Oxidation Reagents

Clean and Highly Selective Oxidation of Alcohols in an Ionic Liquid by Using an Ion-Supported Hypervalent Iodine(III) Reagent

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The oxidation of alcohols to carbonyl compounds plays an important role in organic synthesis, not only in the laboratory but also at the industrial level. Numerous methods are available to accomplish this conversion under various reaction conditions.[1] The demands in recent years for environmentally benign and eco-conscious chemical processes are encouraging chemists to search for clean, high-yielding, highly selective, and economical oxidation methods.[2] In the last decade, in particular, there has been increasing interest in the oxidizing properties of organohypervalent iodine reagents.[3] The extensively studied pentavalent iodine reagents, for example, Dess–Martin periodane (DMP)[4] and its direct precursor *o*-iodoxybenzoic acid (IBX),[5] oxidize alcohols efficiently to carbonyl compounds in organic solvents such as DMSO, CH_2Cl_2, and acetone. Despite their utility and popularity, these iodine(V) oxidants are potentially explosive.[2e] Thus, the readily available and stable iodine(III) oxidants such as iodosobenzene PhIO and diacetoxyiodobenzene $PhI(OAc)_2$ attract much attention. An effective and convenient polymer-supported $PhI(OAc)_2$ reagent was demonstrated by Tohma et al. for the oxidation of alcohols in aqueous media with a potassium bromide catalyst, but primary alcohols were further oxidized to carboxylic acids.[2e] Adam et al. employed Cr^{III}–salen complexes (salen = *N*,*N'*-bis[(2-hydroxyphenyl)methylene]-1,2-ethanediimine) for the selective catalytic oxidation of allylic alcohols to enones by PhIO and $PhI(OAc)_2$ in dichloromethane.[6] However, in view of the carcinogenicity of chromium compounds, environmental and health concerns greatly limit their use. Although the dehydrogenating properties of PhIO and $PhI(OAc)_2$ have been demonstrated in a few cases, only a limited number of clean and selective catalytic oxidations of alcohols to carbonyl compounds have been reported.[7]

Recently, much attention has been focused on the use of ionic liquids as environmentally benign reaction media. Various chemical reactions can be performed in ionic liquids.[8] This fact is attributed to some intriguing properties of ionic liquids, such as high thermal stability, negligible vapor pressure, high loading capacity, and tunable polarity. In view of these distinct advantages, ionic liquids have become an

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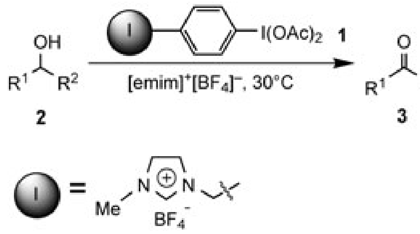
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200461889

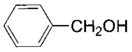
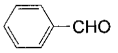
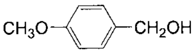
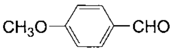
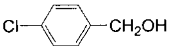
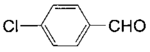
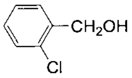
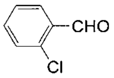
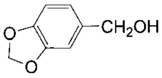
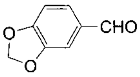
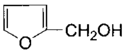
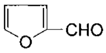
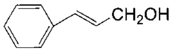
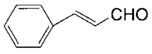
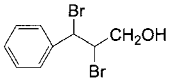
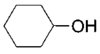
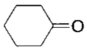
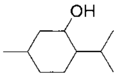
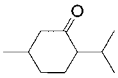
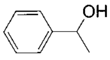
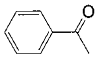
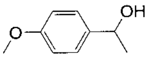
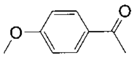
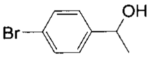
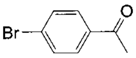
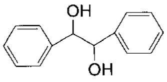
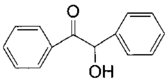
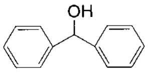
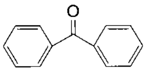
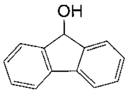
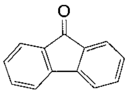
exciting area of research. More recently, ionic liquid formulations have been expanded to include ions with structurally and functionally complex side chains—the so-called "task-specific ionic liquids".[9] Miao and Chan employed ionic liquids as soluble supports for a Suzuki coupling reaction.[10] In comparison with traditional polymer supports or soluble polyethylene glycol (PEG), which has some limitations in loading capacity and solubility,[11] these low-molecular-weight ionic liquids have larger loading capacity and tunable solubility. Herein we report the preparation of 1-(4-diacetoxyiodobenzyl)-3-methylimidazolium tetrafluoroborate ($[dibmim]^+[BF_4]^-$; **1**) and its application in the oxidation of alcohols.

