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A convenient alternative for the selective oxidation of alcohols by silica supported TEMPO using dioxygen as the final oxidant

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ABSTRACT

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Various primary and secondary alcohols were selectively oxidized to the corresponding aldehydes and ketones using silica supported TEMPO as a heterogeneous catalyst and nitrosonium tetrafluoroborate as a cocatalyst. No over-oxidation of aldehydes to acids, nitration processes or oxidation of double bonds was observed. The reported procedure is very convenient, and uses mild experimental conditions (room temperature and dioxygen as the terminal oxidant). Furthermore, the reactions proceeded cleanly and the isolation of the desired compounds required minimal work-up. A mechanistic pathway has been proposed, in which nitrogen oxides and oxoammonium ions act as an electron transfer double bridge.

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1

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1. Introduction

Oxidation processes often require harsh experimental conditions, involving transition metals and strong acids.¹ The oxidation of alcohols leads in the first step to the formation of the corresponding aldehydes or ketones and in the second step aldehydes can be converted into carboxylic acids by common oxidants, including air. Frequently, alcohol oxidation cannot be stopped at the carbonyl derivative, therefore selective oxidation methods are highly desirable.² Many syntheses of medicines or other fine chemicals require aldehydes and ketones as intermediates ³ and there is a high demand for specific aldehydes and ketones: for example, menthone and octanal are used in the fragrance industry, while cyclohexanone is a precursor in the plastic industry.

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Tetrahedron Letters

Jones reagent (CrO₃, aq. H₂SO₄) and pyridinium dichromate (*Cornforth reagent*, PDC) are some of the most used oxidants. Because a stoichiometric amount of reagents is needed to convert primary alcohols into aldehydes,¹⁻⁴ isolation of the desired compound from the reaction mixture requires extensive work-up and generates a large amount of toxic chemical waste. Nowadays the literature data is rich in novel methods using transition-metal-free aerobic oxidation, i.e. those involving hypervalent iodine compounds (*Dess-Martin oxidation*), oxalyl chloride/DMSO (*Swern oxidation*), sodium hypochlorite, nitric acid or its salts, and nitroxide free radicals.¹⁻¹⁰



Figure 1. Acid-base and redox processes of TEMPO free radical (H may stand also for $H^+ + e^-$).

One of the commonly used compounds for oxidation is the stable free radical 2,2,6,6-tetramethylpiperidinyloxy (TEMPO).¹¹⁻ Although it possess an unpaired electron, this chemical is

5

stable under normal conditions, and does not dimerize or react with dioxygen from the air. This free radical can be involved in acid-base and redox type processes, as shown in Figure 1. The oxoammonium salt of TEMPO is also well known as a strong yet specific oxidant.¹⁵

On the other hand, TEMPO is often used in combination with transition metals and seldomly with metal-free cocatalysts. For example, copper, iron, manganese and silver have commonly been used as transition metal cocatalysts,¹⁶⁻¹⁹ while halogens and/or acids have been employed in the metal-free systems.^{20,21} Furthermore, iron oxide nanoparticles together with TEMPO (free or covalently attached) were employed as catalytic systems for the oxidation of benzylic alcohols.²²⁻²⁴

A breakthrough in such systems was the use of nitrogen oxides as mediators between dioxygen and TEMPO.^{6,11,13,20,25,26} Initially, NO_x was obtained in situ from sodium nitrite and acetic acid, but the drawbacks associated with removing acetic acid from the reaction led to the use of gaseous NO_x. However, working with gaseous NO_x represents a problematic issue from a practical point of view. This inconvenience was recently overcome by our group by absorbing gaseous NO_x onto silica supported TEMPO, thus yielding as an easily handled solid catalyst which does not require either an additional cocatalyst or acid.²⁶ Bobbitt's (4-acetamido-2,2,6,6an salt tetramethylpiperidine-1-oxoammonium tetrafluoroborate),² a inexpensive TEMPO derivative, can be easily prepared in a green manner, using water as the solvent and minimising the use of environmentally unfriendly materials. Such oxoammonium salts are metal-free, nontoxic and, after use, the spent oxidant can be recovered and reused, thereby making the process recyclable.²⁷

Heterogeneous catalysts are preferred in large scale or industrial applications. Therefore, in this work we continue our research into conducting practical oxidations of different types of alcohols employing new NO_x and TEMPO based systems. The newly developed metal-free system employing commercially available silica supported TEMPO as the catalyst and a nitrosonium tetrafluoroborate cocatalyst could be used under very mild reaction conditions to obtain a variety of aldehydes or ketones in high yields.

