

## From Azides to Nitro Compounds in a Few Seconds Using HOF·CH<sub>3</sub>CN

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Professor Sharpless, the 2001 Nobel Laureate, stated in a recent paper that azides “usually make fleeting appearance in organic synthesis” mainly because of “irrational fear”.<sup>1</sup> Their chemistry is indeed conspicuously underdeveloped and mainly associated with reduction to amines. The “opposite” reaction, namely oxidation to nitro compounds, is practically unknown with the exception of Corey’s multistep method of converting the azides first to phosphine imines (RN<sub>3</sub> → RN=PR<sub>3</sub>) followed by ozone oxidation. The nitro derivatives thus obtained (40–70% yield) were accompanied by the corresponding phosphine oxides as well as by aldehydes, which in certain cases were the sole products.<sup>2</sup>

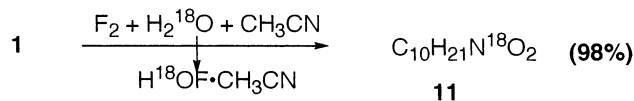
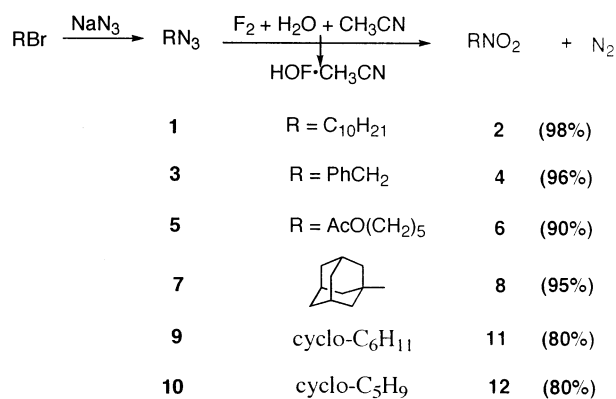
Some years ago we developed the HOF·CH<sub>3</sub>CN complex, simply by bubbling diluted fluorine (commercially available) through aqueous acetonitrile.<sup>3</sup> This oxygen-transfer agent was used for epoxidations of various types of olefins,<sup>4</sup> oxidation of alcohols<sup>5</sup> and methyl ethers<sup>6</sup> to ketones as well as the conversion of ketones to esters via the Bayer–Villiger reaction,<sup>5</sup> oxidation of sulfides, including electron-depleted ones, to sulfones,<sup>7</sup> and much more.<sup>8</sup> This reagent has also been used to convert primary amines<sup>9</sup> and even amino acids<sup>10</sup> to the corresponding nitro compounds. HOF·CH<sub>3</sub>CN was also reacted with tertiary amines to produce *N*-oxides,<sup>11</sup> and reacts with 1,10-phenanthroline<sup>12</sup> to furnish the *N,N'*-dioxide, a compound which has eluded synthesis for more than 50 years. These processes strongly supported the notion that the oxygen atom of this reagent is a very strong electrophile indeed. This and the fact that many transformations could be accomplished only by HOF·CH<sub>3</sub>CN and not by any other oxygen-transfer agent encouraged us to examine if the carbon-bonded nitrogen of azides would be nucleophilic enough to interact with the oxygen atom of HOF·CH<sub>3</sub>CN. One quick experiment was enough to provide an encouraging answer.

1-Azidodecane (**1**) was easily prepared from bromodecane and sodium azide in excellent yields following a literature procedure.<sup>13</sup> A solution of 3 mol equiv of HOF·CH<sub>3</sub>CN was then added to a methylene chloride solution of **1** at 0 °C. A release of N<sub>2</sub> was immediately observed, and in a few seconds the reaction was over, forming 1-nitrodecane (**2**)<sup>14</sup> in 92% yield.<sup>15</sup>

The speed of the reaction made us wonder if other oxygen-transfer agents would be as effective as HOF·CH<sub>3</sub>CN. We refluxed methylene chloride solutions of **1** with 8 mol equiv of MCPBA for 6 h and recovered more than 98% of the starting material. 1-Azidodecane (**1**) was quantitatively recovered also after treatment with 14 mol equiv of dimethyldioxirane (DMDO) for several hours. It seems that HOF·CH<sub>3</sub>CN is a stand-alone oxygen-transfer agent when the transformation of azides to nitro compounds is in question.

