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Facile Oxidation of Primary Amines to Nitriles Using an Oxoammonium Salt

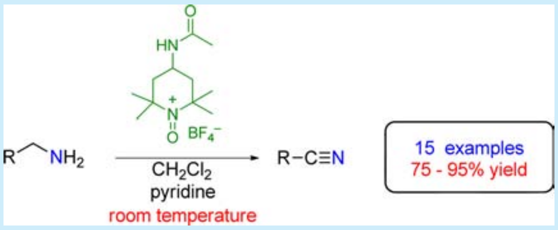
Kyle M. Lambert,[†] James M. Bobbitt,[†] Sherif A. Eldirany,[†] Kenneth B. Wiberg,*[,‡] and William F. Bailey*[,†]

[†]Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269, United States

[‡]Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

Ⓢ *Supporting Information*

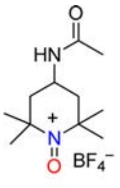
ABSTRACT: The oxidation of primary amines using a stoichiometric quantity of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**) in CH_2Cl_2–pyridine solvent at room temperature or at gentle reflux affords nitriles in good yield under mild conditions. The mechanism of the oxidation, which has been investigated computationally, involves a hydride transfer from the amine to the oxygen atom of **1** as the rate-limiting step.



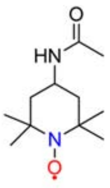
Amines are acutely sensitive to oxidation, and a host of products may be generated depending on the oxidant. A particularly challenging oxidation is the conversion of a primary amine to a nitrile ($RCH_2NH_2 \rightarrow RCN$). This transformation, which formally involves a double dehydrogenation, has been accomplished in a variety of ways[1] including transition-metal catalyzed dehydrogenation,[2] and aerobic oxidation catalyzed by transition metals.[3] More recently, catalytic systems for aerobic oxidation of amines to nitriles have been developed that involve catalytic quantities of a nitroxide, a base, cuprous iodide, and an appropriate ligand for the metal.[4] In this connection, we were intrigued by reports on the oxidation of amines to nitriles by the oxoammonium cation generated from TEMPO by electrochemical oxidation.[5]

Herein we report that the oxidation of a primary amine to the corresponding nitrile may be accomplished expediently, and in high yield using a stoichiometric quantity of a readily available oxoammonium salt (**1**). As detailed below, the oxidation proceeds under mild conditions using inexpensive reagents via a well-defined process. Moreover, the reduced oxidant (**2**), a stable nitroxide, may be recovered and recycled using commercial bleach to regenerate the oxoammonium salt.

The oxoammonium salt, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**), is a stable, highly crystalline, yellow solid. The salt is commercially available. Alternatively, it is easily prepared in a few simple steps from 4-amino-2,2,6,6-tetramethylpiperidine and inexpensive reagents in multimole quantities.[6]



1



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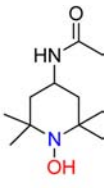

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Oxidation of primary amines to nitriles using **1** is accomplished as follows: slow addition (syringe pump; 15–20 mL/h) of an approximately 0.5 M solution of the amine in dry methylene chloride to a stirred slurry of 4 molar equiv of **1** in dry methylene chloride (150 mL per 10 mmol of amine) containing 8 molar equiv of dry pyridine followed by stirring the reaction mixture at room temperature or at gentle reflux under an atmosphere of nitrogen for a period of time. A simple extractive workup affords essentially pure nitriles, without the need for chromatographic purification, in good to excellent yield as evidenced by the results presented in Table 1.

