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# C–N bond formation followed by N–Cl bond breaking. One more and unexpected case of the formation of a hydroxamic group via heterolytic bond cleavage

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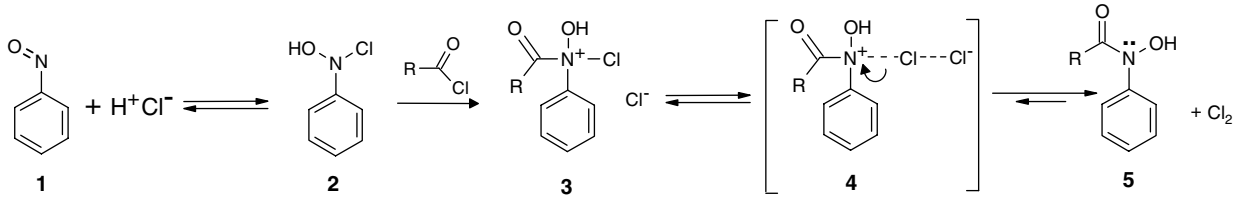
**Abstract**—An unexpected and previously unknown reaction sequence in the interactions of the acyl halides with nitrosobenzenes, which involves carbon–nitrogen bond formation followed by heterolytic nitrogen–chlorine bond cleavage giving the corresponding unsubstituted *N*-phenylalkylhydroxamic acids (or *N*-phenylarylhydroxamic acids) and chlorine as the products has been observed. The kinetic and other evidence obtained suggest that the carbon–nitrogen bond formation is the consequence of a nucleophilic interaction of an *N*-phenylchlorohydroxylamine intermediate, formed in the first reaction step, with the acyl halide in the second step of the complex sequence, which leads to an *N*-acyl-*N*-chlorophenylhydroxylamine cation intermediate. The key reaction step involves the interaction of an *N*-acyl-*N*-chlorophenylhydroxylamine cation intermediate with chloride ion, which leads to the N–Cl heterolytic bond cleavage and the final formation of the hydroxamic group and a molecule of chlorine.


Many important processes in organic chemistry and biochemistry involve C–N bond formation as the fundamental reaction step.[1,2] Interactions of nitrogen nucleophiles with a carbonyl group involving carbon–nitrogen bond formation probably take the position of central significance among these processes. The interactions of the *C*-nitroso group with the carbonyl group of some aldehydes and α-oxo acids present a rather special case among the processes involving the interactions of nitrogen nucleophiles and carbonyl groups and we have been interested in this field for some time.[3–9] The reactions are complex, and ordinarily the first step involves carbon–nitrogen bond formation while the final products are the corresponding hydroxamic acids. The acids belong to a class of compounds of great biomedicinal and industrial significance.[10,11]

We report here the observation of an unprecedented case of the formation of a hydroxamic group resulting from an unexpected and previously unknown reaction sequence in the interactions of the acyl halides with nitrosobenzenes, which involves carbon–nitrogen bond formation followed by heterolytic nitrogen–chlorine bond cleavage. The final products in the complex reaction are the corresponding unsubstituted *N*-phenylalkyl and *N*-phenylarylhydroxamic acids and chlorine (Scheme 1). The final formation of the hydroxamic group at the expense of the oxidation of chlorine in a




**Scheme 1.**

*Keywords*: *C*-Nitroso group; Acyl chlorides; Hydroxamates; N–Cl bond; Kinetics; Mechanism.
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reaction has never previously been observed. The above-mentioned formation of hydroxamic acids via the nucleophilic interaction of a *C*-nitroso group with the carbonyl group of aldehydes[4–6] and α-oxo acids[3,4,6] involves heterolytic C–H or C–C bond cleavage (proton transfer from the carbon[5,7] or decarboxylation[3,4,6]) at the *carbonyl group* to give the electron pair needed for the final formation of the hydroxamic group. Such a heterolytic bond cleavage however cannot be expected in the case of acyl chlorides.

