



An unusual case of carbon–nitrogen bond formation. Reactivity of a C-nitroso group toward acyl chlorides

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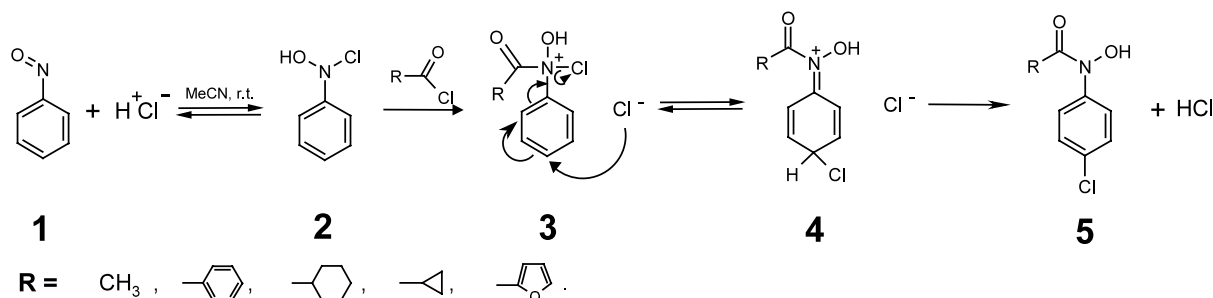
Abstract—Acyl chlorides react with nitrosobenzene in 99.9% acetonitrile and in the presence of catalytic amounts of HCl giving the corresponding *N-p*-chlorophenylhydroxamic acids. The spectroscopic and kinetic evidence obtained indicates that the reaction is initiated by the formation of an *N*-chlorohydroxylamine intermediate from nitrosobenzene and hydrochloride in the first, slow step of the process. The nucleophilic *N*-chlorohydroxylamine intermediate reacts with acyl chloride (or possibly an acyl cation–chloride ion pair) to give the addition acylnitroso intermediate which undergoes to nucleophilic attack by chloride ion at the *para* position of the phenyl moiety and, after proton transfer from carbon, the corresponding *N-p*-chlorophenylhydroxamic acid is formed. © 2001 Elsevier Science Ltd. All rights reserved.

Formation of a carbon–nitrogen bond is among the most important fundamental processes in organic chemistry and biochemistry. For example, many important chemical and biochemical processes are initiated by the addition of a nitrogen nucleophile to a carbonyl group.^{1,2} Recently, we have investigated a more special case of the nucleophilic interaction of a C-nitroso group with the carbonyl group of some aldehydes and α -oxo acids.^{3–9} The interactions involve the formation of a C–N bond, while the reaction products are hydroxamic acids. The acids are of considerable importance due to their numerous industrial and pharmaceutical applications.^{10–14}

We report here the surprising observation that acyl chlorides can interact with nitrosobenzene leading to

C–N bond formation, where the corresponding *N-p*-chlorophenylhydroxamic acids are the products of the reaction (Scheme 1). This previously unknown reaction seems to be quite unexpected. Namely, the above mentioned formation of hydroxamic acids via the nucleophilic interaction of the 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. The possibility of such a heterolytic bond cleavage, however, does not exist in the case of acyl chlorides.

Our observations are as follows:



Scheme 1.

Keywords: C-nitroso group; acyl chlorides; hydroxamates; kinetics; mechanism.

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1. Acyl chlorides react with nitrosobenzene in 99.9% acetonitrile and in the presence of catalytic amounts of HCl giving the corresponding *N-p*-chlorophenylhydroxamic acids (Scheme 1). Under the conditions employed in the kinetic investigation the reaction goes to completion, as shown spectroscopically (Fig. 1). The evidence is corroborated by the product analysis.[†] The spectroscopic evidence does not suggest the accumulation of any intermediate in the reaction. In the absence of HCl, the reaction is negligibly slow.[‡]
2. The observed kinetics for the hydroxamic acid formation were of the first order with respect to the

