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TEMPO-Catalyzed Aerobic Oxidation of Alcohols to Aldehydes and Ketones in Ionic Liquid [bmim][PF_6]

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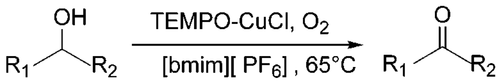
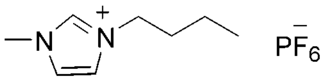
ABSTRACT



R_1= aryls, alkyls ; R_2= H, alkyls

A simple and mild TEMPO–CuCl catalyzed aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones in ionic liquid [bmim][PF_6] with no trace of overoxidation to carboxylic acids has been developed. The product can be isolated by a simple extraction with organic solvent, and the ionic liquid can be recycled or reused.

Room temperature ionic liquids are composed only of ions. They are usually salts of organic cations, and the 1-butyl-3-methylimidazolium salt **1** (Figure 1) is a representative example. They are compounds that are generally liquid at (or close to) room temperature and are highly polar yet noncoordinating. They have essentially no vapor pressure and a good thermal stability. They dissolve many organic and organometallic compounds. However, it is possible to perform a fine-tuning of their miscibility with water and common organic solvents simply by changing the length of the side chains or the nature of the organic cation and the inorganic anion. Such compounds appear very attractive as novel reaction media toward greener processes in organic synthesis.[1] Their unique properties have been already reflected by their use in a wide range of stoichiometric, as well as catalytic reactions.[1]



[bmim][PF_6]

1

Figure 1.

Oxidation of alcohols to the corresponding aldehydes and ketones is one of the most important functional group transformations in organic synthesis. Several catalytic processes using transition metal complexes have been reported using a stoichiometric amount of terminal oxidant.[2] As an alternative, TEMPO has emerged as the catalyst of choice for the mild and selective oxidation of alcohols to the corresponding aldehydes and ketones.[3,4] These transformations employed a catalytic amount of TEMPO and stoichiometric amount of terminal oxidant, but air or molecular

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(1) For recent reviews, see: (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. (c) Sheldon, R. A. *Chem. Commun.* **2001**, 2399 and references therein.

(2) For recent examples, see: (a) Miyata, A.; Murakami, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 7067. (b) Lee, M.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7507. (c) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620. (d) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766 and references therein.

(3) Semmelhack, F. M.; Schmidt, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374.

(4) (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (b) de Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974. (c) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (d) Bolm, C.; Magnus, A. S.; Hilderbrand, J. P. *Org. Lett.* **2000**, *2*, 1173. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041.

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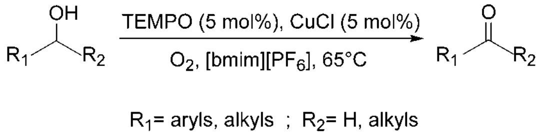
oxygen is desirable from an environmental and economic point of view to replace the chemical oxidant.

Little attention has been paid, to date, to performing catalytic oxidation in ionic liquids despite the economical importance of such reactions.[1b,c] Aerobic oxidation of aromatic aldehydes to the corresponding carboxylic acids using Ni(acac)$_2$ and O_2 in [bmim][PF$_6$]has been reported.[5] Recently it has been demonstrated that ionic liquids can be employed in the oxidation of alcohols, for the extraction and recycling of the TPAP catalyst, without significant loss of activity.[6] To be mentioned are the uses of ionic liquids in catalytic epoxidation[7,8] and their role to remove or extract excess MnO$_2$ in the oxidation of codeine methyl ether to thebaine.[9]

In continuation of our interest in the use of air- and moisture-stable ionic liquids in organic synthesis[10] and taking into account the good solubility of gases (including O_2) in these ionic solvents, it appeared to us that they should be a reaction medium of choice for aerobic oxidation. We report herein a mild and effective procedure for the oxidation of primary and secondary alcohols to the aldehydes and ketones with good to excellent conversion, using a catalyst mixture of TEMPO−CuCl[11] in 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF$_6$][12] (Scheme 1). Furthermore, we demonstrate the possibility of recycling and reuse of the ionic solvent.