 Table 1. Oxidation of various alcohols using silica supported TEMPO as a catalyst and nitrogen dioxide or nitrosonium tetrafluoroborate as a cocatalyst

Entry	Substrate	Product	Cocatalyst	Molar ratio: substrate/ catalyst/ cocatalyst	Time (h)	Yield (%)
1			NO ₂	1/02/02	4	8
2			1102	1/ 0.2 / 0.2	16	40
3	-он			1/ 0.1 /0.1		8
4			$NO^+BE_4^-$	1/ 0.2 /0.1	4	18
5			110 214	1/0.1/0.2		18
6				1/ 0.2 /0.2		97
8	ОН /	$ \sim $	NO_2	1/ 0.2 /0.2	4 16	
9			NO^+BF_4	1/ 0.2 /0.2	16	50
10	Сон	\square	NO ₂	1/ 0.2 /0.2	16	9
11		∽ó °õ	$NO^{+}BF_{4}^{-}$	1/ 0.2 /0.2	16	27
12	ОН		NO ₂	1/ 0.2 /0.2	4	0
13					16	1
14	\sim	\sim	$NO^+BF_4^-$	1/ 0.1 /0.1	16	25
15			no Br4	1/ 0.2 /0.2	16	38
16	\sim	\sim	NO_2	1/0.2/0.2	4	40
17			1.02	1, 0.2, 0.2	16	60
18			$NO^+BF_4^-$	1/ 0.2 /0.2	16	93
19		H	NO ⁺ BF ₄	1/ 0.2 /0.2	4	99
17					·	
20		0 H H			16	90
21	OHOH		NO ⁺ BE/ ⁻	1/02/02	1	73
22			NO DI ₄	1/ 0.2/0.2	2	92
23	CH3	CH3	$NO^+BF_4^-$	1/ 0.2 /0.2	1	100
24				1/ 0.1 /0.1	2	100
25	OH		$NO^{+}BF_{4}^{-}$	1/ 0.2 /0.2	1	50
26					2	67
27			NO_2	1/0.1/0.1	72	99
28	он но		$NO^+BF_4^-$	1/ 0.2 /0.2	16	99

General conditions: DCM (5 mL), room temperature, dioxygen (balloon), isolated yield.

2. Results and discussion

As part of our interest in organic reactions mediated by stable free radicals, we continued our studies aimed at finding improved and cost-effective strategies for the selective oxidation of a range of different alcohols (primary, secondary, aliphatic, aromatic, and cyclic) to the corresponding aldehydes and ketones.

We started this study with the previously described catalyst $(NO_2 \text{ on silica supported TEMPO)}$,²⁶ and employing more complicated substrates, known for their lower reactivity and containing moieties that were also suitable for oxidation such as double bonds (Table 1). Besides the previously explored activated phenyl alcohols the types of alcohols used was enlarged from simple ones (1-octanol or cyclohexanol) to steroids (i.e. testosterone) or hetero-alcohols (furan and pyridine derivatives).

Previously used activated alcohols (benzylic alcohol, 1phenylethanol and diphenylcarbinol) afforded the corresponding aldehyde and ketones in over 90% yields after 24 h using NO₂ as a cocatalyst).²⁶ Using nitrosonium tetrafluoroborate as a cocatalyst, similar results were obtained in much shorter times: 92% for benzaldehyde (Table 1 Entry 22, 2 h), 100% for acetophenone (Entry 24, 1 h), and 67% for diphenylketone (Entry 26, 2 h).

Encouraged by these results, we attempted to extend the process to a wider range of alcohols. Initially, a series of reactions were performed using cyclohexanol, menthol, furfuryl alcohol and 1-octanol, using both NO_2 and nitrosonium tetrafluoroborate as a cocatalyst. Different ratios between substrate, catalyst and cocatalyst were studied, as well as different reaction times. As a general rule, longer reaction times as well as increased amounts of catalyst or cocatalyst improved the yields of oxidation (Table 1).

Interestingly, nitrosonium tetrafluoroborate appeared to be a far better cocatalyst than NO₂. In the case of cyclohexanol, after 4 h, the reaction using NO₂ proceeded to only 8% conversion into cyclohexanone (Entry 1), while nitrosonium tetrafluoroborate gave a yield of 97% (Entry 6). For menthol, no oxidation was observed in the case of NO₂ (Entry 7), even after 16 h (Entry 8), while nitrosonium tetrafluoroborate gave menthone in 50% yield after 16 h (Entry 9). Similar results were obtained for furfuryl

Tetrahedron

alcohol, where the yield increased from 9% (Entry 9) to 27% (Entry 10), and for 1-octanol where the yield increased from 1% to 38% (Entries 13 and 15). As no side reactions were noticed, we proposed that a slow conversion took place. It was previously noted that TEMPO was not a good catalyst for the oxidation of aliphatic alcohols, and an AZADO free radical, a less hindered nitroxide with an adamantane-like structure and hence being more reactive, needed to be used for better results.^{20,21}

Using more complicated substrates, the same trend was observed with yields over 90% (Entry 18, 93%; Entry 19, 99%). The same result was obtained in the case of a dialcohol (yield 99%, Entry 27 and 28).

