Inexpensive and tuneable protic ionic liquids based on sulfuric acid for the biphasic synthesis of alkyl levulinates

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\textbf{A B S T R A C T}

Alkyl levulinates are bio-derived chemicals, increasingly popular for their uses as solvents, additives and intermediates. However, efficient and recyclable catalysts for their synthesis are still the subject of intensive research. In this study, a wide range of alkyl levulinates was synthesized under mild conditions (room temperature, atmospheric pressure), using inexpensive and efficient Bronsted acidic ionic liquids (ILs) based on sulfuric acid and off-the-shelf bases. Acidity of the ILs was closely related to their activity. The ILs could be easily separated and recycled, without significant changes in conversion or selectivity over 10 cycles (yields ca. 90–95%). Under optimized conditions, a 99% yield of pentyl levulinate (model reaction) was achieved. The method was demonstrated to be efficient in the synthesis of levulinates of C1-C16 linear, branched and cyclic alcohols. This innovative, green route to alkyl levulinates fits well within the sustainable development strategy.

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\section*{1. Introduction}

Levulinic acid esters are biomass derivatives that attracted considerable attention as raw materials or bio-platform chemicals for the production of fuel additives, solvents, fragrances, plasticizers, pharmaceuticals as well as wide range of fine chemicals [Fig. 1] [1–16].

Their physicochemical properties include low vapor pressure and low viscosity, low toxicity, high lubricity, very good thermal stability, biodegradability and pleasant smell, making them very attractive alternatives to chemicals derived from crude oil [17–28]. Importantly, the physicochemical properties of levulinate esters can be altered and fine-tuned by changing the structure of the alcohol [29].

A wide range of synthetic strategies to produce levulinates has been reported in the literature, with current approaches aiming for efficient, inexpensive and environmentally friendly technologies [21,30–33]. One of the most prominent methods is the esterification of levulinic acid (LA) with an alcohol. The starting material - levulinic acid - was recognised by the US Department of Energy as one of the top bio-based platform chemicals for the future [1]. It can be produced by the transformation of lignocellulosic biomass, cellulose, saccharides or furfuryl alcohol (via hydrolysis) [34].

The esterification reaction can be catalyzed with a homogeneous acidic catalyst, a heterogeneous catalyst, or an enzyme (e.g. Candida antarctica B lipase). Strong mineral acids, such as sulfuric or hydrochloric, are the most common homogeneous catalysts [35,36]. Popular for their low price, they pose difficulties with product separation and purification, because of their miscibility with the reaction medium. Further issues include great water consumption, long reaction time and harsh reaction conditions, especially high temperature and/or pressure [31,35]. Finally, mineral acids are corrosive and generate large amounts of waste, chiefly salts formed during their neutralization [37]. The two alternatives to mineral acid catalysis: solid acids and enzymes, also come with certain drawbacks. Heterogeneous catalysts, such as heteropolyacids (HPAs), zeolites and sulfonated materials, offer benefits in terms of facile separation from reaction mixture and good recyclability, lower corrosivity and no need for the neutralization step [37–41].
ammonium hydrogen sulfate, \([\text{NE}_{3}\text{Bu-SO}_3\text{H}][\text{HSO}_4]\), was used as a catalyst \cite{45,58}. There are only few reports that investigate the catalytic reaction of HPA after two cycles \cite{45}. Zeolites, while having good surface area and no solubility issues, may undergo stepwise inactivation, observed after few cycles, and thus require additional step of activation \cite{42}. Finally, enzymatic reaction in the presence of lipases has been recently studied \cite{43,44}. Despite several advantages of using enzymes, such as low energy demand and high selectivity, these catalysts are often expensive and sensitive to a number of reaction parameters, including temperature, pH, or the presence of some chemicals which can act as inhibitors.