The stoichiometry of the overall process, depicted in Scheme 1, eq 1, requires explanation. For the stepwise oxidation of the amine to an aldimine (Scheme 1, eq 2) and then to the nitrile (Scheme 1, eq 3), 2 molar equiv of **1** are required. However, in the presence of base, **1** and the hydroxylamine (**3**) synproportionate (Scheme 1, eq 4) to give 2 molar equiv of nitroxide (**2**).[7] Thus, a total of 4 molar equiv of **1** are required for the transformation and the product mixture consists of nitrile (Table 1), pyridinium tetrafluoroborate, and nitroxide **2**. Although only 4 molar equiv of pyridine would seem to be required for the transformation, an excess of pyridine was used so as to avoid protonation of the amine substrate. It is important to note, as detailed in the Supporting Information, that the nitroxide may be recovered with 70–80% efficiency and recycled to give **1**.

The results summarized in Table 1 demonstrate that the oxidation protocol is a robust one. Benzylic and allylic amines are oxidized more quickly than aliphatic amines, typically 12 h at room temperature for benzylic amines and 24–36 h at room temperature for aliphatic amines. Benzylic amines bearing strongly electron-withdrawing substituents are, however, oxidized rather slowly (Table 1, entries 7 and 9). Sluggish

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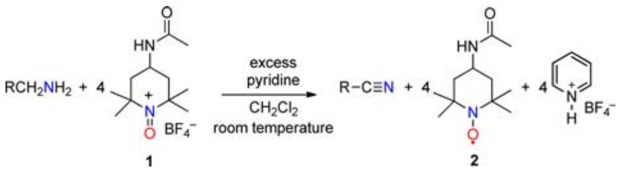
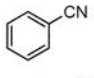
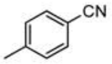
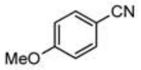
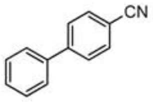
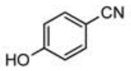
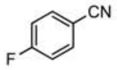
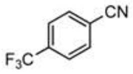
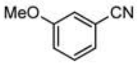
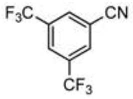
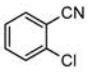
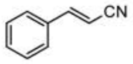
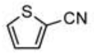
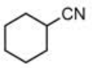
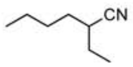
Table 1. Oxidation of Primary Amines to Nitriles (Scheme 1, eq 1)[a]

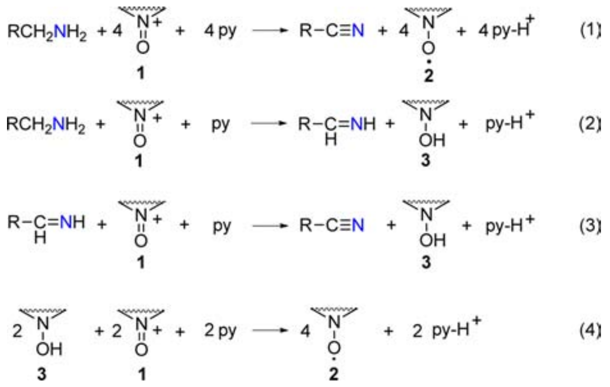


entry	nitrile	time,[b] h	yield,[c] %
1		12	92
2		12	93
3		12	86
4		12	90
5		12	86
6		12	73
7		24	89
8		12	87
9		24[d]	75[d]
10		12	90
11		14	91
12		14	92
13		36, 14[d]	93, 88[d]
14		24, 12[d]	95, 92[d]
15		24	84

[a] All reactions were conducted on a 10 mmol scale. [b] Time reaction mixture was stirred at room temperature or reflux. [c] Isolated yield of chromatographically pure product. [d] Reaction mixture was heated at gentle reflux.

oxidations may be accelerated, with little loss in yield, by simply heating the reaction mixture at gentle reflux (Table 1, entries 9, 13, and 14).

Scheme 1. Overall Process



The successful oxidation of primary amines to nitriles by **1** requires that the amine dissolved in CH_2Cl_2 (typically a 0.5 M solution) be added slowly to the reaction mixture. An addition rate of 20 mL/h was found to be appropriate for the oxidation of relatively reactive amines while a slower rate of 15 mL/h was employed for the oxidation of less reactive substrates such as aliphatic amines. When the amine is added too quickly to the oxidant, it reacts fairly rapidly with the aldimine intermediate to give the symmetrical imine ($RCH{=}NCH_2R$).[8] Control experiments demonstrated that the imine does not react with **1**.

