Synthetic Methods

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Access to Nitriles from Aldehydes Mediated by an Oxoammonium Salt**

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Abstract: *A scalable, high yielding, rapid route to access an array of nitriles from aldehydes mediated by an oxoammonium salt (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) and hexamethyldisilazane (HMDS) as an ammonia surrogate has been developed. The reaction likely involves two distinct chemical transformations: reversible silyl-imine formation between HMDS and an aldehyde, followed by oxidation mediated by the oxoammonium salt and desilylation to furnish a nitrile. The spent oxidant can be easily recovered and used to regenerate the oxoammonium salt oxidant.*

The nitrile group is a highly useful motif to synthetic organic chemists and it can be readily converted into various valuable heterocycles and functional groups such as amines, amides, carboxylic acids, or esters.[1] Additionally, nitriles are prized in their own right as they commonly appear in fine chemicals and can be found in a number of pharmaceutical and agrochemical compounds.[1,2] The most common approach to the preparation of nitriles involves substitution reactions of organic halides with a cyanide source.[1] While a very practical and inexpensive route, utilization of toxic cyanide can prove problematic on scale up. Alternatively, some organic cyanide sources have been explored with great success.[3] Rather than incorporating the nitrile functionality directly, various nitrogen-containing functionalities can be converted into nitriles. Dehydration of amides is one such approach, but often requires harsh reaction conditions (e.g. P_2O_5 and high temperatures).[4] By using a variety of metal- or nonmetal-based oxidants, primary amines can undergo a double oxidation to afford nitriles.[5,6] More recently, attention has turned to converting readily accessible functionalities (e.g. aldehydes and alcohols) into nitriles. The most typical approach is to use hydroxylamine to form an oxime followed by a dehydration reaction.[7] Again, scalability is limited because of the inherent instability of hydroxylamine. An attractive alternative is to perform direct oxidative nitrile synthesis by exposure of an alcohol or aldehyde to ammonia and an oxidant. This transformation has been accomplished both stoichiometrically[8] and catalytically[9]

Recently we engaged in an investigation probing the use of the oxoammonium salt 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (Bobbitt's Salt; **1a**) for oxidative amidation of **2a**. We initially attempted to use our previously optimized reaction conditions for the oxidative esterification of aldehydes (Figure 1a),[10a] but instead replacing hexafluoroisopropanol (HFIP) by hexamethyldisilazane (HMDS) as the coupling partner (Figure 1b). HMDS was employed as a nitrogen source since no appreciable reaction occurs upon exposure of HMDS to **1a**, unlike with aqueous ammonia. Rather than obtaining amidation, we serendipitously discovered a route to rapidly and efficiently access the nitrile **3a** (Figure 1c), albeit a process that was exothermic. Given the advantages of oxoammonium salt

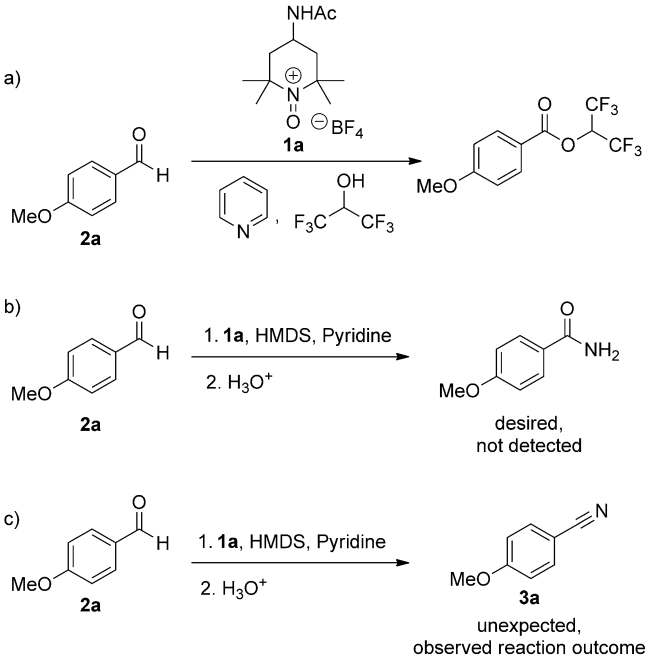

Figure 1. Serendipitous nitrile formation during oxidative amidation attempts.

