N-Arylhydroxamic Acids: Reaction of Nitroso Aromatics with α-Oxo Acids

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A practical and high-yielding route to *N*-arylhydroxamic acids from nitroso aromatics and α-oxo acids **1a–d** is described. In aqueous and acetic acid containing media, the reactions exhibit second-order reaction kinetics overall. In the aqueous medium, the rate constant (k_{obsd}) for *N*-phenylacetohydroxamic acid (**8b**) formation increased with increasing [H_3O^+], though there were some side pathways involving azoxybenzene formation. In general, k_{obsd} for the reaction in the acetic acid containing medium was about one-tenth of that in HCl at pH 0.6. On a preparative scale, acetic acid is better than HCl, in that both reactants showed sufficient solubilities in acetic acid for a high reaction velocity and no side reaction was detected. With this method, the proximate carcinogens, *N*-(4-biphenylyl)acetohydroxamic acid (**12b**) and *N*-(2-fluorenyl)acetohydroxamic acid (**13b**), could be easily prepared. Under both conditions, the order of k_{obsd} for the reactions of nitrosobenzene (**2**) with α-oxo acids **1a–d** was glyoxylic (**1a**) > pyruvic (**1b**) ≥ 2-oxobutyric (**1c**) > benzoylformic (**1d**) acid. For the reactions of substituted nitrosobenzenes **3–6** with pyruvic acid (**1b**), the order of k_{obsd} was *p*-phenyl (**6**) > unsubstituted (**2**) > *p*-chloro (**5**) > *m*-chloro (**4**) ≫ *o*-chloro (**3**) nitrosobenzene. The negative Hammett reaction constant value obtained indicates that an electron-donating substituent is preferable for the reaction. The reaction mechanism and other factors affecting *N*-arylhydroxamic acid formation are also discussed.

Introduction

Arylhydroxamic acids have not only been used as antibiotics[1] and metal chelators[2,3] but are also known to be proximate carcinogens.[4,5] As to the carcinogenicity of *N*-substituted aromatics, biosynthetic studies on *N*-arylacetohydroxamic acids have demonstrated three types of pathways leading to their formation, i.e., acetylation of *N*-arylhydroxylamines,[6] direct *N*-hydroxylation of *N*-arylacetamides,[7] and a thiamine enzyme mediated reaction from nitroso aromatics and pyruvic acid.[8,9]

Three types of chemical synthetic methods, which coincidentally correspond to the abovementioned three biosynthetic pathways, for *N*-arylhydroxamic acids have been reported. The first method involves acylation of *N*-arylhydroxylamines[10-12] and the second oxidation of arylacylamides.[13] However, a disadvantage of these methods is their poor yields, which are due to decomposition of the labile *N*-arylhydroxylamines for the first method and a low rate constant for the second. In order to avoid exposure of people to carcinogenic compounds, the synthesis of such proximate carcinogens should involve a simple procedure.

The third chemical method, which satisfies the latter requirement, corresponds to the biochemical reaction mediated by the thiamine enzyme. This method, however, has been reported to be highly specific for glyoxylic acid, in that no analogous reaction was observed with pyruvic acid.[14] Although arylpyruvic acids have recently been shown to react with *p*-nitroso-*N*,*N*-dimethylaniline to produce the corresponding *N*-[*p*-(dimethylamino)phenyl]arylacetohydroxamic acids,[15] an attempt to obtain *N*-arylacetohydroxamic acids through the reaction of nitroso aromatics with pyruvic acid was unsuccessful.

We present here a general and useful method for the synthesis of *N*-arylhydroxamic acids **8–13** from nitroso aromatics **2–7** and α-oxo acids **1a–d**, including pyruvic and glyoxylic acids, and factors affecting the reaction.

Experimental Section

All melting points were determined by the capillary method and are uncorrected. ^1H NMR spectra were recorded with a JEOL-GX270 spectrometer with tetramethylsilane as the internal standard.

Chemicals. Glyoxylic acid and sodium pyruvate were purchased from Merck and Wako Chemicals Industry Co. (Osaka, Japan), respectively. Sodium 2-oxobutyrate was purchased from Nakarai Chemical Co. (Kyoto, Japan). Benzoylformic acid and nitrosobenzene were obtained from Tokyo Kasei Co. (Tokyo, Japan). Monochloronitrosobenzenes **3–5**,[16] 4-nitrosobiphenyl (**6**),[17] and 2-nitrosofluorene (**7**)[17] were synthesized as described. All other chemicals were of reagent grade.

