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Short communication

Ionic liquid anchored substrate for enzyme catalysed kinetic resolution

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Abstract

A hydroxyl group appended task specific ionic liquid was designed and synthesised. The ionic liquid was used as a vehicle for the substrate of our interest for lipase catalysed kinetic resolution. The ionic liquid anchored ibuprofen underwent *Candida antarctica* lipase catalysed hydrolysis yielding the *S*-enantiomer. The strategy facilitated easy post-resolution isolation of the enantiomers and also carries the prospect of recyclability.

Keywords: Task specific ionic liquids; Ibuprofen; Resolution; Enantioselective hydrolysis

1. Introduction

The earliest ionic liquids in the literature that were probably created unintentionally in the late 19th century, have advanced greatly due to the persistent efforts of the chemists from the materials with potential electrochemical applications to a tantalising new repertoire of solvents [1–3]. The research in this domain has grown by leaps and bounds, unraveling the countless variations of these liquids with several fascinating properties [4]. A negligibly small vapor pressure at ambient temperature, high thermal stability, high ionic conductivity, incredible solvating ability and above all tunability in an ensemble seem to turn these liquids into the future workhorse solvents for virtually any chemical process, you name it. Ionic liquids in the 21st century have gone beyond what they were a decade back. The worth of these compounds is not limited to their applications as mere solvents. The integrated efforts of renowned scientists of wide inter-disciplinarity have diversified the application zone of ionic liquids into several fields such as catalysis, extraction technologies, biotechnologies, fuel cells, nuclear waste treatment, material science, electrochemistry, batteries, etc. [5].

Pioneering work of Davis has led to the development of a branch of ionic liquids designed for a specific task referred to as Task Specific Ionic Liquids, TSILs [6]. This is one avenue of research that is growing at the rapid pace these days, as it makes more sense to tailor ionic liquids for a specific purpose than to randomly synthesise several hundreds of ionic liquids which might turn out to be useful in the end. The core concept involves designing the ionic liquids with the appended functional group for the desired task. Lately, there has been more emphasis on synthesising TSILs with appended co-ordinating functional groups to facilitate the extraction of metal ions or fabricating scavengers. The limitations concerning the chemistry with insoluble supports have been greatly over come by the development of the soluble supports such as polyethylene glycol, fluorous phase and to some extent by using the solvents with the switachable polarity. These developments are/were targeted to eliminate the disadvantages such as long reaction time and excess reagent requirement associated with the use of insoluble supports and at the same time facilitate the process of product separation. With the development of ionic liquids as the neoteric solvents for a number of reactions, the need for the new class of TSILs has been realised. The IL-supported catalysts [7–10], reagents [11,12] and substrates [13,14] have been developed in order to explore the possible advantages these novel strategies can offer over the conventional procedures involving the unsupported counterparts. The area of enzyme catalysed reactions in ionic liquids has witnessed enormous growth since Sheldon and co-workers first demonstrated the use of pure ionic liquids for these reactions [15]. The ability of ionic liquids to efficiently mediate the enantioselective processes catalysed by enzymes was independently reported by Itoh et al. [16] and Kragl and co-workers et al. [17]. Our ongoing investigations on the enzyme catalysed reactions in ionic liquids and interest in task specific

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ionic liquids resulted in conglomeration of these ideas for an altogether different purpose [18–20]. The ability of enzymes to catalyse synthetic organic reactions with high level of activity, selectivity (enantio-, regio- and chemoselectivity) and stability have been distinctly demonstrated in ionic liquids [21–24]. Although the use of IL-coated enzymes (IL as a support for enzymes) for the biocatalytic process has been demonstrated [25], to the best of our knowledge, there is no example to date of covalently anchoring the molecule of interest to ionic liquid for its kinetic resolution. So infact, we decided to make an ionic liquid that can be fed to the enzymes as substrate for kinetic resolution. The idea was conceptualised to test the potential of enzymes to accept ionic liquid as substrate, the concept which we believe would go long way in design of the biodegradable ionic liquids, especially at the time when questions are being raised about their environmental impact.

