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# A novel and efficient ionic liquid supported synthesis of oligosaccharides

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**Abstract**—A novel and efficient ionic liquid supported synthesis of oligosaccharides with a general protocol of coupling and purification is described. The method represents an attractive alternative to the classical solid- and fluorous-phase synthesis strategies and combines the advantage of performing homogeneous chemistry on a relatively large scale while avoiding large excesses of reagents.


Increased awareness of the biological and therapeutic importance of oligosaccharides has stimulated the development of efficient methods for synthesis of these compounds. Different strategies for the assembly of oligosaccharides on polymeric supports have proven to be the most challenging task and have recently received much attention.[1] The solid-phase approach is attractive due to the facile purification process of removing the excess reagents and side products, which allows for the ease of product isolation and makes automation possible.[2] On the other hand, the soluble polymers such as polyethylene glycol (PEG), polyvinyl alcohol and other ingenious variants of these polymers have received considerable attention because of their homogeneous phase chemistry strategies, which have been employed successfully in the synthesis of oligopeptides[2] and oligosaccharides.[3] However, there were some limitations such as low loading capacity, limited solubility during the reaction processes, aqueous solubility, and insolubility in ether solvents.[4] Recently, ionic liquids (ILs) have attracted considerable interest as environmentally benign reaction media because of their many fascinating and intriguing properties.[5] Numerous chemical reactions, including some enzymatic reactions, can be carried out in ionic liquids.[6] An attractive feature of ionic liquids is that their solubility can be tuned readily. Therefore, phase separation from organic solvent or aqueous phase is allowed depending on the choice of cations and anions. This suggests the possibility of using these small molecular ionic liquids as soluble supports for organic synthesis. Substrates anchored on ionic liquids are expected to retain their reactivity, as in solution reactions, and allowed the use of conventional spectroscopic analysis during the synthetic process. Several groups have demonstrated the feasibility of ionic liquid supported organic synthesis of small molecules[7] and peptides,[8] in which the excess reagents and by-products in the multistep reactions can be removed easily by simple washing with a solvent. Herein, we describe an ionic liquid supported synthesis of oligosaccharides. To the best of our knowledge, this is the first report on the synthesis of oligosaccharides utilizing IL support strategy.

As shown in Scheme 1, the 4-OH of phenyl 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**1**), which was prepared from D-glucose in six steps according to the published methods,[9,10] was esterified with chloroacetyl chloride in the presence of pyridine. The resulting ester **2** was immobilized to *N*-methylimidazole via a nucleophilic substitution reaction to give the ionic liquid bounded glucoside **3**. Then the anion $Cl^-$ of **3** was exchanged to anion $PF_6^-$ to afford the ionic liquid bounded glucoside **4**. The subsequent deprotection of TBDMS group was readily performed using concentrated HCl at room temperature to give the corresponding glucoside **5**. With ionic liquid supported **5** in hand, we coupled it with different glycosyl donors **6a**–**f**, that had been activated with trichloroacetimidates,