HPLC Analysis. HPLC was performed with a Shimadzu LC-5A liquid chromatograph equipped with an SPD-2A spectrophotometric detector, an SIL-1A LC injector, and a column of LiChrosorb RP-8 (7 μm) (Merck; 4.0 × 250 mm id). The flow rate was 1 mL/min (1.5 mL for *N*-(4-biphenylyl)acetohydroxamic acid (**12b**) and *N*-(2-fluorenyl)acetohydroxamic acid (**13b**) formation) and the eluants, containing 0.01% (w/v) desferal mesylate,[18] were as follows: CH_3CN/H_2O, the ratio being 1:1 (v/v) for the formation of *N*-arylhydroxamic acids **8a–d** and **9–13b** and the hydrolysis of *N*-phenylhydroxamic acids **8a–d** and 9:11 (v/v) for the formation of *N*-(chlorophenyl)formohydroxamic acids **9–11a**. *N*-Arylhydroxamic acids and nitroso and azoxy compounds were monitored at 260 nm, 260 nm (or 322 nm), and 322 nm, respectively.

Kinetic Experiments on the Formation of *N*-Arylhydroxamic Acids. 1. In pH 0.3–7.0 Solutions. Kinetic measurements were performed at 30 °C in a shaking water bath, over the pH range of 0.3–7.0, in HCl solutions (1 M for pH 0.3 and 0.5 M for pH 0.6) and in HCl/KCl (0.17 M for pH 1.0 and

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0.01 M for pH 2.4), sodium tartrate (0.1 M for pH 2.9 and 4.7) and potassium phosphate (0.18 M for pH 7.0) buffers. The standard reaction mixture consisted of an HCl solution or a buffer (1.7 mL), an aqueous solution of an α-oxo acid (0.2 mL) (final concentration, 2–100 mM), and diglyme (0.1 mL) containing a nitroso compound (final concentration, 0.1–10.7 mM). Except for the pH 0.3 HCl solution, all solutions containing buffers and HCl were maintained at 0.4 M ionic strength, with NaCl and KCl for the tartrate and phosphate buffers, respectively. The reactions were started by the addition of the diglyme solution. At suitable intervals, 0.2-mL aliquots were taken and added to an aqueous K_2HPO_4 solution (0.1 mL) of an appropriate concentration to adjust the pH to 6.8. Each mixture was immediately agitated for 10 min with 0.3 mL of isopropyl ether (purified by passage through a basic aluminum oxide column) saturated with 0.5 M HCl/2 M K_2HPO_4 (2:1, v/v). After brief centrifugation, 10 μL of the organic layer was analyzed by HPLC.

2. In Aqueous Acetic Acid. Kinetic measurements were performed at a controlled temperature (25 ± 2 °C). Each reaction was initiated by the addition of an aqueous solution of an α-oxo acid (**1a** or **1d**) (0.5 mL), unless otherwise stated, to glacial acetic acid (1 mL) containing a nitroso compound. In the cases of sodium pyruvate (**1b**) and sodium 2-oxobutyrate (**1c**), 0.5 mL of a 5 M HCl solution (equivalent to sodium ions) was used. Each reaction mixture, in a test tube stoppered with a marble, was magnetically stirred. At suitable intervals, 50- or 100-μL aliquots were taken and added to 5 mL of CH_3CN or the HPLC eluant, and then 10 μL of the resulting mixture was analyzed by HPLC.

Kinetic Experiments on the Hydrolysis of *N*-Phenylhydroxamic Acids. Kinetic measurements at pH 0.6 were performed at 30 °C in a shaking water bath. The reaction mixture consisted of diglyme (0.1 mL) containing an *N*-phenylhydroxamic acid, 0.5 M HCl (1.7 mL), and H_2O (0.2 mL). The reaction was initiated by the addition of the diglyme solution. At suitable intervals, 0.2-mL aliquots were removed for HPLC analysis as described for the kinetic experiments in pH 0.3–7.0 solutions.

