



Epoxidation of electrophilic alkenes in ionic liquids

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A fast and efficient procedure is proposed for the epoxidation of electrophilic alkenes, the structures of which resemble the vitamin K class, in ionic liquids as solvents and using aqueous basic solutions of hydrogen peroxide as oxidant. Yields of epoxides ranging from very good to almost quantitative are observed for all the substrates analysed.

Introduction

Over recent years, one of the most imperative issue for chemists is the search of clean or green chemical transformations. In particular, waste minimisation/reduction is strongly recommended in order to achieve new attractive industrial processes. In general the use of volatile molecular solvents is one of the most significant sources of chemical waste in the fine chemicals and pharmaceuticals industry. Because of their peculiar properties ionic liquids (IL) have been proposed as novel and environmentally benign reaction media for organic synthesis. Selected examples include dimerization of alkenes,¹ Friedel–Craft reactions,² Diels–Alder cycloadditions,³ hydrogenation reactions,⁴ Heck C–C coupling reaction,⁵ asymmetric epoxidation using chiral (salen)Mn complexes as catalysts⁶ and bromination of double and triple bonds.⁷ For an extensive collection of references, interested readers are referred to very recent reviews.^{8–11}

It is of note that, with very few exceptions,^{6,12–14} the exploitation of IL as solvents for oxidation reactions is still at an

initial stage. A recent paper from Sheldon *et al.*¹⁵ reports the epoxidation of cyclohexene in IL with a peracid formed through perhydrolysis carried out by *Candida antarctica* lipase. Yet, to the best of our knowledge, there are no references concerning the use of aqueous solutions of hydrogen peroxide as oxidants in the absence of metal catalysts.

Hydrogen peroxide has recently regained importance as an oxidant in both the industrial and academic community.¹⁶ The main reasons are related to ‘regulatory forces causing the chemical industry to reduce, and in some instances eliminate, environmental pollution’, and to the fact that the chemical industry is now capable of employing H₂O₂ in a safer, more efficient and innovative manner.¹⁶

Here we present preliminary data on a fast and efficient procedure for epoxidation of electrophilic alkenes in ionic liquids as solvents by using an aqueous solution of hydrogen peroxide in the presence of base catalysis. With this procedure, which couples the use of a ‘green oxidant’ with ‘green solvents’, new routes for industrially appealing oxidations are envisaged.

Results and discussion

Epoxidation reactions were carried out at room temperature, or below, utilizing 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆] (not miscible with water) and 1-butyl-

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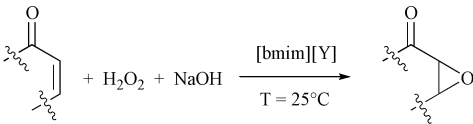
Green Context

A combination of green techniques will often be required to effectively improve the environmental performance of chemical reactions. Here we see the successful combination of one of the newer and less environmentally threatening solvents with one of the safer and least wasteful oxidants. Epoxidations of electrophilic alkenes can be carried out using a mixture of an ionic liquid containing the substrate and aqueous hydrogen peroxide in the presence of a simple base such as sodium hydroxide. No competing hydrolysis reactions are observed and the products which are generally obtained in high yields with only small excesses of oxidant, are easily extracted using an immiscible solvents. **JHC**

3-methylimidazolium tetrafluoroborate [bmim][BF₄], (hygroscopic) solvents. These ILs were chosen on the basis of their availability and stability in the presence of oxygen and water. All the substrates of choice are formally related to the structure of the vitamin K class,¹⁷ prothrombogenic and antihemorrhagic derivatives. The vitamin K epoxides are also very important because of their higher stability to light as compared to the non-oxidized derivatives.

A typical reaction was carried out at 25 °C by dissolving 1 mmol of the substrate in 1 mL of the IL. The mixture was kept under vigorous stirring and 0.3 mL of a commercially available aqueous solution of H₂O₂ (30% w/v) 3 mmol, containing 2 mmol of NaOH, was subsequently added. The course of the reaction was monitored with GC analysis (see Experimental for details). Chromatographic, and in some cases ¹H NMR, comparison with epoxides obtained in the classical reaction carried out with H₂O₂/HO[−] in water¹⁷ was used to identify the products. The data are collected in Table 1.

Table 1 Room temperature base catalyzed oxidation of electrophilic alkenes with hydrogen peroxide in ionic liquids as solvents



No.	Substrate	[Y [−]]	H ₂ O ₂ /mmol	Time/min	Yield ^a (%)
1		[PF ₆ [−]]	3	2	99
		[BF ₄ [−]]	3	2	99
2		[BF ₆ [−]]	3	2	99
		[BF ₄ [−]]	3	2	97
3		[BF ₆ [−]]	9 ^b	180	80
4		[BF ₆ [−]]	3	15	90
5		[BF ₆ [−]]	3	60	99
6		[BF ₆ [−]]	3	5	99
		[BF ₄ [−]]	3	5	99

^a No products other than epoxides were detected by GC analysis for all the substrates. In reactions 3 and 4 the substrate is the only other peak detected by GC.^b Carried out by adding two additional subsequent portions of hydrogen peroxide.

Interestingly, with our procedure almost quantitative production of the epoxides is obtained, with the less hindered substrates, in the time required for the addition of a small excess of the oxidant. More substituted compounds require either longer reaction times or, as in the case of 3,5,5-trimethyl-2-cyclohexen-1-one (isophorone), the addition of a larger excess of H₂O₂ to complete the oxidation.

The epoxidation rate observed for the substrates reported in Table 1 with the procedure presented here, *i.e.* the use of ILs as solvents, can be compared with the reaction rate of the classical reactions performed in water.¹⁸ Preliminary kinetic data indicate that the epoxidation rate observed in [bmim][PF₆], using 2-cyclohexen-1-one as a model alkene, is significantly higher than that obtained in water. A detailed kinetic analysis, actually underway in our laboratories, is clearly necessary for a more precise comparison of the rates, as well as for offering an explanation for the differences in reactivity observed with some hindered substrates.

Conclusions

In summary, the oxidation procedure presented above is characterised by several advantages with respect to classical methods for epoxidation of electrophilic alkenes. In particular, a new class of 'green solvents' and an environmentally benign and cheap oxidant are used. Complete consumption of the reactant is observed with small excesses of peroxide. An advantage over the epoxidation reactions carried out in aqueous systems is that no hydrolysis of the epoxides has been detected. Products are easily separated from the oxidation mixture by simple extraction with an immiscible solvent. Clearly a further improvement of the procedure can be envisaged on a large-scale system where the products may be either distilled from the reaction mixture or extracted with supercritical CO₂.

Experimental

In a standard epoxidation procedure, 1 mmol of the unsaturated compound was dissolved at room temperature in the ionic liquid (1 mL) and 0.3 mL of 30% aqueous hydrogen peroxide (3 mmol) containing sodium hydroxide (2 mmol) were subsequently added under vigorous stirring. The completion of the reaction was determined by controlling the entire consumption of the substrate *via* TLC. Products were then extracted at the end of the reaction by three subsequent additions of ethyl acetate (2 mL). The combined extracts were analyzed by GC using a Megadex DETTBS column. No products other than epoxides were observed with all substrates. The epoxides were identified by comparison with those obtained in the classical reaction carried out with H₂O₂/HO[−] in water.¹⁷ In the case of 2-cyclohexen-1-one and 3,5,5-trimethyl-2-cyclohexen-1-one (isophorone), the reactions were carried out on a larger scale (5.2 mmol) and the epoxides were isolated and identified on the basis of the ¹H NMR spectra of the crude extracts.

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