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# $NaNO_2$-Mediated Transformation of Aliphatic Secondary Nitroalkanes into Ketones or Oximes under Neutral, Aqueous Conditions: How the Nitro Derivative Catalyzes Its Own Transformation

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The nitrosation of secondary nitro derivatives into ketones or oximes depending on the nitro substituents has been reinvestigated. The reaction efficiently takes place under neutral conditions, thus allowing acid-sensitive substrates to be converted in very good yields. The generation of nitrosating species under such mild conditions is unprecedented. Mechanistic investigations strongly suggest that they result from the nucleophilic attack of the nitrite anion on the *aci*-nitro(nate) form of the secondary nitroalkane. The latter acts in turn as an autocatalyst for its own transformation by means of the nitrosating species generated in situ from it.

The chemistry of aliphatic nitro derivatives relies largely on the electron-withdrawing character of the nitro group.[1-3] Stabilized anions of nitroalkanes have, for instance, been extensively used in the Michael,[4] Henry,[5] and Knœvenagel reactions.[6] Starting from primary nitroalkanes, these reactions afford valuable secondary nitro derivatives which can eventually be converted into ketones. Several methods have indeed been reported to transform secondary nitro derivatives into ketones.[7] As of yet, none of them have proven general owing to oxidative and/or acidic conditions or broad functional group incompatibility.[8]

Kornblum first reported that secondary aliphatic nitroalkanes react with ethyl nitrite to give the corresponding ketones.[9,10] This transformation involves the nitrosation[11,12] of the *aci*-nitronate—generated from the nitroalkane and $NaNO_2$ which acts as a base—with ethyl nitrite. Similarly, we reported the efficient nitrosation of primary nitroalkanes into acids.[13] In that case, the nitrosating species are generated in situ under weakly acidic conditions from the readily available sodium nitrite and acetic acid. We then sought to expand this strategy to secondary nitro derivatives and found that in marked contrast to primary nitroalkanes[13] secondary derivatives do not require any acid catalysis. Depending on the substituents of the nitroalkane, the corresponding ketones or oximes are obtained in good yields under neutral, aqueous conditions (Scheme 1).

Mechanistic investigations allowed us to propose a general mechanism for this transformation and to shed light on the striking reactivity observed in the absence of acid and on the important substituent dependence of this reaction.

## Results

The commercially available nitrocyclohexane was first reacted under our previously reported conditions used with primary nitroalkanes, i.e., 2 equiv of sodium nitrite and 10 equiv of acetic acid in hot DMSO.[13] The cyclohexanone is obtained in 86% yield under these conditions (Table 1, entry 1).

The optimum temperature is in the range of 40−65 °C. At lower temperature, cyclohexanone is obtained in low yield (result not shown) and the amount of cyclohexanone oxime increases with increasing temperatures (entry 2). No significant loss of reactivity is observed with water as a cosolvent (entry 3) or in an alcoholic solvent (entry 4). More interestingly, the transformation turned out to be feasible under neutral conditions, i.e., with $H_2O$ as the only $H^+$ supply (entry 5). Yet, the reaction is clearly

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(1) Adams, J. P.; Paterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695−3705.

(2) Ono, N. *The nitro group in organic synthesis*; John Wiley: New York, 2001.

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(6) Carey, F. A.; Sundberg, R. J. In *Advanced organic chemistry part B*, 4th ed.; Plenum: New York, 2001; pp 100−101.

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(8) A very mild transformation of secondary nitro derivatives into ketones using DBU in acetonitrile has been published in the course of the redaction of this article. See: Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233−5235.

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(10) Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418−1420.

(11) Williams, D. L. H. In *Nitrosation*; Cambridge University Press: Cambridge, 1986; pp 36−57.

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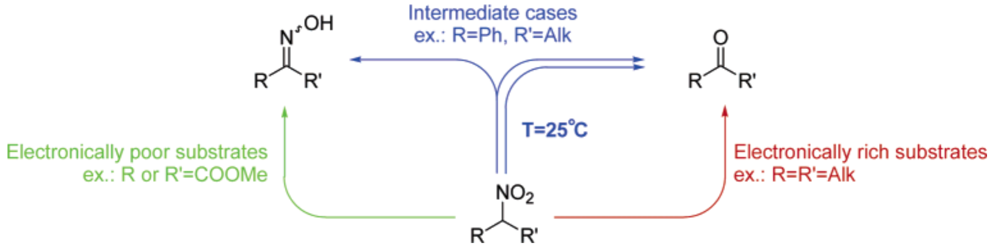
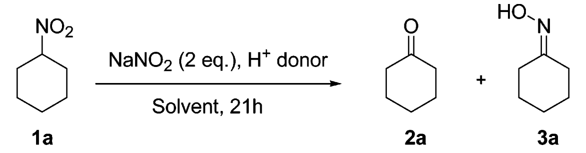
**SCHEME 1. General Transformation of Secondary Nitro Derivatives into Ketones or Oximes[a]**