The only byproduct detected in any product mixtures was a small amount of aldehyde presumably generated by hydrolysis of the aldimine intermediate by adventitious water present in the reaction mixture.[9] The aldimines derived from the more reactive benzylic amines were particularly prone to hydrolysis by trace water present in reaction mixtures. If care is not taken to dry solvent and reagents (particularly salt **1**), the aldehyde may become a major component of the reaction product.

In an effort to gain some insight into the mechanism of the oxidation, the reaction was studied computationally at the B3LYP/6-311+G* level both for the optimizations and for calculation of the thermal corrections; all of the following data are for 298 K. The calculated results are of course for the gas phase, but they would be expected to reasonably represent the trend in energies for the solution phase. It is very difficult to calculate free energies in solution since the major thermal correction for the gas phase results from translation, which in solution becomes diffusion, a more difficult phenomenon to model.

The oxidation was modeled using ethylamine as the substrate and the 2,2,6,6-tetramethylpiperidine-1- oxoammonium cation ($TEMP{=}O^+$) as the oxidant. The results of these studies are summarized diagrammatically in Figure 1, and details are provided in the Supporting Information.

The oxoammonium cation was found to form an intermediate dipole-stabilized prereaction complex with the amine ($\Delta G° = 2$ kcal/mol). This was followed by the first oxidation step involving transfer of a hydride from the α-carbon of the amine to the oxygen of $TEMP{=}O^+$ and formation of a C=N bond. The transition state for this process had one imaginary frequency ($1047i$ cm^{-1}) and an activation free energy of $\Delta G^‡ = 15.8$ kcal/mol relative to the reactants. The product, the protonated aldimine, was less stable than the reactants by $\Delta G° = 7.8$ kcal/mol, but with transfer of the acidic proton to pyridine, the product aldimine and pyridinium cation are more stable than the reactants by $\Delta G° = -1.8$ kcal/mol.

The second step of the oxidation was initially modeled by computing the activation energy for hydride transfer from the α-carbon of the aldimine to the oxygen of the oxoammonium cation. This reaction leads to a high $\Delta G^‡ = 31.8$ kcal/mol

