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Hydroxylamine as a Source for Nitric Oxide in Metal-Free 2,2,6,6-Tetramethylpiperidine *N*-Oxyl Radical (TEMPO) Catalyzed Aerobic Oxidation of Alcohols

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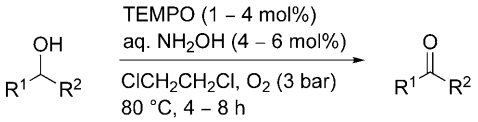
Abstract: The communication reports on the metal-free 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO) catalyzed aerobic oxidation of various alcohols to aldehydes and ketones. A novel catalyst system that uses 1–4 mol% of TEMPO in combination with 4–6 mol% of aqueous hydroxylamine is introduced. No other additives are necessary and corrosive by-products are not formed during oxidation. Nitric oxide which is important for the catalytic cycle is generated *in situ* by reaction of the hydroxylamine with TEMPO. A catalytic cycle for the overall oxidation process is suggested.

Keywords: aerobic oxidation; alcohols; catalysis; hydroxylamine; nitric oxide; 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)

The persistent nitroxide TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl radical) and derivatives thereof are highly valuable organocatalysts for the conversion of primary and secondary alcohols to the corresponding carbonyl compounds.[1] The catalytically active species in most of these reactions is not the nitroxide itself, but its oxidized form, the corresponding *N*-oxoammonium salt. In practice, the oxoammonium salt is generated *in situ* by one-electron oxidation using various organic[2] or inorganic[3] cooxidants. This allows the nitroxide to be used as a catalyst in these oxidations. Although sodium hypochlorite has been highly successfully used as a cooxidant (Anelli conditions),[3a] the identification of cheap and environmental more friendly alternatives is important and currently an active research area. As a result, dioxygen has been investigated as a terminal oxidant in nitroxide-based oxidation protocols.[4] Nitroxides in combination with transition metal catalysts have been successfully applied for oxidation of a broad range of alcohols.[5] Besides other cocatalysts,[6] iron(III)[7] and copper(II)[8] salts have been intensively studied along this line. Furthermore, heterogeneous nitroxide-based catalysts, that might be useful for industrial applications, have gained high visibility.[9]

A first metal-free aerobic oxidation protocol, which uses TEMPO as a catalyst and $NaNO_2/Br_2$ as cooxidants, was reported in 2004.[10] $NaNO_2$ acts as a precursor for nitric oxide which is rapidly oxidized by dioxygen to generate nitrogen dioxide. NO_2 reacts with HBr to regenerate bromine that oxidizes TEMPO to its *N*-oxoammonium bromide salt and HBr. The oxoammonium salt is capable of oxidizing the substrate alcohol. However, the use of bromine and the formation of HBr during oxidation make this and related protocols less attractive for industrial applications.[11] Nevertheless, the use of $NaNO_2$ in these aerobic oxidation processes has found high impact and several variants of that protocol have been developed.[12] To simplify the complicated four-component catalytic system, other sources for nitric oxide have been found. For example, *tert*-butyl nitrite (TBN) was shown to be an efficient additive for alcohol oxidation in combination with TEMPO and dioxygen.[13] Furthermore, the application of hydroxylamine as an NO source was reported very recently.[14] $KBrO_3$ was used to generate both NO_2 and NO from hydroxylamine hydrochloride. The bromate is decomposed to bromide anions providing all necessary components for the generation of *N*-oxoammonium bromides. However, corrosive by-products are formed using this protocol.

Herein we report a new catalyst system for the aerobic alcohol oxidation that uses TEMPO and an aqueous solution of hydroxylamine as catalysts without any other additives (Scheme 1). It is important to note that corrosive HBr is not formed during alcohol



Scheme 1. TEMPO-catalyzed aerobic alcohol oxidation in the presence of hydroxylamine.

oxidation and water is the only side product in these reactions.

Based on our observation that TEMPO is reduced to its corresponding hydroxylamine in the presence of hydroxylamine, we thought that NH_2OH might act as a clean source for NO upon reaction with TEMPO.

First experiments were performed in dichloromethane at room temperature using benzyl alcohol as a test substrate.

