ChemistryOpen

Research Article
doi.org/10.1002/open.202200135

Chemistry Europe
European Chemical Societies Publishing

www.chemistryopen.org

Novel Glucosylimidazolium Ionic-Liquid-Supported Novozym 435 Catalysts – A Proof of Concept for an Acrylation Reaction

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A series of novel ionic liquids based on glucose was synthesized in high yields in simple two or three-step reaction procedures. These carbohydrate-based ionic liquids were studied and compared to commercially available imidazolium-based ionic liquids as supports for Novozym 435 in the acrylation of *n*-butanol. A direct correlation between the availability of hydroxy groups and the overall activity as well as an enhanced recyclability of the biocatalyst has been found for the glucose-based ionic liquids.

Introduction

Among the wide array of enzyme classes, lipases are the most commonly used enzymes.[1,2] Their biological function is the hydrolysis of triglycerides, but they are also more broadly used for many types of hydrolysis[3–4] and esterification reactions.[5–7] In general, biocatalysis is considered as one of the main constituents of the "Twelve Principles of Green Chemistry",[8] since enzymes usually work in an aqueous medium under mild reaction conditions, while also being selective and specific towards their substrates and thus making additional protection/deprotection steps obsolete.[9] On the other hand, however, enzymes are often only moderately stable even under physiological conditions and may suffer from product inhibitions.[10] A typical tool for biocatalysts to enhance the stability and performance of an enzyme is immobilization.[11] In this field, Novozym 435, which is the lipase B from *Candida antarctica* (CALB), immobilized on a macroporous acrylic polymer resin, is the most widely used immobilized biocatalyst.[11] Other lipase-mediated reactions usually need to compete with CALB due to its exceptional high thermo- and pH-stability as well as the high affinity towards esters, amides and thiols.[12]

As part of our continued interest in optimizing the syntheses and applications of carbohydrate-based ionic liquids (CHILs),[13–15] a rapidly growing topic in the recent years,[16] we were investigating the use of CHILs in biocatalysis. Ionic liquids are generally well-known in biocatalysis, for example as reaction medium[17] or as support for the immobilized enzymes,[18] amongst other uses. Recent work from Boncel, Chrobok et al. showcases the immobilization of CALB on carbon nanotubes supported by several ionic liquids.[19] Among their tests with mostly imidazolium-based ionic liquids. two examples of carbohydrate-based ionic liquids particularly sparked our interest.

In the present work, we decided to investigate the relationships between the structure of the CHILs used for the IL support and the overall activity of the immobilized enzyme. Due to its industrial relevance, as well as to maintain comparability with aforementioned work of Boncel, Chrobok et al., we chose the model reaction between *n*-butanol and acrylic acid,[20–21] in our case catalyzed by IL-supported Novozym 435, as the basis of this project.

Results and Discussion

The first part of this project was the synthesis of a series of novel carbohydrate-based ionic liquids. Recently, our group published a straightforward and highly efficient synthesis of glucosylimidazolium iodide **3a** from the corresponding 6-iodo derivative of methyl α-D-glucopyranoside.[13] Herein, we reproduced our previous work and greatly expanded its scope (Schemes 1 and 2).

It is also noteworthy that, previously,[13] we synthesized **3a** from **2** in a high excess of methylimidazole as solvent. While this procedure also led to 99% yield, the work-up and removal of the excess of methylimidazole was difficult to reproduce. We optimized this strategy in this work by using only a small excess of the corresponding imidazole with DMF as solvent, followed by the precipitation of the products **3a** and **4**–**6** using ethyl acetate.

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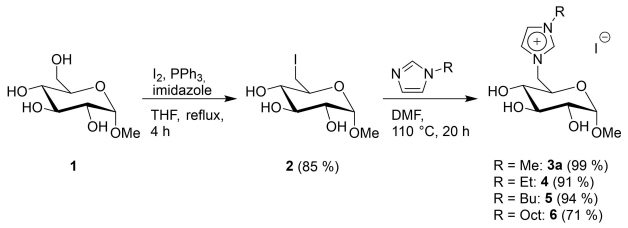
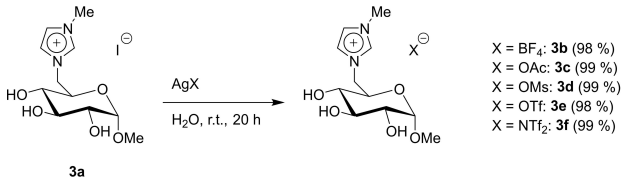
Supporting information for this article is available on the WWW under https://doi.org/10.1002/open.202200135



Scheme 1. Synthesis of four glucosylimidazolium products with varying alkyl chains.

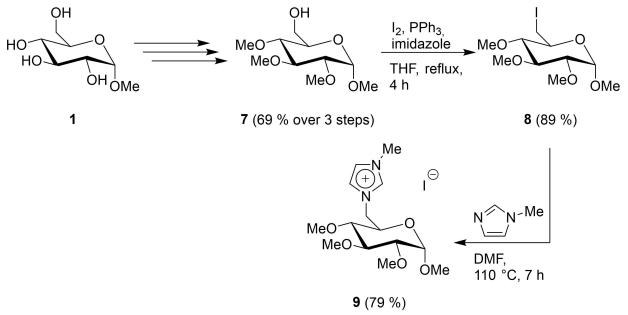


Scheme 2. Anion exchange reactions starting from **3 a**.

Due to the hydrophobic nature of the biocatalytic reaction to be investigated (esterification of *n*-butanol and acrylic acid), we decided to synthesize three new glucosylimidazolium iodide products with ethyl- (**4**), *n*-butyl- (**5**) and *n*-octyl-chains (**6**) at the imidazolium (Scheme 1). All of these reactions proceeded in full conversion, with high yields between 91 and 99%. In contrast, in the case of the **6**, the octyl chain leads to a higher solubility of **6** in ethyl acetate, thus leading to a diminished yield of 71%.