Brønsted acidic ionic liquids have been explored as an alternative to mineral acids in esterification reactions \cite{45-48}. In contrast to solid-state catalysts and enzymatic reactions, ionic liquids may offer the advantage of a drop-in solution in reactors designed for conventional liquid acids. They can be used as acidic catalysts or combine the roles of a catalyst and a solvent. Other noted benefits include low vapor pressure, thermal stability and tune ability of physicochemical properties modifying their cations and/or anions \cite{49-56}. At the same time, ionic liquid-based processes posed their own drawbacks, which were very much dependent on the ionic liquid used. In some cases, prohibitively expensive (requiring multi-step syntheses) ionic liquid were employed, or efficient recycling has not been demonstrated. Alternatively, recycling strategies were time-consuming and economically inefficient (e.g. prolonged heating or evaporation of volatiles under vacuum) \cite{57}. The most promising were examples, where ionic liquids were fine tuned in such way that the product formed a separate phase and could be easily separated by decantation. This was observed in the reaction of acetic acid with \(n\)-butanol in the presence of \(N\)-methyl-2-pyrrolidinium methyl sulfonate or a protic ionic liquid \([\text{Et}_3\text{NH}][\text{(HSO}_4)(\text{H}_2\text{SO}_4)_x]\) \cite{46,58}. There are only few reports that investigate the ionic liquid-catalyzed synthesis of levulinates from levulinic acid \cite{45,46,59}. In an early study, \(N,N,N\)-triethyl-4-sulfobutan-1-ammonium hydrogen sulfate, \([\text{NE}_3\text{Bu-SO}_3\text{H}][\text{HSO}_4]\), was used as a catalyst \cite{45}. Although over 99% yield of ethyl levulinate was achieved after 30 min, the reaction was carried out under pressure (pressure tubes), at a relatively high temperature (140 °C), and the ionic liquid was synthesized via an expensive sulfonate precursor. In a more recent example, sulfonic acid-functionalized benzimidazolium poly (ionic liquid) (SAFBPIL) has been used as a heterogeneous catalyst in the esterification of levulinic acid with ethanol \cite{59}. Again, 99% conversion to ethyl levulinate was obtained at 70 °C, but the reaction took 9 h and required a great excess of alcohol (LA: EA molar ratio 1:10). Moreover, synthesis of this catalyst requires multiple steps (overall yield about 50%), expensive precursors, and is time consuming. Possibly the most promising was the reaction using a simple, protic ionic liquid, \(1\)-methylimidazolium hydrogen sulfate, \([\text{Hmim}][\text{HSO}_4]\), which gave good yields of butyl levulinate (up to 90%), albeit required elevated temperature (90 °C) \cite{48}. In our earlier work, protic ionic liquids based on anionic clusters of sulfuric acid, \([\text{HSO}_4]_x[\text{(H}_2\text{SO}_4)_x]^{-}\) \((x = 0, 1, 2\) were found to be extremely efficient esterification catalysts \cite{58}. Similar ionic liquids, albeit based on a simple hydrogen sulfate anions, were demonstrated to easily phase-separate from levulinate esters, offering promising separation and recycling strategy \cite{48}. Finally, protic ionic liquids based on sulfuric acid and simple amines were explicitly described as economically competitive in comparison with the cheapest acidic catalyst and even solvents \cite{60}. All these factors provided strong motivation to investigate the synthesis of a range of alkyl levulimates using ionic liquids with \([\text{HSO}_4]_x[\text{(H}_2\text{SO}_4)_x]^{-}\) anions (Fig. 2 b).

For the purpose of this study we chose protic ionic liquids with oligomeric anions based on sulfuric acid as catalysts. The choice of those specific materials was justified by few reasons. First of all, protic ionic liquids are easier, more sustainable in synthesis (acid-base reaction) and less expensive than aprotic ones. Secondly, ionic liquids with sulfuric acid have been studied in esterification reaction several times, and the big advantage over the other ILs, lies in the fact, that they are not miscible with product of the reaction – ester. Such biphasic system gives an excellent separation possibility, because the ester can be easily decanted from ILs. Additionally, sulfuric acid itself is a cheap and strong acid with great catalytic properties, so while converted to ionic liquid, results in a powerful, environment friendly Brønsted catalyst, which drives the reversible esterification reaction completely towards the product. On top of that, oligomeric anions increase the acidity of ILs, giving better catalytic properties than mono anion ILs.
2. Materials and methods

2.1. Materials

Methanol, ethanol and propanol (all ≥98%) were purchased from Avantor Chemicals. 1-Methylpyrrolidine, 1-methylimidazole, triethylamine, α-methylpyridine and sulfuric acid (95%) were purchased from Sigma-Aldrich and used as received. Other reagents (all ≥98%) and solvents were purchased from Merck. Chemicals were used without further purification.

2.2. Methods

Protic ionic liquids were synthesized according to the literature procedure [58]. 1 mol eq. of an amine was weighed out into a round-bottomed flask equipped with a stirring bar, placed in an ice bath, and stirred vigorously. Required amount of sulfuric acid (1, 2, or 3 mol eq.) was slowly added to stirred amine, then the mixture was left to react (750 rpm, 1 h, 50 °C). Subsequently, the ionic liquid was dried under high vacuum (50 °C, 10⁻² bar, overnight). All ionic liquids were obtained with near-quantitative yields (97–99%).