[a] Conditions: $NaNO_2$ (2 equiv), $H_2O$/DMSO 1/7 (v/v), 65 °C unless otherwise stated.

**TABLE 1. Nitrosation of Nitrocyclohexane into Cyclohexanone**



| entry | $H^+$ donor (equiv) | $T$ (°C) | solvent | yield[a] (%) 2a | 3a |
|---|---|---|---|---|---|
| 1 | $CH_3COOH$ (1.2) | 65 | DMSO | 86 (35)[b] | <2 |
| 2 | $CH_3COOH$ (1.2) | 95 | DMSO | 85 | 10 |
| 3 | $CH_3COOH$ (10) | 65 | $DMSO_{50\%}$ | 82 | <2 |
| 4 | $CH_3COOH$ (5) | 70 | $EtOH_{65\%}$ | 78 | 0 |
| 5 | $H_2O$ (excess) | 69 | DMSO | 85 (12) | <2 |

[a] Yields based on GC analysis of the reaction mixture with naphthalene as an internal standard. [b] Yields in parentheses refer to the yields obtained after 2 h.

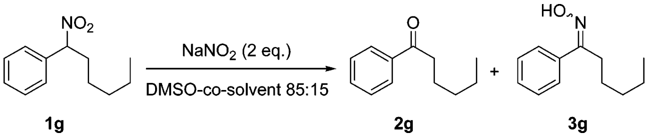
$H^+$ catalyzed as shown by the yields obtained after 2 h (lines 1 and 5, yields in parentheses).

These conditions—$NaNO_2$ (2 equiv), $H_2O$/DMSO 1/7 (v/v), 65 °C—proved quite general (Table 2). On one hand, electronically rich nitro **1b**−**d** are converted to the ketones **2b**−**d** in good yields (Table 2, entries 1−3). Interestingly, no protecting group is required for alcohol **1b** and ketone **1c** (entries 1 and 2), and the silyl ether of **1d** is not cleaved under these conditions so that ketone **2d** is obtained in very good yield (entry 3).[14]

In contrast, electronically poor α-nitroesters **1e** and **1f** yield the oxime quantitatively (entries 4 and 5).[15] 1-Phenylnitrohexane **1g** exhibits an intermediate reactivity and invariably yields a 35:65 mixture of oxime and ketone at 65 °C (entry 6). Neither the use of an excess of $NaNO_2$ nor the use of acetic acid instead of water (Table 3, entry 2) increased the yield of ketone **2g**. In the latter case, the oxime partially undergoes a Beckman rearrangement as a consequence of the more acidic medium. Nevertheless, we found that **2g** can be obtained quantitatively if the reaction is carried out at room temperature (Table 3, entry 3).

At this point, several observations are worth noting. First, one can reasonably question the involvement of nitrosating species under neutral conditions. Indeed, in contrast to acetic acid ($pK_a = 4.8$), water alone is not acidic enough to generate such $NO^+$-like species from sodium nitrite ($pK_a = 3.3$).[11,12] Furthermore, both the striking substituent effect that governs the oxime/ketone product distribution of the reaction and the critical influence of the temperature on the formation of **2g** need to be explained. Therefore, we explored in detail the mechanism responsible for the formation of cyclohexanone from nitrocyclohexane under our standard conditions; our results are presented in the following section.

**TABLE 3. Influence of the Temperature and Acid Strength in the Synthesis of 2g**



| entry | cosolvent | $T$ (°C) | time (h) | yield (%) 2g | 3g |
|---|---|---|---|---|---|
| 1 | $H_2O$ | 71 | 72 | 65 | 35 |
| 2 | $CH_3COOH$ | 70 | 14 | 45[a] | 15[a] |
| 3 | $H_2O$ | 20 | 148 | 100 | 0 |

[a] The oxime partially undergoes a Beckman rearrangement under these conditions (yield ca. 15%).