The only limitation of this reaction is the ability of making the azides, but once they are at hand the rest is easy. Although HOF·CH<sub>3</sub>CN is known to react with aromatic rings,<sup>16</sup> this reaction is relatively slow, and therefore the ring in benzyl azide (**3**)<sup>13</sup> will not interfere with the immediate reaction of the azido moiety to give almost quantitatively α-nitrotoluene (**4**). Neither will an ester group, which remains intact for the duration of the reaction. 5-Azidopentyl acetate (**5**), obtained in 94% yield from 5-bromopentyl acetate, was quickly converted to 5-nitropentyl acetate (**6**)<sup>17</sup> in 90% yield. HOF·CH<sub>3</sub>CN is able to substitute tertiary hydrogens with a hydroxyl group<sup>18</sup> in a slow reaction. It is not surprising then to find that 1-azidoadamantane (**7**) was converted to 1-nitroadamantane (**8**)<sup>19</sup> in 95% yield without affecting the three tertiary hydrogens found in the starting azide. Secondary azides are excellent substrates as well. Preparing cyclohexyl (**9**) and cyclopentyl (**10**) azides from the corresponding bromides is straightforward,<sup>13</sup> and again a 5-s, 0 °C reaction with 3 mol equiv of the reagent is all it takes to obtain nitrocyclohexane (**11**) and nitrocyclopentane (**12**) in good yields.

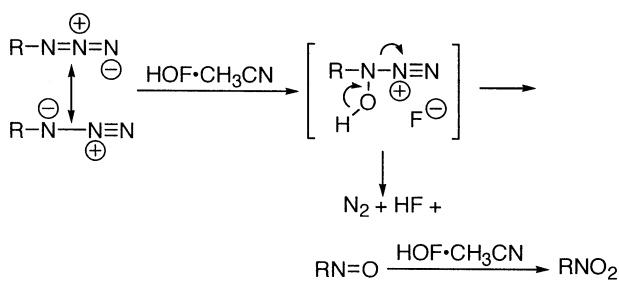
One of the advantages of HOF·CH<sub>3</sub>CN is that its electrophilic oxygen comes from water, which is the best source for all oxygen isotopes. We have passed fluorine through a solution of acetonitrile and H<sub>2</sub><sup>18</sup>O and obtained H<sup>18</sup>OF·CH<sub>3</sub>CN, which was reacted with **1**. HRMS (CI) data [*m/z* = 190.157446, calcd for C<sub>10</sub>H<sub>21</sub>N<sup>18</sup>O<sub>2</sub> (M – 1) 190.15789] confirmed that the two oxygen atoms of the nitrodecane (**11**, 98% yield) are the expected [18]O isotope.



The reaction works also with aromatic azides, although it is not as practical as the reaction with the aliphatic ones, mainly because these azides are usually made from the corresponding aromatic amines, which are themselves excellent substrates for oxidation by HOF·CH<sub>3</sub>CN to the nitro derivatives.<sup>9a</sup> Still, the reactions of aromatic azides could shed light on the mechanism of this reaction.

In contrast to the short reaction times required for oxidation of aliphatic azides, conversion of azidobenzene (**12**) to nitrobenzene (**13**) required almost an hour. On the other hand, nitrosobenzene (**14**) was oxidized by HOF·CH<sub>3</sub>CN immediately. The more electron-rich carbon-bonded nitrogen of 4-methoxyazidobenzene (**15**) reacted considerably faster than **12** (10 min versus 1 h), to give 4-nitroani-

sole in 65% yield. What is more, one could clearly observe the development of an intensive blue color of the nitroso derivative (17) which was formed and then disappeared after a few seconds. It should be noted that 4-azidonitrobenzene (18) was found to be unreactive toward the electrophilic oxygen of the reagent because of the low electron density of the carbon-bonded azido nitrogen. These observations support a two-step reaction mechanism. The first and rate-limiting step involves attack of the electrophilic oxygen on the relatively electron-rich azido nitrogen, resulting in formation of a nitroso compound,  $N_2$ , and HF. Consequently, the respective nitroso reacts fast with an additional molecule of  $HOF \cdot CH_3CN$  to form the desired nitro compound.