2.3. Synthesis of levulinate esters

In a typical procedure, levulinic acid (14.7 mmol, 1.0 eq.), ionic liquid (0.01–1.0 eq.) and alcohol (1.0–3.0 eq.) were placed in a round-bottomed flask, equipped with a magnetic stirring bar. The mixture was stirred vigorously under pre-set reaction conditions (750 rpm, 5–120 h, at 0, 25, 50 or 100 °C). The progress of the reaction was monitored by GC and TLC analyses. In most cases, a biphasic system was formed, and the upper organic phase, containing excess of alcohol and ester, was decanted. In a few cases of incomplete separation of the organic phase, the esters were isolated by extraction with hexane or chloroform. The excess alcohol (and solvent, if used) was evaporated under reduced pressure. The procedure for cetyl levulinate synthesis, required dissolution of the solid cetyl alcohol in diisopropyl ether before reaction.
Recycling of ionic liquids was studied using a model reaction of pentyl levulinate synthesis, in the presence of [Hmim][\(\text{HSO}_4\)]\(\text{H}_2\text{SO}_4\)]\(_2\). Levulinic acid (44.2 mmol, 1.0 eq.), [Hmim][\(\text{HSO}_4\)]\(\text{H}_2\text{SO}_4\)]\(_2\) (5.3 mmol, 0.12 eq.) and pentanol (88.4 mmol, 2.0 eq.) were placed in a round-bottomed flask (25 mL), equipped with a magnetic stirring bar and stirred vigorously (750 rpm, 5 h, 25 °C). After that, the upper layer containing ester and excess of alcohol was decanted and analysed by \(^1\)H and \(^{13}\)C NMR spectroscopy. The lower phase, containing ionic liquid and water, was stirred under vacuum (60 °C, 10 \(^-2\) bar, 8 h) in order to remove water, following which the ionic liquid was re-used in the next esterification reaction.

2.4. Analysis

The purity and structure of the synthesized ionic liquids were confirmed by \(^1\)H NMR spectroscopy (Agilent 400 MHz spectrometer). \(^1\)H and \(^{13}\)C NMR spectra of levulinates were recorded on the Agilent 400 MHz or Varian 600 MHz spectrometers. Thin-layer chromatography (TLC) was carried out using silica gel F254 Merck plates. The mobile phase contained hexane:ethyl acetate (v/v 1:1 or 3:1). GC analysis was performed on the Schimadzu GC-2010 Plus chromatograph, equipped with an SPB™-5 column (30 m x 0.2 mm x 0.2 μm). Spectroscopic data as well as more details about TLC analysis are given in the Supporting materials.

3. Results and discussion

3.1. Synthesis and characterization of ionic liquids

Bronsted acidic ionic liquids used in this study were prepared by the proton transfer between sulfuric acid and an amine. Selected amines represent a variety of structures, which led to generating aliphatic, acyclic and aromatic cations: 1-methylimidazolium, \(N,N,N\)-triethylammonium and \(2\)-methylpyridinium (Fig. 3).

When using equimolar ratio of sulfuric acid to amine (\(\chi_{\text{H}_2\text{SO}_4}=0.50\)), the hydrogen sulfate anion, \([\text{HSO}_4]^-\), was formed. In excess of sulfuric acid (\(\chi_{\text{H}_2\text{SO}_4}>0.50\)), the anionic species were of the general formula \([\text{HSO}_4\text{H}_2\text{SO}_4]^- (x = 1 \text{ or } 2)\). These anions were initially suggested to have the form of hydrogen-bonded clusters of \([\text{HSO}_4]\) and sulfuric acid (Fig. 4), their nominal size depending on the molar ratio of the acid, \(\chi_{\text{H}_2\text{SO}_4}\) [58].

However, this “cluster” view appears now to be obsolete, our recent results (in preparation) suggesting that a more truthful image is a hydrogen-bonded network of sulfuric acid molecules and hydrogen sulfate anions, with net negative charge, and protonated bases in transient cavities throughout the network. This is in analogy to our published study of pyridine in acetic acid [53], albeit in case of sulfuric acid, the bases remain fully protonated.

Acidity of these ionic liquids, previously quantified using Gutmann acceptor number (AN), was in the range of 65.5–121.5, and could be tailored by altering \(\chi_{\text{H}_2\text{SO}_4}\). For \(\chi_{\text{H}_2\text{SO}_4}=0.50\), ANs were towards the lower end of this range, indicating medium acidity strength. For \(\chi_{\text{H}_2\text{SO}_4}=0.75\), ANs reached 120 or more, comparable to values for other strong acids (\(\text{AN}_{\text{CF}_3\text{COOH}}=105.5, \text{AN}_{\text{CF}_3\text{SO}_3\text{H}}=129.1\)) [61]. Although this high acidity could be interpreted as \([\text{Hbase}]\text{[HSO}_4]\) salts dissolved in sulfuric acid, it was noted that phase behaviour of these ionic liquids was very different than that of bulk sulfuric acid. Furthermore, their catalytic activity was strongly cation-dependent, even in the presence of large excess of sulfuric acid, which made the cation selection an important aspect of the catalyst tuning process [58,60,62].