Then, to further investigate the effect of the different anions on the IL-supported Novozym 435 catalysts, we performed several anion exchange reactions with **3 a**. The iodide anion of **3 a** enables a simple reaction procedure by using an equivalent amount of a silver salt of choice to achieve the desired product. We chose the anions tetrafluoroborate **3 b**, acetate **3 c**, mesylate **3 d**, triflate **3 e** and bis-triflylimide **3 f** (Scheme 2).

Lastly, we aimed to synthesize a glucosylimidazolium product in which all hydroxy groups are methylated. In our first attempt, we tried to methylate **2** with methyl iodide, using different bases like sodium hydride or triethylamine at varying temperatures. All reactions led to inseparable mixtures of unidentified carbohydrate products. Thus, we had to take a longer route to synthesize **9** (Scheme 3).



Scheme 3. Five-step synthesis of the permethylated glucosylimidazolium **9**.

Starting with a synthetic strategy previously published by our group,[15] the commercially available **1** was firstly protected with a trityl group in position 6, then permethylated using methyl iodide and sodium hydride and finally converted to **7** by removal of the trityl protecting group. With **7**, a permethylated glucopyranoside with only a single free hydroxy group in position 6, in hand, the Appel reaction leading to product **8** proceeded smoothly in 89% yield. This marks an alternative and more efficient strategy towards **8** than previously published by Kuzuhara et al. who converted **7** to a 6-tosylated intermediate (53% yield) which was followingly converted to **8** using sodium iodide (49% yield).[22]

Finally, the reaction of **8** with *N*-methylimidazole lead to the desired ionic liquid **9** in 79% yield. In this case, a precipitation of the product from the reaction procedure, as reported for **3 a**, **4**, **5**, and **6**, was not possible, since **9** is fully soluble in ethyl acetate. Thus, product **9** was purified through column chromatography.

To identify our products as ionic liquids, which are by definition salts with a melting point under 100 °C, the melting points of all 10 ionic products were measured (Table 1). The data shows that only two of the salts cannot be defined as ILs, namely **3 a** and **4**, although the melting point of **4** is close to 100 °C. All other eight products are either viscous liquids at room temperature (the triflate and bis-triflylimide products **3 e** and **3 f** as well as the butyl- and octyl-chain products **5** and **6**) or exhibit melting points only close above room temperature, ranging from 30 to 41 °C.

After successfully synthesizing ten CHILs, nine of which were previously unreported in literature, we used these products as well as five additional conventional imidazolium-based ionic liquids for the preparation of the IL-supported Novozym 435 catalysts. Since our goal for the biocatalytic acrylation was to investigate the influence of the IL coating on the yield of the reaction, we had to choose the conventional imidazolium ILs with a high comparability towards our CHILs in mind. Thus, we decided to use EMIM-I, EMIM-BF_4, EMIM-NTf_2, HO-EMIM-I and HO-EMIM-NTf_2 (Figure 1).

Most of these ILs were commercially available; only HO-EMIM-I had to be synthesized, which was prepared from *N*-methylimidazole and 2-iodoethanol in 97% yield, following a reaction procedure from Kitaoka et al. who had previously synthesized the similar bromide salt.[23]

Table 1. Physical appearance and melting points of the glucosylimidazolium products.

Product	Code name	Physical appearance	Melting point [°C]
3 a	GMIM-I	light-brown solid	172–173
3 b	GMIM-BF_4	yellow solid	30–31
3 c	GMIM-OAc	yellow solid	39–40
3 d	GMIM-OMs	orange solid	36–38
3 e	GMIM-OTf	yellow liquid	/
3 f	GMIM-NTf_2	yellow liquid	/
4	GEIM-I	off-white solid	99–101
5	GBIM-I	orange liquid	/
6	GOIM-I	orange liquid	/
9	Me-GMIM-I	orange solid	40–41

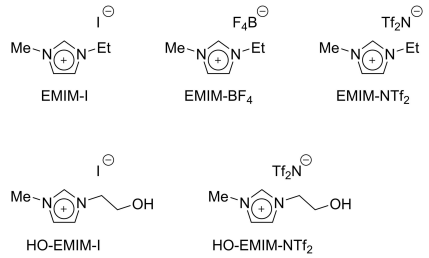


Figure 1. Conventional imidazolium-based ILs used in this study.

In the next step, we prepared our IL-supported Novozym 435 biocatalyst. For this, we used a modified version of the procedure by Iborra et al.[24] The Novozym 435 and the ionic liquid were gently stirred at room temperature in an orbital shaker, followed by filtration and drying of the biocatalyst. The uptake of the IL on the Novozym 435 was calculated through the residual IL remaining in the filtrate.

