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A Versatile and Highly Selective Hypervalent Iodine (III)/ 2,2,6,6-Tetramethyl-1-piperidinyloxyl-Mediated Oxidation of Alcohols to Carbonyl Compounds

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Catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) are used in combination with [bis(acetoxy)iodo]benzene (BAIB) as a stoichiometric oxidant in the conversion of primary and secondary alcohols to carbonyl compounds. This procedure works efficiently at room temperature in almost all common solvents and neat in some cases. This process exhibits a very high degree of selectivity for the oxidation of primary alcohols to aldehydes, without any noticeable overoxidation to carboxyl compounds, and a high chemoselectivity in the presence of either secondary alcohols or of other oxidizable moieties. This procedure allows an easy, convenient, high-yielding method for the oxidation of alcohols starting from commercially available compounds.

Introduction

In the last decade there has been increasing interest by organic chemists in the oxidizing properties of hypervalent iodine compounds.[1] Various iodo(V)-based reagents, the 12-I-5 Dess−Martin periodane (DMP, 1,1,1-triacetoxy-1,1-dihydro-1,2-benzodoxol-3*H*-one)[2] and its direct precursor the 10-I-4 iodinane oxide (IBX, 1-hydroxy-1,2- benzodoxol-3*H*-one 1-oxide, *o*-iodoxybenzoic acid),[3] have been utilized for the efficient oxidation of alcohols to carbonyl compounds. Although the dehydrogenating properties of the 10-I-3 derivatives (BTIB, [bis(1,1,1-trifluoroacetoxy)iodo]benzene; BAIB, [bis(acetoxy)iodo]benzene)[1e,f] have been demonstrated in a number of cases, only a few selective examples describe the oxidation of alcohols.[4] Due to the permanent demand of selective methods for synthetic chemists, protocols for the oxidation of alcoholic moieties able to discriminate between various functional groups remain a challenge. Recently *N*-oxoammonium salts have been demonstrated to be useful reagents for the transformation of alcohols.[5] They have been used stoichiometrically either in isolated form[6] or generated *in situ* via acid-catalyzed dismutation.[7] A number of oxidants, including *m*-chloroperbenzoic acid,[8] high-valent metal salts,[9] sodium bromite,[10] sodium or calcium hypochlorite,[11] *N*-chlorosuccinimide,[12] and electrooxidation,[13] have been used.

Results and Discussion

In this paper we wish to describe a novel, high-selective *N*-oxoammonium salt-based oxidation protocol, where catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) are used in combination with BAIB as stoichiometric oxidants (Scheme 1).[14] This procedure works

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Table 1. Oxidation of Alcohols with BAIB/TEMPO

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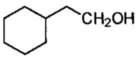
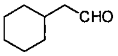
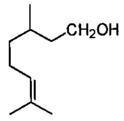
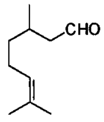
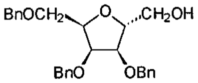
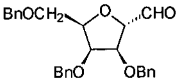
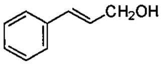
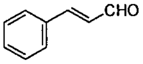
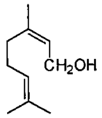
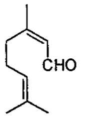
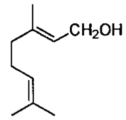
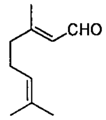
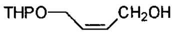
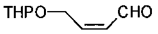
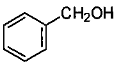
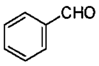
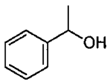
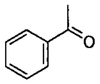
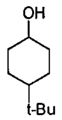
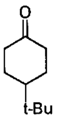
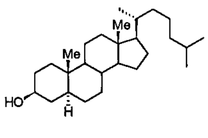
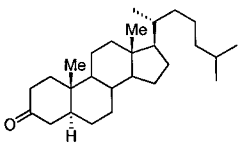
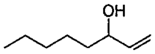
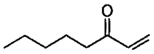
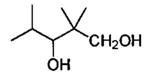
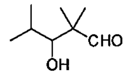
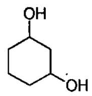
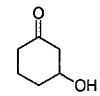
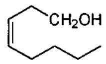
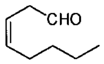
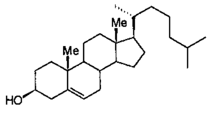
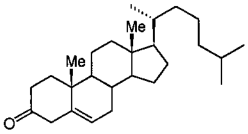
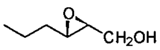
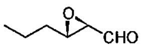
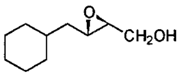
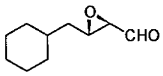
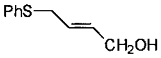
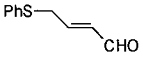
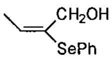
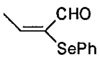
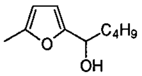
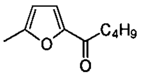
1			2.5	80
2			0.5	90
3			15	75
4			1	95
5			1.5	95
6			0.1	95
7			0.2	95[b]
8			0.5	95
9			1.5	95
10			7	90
11			5	80
12			2.5	95
13			2.5	70
14			8	90
15			2.5	95
16			5	80
17			1	70
18			2	75
19			1	70
20			15	55
21			3	95