However, in the recently reported[12] interaction of acyl chlorides with nitrosobenzene, the electron pair needed in that key step for the final formation of the hydroxamic group arises by proton transfer from the *para*-position of the phenyl moiety interconnected with the addition of the chloride ion at the same carbon, which leads to the completion of the incipient hydroxamic group. As a consequence, the only products in the reaction are the corresponding substituted *N*-*p*-chlorophenylalkyl or *N*-*p*-chlorophenylaryl hydroxamic acids. In contrast, the products in the interaction reported here are the corresponding unsubstituted *N*-*p*-phenylalkyl or *N*-*p*-phenylarylhydroxamic acids. We have observed the following:

(1) Unsubstituted *N*-phenylalkyl and *N*-phenylarylhydroxamic acids (**5** in Scheme 1) and chlorine (bromine in the case of acyl bromides) were the products of the interactions of the acyl halides and nitrosobenzene in pure acetonitrile[†,‡] providing that the nitroso compound was present in a large excess over HCl in the reaction mixture.[§] Thus, for example, at the ratio [PhNO]/[HCl] of ≈180, and [PhNO] = 0.3 M, the yield of unsubstituted *N*-phenylalkylhydroxamic acids was 98%, while only 1% of the corresponding *p*-chloro substituted acid was formed, as evidenced by HPLC (see also Fig. 1).

(2) The formation of chlorine in the reaction was substantiated both qualitatively and quantitatively using the fast redox reaction with $I^-$ in chloroform.[¶] The known phenomenon of some positive charge on the chlorine in an N–Cl bond[13,14] may be significant here. In addition, the presence of an electron-withdrawing group on the nitrogen of the *N*-acyl-*N*-chlorophenylhydroxylamine cationic intermediate possibly enhances the charge separation between the nitrogen and chlorine of that N–Cl bond.

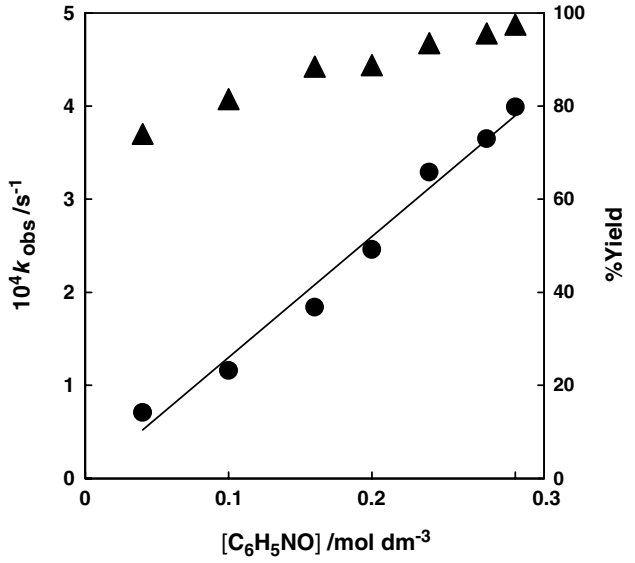


**Figure 1.** Dependence of the observed rate constants for the formation of unsubstituted *N*-phenylacetohydroxamic acid on the concentration of nitrosobenzene in excess (solid circles) along with the yield obtained of the unsubstituted acid (solid triangles, right-hand vertical axis) at 25 °C. Acetyl chloride and HCl were $5\times10^{-3}$ and $1.67\times10^{-3}$ M, respectively, throughout. Pseudo-first-order rate constants were determined using an HPLC system (Spectra Physics) and are the average of several runs. Good first-order kinetics were obtained for 3–5 half lives. The appropriate aliquots of the reaction mixture were diluted with mobile phase buffer ($NH_4HCOO$ buffer pH 3.5:methanol, 40:60, 60:40, or 70:30) to ensure the reaction was stopped and then purified by chromatography on a Restek UltraIBD HPLC column and detected by the monitoring of absorbance at 254 nm. The amounts of the product hydroxamic acids were determined using the standard samples of the corresponding acid and *p*-nitrotoluene or *m*-nitrotoluene as the internal standards. Ordinarily, the overall yield of both unsubstituted and the corresponding substituted acid were as high as 95% or more.

