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Sustainable vanadium(V)-catalyzed oxybromination of styrene: Two-phase system versus ionic liquids*

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Abstract: Oxybromination reaction of styrene was performed in a two-phase system of water/ionic liquids (ILs). The aim of the work was to make the mild and efficient two-phase system previously developed for the vanadium(V)-catalyzed oxybromination of alkenes, inspired by the activity of haloperoxidase enzymes, even more interesting from a sustainable point of view. As in that case, a brominating intermediate was formed from the metal catalyst, H_2O_2, and bromide ion in the acid aqueous phase, but chlorinated solvents were replaced with ILs.

$[bmim^+][PF_6^-]$, $[bm_2im^+][PF_6^-]$, $[bmim^+][BF_4^-]$, $[bmim^+][CF_3SO_3^-]$, and $[bmim^+][(CF_3SO_2)_2N^-]$ were tested. We report on interesting results in terms of reaction rates and selectivities.

Keywords: Vanadium; hydrogen peroxide; oxidation; ionic liquids; styrene; oxybromination.

INTRODUCTION

Vanadium-dependent bromoperoxidase enzymes (V-BrPO) catalyze the oxidation of bromide ion by hydrogen peroxide [1–3]. These enzymes are known to play a major role in the biosynthesis of brominated compounds. The catalytic effect is related to the formation in the active site of the enzyme of a peroxo vanadium species that is a much stronger oxidant as compared with H_2O_2. This peroxo derivative oxidizes the bromide ion to form a brominating intermediate which, in turn, brominates the organic substrate. Following the hypothesis that the brominating intermediate is formed in the hydrophilic portion of the enzyme, while the functionalization of the substrate takes place in a hydrophobic part of the active site, we have selected a vanadium-based two-phase system (water/chlorinated solvents) for bromination and oxybromination of aromatic and unsaturated organic molecules [4–6]. Our procedure operates in mild conditions and uses a sustainable oxidant, H_2O_2, and a sustainable source of positive bromine such as KBr. As indicated in Fig. 1, the acid aqueous phase contains the vanadium catalyst, hydrogen peroxide, and bromide ions. The organic substrate, on the other hand, is dissolved in the molecular solvent. In the course of our studies, by combining reactivity analysis with spectroscopic techniques, mainly ^{51}V NMR [7], we have been able to identify monoperoxo vanadium complexes as the competent oxidant of bromide ion, while the diperoxo vanadium species likely acts as a reservoir of the active oxidant. When alkenes are used as substrates, two products are usually observed: bromohydrin and dibromide [8]. To note, the reaction is typically characterized by a good degree of selectivity to-

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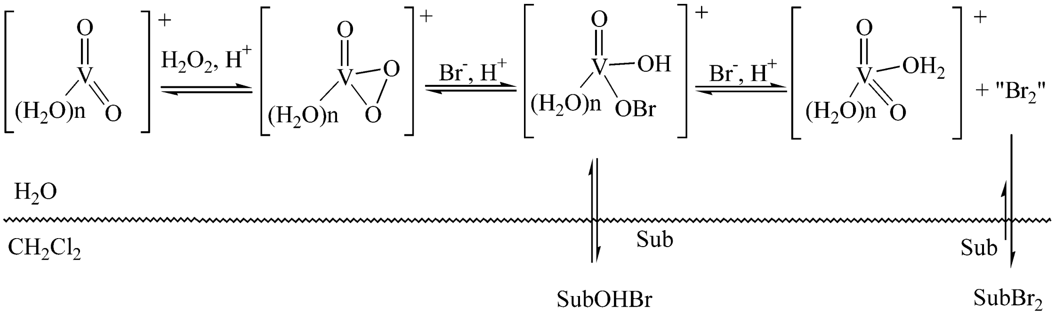


Fig. 1 V-catalyzed oxybromination reaction in a two-phase system.

ward formation of the bromohydrin. In that respect, we observed that (i) the product yields depend on the rate of stirring, (ii) other classical brominating systems produce selectively dibromide, (iii) there is evidence for substrate coordination, (iv) more nucleophilic substrates favor the formation of bromohydrin, and (v) Hammett correlations indicate two parallel processes. Consequently, our mechanistic proposal involves two intermediates, as indicated in Fig. 1, the first one, a vanadium-bound hypobromite ion, responsible for the formation of bromohydrin and the second one, bromine, in charge of the formation of dibromo compounds [8].