Table 2. IL content of the IL supported Novozym 435 biocatalysts and yields of the *n*-butyl acrylate.[a]

Entry	Code name	IL content [μmol g^{-1}]	Average yield of *n*-butyl acrylate[b]
1	Novozym 435	/	55% (±2.5)
2	N435-GMIM-I (**3a**)	86.3	67% (±2.0)
3	N435-GMIM-BF_4 (**3b**)	143.4	6% (±0.5)
4	N435-GMIM-OAc (**3c**)	141.1	64% (±2.7)
5	N435-GMIM-OMs (**3d**)	67.0	59% (±3.9)
6	N435-GMIM-OTf (**3e**)	68.8	61% (±1.9)
7	N435-GMIM-NTf_2 (**3f**)	88.7	64% (±2.8)
8	N435-GEIM-I (**4**)	153.0	67% (±1.1)
9	N435-GBIM-I (**5**)	141.9	64% (±1.2)
10	N435-GOIM-I (**6**)	47.0	63% (±0.5)
11	N435-Me-GMIM-I (**9**)	110.1	58% (±0.3)
12	N435-EMIM-I	57.9	55% (±3.0)
13	N435-EMIM-BF_4	73.2	44% (±1.4)
14	N435-EMIM-NTf_2	62.4	60% (±0.7)
15	N435-HO-EMIM-I	76.1	67% (±1.1)
16	N435-HO-EMIM-NTf_2	68.0	67% (±1.2)

[a] 1 mL reaction volume containing acrylic acid (1 M, 1 mmol, 68.6 μL), *n*-butanol (2 M, 2 mmol, 183 μL), cyclohexane (748 μL), N435-biocatalyst (150 mg), 24 h, 25 °C. [b] Determined by GC, with five individual samples taken from each reaction. Standard deviation of average yield in brackets.

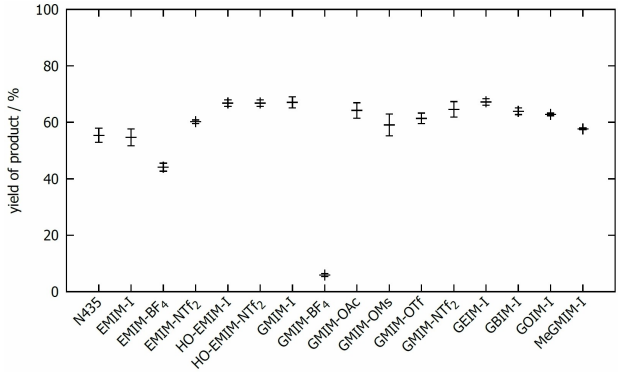


Figure 2. Yield of *n*-butyl acrylate for the reaction of acrylic acid and *n*-butanol with Novozym 435 (N435) and each of the ILs tested in this study. Reaction conditions: 1 mL reaction volume containing acrylic acid (1 M, 1 mmol, 68.6 μL), *n*-butanol (2 M, 2 mmol, 183 μL), cyclohexane (748 μL), N435-biocatalyst (150 mg), 24 h, 25 °C.

With the prepared IL-supported biocatalyst in hand, we performed our proof-of-concept acrylation reactions with *n*-butanol and acrylic acid in cyclohexane, akin to previously reported reaction conditions.[19] An overview of all yields can be found in Table 2, as well as visualized in Figure 2.

Looking at the performance of Novozym 435 without any IL support, the yield of *n*-butyl acrylate is at 55% (Table 2, entry 1). It is noteworthy that for the same reaction under overall similar reaction conditions, with the only difference being a lower substrate concentration, a yield of *n*-butyl acrylate of 74% was previously reported.[19] Our value of 55% was individually confirmed with two different batches of Novozym 435.

Only two of the tested ILs lead to yields lower than the 55% given by Novozym 435, which are the two tetrafluoroborate ILs GMIM-BF_4 **3b** and EMIM-BF_4 with 6 and 44% yield, respectively (Table 2, entries 3 and 13). Similarly, the BF_4 ionic liquid tested by Boncel, Chrobok et al. also led to their worst reported performance,[19] thus clearly showcasing a generally negative influence of the tetrafluoroborate anion independent of the corresponding IL cation. A similar behavior was observed by Queirós et al., where the tetrafluoroborate anion showed the highest toxicity inflicted to bacteria because of fluoride dissociation.[25]

All other IL-supported Novozym 435 biocatalysts led to a similar or overall higher yield of *n*-butyl acrylate than with non-IL-supported Novozym 435, with the highest yields at 67%. Overall, besides the aforementioned negative effect of the BF_4-containing ILs, no clear influence of the anion on the reaction performance could be found. There are only small differences, like EMIM-I with 55% yield in comparison to EMIM-NTf_2 with 60% yield (Table 2, entries 12 and 14) or GMIM-OMs **3d** having the worst (59%) and GMIM-I **3a** the highest (67%) performance out of the six GMIM-based ILs (Table 2, entries 2–7).

From all the data, there is one clear influence we found: The availability of at least one hydroxy group in the IL leads to a higher yield. This most clearly visible when comparing EMIM-I with its 55% to HO-EMIM-I and its 67% yield (Table 2, entries 12 and 15). The only difference between these two ILs is a single hydroxy function. The same trend is also reconfirmed with the glucosylimidazolium-based ILs **3a** and **9**, whose difference lies in free and methylated OH groups, respectively (Table 2, entries 2 and 11).

Overall, four of the tested novel IL-supported Novozym 435 biocatalysts led to the highest yield of *n*-butyl acrylate of 67% at the given reaction conditions. These are GMIM-I **3a**, GEIM-I **4**, HO-EMIM-I and HO-EMIM-NTf_2 (Table 2, entries 2, 8 and 15–16). Out of these four, GMIM-I **3a** and the two HO-EMIM ILs had overall similar IL contents on the Novozym 435, ranging from 68 to 86 μmol IL per 1 gram of Novozym 435. Only GEIM-I **4** has a notably higher IL content of 153 μmol g^{-1}. Thus, the similar performance of **4** in comparison to the other three best-performing ILs may be attributed to the higher IL content and not to the properties of **4** itself.

However, when evaluating which of the ILs is objectively the best in this study, other factors than only the yield have to

be considered. One such factor is the availability/ effectiveness of the synthesis of the ionic liquid. Here, out of the aforementioned four best salts (**3a**, **4**, HO-EMIM-I and -NTf_2), only HO-EMIM-NTf_2 is commercially available. When looking at the synthesis, both **3a** and **4** can be prepared in simple two-step procedures in high yields over 90%. HO-EMIM-I is also fairly straightforward to synthesize, however, it needs an extensive heating time.