Preparative Synthesis. To glacial acetic acid (20 mL) containing a nitroso compound (20 mmol) was added 10 mL of an aqueous solution of sodium pyruvate (**1b**) (50 mmol) neutralized with 5 M HCl, but glyoxylic acid monohydrate (**1a**) was dissolved in 10 mL of glacial acetic acid. The mixture was stirred at room temperature until the nitroso compound had been completely consumed, as determined by HPLC. After treatment with NH_4HCO_3 (50 mmol), the mixture was evaporated under reduced pressure. The residue was dissolved in 1 M NaOH (50 mL) and the resulting solution was washed with Et_2O (3 × 10 mL). The pH of the aqueous phase was adjusted with 5 M H_3PO_4 to 5.5 in an ice bath, followed by extraction with Et_2O (3 × 40 mL). The combined ethereal extracts were dried over Na_2SO_4 and then evaporated under reduced pressure to give the crude product, which was recrystallized as described below.

N-(*o*-Chlorophenyl)acetohydroxamic acid (**9b**) was prepared from *N*-(*o*-chlorophenyl)hydroxylamine and acetyl chloride as described elsewhere.[19] All other *N*-arylhydroxamic acids synthesized from the corresponding nitroso compounds and α-oxo acids were characterized by means of elemental and spectral analyses. The required reaction times for, and yields, melting points, results of elemental analyses, and spectral data of typical compounds were as follows.

***N*-Phenylformohydroxamic acid (8a)**: reaction time was 0.5 h; the yield was 95%; mp 67–69 °C (colorless plates from benzene/hexane) (lit.[14] mp 67–69 °C). Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.65; H, 5.10; N, 10.27. ^1H NMR ($CDCl_3$, δ): 7.27–7.46 (m, 5 H), 8.51 (s, 1 H), and 9.50 (br s, 1 H). UV (EtOH): λ_{max} 253 nm (ε 11 200).

***N*-Phenylacetohydroxamic acid (8b)**: 2 h; 93%; mp 66–67 °C (colorless prisms from benzene/hexane) (lit.[20] mp 67 °C). Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.70; H, 6.00; N, 9.27. ^1H NMR (DMSO-d_6, δ): 2.20 (s, 3 H), 7.11–7.39 (m, 3 H), 7.63 (d, 2 H, J = 8.6 Hz), and 10.59 (s, 1 H). UV (EtOH): λ_{max} 254 nm (ε 9900).

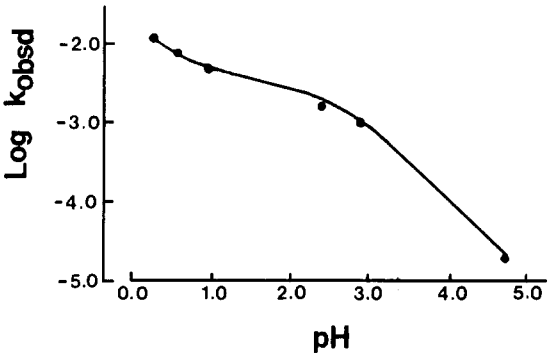


Figure 1. Plot of log k_{obsd} vs pH for the formation of *N*-phenylacetohydroxamic acid (**8b**). The solid line represents the theoretical plot of log k_{calcd} calculated using eq 2, where k_1 = 3.5 × 10^{-3} M^{-1} s^{-1}, k_2 = 1.9 × 10^{-2} M^{-2} s^{-1}, and K_a = 3.1 × 10^{-3} M.

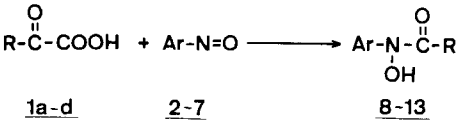
***N*-(*o*-Chlorophenyl)formohydroxamic acid (9a)**: 17 h; 88%; mp 76–77 °C (colorless prisms from benzene/hexane) (lit.[21] mp 80 °C). Anal. Calcd for $C_7H_6NO_2Cl$: C, 49.00; H, 3.52; N, 8.16; Cl, 20.66. Found: C, 49.05; H, 3.49; N, 8.08; Cl, 20.79. ^1H NMR ($CDCl_3$, δ): 7.34–7.41 (m, 2 H), 7.48–7.56 (m, 2 H), 8.23 (s, 1 H), and 9.57 (br s, 1 H). UV (EtOH): λ_{max} 249 nm (ε 4600).