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oxidants, namely that they are environmentally benign, recyclable, and metal-free species which can facilitate oxidation under extremely mild reaction conditions, and our interest in enhancing the profile of oxoammonium salt-based transformations, we elected to advance this unusual outcome into a general methodology for the direct synthesis of nitriles from aldehydes.[10]

To understand our unexpected result better, we systematically examined the role of each of the reaction components. This study also served as an opportunity to optimize reaction conditions. First, to control the observed exotherm when utilizing the oxidative esterification conditions for this transformation, we decided to conduct the reaction in CH_2Cl_2. This solvent served as a thermal sink and no exotherm was observed at an aldehyde concentration of 0.5 M. We quickly found that pyridine was not essential for nitrile formation as the reaction proceeded readily in its absence. This observation eliminated the possibility of an acyl pyridinium intermediate which was posited by Bobbitt et al. as the key intermediate during oxidative esterification reactions mediated by **1a**.[10b] Variation of the loading of **1a** and HMDS provided further critical mechanistic insight. The use of 0.5 equivalents as opposed to 1 equivalents of **1a** in the presence of three equivalents of HMDS gave starkly different results. In the case of the former, one would expect only to obtain about 25% conversion into the nitrile because of the known comproportionation of **1a** under basic conditions.[10b] While this was confirmed by ^{1}H NMR spectroscopy, an additional 25% of **2a** was consumed and the formation of another compound was observed. This compound was later identified as the N-(trimethylsilyl)imine of **2a**. In contrast, use of 1 equivalent of **1a** afforded complete consumption of **2a** in addition to the formation of equal amounts of **3a** and the imine. By employing two or more equivalents of **1a**, we were able to obtain **3a** as the sole product. The absence of the imine at higher loadings of **1a** suggested to us that it was the likely reaction intermediate, and that it was the species undergoing oxidation during the course of the reaction.

This conclusion was further evidenced by a recent report by Wiberg, Bailey, and co-workers who stated that oxidation of imines by **1a** is highly favorable and exothermic (Figure 2a).[6] We confirmed that such imines could be oxidized with **1a** by independently preparing **4** and subjecting it to our reaction conditions. We observed a highly exothermic reaction, with benzonitrile and Me_3Si-F being the observed major products (Figure 2b).

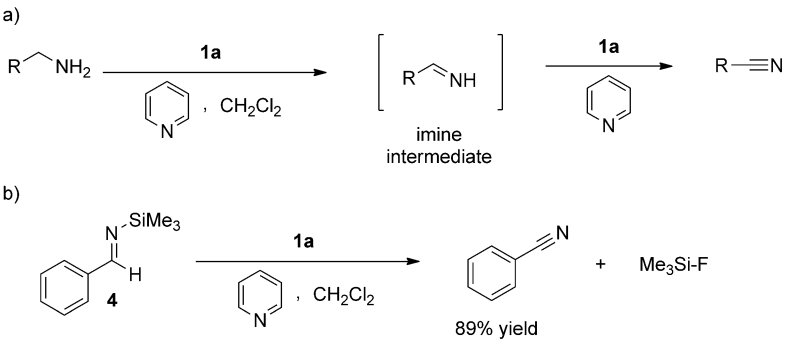


Figure 2. Reported amine oxidation mediated by **1a** and the oxidation of a plausible mechanistic intermediate.

The formation of Me_3Si-F was also observed when **2a** was treated with **1a**. Use of the perchlorate salt of **1a** strictly gave Me_3Si-OH and $(Me_3Si)_2O$ as the reaction by-products. Next, HMDS loading was varied. At only 1 equivalent of HMDS and 2 equivalents of **1a**, a 50% conversion into **3a** was achieved, with the remainder being **2a** and no intermediate imine detected. Use of 2 equivalents or more of HMDS gave sole conversion into **3a**.

With these data in hand, we were able to construct a plausible reaction mechanism (Figure 3). We speculate that numerous pathways are available for the formation of the N-trimethylsilyl imine of **2a** from HMDS and small amounts form during the course of the reaction. Rapid oxidation of the imine would forge the remaining C–N bond, thus furnishing the nitrilium ion which, in the presence of the now naked tetrafluoroborate anion, would decompose to BF_3 and Me_3Si-F. Given the strength of Si–F bond and the computed exothermic nature of nitrilium deprotonation during our

