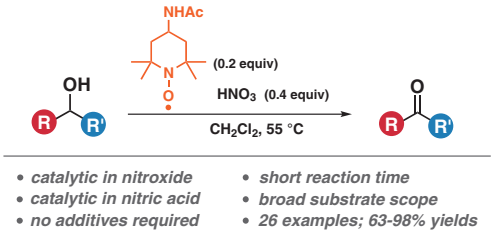
Oxidation of Alcohols to Aldehydes and Ketones Using a Catalytic Pairing of a Nitroxide and Nitric Acid

Manisha Sharma
Arturo León Sandoval
Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06269, USA
nicholas.leadbeater@uconn.edu



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Abstract A methodology for the oxidation of alcohols to aldehydes and ketones is presented. The approach employs catalytic quantities of a nitroxide and nitric acid, with no additives or metal catalysts being required. It proves effective for a range of aromatic, heteroaromatic, and aliphatic alcohol substrates, the desired products being formed in good to excellent yield. In the case of primary alcohols, the oxidation can be stopped at the aldehyde without concomitant formation of the corresponding carboxylic acid.

Key words oxidation, nitroxide, nitric acid, aldehydes, ketones, alcohols

Oxidation plays a central role in preparative organic chemistry, none more so than for the conversion of alcohols into aldehydes, ketones, and carboxylic acids.[1] To this end, both stoichiometric and catalytic approaches can be taken. Oxoammonium salts prove to be particularly attractive reagents for stoichiometric oxidation reactions,[2] 4-acetamido-2,2,6,6-tetramethylpiperidin-1-oxoammonium tetrafluoroborate salt (**1**) being the most widely used example (Figure 1).[3,4] It is a recyclable, metal-free species that can affect reactions using either a mildly acidic or basic route. While when using a base, the substrate scope is often broader and reaction times are shorter, a drawback is that a superstoichiometric quantity of **1** is needed since the spent oxidant, hydroxylammonium salt **2**, undergoes a comproportionation reaction with **1** to generate nitroxide **3**.[5] A consequence of this is that a sacrificial equivalent of **1** is required to achieve complete oxidation of the substrate.

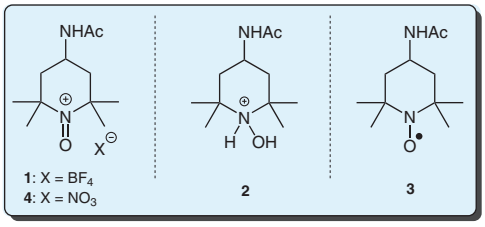
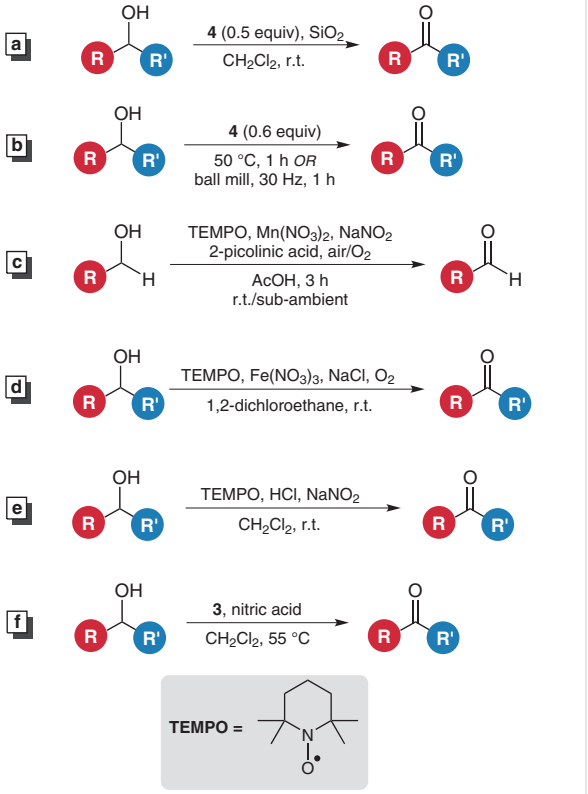