We herein report the synthesis of a hydroxyl group appended butylmethylimidazolium hexafluorophosphate ionic liquid *via* a simple strategy. The molecule of interest, i.e. (±)-ibuprofen was then anchored covalently to the ionic liquid for the purpose of lipase catalysed kinetic resolution. The hexafluorophosphate based ionic liquid was chosen for the study as it belongs to the class of neutral, hydrophobic category of ionic liquids, which are easy to prepare, purify and handle. Moreover, these facilitate easy isolation of compounds by extraction with organic solvents. Another critical reason behind the choice of this ionic liquid was the fact that this class of ionic liquids have proven to be efficient solvent system for the lipase catalysed reactions [18–20].

2. Results and discussions

2.1. Synthesis of ionic liquid anchored ibuprofen

We intended to anchor ibuprofen on the ionic liquid *via* ester linkage so that it can be hydrolysed enantioselectively with the aid of lipases. The hydroxyl group on the ionic liquid has to be on the cation part as hexafluorophosphate based ionic liquid was chosen for the study. For the purpose of enzymatic hydrolysis, we thought it would be worthwhile to place the hydroxyl group at the terminus of the reasonably long alkyl chain so that the substrate mimics the much explored ordinary alkyl ester of ibuprofen in terms of stereo-electronics and kinetics of the lipase catalysed hydrolysis. Ibuprofen, being one of the most widely marketed non-steroidal anti-inflammatory drugs was intentionally chosen for the study as its success would widen the scope of strategy for resolution of not only other NSAID class of drugs but also other commercially important bioactive carboxylic acids. Besides, the lipase-catalysed kinetic resolution of ibuprofen is very well-studied example [26,27]. The kinetic resolution of ibuprofen has also been studied in ionic liquids by enantioselective esterification approach, wherein the ionic liquids are reported to enhance the enantioselectivity of the process [28]. Based on these presumptions; we arrived at the target **1** as shown in Fig. 1. The alkyl chain comprising of four carbons was a viable option from standpoint of kinetic resolution as the substrate would resemble vaguely to the (ω-functionalised) butyl ester of ibuprofen and also the ionic liquid would resemble one of the most widely used 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid, [bmim]PF_6. Moreover, synthetically,

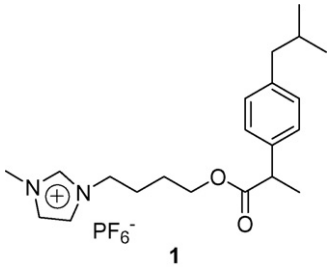
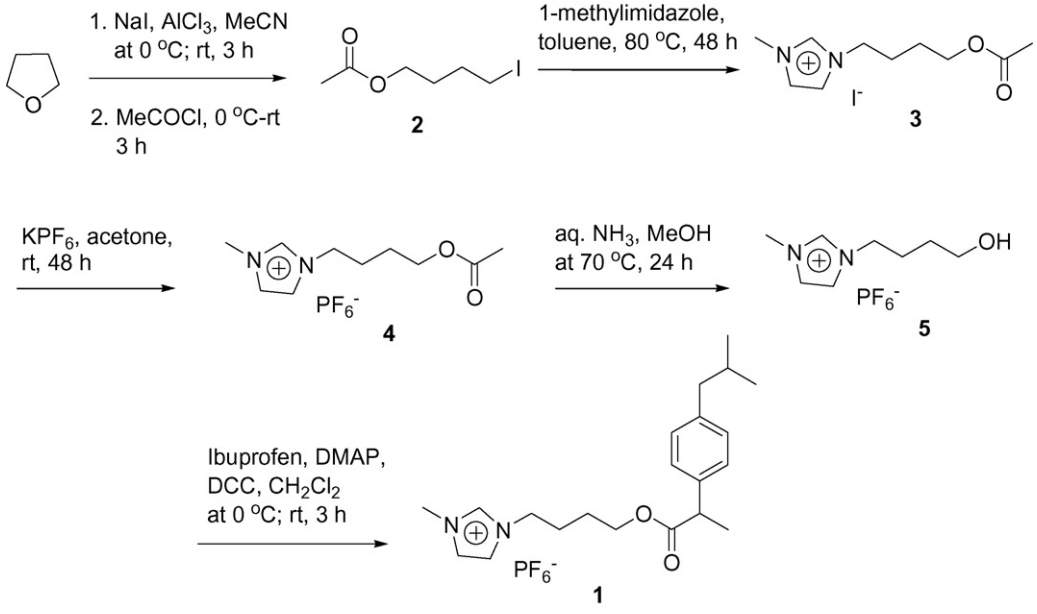


Fig. 1. Ibuprofen anchored ionic liquid for the lipase catalysed kinetic resolution.