Compound **1** was readily synthesized by reaction of 1-methylimidazole with 4-bromomethyliodobenzene and then oxidation with peracetic acid (30% H_2O_2 and acetic anhydride). The oxidation of alcohols using $[dibmim]^+[BF_4]^-$ as an oxidant was conducted in the ionic liquid $[emim]^+[BF_4]^-$ (1-ethyl-3-methylimidazolium tetrafluoroborate; Scheme 1) in the presence of a low concentration of bromide ions under mild conditions (30 °C, a 1:1.4 ratio of substrate **2**:oxidant **1**; (Table 1).



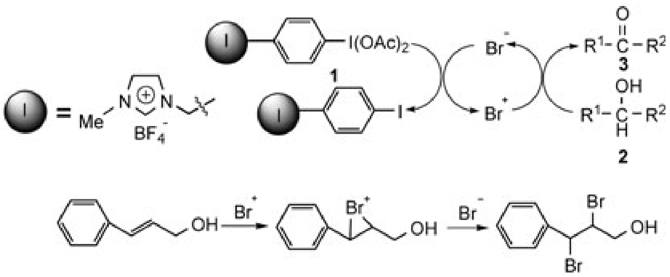
Scheme 1. Selective oxidation by $[dibmim]^+[BF_4]^-$ (**1**) in $[emim]^+[BF_4]^-$ of alcohol substrates (**2**) to give carbonyl compounds (**3**).

Table 1: Oxidation of alcohols with $[dibmim]^+[BF_4]^-$ in $[emim]^+[BF_4]^-$.

Entry	Substrate		Product		*t* [h]	Yield [%][a]
1		**2a**		**3a**	3	92[b]
2		**2b**		**3b**	3	95
3		**2c**		**3c**	3	91
4		**2d**		**3d**	3	89
5		**2e**		**3e**	3	57
6		**2f**		**3f**	3	94[b]
7		**2g**		**3g**	4	<5
				**3g′**		93
8		**2h**		**3h**	16	95
9		**2i**		**3i**	18	75[c]
10		**2j**		**3j**	4	90[b]
11		**2k**		**3k**	5	94
12		**2l**		**3l**	5	96
13		**2m**		**3m**	2	93
14		**2n**		**3n**	9	98[c]
15		**2o**		**3o**	12	98[c]

[a] Yields of isolated product after chromatographic purification unless otherwise noted. [b] Yields were determined by ^1H NMR spectrometry. [c] Ten drops of acetonitrile were added to increase the solubility of substrates.

A variety of primary and secondary alcohols were oxidized to carbonyl compounds in moderate to excellent yields at room temperature. The reactions were performed in a flask without any particular precautions. Under these conditions primary alcohols (Table 1, entries 1–6) were oxidized in less than four hours to the corresponding aldehydes in 57–95 % yields without any noticeable overoxidation to the carboxylic acids. Secondary alcohols (Table 1, entries 8–15) were oxidized to the corresponding ketones over longer reaction times except for entry 13. The oxidation was relatively sluggish (16–18 h) and needed two equivalents of oxidant for the unactivated, alicyclic substrates (Table 1, entries 8 and 9). Notably, cinnamyl alcohol (Table 1, entry 7) was mainly converted into the double-bond addition product. It has been suggested that the oxidation of alcohols is catalyzed by a small amount of bromide ion remaining in the $[emim]^+[BF_4]^-$.[12] A possible mechanism for the oxidation of alcohols with $[dibmim]^+[BF_4]^-$ is described in Scheme 2. The bromide ion present in the $[emim]^+[BF_4]^-$ seems to be oxidized by $[dibmim]^+[BF_4]^-$ to form a highly active intermediate Br^+ ion, probably in the form of acetyl hypobromite or the bromate(I) complex reported by Kirschning and coworkers,[13] which reacts with alcohols to produce the corresponding carbonyl compounds with regeneration of the bromide ion.[14] The Br^+ ion attacks a C=C bond of a substrate preferentially, so the main product from the oxidation of cinnamyl alcohol is 2,3-dibromo-3-phenylpropanol.

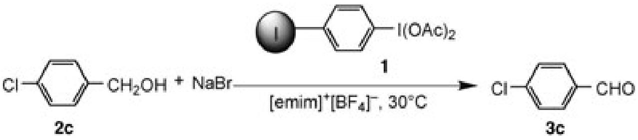


Scheme 2. A possible mechanism for the oxidation of substrates by $[dibmim]^+[BF_4]^-$.