**Mechanistic Investigations.** We propose the mechanism depicted in Scheme 2 for the conversion of secondary nitro derivatives into ketones and/or oximes when treated with 2 equiv of $NaNO_2$ in aqueous DMSO at 65 °C.

We believe three different paths account for the conversion of secondary nitro derivatives into ketones under our neutral conditions (paths **A**−**C**, Scheme 2). In path **A**, the sodium nitrite acts as an O-nucleophile and adds to the *aci*-nitro eventually giving the ketone in a straightforward way. Similar mechanisms were actually postulated for the hydration and the addition of oxone to *aci*-nitro derivatives.[17,18] As pointed out by one reviewer, homolytic cleavage of intermediate **5** to give the ketone and two molecules of nitrogen monoxide is also likely. Alternatively, the N-nitration of the *aci*-nitro yields the pseudonitrole **4** which further evolves to the oxime or the ketone depending on the nitro substituents (path **B**). As evidenced by our mechanism, nitrosating species such as $N_2O_4$ and $N_2O_3$, or others,[16] are formed in the course of the reaction from the pseudonitrole **4** and intermediate **5** (see reactions **II** and **III** in Scheme 2). Alternatively, the *aci*-nitro(nate) can be directly nitro-

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(14) This result is noteworthy since the silyl ether bond is cleaved under the conditions used to convert primary nitro derivatives into acids, i.e., in the presence of acetic acid instead of water.

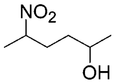
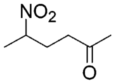
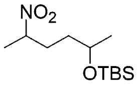
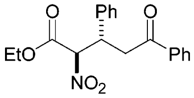
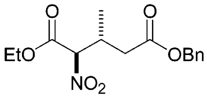
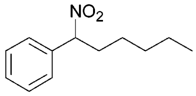
(15) Kornblum, N.; Eicher, J. H. *J. Am. Chem. Soc.* **1956**, *78*, 1494−1497.

(16) Williams, D. L. H. In *Nitrosation*; Cambridge University Press: Cambridge, 1986; Vol. Chapter 1, pp 1−35.

(17) White, E. H.; Considine, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 626−630.

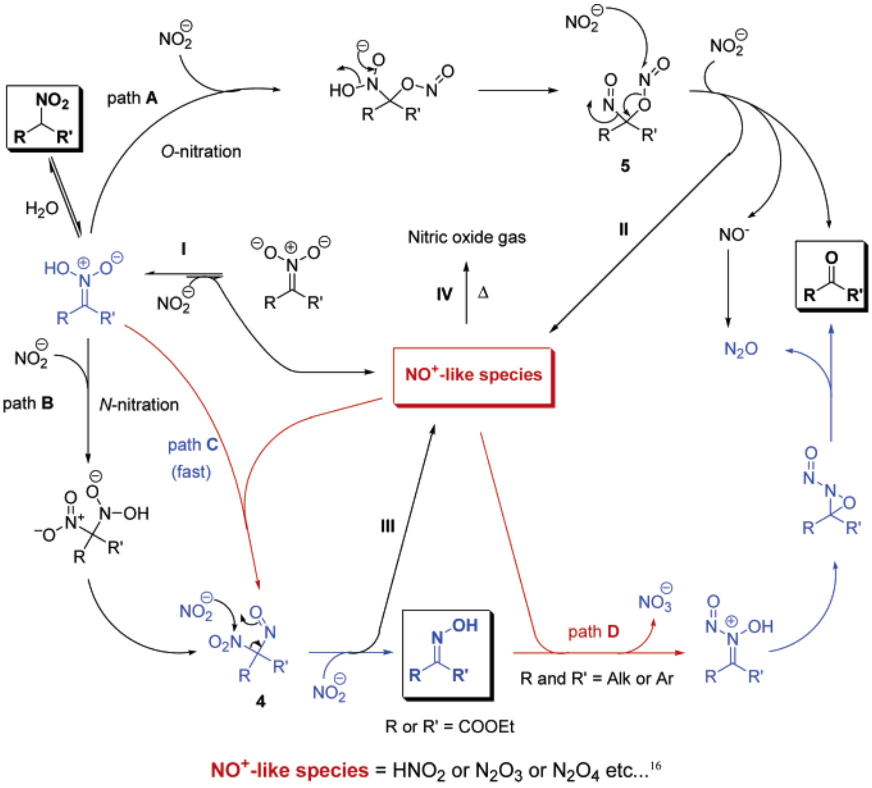
(18) Cundall, R. B.; Locke, A. W. *J. Chem. Soc. B* **1968**, 98−103.