Scheme 1. Synthesis of ibuprofen-anchored ionic liquid.

1,4-bifunctionalised alkyl chain can be accessed from cheap and common organic solvent, tetrahydrofuran.

The cyclic ether ring opening reaction on tetrahydrofuran was carried out by using NaI, acetyl chloride and $AlCl_3$ as a Lewis acid to yield the iodoacetate **2** in 98% yields (Scheme 1). The iodoacetate **2** was used for the quaternisation of *N*-methylimidazole, to result in the formation of the quaternary iodide salt **3** in 94% yields. The metathesis of the iodide salt **3** in acetone with KPF_6 resulted in ionic liquid **4** in 90% yields. The deacetylation of **4** was effected using excess of aqueous ammonia (25%) in methanol to yield the –OH functionalised imidazolium based ionic liquid **5** in 95% yields. Finally the –OH functionalised ionic liquid **5** was subjected to esterification reaction with racemic ibuprofen using DCC as coupling agent in presence of the catalytic amount of DMAP. The esterification reaction fetched 84% yield of the product **1** obtained after column chromatography.

2.2. Lipase catalysed hydrolysis of ionic liquid anchored ibuprofen

Once the synthesis of the target was achieved, the most critical step was to evaluate if compound **1** underwent lipase catalysed hydrolysis as such reactions are substrate specific and sometimes even subtle changes in the structure of the substrate might result in unfavorable results. So systematic screening experiments were performed with several available lipases like *Pseudomonas cepacia* (now also know as *Burkholderia cepacia*) lipases supported on celite, PS-C and diatomite, PS-D, *Candida cylindracea* and *Candida antarctica*. Out of four types of lipases screened, only *Candida antarctica* lipase showed the hydrolytic activity in dimethyl sulfoxide in a preliminary experiment with aqueous 0.1 M phosphate buffer at room temperature (Scheme 2). Several other non-polar as well as polar organic solvents, such as n-hexane, dichloromethane, tetrahydrofuran, dioxane and dimethyl sulfoxide along with aq. phosphate buffer were investigated as the reaction media. Hydrolysis was observed only in dimethyl sulfoxide solvent and 0.1 M phosphate buffer (1:1 v/v ratio) after 24 h at room temperature. The ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim]PF_6 and 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF_4 were also investigated as reaction media along with phosphate buffer for the lipase catalysed reaction. The hydrolysis reaction was observed in these ionic liquids, the rates were slightly slower than that in dimethyl sulfoxide. The rationale behind the idea was to exploit both enzymes as well as ionic liquids to achieve the task of kinetic resolution of racemic ibuprofen. Anchoring the substrate to ionic liquid did make the task of post-resolution separation of enantiomers relatively easy. The substrate **1** is soluble in both in DMSO and [bmim]PF_6. The hydrolysed enantiomer was simply extracted with diethyl ether and the rest of the reaction mixture was subjected to chemical hydrolysis with aq. K_2CO_3 to recover the other enantiomer. The –OH appended ionic liquid (in ionic liquid reaction medium) was then ready again for another cycle or totally different task. The enantioselectivity of the hydrolysis was monitored in an unoptimised experiment in dimethyl sulfoxide after 24 h. The *S*-(+)-ibuprofen was obtained with the reasonably good optical purity, i.e. 86% ee with the isolated yield of 87% of theory ($E = 35$). The experiment in ionic liquid [bmim]PF_6 as the reaction medium after 26 h yielded the product in comparable optical yields, i.e. 80% ee. The isolated yield in this case was 80% of theory. In order to investigate the effect of the ionic liquid auxiliary on the reaction rate and activity, *n*-butyl ester of the (±)-ibuprofen was subjected to the enzyme mediated hydrolysis in DMSO and the reaction was monitored by TLC. The rate of hydrolysis of **1** is comparable to the rate of hydrolysis of the *n*-butyl ester of the (±)-ibuprofen.