3.2. The influence of the ionic liquid catalyst structure on the esterification of levulinic acid with pentanol

The influence of different protic cations and different \(\chi_{\text{H}_2\text{SO}_4}\) values was investigated in a model reaction, namely esterification of levulinic acid with pentyl alcohol (Fig. 5). Protonic ionic liquids based on four cations: \([\text{Hmim}]^+, [\text{Hmpyr}]^+, [\text{Hmpy}]^+\) and \([\text{Et}_3\text{NH}]^+\), with acidity tuned by altering the sulfuric acid ratio (\(\chi_{\text{H}_2\text{SO}_4}\)), were studied.

Initially, all reactants combined ionic liquids formed homogenous mixtures. As reaction progressed, the formation of a second phase was observed (Fig. 6), identified to be the ester product, while levulinic acid was completely dissolved in the ionic liquid phase.

This was a very encouraging observation, expected to shift the reaction equilibrium towards products and bearing a promise of facile separation and recycling of the ionic liquid catalyst.

All reactions were allowed to proceed for 5 h, under very mild conditions (25 °C, ambient pressure), before the upper layer was decanted. The ester was isolated by extraction with hexane, following the decantation. Isolated yields of pentyl levulinate, achieved for ionic liquids with the four different cations and three \(\text{H}_2\text{SO}_4\) loadings (\(\chi_{\text{H}_2\text{SO}_4}=0.50, 0.60\) and 0.75), are compared in Fig. 7.

Ionic liquids with moderately acidic \([\text{HSO}_4]^-\) anion were poor catalysts (2–24% isolated yields of pentyl levulinate), which can be attributed not only to lower acidities (as measured by AN), but also to higher viscosities, which hindered the mass transport. Conversion achieved using [Hmim][\text{HSO}_4] was lower than that reported in the literature [48] however, the literature reaction was carried out at 90 °C, which would have improved both the kinetics and the mass transport. Furthermore, in contrast to the literature claim, the ester could not be isolated by simple decantation from over the [Hmim][\text{HSO}_4] layer in the presence of excess alcohol. Both this and our earlier work [58] have shown that butanol is not, in fact, miscible with [Hmim][\text{HSO}_4].

Fig. 3. Protonic cations of ionic liquids used in this work.
Ionic liquids with excess of sulfuric acid ($\chi_{\text{H2SO4}} = 0.60$ and $\chi_{\text{H2SO4}} = 0.75$) performed very well, delivering yields up to 91% of isolated ester under extremely mild conditions. In all cases, slightly better results were obtained with the highest sulfuric acid ratio, $\chi_{\text{H2SO4}} = 0.75$. Cations had only minor influence on the overall catalytic performance of the studied ionic liquids, with [Hmim]$^+$ giving the best result (91% yield of isolated ester).

3.3. The influence of the ionic liquid catalyst loading on the esterification of levulinic acid with pentanol

It is well known that acidic ionic liquids could influence the reaction by their catalytic activity, but also through solvation. To explore both of these influences, the best-performing ionic liquid, [Hmim]$	ext{[(HSO4)\,(H2SO4)2]}$, was screened at a range of loadings with respect to the levulinic acid: 1, 10, 12, 25, 50 and 100 mol% (Table 1). Increasing the catalyst loading from 1 to 10 mol%, and then to 12 mol%, resulted in improved performance, but further increases did not result in further rise of isolated yields. In consequence, the 12 mol% loading was recognised as optimal, with 96% yield of pentyl levulinate. This amount of the ionic liquid can be considered catalytic, and at the same time it was sufficient to form the two-phase system, enhancing phase separation of the ester product.

3.4. The influence of reactants ratio on the esterification of levulinic acid with pentanol

The influence of the alcohol excess was investigated by varying the LA:pentyl alcohol ratio between 1:1 and 1:3, using the optimum 12 mol% loading of [Hmim]$	ext{[(HSO4)\,(H2SO4)2]}$ (Fig. 8). Using equimolar ratio of reactants, it was found impossible to reach 90% conversion; with increasing excess of alcohol, the reaction kinetics and overall yields improved gradually. The 1:2 excess of pentanol with respect to levulinic acid allowed for the complete conversion of the acid and gave 97–99% yield of pentyl levulinate. Further increase of pentanol excess to 1:3 did not influence the reaction rate or the ester yield.