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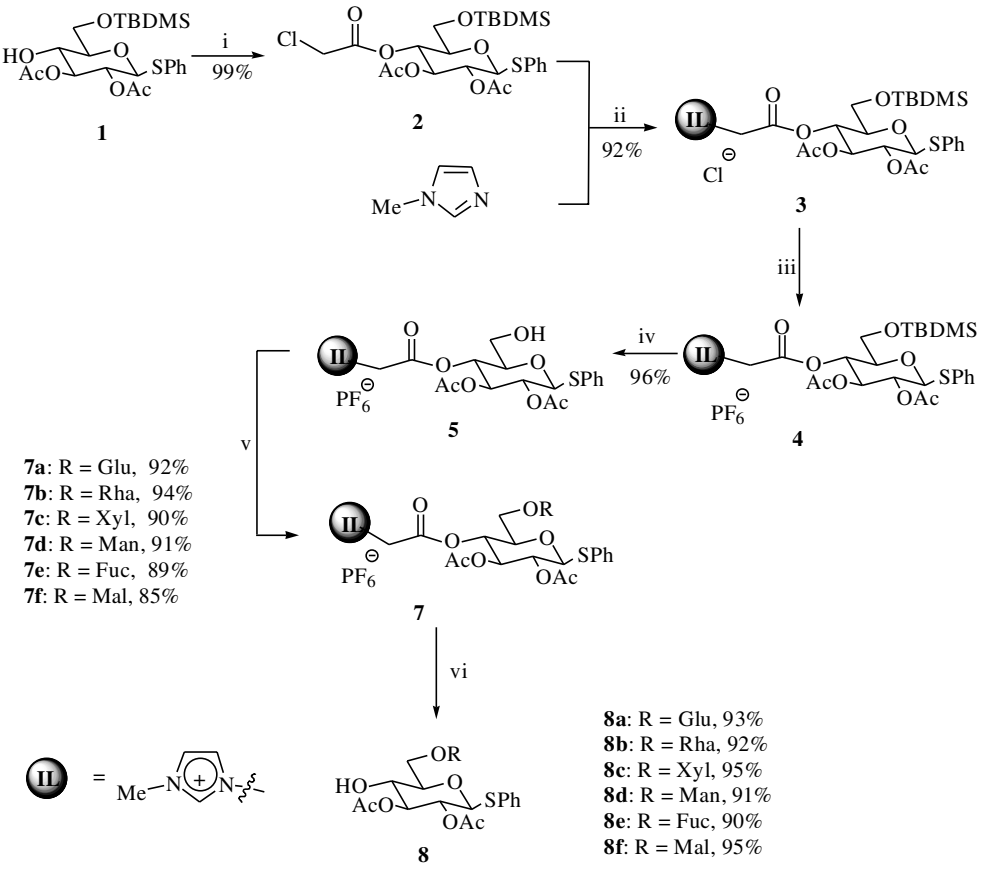



**Scheme 1.** Reagents and conditions: (i) $ClCH_2COCl$ (1.2 equiv), Py (1.5 equiv), $CH_2Cl_2$, 0 °C, 30 min; (ii) *N*-methylimidazole (1.0 equiv), $CH_3CN$, $N_2$, 80 °C, 12 h; (iii) $KPF_6$ (1.0 equiv), $CH_3CN$, rt, 24 h; (iv) concd HCl, THF, 15–30 min; (v) **6** (3.0 equiv), TMSOTf (cat.), 4 Å MS, $CH_2Cl_2$, $N_2$, −40 to 0 °C, 2 h; (vi) saturated aq $NaHCO_3$ (2 mL), TBAB (0.1 g), $Et_2O$, 15 min.

**Table 1.** Ionic-liquid-supported synthesis of oligosaccharides

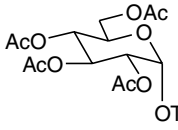
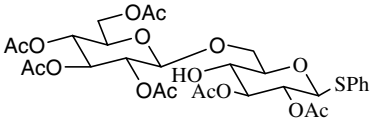
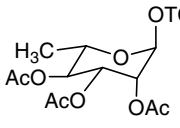
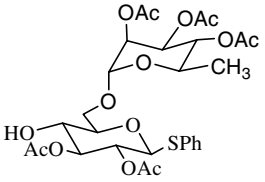
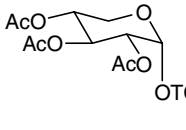
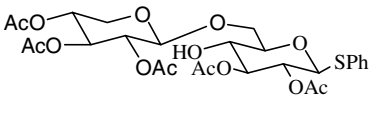
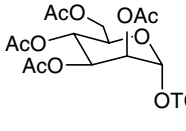
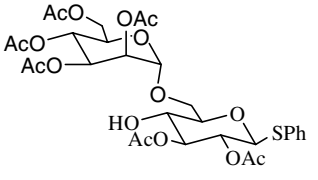
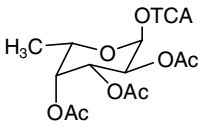
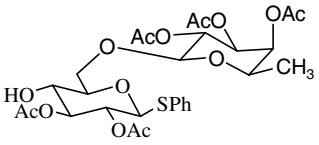
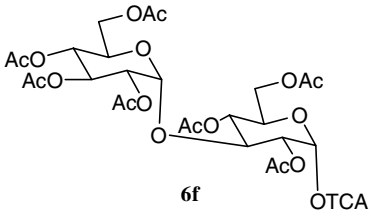
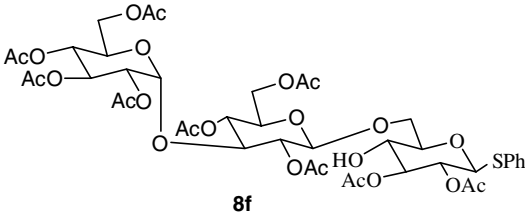
| Entry | R | Product | Yield[a] (%) | Purity[b] (%) |
|---|---|---|---|---|
| 1 |  **6a** |  **8a** | 85 | 95 |
| 2 |  **6b** |  **8b** | 86 | 93 |
| 3 |  **6c** |  **8c** | 86 | 92 |
| 4 |  **6d** |  **8d** | 83 | 92 |