***N*-(4-Biphenylyl)acetohydroxamic acid (12b)**: 2 h; 80%; mp 147–148 °C (white needles from benzene/hexane) (lit.[22] mp 147–148 °C). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.70; H, 5.76; N, 6.11. ^1H NMR (DMSO-d_6, δ): 2.24 (s, 3 H), 7.45–7.72 (m, 9 H), and 10.65 (s, 1 H). UV (EtOH): λ_{max} 280 nm (ε 22 000).

***N*-(2-Fluorenyl)acetohydroxamic acid (13b)**: 0.5 h; 84%; mp 148–149 °C (pale yellow needles from EtOAc/hexane) (lit.[22] mp 148–151 °C). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 74.90; H, 5.42; N, 5.89. ^1H NMR (DMSO-d_6, δ): 2.22 (s, 3 H), 3.93 (s, 2 H), 7.29–7.40 (m, 2 H), 7.55–7.65 (m, 2 H), 7.84–7.88 (m, 3 H), and 10.66 (s, 1 H). UV (EtOH): λ_{max} 291 nm (ε 22 400) and 302 nm (ε 18 800).

Results and Discussion

The aim of the present investigation was to find a practical approach for the synthesis of *N*-arylhydroxamic acids. To this end, we began our studies by preparing *N*-phenylacetohydroxamic acid (**8b**) from nitrosobenzene (**2**) and pyruvic acid (**1b**). In the pH range of 0.3–4.7, this



1a-d 2-7 8-13

R		Ar		
a	H	2	C_6H_5	8a-d
b	CH_3	3	o-ClC_6H_4	9a,b
c	C_2H_5	4	m-ClC_6H_4	10a,b
d	C_6H_5	5	p-ClC_6H_4	11a,b
		6	4-Biphenylyl	12b
		7	2-Fluorenyl	13b

reaction afforded compound **8b** and azoxybenzene, which accounted for a significant proportion of the products at lower pH. The reaction kinetics of the formation of compound **8b** are second order overall and first order with respect to both nitrosobenzene (**2**) and pyruvic acid (**1b**). The logarithms of k_{obsd} (the observed second-order rate constants) are plotted vs pH in Figure 1. It is obvious that the reaction rate is pH dependent in this range, increasing

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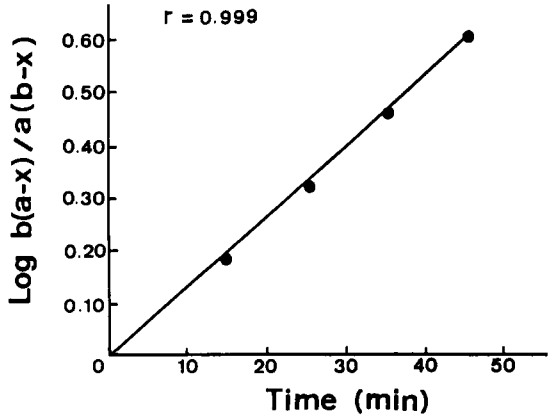

Figure 2. Plot of the second-order rate equation vs time for the formation of *N*-phenylacetohydroxamic acid in aqueous acetic acid. *a* is the initial concentration of pyruvic acid, which was 1.68 M; *b* is the initial concentration of nitrosobenzene, which was 0.67 M; and *x* is the amount of product at the time.

as the pH decreases. Since the reaction was very slow at pH 7.0 (data not shown), the active species is thought to be undissociated pyruvic acid (PA). In the pH range of 0.3–4.7, the overall velocity of the reaction, v, may be represented by eq 1. By expressing PA in terms of $[\mathbf{1b}]_t$

$$v = k_1[\mathrm{PA}][\mathbf{2}] + k_2[\mathrm{H^+}][\mathrm{PA}][\mathbf{2}] \quad (1)$$

(t denotes the total analytical concentration), v is given by eq 2. In eq 2, K_a is the acid dissociation constant for

$$v = k[\mathbf{1b}]_t[\mathbf{2}], \text{ where } k = \frac{k_1[\mathrm{H^+}] + k_2[\mathrm{H^+}]^2}{[\mathrm{H^+}] + K_a} \quad (2)$$

PA. The computed k_1, k_2, and K_a are shown in the legend for Figure 1. The value of K_a agrees reasonably well with the reported one (pK_a = 2.40 ± 0.01 at 25 °C).[23]

