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Acylation of Amines and Alcohols by Anodic Oxidation of *N*-Phenyl-hydroxamic Acids

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The electrochemical acylation of amines and alcohols is described. The yield of products from the electrochemical reaction is markedly improved by the use of *N*-phenyl derivatives of hydroxamic acids in place of the *N*-hydrogen counterparts.

Keywords——anodic oxidation; acylation of amine and alcohol; *N*-phenylhydroxamic acid; acetonitrile; glassy-carbon electrode

In the previous communication,[1] we described a method for the benzoylation, acetylation and ethylaminocarbonylation of amines and alcohols by the anodic oxidation of hydroxamic acid derivatives (HA), *i.e.*, benzohydroxamic acid (BHA) and acetohydroxamic acid (AHA), and *N*-ethyl-*N'*-hydroxyurea (EHU), respectively. The reaction was performed in an organic solvent under very mild conditions and fairly good yields were obtained without competitive oxidation of amines. The benzoylation of some amines with strong basicity, however, was not satisfactory as compared with the ethylaminocarbonylation of the amines.

In the present paper, we show that the *N*-phenyl derivatives of hydroxamic acids give better results in the above reaction.

Results and Discussion

In the presence of amines, HA and EHU are oxidized at lower potentials (E_{pe}) than the original potentials (E_{pl}), since they form hydrogen-bonded complexes with the added amines.[1–3] Under the conditions used, it was expected that amines with larger basicity would give higher yields of amide or urea. This was true in the oxidation of EHU, but not in that of BHA.[1] When an amine with a pKa value larger than about ten was added in excess to 10 mM BHA dissolved in acetonitrile containing about 0.1 M sodium perchlorate, a white precipitate appeared immediately. The precipitate was analyzed and found to be the sodium salt of BHA, $C_6H_5CONHONa$. The low yield of benzoylamines should thus be attributable in part to the decrease in the concentration of BHA. The yield of benzoylamines was, however, not improved even when the supporting electrolyte $NaClO_4$ was replaced by $Et(nBu)_3NBF_4$ to avoid the precipitation of the salt. Since *N*-phenyl-BHA is a weaker acid ($pK_a=9.15$)[3] than BHA ($pK_a=8.80$)[3] and is not expected to form an insoluble sodium salt, the former was tested in place of BHA. The effects of the *N*-phenyl group on the oxidation potential and on the yields of the reaction products from amines and alcohols were also investigated with AHA and 2-MeO-BHA.

As shown in Table I, E_{pl} and E_{pe} values of the *N*-phenyl derivatives of BHA, 2-MeO-BHA and AHA are lower than those of the corresponding acids without the *N*-phenyl group.

Electrolysis was performed potentiostatically at E_{pe} in acetonitrile containing 0.1 M $NaClO_4$ by two methods; i) with about 10^{-2} M acid and an equimolar amount of nucleophile in the presence or absence of excess pyridine, ii) with about 10^{-2} M acid and about four-fold excess of nucleophile. The results are summarized in Table II. The yields of the amides and esters are markedly increased by the introduction of an *N*-phenyl group at the nitrogen of the

TABLE I. Cyclic Voltammetric Data for HA and *N*-Phenyl-HA

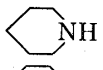
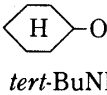
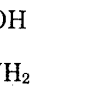
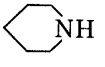
	E_{pl} [a]	E_{pe} [b]
BHA	1.35	0.60
N-Phenyl-BHA	1.05	0.40
2-MeO-BHA	1.44	0.25
N-Phenyl-2-MeO-BHA	1.26	0.20
AHA	1.65	0.45
N-Phenyl-AHA	1.15	0.15

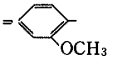
a) V *vs.* SCE.
b) Peak potential of an extra wave appearing on addition of excess piperidine.

acids, and the selectivity of acylation which involves only the amino group of ethanolamine is retained.[1] In the oxidation of 2-MeO-BHA in the presence of *tert*-$BuNH_2$ or piperidine and the oxidation of AHA in the presence of iso-$PrNH_2$ the current decreased to the background considerably before 2F/mole has been consumed (Table II). This current decrease was probably because of the adsorption of insoluble sodium hydroxamate on the surface of the electrode. The use of *N*-phenyl derivatives of 2-MeO–BHA and AHA avoided this problem to some extent.