**TABLE 2. Reaction of Various Secondary Nitroalkanes under Standard Conditions[a]**

| entry | substrate | | yield (%)[b] ketones **2b-g** | yield (%)[b] oximes **3b-g** |
|---|---|---|---|---|
| 1 |  | **1b** | 75 | nd[c] |
| 2 |  | **1c** | 75 | nd |
| 3 |  | **1d** | 86 | nd |
| 4 |  | **1e** | nd | 100 |
| 5 |  | **1f** | nd | 100 |
| 6 |  | **1g** | 65 | 35 |

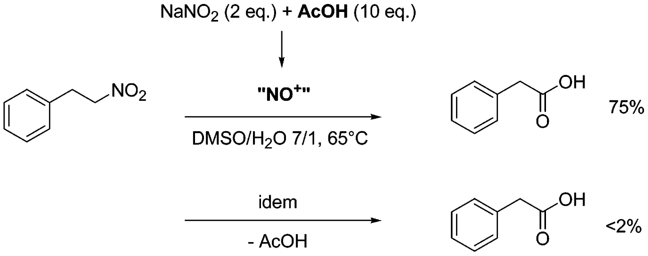
[a] Conditions: NaNO$_2$ (2 equiv), H$_2$O/DMSO 1/7 (v/v), 65 °C. [b] Isolated yields. [c] Not detected.

**SCHEME 2. Proposed General Mechanism for the Conversion of Secondary Nitro Derivatives into Ketones or Oximes[a]**



[a] The original Kornblum mechanism is shown in blue.

**SCHEME 3. Nitrosated Species Are Needed To Convert Primary Nitro Derivatives into Acids**



sated by these nitrosating species (path **C**) as already evidenced by Kornblum, thus overtaking path **B**.[10] The final ketone/oxime ratio obtained at the end of the reaction largely depends on the propensity of the oxime to react with such species (path **D**). While electronically rich oximes are easily nitrosated to the corresponding ketones, electronically poor ones are not and are obtained as the sole product.

## Discussion

While under acidic conditions the protonation of NaNO$_2$ is responsible for the formation of NO$^+$-like species[11,12] and in turn the reactivity observed with primary nitroalkanes,[13] the anionic character of the nitrite remains unaltered under our neutral conditions. Thus, it is likely to act as a powerful nucleophile toward the *aci*-nitro, and both the O- and N-nitrations of the latter can be anticipated by virtue of the ambident character of the nitrite ion. Several experimental observations support this hypothesis and prove that nitrosating species are actually formed in the course of the reaction under neutral, aqueous conditions.

First, primary derivatives such as 2-phenylnitroethane are not reactive and do not give the corresponding acid unless acidic conditions are employed (Scheme 3).

Thus, if primary nitroalkanes do require the formation of nitrosating species from NaNO$_2$ and acetic acid to afford the corresponding acid, secondary derivatives do not. This result can be explained on the basis of the nitro−*aci*-nitro equilibrium unfavorable to the latter with primary derivatives;[19] the amount of the *aci*-nitro form in solution is then too low to observe the nucleophilic attack of the nitrite (paths **A** and **B**). The same observation goes for the intermediately formed cyclohexanone oxime that is not transformed into cyclohexanone under our standard conditions unless acetic acid is added to the solution (Scheme 4).[20]

This result is in agreement with our mechanism, as the oxime−ketone transformation requires nitrosating species previously formed from the intermediates **4** and **5** (see path **D**, Scheme 2). Therefore, those species must somehow be formed from the nitro derivative itself. To further evidence the ability of the nitro derivative to act as the actual NO$^+$ supply, we carried out the same test reaction in the presence of an external secondary nitro derivative, namely 2-nitropropane (Scheme 5).

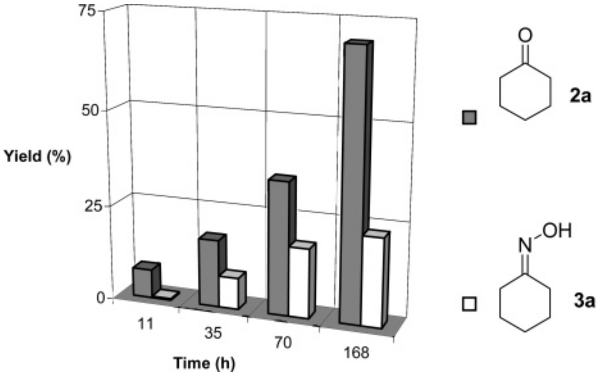


**FIGURE 1.** Nitrosation of **1a** in the presence of *N*,*N*-dimethylaniline. Conditions: NaNO$_2$ (4 equiv), *N*,*N*-dimethylaniline (2 equiv), DMSO/H$_2$O 1.4/0.2, 70 °C.