When acetic acid was used as the reaction solvent, nitrosobenzene (**2**) reacted with pyruvic acid (**1b**) in a second-order manner to give *N*-phenylacetohydroxamic acid (**8b**) (Figure 2). A reaction in an HCl solution can be affected by the problems of the low solubility of nitroso aromatics and side reactions on a preparative scale. Although k_{obsd} of the formation of *N*-arylacetohydroxamic acids corresponding to nitroso aromatics **2–6** in aqueous acetic acid were 1 order of magnitude smaller than those in HCl at pH 0.6 (Table I), the reactions in aqueous acetic acid were highly selective as to the formation of *N*-arylacetohydroxamic acids **8–13b** with no side reaction product, enhancement of the reaction velocity being enough for the reaction to proceed to completion based on nitroso aromatics, including 2-nitrosofluorene (**7**) (see Experimental Section), with higher concentrations of both reactants than in HCl. The use of this method was extended to the synthesis of *N*-arylhydroxamic acids from nitroso aromatics and α-oxo acids other than pyruvic acid (**1b**), which will be discussed later.

As to the effects of ring substituents of nitrosobenzenes on the formation of the corresponding *N*-arylacetohydroxamic acids, the order of k_{obsd} values in both media (see Table I) was as follows: *p*-phenyl (**6**) > unsubstituted (**2**) > *p*-chloro (**5**) > *m*-chloro (**4**) ≫ *o*-chloro (**3**) nitrosobenzene. In the case of *o*-chloronitrosobenzene (**3**), the formation of *N*-(*o*-chlorophenyl)acetohydroxamic acid (**9b**) was not detected in HCl due to the limited solubility of compound **3**. No correlation was found between the k_{obsd}

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Table I. Rate Constants, k_{obsd} (M^{-1} s^{-1}), for the Reaction of Nitrosobenzenes with Pyruvic Acid

nitroso compd	k_{obsd} in HCl at pH 0.6	k_{obsd} in aqueous AcOH	π_0,[a] V
2	(7.7 ± 0.7) × 10^{-3}	(5.3 ± 0.1) × 10^{-4}	0.582
3	ND[b]	ca. 1 × 10^{-7}	0.598
4	(1.3 ± 0.1) × 10^{-3}	(1.3 ± 0.1) × 10^{-4}	0.583
5	(5.0 ± 0.4) × 10^{-3}	(3.8 ± 0.3) × 10^{-4}	0.576
6	(2.1 ± 0.2) × 10^{-2}	(2.5 ± 0.1) × 10^{-3}	

[a] Vs NHE in 0.1 N HCl in 50% acetone–water at 50 °C (from ref. 16). [b] ND means not detectable.

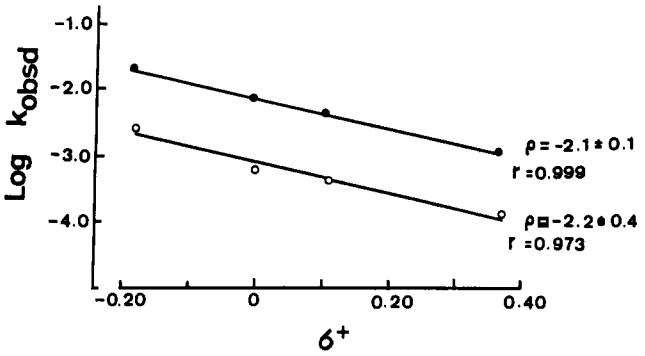

Figure 3. Correlation of log k_{obsd} for the formation of *N*-arylacetohydroxamic acids vs Brown's σ^+ constants. Open circles, in aqueous acetic acid; closed circles, in HCl at pH 0.6.

