals Ind., Ltd.).

Apparatus and Procedures; Cyclic Voltammetry——Cyclic voltammetry was performed with a three-electrode system employing a linear scanning unit (Hokuto Denko Co., model HB 101) equipped with a potentiostat (Hokuto Denko Co., model PS-500B). The electrode system consisted of a glassy-carbon indicator electrode (3 mm i.d.), a glassy-carbon counter electrode and a saturated calomel reference electrode (SCE). Measurements were carried out at

TABLE IV. Properties of Amides, Lactams and Imides

Compd.	mp or bp °C (Recryst. solvent or pressure)	Elemental analysis % Found (Calcd)		
		C	H	N
$(MeCO)_2NEt$	bp 96—98 (25 mmHg)	55.43	8.75	10.73
		(55.79	8.58	10.85)
1	bp 87—89 (6 mmHg)	63.43	10.11	12.19
		(63.68	9.80	12.39)
2	bp 152—153 (3 mmHg)	75.58	7.52	7.87
		(75.40	7.48	7.99)
3	mp 41—42 (from *n*-hexane)	76.20	8.12	7.46
		(76.15	7.99	7.40)
7	mp 67—68 (from iso-PrOH)	52.91	6.18	12.57
		(53.09	6.24	12.38)
9	mp 101 (from iso-PrOH)	69.98	5.82	7.51
		(69.82	5.86	7.40)
11	bp 87 (3.5 mmHg)	56.48	7.19	10.55
		(56.68	7.14	11.02)
12	mp 91—92 (from *n*-hexane)	69.92	5.68	7.37
		(69.82	5.86	7.40)
13	mp 104—106 (from $CHCl_3$–pet. ether)	70.72	6.44	6.82
		(70.91	6.45	6.89)

25 ± 0.05 °C with a substrate concentration of *ca.* 5 mM and a sweep rate of 0.05 V s^{-1}.

Controlled Potential Electrolysis——Controlled potential electrolysis was carried out with a Hokuto Denko HA 101 potentiostat; the current was recorded on a Toa Dempa EPR-2TB recorder and the quantity of electricity consumed was measured with a Hokuto Denko HF-102 coulombmeter. The electrolyses were generally performed with 20 mM substrate, 5 mM NHPI and 53 mM pyridine in 20 ml of acetonitrile containing 0.1 M $NaClO_4$ using an H-type divided cell with a glassy-carbon plate (3 cm × 1.5 cm) electrode, at 0.85 V *vs.* SCE with mechanical stirring under a stream of oxygen.

Materials——Physical data of the starting materials and authentic samples prepared are summarized in Table IV. Compounds **1**, **2** and **3** were prepared by the reaction of piperidine or pyrrolidine with the corresponding acid chloride in methylene chloride in the presence of triethylamine and purified by distillation (**1** and **2**) or recrystallization from *n*-hexane (**3**).

Authentic samples of diacetamide and **8** were purchased from Aldrich Chemical Co., and Tokyo Kasei Kogyo Co., respectively. All materials were of reagent (or equivalent) grade and were used as received from the commercial source. *N*-Ethylacetamide,[7] **7**,[8] **9**,[9] **11**,[7] **12**[7] and **13**[7] were prepared according to the reported methods.

Products Analysis——Identification of the oxidation products (**7** and **11**) was done by comparison of the spectroscopic (IR and ^{1}H-NMR) data of the products isolated from the electrolyzed solution by column chromatography with those of authentic samples. Other products were identified by comparison of the retention times on GLC or HPLC with those of authentic samples using the solution after electrolysis. All GLC analyses of products were done on 1 m × 3 mm i.d. or 2 m × 3 mm i.d. stainless steel columns packed with 10% PEG 20M or PEG 6000 (treated with KOH) on Celite 545. All HPLC analyses were performed using a bonded-phase cartridge C_{18}, Radial-PAK A (Waters Associates, Inc.) with 60% (v/v) −80% (v/v) aqueous acetonitrile as the eluent.

References and Notes

1) T. Shono, *Tetrahedron*, **40**, 811 (1984) and references cited therein.
2) *a*) Y. Ban, T. Wakamatsu, and M. Mori, *Heterocycles*, **6**, 1171 (1979); *b*) M. Okita, T. Wakamatsu, and Y. Ban, *J. Chem. Soc., Chem. Commun.*, **1979**, 749; *c*) M. Okita, T. Wakamatsu, M. Mori, and Y. Ban, *Heterocycles*, **14**, 1089 (1980).
3) *a*) M. Masui, S. Hara, T. Ueshima, T. Kawaguchi, and S. Ozaki, *Chem. Pharm. Bull.*, **31**, 4209 (1983); *b*) M. Masui, K. Hosomi, T. Tsuchida, and S. Ozaki, *ibid.*, **33**, 4798 (1985); *c*) Unpublished data.
4) J. M. Pavlik and S. Tantayann, *J. Am. Chem. Soc.*, **103**, 6755 (1981).

5) H. Sakurai and K. Tokumaru, "Chemistry of Free Radical," Nankodo, Tokyo, 1967, p. 23.
6) J. Hine, "Physical Organic Chemistry," 2nd ed. McGraw-Hill, New York, 1962, Chap. 7-3 and 21-2.
7) O. L. Volker, *Synthesis*, **1979**, 387.
8) W. Flitsch, *Chem. Ber.*, **97**, 1542 (1964).
9) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 1744 (1964).