[a] The reported yields refer to isolated, chromatographically pure or recrystallized compounds. All the structures have been confirmed by IR, ^{1}H-NMR, and ^{13}C-NMR analysis. [b] Solvent: CH_3CN/aqueous buffer, pH 7 (1/1).

Scheme 1. Oxidation of Alcohols with BAIB/TEMPO

$$PhI(OAc)_2 + RR'CHOH \xrightarrow[CH_2Cl_2]{\text{TEMPO (cat.)}} PhI + RR'CO + 2\,AcOH$$

efficiently at room temperature in CH_2Cl_2 (and also in almost all common solvents and neat in some cases)[15] at high concentrations (>1 M) and can be performed in an open flask without any particular precaution, *e.g.*, inert atmosphere or dry solvent. Under these conditions primary alcohols (Table 1, entries 1−3) are oxidized in less than 2 h to the corresponding aldehydes without any noticeable overoxidation to the carboxylic acids, even with an excess of BAIB. No oxidation process was observed in the absence of the TEMPO. Primary allylic and benzylic alcohols (entries 4−8) are rapidly oxidized to aldehydes. It should be noticed that the easily isomerizable[16] *Z* configuration of the nerol (entry 5) is recovered unchanged from the reaction medium. Secondary alcohols (entries 9−12) are oxidized to the corresponding ketones in longer reaction times. No isomerization to the α,β-unsaturated aldehydes is noted for secondary allylic alcohols.[17] 1,2-Diols are cleaved to the corresponding aldehydes;[18] meanwhile the 1,3-diols (entries 13 and 14) are converted to 1,3-hydroxycarbonyl compounds. Since acetic acid is developed during the reaction, the oxidation of alcohols with acid labile groups is an important target. Homoallylic substrates (entries 15 and 16) are cleanly oxidized to the corresponding carbonyl compounds without transposition of the double bond to the conjugated position. The optically pure 2*S*,3*R* epoxides (entries 17 and 18), prepared according to the Sharpless protocol,[19] are rapidly oxidized to epoxy aldehydes in high yields, without epimerization at the C2 carbon.[20] Under the standard reaction conditions, entry 7 undergoes a furanization process; however, performing the reaction in a 1/1 CH_3CN/aqueous buffer at pH 7 solvent mixture, the corresponding aldehyde is recovered in excellent yield, without *E*−*Z* isomerization.[21] Selenium or sulfur functional groups have been reported to be oxidized by both iodine(III)[4c,22] compounds and TEMPO/primary oxidant systems.[5] Our reactive system exhibits high chemoselectivity toward the alcoholic moiety even in the presence of these heteroatoms (entries 19−20). We have already

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[15] When the alcohol is liquid the reaction can be performed without any solvent under strong agitation at 0 °C. Benzyl alcohol, 1-phenylethanol, and geraniol were efficiently oxidized under this condition.