values obtained and the oxidation–reduction potentials (π_0)[16] of the nitroso compounds. On Hammett plottings[24] (Figure 3), the correlation of the k_{obsd} values with Brown's σ^+ constants is better than with σ values (data not shown). From the negative ρ values in Figure 3, it is suggested that the formation of *N*-arylacetohydroxamic acids proceeds via a nucleophilic attack by nitroso aromatics on pyruvic acid (**1b**). It has been reported[25,26] that an important feature (which has no equivalent in nitrobenzene) of nitrosobenzene (**2**) is the lone pair on the nitrogen, which produces the strongest negative electrostatic potential in the molecule, which should be regarded as a very reactive site for electrophiles. When nitrobenzene instead of nitrosobenzene (**2**) was treated with pyruvic acid (**1b**) in aqueous acetic acid, neither the formation of *N*-phenylacetohydroxamic acid (**8b**) nor a decrease in nitrobenzene was detected until 2 h. This also suggests that the formation of *N*-arylacetohydroxamic acids proceeds via the nucleophilic attack by the nitroso nitrogen on the carbonyl carbon of an α-oxo acid. The extremely decreased activity of *o*-chloronitrosobenzene (**3**) is thought to be partly due to the inductive effect of the ortho chlorine substituent, which reduces the nucleophilicity of the nitrogen atom, but mainly to the steric effect, from the following: in the ^{1}H NMR spectra of the nitroso compounds **2–5** in AcOH-d_4, an abnormal chemical shift (δ 6.22 for **3** and δ 7.77–8.06 for others, ca. 1.7 ppm upfield) assigned to a proton at the ortho position to the nitroso group was only observed for *o*-chloronitrosobenzene (**3**), which indicates that this compound exists as an anti conformer, where the oxygen atom of the nitroso group is on the opposite side to the chlorine substituent, as reported for other ortho-substituted nitrosobenzenes.[27–29] Thus, the ortho chlorine substituent

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Table II. Rate Constants, k_{obsd} (M^{-1} s^{-1}), for the Reaction of Substituted Nitrosobenzenes with Glyoxylic Acid in Acetic Acid

nitroso compd	k_{obsd}
2	$(1.3 \pm 0.1) \times 10^{-2}$
3	$(3.5 \pm 0.1) \times 10^{-5}$
4	$(3.3 \pm 0.2) \times 10^{-2}$
5	$(1.1 \pm 0.1) \times 10^{-2}$

would sterically hinder the nucleophilic attack by the nitroso nitrogen. In the reaction of nitroso aromatics **2–5** with glyoxylic acid (**1a**) in acetic acid without water, a rate constant of the same order (Table II) as in the case of pyruvic acid (**1b**) in aqueous acetic acid was obtained.

Reaction of Nitrosobenzene (2) with α-Oxo Acids 1a–d. Besides pyruvic acid (**1b**), other α-oxo acids, i.e., glyoxylic acid (**1a**), 2-oxobutyric acid (**1c**), and benzoylformic acid (**1d**), reacted with nitrosobenzene (**2**) in both HCl at pH 0.6 and aqueous acetic acid, although the order of k_{obsd} ranged from 10^{-5} to 10^{-2} M^{-1} s^{-1} (Table III). Excellent correlations of log k_{obsd} in HCl (eq 3; $r = 0.999$) and in aqueous acetic acid (eq 4; $r = 0.999$) vs the σ^* and E_s parameters were observed on application of the Taft equation.[32] Although the correlations of log k_{obsd} with the

$$\log k_{obsd} = \underset{(0.116)}{0.329\sigma^*} + \underset{(1.034)}{0.644E_s} - 2.155 \quad (3)$$

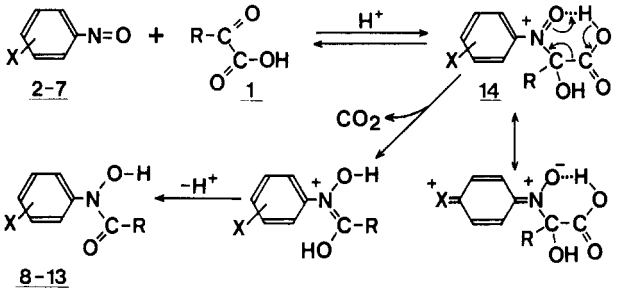
$$\log k_{obsd} = \underset{(0.127)}{0.307\sigma^*} + \underset{(1.037)}{0.551E_s} - 3.288 \quad (4)$$

σ^* parameter alone are very poor or nonexistent, the data are well correlated with the E_s parameter alone ($r = 0.994$ and 0.993 for log k_{obsd} obtained in HCl and aqueous acetic acid, respectively). In both media, the steric effect was found to be more important than the polar effect from their standard partial regression coefficients, shown in parentheses in the above equations. These results, therefore, show that steric effects, as measured as E_s, are significant and that the reaction velocity decreases as E_s becomes smaller, decreasing E_s values presumably corresponding to an increasing effective steric bulk.