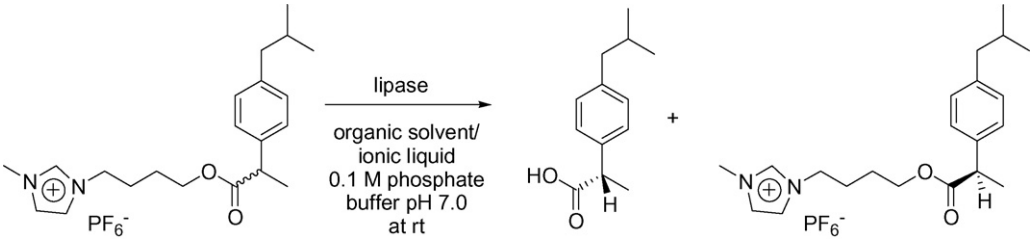
3. Experimental

3.1. Materials and methods

Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen before use. Toluene, acetonitrile and dichloromethane were distilled from CaH_2 under nitrogen. All other commercial reagents were used without any purification unless otherwise indicated.

The analytical thin layer chromatography (TLC) was performed on silica gel plates with QF-254 and TLC visualisation was done by using one or more of the method(s) including UV-light, phosphomolybdic acid as color developing agent and iodine. The flash column chromatography was performed using 230–400 mesh silica gel.

^1H, ^{13}C, ^{19}F and ^{31}P NMR spectra were acquired on Bruker/Tecmag AC-250 MHz (250 MHz ^1H, 63 MHz ^{13}C, 101 MHz ^{31}P, 235 MHz ^{19}F) spectrophotometer. For ^1H and ^{13}C NMR, when $CDCl_3$ was used as a solvent, the chemical shifts (δ) are reported in ppm with respect to TMS as an internal standard (0.00 ppm, ^1H and ^{13}C) and where DMSO d_6 was used as a solvent, the chem-



Scheme 2. Lipase-catalysed enantioselective hydrolysis of ionic liquid anchored ibuprofen ester.

ical shifts are reported in ppm relative to DMSO d_6 (2.50 ppm ^{1}H, 39.52 ppm ^{13}C). The chemical shifts in ^{31}P NMR spectra are reported in ppm with respect to aq. 85% H_3PO_3 as external standard (0.00 ppm ^{31}P) and in ^{19}F NMR spectra with respect to 0.5% $CF_3C_6H_5$ in $CDCl_3$ as external standard (63.72 ppm ^{19}F). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet) and bs (broad singlet). The coupling constants (J) are reported in Hz.

3.2. Experimental procedures for the synthesis of **2–5** and **1**

3.2.1. Synthesis of **2**

To a well stirred suspension of NaI (18.75 g, 125 mmol) and $AlCl_3$ (33.38 g, 250 mmol), in dry acetonitrile (200 mL) maintained at 0 °C, was added dry tetrahydrofuran (9.00 g, 10.15 mL, 125 mmol), over a period of 10 min. The reaction was stirred for 3 h at room temperature. Subsequently, the reaction mixture was cooled at 0 °C and acetyl chloride (14.72 g, 13.33 mL, 187.5 mmol) was gradually added with stirring over a period of 30 min. The stirring was continued for 3 h at room temperature. The resulting solution was partitioned with excess of water and $CHCl_3$ (200 mL). The $CHCl_3$ layer was washed with aqueous $Na_2S_2O_3$ (100 mL of 5% solution) and subsequently with excess of water, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to yield 29.65 g (98% yield) of pale yellow liquid. IR (neat): υ 2957, 1738, 1431, 1387, 1366, 1241, 1178, 1035, 947, 891, 744, 634, 606 and 512 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69–1.81 (m, 2H, AcO-CH_2-CH_2-CH_2-CH_2-I), 1.85–1.97 (m, 2H, AcO-CH_2-CH_2-CH_2-CH_2-I), 2.06 (s, 3H, CH_3-CO-O-), 3.20–3.25 (t, J = 6.6 Hz, 2H, AcO-CH_2-CH_2-CH_2-CH_2-I) and 4.06–4.11 (t, J = 6.3 Hz, 2H, AcO-CH_2-CH_2-CH_2-CH_2-I) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 6.05, 20.95, 29.48, 29.91, 63.17 and 170.93 ppm; MS: *m/z* 183 (100%, [M-(OCOCH$_3$)]$^+$) and 115 (42%, [M-I]$^+$) amu.