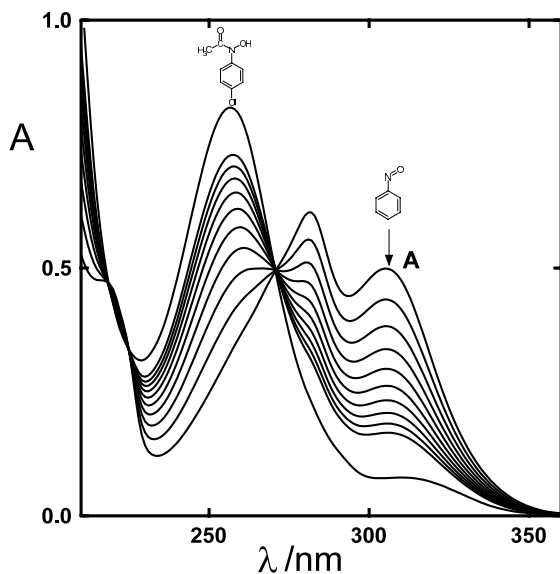


Figure 1. Change in the UV spectrum of the reaction mixture containing $0.007 \text{ mol dm}^{-3} \text{ CH}_3\text{COCl}$, $10^{-4} \text{ mol dm}^{-3} \text{ C}_6\text{H}_5\text{NO}$ and $0.03 \text{ mol dm}^{-3} \text{ HCl}$ in 99.9% acetonitrile, at 25.0°C . Scans (from A downward): 0, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 160 min. The spectra of acetyl chloride were subtracted for clarity.

[†] All the quoted hydroxamic acids were isolated and characterised using CHN analysis, NMR, IR and UV-vis spectroscopy. The evidence obtained was in accordance with published data (see Ref. 4). Thus, for example, for *N-p*-chlorophenylcyclopropylhydroxamic acid we obtained: mp $114\text{--}117^\circ\text{C}$; elemental analysis calcd for $\text{C}_{10}\text{H}_{10}\text{ClNO}_2$: C, 56.75; H, 4.76; N, 6.62; R, 31.87; found: C, 57.76; H, 4.90; N, 6.68; R, 30.66%; $^1\text{H NMR}$ (DMSO, 300 MHz): δ 0.87 (4H, d, $J=8$ Hz), 2.50 (1H, s), 7.41 (2H, d, $J=9$), 7.66 (2H, d, $J=9$), 10.84 (1H, s); $^{13}\text{C NMR}$ (DMSO, 300 MHz): δ 172.8, 140.9, 128.4, 128.3, 121.9, 11.3, 8.4; IR (KBr, cm^{-1}): 3100.6, 2893.9, 1617.9, 1487.2, 1430.4, 1338.1, 1315.6, 1292.6, 1095.5, 1068.2, 936.6, 828.2, 752.8, 481.3; For *N-p*-chlorophenylacetohydroxamic acid we obtained: mp $72\text{--}73^\circ\text{C}$; elemental analysis calcd for $\text{C}_8\text{H}_8\text{ClNO}_2$: C, 51.77; H, 4.34; N, 7.55; R, 36.34; found: C, 51.63; H, 4.42; N, 7.68; R, 36.27%; $^1\text{H NMR}$ (DMSO, 300 MHz): δ 2.20 (3H, s), 7.39 (2H, d, $J=9$), 7.66 (2H, d, $J=9$), 10.69 (1H, s); $^{13}\text{C NMR}$ (DMSO, 300 MHz): δ 170.3, 140.6, 131.7, 128.4, 121.4, 23.4; IR (KBr, cm^{-1}): 3135.9, 2894.4, 1623.6, 1485.9, 1381.4, 1095.8, 1013.6, 829.1, 741.3, 497.7; UV-vis (MeCN): $\lambda_{\text{max}}=256 \text{ nm}$, $\epsilon_{256 \text{ nm}}=9984 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$.

[‡] Traces of water (0.03%) were present in acetonitrile which could lead to the very small amounts of HCl due to slow hydrolysis of acetyl chloride.

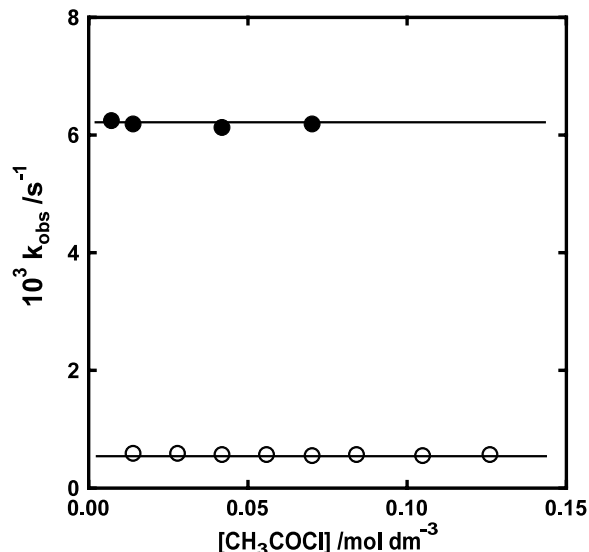


Figure 2. The dependence of the k_{obs} versus acetyl chloride concentration for the reaction of acetyl chloride with nitrosobenzene in 99.9% acetonitrile at 25.0°C . ○: at $0.031 \text{ mol dm}^{-3}$ of HCl. ●: at $0.150 \text{ mol dm}^{-3}$ of HCl. Nitrosobenzene: $10^{-4} \text{ mol dm}^{-3}$ (see also Fig. 3 for the remaining details).