(3) The observed pseudo-first-order rate constants for the formation of *N*-phenylacetohydroxamic acid depend linearly on the concentration of nitrosobenzene in excess (Fig. 1). The corresponding linear dependence on the HCl concentration in the reaction was obtained (Figs. 2 and 3 inset). Under the conditions employed, the rate dependencies obtained for the formation of unsubstituted *N*-phenylacetohydroxamic acid should be consistent with the rate law: $k_{obs} = k$ [PhNO][HCl]. At constant concentration of the nitroso compound in excess, the fraction of the unsubstituted *N*-phenylacetohydroxamic acid versus corresponding substituted *N*-*p*-chlorophenylacetohydroxamic acid increases as the observed rate constant for the formation of the unsubstituted acid increases (see Fig. 2). This finding is consistent with the existence of two concurrent processes.

(4) A kinetic deuterium isotope effect $k_{obs}$(HCl)/$k_{obs}$(DCl) of 0.81 (0.02) for the formation of the

[†] Acetonitrile (99.9%, HPLC grade) and an acetonitrile solution of dry HCl were used in all the experiments.

[‡] For example, a simple preparative procedure, which includes interaction of 0.1 M of nitrosobenzene with 0.005 M HCl and 0.01 M of acetyl chloride in acetonitrile for 1 h gave, after working-up with aqueous $NaHCO_3$, extraction with dichloromethane, drying, and purification (TLC or HPLC) *N*-phenylacetohydroxamic acid (as substantiated by $^1H$, see, for example, Ref. 15, and $^{13}C$ NMR spectroscopy) in 92% yield.

[§] The only products we observed under the conditions applied in the previous kinetic investigation[12] of the interaction, where the range of concentration of nitrosobenzene applied was necessarily determined by the magnitude of molar absorbance of nitrosobenzenes and the limitations of available spectroscopic method, were the corresponding *N*-*p*-chlorophenylalkylhydroxamic acids.

[¶] The molar absorbance coefficient of the $I_3^-$ complex in chloroform is $2.72\times10^4$ at 364 nm. As the source of iodide ions, tetraethylammonium iodide was used. At the ratio of iodide/chlorine of 250 used in the procedure, the oxidation of the iodide is almost instantaneous.

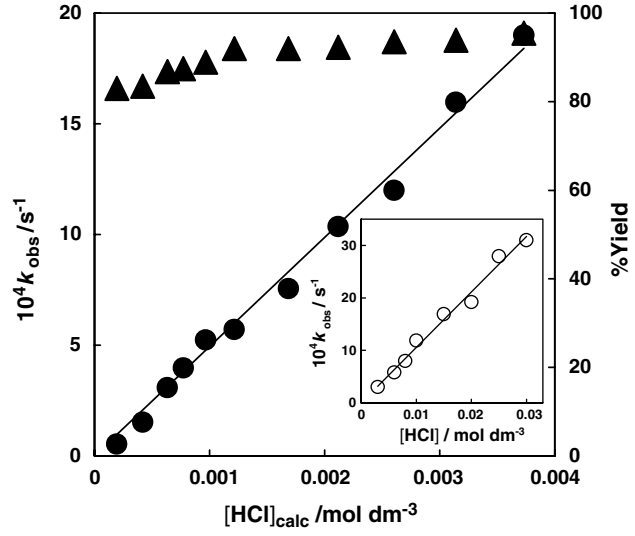


**Figure 2.** Dependence of the observed rate constants for the formation of unsubstituted *N*-phenylacetohydroxamic acid on the effective concentration of HCl (solid circles) along with the obtained yield of the unsubstituted acid (solid triangles, right-hand vertical axis). At 25 °C. The effective concentrations of HCl were calculated from the corresponding total concentrations using the value of 450 $M^{-1}$ for the association constant between HCl and acetyl chloride in 99.9% acetonitrile (see text). Concentrations of nitrosobenzene and acetyl chloride were 0.200 and 0.010 M, respectively, throughout. Rate constants were determined as described above (see Fig. 1). Inset: Dependence of the observed rate constants for the formation of unsubstituted *N*-phenylacetohydroxamic acid on the concentration of HCl in excess over acetyl chloride. Concentrations of nitrosobenzene and acetyl chloride were 0.050 and 0.003 M, respectively, throughout.

