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A novel method for the synthesis of 2-imidazolones

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ABSTRACT

The superoxide ion electrochemically generated by reduction of oxygen, or chemically generated by dissolving potassium superoxide in ionic liquids, reacts with alkyl imidazolium cations of imidazolium-based ionic liquids at room temperature and atmospheric pressure to give the corresponding 2-imidazolones in excellent yields.

2-Imidazolones, for example, 1-butyl-3-methylimidazolone, are useful as intermediates for polymers, agrochemicals, and pharmaceutical compounds.[1] In addition, they possess interesting biological activities. Several derivatives of 2-imidazolone are biotin antagonists in biological systems, amongst which are compounds capable of inhibiting the growth of malignant tumors.[2] Moreover, some 2-imidazolone compounds are anti-inflammatory agents and are useful for the treatment of dermatitis, inflammation of joints, and similar conditions which are usually responsive to known anti-inflammatory agents. They also possess antipyretic and analgesic properties and are thus particularly useful in the treatment of inflammatory conditions in which an increase in body temperature and pain, or excessive discomfort are present. These compounds appear to be well tolerated and do not cause undesirable side effects such as allergic reactions.[3]

The simple heterocycle, 1,3-dihydro-2*H*-imidazol-2-one has proved to be a promising building block for 1,2-diamine skeletons,[4] which are found as structural units in bioactive compounds of medicinal interest,[5] and chelating ligands for metal catalysts.[6] Seo et al. reported on the preparation of versatile chiral synthons for 1,2-diamines, (4*S*,5*S*)-, and (4*R*,5*R*)-4,5-dimethoxy-2-imidazolidinone derivatives, using 1,3-dihydro-2*H*-imidazol-2-one as the starting material.[7] They showed that both methoxy groups of the synthons could readily be replaced with primary to tertiary alkyl groups and aryl moieties with full retention of configuration in a stepwise manner. Subsequent ring opening provides a versatile route to optically active *threo*-1,2-diamines. However, it should be noted that the reported synthesis of the chiral synthons involves an efficient, but rather tedious optical resolution step. Kuneida reviewed the use of 1,3-dihydro-2*H*-imidazol-2-one as a building block for chiral polyfunctional compounds as well as chiral heterocyclic auxiliaries for asymmetric synthesis.[8] Simple five-membered heterocycles such as 2-oxazolone, 1,3-dihydro-2*H*-imidazol-2-one, and 2-thiazolone show interesting behavior toward polymerization and condensation, leading to homopolymers and telomers, as well as condensation reagents.[9] Several synthetic procedures for 2-imidazolones have been reported in the literature.[10] Lipshutz et al. showed that N-SEM-protected imidazoles could be sequentially derivatized at the 2- and 5-positions in a one-pot operation. Quenching with selected peroxides following initial lithiation led directly to imidazolones.[11] All the reported synthetic procedures are complicated and utilize expensive reagents. In addition, the maximum yield in most cases was less than 80%.[12]

Generation of the superoxide ion ($O_2{}^{\cdot -}$) by electrochemical reduction of oxygen in aprotic solvents and ionic liquids (ILs) has gained increased importance due to its many potential applications, Eq. (1).[13–31]