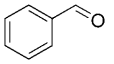
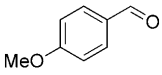
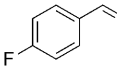
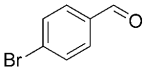
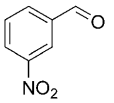
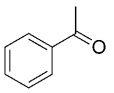
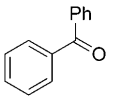
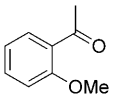
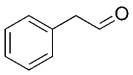
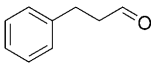
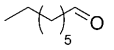
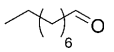
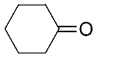
We found that with 40 mol% of TEMPO and 40 mol% of an aqueous solution of hydroxylamine (50 wt%) under an atmosphere of O_2 (balloon technique) at room temperature, benzaldehyde was quantitatively formed within 12 h. In α,α,α-trifluorotoluene, or a mixture of acetonitrile and water (3:1), or an aqueous phosphate buffer, the oxidation did not work. Benzaldehyde was formed quantitatively using 1,2-dichloroethane (DCE) as a solvent under otherwise identical conditions. In refluxing DCE the reaction time was decreased to 4 h (100% conversion). Surprisingly, the oxidation did not proceed efficiently using hydroxylamine hydrochloride and NEt_3 in place of salt-free aqueous hydroxylamine as additives.

Unfortunately, lowering the amount of catalysts led to a significantly reduced yield. For example, using TEMPO (5 mol%) and NH_2OH (10 mol%), catalysis stopped at low conversion (13%). At this place we have to mention that all initial reactions were conducted in Schlenk flasks using balloon technique. The head space of the reaction mixture was exchanged several times by flushing dioxgen through the flask.

We made the important observation that, in some cases, results using this experimental set-up were not reproducible. We believed that this was due to the fact that the catalytically active NO and NO_2 (see discussion on the mechanism below) were removed from the reaction mixture while flushing the head space with O_2. Therefore, we decided to continue our optimization studies in a stainless steel autoclave to prevent leakage of NO and NO_2. A constant O_2 pressure of 3 bar was used in most experiments.

To our delight, with 1 mol% TEMPO and 4 mol% hydroxylamine near quantitative benzaldehyde formation at 80 °C for 4 h was achieved (Table 1, entry 1). TEMPO could be replaced by the less expensive 4-acetamido-TEMPO without affecting the yield. The O_2 pressure seemed not to influence reaction outcome to a large extent, since full conversion was also achieved with 2 or 4 bar of dioxygen under otherwise identical conditions. A further lowering of the TEMPO loading to 0.5 mol% in combination with 4 mol% of NH_2OH did not allow for quantitative oxidation (64%). Moreover, using 1 mol% of TEMPO and 2 mol% of NH_2OH, conversion was also not complete (83%). The electron-rich *para*-methoxybenzyl alcohol was quantitatively oxidized under optimized conditions (entry 2). However, benzyl alcohol derivatives bearing electron-withdrawing substituents were less reactive and TEMPO loading had to be increased to 2 mol% in order to reach full conversion (entries 3–5). Under the same conditions, secondary benzyl alcohols were quantitatively oxidized to the

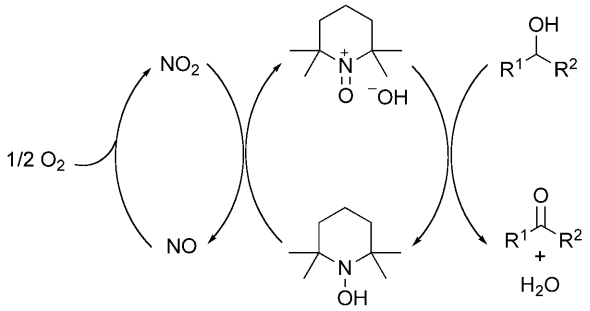
Table 1. TEMPO/NH_2OH-catalyzed aerobic oxidation of alcohols.[a]

Entry	Product	TEMPO [mol%]	NH_2OH [mol%]	Time [h]	Yield [%][b]
1		1	4	4	100[c] (97)
2		1	4	4	100 (97)
3		2	4	4	100 (95)
4		2	4	4	100 (98)
5		2	4	4	100 (99)
6		2	4	6	100 (94)
7		2	4	6	100 (97)
8		2	4	6	100 (99)
9		4	6	3	91 (63)
10		4	6	6	100[c] (91)
11		4	6	6	100 (87)
12		4	6	6	100 (90)
13		4	6	8	40 (21)

[a] All reactions carried out on a 20 mmol scale of the corresponding alcohol in DCE at 80 °C and a pressure of 3 bar of O_2.

[b] GC conversion (isolated yield).

[c] Full conversion was also achieved using 4-acetamido-TEMPO as the nitroxide catalyst.



Scheme 2. Catalytic cycle.

corresponding ketones (entries 6–8). As expected, aliphatic alcohols, such as 2-phenylpropan-1-ol, were more difficult to oxidize. We found that 4 mol% of TEMPO and 6 mol% of NH_2OH were necessary for high conversion (entry 9). With this substrate we noted oxidative C–C bond cleavage of phenylacetaldehyde to benzaldehyde under the applied conditions. Therefore, reaction was stopped at 91% conversion (3 h). Transformation of phenylacetaldehyde to benzaldehyde has been reported.[15] Other primary aliphatic alcohols were cleanly oxidized within 6 h (entries 10–12). Under these conditions, oxidation of secondary alcohols as exemplified for cyclohexanol was not efficient (entry 13).