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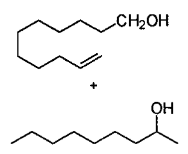
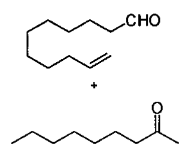
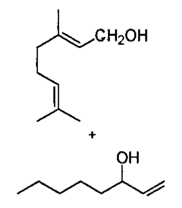
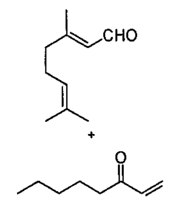
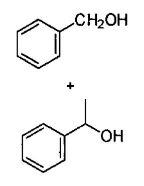
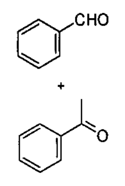
Table 2, Oxidations of Primary Alcohols in the Presence of Secondary Alcohols[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1			0.5	>99 Not detectable
2			0.1	>99 Not detectable
3			0.5	>99 Not detectable

[a] The reactions were carried out on a 1:1 mixture of primary and secondary alcohols, on a 1 mmol scale. [b] The yields were determined by ^{1}H-NMR spectroscopy and confirmed by GC analysis.

Table 3. Solvent Influence on the Reaction[a]

solvent	dielectric constant	conversion after 1 h (%)[b]
n-hexane	1.9	50
Et_2O	3.8	50
AcOH	6.4	90
CH_2Cl_2	8.9	70
pyridine	12.9	<1[c]
CH_3CN	35.9	80
DMSO	46.4	90

[a] The reactions were performed on a 1 mmol scale under standard conditions. [b] Conversions refer to 2-cyclohexylethanol and were determined by GC analysis. [c] Less than 5% after 1 week.

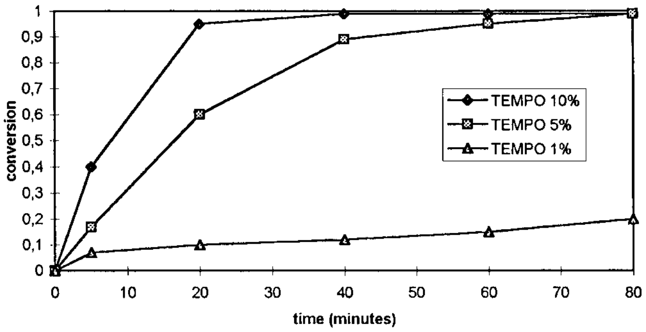
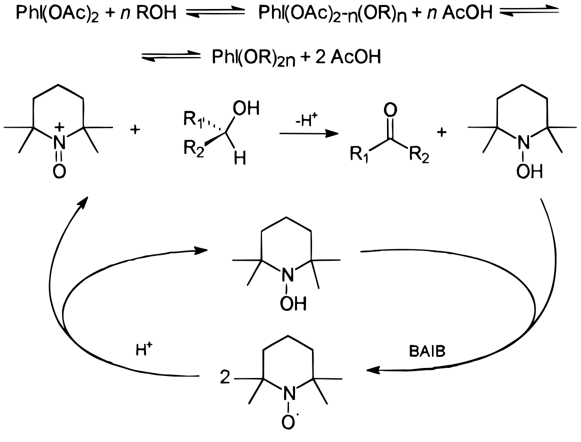


Figure 1. Catalyst efficiency. The reactions were performed on a 1 mmol scale under standard conditions. Conversions refer to benzyl alcohol and were determined by GC analysis.

Scheme 2. Proposed Reaction Pathway for the Oxidation of Alcohols with BAIB/TEMPO



reported that 1-(5-methyl-2-furyl)alcohols are smoothly converted to pyranones with BAIB.[23] Under these new reaction conditions they are selectively transformed to furyl ketones (entry 21).[24]

The different reaction rates between primary and secondary alcoholic functions suggest a possible chemoselectivity. In fact, the competing reaction of a 1:1 mixture of 10-undecen-1-ol and 2-octanol using 1 equiv of BAIB resulted in the complete conversion of the primary alcohol into aldehyde, whereas no ketone could be detected (Table 2, entry 1). The competitive oxidation of allylic and benzylic alcohols exhibits a similar degree of selectivity (Table 2, entries 2 and 3). Entry 13 (Table 1) is an example of regioselectivity between primary and secondary alcoholic functions, which is achieved in 70% yield.