Figure 1 Oxoammonium salts **1** and **4**, hydroxylammonium **2**, and nitroxide **3**

Our group has investigated the use of oxoammonium salts bearing anions other than tetrafluoroborate.[6] When employing **4**, the nitrate anion analogue of **1**, it is possible to oxidize alcohols to the corresponding carbonyl compounds very effectively.[7–9] These transformations can be performed using 0.5–0.6 equiv of **4** and the substrate scope proves to be quite broad. The reactions can be performed in solvent with silica gel as an additive (Scheme 1a)[9] or under solvent-free or mechanochemical conditions without the need for additives (Scheme 1b).[7]

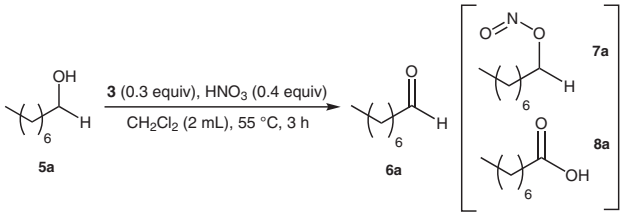
In **4**, the nitrate counterion is not innocent and instead plays a role in the reaction mechanism.[7,9] This is not totally unexpected. There is precedent for the oxidation of alcohols in a catalytic manner using nitroxides in the presence of nitrogen oxide (NO_x) co-catalysts, with oxygen being the terminal oxidant (Scheme 1c–e).[10–17] Mechanistically, these processes involve a NO/NO_2 redox couple linked to a hydroxylamine/oxoammonium cycle. They generally involve the addition of sodium nitrite, the use of a metal co-catalyst, or both. As an alternative approach, we posited that we could form **4** *in situ* from **3** by the addition of nitric acid and so decided to explore this path. It would offer a simple, easy method for oxidation of a range of alcohol substrates with no need for a metal co-catalyst. Our results are presented here (Scheme 1f).



Scheme 1 (a) Oxidation using oxoammonium salt **4** in dichloromethane;[9] (b) solvent-free and mechanochemical oxidation using oxoammonium salt **4**;[7] (c) oxidation using TEMPO, sodium nitrite, and a manganese catalyst;[16] (d) oxidation using TEMPO, sodium chloride, and an iron catalyst;[17] (e) oxidation using TEMPO, sodium nitrite, and hydrochloric acid;[15] (f) this work.

In order to optimize reaction conditions for the oxidation of alcohols to aldehydes and ketones, we decided to use 1-octanol (**5a**) as a model substrate. As a starting point, we chose reaction conditions similar to those employed in our other oxidative transformations using **4**,[7,9] but this time starting with **3**. We chose to use 2 mmol of the alcohol substrate, 0.3 equiv of **3**, in 2 mL of dichloromethane, and heating the reaction mixture at 55 °C for 3 h. With the addition of 0.4 equiv of nitric acid, we observed a 69% conversion into 1-octanal (**6a**) along with 12% of the nitroso intermediate (**7a**) and 8% of octanoic acid (**8a**, Table 1, entry 1). Unlike our methodology using **4**, the addition of 1 wt. equiv of silica gel did not have a positive effect on product conversion when starting with **3** (entry 2). We posited that reducing the quantity of nitric acid used may lead to a concomitant decrease in carboxylic acid formation. This was not the case when using 0.3 equiv of nitric acid, but product conversion was increased to 75% due to less of the nitroso intermediate **7a** (entry 3). Reducing the nitric acid loading further to 0.2 equiv did not increase product conversion further, but in this case, we did see less **8a** being formed (entry 4). Increasing the quantity of **3** from 0.3 equiv to 0.4 equiv did lead to a concomitant increase in product conversion when using 0.2 or 0.3 equiv of nitric acid (entries 5 and 6). However, when increasing the amount of nitric acid used to 0.4 equiv product conversion decreased due to the competitive formation of the off-target carboxylic acid **8a** (entry 7). Next, we probed the effect of decreasing the loading of **3** on the outcome of the reaction. When using 0.2 equiv of **3** and varying the loading of nitric acid from 0.2 equiv to 0.4 equiv, we could improve the product conversion to 80% when using the higher amount of nitric acid (entries 8–10). Looking next at reaction time and temperature, 3 h proved optimal when operating at 55 °C (entries 11 and 12). Performing the reaction at room temperature instead of at 55 °C was not effective (entries 13 and 14). We performed the