$$O_2 + e^- \rightarrow O_2{}^{\cdot -} \qquad (1)$$

We were the first to report the generation of stable $O_2{}^{\cdot -}$ in imidazolium-based ILs.[20,21] The $O_2{}^{\cdot -}$ ion was then used for the destruction of chlorinated hydrocarbons, reduction of carbon dioxide, and the synthesis of ketones and carboxylic acids from the corresponding secondary and primary alcohols, respectively. It was reported in the literature that the positive charge density on the carbon atom at position 2 (C-2) in the imidazolium ring of ILs is greater than that at the other positions.[26] Various research groups have observed that electro-generated $O_2{}^{\cdot -}$ undergoes ion pairing with the imidazolium cation of ILs and that the degree of association of $O_2{}^{\cdot -}$ with the 1-ethyl-3-methylimidazolium cation in dimethyl sulfoxide is comparable to that of $O_2{}^{\cdot -}$ with H_2O.[30] Such ion pairing may ultimately lead to nucleophilic attack on C-2 of the imidazolium cation by $O_2{}^{\cdot -}$ to form a complex or a new product.[32–34] Islam et al. studied the stability of the superoxide ion generated chemically by dissolving KO_2 in anhydrous dimethylsulfoxide containing imidazolium cation-based ILs using UV–visible, NMR, and voltammetric techniques, and an ab initio molecular orbital calculation.[35] UV–visible spectroscopic and cyclic voltammetric measurements revealed that the $O_2{}^{\cdot -}$ species reacted

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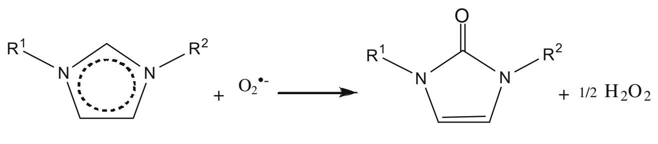
with the imidazolium cations of ILs to form hydrogen peroxide. Based on molecular orbital calculations, Islam et al. suggested that the $O_2^{\cdot-}$ species attacked the 2-position of the imidazolium ring to form an ion pair complex in which one oxygen atom was bound to C-2 and the other to the hydrogen atom of the $-CH_3$ group attached to C-2. Eventually, the ion pair complex of the imidazolium cation and $O_2^{\cdot-}$ species undergoes a ring-opening reaction as evidenced by ^1H NMR measurements.

As mentioned before, we used $O_2^{\cdot-}$ for different applications with 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][HFP], and 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [bdmim][HFP]. Although the yields were high in these reactions, GC–MS analysis indicated the presence of an unexpected compound. Careful analysis of the mass spectrum of the compound revealed it to be 2-imidazolone resulting from the reaction of the superoxide ion with the cation of the IL. Farmer and Welton reported similar results for the oxidation of benzyl alcohol in 1-butyl-3-methylimidazolium bis[trifluoromethanesulfonyl]imide using ruthenium catalysts.[36] They detected the presence of 1-butyl-3-methylimidazolidone and 1-butyl-3-methylimidazolidine-2,4,5-trione in the ether extract of the reaction products. However, all their attempts to isolate and quantify these products failed. They also reported that when 1-butyl-2,3-dimethylimidazolium bis[trifluoromethanesulfonyl]imide was used to block the C-2 position, no apparent oxidation of the IL was detected.[36] In order to confirm that $O_2^{\cdot-}$ reacts with the imidazolium cation of ILs as shown in Scheme 1, the bulk reaction of the $O_2^{\cdot-}$ species with the imidazolium cation was carried out and the product was extracted using diethyl ether. GC–MS and FTIR were used to identify the products. It should be noted that the production of H_2O_2 as a result of the reaction of the superoxide ion with the imidazolium cation of ILs was reported by Islam et al.[35]

The results of these analyses are shown in the Supplementary data. The reaction yield and purity of the isolated 2-imidazolones are listed in Table 1.

The yield is based on the amount of superoxide generated electrochemically or chemically and on the assumption of a 1:1 stoichiometric ratio for the reaction shown in Scheme 1. The reactions took place under ambient conditions, that is, the temperature was about 25 °C and the pressure was about 99 kPa.

It can be seen from Table 1 that the anion of the IL does not have any effect on the yield provided that it does not produce by-products that react with the superoxide ion, for example, hexafluorophosphate. It should be noted that in all cases, no by-products were detected. The small peaks shown in Figure S3 (Supplementary data) are due to the impurities present in the IL as confirmed by GC–MS. We also conducted several experiments to synthesize 2-imidazolone on a preparative scale. The results showed that neither the yield nor the purity of the product decreased significantly (Table 1, entry 3).