Recently, evidence on the formation of the vanadium-bound hypobromite intermediate has been obtained by using electrospray ionization/mass spectrometry (ESI/MS) technique [8].

From a synthetic point of view, it can be recalled here that with several different alkenes, depending on the experimental conditions, yields reaching up to 98 %, together with high selectivity toward formation of bromohydrin, have been obtained [4,5]. Figure 2 contains the data referring to reaction with styrene in selected reaction conditions [5].

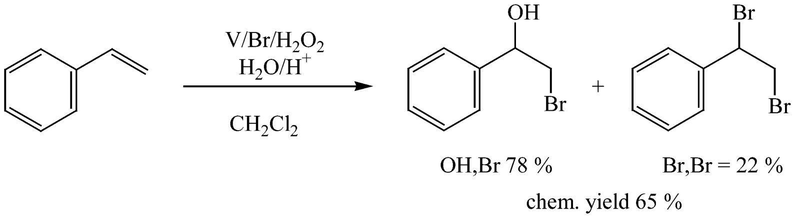
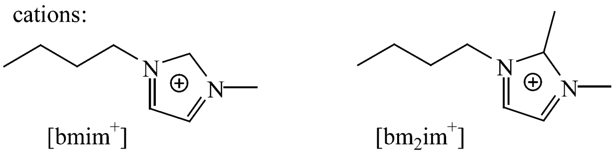


Fig. 2 V-catalyzed oxybromination of styrene in a two-phase system. Sub = 0.01 mol L^{-1}, V = 0.01 mol L^{-1}, Br^{-} = 0.05 mol L^{-1}, H_2O_2 = 0.01 mol L^{-1}, pH = 1($HClO_4$), 25 °C, 1000 rpm stirring rate, 24 h.

As indicated by the data so far summarized, this oxybromination procedure is reasonably interesting from a sustainability point of view. However, in order to render it even more attractive, we decided to replace the chlorinated organic solvents with ionic liquids (ILs). Because of their peculiar properties, ILs have been recently proposed as novel and environmentally benign reaction media for several organic syntheses [9–11]. *N*-alkylpyridium and *N,N'*-dialkyl imidazolium cations coupled with a variety of inorganic anions have been, in fact, used as suitable solvents for several organic reactions as well as in catalytic processes: Friedel–Craft reactions [12], Diels–Alder cycloadditions [13], metal-catalyzed hydrogenations [14], Mn-catalyzed asymmetric epoxidation [15], and bromination of double and triple bonds [16] are just a few examples in this quite new field.

In the course of our study, we focused our attention on some hydrophilic and hydrophobic ILs [18]. In particular, we chose 1-butyl-3-methylimidazolium, [$bmim^+$], and 1-butyl-2,3-dimethylimidazolium, [bm_2im^+], cations and tetrafluoborate, [BF_4^-], hexafluorophosphate, [PF_6^-], triflate, [$CF_3SO_3^-$], and bistrifluoromethanesulfonimide anions, [$(CF_3SO_2)_2N^-$]. Thus, the following ILs—

$[bmim^+][PF_6^-]$, $[bm_2im^+][PF_6^-]$, $[bmim^+][BF_4^-]$, $[bmim^+][CF_3SO_3^-]$, and $[bmim^+][(CF_3SO_2)_2N^-]$—were tested for performing the title reaction. In Fig. 3, the structures of the ILs used are collected. We present some interesting results on a faster and more efficient procedure for oxybromination of styrene, particularly when hydrophobic ILs are used.



anions: $[PF_6^-]$, $[BF_4^-]$,$[CF_3SO_3^-]$ $[(CF_3SO_2)_2N^-]$

$[bmim^+][BF_4^-]$, $[bmim^+][CF_3SO_3^-]$: hydrophilic
$[bmim^+][PF_6^-]$, $[bm_2im^+][PF_6^-]$, $[bmim^+][(CF_3SO_2)_2N^-]$: hydrophobic

Fig. 3 Hydrophilic and hydrophobic ILs used.