Table 1 Optimization of Reaction Conditions[a]



Entry	Deviation from above	**6a**:**7a**:**8a** (%)[b,c]
1	none	69:12:8
2	addition of 1 wt equiv silica gel	65:15:7
3	0.3 equiv nitric acid	75:9:7
4	0.2 equiv nitric acid	74:15:3
5	0.4 equiv **3**, 0.2 equiv nitric acid	72:8:4
6	0.4 equiv **3**, 0.3 equiv nitric acid	80:4:8
7	0.4 equiv **3**, 0.4 equiv nitric acid	75:4:11
8	0.2 equiv **3**, 0.2 equiv nitric acid	72:15:4
9	0.2 equiv **3**, 0.3 equiv nitric acid	76:10:9
10	0.2 equiv **3**, 0.4 equiv nitric acid	80:7:13
11	0.2 equiv **3**, 0.4 equiv nitric acid, 1 h	57:36:4
12	0.2 equiv **3**, 0.4 equiv nitric acid, 2 h	73:12:15
13	0.2 equiv **3**, 0.4 equiv nitric acid, no heating	55:21:10
14	0.3 equiv **3**, 0.4 equiv nitric acid, no heating	55:19:11
15	acetonitrile as solvent	53:10:29
16	0.2 equiv **3**, 0.4 equiv nitric acid, 0.1 equiv $NaNO_2$	73:7:10
17	0.3 equiv **3**, no nitric acid	0:0:0
18	no **3**, 0.4 equiv nitric acid	0:0:0

[a] Reaction performed in a sealed vial using **5a** (2 mmol, 1 equiv).
[b] Product conversion determined by ^{1}H NMR spectroscopy.
[c] Remaining mass balance is unreacted starting material and uncharacterized byproducts.

reaction using acetonitrile as the solvent but found the outcome was inferior to that when employing dichloromethane (entry 15).

In certain cases, benzylic alcohols can be oxidized to carbonyl compounds using nitric acid without any additional reagents being required.[17] As stated earlier, depending on the conditions used, either the nitrite ion, $[NO_2]^-$, or nitrogen dioxide, NO_2, is proposed as the key oxidizing species.[18] We wanted to see whether the addition of a nitrite source to our reaction mixture would have a positive impact on product conversion. To do this, we performed our reaction at a loading of 0.2 equiv of **3** and 0.4 equiv nitric acid, with the addition of 0.1 equiv of sodium nitrite. This did not improve the outcome (entry 16).