Another highly important factor to consider is the toxicity of the IL. It has been apparent in the literature of the recent years that many conventional imidazolium-based ionic liquids suffer from a high (eco)toxicity.[26–27] On the other hand, glucopyranoside-based ionic liquids with an overall similar chemical structure to the ones featured in this study have been proven to possess an enhanced biocompatibility.[15] Biocompatibility tests for the glucosylimidazolium CHILs featured in this study are currently also under preparation.

The final part of this study, and with this the final factor to decide on the objectively best IL-supported catalyst in this work, was biocatalyst recycling. For both **3a** and HO-EMIM-NTf_2, which we chose as the best representatives for each class of either conventional imidazolium-based ionic liquids or glucosylimidazolium-based ionic liquids, the used IL-supported Novozym 435 was collected by filtration after reaction, re-dried and then used for the next reaction, with ten cycles each. Here, we could find some drastic differences in the performance of each biocatalyst (Figure 3). The yield of *n*-butyl acrylate achieved by N435-HO-EMIM-NTf_2 was stable for four cycles and then quickly fell to only 26% yield after ten cycles. The glucosylimidazolium iodide-supported Novozym 435, however, maintains its performance nearly unchanged for the tested ten cycles, lowering to only 62% from the initial 67%, marking **3a** as the overall best support material for this type of reaction.

In a final note, it should be pointed out that the IL-supported immobilized CALB on carbon nanotubes catalysts, which were recently tested for similar biocatalytic acrylation studies,[19] show an overall higher first-cycle performance (up to 99%) than the IL-supported Novozym 435 biocatalysts in this work. However, they are not reliably recyclable and lose their high performance after only 2–3 cycles while furthermore needing a more complex catalyst preparation.

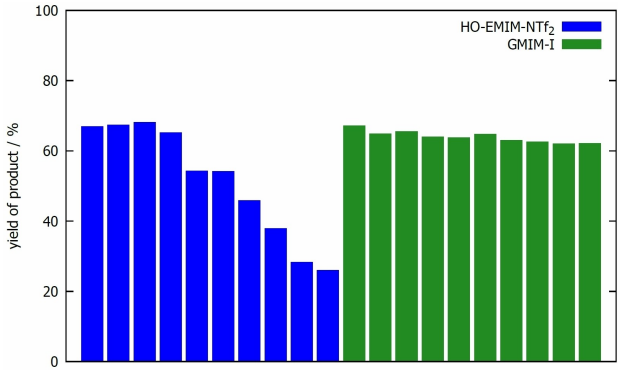


Figure 3. Recyling experiments with HO-EMIM-NTf_2 and GMIM-I-supported Novozym 435, ten cycles each.

Conclusion

Overall, ten glucosylimidazolium products have been synthesized as part of this study, nine of which had not been reported in literature before. Their synthesis is highly optimized, needing only two or three steps with yields mostly over 90%. Their thermal data shows that eight of the ten products can be classified as ionic liquids. These ten novel CHILs were comparatively studied, beside five conventional imidazolium-based ionic liquids, as supports for Novozym 435 in the reaction between *n*-butanol and acrylic acid.

The direct comparison between all ionic liquids allowed to define a number of trends: First, nearly every IL support leads a generally higher yield than obtained from using the non-IL-supported Novozym 435. Second, the anion of the IL has only a low influence on the overall yield, with the exception of tetrafluoroborate, which always seems to lead to a diminished performance. And third, the availability of at least one free hydroxy group clearly enhances the activity and yield.

Finally, recycling studies performed for two of the best salts in this study, which are the glucosylimidazolium salt GMIM-I **3a** and the commercially available ionic liquid HO-EMIM-NTf_2, have proven a high catalyst recyclability for the glucosylimidazolium salt **3a**.

Experimental Section

All reagents and solvents were purchased from commercial sources and used as received without further purification, if not stated otherwise. The NMR spectra were recorded on a Bruker AVANCE 300 III or 500. All chemical shifts are reported in ppm. $CDCl_3$ was calibrated as 7.27 ppm (^{1}H) and 77.00 ppm (^{13}C). DMSO-d_6 was calibrated as 2.49 ppm (^{1}H) and 39.50 (^{13}C). D_2O was calibrated as 4.80 (^{1}H). ESI-MS were measured an Agilent 1200/6210 Time-of-Flight LC-MS or an Thermo Scientific Exactive ESI/DART FTMS. The specific rotations were measured with a Dr. Kernchen Gyromat-HP Digital Automatic Polarimeter with concentrations given in mg/mL. Biocatalytic experiments were carried out in a Biosan TS-100 thermo-shaker. Conversion was measured with a Trace 1310 gas chromatograph by Thermo Scientific, equipped with a 1300 flame ionization detector and an Agilent HP-5 column (30 m × 0.25 mm × 0.25 μm). For the internal standard, 20 mM *n*-decane in cyclohexane has been used in all measurements. Temperatures of injector and detector were set to 250 °C.

Biocatalyst preparation

Acetonitrile (30 mL) was added to Novozym 435 (1.0 g) and the ionic liquids (0.3 g) in a 30 mL glass vial. The reaction was gently stirred at room temperature for 30 min in an orbital shaker. The biocatalyst was dried under high vacuum after filtration. The acetonitrile in the collected filtrate was removed by rotary evaporator to determine the residual IL not adsorbed onto the biocatalyst.