We suggest the following catalytic cycle for oxidation of alcohols under the applied conditions (Scheme 2). NO is probably generated by oxidation of H_2NOH with TEMPO *via* H-transfer reactions to give TEMPOH. Reaction of NO with O_2 provides NO_2,[13] which reacts with TEMPOH to give NO and the TEMPO oxoammonium salt. This salt then reacts with the substrate alcohol to give the corresponding aldehyde or ketone.[1] Environmentally friendly water is the sole by-product formed in this process.

TEMPO has a dual role in our proposed catalytic cycle: a) it acts as an oxidant to generate the active cooxidant (NO) and b) it acts as precursor for the *N*-oxoammonium cation. We were able to qualitatively prove the formation of nitric oxide in the reaction of TEMPO with hydroxylamine by running the TEMPO-mediated hydroxylamine decomposition in the presence of 2,3-diaminonaphthalene (DAN). DAN is a well accepted probe for nitric oxide, mostly applied in biochemistry.[16] Upon treatment with nitrosating agents in acidic media, DAN is smoothly converted to the highly fluorescent 2,3-naphthotriazole (NAT).[17] Indeed, small amounts of NAT were formed when DAN was added to a solution of TEMPO and hydroxylamine in dichloromethane at room temperature under an oxygen atmosphere. Analysis by ESI-mass spectrometry and fluorescence spectroscopy unambiguously confirmed the formation of NAT.

In summary, we have reported a new catalyst system for the TEMPO-catalyzed aerobic oxidation of alcohols. The process uses commercially available catalysts, namely TEMPO and aqueous hydroxylamine. Various primary and secondary alcohols can be oxidized with this procedure. No corrosive acids are generated during oxidation and water is the only side product formed.

Experimental Section

General Remarks

All autoclave reactions were performed in a stainless steel autoclave (Roth high pressure laboratory autoclave model 2 equipped with two needle valves for charging and depressurization) with an operating volume of 300 mL. Dichloromethane (DCM) was freshly distilled from P_2O_5 under an argon atmosphere. 1,2-Dichloroethane (DCE, 99.8+%, extra pure) was purchased from Acros Organics and was used as received. Hydroxylamine solution (50 wt% in H_2O, 99.999%) was purchased from Sigma Aldrich and was used as received. All other chemicals were purchased from Sigma Aldrich, Acros Organics, and Fluka and were used as received. Gas chromatography (GC) was performed on a Hewlett Packard 6890 chromatograph equipped with a HP-5 column (30 m × 0.32 mm, film thickness 0.25 μm) using H_2 (*ca.* 1 bar) as carrying gas. GC/MS (EI, 70 eV) was performed on a combined set-up of an Agilent 6890N chromatograph equipped with a HP-5 column using helium (*ca.* 1 bar) as carrying gas and a Waters-Micromass Quattro Micro spectrometer. ^{1}H NMR (300 MHz) spectra were recorded on a Bruker DPX 300 spectrometer. HR-MS ESI (*m*/*z*) were recorded on a Bruker MicroTof or an Orbitrap LTQ XL (Nanospray) of Thermo Scientific. Fluorescence emission spectra were recorded on an AMINCO-Bowman Series 2 (AB2) spectrometer of Thermo Fisher Scientific Inc. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates; detection with UV light or by dipping into a solution of $KMnO_4$ (1.5 g) and $NaHCO_3$ (5.0 g) in H_2O (0.40 L) followed by heating. FC was carried out on Merck silica gel 60 (40–63 μm) with an argon excess pressure of about 0.4 bar.

Typical Procedure for Alcohol Oxidation

Oxidation of benzyl alcohol: Benzyl alcohol (2.07 mL, 20.0 mmol, 1 equiv.) was added to a glass barrel equipped with a stirring bar and dissolved in DCE (20 mL). After addition of TEMPO (31.3 mg, 0.200 mmol, 1 mol%) and a solution of NH_2OH (53 μL, 0.80 mmol, 4 mol%, 50 wt% in H_2O) the barrel was quickly embedded into a stainless steel autoclave which was instantaneously closed and charged with dioxygen (3 bar). The reaction mixture was then vigorously stirred (1500 rpm) at 80 °C for 4 h. After cooling to room temperature, careful depressurization and GC analysis, the solvent was removed under reduced pressure to afford after purification by FC (SiO_2) benzaldehyde which was analyzed by ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.02$ (s, 1H, CH), 7.95–7.83 (m, 2H, aryl-H), 7.70–7.58 (m, 1H, aryl-H), 7.58–7.47 (m, 2H, aryl-H). Spec-

troscopic data are in agreement with those reported in the literature.[18]

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