3.5. The influence of reaction temperature on the esterification of levulinic acid with pentanol

Esterification of levulinic acid with pentanol, in the presence of [Hmim]$	ext{[(HSO4)\,(H2SO4)2]}$ (12 mol% IL, 2 mol eq. alcohol), was screened at a range of reaction temperatures, from 25 to 75°C (Fig. 9).

At room temperature (25°C), full conversion of LA and the product yield of >97% was reached after 5 h. As expected, increased temperature enhanced the reaction rate, and at 75°C the pentyl levulinate yield of ca. 99% was reached after 30 min. Changes in the reaction temperature had no effect on selectivity, which – when future continuous process is considered - offers the potential of adjusting temperature/residence time parameters based on techno-economic evaluation, without compromising product quality.

3.6. Recycling of the ionic liquid catalyst

The key advantages of using ionic liquids with the [HSO4$^-$\,(H2SO4)2]$^–\,$ anions lie not only with their very high catalytic activity or the fact that the product forms a separate layer, but also in their easy recycling. Ten consecutive cycles of the model esterification of levulinic acid with pentanol were carried out at room temperature, in the presence of the same sample of [Hmim]$	ext{[(HSO4)\,(H2SO4)2]}$ (Fig. 10). After each cycle, the upper ester layer was decanted, leaving the lower layer with ionic liquid, water formed during the reaction and traces of unreacted alcohol (complete conversion of levulinic acid was observed in all cycles). The NMR analysis of the organic phase, after separation of ionic liquid revealed, that it contained a little amount of water (2.6–3.8 mol% depending on the cycle; $^1$H NMR in Supplementary Materials). Since the ratio of substrates was 2:1 (alcohol:levulinic acid), we have observed, that in the post-reaction organic layer, the ratio of product (pentyl levulinate) to unreacted alcohol was ~1:1. Both water and traces of starting materials in the lower layer were removed by vacuum distillation, with no loss of the ionic liquid over the 10 consecutive cycles.
cycles. Catalytic activity of the IL, although fluctuating within the error bars, remained stable for all ten runs. The experiments on the influence of small amount of water on the IL catalytic activity, performed with one of the ILs used in our research \([\text{Et}_3\text{N}]\)(\text{HSO}_4)(\text{H}_2\text{SO}_4)_2\) revealed, that upon recycling, it was not possible to completely remove the entire water from IL, even when the high vacuum distillation was used. Up to 10% of water could be incorporated in the structure of IL, without changing the activity of IL. Additionally, the experiments where the water was added stepwise to the dry IL (~10%) also confirmed that finding (NMR details in Supporting materials). The NMR analysis also proved that no free H\text{SO}_4 was present in the recycled IL. The main source of the discrepancies is most likely losses during decantation of the ester phase at a relatively small scale (15.3 mL of reaction mixture, 1.2 mL of ionic liquid). This hypothesis was also proven by the research on n-butyl levulinate in larger scale (1000 mL of reaction mixture) where the yield of isolated product was stable for 11 cycles (~92–94%; data in preparation for publication).

3.7. Substrate scope

In order to demonstrate robustness of this new, very promising approach to levulinate synthesis, a wide range of aliphatic (C1-C16) and cyclic (C5) alcohols were tested, using \([\text{Hmim}]\)(\text{HSO}_4)(\text{H}_2\text{SO}_4)_2\) as the catalyst (Fig. 11).

All relatively short, aliphatic, primary linear alcohols (C1-C8) gave high yields of the corresponding levulinates (81–91%). A primary alcohol with branched carbon chain (2-ethylhexanol) was also efficiently converted to its levulinic ester (87%). The longer-chained cetyl alcohol (C16) gave lower yield (61%), which was likely the combination of several factors. The alcohol itself was poorly soluble in the reaction mixture, which necessitated its dissolution in diisopropyl ether prior to reaction, and the product separation was very problematic, due to its surfactant properties (foamy mixture formation). Cyclic alcohols gave slightly lower ester yields than analogous linear alcohols with the same number of carbon atoms (79% recorded for cyclopentanol). As expected, the lowest yields were obtained for secondary alcohols, with 49% for isopropanol and 59% for 2-pentanol. All these outcomes are consistent with conventional esterification reaction of carboxylic acids with alcohols.

4. Conclusion

A new, efficient and economically-viable route to valuable intermediates, levulinate esters, has been developed. The catalysts, protic ionic...
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Appendix A. Supplementary data

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