Novel Transformation of Primary Nitroalkanes and Primary Alkyl Bromides to the Corresponding Carboxylic Acids

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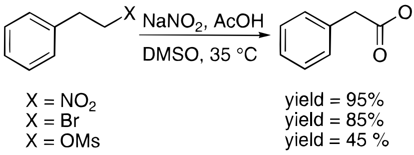
Nitro compounds are very potent intermediates in organic synthesis.[1] However, there are strikingly few examples of naturally occuring aliphatic nitro compounds or of synthetic products that have found significant biological use. For this reason, the transformation of nitro compounds into other functionalities is crucial. The conversion to aldehydes[2] (the Nef reaction) and the reduction to the amine[3] appear to be the most useful transformations of primary nitroalkanes.

The oxidation of primary nitro compounds to carboxylic acids is rarely useful. This transformation is generally carried out in strongly acidic, aqueous media[4] or by using strong oxidants such as permanganate[5] or molybdate.[6]

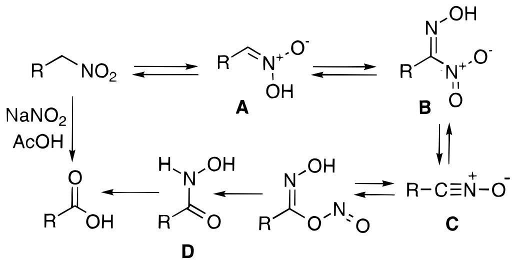
In 1956, Kornblum et al.[7] reported the oxidation of nitroparaffins using a mixture of nitrite ester and sodium nitrite. However, the reaction was prone to poor yields (between 9 and 52%) and long reaction times. The reaction was postulated to proceed *via* the formation of a nitrolic acid, which reportedly is highly unstable. Nitrite ester was thought to act as an electrophilic nitrosonium ion equivalent and sodium nitrite as a base. This lack of mechanistic undersanding as well as poor yields prevented this reaction from any significant application.

Forty years later, we report a very efficient related reaction using a mixture of sodium nitrite and acetic acid in DMSO (Scheme 1). Investigation of the mechanism enabled us to prove that nitrolic acids are stable and easily accessible compounds.

Scheme 1



Scheme 2



The treatment of 2-phenylnitroethane with sodium nitrite and acetic acid in dimethyl sulfoxide at 35 °C quantitatively led to the corresponding carboxylic acid.[8] It is known that primary bromides and primary mesylates can be converted to the corresponding nitro compounds by the action of sodium nitrite in DMSO.[1] However, in the presence of acetic acid and excess sodium nitrite, the nitro derivative was not isolated and the reaction directly gave the carboxylic acid in 85% yield. The formation of a small amount of alcohol was also observed, and is presumably due to the hydrolysis of the unavoidable nitrite compound, a byproduct arising from the O-alkylation of sodium nitrite. This reaction is, to our knowledge, the only synthetically useful one-pot oxidation of primary bromides to the corresponding carboxylic acids. To account for this transformation we propose a mechanism analogous to that described when the reaction is carried out under strongly acidic conditions[9] (Scheme 2).

Under acidic conditions the nitroalkane is in equilibrium with the *aci* form **A** that reacts with a nitrosating agent to form the corresponding nitrolic acid **B**. The further transformation of the nitrolic acid **B** into the hydroxamic acid **D** proceeds *via* the formation of a reactive nitrile oxide intermediate **C**. By nucleophilic attack of sodium nitrite, **C** is converted into **D**, which is readily hydrolyzed to yield the carboxylic acid.

To prove that under our conditions the reaction proceeds *via* the same intermediate, we intercepted or isolated several of these intermediates.

Nitrolic acids were first reported by Meyer in 1873[10] but have, apparently, fallen into disuse.[11] This might be due to the lack of a reliable preparative method and to the conviction that these are unstable compounds. The nitrolic acid intermediates **B** were isolated[12] simply by carrying out the reaction at 18 °C instead of 35 °C (Scheme 3).

Nitrolic acids appear to be stable compounds that can be purified by silica gel chromatography. Heating at 60

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(8) **Typical Procedure.** A solution of the nitroalkane (1 mmol), sodium nitrite (3 mmol), and acetic acid (10 mmol) in dimethyl sulfoxide (2 mL) was stirred at 35 °C for 6 h. After acidification with a 10% aqueous solution of hydrochloric acid, the product was extracted several times with ether and purified by silica gel chromatography.

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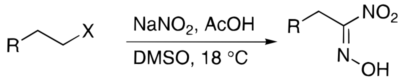
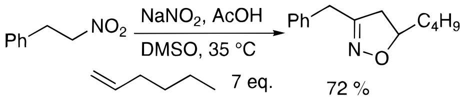
Scheme 3



R	X	Yield
C_6H_{13}	NO_2	85 %
Ph	NO_2	82 %
Ph	Br	78 %

Scheme 4



°C for 3 h did not lead to significant decomposition. However, when these compounds were subjected to acetic acid and sodium nitrite in dimethyl sulfoxide at 35 °C, the nitrolic acids **B** quantitatively afforded the corresponding carboxylic acids.