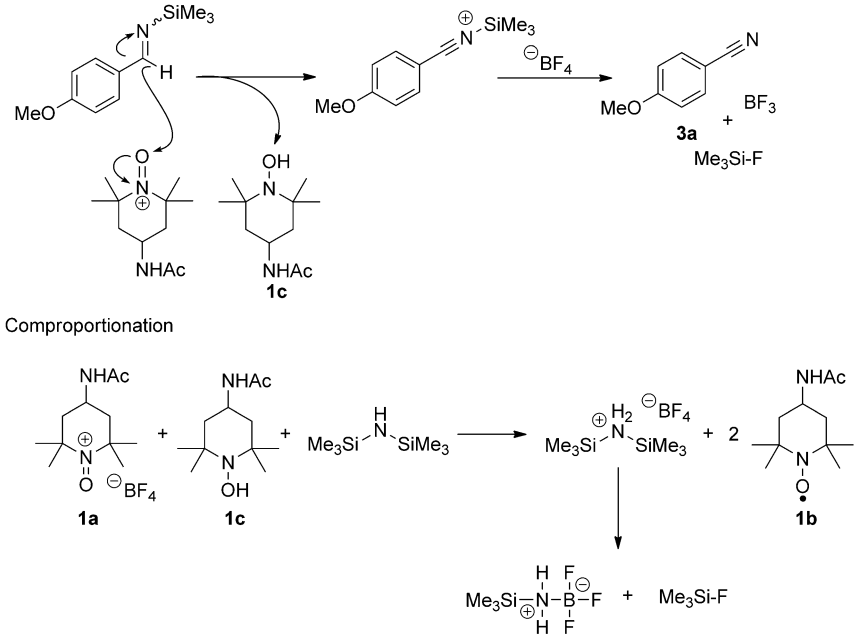
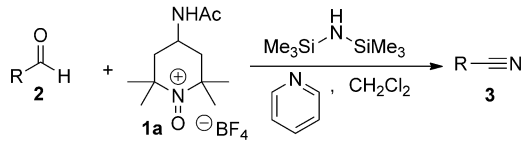
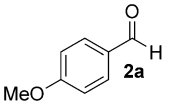
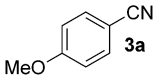
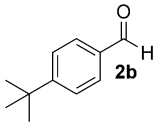
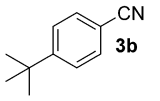
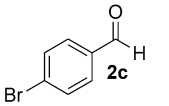
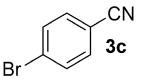
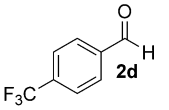
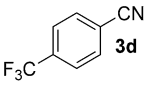
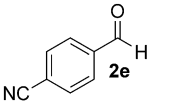
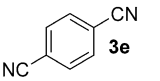
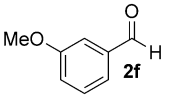
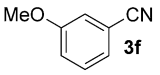
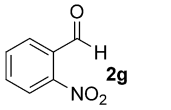
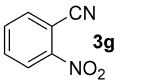
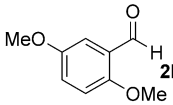
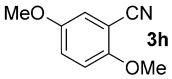
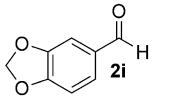
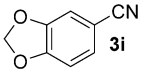
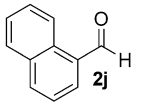
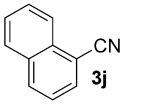
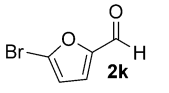
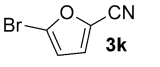
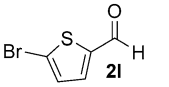
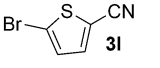
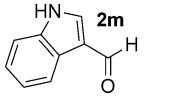
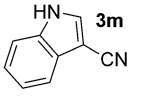
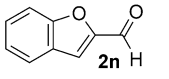
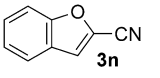
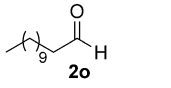
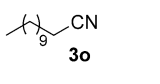


Figure 3. Plausible reaction mechanism.

Table 1: Scope of oxidative formation of nitriles[a].