Silica is a very good support for TEMPO, as it is stable over a wide pH range and can be easily modified using silica-coupling reagents. Additionally, it is a solid that can be simply recovered and used repeatedly. Previously it was shown that the silica supported TEMPO/ NOx system could be used in a second oxidation reaction without the need to be reactivated by passing through nitrogen dioxide, but its efficiency decreased, requiring longer reaction times.²⁶ The efficiency of the recycled silica supported TEMPO in the new system remained very similar to fresh catalyst, requiring only the addition of nitrosonium tetrafluoroborate.

As a model we reproduced Entry 23 and recycled the catalyst (Figure 2). Notably, after 4 reactions, the silica supported TEMPO kept its original activity. However, after the 4th reaction the yield fell below 70% and the catalyst needed to be restored by washing with water or methanol. This loss of activity was probably due to the accumulation of solid residues on the silica (i.e. tetrafluoroborate salts) that were not removed by washing with DCM, but were more easily soluble in water or methanol. No TEMPO leaking from the silica was observed by TLC or ESR. The simple separation of the solid heterocatalyst from the reaction process and its high activity during reuse represents an economic improvement

Literature data generally shows two types of mechanisms for such selective oxidations mediated by TEMPO, involving two different pathways: i) *in situ* generation of the oxoammonium cation,^{5,20} and ii) a complicated cooperative redox mechanism involving transition metals.²⁸ A simple method to determine the correct mechanism is to compare the redox potential of the TEMPO⁺/TEMPO couple with the involved partner oxidant used as a cocatalyst. However, this cannot be taken as absolute proof because the metal ion can alter the reactivity of the TEMPO free radical.²⁹

For the first pathway, it is compulsory to conduct the reaction in the presence of an oxidant which is able to convert the nitroxide free radical into its oxoammonium cation. If the cocatalyst cannot directly oxidize TEMPO (i.e. copper salts), a complicated concerted two-electron alcohol oxidation takes place. Very recently, this issue was resolved, reconciling a collection of diverse and seemingly contradictory experimental and computational data reported previously in the literature.²⁸



Figure 2. Efficiency of the recovered catalyst (Entry 23). Grey columns- after washing with DCM. Black column- after washing with water.

Nevertheless, in our case, the oxoammonium cation is the intermediate oxidant, as the NO⁺/NO redox pair in the presence of TEMPO has been proven to be able to oxidize alcohols in an anaerobic system.⁹ Therefore, nitrosonium tetrafluoroborate oxidizes TEMPO into the corresponding oxoammonium cation, yielding NO at the same time (Scheme 1).



Scheme 1. Proposed mechanism involving TEMPO and NO_x species

NO reacts easily with dioxygen yielding nitrogen dioxide. It is worth mentioning that dioxygen, nitrogen oxide and nitrogen dioxide are all stable free radicals, as they contain in their molecule an unpaired electron. Nitrogen dioxide oxidises TEMPOH to TEMPO in a first step; of course, it is also possible for this to oxidize TEMPO to TEMPO⁺, thus reforming the active oxidant species. The NO/NO₂ and TEMPO⁺/TEMPO cycles represent two active catalytic processes, acting as an electron transfer double bridge. On the other hand, dioxygen is the final oxidant and water the by-product of oxidation (Scheme 1). The solid TEMPO catalyst operates as a trap for NO_x, and these represent the species that activate dioxygen.^{26,30}

Overall, the catalytic system involving NO_x as an unconventional oxidant is a very promising alternative for the oxidation of a broad array of alcohols with minimal workup.

3. Conclusions

Silica immobilized TEMPO as a catalyst in conjunction with nitrosonium tetrafluoroborate as cocatalyst was shown to selectively convert a wide range of alcohols into the corresponding aldehydes or ketones. The process minimizes the drawbacks of classical oxidation systems (acidic media, halogens, transition metals, or gaseous nitrogen oxides), proceeding at room temperature under metal, acid and halogen free conditions. Dioxygen is the final oxidant and water is obtained as a by-product. The solid catalyst can be easily recovered and reused directly. This system, which is the first time that nitrosonium tetrafluoroborate has been used as a cocatalyst, represents a good alternative for selective alcohol oxidation.

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4

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Supplementary Material

Experimental details and typical NMR spectra of the reaction products.

Graphical Abstract



6

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Highlights:

- Unconventional oxidation of alcohols to the corresponding aldehydes or ketones; •
- Clean reactions with minimal work-up in high yields, at room temperature; •
- Supported TEMPO free radical as heterogeneous catalyst;
- First time nitrosonium tetrafluoroborate used as cocatalsyt; •
- Mechanistic pathway involves nitrogen oxides and oxoammonium ions. •