<b>12</b>	R = Ph	<b>14</b> (green)	<b>13</b> (65%)
<b>15</b>	R = 4-MeOC <sub>6</sub> H <sub>4</sub>	<b>17</b> (blue)	<b>16</b> (65%)
<b>18</b>	R = 4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	no reaction	

In conclusion, we have demonstrated that the  $HOF \cdot CH_3CN$  is probably the best oxygen-transfer agent chemistry has to offer. It is capable of transformations which cannot be completed by any other reagent, and the reaction  $RN_3 \rightarrow RNO_2$  is an important example. The only "problem" with this agent is the reluctance of some chemists to work with  $F_2$ . This should not be so. Today, prediluted fluorine is commercially available, and the work with it is as easy as turning a valve on and off. All reaction vessels are standard glassware, and a simple basic trap takes care of small amounts of  $F_2$  which had not reacted with water. Twenty years ago, only a handful of organic laboratories were working with this

element. Today there are more than a hundred. We hope this work will contribute to increase this number.

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#### References

- (1) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
- (2) Corey E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682.
- (3) Rozen, S.; Brand, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 5, 554.
- (4) (a) Rozen, S.; Kol, M. *J. Org. Chem.* **1990**, *55*, 5155. (b) Hung, M. H.; Smart, B. E.; Feiring, A. E.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 3187. (c) Rozen, S.; Bareket, Y.; Dayan, S. *Tetrahedron Lett.* **1996**, *37*, 531. (d) Dayan, S.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2000**, *65*, 8816.
- (5) Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169.
- (6) Rozen, S.; Dayan, S.; Bareket, Y. *J. Org. Chem.* **1995**, *60*, 8267.
- (7) (a) Rozen, S.; Bareket, Y. *J. Org. Chem.* **1997**, *62*, 1457. (b) Toyota, A.; Ono, Y.; Chiba, J.; Sugihara, T.; Kaneko, C. *Chem. Pharm. Bull.* **1996**, *44*, 703.
- (8) (a) Rozen, S. *Acc. Chem. Res.* **1996**, *29*, 243. (b) Rozen, S. *Pure Appl. Chem.* **1999**, *71*, 481.
- (9) (a) Kol, M.; Rozen, S. *J. Chem. Soc., Chem. Commun.* **1991**, 567. (b) Rozen, S.; Kol, M. *J. Org. Chem.* **1992**, *57*, 7342. (c) Dirk, S. M.; Mickelson, E. T.; Henderson, J. C.; Tour, J. M. *Org. Lett.* **2000**, *2*, 3405.
- (10) Rozen, S.; Bar-Haim, A.; Mishani, E. *J. Org. Chem.* **1994**, *59*, 1208.
- (11) (a) Dayan, S.; Kol, M.; Rozen, S. *Synthesis* **1999**, 1427. (b) Chavez, D. E.; Hiskey, M. A. *J. Energ. Mater.* **1999**, *17*, 357.
- (12) Rozen, S.; Dayan, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3471.
- (13) Alvarez, G. S.; Alvarez, M. T. *Synthesis* **1997**, 413.
- (14) Crandalland, J. K.; Reix, T. *J. Org. Chem.* **1992**, *57*, 6759.
- (15) General procedure for working with fluorine: Fluorine is a strong oxidant and a very corrosive material. It should be used only with an appropriate vacuum line, such as the one described in ref 11a. For the occasional user, however, various premixed mixtures of  $F_2$  in inert gases are commercially available, simplifying the process. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no bad experiences working with it. General procedure for producing the  $HOF \cdot CH_3CN$  complex: Mixtures of 10–15%  $F_2$  with nitrogen were used in this work. They were passed at a rate of about 400 mL/min through a cold ( $-10^\circ C$ ) mixture of 60 mL of  $CH_3CN$  and 6 mL of  $H_2O$ . The development of the oxidizing power was monitored by reacting aliquots with acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.4–0.6 mol/L. With the exception of the [ $^{18}O$ ]-labeled **11**, the final nitro products are known. Their spectral properties are in full agreement with those described in the literature.
- (16) Kol, M.; Rozen, S. *J. Org. Chem.* **1993**, *58*, 1593.
- (17) Compound **6** was made previously in 42% yield in a 3-day reaction: Zee-Cheng, K. Y.; Cheng, C. C. *J. Med. Chem.* **1969**, *12*, 157.
- (18) Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325.
- (19) Krishnamurthy, V. V.; Iyer, P. S.; Olah, G. A. *J. Org. Chem.* **1983**, *48*, 3373.

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