N-Phenyl-2-MeO-BHA produced much larger amount of methyl-2-MeO-benzoate than 2-MeO-BHA did in the oxidation performed in methanol for example, in which no precipitate

TABLE II. Products from Electrolysis of BHA, 2-MeO-BHA and AHA (Group A) and their *N*-Phenyl Derivatives (Group B) in the Presence of Amine or Alcohol

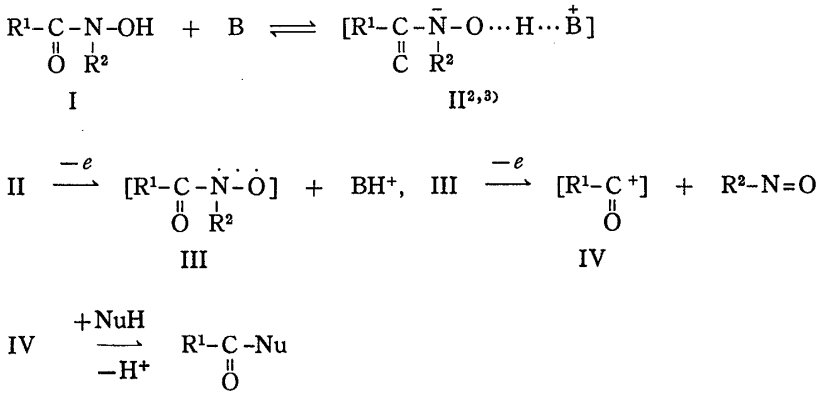
HA	Amine or alcohol	Group A				Group B		
		$E_{app.}$ [a]	n [b]	Products	Yield (%) [c]	$E_{app.}$ [a]	n [b]	Yield (%) [c]
BHA or *N*-Phenyl-BHA	$MeNH_2$	0.40	2.2	$C_6H_5CONHMe$	59[d]	0.40[d] (0.65)[e]	3.1[d] (2.1)[e]	93[d] (74)[e]
	iso-Pr NH_2	0.40	2.1	C_6H_5CONHiso-Pr	59[d]	0.40[d] (0.65)[e]	3.1[d] (2.5)[e]	85[d] (82)[e]
		0.60	3.0	C_6H_5CO	26[d]	0.40[d] (0.65)[e]	3.0[d] (2.4)[e]	71[d] (60)[e]
		[f]	2.6	$C_6H_5CO_2$ 	31[f]	[f]	3.0	57[f]
2-MeO-BHA or *N*-Phenyl-2-MeO-BHA	*tert*-$BuNH_2$	0.30	0.6[g]	RCONH*tert*-Bu[h]	10[i]	0.25	1.0[g]	54[i]
		0.25	1.3[g]	RCO  [h]	15[i]	0.25	1.7	74[i]
	$HOCH_2CH_2NH_2$	0.26	1.7	$HOCH_2CH_2$ [h] NHCOR	52[i]	0.25	1.8	85[i]
	MeOH	1.20	1.8	RCOOMe[h]	50[j]	1.05	1.8	87[j]
AHA or *N*-Phenyl-AHA	$C_6H_5CH_2NH_2$	0.75	4.6[d] (3.6)[e]	$MeCONHCH_2C_6H_5$	66[d] (65)[e]	0.40[d]	5.2[d]	83[d]
	iso-Pr NH_2	0.56[d] (0.71)[e]	1.0[g] (1.8)	MeCONHiso-Pr	25[d] (28)[e]	0.25[d]	2.7[d]	88[d]

a) Applied potential, V *vs.* SCE.
b) Faradays passed per mole of the substrate.
c) Mole per cent of the acids.
d) Electrolyzed with about four-fold excess of amine.
e) Electrolyzed with an equimolar quantity of amine in the presence of about four-fold excess of pyridine.
f) Electrolyzed with a constant current of 5 mA/cm² in the presence of about four-fold excess of  and CF_3COOH.
g) Electrolysis did not proceed further when the electricity consumption (F/mol) reached the value described in the Table.
h) R = 
i) Electrolyzed with an equimolar amount of amine.
j) Electrolyzed in methanol.

was formed. The results suggest that the introduction of a phenyl group at the nitrogen atom of the acids has another effect on the oxidative acylation besides preventing the formation of insoluble salt.