3.2.2. Synthesis of **3**

A mixture of *N*-methylimidazole (9.02 g, 8.71 mL, 110 mmol) and iodoacetate ester **2** (24.20 g, 100 mmol) in dry toluene (100 mL) was heated at 80 °C for 48 h to obtain a viscous liquid forming the lower layer. The reaction mixture was refrigerated at 0 °C overnight to yield the solid quaternary iodide. The toluene layer was decanted and the solid was washed with several portions of diethyl ether (3 × 10 mL). The yield of the product was 30.46 g (94% yield). IR (neat): υ 3150, 3082, 2954, 1729, 1626, 1573, 1460, 1368, 1249, 1167, 1044, 959, 832, 753, 620 and 525 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69–1.81 (m, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OAc), 2.00–2.12 (m, 5H, ImN-CH_2-CH_2-CH_2-CH_2-OCO-CH_3), 4.08–4.13 (m, 5H, ImN-CH_3 and ImN-CH_2-CH_2-CH_2-CH_2-OAc), 4.42–4.48 (t, J = 7.4 Hz, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OAc), 7.68–7.69 (m, 1H, 1× -CH arom), 7.72–7.73 (m, 1H, 1× -CH arom) and 9.71 (s, 1H, 1× -CH arom) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.28, 25.30, 27.02, 37.24, 49.56, 63.43, 122.64, 123.96, 136.43 and 171.28 ppm; ESI MS: positive mode: *m/z* 197.0 (100%, $[C_{10}H_{17}N_2O_2]^+$), 198.1 (13%, $[C_{10}H_{17}N_2O_2 + 1]^+$) amu and negative mode: *m/z* 126.8 (100%, [I]$^-$) amu.

3.2.3. Synthesis of **4**

To the solution of **3** (22.68 g, 70 mmol) in dry acetone (200 mL) was added powdered KPF_6 (25.90 g, 140 mmol) and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was filtered and the filtrate upon evaporation of acetone under reduced pressure gave a pale yellow ionic liquid. The crude ionic liquid was passed through alumina (80 g) in a column and eluted with MeOH. The resultant solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The yield of the resulting product was 21.55 g (90% yield). The ionic liquid obtained upon elution with methanol is halide free (indicated by the $AgNO_3$ test). IR (neat): υ 3170, 3124, 2965, 1731, 1577, 1459, 1432, 1389, 1369, 1249, 1169, 1047, 842, 752, 624 and 558 cm^{-1}; ^{1}H NMR (250 MHz, DMSO d_6): δ 1.50–1.62 (m, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OAc), 1.79–1.90 (m, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OAc), 2.01 (s, 3H, -OCO-CH_3), 3.85 (s, 3H, ImN-CH_3), 3.99–4.05 (t, J = 6.5 Hz, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OAc), 4.16–4.22 (t, J = 7.0 Hz, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OAc), 7.68–7.69 (m, 1H, 1 × -CH arom), 7.74–7.76 (m, 1H, 1 × -CH arom) and 9.08 (s, 1H, 1 × -CH arom) ppm; ^{13}C NMR (63 MHz, DMSO d_6): δ 20.68, 24.81, 26.14, 35.75, 48.38, 63.08, 122.23, 123.67, 136.59 and 170.44 ppm; ^{31}P NMR (101 MHz, DMSO d_6): −159.97 to −117.88 ppm (septet); ^{19}F NMR (235 MHz, DMSO d_6): −67.87 to −64.85 ppm (doublet); ESI MS: positive mode: *m/z* 197.0 (100%, $[C_{10}H_{17}N_2O_2]^+$), 198.1 (12%, $[C_{10}H_{17}N_2O_2 + 1]^+$)amu and negative mode: *m/z* 144.7 (100%, $[PF_6]^-$) amu.