Method for GC determination of the yield *n*–butyl acrylate

Cyclohexane (748 μL), acrylic acid (68.6 μL), *n*-butanol (183 μL) and the biocatalyst (150 mg) were placed into a 2 mL Eppendorf Tube for 24 h at 25 °C. Reaction progress was controlled by GC analysis. A

200 μL sample was withdrawn from the reaction and further diluted with 1 mL cyclohexane and 200 μL internal standard.

Temperature program for GC started at 75 °C, followed by a heating rate of 5 K/min to 110 °C and 30 K/min to 140 °C.

Methyl 6-iodo-α-D-glucopyranoside 2

2 was prepared according to Ref. [13].

1-(Methyl α-D-glucopyranosid-6-yl)-3-methylimidazolium iodide 3 a

The synthesis of product **3 a** was modified from a previous work of our group.[13] **2** (3.649 g, 12.0 mmol) and *N*-methylimidazole (1.642 g, 20.0 mmol) were dissolved in DMF (20 mL) and stirred at 110 °C for 20 hours. After cooling down, ethyl acetate (160 mL) was added and the flask was stored in a fridge overnight. The solvent was decanted and the precipitated solid was washed with ethyl acetate (3×40 mL) and dried under high vacuum to isolate the product as a light-brown solid (4.574 g, 99 %). m.p.: 172–173 °C. $[\alpha]_D^{25} = +63.4$ (c = 1.8, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 3.26–3.32 (m, 1H); 3.31 (s, 3H, OCH_3); 3.63 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.72–3.78 (m, 1H); 3.94–3.98 (m, 1H); 4.00 (s, 3H, NCH_3); 4.50 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.3 Hz, H-6a); 4.69 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.5 Hz, H-6b); 4.89 (d, 1H, ^3J = 3.7 Hz, H-1); 7.55 (d, 1H, ^3J = 2.0 Hz, H_{Ar}); 7.64 (d, 1H, ^3J = 2.0 Hz, H_{Ar}); 8.89 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 36.1 (NCH_3); 49.9 (C-6); 55.2 (OCH_3); 69.4, 70.5, 71.0, 72.9 (C-2, C-3, C-4, C-5); 99.3 (C-1); 123.2, 123.6, 137.0 (CH_{Ar}). HRMS (ESI, *m/z*): Calculated for $C_{11}H_{19}N_2O_5^+$, 259.1294; measured 259.1299. Calculated for I^-, 126.9045; measured 126.9047.

1-(Methyl α-D-glucopyranosid-6-yl)-3-methylimidazolium tetrafluoroborate 3 b

3 a (1 mmol, 386 mg) and silver tetrafluoroborate (1 mmol, 195 mg) were suspended in water (5 mL) and stirred for 20 h. The product was obtained as a yellow solid (340 mg, 98 %) after filtration and removal of water. m.p.: 30–31 °C. $[\alpha]_D^{26} = +75.4$ (c = 6.1, H_2O). ^{1}H NMR (300 MHz, D_2O): 3.23 (dd, 1H, ^3J = 10.0 Hz, ^3J = 9.0 Hz); 3.27 (s, 3H, OCH_3); 3.57 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.67–3.74 (m, 1H); 3.89–3.96 (m, 1H); 3.95 (s, 3H, NCH_3); 4.45 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.4 Hz, H-6a); 4.64 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.5 Hz, H-6b); 4.84 (d, 1H, ^3J = 3.8 Hz, H-1); 7.50–7.51 (m, 1H, H_{Ar}); 7.58–7.60 (m, 1H, H_{Ar}); 8.82 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 35.7 (NCH_3); 49.8 (C-6); 55.0 (OCH_3); 69.4, 70.4, 71.0, 72.9 (C-2, C-3, C-4, C-5); 99.3 (C-1); 123.2, 123.5, 137.0 (CH_{Ar}). ^{19}F NMR (282 MHz, D_2O): δ = −150.38 (s, ^{10}B-coupling signal), −150.43 (q, ^1J = 1.3 Hz, ^{11}B-coupling signal). HRMS (ESI, *m/z*): Calculated for $C_{11}H_{19}N_2O_5^+$, 259.1294; measured 259.1297. Calculated for BF_4^-, 86.0066; measured 86.0070.

1-(Methyl α-D-glucopyranosid-6-yl)-3-methylimidazolium acetate 3 c

3 a (1 mmol, 386 mg) and silver acetate (1 mmol, 167 mg) were suspended in water (5 mL) and stirred for 20 h. The product was obtained as a yellow solid (315 mg, 99 %) after filtration and removal of water. m.p.: 39–40 °C. $[\alpha]_D^{27} = +64.7$ (c = 1.0, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.93 (s, 3H, CH_3); 3.21 (dd, 1H, ^{3}J = 10.0 Hz, ^{3}J = 9.0 Hz); 3.26 (s, 3H, OCH_3); 3.55 (dd, 1H, ^{3}J = 9.8 Hz, ^{3}J = 3.8 Hz, H-2); 3.66–3.72 (m, 1H); 3.87–3.92 (m, 1H); 3.94 (s, 3H, NCH_3); 4.44 (dd, 1H, ^{2}J = 14.6 Hz, ^{3}J = 7.4 Hz, H-6a); 4.63 (dd, 1H, ^{2}J = 14.6 Hz, ^{3}J = 2.5 Hz, H-6b); 4.83 (d, 1H, ^{3}J = 3.8 Hz, H-1); 7.49–7.50 (m, 1H, H_{Ar}); 7.58–7.59 (m, 1H, H_{Ar}); 8.82 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 23.2 (CH_3); 35.7 (NCH_3); 49.8 (C-6); 54.9 (OCH_3); 69.4, 70.4, 71.0, 72.8 (C-2, C-3, C-4, C-5); 99.3 (C-1); 123.1, 123.5, 137.0 (CH_{Ar}); 181.4 (C=O). HRMS (ESI, *m/z*): Calculated for $C_{11}H_{19}N_2O_5^+$, 259.1294; measured 259.1298.