RESULTS AND DISCUSSION

The oxybromination reactions were carried out at room temperature by using the different hydrophilic and hydrophobic ILs in order to determine first of all which system, homogeneous versus a two-phase one, is superior. The two-phase option is obviously due, as in the case of the chlorinated solvents, to the use of aqueous solutions of hydrogen peroxide as primary oxidant. The ILs indicated above were chosen on the basis of their availability and stability in the presence of an oxidant and water. In several cases, irreproducible results were obtained by using commercial ILs. This fact is likely due to an insufficient purity of the samples used. Such an aspect has been already addressed on other occasions by several authors [17]. Therefore, in order to have ILs with appropriate purity, we synthesized our solvents [19].

Styrene was used as model organic substrate. As a first attempt, a homogeneous system was investigated by using $[bmim^+][BF_4^-]$ and $[bmim^+][CF_3SO_3^-]$ solvents [25].

The results obtained, together with those referring to the classical reaction carried out in H_2O/CH_2Cl_2 two-phase system repeated in the course of this work, are collated in Table 1.

Table 1 V-catalyzed oxybromination of styrene with H_2O_2 and KBr in hydrophilic IL[a].

Solvent(s)	Time h	Yield %	OH,Br:Br,Br %
H_2O/CH_2Cl_2[a]	24	65	78:22
$[bmim^+][BF_4^-]$[b]	2	27	58:42
$[bmim^+][CF_3SO_3^-]$[b]	2	68	79:21

[a] NH_4VO_3 = 0.01 mol L^{-1}, H_2O_2 = 0.01 mol L–1, KBr = 0.05 mol L^{-1}, styrene = 0.01 mol L^{-1}, pH ca. 1 ($HClO_4$), room temperature.
[b] NH_4VO_3 = 0.01 mol L^{-1}, H_2O_2 = 0.02 mol L–1, KBr = 0.1 mol L^{-1}, styrene = 0.02 mol L^{-1}, pH ca. 1 ($HClO_4$), room temperature.

As seen from the data in Table 1, the outcome of the reaction carried out in $[bmim^+][BF_4^-]$ is poor in terms of both yield and selectivity. On the other hand, in comparison with the classical reaction, no improvement was observed with $[bmim^+][CF_3SO_3^-]$ other than a shortening of the reaction time. This approach was therefore discarded, also considering that on some occasions precipitation of salts was observed, thus, the unrewarding results obtained may be also due to a lower actual concentration of the reagents.

Thus, we focused our attention on a two-phase system employing the hydrophobic ILs indicated in Fig. 2. In particular, $[bmim^+][PF_6^-]$ was chosen as a model IL to optimize the reaction conditions [26]. Table 2 contains the results obtained in the course of this exploration. For comparison purposes, the first two lines again refer to the classical two-phase reaction with molecular solvents.

Table 2 V-catalyzed oxybromination of styrene with H_2O_2 and KBr in a two-phase system $H_2O/[bmim^+][PF_6^-]$[a].

Run	Styrene mol L^{-1}	Br^- mol L^{-1}	VO_3^- mol L^{-1}	H_2O_2 mol L^{-1}	Time h	Yield %	OH,Br:Br,Br
1	0.01[b]	0.05	0.01	0.01	24	65	78:22
2	0.02[b]	0.10	0.02	0.02	2	81	43:57
3	0.04	0.10	0.01	0.02	4	96	97:3
4	0.02	0.10	0.01	0.02	4	96	98:2
5	0.02	0.05	0.01	0.02	4	68	97:3
6	0.02	0.10	0.02	0.02	2	>99	98:2
7	0.02	0.10	0.001	0.02	24	87	96:4

[a] NH_4VO_3 as V precursor, water at pH ca. 1 ($HClO_4$), room temperature.