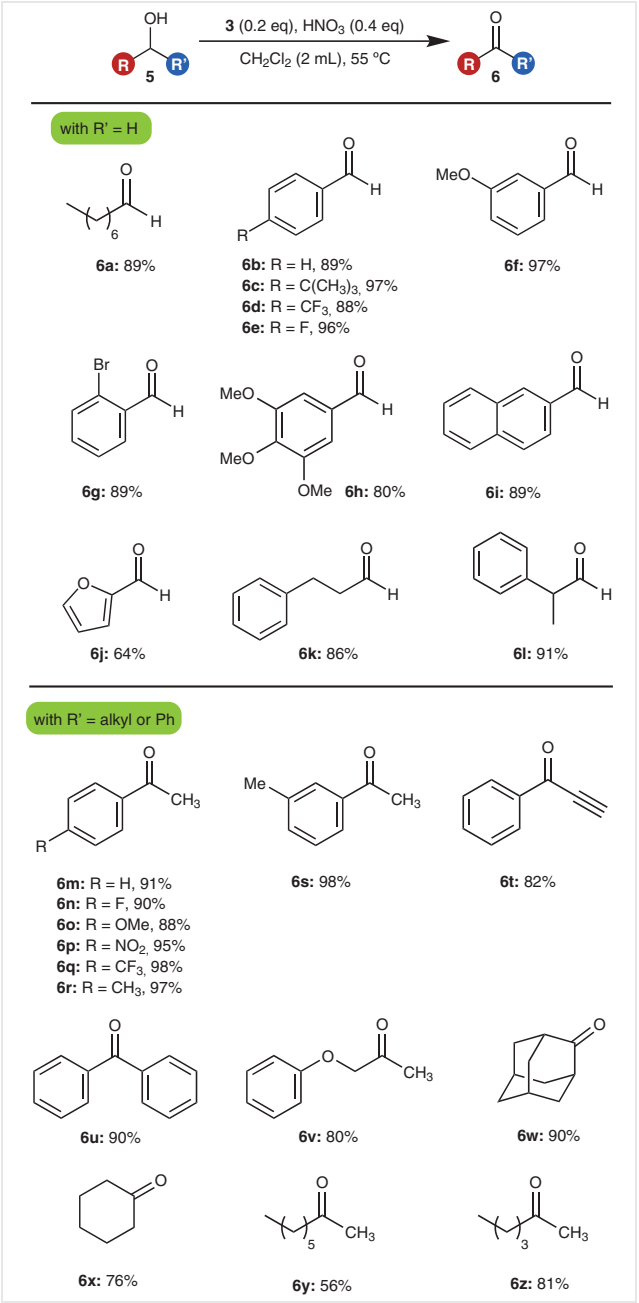
To conclude our optimization process, we wanted to confirm that both **3** and nitric acid were essential. We found that indeed they were running the reaction in the absence of either of these components did not yield any product (entries 17 and 18). Our optimal conditions are: alcohol (2 mmol) **3** (0.2 equiv), nitric acid (0.4 equiv), in 2 mL dichloromethane, heating at 55 °C for 3 h.

We also devised a product-purification strategy. Upon completion of the reaction, the product mixture was loaded onto a pad of silica gel. Diethyl ether or dichloromethane was passed through the silica gel, first eluting any unreacted alcohol and then the product. The nitroso intermediate and any carboxylic acid formed in the reaction remained adsorbed on the silica. The solvent was then removed from the filtrate of the product under vacuum, affording **6a** in pure form.

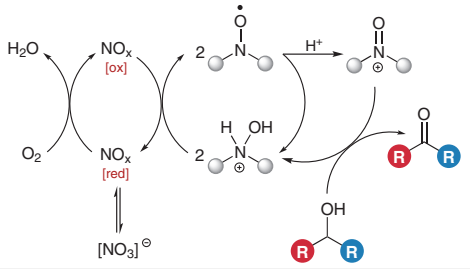
Having optimized the reaction, we next performed a substrate screen of primary alcohols (Scheme 2).[3,4] A range of benzyl alcohols bearing electronically different substituents were examined first. All could be converted into the corresponding aldehydes, with yields ranging from good to excellent (**6b–h**). A representative polysubstituted substrate afforded the expected aldehyde (**6i**), as did a heteroaromatic example (**6j**). In the case of the latter, the isolated product yield was modest due to competitive side reactions that occurred. We also evaluated two compounds with nonconjugated systems, along with 1-octanol, the aldehydes being obtained in good yields (**6a**, **6k**, and **6l**).

Building on the success of converting primary alcohols into aldehydes, we decided to test the approach for the oxidation of secondary alcohols to ketones. Again, benzyl alcohols bearing electron-donating and electron-withdrawing substituents were readily oxidized (**6m–u**). We also screened representative aliphatic secondary alcohols, and all could be oxidized to the desired ketones in moderate to good yields (**6v–z**).