1-(Methyl α-D-glucopyranosid-6-yl)-3-methylimidazolium methanesulfonate 3 d

3 a (1 mmol, 386 mg) and silver methanesulfonate (1 mmol, 203 mg) were suspended in water (5 mL) and stirred for 20 h. The product was achieved as an orange solid (349 mg, 99 %) after filtration and removal of water. m.p.: 36–38 °C. $[\alpha]_D^{25} = +76.7$ (c = 1.3, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 2.84 (s, 3H, CH_3); 3.22 (dd, 1H, ^3J = 10.0 Hz, ^3J = 9.1 Hz); 3.27 (s, 3H, OCH_3); 3.56 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.67–3.73 (m, 1H); 3.89–3.93 (m, 1H); 3.95 (s, 3H, NCH_3); 4.45 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.4 Hz, H-6a); 4.64 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.5 Hz, H-6b); 4.84 (d, 1H, ^3J = 3.8 Hz, H-1); 7.50–7.51 (m, 1H, H_{Ar}); 7.59–7.60 (m, 1H, H_{Ar}); 8.83 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 35.8 (NCH_3); 38.4 (CH_3); 49.8 (C-6); 55.0 (OCH_3); 69.4, 70.4, 71.0, 72.9 (C-2, C-3, C-4, C-5); 99.3 (C-1); 123.2, 123.5, 137.0 (CH_{Ar}). HRMS (ESI, *m/z*): Calculated for $C_{11}H_{19}N_2O_5^+$, 259.1294; measured 259.1298. Calculated for $CH_3O_3S^-$, 94.9803; measured 94.9802.

1-(Methyl α-D-glucopyranosid-6-yl)-3-methylimidazolium trifluoromethanesulfonate 3 e

3 a (1 mmol, 386 mg) and silver trifluoromethanesulfonate (1 mmol, 257 mg) were suspended in water (5 mL) and stirred for 20 h. The product was obtained as a viscous yellow viscous liquid (398 mg, 98 %) after filtration and removal of water. $[\alpha]_D^{26} = +126.8$ (c = 0.6, H_2O). ^{1}H NMR (300 MHz, D_2O): 3.22 (dd, 1H, ^3J = 10.0 Hz, ^3J = 9.0 Hz); 3.27 (s, 3H, OCH_3); 3.57 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.67–3.74 (m, 1H); 3.89–3.93 (m, 1H); 3.95 (s, 3H, NCH_3); 4.45 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.4 Hz, H-6a); 4.64 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.5 Hz, H-6b); 4.84 (d, 1H, ^3J = 3.8 Hz, H-1); 7.50–7.51 (m, 1H, H_{Ar}); 7.59–7.60 (m, 1H, H_{Ar}); 8.82 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 35.7 (NCH_3); 49.8 (C-6); 55.0 (OCH_3); 69.4, 70.4, 71.0, 72.9 (C-2, C-3, C-4, C-5); 99.3 (C-1); 119.6 (q, ^1J = 317.4 Hz, CF_3); 123.2, 123.5, 136.9 (CHAr). ^{19}F NMR (282 MHz, D_2O): δ = −78.8. HRMS (ESI, *m/z*): Calculated for $C_{11}H_{19}N_2O_5^+$, 259.1294; measured 259.1297. Calculated for $CF_3O_3S^-$, 148.9520; measured 148.9519.

1-(Methyl α-D-glucopyranosid-6-yl)-3-methylimidazolium bis-(trifluoromethanesulfonyl)-imide 3 f

3 a (1 mmol, 386 mg) and silver bis-(trifluoromethanesulfonyl)-imide (1 mmol, 388 mg) were suspended in water (5 mL) and stirred for 20 h. The product was obtained as a viscous red viscous liquid (533 mg, 99 %) after filtration and removal of water. $[\alpha]_D^{25} = +55.8$ (c = 2.1, H_2O). ^{1}H NMR (300 MHz, D_2O): 3.23 (dd, 1H, ^3J = 10.0 Hz, ^3J = 9.0 Hz); 3.27 (s, 3H, OCH_3); 3.57 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.67–3.74 (m, 1H); 3.89–3.93 (m, 1H); 3.95 (s, 3H, NCH_3); 4.45 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.4 Hz, H-6a); 4.64 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.6 Hz, H-6b); 4.84 (d, 1H, ^3J = 3.8 Hz, H-1); 7.50–7.51 (m, 1H, H_{Ar}); 7.59–7.60 (m, 1H, H_{Ar}); 8.82 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 35.7 (NCH_3); 49.8 (C-6); 55.0 (OCH_3); 69.4, 70.5, 71.0, 72.9 (C-2, C-3, C-4, C-5); 99.3 (C-1); 119.2 (q, ^1J = 319.8 Hz, CF_3); 123.2, 123.5, 136.9 (CH_{Ar}). ^{19}F NMR (282 MHz, D_2O): δ = −79.2. HRMS (ESI, *m/z*): Calculated for $C_{11}H_{19}N_2O_5^+$, 259.1294; measured 259.1293. Calculated for $C_2F_6NO_4S_2^-$, 279.9173; measured 279.9174.