[b] Reaction carried out in the classical two-phase conditions: H_2O/CH_2Cl_2, water at pH ca. 1 ($HClO_4$), room temperature.

The first comment that can be offered with respect to the data reported in the table is related to the rate of the reaction. In fact, by comparing entries 2 and 6, which have the same concentration of all reagents, it appears that the rate of consumption of the oxidant is not greatly affected by the change of the solvent. Moreover, as already observed with molecular solvents, the reaction rate is essentially determined by the concentration of the peroxo vanadium species, while no detectable effects have been detected by lowering by a factor of 2 the substrate concentration, entries 3 and 4.

Taking into account this aspect and also the fact that in ILs, which generally show much better solvent properties, higher concentration can be achieved, we have worked with a higher concentration of reagents, and in particular of styrene.

The most intriguing result obtained refers to the observation that in ILs much higher yields and synthetically interesting selectivities are obtained in all cases. If again the comparison is made between entries 2 and 6, an increase of the yield from 81 % to an almost quantitative one is detected, together with a much better selectivity toward the formation of bromohydrin. The preferential formation of dibromo derivative, observed when chlorinated solvents are used, can be ascribed to a less polar environment, which likely favors the formation of molecular bromine.

Interestingly enough, a 10 times lowering of the vanadium concentration still leads to good results in reasonable reaction time.

With these results in hands, we moved to analyze the course of the reactions in the other hydrophobic IL objects of this study. Table 3 collects the outcome of the reactions in $[bmim^+][(CF_3SO_2)_2N^-]$ and $[bm_2im^+][PF_6^-]$ in comparison with that obtained in $[bmim^+][PF_6^-]$, using the reaction conditions of entry 4 in Table 2. At first glance, it appears that with all three ILs used very good results are achieved in terms of chemical yields, selectivities, and reaction rates.

Table 3 V-catalyzed oxybromination of styrene with H_2O_2 and KBr in a two-phase system H_2O/IL[a].

IL	Time h	Yield %	OH,Br:Br,Br
CH_2Cl_2[b]	24	65	78:22
$[bmim^+][PF_6^-]$	4	96	98:2
$[bmim^+][(CF_3SO_2)_2N^-]$	6	92	97:3
$[bm_2im^+][PF_6^-]$	4	>99	94:6

[a] NH_4VO_3 as vanadium precursor, water at pH ca. 1 ($HClO_4$), room temperature, $VO_3^- = 0.01$ mol L^{-1}, $H_2O_2 = 0.02$ mol L^{-1}, KBr = 0.1 mol L^{-1}, styrene = 0.02 mol L^{-1}.

[b] Control conditions with molecular solvent.

Indeed, no big differences between the solvents are observed, even though a somewhat detectable trend, as far as the chemical yield is concerned, may be distinguished. In fact, from the 92 % in 6 h obtained in $[bmim^+][(CF_3SO_2)_2N^-]$, an excellent, almost quantitative yield in 4 h was observed in $[bm_2im^+][PF_6^-]$.

Even though further studies are required, and in particular an extension of the number of ILs is fundamental in order to draw a complete description of the effects of these media on the oxybromination reaction, some preliminary comments can be offered. A first important point is related to the selectivity attainable working with a two-phase water/ILs system. In fact, in the present conditions, the functionalization of the substrate takes place in a much more polar phase [27], i.e., the IL phase. This fact likely causes a less favorable distribution of bromine between the two phases, thus determining a very low actual concentration of bromine in the IL phase, which implies that the pathway toward the formation of dibromo derivative, see Fig. 1, becomes, in some cases, almost negligible.

Several studies [27–29] are now appearing with the aim to define the solvent properties for ILs, however, our data are related to a limited number of solvents and it is very difficult at this point to completely understand the effect of the ionic solvent in the transfer of the active brominating species from water. On the basis of the collected data, this process appears to be more facile with respect to what is observed with a molecular solvent such as $CHCl_3$ or $CHCl_2$. However, correlation with solvent parameters [17], such as those of Kamlet-Taft or of Reichardt, is not yet feasible, particularly because of the limited number of ILs used in the present work.