**Table 1** (*continued*)

| Entry | R | Product | Yield[a] (%) | Purity[b] (%) |
|---|---|---|---|---|
| 5 |  **6e** |  **8e** | 80 | 90 |
| 6 |  **6f** |  **8f** | 81 | 94 |

[a] Isolated yields are based on the conversion of **5**.
[b] Purity are detected by HPLC.

to provide five disaccharides **7a**–**e** and one trisaccharide **7f**. Finally, cleavage of the ester linkage with saturated aqueous sodium bicarbonate solution in the presence of TBAB and solvent extraction gave the corresponding free disaccharides **8a**–**e** and trisaccharide **8f** in high yields with excellent purities.[11] The results are summarized in Table 1.

As a suitable model reaction for ionic liquid-phase-supported organic synthesis, we have chosen to use chloroacetyl chloride bound to the ionic liquid moiety. It was stable in a series of reactions and it could be cleaved in a short time (15 min) under mild conditions (e.g., TBAB/aq $NaHCO_3$/$Et_2O$). After being unbound, the oligosaccharide products were transferred into organic phase giving high purity as shown in HPLC analysis, so further chromatography is not necessary.

All of the ionic liquid supported oligosaccharides prepared thus far are soluble in polar organic solvents such as acetone, acetonitrile, methanol, chloroform, and dichloromethane, but are essentially not soluble in diethyl ether or hexane. During the whole synthetic sequence, every IL-bounded intermediate could be purified by consecutively washing with diethyl ether and EtOAc, in which the excess reagents and by-products were removed. It is noteworthy that all of the intermediates, including the IL-bounded saccharides, and final products could be confirmed with $^1H$ NMR, $^{13}C$ NMR and MS in our procedure.[12] The mass spectra of the ionic liquid supported saccharides **3**–**7** were helpful for the structural characterization because the peak corresponding to the cation bearing the saccharides was detected easily as the most intense peak in the spectrum.

In summary, we have developed a novel ionic liquid supported synthesis of oligosaccharides. Using this procedure, the intermediates could be purified by simple washing. This strategy provides a fast and efficient approach to diversify the oligosaccharides for biological testing. Our method represents an attractive alternative to the classical solid- and fluorous-phase synthesis strategies and combines the advantage of performing homogeneous chemistry on a relatively large scale while avoiding large excesses of reagents. Expansion of the method presented here towards differently functionalized ionic supports and the synthesis of more complex target molecules are currently being pursued.