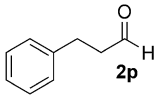
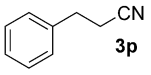
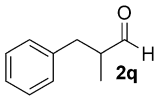
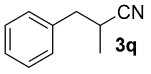
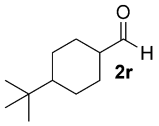
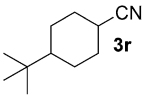
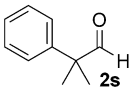
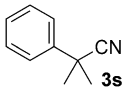
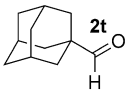
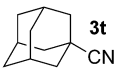
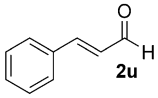
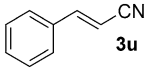
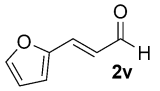
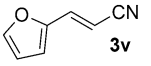
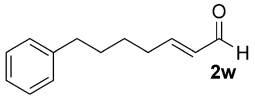
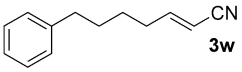
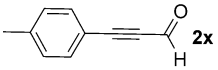
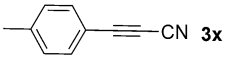
Entry[a]	Aldehyde	Nitrile	*t* [h]	Yield [%][b]
1			1	95 (90)[c]
2			4	97 (88)[c]
3			24	75
4			36	51[d]
5			36	69
6			12	91
7			24	80
8			4	88
9			12	93
10			12	88
11			12	82
12			12	69
13			2	67
14			12	75
15			1	80

prior[6] investigation, this step likely explains the observed highly exothermic character of this reaction. The known[10b] comproportionation of **1a** under basic conditions explains the requirement for 2 equivalents of **1a** and HMDS as well as the formation of **1b**.

By using the mechanism as a guide, we treated **2a** with 2.5 equivalents of HMDS and **1a** in CH_2Cl_2. Additionally, to prevent unwanted side reactions, 1.1 equivalents of pyridine were added. While not mechanistically necessary, pyridine is an excellent means to sequester the BF_3 generated during the course of the reaction. We obtained complete conversion into **3a** after only 1 hour at room temperature. Isolation of **3a** proved simple and we obtained a 95% yield of **3a** (Table 1, entry 1). Next we turned our attention to survey the scope of the reaction. The initial focus centered on aryl aldehydes as a means of assessing the electronic and steric constraints governing this reaction. Both electron-rich (entries 1,2,8, and 9) and electron-poor (entries 3–7) benzaldehyde derivatives all underwent rapid oxidation and gave fair to excellent yields of their corresponding nitriles. Scale-up to a 50 mmol scale proved facile and neither compromised yield nor changed the impurity profile (entries 1 and 2). However, on such scales, thermal moderation was required and was easily accomplished using a room temperature water bath.

The electronic and steric constraints of the aryl systems had a notable effect both on yield and on reaction rate. Substrates with electron-rich aryl rings reached completion at a much faster rate than those bearing electron-withdrawing groups. In certain cases (entries 3–5 and 7), we were unable to achieve complete conversion in less than 36 h using our optimized reaction conditions. Premature quenching of the reaction mixture led to hydrolysis of the intermediate imine, thus diminishing yield and furnishing the starting aldehyde as a contaminant (typically $< 10\%$ by ^{1}H NMR spectroscopy). This contaminant could easily be removed by simply stirring the crude reaction mixture overnight in Et_2O in the presence of a commercially available silica-bound amine-based scavenger.[11] In addition, a known side reaction involving nitriles and the hydroxylamine **1c** (formed during the reaction; see Figure 3) had a deleterious effect on yield in very electron-poor systems (entry 4). Discovered by Endo and coworkers, hydroxylamines of the tetramethylpiperidinyl scaffold react rapidly with electron-poor nitriles to give amides (Figure 4).[11] Moreover, Endo found the reaction is significantly accelerated under basic conditions, thus explaining the observed amide by-product and hence the greatly diminished yield of **3d**.[11] Interestingly, the steric constraints of **3g** (entry 7) must deter this process

Table 1: (Continued)

Entry[a]	Aldehyde	Nitrile	*t* [h]	Yield [%][b]
16	 **2p**	 **3p**	1	71[e]
17	 **2q**	 **3q**	4	72
18	 **2r**	 **3r**	2	96
19	 **2s**	 **3s**	32	80
20	 **2t**	 **3t**	1	82
21	 **2u**	 **3u**	2	86
22	 **2v**	 **3v**	12	78[f]
23	 **2w**	 **3w**	–	–[g]
24	 **2x**	 **3x**	1	79

[a] Reaction conditions unless otherwise noted: aldehyde in CH_2Cl_2 (10 mmol, 1 equiv, 0.5 M), HMDS (25 mmol, 2.5 equiv), pyridine (11 mmol, 1.1 equiv), **1a** (25 mmol, 2.5 equiv) [b] Yield of isolated product. [c] Yield on 50 mmol scale. [d] A 50:50 mixture by volume of Et_2O and CH_2Cl_2 was used as the solvent. [e] HMDS was added dropwise to the reaction mixture. [f] Reaction was run at 0.1 M to prevent polymerization. [g] Complex mixture observed.