In these experiments, sodium pyruvate and sodium 2-oxobutyrate were used, so kinetic experiments in acetic acid were performed with an HCl solution (equivalent to sodium ions). The presence of water in the reaction mixture affected the reaction velocity; the rate constant of the reaction of nitrosobenzene (**2**) with glyoxylic acid (**1a**) in acetic acid without water (Table II) was about 4-fold greater than that observed in aqueous acetic acid (Table III). Therefore, the reaction of nitroso aromatics with α-oxo acids in acetic acid without water is favorable for the synthesis of *N*-arylhydroxamic acids, if free α-oxo acids are available.

Hydrolysis of *N*-Phenylhydroxamic Acids in HCl Solutions. On the reaction of nitroso aromatics with α-oxo acids, azoxy compounds were only detected in the pH 0.3–4.7 solutions. Since it has recently been reported[33] that the hydrolysis of *N*-arylacetohydroxamic acids in aqueous acidic solutions yields the corresponding *N*-arylhydroxylamines, that are further converted through

Scheme I



air oxidation to azoxy compounds, the hydrolysis of *N*-phenylhydroxamic acids **8a–d** in HCl at pH 0.6 was investigated. These compounds were hydrolyzed in a first-order manner to yield several secondary products, including azoxybenzene and the Bamberger rearrangement products of *N*-phenylhydroxylamine, the immediate product of hydrolysis. The acid-catalyzed pseudo-first-order rate constants, k_H, which are listed in Table IV, showed excellent correlation ($r = 0.999$) on application of the Taft equation[32] (eq 5). The steric effect appears to

$$\log k_H = \underset{(0.045)}{0.115\sigma^*} + \underset{(1.014)}{0.577E_s} - 4.481 \quad (5)$$

be more important than the polar effect from their standard partial regression coefficients, shown in parentheses in the above equation. A positive value for δ (steric susceptibility constant) indicates that the reaction velocity decreases with increasing steric hindrance. An analogous result with respect to the steric effect was observed in the acid-catalyzed hydrolysis of aliphatic hydroxamic acids.[34] The fact that *N*-phenylformohydroxamic acid (**8a**) is most susceptible to acid-catalyzed hydrolysis is consistent with the observation that the largest amount of azoxybenzene was formed on the reaction of nitrosobenzene (**2**) with glyoxylic acid (**1a**) in HCl at pH 0.6. Thus, the formation of an azoxy compound, a by-product of the reaction of nitroso aromatics with α-oxo acids in pH 0.3–4.7 solutions, is attributed to the reaction of nitroso aromatics with *N*-arylhydroxylamines formed through the hydrolysis of nascent *N*-arylhydroxamic acids and not through the reduction of nitroso aromatics by α-oxo acids.

Mechanistic Aspects of *N*-Arylhydroxamic Acid Formation. Since Kronja et al.[35] reported that substituted nitrosobenzenes reacted with formaldehyde in an acid-catalyzed reaction, giving *N*-arylformohydroxamic acids, the formation of *N*-phenylhydroxamic acid from nitrosobenzene (**2**) and acetaldehyde was examined in two types of media. In HCl at pH 0.6, acetaldehyde reacted with nitrosobenzene (**2**) to give *N*-phenylacetohydroxamic acid (**8b**) (k_{obsd}, ca. 10^{-4} M^{-1} s^{-1}), while acetaldehyde was not formed from pyruvic acid (**1b**) under the same conditions. While in aqueous acetic acid, acetaldehyde did not react with nitrosobenzene (**2**). Therefore, *N*-phenylhydroxamic acids can be formed through the direct interaction of nitrosobenzene (**2**) and α-oxo acids **1** without a prior decarboxylation step for the latter.

On the basis of the observations mentioned above, a mechanism is proposed for the formation of *N*-arylhydroxamic acids from nitroso aromatics and α-oxo acids, as shown in Scheme I. From the negative values of the Hammett constants (see Figure 3), this reaction is con-

(29) The steric effect of the ortho substituent on *N*-arylacetohydroxamic acids is also briefly discussed in relation to their ^1H NMR and UV spectra (see ref 19).
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Table III. Rate Constants, k_{obsd} (M^{-1} s^{-1}), for the Reaction of Nitrosobenzene with α-Oxo Acids

				in HCl at pH 0.6		in aqueous AcOH	
α-oxo acid	R	σ^* [a]	E_s [a]	log k_{obsd}	log k_{calcd} [b]	log k_{obsd}	log k_{calcd} [c]
1a	H	0.49	1.24	−1.201	−1.196	−2.456	−2.455
1b	CH_3	0	0	−2.114	−2.155	−3.276	−3.288
1c	C_2H_5	−0.10	−0.07	−2.268	−2.233	−3.367	−3.357
1d	C_6H_5	0.60	−2.55	−3.602	−3.600	−4.509	−4.509

[a] The σ^* (polar substituent constant) and E_s (steric substituent constant) values are from ref 30 and 31, respectively. [b,c] Calculated using eq 3 (for b) and eq 4 (for c) using parameters determined by the least-squares method.