3.2.4. Synthesis of **5**

To a solution of **4** (10.26 g, 30 mmol) in methanol (50 mL), was added aq. ammonia (20.4 mL of 25 w% solution, 300 mmol) and the reaction was stirred at 70 °C for 24 h. After the completion of the reaction (indicated by TLC), the solution was evaporated under reduced pressure to get rid of water and MeOH, resulting in the formation of a viscous liquid. The crude ionic liquid was passed through alumina (40 g) in a column and eluted with methanol. The resultant solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The yield of the product was 8.55 g (95% yield). IR (neat): υ 3399, 3172, 3124, 2945, 1665, 1577, 1459, 1430, 1390, 1340, 1169, 1061, 841, 741, 651, 624 and 558 cm^{-1}. ^{1}H NMR (250 MHz, DMSO d_6): δ 1.34–1.45 (m, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OH), 1.76–1.89 (m, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OH), 3.40–3.45 (t, J = 6.3 Hz, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OH), 3.85 (s, 3H, ImN-CH_3), 4.15–4.20 (t, J = 7.3 Hz, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OH), 4.50 (bs, 1H, -OH), 7.67–7.68 (m, 1H, 1× -CH arom), 7.74–7.75 (m, 1H, 1× -CH arom) and 9.08 (s, 1H, 1× -CH arom) ppm; ^{13}C NMR (63 MHz, DMSO d_6): δ 26.44, 28.84, 35.74, 48.79, 59.97, 122.28, 123.62 and 136.54 ppm; ^{31}P NMR (101 MHz, DMSO d_6): −159.97 to −117.88 ppm (septet); ^{19}F NMR (235 MHz, DMSO d_6): −67.91 to −64.89 ppm (doublet); ESI MS: positive mode: *m/z* 155.1 (100%, $[C_8H_{15}N_2O]^+$), 156.1 (9%, $[C_8H_{15}N_2O + 1]^+$) amu and negative mode: *m/z* 144.7 (100%, $[PF_6]^-$) amu.

*3.2.5. Synthesis of **1***

To the solution of (±)-ibuprofen (5.16 g, 24.99 mmol) in anhydrous dichloromethane (100 mL), maintained at 0 °C, was added DMAP (0.203 g, 1.66 mmol) and **5** (5.00 g, 16.66 mmol). To this solution was added a solution of DCC (4.12 g, 19.99 mmol) in anhydrous dichloromethane (20 mL) over a period of 10 min, while maintaining the temperature of the reaction mixture at 0 °C. The stirring was continued at rt for 3 h. The resulting solution was filtered and the precipitate was washed with dichloromethane (5 mL × 10 mL). The organic layer was washed with aqueous 0.5 N HCl (100 mL) and then with aqueous saturated $NaHCO_3$ (100 mL) followed by washings with excess water. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. A 6.84 g (84% yield) of product was obtained upon flash column chromatography (EtOAc:$CHCl_3$, 6:4) as a pale yellow liquid. IR (neat): υ 3165, 3122, 2956, 2870, 1730, 1575, 1512, 1466, 1383, 1336, 1247, 1203, 1168, 1094, 1071, 843, 624 and 558 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.85–0.88 (d, $J = 6.5$ Hz, 6H, Ar-CH_2-$CH(CH_3)_2$), 1.43–1.46 (d, $J = 7.0$ Hz, 3H, -O-CO-CH(CH_3)-Ar), 1.54–1.64 (m, 2H, ImN-CH_2-CH_2-CH_2-CH_2-OCO-), 1.75–1.87 (m, 3H, -CH_2-$CH(CH_3)_2$ and ImN-CH_2-CH_2-CH_2-CH_2-OCO-), 2.40–2.43 (d, $J = 7.0$ Hz, 2H, Ar-CH_2-$CH(CH_3)_2$), 3.65–3.73 (q, $J = 7.1$ Hz, 1H, -O-CO-CH(CH_3)-Ar), 3.83 (s, 3H, ImN-CH_3), 4.02–4.07 (m, 4H, ImN-CH_2-CH_2-CH_2-CH_2-OCO-), 7.06–7.25 (m, 6H, 6× -CH arom.) and 8.37 (s, 1H, 1× -CH arom.) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 18.39, 22.32, 25.04, 26.46, 30.15, 36.07, 44.92, 44.99, 49.32, 63.55, 122.06, 123.68, 127.21, 129.38, 135.80, 137.84, 140.58 and 174.86 ppm; ^{31}P NMR (101 MHz, $CDCl_3$): −164.89 to −122.77 ppm (septet); ^{19}F NMR (235 MHz, $CDCl_3$): −74.54 to −71.52 ppm (doublet); ESI MS: positive mode: *m/z* 343.2 (100%, $[C_{21}H_{31}N_2O_2]^+$), 344.2 (25%, $[C_{21}H_{31}N_2O_2 + 1]^+$) amu and negative mode: *m/z* 144.7 (100%, $[PF_6]^-$) amu.