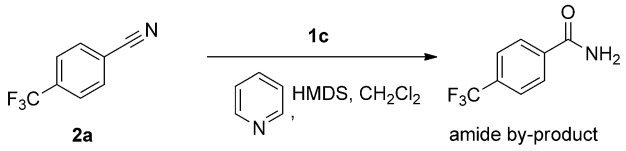


Figure 4. Known reaction of electron-poor nitriles with the hydroxylamine **1c** discovered by Endo and co-workers.

as no amide was observed despite being significantly electron poor. This assertion was further evidenced by the fact that the *para* counterpart to **3g** (not shown) gave the amide as the major product.

We next probed whether polycyclic and heterocyclic systems would be amenable to oxidative nitrile formation. A representative polycyclic example (entry 10) tolerated our reaction conditions, thus giving the corresponding nitrile **3j** in excellent yield. Similarly, an array of heterocycles containing sulfur, oxygen, and nitrogen atoms (entries 11–14) were well-tolerated, thus affording good to excellent yields of nitriles.

Wondering whether our protocol could be extended to aliphatic aldehydes, we initially screened a representative straight chain example (entry 16). Aliphatic aldehydes not bearing an α-substitution were problematic, and is likely due to their propensity to undergo self-aldol reactions in the presence of silylated amines.[12] However, by adding HMDS slowly to the reaction mixture, we were able to avoid this unwanted side reaction and maintain good yield (entries 15 and 16). Next, various aliphatic substrates bearing α-substituents (entries 17–20), whose synthesis would be impractical by classical S_N2 approaches, were screened. We were pleased to find that they all formed the desired nitrile, regardless of substitution pattern. Unsurprisingly, conformational restriction of the α-substituents dramatically increases the reaction rate. Restricted systems (entries 18 and 20) reached completion rapidly, while unrestricted examples (entries 17 and 19) were sluggish. This acceleration in rate is likely due to diminished steric encumbrance by the α-substituents.

We concluded our screen of substrates by studying α,β-unsaturated and propargylic systems (entries 21–24). Cinnamaldehyde (entry 21) successfully converted into its nitrile in excellent yield. When using the optimized reaction conditions, we initially obtained very low yield of **3v** because of polymerization. By performing the reaction at a higher dilution, we successfully converted this aldehyde into its nitrile in good yield (entry 22), albeit at the expense of a longer reaction time. Removing the double bond from conjugation had a deleterious effect on the reaction, with only polymeric material being obtained (entry 23). This is likely a consequence of various Michael additions into the alkene. This observation is in agreement with the findings of Endo[11] as well as our own[10a] investigations. In contrast, a representative conjugated propargylic aldehyde rapidly and cleanly converted into its nitrile (**3x**) in good yield (entry 24).

To expand the utility of our approach, we investigated whether alcohols could be converted directly into nitriles using **1a**. Using a two-step, one-pot procedure, we found that this transformation could indeed be accomplished successfully (Figure 5). First, 4-chlorobenzyl alcohol was oxidized to its aldehyde **2y** under basic conditions.[13] Subsequent addition of HMDS, pyridine, and more **1a** provided the nitrile in excellent yield without the need for isolation and purification of the intermediate aldehyde.

In summary, a methodology for the conversion of an aldehyde into a nitrile facilitated by an oxoammonium salt is described. Using HMDS as a nitrogen source, aldehydes can be converted into nitriles under mild reaction conditions in fair to excellent yield. Both the success and the rate of the reaction are contingent on the formation and subsequent oxidation of the intermediate N-trimethylsilyl imine. The reaction is scalable and the spent oxidant can be recovered.

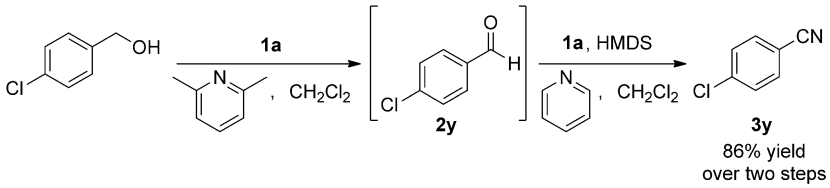


Figure 5. Nitrile synthesis from an alcohol through tandem oxidation.

Alcohols can also be easily converted into nitriles using the conditions outlined here in a two-step, one-pot approach.

Keywords: aldehydes · cyanides · oxidation · reaction mechanisms · synthetic methods

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