A proposed mechanism for the oxidation reaction is shown in Scheme 3. The first step is the dissociation of nitric acid to generate the nitrate anion. This in turn is converted into reduced NO_x species which are oxidized by molecular oxygen. Nitroxide **3** comproportionates to generate oxoammonium and hydroxylammonium cations, the former performing the key transformation; the oxidation of the alcohol substrate to generate the desired aldehyde or ketone product. The hydroxylammonium cation is then converted back into the nitroxide by a NO_x-mediated oxidation process, closing the catalytic cycle.



Scheme 2 Substrate scope for the oxidation of alcohols. Reaction performed in a sealed vial using **5** (2 mmol, 1 equiv). Isolated yields after purification are given.



Scheme 3 Proposed mechanism.

In summary, we have developed a methodology for the oxidation of alcohols to aldehydes and ketones.[20,21] The approach employs catalytic quantities of a nitroxide and nitric acid without any additives or metal catalyst being required. It proves effective for a range of aromatic, heteroaromatic, and aliphatic alcohol substrates, the desired products being formed in good to excellent yield. In the case of primary alcohols, the oxidation can be stopped at the aldehyde without concomitant formation of the corresponding carboxylic acid.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online 577.

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(20) **General Procedure**
To a 4-dram reaction vial equipped with a stir bar were added the starting material (2 mmol, 1 equiv), 4-acetamido-2,2,6,6-tetramethylpiperidin-1-oxyl (ACT, 85mg, 0.2 equiv), 2 mL of dichloromethane, and nitric acid (70%, 0.051 mL, 0.4 equiv). The vial was closed tightly. The contents were then heated in a sand bath at 55 °C. Upon completion, the product mixture was loaded onto a pad of silica gel. Diethyl ether or dichloromethane was passed through the silica gel, first eluting any unreacted alcohol and then the product. The nitroso intermediate and any carboxylic acid formed in the reaction remain adsorbed on the silica. The solvent was then removed from the filtrate of the product under vacuum, affording the aldehyde or ketone in pure form.

(21) **Representative Spectral Data**
Octanal (6a)
Obtained as colorless oil in 3 h (0.233 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (t, *J* = 1.9 Hz, 1 H), 2.41 (td, *J* = 7.3, 1.9 Hz, 2 H), 1.63 (p, *J* = 7.3 Hz, 2 H), 1.30 (dd, *J* = 8.5, 5.4 Hz, 8 H), 0.92 0.84 (m, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.96, 77.33, 77.01, 76.69, 43.92, 31.62, 29.13, 29.01, 22.58, 22.10, 14.04.

4-(Trifluoromethyl)benzaldehyde (6d)
Obtained as light-yellow oil in 1 h (0.306 g, 88%). **¹**H NMR (400 MHz, $CDCl_3$): δ = 10.11 (s, 1 H), 8.01 (d, *J* = 7.9 Hz, 2 H), 7.82 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.04, 129.92, 126.15, 126.11. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.10, –161.64.
Furfural (6j)
Obtained as yellow liquid in 1 h (0.123 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 7.71–7.64 (m, 1 H), 7.25 (dd, *J* = 3.6, 0.8 Hz, 1 H), 6.60 (dd, *J* = 3.6, 1.7 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.88, 153.03, 148.06, 120.91, 112.58.
4-Methoxyacetophenone (6o)
Obtained as a yellow oil in 2 h (0.266 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.89 (m, 2 H), 6.97–6.89 (m, 2 H), 3.87 (s, 3 H), 2.55 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.77, 163.50, 130.59, 130.38, 113.69, 55.47, 26.34.
1-Phenyl-2-propyl-1-one (6t)
Obtained as yellow solid in 1 h (0.212 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.06 (m, 2 H), 7.68–7.59 (m, 1 H), 7.56–7.45 (m, 2 H), 3.44 (s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.41, 136.17, 134.53, 129.72, 128.70, 80.76, 80.29.
2-Adamantanone (6w)
Obtained as white solid in 1 h (0.265 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (d, *J* = 4.7 Hz, 2 H), 2.14–1.96 (m, 12 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 46.98, 39.29, 36.32, 27.46.