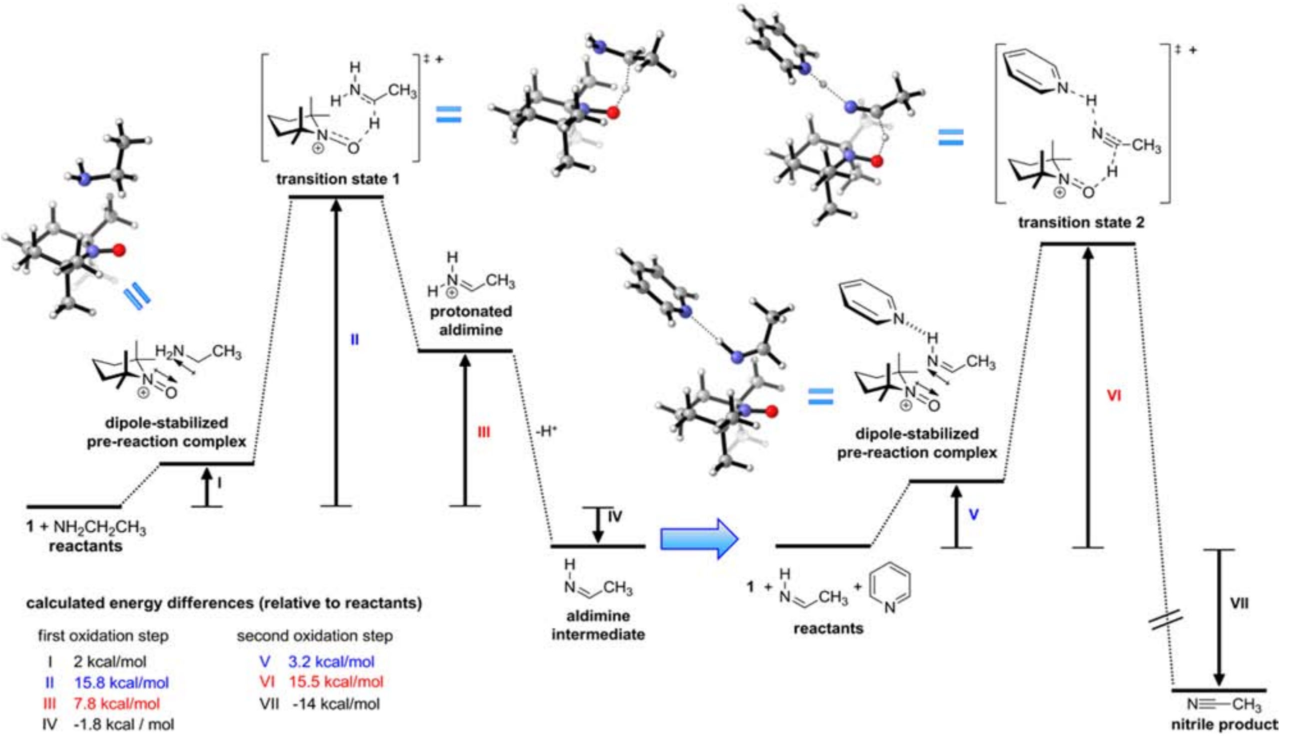


Figure 1. Computed profile (B3LYP/6-311+G*) for the oxidation of primary amines to nitriles.

because it results in a high energy protonated acetonitrile product. Indeed, the latter is calculated to transfer a proton to pyridine with $\Delta G^\circ = -35.5$ kcal/mol. Clearly, pyridine must participate in the oxidation step. This was studied by including pyridine in the reaction of TEMP=O^+ with the aldimine. Gratifyingly, this three-component situation leads to a pre-reaction complex ($\Delta G^\circ = 3.2$ kcal/mol relative to reactants) and a more reasonable activation free energy of $\Delta G^\ddagger = 15.5$ kcal/mol relative to the three reactants. This transition state had one imaginary frequency ($1016i$ cm^{-1}). The overall oxidation of the aldimine to the neutral nitrile was computed to be exothermic by $\Delta G^\circ = -14$ kcal/mol.

The mechanism suggested by these computational studies is analogous to that thought to be responsible for the oxidation of alcohols by the oxoammonium cation in neutral or acidic solution.[10] Both oxidations involve, as the rate-limiting step, transfer of a hydride from the substrate to the oxidant. The development of a partial positive charge on the α-carbon of the amine in the course of the oxidation nicely accounts for the fact that benzylic amines bearing electron-withdrawing substituents react more slowly than those bearing electron-donating groups.

In summary, the oxidation of primary amines at room temperature using oxoammonium salt **1** in methylene chloride–pyridine provides an experimentally simple, mild, and efficient method for the synthesis of nitriles. Moreover, the progress of the oxidation is easily followed visually. The initial yellow slurry of **1** progressively develops a deep-red color, as the concentration of soluble nitroxide **2** in the reaction medium increases. Upon completion of the oxidation, the methylene chloride is deep red and a white precipitate of pyridinium tetrafluoroborate is evident. The color changes associated with the oxidation are illustrated in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedures; product characterization; ^1H, ^{13}C, and ^{19}F NMR spectra of all products; a summary of the calculations, including computed energies and coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: William.Bailey@uconn.edu.
*E-mail: kenneth.wiberg@yale.edu.

Notes

The authors declare no competing financial interest.

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