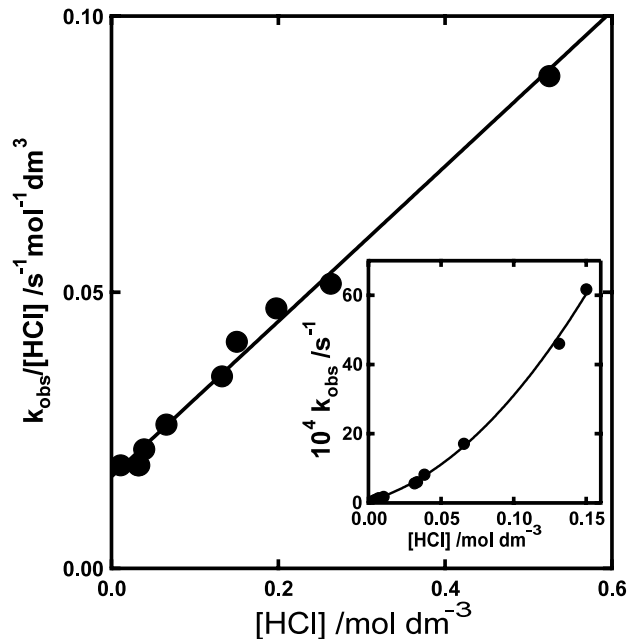


Figure 3. The dependence of the $k_{\text{obs}}/[\text{HCl}]$ versus HCl concentration for the reaction of acetyl chloride with nitrosobenzene in 99.9% acetonitrile at 25.0°C . The observed rate constants were determined spectrophotometrically by following the disappearance of the absorbance of nitrosobenzene at 305 nm (or by following the increase in the absorbance at 256 nm) using a HP 8452 or HP 8453 UV-vis spectrophotometer. Very good first-order kinetics within at least three half-lives of the reaction were obtained. CH_3COCl : $0.007 \text{ mol dm}^{-3}$; $\text{C}_6\text{H}_5\text{NO}$: $10^{-4} \text{ mol dm}^{-3}$; and 0.03 mol dm^{-3} . In order to avoid the use of aqueous HCl, a solution of dry gaseous HCl in 99.9% acetonitrile was used throughout. Inset: The dependence of the k_{obs} versus HCl concentration for the reaction of acetyl chloride with nitrosobenzene in 99.9% acetonitrile at 25.0°C . The reaction conditions were the same as described above.

nitroso compound but did not depend on the concentration of the acyl chloride (Fig. 2) (in the experiments, acyl chloride was always in great excess over the nitrosobenzene concentration). The result is the same regardless of the starting HCl concentration (see Fig. 2) and is consistent with the relatively fast interaction of acetyl chloride or acetyl cation–chloride ion pair with a nucleophilic intermediate (see below) arising from nitrosobenzene and HCl in the preceding slow step of the reaction.

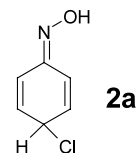
3. The dependence of the observed pseudo first-order rate constants on hydrochloride concentration (Fig. 3) is complex and is consistent with the rate law (Ph = phenyl):

$$\text{Rate} = k_1[\text{HCl}][\text{PhNO}] + k_2[\text{HCl}]^2[\text{PhNO}] \quad (1)$$

4. The values of the parameters k_1 and k_2 are $0.0167 \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$ and $0.140 \text{ s}^{-1} \text{ mol}^{-2} \text{ dm}^6$, respectively. The observed linear term of Eq. (1) requires that the interaction of nitrosobenzene with a single H^+Cl^- ion pair[§] can lead to the reactive intermediate which we describe as *N*-chlorohydroxylamine (**2**). There are a large number of addition reactions of the *C*-nitroso group where the nitroso group acts as an electrophile and the addition of anionic nucleophiles to the nitroso group to give transient intermediates is not unknown.¹⁵ In addition, chloride is in a polar, aprotic solvent such as acetonitrile is strongly desolvated which makes it more basic[¶] and more capable of addition to a nitroso group. The same intermediate can, of course, arise from the interaction of two hydrochloride ion pairs with the nitroso group which corresponds to the quadratic term of Eq. (1). This term could also be consistent with the formation of an alternative, 4-chlorohexadienone oxime intermediate **2a**.