The ionic liquid $[emim]^+[BF_4]^-$ used in the above reactions was prepared by the metathesis of 1-ethyl-3-methylimidazolium bromide with sodium tetrafluoroborate in acetone. However, this method did not remove the bromide ion completely if no further purification procedure was applied. Although the oxidation reaction proceeded in high yield, we were concerned about whether the change in concentration of the bromide ion would lead to overoxidation. Therefore, we investigated the influence of bromide ion concentration on the oxidation result. First, the concentration of bromide ion in $[emim]^+[BF_4]^-$ was measured by Volhard's procedure (Table 2, entry 2) to be 1.82–1.94 % (w/w). The ionic liquid $[emim]^+[BF_4]^-$ was then thoroughly purified through method B reported by Park and Kazlauskas.[12] In the following experiment sodium bromide was taken as the source of the bromide ion.

The oxidation of 4-chlorobenzyl alcohol (**2c**) was examined as a standard substrate while varying the bromide ion concentration from 0 to 10 % (w/w). The reaction was performed in a mixture of purified ionic liquid $[emim]^+[BF_4]^-$ (1.50 g), alcohol (0.5 mmol), and oxidant (0.7 mmol). We were pleased to find that alcohol **2c** was oxidized to aldehyde **3c** in 72–93 % yield (Table 2). A low concentration of bromide ions (Table 2, entry 3, 0.5 %) was unfavorable since it slowed down the reaction rate; the reaction was very slow in the absence of bromide ions (Table 2, entry 1). However, when 10 % of bromide ion (equal to 0.193 g NaBr) was added to 1.50 g of purified $[emim]^+[BF_4]^-$, the solid could not dissolve in the ionic liquid completely, which made the solution too thick to stir efficiently and resulted in a decreased yield. No further oxidation of 4-chlorobenzaldehyde to the corresponding carboxylic acid was observed even after the reaction times were prolonged to 24 hours. We think that in this system the ionic liquid $[emim]^+[BF_4]^-$ plays a very important role in preventing aldehydes from overoxidation to carboxylic acids.[15]

Table 2: The influence of the bromide ion concentration on oxidation.



Entry	Conc. of Br^- [% (w/w)]	t [h]	Yield [%]
1	0.0	24	84
2	ca. 1.9	3	91
3	0.5	3	72
4	1.0	3	92
5	2.0	3	93
6	5.0	3	91
7	10.0	3	83

To evaluate the performance of $[dibmim]^+[BF_4]^-$ we compared it with the widely used oxidant $PhI(OAc)_2$ in $[emim]^+[BF_4]^-$. The results (Table 3) show that the yields of alcohols using $[dibmim]^+[BF_4]^-$ are higher than those with $PhI(OAc)_2$ in the same reaction time. For the primary alcohols (Table 3, entries 1 and 2) with $PhI(OAc)_2$ as the oxidant, an electron-donating group on the aryl ring gives satisfactory yields, but an electron-withdrawing group greatly decreases the yields. Poor yields are obtained in the oxidation of secondary alcohols, which means not only electronic effects

Table 3: Comparison of $[dibmim]^+[BF_4]^-$ with $PhI(OAc)_2$ in $[emim]^+[BF_4]^-$.

Entry	Substrate	Product	t [h]	Yield with $PhI(OAc)_2$ [%]	Yield with $[dibmim]^+[BF_4]^-$ [%]
1	**2b**	**3b**	3	73	95
2	**2c**	**3c**	3	37	91
3	**2k**	**3k**	5	32	94
4	**2l**	**3l**	5	22	96
5	**2n**	**3n**	9	11[a]	98[a]

[a] Ten drops of acetonitrile were added to increase the solubility of the substrates.

(Table 3, entries 3 and 4) but also steric effects (Table 3, entry 5) significantly influence the reaction. However, both primary and secondary alcohols with electron-donating or -withdrawing groups give excellent yields with $[\text{dibmim}]^+[\text{BF}_4]^-$ as the oxidant. Pausacker measured the oxidation rates of isohydrobenzoin by aryl iodosoacetates in acetic acid and found that electron-donating groups present in the aryl moiety decrease the reaction rate, but electron-withdrawing groups increase the rate.[16] The imidazolium cation will act as an electron-withdrawing group in the $[\text{dibmim}]^+[\text{BF}_4]^-$ oxidant, and hence greatly enhance the reaction rate. Therefore, higher yields can be obtained in a shorter reaction time.

In conclusion, we have demonstrated that the dehydrogenating properties of $[\text{dibmim}]^+[\text{BF}_4]^-$ can be used for the oxidation of alcohols to carbonyl compounds. The main features of this process are: 1) a high degree of selectivity for the oxidation of primary alcohols to carbonyl compounds in an ionic liquid; 2) easy workup and environmentally benign—the ion-supported hypervalent iodine(III) reagent can be recovered and reused after oxidation with peracetic acid; and 3) notably, the aldehydes do not undergo further oxidation to carboxylic acids even at longer reaction times. Studies on applications of $[\text{dibmim}]^+[\text{BF}_4]^-$ in other reactions are in progress.

Received: September 3, 2004

Keywords: alcohols · hypervalent compounds · iodine · ionic liquids · oxidation

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