Cyclohexanone is indeed formed in that case. Consequently, the nitro derivative is not only transformed into ketone but is also responsible for the generation of nitrosating species from NaNO$_2$ under neutral, aqueous conditions. Hence, the nitro derivative can be considered as a kind of a catalyst for its own transformation as the nitrosating species formed catalyze the transformation (path **C**, Scheme 2). Yet, one could argue the nitro derivative might simply be acidic enough to promote the generation of nitrosating species from NaNO$_2$ through the simple acid−base reaction between those two species (see the *aci*-nitro−*aci*-nitronate equilibrium **I** in Scheme 2). In that case, path **C** alone (the original Kornblum's mechanism) could account for the transformation of secondary nitro derivatives into ketones. Based on this hypothesis alone, no reaction should take place in the absence of nitrosating species. Yet, the reaction does take place in the presence of *N*,*N*-dimethylaniline—a potent NO$^+$ species scavenger—[21,22] even though excess NaNO$_2$ is needed (Figure 1). Under these conditions, both transformations involving nitrosated species (see red arrows in Scheme 2) are shut down. The only way for the substrate to undergo the transformation is through paths **A** and **B**. Since the oxime and ketone are formed under these conditions, this strongly supports the hypothesis that NaNO$_2$ can act as a nucleophile toward the *aci*-nitro(nate). To the best of our knowledge, this is the first time the nitrite ion has been shown to be able to react as a nucleophile toward a nitroalkane. The aptitude of nitrite ion to act as a nucleophile has been precluded so far by the acidic conditions usually employed to perform such transformations (the nitrite ion is protonated at pH < 3.3). The 7:3 oxime/ketone ratio obtained may in turn reflect the N/O-nitration addition ratio of NaNO$_2$ to the *aci*-nitro (paths **B** and **A**, respectively).[23] This experiment also suggests that nitrosating species are indeed good catalysts for this transformation, the reaction time being much longer in their absence.[24]

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(19) Bordwell, F. G.; Boyler, W. J., Jr.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5926−5932.

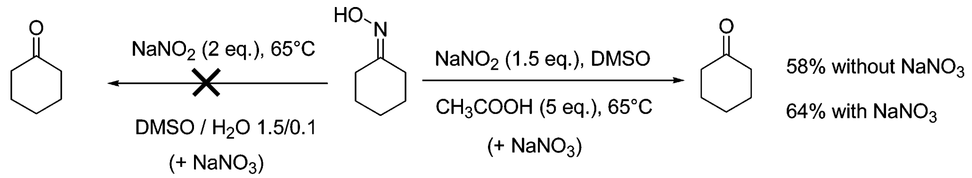
(20) Since sodium nitrate was formed during the course of the reaction, the reactions were also conducted in the presence of this salt.

(21) Liddell, H. F.; Saville, B. *Chem. Ind.* **1957**, 493−494.

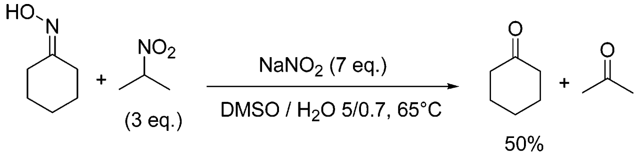
(22) Loeppky, R. N.; Singh, S. K.; Elomari, S.; Hastings, R.; Theiss, T. E. *J. Am. Chem. Soc.* **1998**, *120*, 5193−5202.

(23) While the cyclohexanone **2a** is formed quantitatively in the absence of *N*,*N*-dimethylaniline with a strong nitrosating reagent such as the nitrosyl tetrafluoroborate, it is not detected in the presence of 2 equiv of *N*,*N*-dimethylaniline. As a consequence, the cyclohexanone formed in this test is likely to result from the O-nitration of the *aci*-nitro (path **A**, Scheme 2).