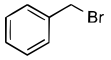
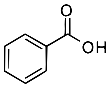
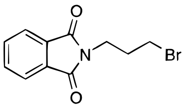
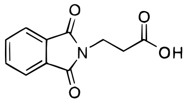
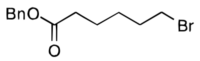
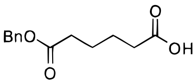
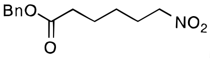
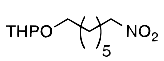
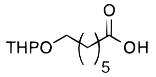
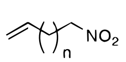
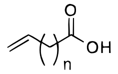
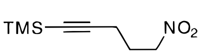
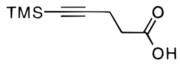
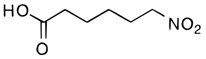
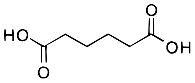
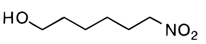
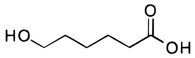
The mechanism for the transformation of **B** into the hydroxamic acid **D** proceeds *via* the formation of a reactive nitrile oxide intermediate **C**. In the presence of an excess of 1-hexene (7 equiv), the postulated nitrile oxide was intercepted and the isoxazole adduct was obtained in 72% yield (Scheme 4).

Under our reaction conditions, an authentic sample of **D** rapidly and quantitatively yielded the corresponding carboxylic acid. Apparently, the solvent is not involved in the transformation, because the reaction could be carried out in either DMF or sulfolane (dipolar aprotic solvents) and consistently afforded the products in excellent yield.

To explain the mildness and the efficiency of this transformation, we postulate that the reaction is not acid-catalyzed, but propelled by an equivalent of nitrosonium ion, generated *in situ* by the reaction of acetic acid with sodium nitrite.[13] To support this postulate, we subjected all the intermediates to several reaction conditions. In each case, the reaction proceeded only if both acetic acid and sodium nitrite were present. Furthermore, in the absence of acetic acid, but with 1 equiv of nitrosonium tetrafluoroborate salt and 1.3 equiv of sodium nitrite, the reaction proceeded readily and the carboxylic acid was isolated in 82% yield. This demonstrates the predominant role of a nitrosonium species in the mechanism.

Several representative substrates were subjected to our reaction conditions. The results obtained are summarized in Table 1.

Table 1.

Entry	Substrate	Product	Yield
1			80 %
2			67 %
3			85 %
4			96 %
5			90 %
6			n=5; 95 % n=3; 89 %
7			98 %
8			95 %
9			72 %

The reaction proceeded smoothly and the products were obtained in over 90% yield starting from the nitro derivatives and about 80% yield starting from the bromides. The mildness of the reaction conditions renders it compatible with many acid- or base-sensitive functionalities. Thus, THP ethers and benzyl esters remained intact (Table 1, entries 3–5). Alkynes and alkenes proved to be stable under the reaction conditions (Table 1, entries 6 and 7), and no cycloadducts were detected. Furthermore, even unprotected acids (Table 1, entry 8) could be transformed. When the reaction was carried out with an unprotected alcohol, the hydroxy acid obtained had to be acetylated to facilitate its purification (Table 1, entry 9).

In summary, we report a useful and new transformation of primary nitroalkanes and primary alkyl bromides into the corresponding carboxylic acids, with very good yield. The reaction proceeded under mild acidic conditions that render it compatible with various sensitive functionalities. This study also provided new conditions for the conversion of primary nitro compounds into the corresponding nitrolic acids. These transformations appear to proceed *via* a novel mechanism that involves the nitrosonium ion as an active species.

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(12) **Typical Procedure.** A solution of 2-nitroethylbenzene (0.15 g, 1 mmol), sodium nitrite (0.14 g, 2 mmol), and acetic acid (0.57 mL, 10 mmol) in dimethyl sulfoxide (2 mL) was stirred at 18 °C for 8 h. The reaction mixture was then diluted with 10 mL of a 10% aqueous solution of hydrochloric acid. The product was extracted with ether (3 × 15 mL). The organic layers were combined, washed with a solution of sodium carbonate, dried over $MgSO_4$, and concentrated under vacuum. Purification by silica gel chromatography yielded 150 mg of 1-nitro-2-phenylethanone oxime as a white solid. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 10.10 (s, 1H, OH); 7.33 (s, 5H); 4.29 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 160.9, 132.5, 128.8, 127.5, 30.0. IR ν (cm^{-1}): 3293.6, 2890.3, 1541.9, 1496.1, 1455.6, 1421.3, 1343.0, 1075.8, 1030.7, 855.6, 736.7, 709.2. MS (CI/NH_3) *m/z* (rel intens): 134 ($M^+ - NO_2$, 60), 151 ($MNH_4^+ - NO_2$, 60), 181 (MH^+, 16), 198 (MNH_4^+, 20).

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