*3.3. Enzymatic hydrolysis of **1***

In a typical experimental procedure, to the solvent (1 mL), **1** (0.1792 g, 0.367 mmol), lipase (450 U) and phosphate buffer of pH 7 (0.1 M, 1 mL) were added and the reaction mixture was stirred for a suitable time at room temperature. The reaction was monitored by TLC. After completion of reaction, the volatile organic solvents (if any) were evaporated under reduced pressure and the product was extracted by adding water (10 mL) and partitioning the reaction mixture with ether (10 mL). The extraction step was repeated with ether (2 mL × 10 mL) and the combined ether extracts were dried over anhydrous Na_2SO_4 concentrated at reduced pressure to obtain the hydrolyzed *S*-(+)-ibuprofen. The unhydrolysed ester **1** remains in [bmim]PF_6 or it remains suspended in the aqueous layer when DMSO was used for the hydrolysis. In the later case, the extraction of the aqueous layer with CH_2Cl_2 (2 mL × 10 mL) followed by drying and evaporation of CH_2Cl_2 yields the unreacted ester. Where as in the former case, the combination of [bmim]PF_6 and **1** is subjected to hydrolysis directly.

3.4. Chemical hydrolysis of unreacted chiral ester

The unreacted ester (or its solution in [bmim]PF_6) recovered from the enzymatic hydrolysis was dissolved in methanol (10 mL) and to this solution was added aqueous methanolic solution of K_2CO_3 (0.100 g in 5 mL of 50% aqueous methanol). The reaction mixture was stirred at room temperature for 6 h. The reaction was monitored and the completion was indicated by TLC. After completion of reaction, methanol was evaporated under reduced pressure and the contents were neutralised (to pH 6) and the product was extracted by adding water (10 mL) and partitioning the reaction mixture with ether (10 mL). The extraction step was repeated with ether (2 × 10 mL) and the combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to obtain the hydrolysed *R*-(-)-ibuprofen.

4. Conclusion

Thus, *via* a very simple, efficient and high yielding protocol the –OH appended ionic liquid was synthesised which, we believe is potentially a very important ionic liquid. The –OH appended ionic liquid due to a synthetically versatile functional group offers various possibilities of covalently anchoring chiral auxillaries, catalysts, reagents, probes, etc to it. This linkage or immobilisation would facilitate the exploitation of advantages of supported chemistry in the ionic liquid phase. Such a scenario, we believe is close to functional ideal. To the best of our knowledge this is the first example of the utilisation of the ionic liquid supported substrate for an enzyme catalysed reaction. Encouraging optical yields were observed in the preliminary unoptimised experiments of lipase catalysed hydrolysis reported here. Nevertheless, the method has lots of room for improvement by fine-tuning of experimental conditions. More work on improvement and extension of this strategy for kinetic resolution of other chiral drugs are underway in our laboratory.

Acknowledgments

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