Furthermore, the increase of the chemical yield seems to be more connected with the viscosity of the medium. In fact, the best chemical yield is obtained with $[bm_2im^+][PF_6^-]$, whose viscosity is not yet determined, but expected to be higher than that of the other solvents used, considering that it melts at about room temperature.

A further aspect needs also to be analyzed, considering the definite effect of the IL anion observed. Experiments aimed at evaluating the nature of the vanadium precursors are, in fact, warranted.

To summarize in a pictorial way, Fig. 4, we believe that the polar environment used and the peculiarity of these "organized" solvents produce initially a higher concentration of the active species in the IL phase, see Fig. 1, thus favoring the first equilibrium depicted in Fig. 4. Secondly, it appears possible that the reaction between the bromiranium species [30], formed upon reaction of the vanadium-bound hypobromite intermediate and the substrate [31], with a vanadium-coordinated molecule of water to form the bromohydrin is facilitated by a slower way out from the organized solvent cage. The net result is thus a more efficient and fast reaction. Clearly, more mechanistic studies are required in order to clarify these points.

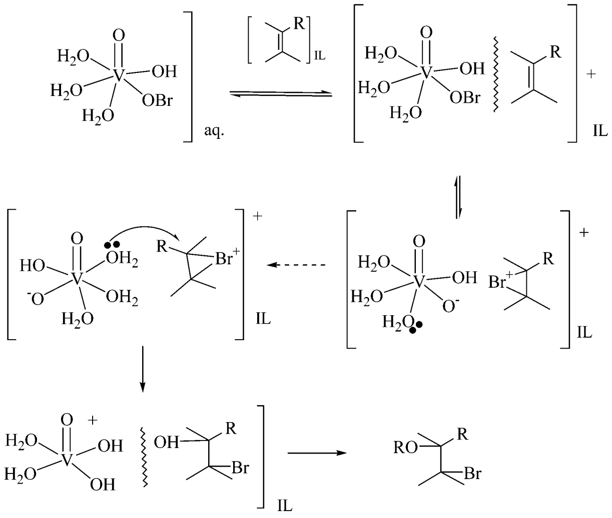


Fig. 4 Proposed steps in the V-catalyzed oxybromination reaction in ILs.

ACKNOWLEDGMENT

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18. The hydrophilic and hydrophobic nomenclature, see ref. [17], is normally used in order to identify ILs which either form a single phase with water or dissolve very small quantity of water, therefore forming two-phase systems.

19. The synthesis of ILs used in this work consisted in two steps. The first is a quaternization reaction between an alkyl-substituted imidazole and an alkyl bromide, to obtain a solid precursor. The second one is a metathesis reaction in which the bromide ion is exchanged by an appropriate anion able to give a liquid product at room temperature. Both these passages were executed following literature procedures [20–24] with appropriate modifications which will be the object of publication elsewhere. Characterization of ILs was made by ^{1}H NMR by comparison with literature data [16], when available.
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25. Reactions in hydrophilic ILs are carried out by dissolving styrene (0.02 mmol) in 1 ml of IL. A small amount (100 µl) of acid (pH = 1, $HClO_4$) aqueous phase containing 0.1 mmol of KBr, 0.01 mmol of NH_4VO_3, and 0.02 mmol of H_2O_2, is then added to IL. The reaction is carried out at room temperature under vigorous stirring; yields and selectivity were calculated, after complete disappearance of oxidant, by GC quantitative analysis (dodecane external standard).
26. In a typical reaction carried out in a two-phase system (H_2O/hydrophobic IL), the acid (pH = 1, $HClO_4$) aqueous phase (1 ml) containing the appropriate concentration of KBr, NH_4VO_3, and H_2O_2, and the IL (1 ml) containing styrene were added together in the reactor at room temperature and vigorously stirred. Yields and selectivity were calculated, after complete disappearance of the oxidant, by GC quantitative analysis (dodecane external standard).
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