A Facile and Eco-Friendly Method for the Synthesis of 1,2-Orthoesters of Carbohydrates in Ionic Liquid

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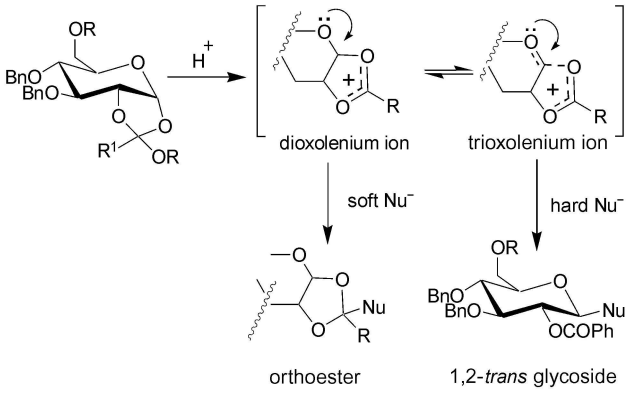
Abstract: A facile method for the synthesis of 1,2-orthoesters of carbohydrates in ionic liquid [bmim]PF_6 is described. The method described herein is simpler, eco-friendly and avoids the addition of quaternary ammonium salts as promoters.

Key words: ionic liquid, 1,2-orthoesters, carbohydrates, glycosyl bromides, quaternary ammonium salts

Technologies based on ionic liquids have become an important area over the last few years.[1] Efforts are going on to make use of the property of ionic liquids to replace the conventional organic solvents used in organic chemistry. Reports indicate that ionic liquids can coordinate with polar molecules very well[2] and in effect this will serve in solubilizing the organic compounds in ionic liquids.

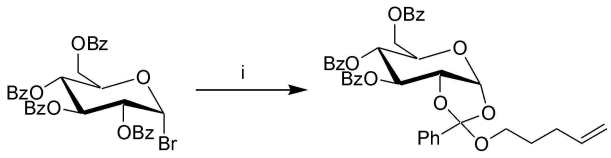
When it comes to polar organic molecules, pre-eminent are the carbohydrates.[3] There has been a resurgence of interest in carbohydrate chemistry in recent years, mainly due to the current developments in glycobiology.[4] The common solvents used in carbohydrate chemistry such as DMF, pyridine, methanol, etc. cause serious environmental problems. An efficient and eco-friendly solvent as a substitute for these solvents is a topic of current interest. Ionic liquids have been used for the acetylation of sugars[5] and glycosyl trichloroacetamidates are known to react smoothly in presence of trimethylsilyl triflate in ionic liquid leading to glycosides and disaccharides.[6]

Cyclic orthoesters are valuable intermediates for a variety of synthetic transformations.[7] In synthetic carbohydrate chemistry, 1,2-orthoesters have been utilized as glycoside donors[3,8] and a number of reports is available on the use of 1,2-orthoesters of carbohydrates in oligosaccharide synthesis. Among various 1,2-orthoesters of carbohydrates, *n*-pentenyl orthoesters (NPOEs)[9] of sugars have received much attention. Fraser-Reid and co-workers have extensively utilized *n*-pentenyl orthoesters (NPOEs) as glycosyl donors in the synthesis of oligosaccharides of biological importance.[10] Upon treatment with a Lewis acid, they are converted into highly stabilized ambident dioxolenium ions. The oxonium ions undergo reaction with nucleophiles at either C-2 or C-4/5 depending on the nature of the nucleophile.[11] Hard nucleophiles such as silyl enol ethers, cuprates and titanium enolates add at C-2 in a kinetically controlled process, whereas soft nucleophiles such as alcohols and phenols add at C-4/5 in a thermodynamic process. The latter has been utilized in the glycosidation reaction. A schematic representation of the process is shown in Scheme 1. 1,2-Orthoesters have also been used as a protecting group for C-1/2 hydroxyl groups.[12]



Scheme 1

1,2-Orthoesters are usually prepared by the reaction of peracetylated or perbenzoylated glycosyl bromides with alcohol in the presence of a quaternary ammonium salt[13] or silver triflate[14] and a base, usually *syn*-collidine or 2,6-lutidine or with alcohol and potassium fluoride.[15] They can also be prepared by the reaction of 1-hydroxy sugars with tetramethyl-α-chloro enamine and alcohol in presence of triethylamine.[16] It is to be noted that in the classical method of preparation of orthoesters, the anomeric bromide is refluxed with alcohol in the presence of 2,6-lutidine in dry dichloromethane for five days.[9,17] The modified method which involves the use of tetrabutylammonium iodide also involves use of dry dichloromethane and refluxing for 24 hours. The major disadvantages of both methods are the use of dry dichloromethane, longer reaction time and cumbersome work-up to remove the dissolved salts.



Scheme 2 *Reagents and conditions*: i) alcohol (1.5 equiv), 2,6-lutidine (2 equiv), [bmim]PF_6, r.t., 8 h.

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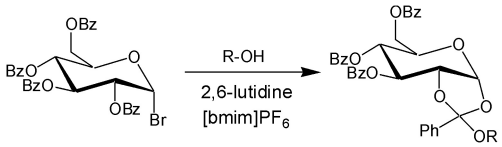
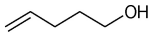
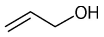
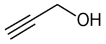
Herein we report a facile method for the synthesis of 1,2-orthoesters of carbohydrates from the corresponding anomeric bromides in ionic liquid [bmim]PF_6 without any promoter.