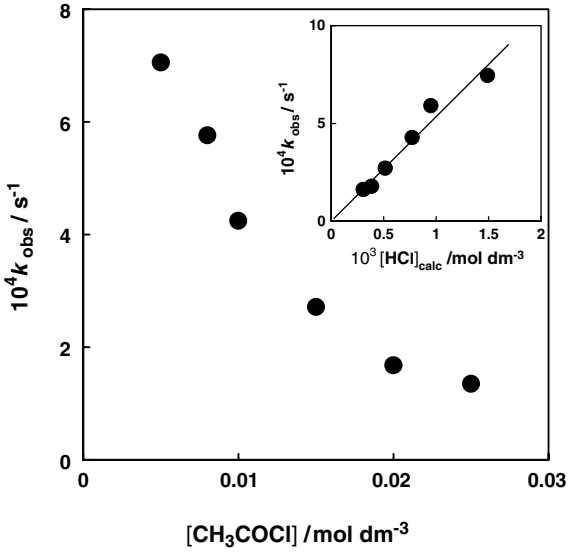


**Figure 3.** Change of the observed rate constants for the formation of unsubstituted *N*-phenylacetohydroxamic acid on the increase in the concentration of acetyl chloride in excess with regard to the HCl concentration. Concentrations of nitrosobenzene and HCl were 0.200 and 0.0033 M, respectively, throughout. Inset: the corresponding dependence of the same observed rate constants on the calculated effective concentration of HCl (see text). Note that the order of appearance of the rate constants is now reversed to show no dependence on the acetyl chloride concentration.

unsubstituted *N*-phenylacetohydroxamic acid in the complex reaction was observed. This result suggests the involvement of a proton transfer in the process and could support the formation of an *N*-chlorophenylhydroxylamine intermediate[12] **2** from the acyl halide and the nitroso compound, assuming that the well known difference in the affinities of a weakly basic substrate toward the proton and its isotope[16] existed in this case. The linear dependencies[‖] (Figs. 1 and 2) of the observed rate constants on the concentrations of nitroso compound and HCl could also be used in support of the proposed formation of the intermediate **2** in the process.

(5) Taking into account the results summarized by Figures 1–3 it seems reasonable to assert that under the conditions employed, the rate constants for the formation of the unsubstituted *N*-phenylacetohydroxamic acid in the reaction do not depend on the concentration of acetyl chloride. The finding would be consistent with a fast nucleophilic interaction of the intermediate **2** with the acyl halide or possibly with protonated acyl halide. Although the *C*-nitroso group could act as a nucleophile,[3–9,17] nitrosobenzene does not react with acyl halides in the absence of HCl (or HBr), which suggests that the other nucleophile should be involved in the C–N bond formation. However, the excess of halide over HCl causes a reduction of the apparent rate constant (Fig. 3). Probably, the apparent decrease is caused by the formation of an association[**] between the acyl halide and HCl, which in turn decreases the effective concentration of the acid. Starting from this assumption, an estimate based on the kinetic results (see Fig. 3) gave, for the association constant, a value of 450 $M^{-1}$. This value is in quite a good agreement with one obtained by comparison of the slopes of linear plots of Figures 1 and 3.

(6) Substituted nitrosobenzenes (*p*-$CH_3$, *p*-Br, *p*-Cl, *m*-Cl) enter the reaction giving the corresponding substituted *N*-phenylhydroxamic acids. Thus, *p*-methylnitrosobenzene gave *p*-methylphenylacetohydroxamic acid in 91% yield. This observation is fully consistent with the proposed mechanism (Scheme 1) since the earlier described concurrent process[12] of substitution by halide ion in the *para*-position and the formation of corresponding *p*-chlorophenylacetohydroxamic acid was not possible in this case.