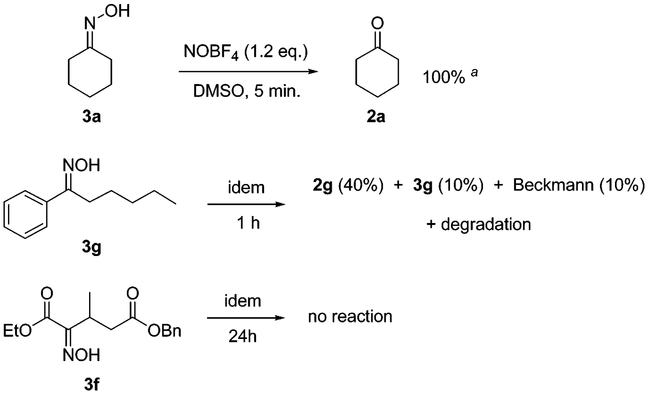
**SCHEME 4 Conversion of Cyclohexanone Oxime into Cyclohexanone Requires Nitrosating Species**



**SCHEME 5. Nitrosating Species Are Formed from the Secondary Nitro Derivative and $NaNO_2$ under Neutral Conditions**



**SCHEME 6. Influence of the Substituents for the Nitrosation of Oximes[a]**



[a] A transient blue color from the pseudonitrole is transiently seen in the course of the reaction.

The reaction is strongly substituent-dependent (Table 2). While electronically poor nitro derivatives such as α-nitroesters **1e** and **1f** yield the oxime quantitatively, cyclohexanone **1g** is formed from the electronically rich nitrocyclohexane. These results emphasize the ease with which the respective oxime intermediates can be nitrosated (Scheme 6).

The more electronically rich the substituents of the oxime, the more nucleophile the oxime (**3a** > **3g** ≫ **3f**) and the easier the nitrosation to the ketone (path **D**, Scheme 2). Besides, most of the nitrosated species formed in the course of the reaction are known to be thermally unstable.[12,16,25] Hence, the thermal decomposition of the different nitrosated species (see reaction **IV** in Scheme 2) competes with the nitrosation of the oxime into ketone (path **D**). This is especially true in the case of a weakly reactive oxime such as **3g**. While nitrosating species are predominantly decomposed at high temperature leading to substantial amounts of the oxime (Table 2, entry 6), the ketone **2g** is formed as the sole product at room temperature where nitrosating species are stable (Table 3, entry 3).

At first glance, the results obtained with α-nitroesters (Table 2, entries 4 and 5) would appear incompatible with our proposed mechanism as no ketone is formed. Even though path **D** is blocked with this substrate, some ketone would at least result from the O-nitration of the derived *aci*-nitro (path **A**, Scheme 2). Nevertheless, as noted by Kornblum,[15] the acidity of these compounds is much greater, thus favoring path **C** over paths **A** and **B**. Furthermore, the addition of $NaNO_2$ to the *aci*-nitro (paths **A** and **B**) are all the more unlikely because the double bond of the corresponding *aci*-nitro is in conjugation with the ester group.

In conclusion, an efficient method to transform secondary nitro compounds into ketones or oximes—depending on the nature of their substituents—under mild conditions was developed. Unlike Kornblum's nitrosation method,[10] small amounts of ketones or oximes result from the direct nitrosation of the *aci*-nitro(nates) in our case. A detailed analysis of the mechanism allowed us to conclude that the nitrite ion acts as a potent nucleophile toward the *aci*-nitro(nate). Not only does the neutral pH employed in our case is important for the nitrite to act as a nucleophile, it also allows the conversion of acid-sensitive substrates such as **1d** and **1g** to take place in high yields. We have also shown that nitrosated species are generated in the course of the reaction from $NaNO_2$ and the secondary nitro derivative. These species are necessary to convert oximes into ketones, and their generation under neutral aqueous conditions is remarkable and unprecedented.

**Acknowledgment.** We thank Byron Purse for reviewing this manuscript and the Ministère de la recherche et de l'enseignement supérieur for financial support through an MRE grant to A.G.

**Supporting Information Available:** Spectroscopic data for compounds **1b**–**d**,**g**, **2b**,**d**, and **3e**,**f**. General procedure for the nitrosation of secondary nitroalkanes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Hugues, E. D.; Ingold, C. K.; Ridd, J. H. *J. Chem. Soc.* **1958**, 88–98.

(26) Seebach, D.; Lehr, F. *Helv. Chim. Acta* **1979**, *62*, 2239–2257.