Table IV. Hydrolysis Rate Constants, k_H (s^{-1}), for N-Phenylhydroxamic Acids in HCl at pH 0.6

hydroxamic acid	R[a]	log k_H	log $k_{H(calcd)}$ [b]
8a	H	−3.721	−3.718
8b	CH_3	−4.456	−4.481
8c	C_2H_5	−4.553	−4.532
8d	C_6H_5	−5.865	−5.864

[a] The σ^* and E_s values used are shown in Table III. [b] Calculated with eq 5 using parameters determined by the least-squares method.

sidered to proceed via an initial nucleophilic attack by nitroso nitrogen on the carbonyl carbon of an α-oxo acid and/or a protonated one. The fact that better correlations have been found using σ^+ values (see Figure 3) indicates the formation of a transient adduct (14), which should be stabilized by an electron-donating para substituent through a resonance effect. The adduct is then converted to the corresponding N-arylhydroxamic acid through decarboxylation, presumably a driving force for the forward reaction. That ethyl pyruvate does not react with nitrosobenzene (data not shown) is explained by the low ability for the corresponding adduct to decarboxylate. It is reasonable to suggest that the initial nucleophilic attack, which is affected by substituents R and X (see Scheme I) through their polar (minor) and steric (major) effects, is the rate-determining step for this overall reaction.

In conclusion, our method should be applicable to the synthesis of various N-arylhydroxamic acids.

Rates and Regioselectivities of the Palladium-Catalyzed Ethynylation of Substituted Bromo- and Dibromobenzenes

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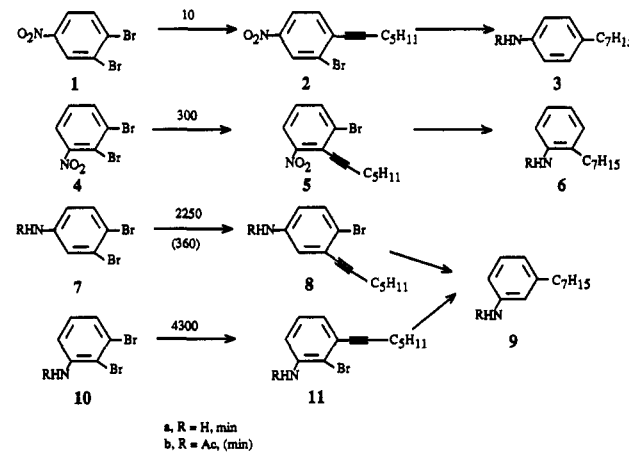
The Pd(0)/Cu_2Br_2-catalyzed ethynylation of 1,2-dibromo-4-nitro- and 1,2-dibromo-3-nitrobenzenes provide rapidly the product in which the bromine para or ortho to the nitro group is displaced, whereas the corresponding dibromoacetamidobenzenes provide the product of meta displacement slowly. Investigation of the rates of a series of para-substituted bromobenzenes indicates that the reaction is zero-order with respect to the heptyne and bromobenzene concentration, with a Hammett ρ value of 2.8.

Introduction

The palladium-catalyzed cross-coupling reactions of aryl halides[1,2] and aryl triflates[3] with alkyl, vinyl, acetylenic, and aryl tin reagents have been shown to proceed in high yields under mild conditions. Also, halopyridine derivatives have been shown[4,5] to undergo a regioselective palladium-catalyzed coupling reaction with terminal acetylenes and aryl zinc halides. We recently described[6] a simple entry into the benzene-o-diyne system similar to the ene–diyne system of several members of a related class of DNA damaging agents, esperamicins[7] and calicheamicins[8] using the Pd(0)-catalyzed coupling of o-dibromobenzene with various terminal acetylenes. The second

Scheme I



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