Prompted by these results, we have analyzed some aspects in order to elucidate the reaction pathway. TEMPO is not directly oxidized by BAIB in CH_2Cl_2.[25] However the corresponding hydroxylamine[26] is converted to the radical. The outcome of the reaction is influenced by the dielectric constant of the medium (Table 3). The results in acetic acid and pyridine are explained by the acid-catalyzed dismutation of TEMPO,[27] favored in the former and inhibited in the latter. Analogous results are obtained with stoichiometric quantities of other organic bases. The reaction proceeds even faster when catalytic amounts of acetic acid are added.

As a result of these experimental observations and according to preceding studies, we are able to propose a possible reaction pathway. After a ligand exchange around the iodine atom,[28] the developed acetic acid catalyzes the dismutation of TEMPO to hydroxylamine and oxoammonium salt.[5] This species is responsible for the selective oxidation of alcohols while being reduced to hydroxylamine. The role of BAIB is to regenerate the TEMPO in order to close the catalytic cycle (Scheme 2). ESR studies demonstrate a direct involvement of the radical species whose signal intensity decreases during the reaction and returns to the initial value at its end.[29]

In order to elucidate the efficiency of the catalyst, we have performed the oxidation of benzyl alcohol at several concentrations of TEMPO (Figure 1). The reaction proceeds even at 10^{-2} mol equiv without any problem except for longer reaction times. This result allowed the scaling up to preparative oxidation reactions (0.1 mol).

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[29] Quantitative ESR studies will be published elsewhere in due course.

Conclusions

In conclusion we have demonstrated that the dehydrogenating properties of BAIB can be used for the TEMPO-mediated oxidation of alcohols to carbonyl compounds. This process exhibits a high degree of *selectivity for the oxidation of primary alcohols to aldehydes,* without any noticeable overoxidation to carboxyl compounds, and a high *chemoselectivity* in the presence of either secondary alcohols or other oxidizable moieties. Furthermore, the procedure reported here allows an *easy, convenient, high-yielding method for the transformation of alcohols starting from commercially available compounds.*

Experimental Section

General Experimental. ^{1}H (200 MHz) and ^{13}C (50MHz) nuclear magnetic resonance spectra were recorded at room temperature in $CDCl_3$ solutions. ESR spectra were recorded at room temperature in CH_2Cl_2 solutions. Mass spectra were obtained on a mass spectrometer using GC−MS coupling. Flash chromatography was executed with Merck Kiesegel 60 (230−400 mesh) using a mixture of ethyl acetate or methylene chloride and hexane as eluants. All commercially available reagents were purchased from Aldrich and used as received. Epoxy alcohols, 2-(phenylseleno)-2-butenal,[30] 4-(phenylthio)-2-buten-1-ol,[31] and 3β,4β-bis(benzyloxy)-5β-[(benzyloxy)methyl]-2,5-anhydro-D-talitol[32] were prepared according to cited literature procedures.

General Procedure for Alcohol Oxidations. BAIB (354 mg, 1.1 mmol) was added to a solution of alcohol (1 mmol) and TEMPO (15 mg, 0.1 mmol) in 1 mL of CH_2Cl_2. The reaction mixture was stirred until the alcohol was no longer detectable (TLC), and then it was diluted with CH_2Cl_2 (5 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography or crystallization afforded pure products.

Intermolecular Competition Experiments. The standard procedure was applied to an equimolecular mixture of primary and secondary alcohols with a stoichiometric amount of BAIB.

Oxidation Products. Aldehydes and ketones obtained by oxidation were characterized by usual spectral data and compared with the literature values.

ESR spectra. ESR spectra were recorded every 15 min on the reaction of benzyl alcohol performed on a 0.5 mmol scale under standard conditions.

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