[‖] Assuming an unfavorable equilibrium for the formation of *N*-chlorophenylhydroxylamine intermediate (which would be in line with our spectroscopic evidence since no change in the spectra of the nitroso compound on the addition of HCl in acetonitrile was observed) the linear dependence of the observed rate constants on the concentration of nitroso compound in excess would be expected.

[**] At present, it is difficult to give any precise account about the nature of the association between acetyl chloride and HCl in dry acetonitrile. We note however that in a separate investigation we have observed that formaldehyde and HCl in dry acetonitrile associate with a constant of the order of $10^4$ $M^{-1}$.

(7) Substituted *N*-*p*-chlorophenylalkylhydroxamic acids or *N*-*p*-bromophenylalkylhydroxamic acids were formed in the interaction of the corresponding unsubstituted acids and chlorine or bromine in acetonitrile,[††] The finding is in support of the mechanism proposed in Scheme 1. The reaction should involve the reverse of the key reaction step of the process of formation of the corresponding unsubstituted hydroxamic acids, that is, the N–Cl heterolytic bond breaking followed by the formation of chlorine and unsubstituted hydroxamic acid.

The picture that emerges from the evidence (Scheme 1) is a complex process, which starts with an initial addition giving chlorophenylhydroxylamine **2**. The intermediate reacts further in a relatively fast step with the acyl halide giving the corresponding *N*-acyl-*N*-chlorophenylhydroxylamine cation intermediate **3**. This intermediate undergoes heterolytic N–Cl bond cleavage mediated by chloride ion (from the $H^+Cl^-$ ion pair[‡‡] or possibly the $Cl^-$ ion resulting from the nucleophilic interaction of acyl chloride with the chlorophenylhydroxylamine), which leads to the formation of the unsubstituted hydroxamic acid and chlorine as the products. This process is much faster than the concurrent process of the formation of the hydroxamic group via the substitution of chloride ion at the *para*-position of the phenyl moiety interconnected with the proton transfer from the same position. Therefore, at the high ratios of [nitroso compound]/[$H^+Cl^-$] almost all the HCl is consumed in the formation of the unsubstituted *N*-phenylalkylhydroxamic (or *N*-phenylarylhydroxamic) acids and $Cl_2$ and the lack of HCl prevents (except to the small extent) the slower concurrent reaction of the formation of ring-chlorinated hydroxamic acid. When excess of HCl is present this concurrent process becomes important. The experiment in which ring-chlorinated hydroxamic acid was obtained from unchlorinated hydroxamic acid and $Cl_2$ (see above) suggests that the reaction sequence $\mathbf{3} \rightarrow \mathbf{4} \rightarrow \mathbf{5}$ (Scheme 1) should be reversible. If this is the case, the key intermediate **3** arises also from the reverse of $\mathbf{3} \rightarrow \mathbf{4} \rightarrow \mathbf{5}$ path, which in presence of HCl also contributes the ring-chlorination process at the *para*-position. Following the evidence obtained it seems reasonable to conclude that the intermediates involved in the first and second steps should be the same as those proposed to be involved in the previously investigated formation of *N*-*p*-chlorophenylalkylhydroxamic acids[12] while the formation of the unsubstituted *N*-phenylalkylhydroxamic acids follows a completely different reaction pathway subsequently.

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[††] For example, performing the reaction for 40 min at 25 °C in a solution containing 0.01 M $Cl_2$ and 0.001 M *N*-phenylacetohydroxamic acid in acetonitrile, HPLC analysis showed that a 4:6 mixture of *N*-*p*-chlorophenylacetohydroxamic acid and the starting unsubstituted *N*-phenylacetohydroxamic acid were obtained. In a control experiment, no change in the spectra of 0.01 M $Cl_2$ and 0.0001 M nitrosobenzene was observed for a period of at least three half lives of the corresponding reaction of nitroso compound with acetyl chloride and HCl. Also, the HPLC evidence with regard to the standard reaction conditions do not show appearance of any other products than hydroxamic acids.

[‡‡] HCl is considered to be an ionic pair in 99.9% acetonitrile.[18]