1-(Methyl α-D-glucopyranosid-6-yl)-3-ethylimidazolium iodide 4

2 (912 mg, 3.0 mmol) and *N*-ethylimidazole (481 mg, 5.0 mmol) were dissolved in DMF (5 mL) and stirred at 110 °C for 20 hours. After cooling down, ethyl acetate (40 mL) was added and the flask was stored in a fridge overnight. The solvent was decanted and the precipitated solid was washed with ethyl acetate (6×10 mL) and dried under high vacuum to yield the product as an off-white solid (1.094 g, 91 %). m.p.: 99–101 °C. $[\alpha]_D^{26} = +46.5$ (c = 1.5, H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 1.53 (t, 3H, ^3J = 7.4 Hz, CH_3); 3.22–3.26 (m, 1H); 3.25 (s, 3H, OCH_3); 3.57 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.68–3.71 (m, 1H); 3.92 (ddd, 1H, ^3J = 10.0 Hz, ^3J = 7.7 Hz, ^3J = 2.4 Hz, H-5); 4.29 (q, 2H, ^3J = 7.4 Hz, NCH_2); 4.44 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.6 Hz, H-6a); 4.64 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.5 Hz, H-6b); 4.84 (d, 1H, ^3J = 3.8 Hz, H-1); 7.57–7.60 (m, 2H, H_{Ar}); 8.90 (s, 1H, H_{Ar}). ^{13}C NMR (125 MHz, D_2O): δ = 14.5 (CH_3); 45.0 (NCH_2); 49.9 (C-6); 55.0 (OCH_3); 69.4, 70.5, 71.0, 72.9 (C-2, C-3, C-4, C-5); 99.3 (C-1); 122.0, 123.2, 136.0 (CH_{Ar}). HRMS (ESI, *m/z*): Calculated for $C_{12}H_{21}N_2O_5^+$, 273.1455; measured 273.1461. Calculated for I^-, 126.9045; measured 126.9047.

1-(Methyl α-D-glucopyranosid-6-yl)-3-butylimidazolium iodide 5

2 (912 mg, 3.0 mmol) and *N*-butylimidazole (621 mg, 5.0 mmol) were dissolved in DMF (5 mL) and stirred at 110 °C for 20 hours. After cooling down, ethyl acetate (40 mL) was added and the flask was stored in a fridge overnight. The solvent was decanted and the precipitated solid was washed with ethyl acetate (6×10 mL) and dried under high vacuum to yield the product as an orange viscous liquid (1.204 g, 94 %). $[\alpha]_D^{26} = +48.2$ (c = 3.2, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 0.95 (t, 3H, ^3J = 7.4 Hz, CH_3); 1.26–1.39 (m, 2H, CH_2); 1.85–1.94 (m, 2H, CH_2); 3.21–3.27 (m, 1H); 3.25 (s, 3H, OCH_3); 3.57 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.67–3.74 (m, 1H); 3.92 (ddd, 1H, ^3J = 10.2 Hz, ^3J = 7.8 Hz, ^3J = 2.6 Hz, H-5); 4.27 (t, 2H, ^3J = 7.0 Hz, NCH_2); 4.44 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.7 Hz, H-6a); 4.66 (dd, 1H, ^2J = 14.5 Hz, ^3J = 2.6 Hz, H-6b); 4.84 (d, 1H, ^3J = 3.8 Hz, H-1); 7.57–7.61 (m, 2H, H_{Ar}); 7.97 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 12.6 (CH_3); 18.7, 31.2, 49.4 (CH_2); 49.9 (C-6); 55.0 (OCH_3); 69.4, 70.6, 71.0, 72.8 (C-2, C-3, C-4, C-5); 99.3 (C-1); 122.3, 123.2, 136.3 (CH_{Ar}). HRMS (ESI, *m/z*): Calculated for $C_{14}H_{25}N_2O_5^+$, 301.1768; measured 301.1763. Calculated for I^-, 126.9045; measured 126.9050.

1-(Methyl α-D-glucopyranosid-6-yl)-3-octylimidazolium iodide 6

2 (912 mg, 3.0 mmol) and *N*-octylimidazole (901 mg, 5.0 mmol) were dissolved in DMF (5 mL) and stirred at 110 °C for 20 hours. After cooling down, ethyl acetate (40 mL) was added and the flask was stored in a fridge overnight. The solvent was decanted and the precipitated solid was washed with ethyl acetate (6×10 mL) and dried under high vacuum to yield the product as an orange viscous liquid (1.033 g, 71 %). $[\alpha]_D^{27} = +50.1$ (c = 1.5, H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 0.88 (t, 3H, ^3J = 7.0 Hz, CH_3); 1.27–1.34 (m, 10H, 5xCH_2); 1.88–1.93 (m, 2H, CH_2); 3.22–3.26 (m, 1H); 3.23 (s, 3H, OCH_3); 3.56 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.8 Hz, H-2); 3.68–3.71 (m, 1H); 3.91 (ddd, 1H, ^3J = 10.2 Hz, ^3J = 7.9 Hz, ^3J = 2.5 Hz, H-5); 4.26 (t, 2H, ^3J = 6.9 Hz, NCH_2); 4.43 (dd, 1H, ^2J = 14.6 Hz, ^3J = 7.8 Hz, H-6a); 4.65 (dd, 1H, ^2J = 14.6 Hz, ^3J = 2.5 Hz, H-6b); 4.82 (d, 1H, ^3J = 3.8 Hz, H-1); 7.57–7.61 (m, 2H, H_{Ar}); 8.91 (s, 1H, H_{Ar}). ^{13}C NMR (125 MHz, D_2O): δ = 13.4 (CH_3); 22.0, 25.2, 27.9, 28.1, 29.1, 30.9 (CH_2); 49.7, 50.0 (CH_2, C-6); 55.0 (OCH_3); 69.4, 70.6, 71.0, 72.8 (C-2, C-3, C-4, C-5); 99.3 (C-1); 122.3, 123.2, 136.4 (CH_{Ar}). HRMS (ESI, *m/z*): Calculated for $C_{18}H_{33}N_2O_5^+$, 357.2394; measured 357.2397. Calculated for I^-, 126.9045; measured 126.9051.