Although the electrolysis performed in the presence of about four-fold excess of amines usually gave a higher yield of amides based on HA, n values in some of the electrolyses exceeded two, and sometimes reached about three. This low current yield may be a result of partial oxidation of added amines in the last stage of the electrolysis. This could be overcome ($n \simeq 2$) by the use of excess pyridine ($E_{pl} > 1.90$ V) in place of excess amines. Pyridine is thought to act as a catalyst for the acylation and as a base to make the oxidation potential of HA lower in the electrolysis.

On the basis of the proposed oxidation mechanism of the acids[4] and the present results, the following reaction scheme is proposed.



where $R^1 = C_6H_5$, 2-MeO-C_6H_4 or CH_3, $R^2 = H$ or C_6H_5 and NuH = amine or alcohol. It is not clear, however, whether the attack of nucleophile on the acyl carbon occurs before or after the C–N bond fission. The present results show that the yields of the acylated products are higher when the leaving group is nitrosobenzene, but are independent of the base strength of nucleophile, and thus it is likely that the C–N bond is cleaved before the addition of nucleophile, as in an S_N1 reaction.

Experimental

Materials——Benzohydroxamic acid,[5] *N*-phenyl benzohydroxamic acid,[6] acetohydroxamic acid[5] and *N*-phenyl acetohydroxamic acid[7] were prepared according to the literatures.

N-(2-Methoxybenzoyl)-hydroxylamine (2-MeO-BHA): A solution of 0.7 g (18 mmol) of NaOH in 10 ml of water was added dropwise under a stream of nitrogen to 20 ml of water–ether 1: 1 mixture containing 1.3 g (18 mmol) of $NH_2OH \cdot HCl$ with mechanical stirring. The mixture was cooled to 0°C, then 1 g (9.5 mmol) of Na_2CO_3 in 5 ml of water and 2 g (12 mmol) of 2-MeO-C_6H_4COCl prepared by the method of Keumi[8] in dry ether were added dropwise. The mixture was stirred for 1 h at 0°C then for a further 3 h at r.t. The precipitated crystals were collected and recrystallized from ethyl acetate, to provide needles (1.35 g, 66%). mp 125°C. $C_8H_9NO_3$ requires C, 57.48; H, 5.43; N, 8.38. Found: C, 57.57; H, 5.42; N, 8.33. δ (CD_3CN) 3.92 (3H, s, $-OCH_3$) 6.8—8.1 (4H, m, $-C_6H_4-$) 8.5—9.5 (2H, br, –NH and –OH). *N*-(2-Methoxybenzoyl)-*N*-phenylhydroxylamine (*N*-phenyl-2-MeO-BHA): Sodium carbonate (3 g, 28 mmol) suspended in dry chloroform was added to dry chloroform solution of phenylhydroxylamine (2.2 g, 20 mmol) at 0°C under mechanical stirring, then 2-MeOH-C_6H_4COCl (3.4 g, 20 mmol) in dry chloroform was added dropwise to the mixture. The whole was stirred for 1 h at 0°C and then for 1 h at r.t. Concentration of the chloroform layer under reduced pressure gave a viscous oil, which solidified on cooling. The solid was recrystallized from water–methanol (2 g, 45%). mp 115°C. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39; N, 5.76. Found: C, 68.97; H, 5.34; N, 5.83. δ (CD_3CN) 3.65 (3H, s, $-OCH_3$) 6.7—7.7 (10H, m, $-C_6H_5$, $-C_6H_4-$ and –OH).

Benzamides and acetamides were prepared by the standard method.[9] *N-tert*-Butyl-2-methoxybenzamide and 1-(2-methoxybenzoyl)-piperidine were prepared by the reaction of 2-MeO-C_6H_4COCl with the corresponding amine in the manner described in the case of *N*-phenyl-2-MeO-BHA. *N-tert*-Butyl-2-methoxy-