However, only a minor contribution of that intermediate to the overall process is expected, due to its greater basicity (and subsequent protonation) in comparison to *N*-chlorohydroxylamine.^{||} On the other hand, the change in the spectra of the reactants and products during the course of the reaction remained the same when 0.15 M of water was added to the reaction mixture. Taking into account that nitrosobenzene is a relatively weak nucleophile, it seems highly unlikely that, under the conditions employed in the kinetic experiments (10^{-4} M of nitroso compound), nitrosobenzene alone could compete with water (being in 1500-fold excess over

the nitrosobenzene concentration) for the acyl chloride. Hydrolysis of acyl chloride was the only reaction observed when the water content in the reaction mixture exceeded a few percent, obviously because the formation of the intermediate arising from nitrosobenzene is much slower than the reaction of acetyl chloride with water. Therefore, it seems reasonable to conclude that a species much more nucleophilic than nitrosobenzene should be involved in the process of formation of hydroxamic acid.



5. An inverse isotope effect $k_{\text{H}}/k_{\text{D}}$ of 0.80 (0.19) between DCl and HCl in the reaction was observed. The effect is relatively small in comparison to the ordinary solvent isotope effects arising from the difference between the $\text{p}K_{\text{a}}^{\text{H}}$ and $\text{p}K_{\text{a}}^{\text{D}}$ values of a protonated/deuterated species involved in the process.¹⁸ However, the observation probably suggests the involvement of the proton transfer in the formation of the intermediate (**2**) from HCl and nitrosobenzene.
6. Addition of chloride ion (benzyltrimethylammonium chloride)^{¶¶} enhances the observed rate constants of the reaction. This fact cannot be ascribed unequivocally in favour of the proposal that *N*-*p*-chlorophenylhydroxylamine is the reactive intermediate arising from nitrosobenzene and HCl. The observation is not inconsistent with nucleophilic attack of the chloride at the *para* position of the phenyl moiety of the addition intermediate (**3**). At present, there is not enough evidence to decide which process predominates in the reaction. With regard to the established rate law (Eq. (1)), the observation could also mean that (in the absence of the added quaternary salt) the chloride ion was principally transferred within the same encounter pair of the intermediate (**3**). The observed rate constants decrease when the concentrations of the added quaternary chloride approaches that of HCl, probably because of the formation of HCl_2^- homoconjugate complex.^{**}
7. A substrate KIE between nitrosobenzene and nitrosobenzene- d_5 , $k_{\text{H}}/k_{\text{D}}$ of 1.25 (0.21) in the reaction was observed. The effect is quite small and could be consistent with a fine balance between the rates of the initial and the final step (proton transfer from the carbon) of the reaction.
8. The Arrhenius plot of $\log k_{\text{obs}}$ versus $1/T$ is slightly curved which is what is expected if more than one process takes place in the reaction system.
9. Addition of the less polar solvent diminishes the rate of the reaction in accordance with the expectation that the dissociation of the HCl ion pair in the transition state for the formation of the intermediate (**2**) is of importance for the reaction. The rate is

[§] Our conductimetric measurements indicate that HCl should be present in 99.9% acetonitrile (used in all the experiments), exclusively, in the form of an ion pair (or possibly hydrogen-bonded ion pair) whilst the measurements suggest that benzyltrimethylammonium chloride is (in the same solvent) substantially dissociated.

[¶] For example, the $\text{p}K_{\text{a}}$ of HCl in another polar aprotic solvent, dimethyl sulfoxide, is 1.8 (see Ref. 16).

^{||} Phenylhydroxylamine, for instance, did not react with acetyl chloride when added to the reaction mixture, obviously because of only a minute fraction of unprotonated amine can exist under the acidic conditions. On the other hand, *N*-chlorophenylhydroxylamine should be much less basic, but nevertheless, strongly nucleophilic (cf. the case of the 'α-effect' nucleophiles¹⁷).

^{**} See for example Ref. 19.

halved by the addition of 80% of dioxane and is retarded to a somewhat lesser extent by the addition of dichloromethane.

The evidence obtained is summarised in Scheme 1. The reaction presents a new route for obtaining various hydroxamic acids using acyl chlorides, especially in the cases where acidic conditions are desired or cannot be avoided. An example is the derivatisation of *N*-(benzotriazolylcarbonyl) amino acid chlorides into the corresponding aminohydroxamic acid derivatives which is not possible under the basic conditions (where the benzotriazolyl group would be eliminated) usually used in order to introduce the desired hydroxamic functionality.^{††}

Acknowledgements

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^{††} In a separate study, one of us (M.L.) had used such a procedure in the successful attempt to synthesise new 1,2,5-oxadiazine derivatives starting from *N*-(1-benzotriazolylcarbonyl)aminohydroxamic acids.

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