Scheme 1. Synthesis of 2-imidazolones by reaction of a superoxide ion with the imidazolium cation of the IL.

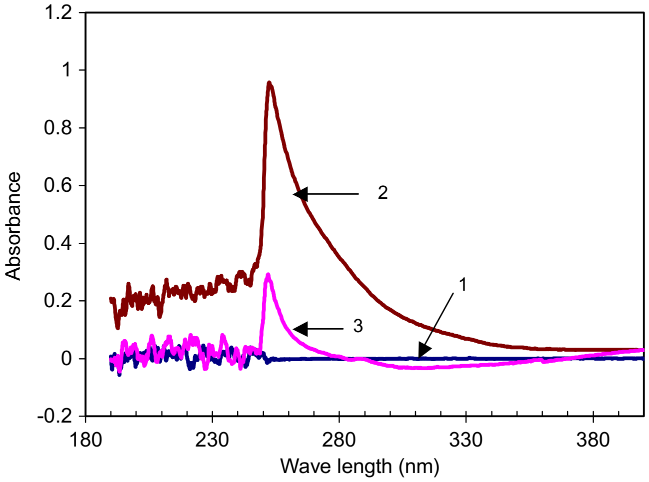


Figure 1. UV–vis spectra for electrochemically generated $O_2^{\cdot-}$ in [bmim][HFP] after passing 170 C of charge, (1) baseline, (2) after 30 min, and (3) after 16 h.

In order to determine an approximate value for the rate constant of the pseudo first order reaction of the superoxide ion with the cation of the IL, we measured the change of concentration of the generated $O_2^{\cdot-}$ in [bmim][HFP] and 1-ethyl-3-methylimidazolium ethylsulfate as a function of time using a UV–vis spectrometer (Fig. 1).[37] Typically, about 0.1 mL of the IL containing chemically or electrochemically generated $O_2^{\cdot-}$ was withdrawn at different time intervals. The sample was dissolved in about 1 mL of ethyl acetate and the UV–vis spectrum was measured over the range 400–190 nm. The estimated values of the rate constants at 25 °C are $2.1 \times 10^{-5}\ s^{-1}$ and $1.7 \times 10^{-5}\ s^{-1}$, respectively. These values are two orders of magnitude smaller than those reported by Islam et al. for the reaction of the superoxide ion with 1-butyl-2,3-dimethylimidazolium tetrafluoroborate in anhydrous dimethylsulfoxide.[35]

In summary, we have described a simple and efficient method for the synthesis of 2-imidazolones by the reaction of a superoxide ion with the cations of imidazolium-based ILs. Both the yield and purity of the isolated products were excellent.

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Table 1
2-Imidazolones obtained via the reaction of a superoxide ion with ILs

Entry	Ionic liquid	Product	Yield% (mg)	Purity of isolated product (%)
1	1-Butyl-3-methylimidazolium hexafluorophosphate	1-Butyl-3-methyl-2-imidazolone	95 (1.1)	97
2	1-Ethyl-3-methylimidazolium ethylsulfate	1-Ethyl-3-methyl-2-imidazolone	97 (0.9)	97
3	1-Ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	1-Ethyl-3-methyl-2-imidazolone	98 (0.8)	98
			96 (723)	98
3	1-Hexyl-3-methylimidazolium chloride	1-Hexyl-3-methyl-2-imidazolone	96 (1.3)	98
4	1-Octyl-3-methylimidazolium chloride	1-Octyl-3-methyl-2-imidazolone	96 (0.7)	98
5	1,3-Dimethylimidazolium diphosphate	1,3-Dimethyl-2-imidazolone	97 (0.7)	98
6	1,3-Dimethylimidazolium trifluoromethanesulfonate	1,3-Dimethyl-2-imidazolone	97 (0.8)	98

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.030.

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