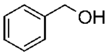
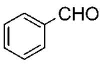
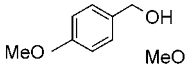
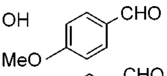
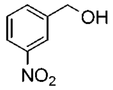
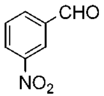
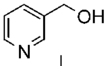
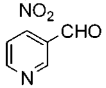
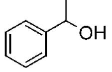
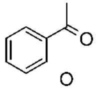
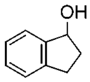
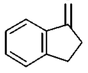
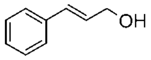
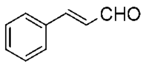
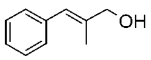
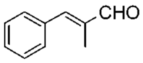
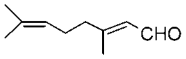
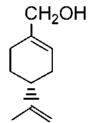
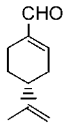
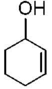
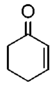
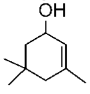
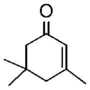
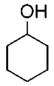
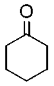
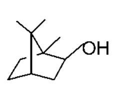
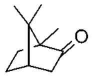
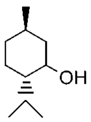
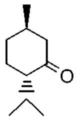
Scheme 1



As indicated in Table 1, various types of benzylic, allylic, and aliphatic alcohols, both primary and secondary, have been successfully used. The procedure is very simple, and it has to be noted that the reaction is performed directly under O_2 atmosphere. No bubbling of O_2 is necessary, and this is probably due to the good solubility of O_2 in the ionic liquid. The products were isolated by simple extraction with ether and purified by passing through short silica gel column. Reactions were monitored by GC, and no trace of overoxidation to carboxylic acid was detected.

From the data in Table 1,[13] it is clear that the conversion of benzylic and allylic alcohols to the corresponding carbonyl compounds[14] is faster and more efficient, whereas the aliphatic alcohols reacted more slowly and in a few cases the reactions were incomplete (entries 15−19). This is in agreement with reactions performed in classical organic

Table 1. Conversion of Alcohols to Aldehydes and Ketones

entry	alcohol	product	time/h	conversion[a]	yield[b]
1			15	98	72
2			9[c]	98	73
3			16	97	90
4			15	97	96
5			36	96	75
6			83	98	73
7			42[d]	98	72
8			30	96	91
9			20	98	75
10			29	97	78
11	geraniol		18	98	85
12			16	98	90
13			24	98	75
14			28	90	60
15	n-C_7H_{15}-CH_2OH	n-$C_7H_{15}CHO$	30	70	
16			60	90	
17			36[d]	98	50
18			48	30	
19			48	no reaction	

[a] GC conversion. [b] Isolated yield. [c] Reaction was carried out at 50 °C with 10% catalyst. [d] 10% catalyst was used.

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(5) Howarth, J. *Tetrahedron Lett*. **2000**, *41*, 6627.

(6) Ley, S. V.; Ramarao, C.; Smith, M. D. *Chem. Commun*. **2001**, 2278.

(7) Owens, G. S.; Abu-Omar, M. M. *Chem. Commun*. **2000**, 1165.

(8) Song, C. E.; Roh, E. J. *Chem. Commun*. **2000**, 837.

(9) Singer, R. D.; Scammells, P. J. *Tetrahedron Lett*. **2001**, *42*, 6831.

(10) Le Boulaire, V.; Gree, R. *Chem. Commun*. **2000**, 2195.

(11) It has to be noted that both TEMPO and CuCl are completely soluble in the ionic solvent [bmim][PF$_6$] under our reaction conditions (see representative experimental procedure).

(12) For the synthesis of **1**, see: Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D. *Chem. Commun*. **1994**, 299.

(13) **Representative Experimental Procedure.** A mixture of benzyl alcohol (108 mg, 1.0 mmol), TEMPO (7.8 mg, O. O5 mmol), and CuCl (4.95 mg, 0.05 mmol) in [bmim][PF$_6$] (1.5 mL) was heated at 65 °C under magnetic stirring for 15 h under O_2 (1 atm.). The reaction mixture was extracted with diethyl ether (3 × 8 mL). The ether layer was concentrated in vacuo. Filtration of the extract over short silica gel pad afforded benzaldehyde (76.5 mg, yield 72%).

solvents and was attributed to the instability of nitrosonium ion in the presence of aliphatic aldehydes and oxygen.[3] By using Mn $(NO_3)_2-Co(NO_3)_2$ or Mn $(NO_3)_2-Cu(NO_3)_2$, very low conversions (≤2%) of octanol to octanal were obtained in [bmim][PF_6], contrary to the excellent results in AcOH.[15] As expected, the conversion of secondary alcohols took a longer time as compared to primary alcohols. Cyclohexenol (entry 13) was almost inert to oxidation in DMF,[3] but in ionic liquid the conversion to cyclohexenone was found to be good. In the case of entry 19, the reaction did not proceed at all as the solubility of this alcohol was poor in the ionic solvent. The reaction time can be reduced by increasing the catalyst quantity, which was shown in entries 2, 7, and 17. The careful study of ^1H and ^{13}C NMR spectra of the ionic liquid after extraction of the product indicated no trace of the reactants and products left in the solvent, so it can be reused for different reactions.[16]

One of the main aims of using ionic liquid as reaction medium was to study the possibility of its recycle and reuse, for the same as well as different types of reactions. We found that the recycling of the ionic liquid is viable, and it was recycled for the oxidation of benzyl alcohol to benzaldehyde.[17] The reaction was carried out eight times in consecutive runs with only a slight decrease in isolated yields (Table 2).