Methyl 6-iodo-2,3,4-O-methyl-α-D-glucopyranoside 8

Methyl 2,3,4-O-methyl-α-D-glucopyranoside **7**, which was used as the starting material of this synthesis, was synthesized in three steps following a previously published procedure of our group.[15] This procedure is comprised of the 6-tritylation of methyl α-D-glucopyranoside, followed by the permethylation of the hydroxy groups using sodium hydride and methyl iodide and, finally, followed by the removal of the trityl protecting group using acetic acid.

7 (960 mg, 4.06 mmol), triphenylphosphine (1.597 g, 6.09 mmol), iodine (1.546 g, 6.09 mmol) and imidazole (552 mg, 8.12 mmol) were refluxed in THF (25 mL) for 4 h. The resulting solid was filtered off, the solvent was removed and the product was obtained as a colourless liquid (1.256 g, 89 %) after column chromatography (heptane/ethyl acetate 7:1 to 4:1). $[\alpha]_D^{27} = +142.5$ (c = 2.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.94–3.00 (m, 1H); 3.20 (dd, 1H, ^3J = 9.6 Hz, ^3J = 3.6 Hz, H-2); 3.29–3.39 (m, 2H); 3.46 (s, 3H, OCH_3); 3.50–3.56 (m, 2H); 3.52 (s, 3H, OCH_3); 3.61 (s, 3H, OCH_3); 3.62 (s, 3H, OCH_3); 4.82 (d, 1H, ^3J = 3.6 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.5 (C-6); 55.5, 59.0, 60.8, 60.9 (OCH_3); 69.3, 81.8, 83.1, 83.4 (C-2, C-3, C-4, C-5); 97.5 (C-1). HRMS (ESI, *m/z*): Calculated for $C_{10}H_{19}IO_5 + Na^+$, 369.0169; measured 369.0175.

1-(Methyl 2,3,4-O-methyl-α-D-glucopyranosid-6-yl)-3-methylimidazolium iodide 9

8 (1.038 g, 3.0 mmol) and *N*-methylimidazole (411 mg, 5.0 mmol) were dissolved in DMF (5 mL) and stirred at 110 °C for 20 hours. The solvent was removed and the product was obtained as an orange solid (1.020 g, 79 %) after column chromatography (first ethyl acetate to remove remaining *N*-methylimidazole, then MeOH to collect the product). m.p.: 40–41 °C. $[\alpha]_D^{24} = +55.6$ (c = 3.4, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 3.21 (dd, 1H, ^3J = 9.9 Hz, ^3J = 9.0 Hz); 3.23 (s, 3H, OCH_3); 3.43 (dd, 1H, ^3J = 9.8 Hz, ^3J = 3.7 Hz, H-2); 3.51 (s, 3H, OCH_3); 3.56–3.62 (m, 1H); 3.64 (s, 3H, OCH_3); 3.65 (s, 3H, OCH_3); 3.89–3.95 (m, 1H); 3.96 (s, 3H, NCH_3); 4.46 (dd, 1H, ^2J = 14.5 Hz, ^3J = 8.1 Hz, H-6a); 4.66 (dd, 1H, ^2J = 14.5 Hz, ^3J = 2.5 Hz, H-6b); 5.05 (d, 1H, ^3J = 3.6 Hz, H-1); 7.52 (t, 1H, ^3J = 1.8 Hz, H_{Ar}); 7.62 (d, 1H, ^3J = 1.8 Hz, H_{Ar}); 8.86 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 35.9 (NCH_3); 49.7 (C-6); 54.8, 58.0, 60.0, 60.1 (OCH_3); 68.5, 79.6, 79.9, 82.1 (C-2, C-3, C-4, C-5); 96.6 (C-1); 123.1, 123–6 (CH_{Ar}). HRMS (ESI, *m/z*): Calculated for $C_{14}H_{25}N_2O_5^+$, 301.1768; measured 301.1761. Calculated for I^-, 126.9045; measured 126.9044.

1-(2-Hydroxyethyl)-3-methylimidazolium iodide [HO-EMIM-I]

N-methylimidazole (7.4 mL, 93 mmol) and 2-iodoethanol (8.5 mL, 110 mmol) were refluxed in acetonitrile (50 mL) for 72 hours. The solvent was removed and water (50 mL) was added. The aqueous phase was washed with ethyl acetate (4×50 mL). After the removal of the water, the product was kept under high vacuum for 24 hours. The product was obtained as a white solid (22.955 g, 97 %). m.p.: 68–69 °C. ^{1}H NMR (300 MHz, D_2O): δ = 3.98 (s, 3H, CH_3); 3.99–4.02 (m, 2H, CH_2); 4.38–4.41 (m, 2H, CH_2); 7.53 (t, 1H, ^3J = 1.8 Hz, H_{Ar}); 7.59 (t, 1H, ^3J = 1.8 Hz, H_{Ar}); 8.83 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, D_2O): δ = 35.9 (CH_3); 51.6, 59.8 (CH_2); 122.5, 123.7, 136.4 (CH_{Ar}).

Acknowledgements

Financial support by the NFDI4Cat (DFG project number 441926934) as well by the Leibniz Association and the Leibniz Science Campus ComBioCat is gratefully acknowledged by the

authors. We thank Prof. Udo Kragl for the fruitful discussions on this topic.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: acrylic acid · carbohydrate · lipase · novozym 435 · supported ionic liquid phase

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Manuscript received: June 16, 2022
Revised manuscript received: July 7, 2022