## Acknowledgments

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11. Typical procedure for the synthesis of **8a**: To a stirred solution of phenyl 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside **1** (1.0 mmol) and Py (1.5 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise chloroacetyl chloride (1.2 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C over 30 min. The mixture was poured into water (5 mL), quickly washed with dilute HCl, saturated aqueous $NaHCO_3$ solution and water, and dried over anhydrous $Na_2SO_4$. After evaporation in vacuo, the residue was chromatographed on silica gel with hexane–EtOAc (2:1) to give pure **2**. A solution of **2** (1.0 mmol) and *N*-methylimidazole (1.0 mmol) in $CH_3CN$ (15 mL) was stirred at 80 °C for 24 h. $KPF_6$ (1.0 mmol) was added and the mixture was stirred for another 24 h. After it was filtered and evaporated in vacuo, the residue was washed with $Et_2O$ ($3 \times 5$ mL) and then EtOAc ($3 \times 5$ mL) to give **4**, which was used directly for the next reaction. The ionic liquid **4** was dissolved in THF (10 mL), followed by the addition of two drops of concd HCl, and stirred for 15 min. After evaporated in vacuo, the residue was washed twice with $Et_2O$ ($3 \times 5$ mL) and dried in vacuo to yield the ionic liquid **5**. To a mixture of **5** (0.25 mmol), O-acetylated monosaccharide trichloroacetimidate donor (0.75 mmol) and 4 Å MS (1 g) in dry $CH_2Cl_2$ (20 mL) was added dropwise trimethylsilyl triflate (0.06 mmol) in dry $CH_2Cl_2$ (2 mL) under nitrogen at −40 °C, and then the reaction temperature was allowed to increase to 0 °C. The mixture was filtered and the solvent was removed under vacuum. The residue was washed with $Et_2O$ (5 mL), and then dissolved in $CH_2Cl_2$ (1 mL) and washed with $Et_2O$ ($3 \times 5$ mL) to afford the ionic liquid supported disaccharide **7a**. To a solution of **7a** (0.2 mmol) in $Et_2O/H_2O$ (1:1, 3.0 mL) was added saturated aqueous $NaHCO_3$ solution (2 mL) and TBAB (0.1 g). The mixture was stirred at room temperature for 30 min. The $Et_2O$ phase was filtered through a short pad of silica gel. Removal of the solvent gave free disaccharide **8a** as a white solid. All products gave satisfactory $^1H$ NMR, $^{13}C$ NMR, H–H COSY and HMQC.
12. All compounds reported here were duly characterized. Selected data: **7b**: $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 6.2$ Hz, 3H), 1.95 (s, 3H), 2.03 (s, 3H), 2.05 (s, 6H), 2.11 (s, 3H), 3.80 (d, $J = 10.0$ Hz, 1H), 4.00–3.94 (m, 5H), 4.70 (d, $J = 10.0$ Hz, 1H), 4.90 (t, $J = 9.6$ Hz, 1H), 4.96 (s, 1H), 5.03 (t, $J = 10.0$ Hz, 1H), 5.22–5.14 (m, 4H), 5.30–5.26 (m, 2H), 6.04 (d, $J = 17.6$ Hz, 1H), 7.32–7.30 (m, 4H). 7.45–7.44 (m, 2H), 7.67 (s, 1H), 10.12 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 17.8$, 20.96, 20.97, 21.02, 21.05, 21.2, 36.6, 66.3, 66.7, 69.2, 69.4, 70.1, 70.2, 70.7, 73.4, 75.9, 83.8, 97.8, 118.7, 124.1, 128.5, 129.8, 131.9, 132.3, 138.3, 138.4, 166.5, 169.7, 170.34, 170.36, 170.42, 170.43; ESI (MS): $m/z = 751$ $[M-PF_6]^+$.
Compound **8b**: mp: 70–72 °C; $[\alpha]_D^{20}$ −50.4 (*c* 1.05, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 1.21$ (d, $J_{5,6} = 9.6$ Hz, 3H, H-6, Rha), 2.01 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_3$), 3.02 (d, $J = 2.6$ Hz, 1H, 4-OH, Glu), 3.57–3.54 (m, 1H, H-5, Glu), 3.76–3.70 (m, 2H, H-4, H-6a, Glu), 4.04–3.97 (m, 2H, H-6b, Glu, H-5, Rha), 4.71 (d, $J = 10.0$ Hz, 1H, H-1, Glu), 4.79 (d, $J = 0.5$ Hz, 1H, H-1, Rha), 4.92 (d, $J = 9.5$ Hz, 1H, H-2, Glu), 5.10–5.02 (m, 2H, H-3, Glu, H-4, Rha), 5.26 (d, $J = 3.5$ Hz, 1H, H-3, Rha), 5.28 (t, $J = 1.4$ Hz, 1H, H-2, Rha), 7.35–7.29 (m, 3H), 7.47–7.35 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 17.6$ (C-6, Rha), 21.00 ($COCH_3$), 21.03 ($COCH_3$), 21.09 ($COCH_3$), 21.15 ($COCH_3$), 66.7 (C-6, Glu), 66.8, 68.8, 68.9, 69.4, 69.6, 70.0, 71.0, 77.5, 79.0, 86.0 (C-1, Glu), 98.0 (C-1, Rha), 128.4, 129.2, 132.4, 132.6, 169.7, 170.3, 170.4, 171.9; ESI (MS): $m/z = 650.9$ $[M+Na]^+$.