benzamide was recrystallized from water–methanol. mp 53°C. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76. Found: C, 69.19; H, 8.25; N, 6.68. δ (CD_3CN) 1.42 (9H, s, $-Bu^t$) 3.87 (3H, s, $-OCH_3$) 6.7—8.2 (5H, m, $-C_6H_4-$ and $-NH-$). 1-(2-Methoxybenzoyl)-piperidine was purified by silica gel thin layer chromatography (TLC). mp 46°C. $C_{13}H_{17}NO_2$ requires C, 71.20; H, 7.82; N, 6.39. Found: C, 71.25; H, 7.92; N, 6.28. δ (CD_3CN) 1.1—1.8 (6H, br, $\overset{|}{N}H-CH_2-CH_2-\overset{|}{}$) 3.10 and 3.60 (2H×2, br, $\overset{|}{N}H-CH_2-\overset{|}{}$). *N*-(2-Hydroxyethyl)-2-methoxybenzamide: The viscous oil obtained by the reaction of ethanolamine (0.7 g, 12 mmol) with 2-MeO-C_6H_5COCl (2 g, 12 mmol) in the manner described in the case of *N*-phenyl-2-MeO-BHA was found by TLC to contain two compounds A and B, which were separated by silica gel column chromatography using chloroform as an eluent. Compound A (smaller *Rf* value) was *N*-(2-hydroxyethyl)-2-MeO-benzamide (0.55 g, 24%). $C_{10}H_{13}NO_3$ requires C, 61.52; H, 6.71; N, 7.18. Found: C, 61.30; H, 6.67; N, 7.07. δ (DMSO-d_6) 3.2—3.7 (5H, m, $-CH_2\times2$ and $-OH$) 3.90 (3H, s, $-OCH_3$) 4.80 (1H, t, J=6 Hz, $-CONH-$) 6.9—7.9 (4H, m, $-C_6H_4-$). The spectroscopic data on compound B (larger *Rf* value) showed that compound B is *N*-[2-(2-methoxybenzoyloxy)ethyl]-2-methoxybenzamide. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (–OCO–), 1645 (–CONH–). δ (CD_3CN) 3.80 (3H, s, $-OCH_3$) 3.86 (3H, s, $-OCH_3$) 6.8—8.3 (8H, m, $-C_6H_4-\times2$).

Products Analysis——Benzoylamines, 2-MeO-benzoylamines and acetylamines were isolated as described below and identified by comparing their IR and NMR spectra with those of authentic samples. The solution from electrolysis was concentrated by evaporation under reduced pressure. Chloroform was added to the residue, and the solution was washed with dilute HCl solution. The chloroform layer was dried over Na_2SO_4 and concentrated, and the amides were separated from the residue by silica gel column or TLC.

Benzoylamines, *N*-benzylacetamides and 2-MeO-benzoylamine were determined by the use of high performance liquid chromatograph (Waters model 6000) with a spectrometric detector (JASCO UVIDEC-1) using a bonded-phase cartridge, Radial-PAK A (Waters Associates, Inc.) with 70% (v/v) aqueous methanol and a 1: 1 mixture of acetonitrile and 0.2 M triethylamine phosphate buffer (pH 3) as eluents.

N-Isopropylacetamide was determined by gas liquid chromatography (GLC) using a stainless steel column (2×3 mm ϕ) packed with PEG 20M (Nishio Kogyō) and maintained at 160°C.

Sodium Benzohydroxamate: The white precipitate appearing on addition of excess methylamine to an acetonitrile solution containing about 10 mM BHA and 0.1 M $NaClO_4$ was recrystallized from ethanol. The melting point of the precipitate was over 295°C. The characteristic frequencies in the infrared (IR) spectrum of the precipitate were in accord with those of authentic benzohydroxamic acid in dioxane containing an equivalent amount of CH_3ONa.[10] *Anal.* Calcd for $C_{17}H_6NNaO_2$: C, 52.83; H, 3.80; N, 8.80. Found: C, 52.82; H, 4.20; N, 8.98.

Apparatus and Procedures——Cyclic Voltammetry: Cyclic voltammetry was performed using a three-electrode system consisting of a glassy-carbon working electrode, an SCE reference electrode and a glassy-carbon counter electrode at 25° with a scan rate of 0.05 V s^{-1}. The values of E_{pl} and E_{pe} were measured in acetonitrile containing 0.1 M $NaClO_4$ using 5 mM HA, and 5 mM HA with about four-fold excess of amine, respectively.

Controlled Potential Electrolysis: Controlled potential electrolysis was performed with a Hokuto Denko HA 101 potentiostat using 10 mM HA in 40 ml of electrolyte (CH_3CN–0.1 M $NaClO_4$) and an equimolar or excess amount of amine in an undivided cell at a glassy-carbon plate (2 cm×3 cm) or a rectified vitreous carbon electrode (45S, 1.8 cm×2.0 cm×0.8 cm).

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