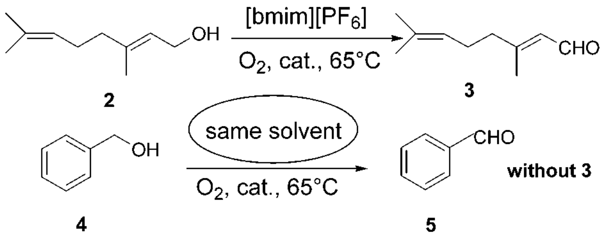
Table 2. Reuse of the Solvent for the Oxidation of Benzyl Alcohol to Benzaldehyde

	run							
	1	2	3	4	5	6	7	8
yield (%)	72	70	68	70	65	64	62	60

Furthermore, a direct distillation of the carbonyl compounds from the reaction mixture appears very attractive in the case of derivatives that are volatile enough. This was demonstrated with benzyl alcohol, affording benzaldehyde in a 76% yield (by bulb to bulb distillation in vacuo, on a 5 mmol scale). Here again, the ionic solvent could be recycled after performing simple washing with ether and then water.

In addition to the recycling of the ionic liquid for the same reaction it was also appropriate to check the viability of reusing it for different types of substrates. This was demonstrated in two different sets of reactions (Scheme 2):

Scheme 2



(i) After the oxidation of geraniol (Table 1, entry 11) to the corresponding aldehyde, the recovered solvent was reused for the oxidation of benzyl alcohol to benzaldehyde, and the ^1H, ^{13}C and GC analysis of the product indicated no contamination of the earlier product (≤2%).

(ii) This result was further confirmed by performing one more set of reactions using the recovered solvent from cinnamyl alcohol oxidation (Table 1, entry 9), and reused for the oxidation of benzyl alcohol, it gave similar results.

At this stage, it proved to be possible to recycle only the ionic solvent, and the immobilization of the catalytic system in the ionic liquid was not successful. This may be due to the decomposition of the catalyst during the oxidation[18] as well as extraction of this reagent at the end of the reaction.[19] Studies are underway to modify the catalytic system to allow for recycling.

In conclusion, we have demonstrated the efficient aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones by using TEMPO−CuCl catalyst system in [bmim][PF_6].[20] The benzylic and allylic alcohols were oxidized with excellent conversions, whereas aliphatic alcohols were slow and less reactive. The reaction conditions are simple and mild, and the solvent can be recycled and reused.

Acknowledgment. The authors thank CNRS for the award of a research associate position to I.A.A.

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[14] All of the isolated compounds (purity >98% checked by NMR and GC) have spectral data in agreement with the literature. Furthermore, in all cases except entries 8, 10, and 15 where the compounds were not readily available, all carbonyl derivatives have shown identity (GC, NMR) with authentic samples.

[15] Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett*. **2001**, *42*, 6651.

[16] It has to be noted that in the NMR spectra of **1** large areas are available to detect the reaction products. For instance, when using ^1H NMR (in acetone-d_6) the zone between 4.5 and 15 ppm is very convenient since **1** has only three sharp singlets at 7.6, 7.7, and 8.8 ppm corresponding to the imidazolium protons. Similarly, in the ^{13}C NMR spectrum between 50 and 250 ppm there are only three peaks at 123.2, 124.5, and 137.2 ppm corresponding to the imidazolium carbons.

[17] After the extraction, the ionic solvents was washed with water (10 mL) and dried at 70 °C for 7 h under high vacuum before next run.

[18] GC analysis of the reaction mixture at different intervals showed a slow degradation of the catalyst (TEMPO).

[19] The catalyst being extracted along with the product, after three extractions the ionic liquid was left with no trace of catalyst.

[20] Furthermore, it has to be noted that this reaction can be performed directly in air atmosphere. However, in that case the reaction is slower: under similar conditions it took 45 h for the oxidation of benzyl alcohol to benzaldehyde instead of 15 h in O_2 atmosphere (Table 1).