Our studies were initiated with the reaction of perbenzoylated glucopyranosyl bromide with 4-penten-1-ol in presence of 2,6-lutidine in ionic liquid [bmim]PF_6. The reaction proceeded smoothly at room temperature (8 h) affording the glucose pentenyl orthoester in 80% yield (Scheme 2). The product was separated from the reaction mixture by extraction with diethyl ether, followed by purification by silica gel column chromatography (if needed). The water and diethyl ether insoluble ionic liquid was washed with water followed by diethyl ether, dried in vacuo and reused. Similar results were obtained with various other alcohols and the results obtained with glucopyranosyl bromide are summarized in Table 1.

Table 1 Synthesis of 1,2-Orthoesters of Glucose in Ionic Liquid



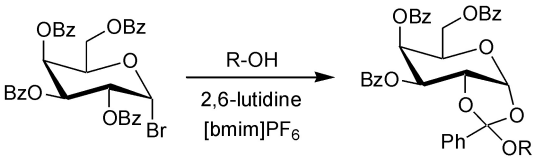
No	Alcohol (R-OH)	Yield (%)
1		80[a]
2		64[a]
3		58[a]
4	1-Butanol	60[a]
5	Isopropanol	52[b]
6	Isooctanol	77[b]
7	Benzyl alcohol	59[a]

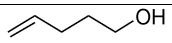
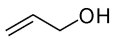
[a] Alcohol (1.5 equiv), 2,6-lutidine (2 equiv), [bmim]PF_6, r.t., 8 h.
[b] Alcohol (1.5 equiv), 2,6-lutidine (2 equiv), [bmim]PF_6, 45 °C, 3 h.

To establish the feasibility of this reaction as a general method for the synthesis of 1,2-orthoesters, we have carried out the preparation of galactose and mannose orthoesters and the results are summarized in Table 2 and Table 3.

The results show that the present method can be used for the synthesis of 1,2-orthoesters of carbohydrates with a wide range of alcohols. Since quaternary ammonium salts are not used in the reaction, the work-up of the reaction is very simple and the ionic liquid can be reused by washing with water and diethyl ether followed by drying in vacuo. In conclusion, we have developed a facile and eco-friendly method for the synthesis of 1,2-orthoesters of carbohydrates in ionic liquid [bmim]PF_6. The method is much simpler and the solvent can be reused any number of times.

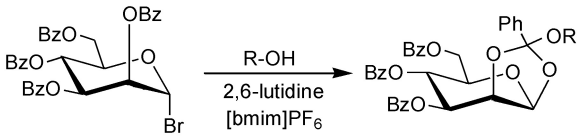
Table 2 Synthesis of 1,2-Orthoesters of Galactose in Ionic Liquid[a]

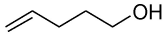
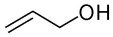


No	Alcohol (R-OH)	Yield (%)
1		75
2		68
3	Isopropanol	69
4	Isooctanol	82

[a] Alcohol (1.5 equiv), 2,6-lutidine (2 equiv), [bmim]PF_6, r.t., 8 h.

Table 3 Synthesis of 1,2-Orthoesters of Mannose in Ionic Liquid[a]



No	Alcohol (R-OH)	Yield (%)
1		70
2		90
3	Isopropanol	59

[a] Alcohol (1.5 equiv), 2,6-lutidine (2 equiv), [bmim]PF_6, r.t., 8 h.

Experimental

A Typical Experimental Procedure for 3,4,6-Tribenzoyl Glucose Pentenyl Orthoester[18]

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosylbromide (0.20 g, 0.30 mmol) was dissolved in ionic liquid [bmim]PF_6 (2 mL). 2,6-Lutidine (0.07 mL, 0.60 mmol) was added to it followed by 4-penten-1-ol (0.05 mL, 0.46 mmol). The reaction mixture was stirred at r.t. for 8 h. The reaction mixture was extracted with Et_2O, dried over Na_2SO_4 and the solvent was evaporated off completely. The crude sample on purification by silica gel column chromatography afforded the pure substance as a viscous liquid (0.16 g, 80%).

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(18) Spectral data for some key compounds.
(a) **3,4,6,-Tri-*O*-benzoyl Glucopyranosyl *n*-Pentenyl Orthoester**:
R_f = 0.2926 (25% EtOAc–hexane). IR (neat): ν_{max} = 3070, 2449, 1740, 1644, 1612, 1460, 1275, 1109, 976, 925, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–8.60 (m, 20 H), 6.01 (d, 1 H, *J* = 5.2 Hz), 5.84–5.67 (m, 1 H), 5.47 (d, 1 H, *J* = 8.7 Hz), 4.97 (d, 1 H, *J* = 1.5 Hz), 4.92 (d, 1 H, *J* = 1.3 Hz), 4.74 (dd, 1 H, *J* = 3.4, 7.2 Hz), 4.51 (dd, 1 H, *J* = 4.8, 12.0 Hz), 3.29–3.37 (m, 2 H), 2.01–2.09 (m, 2 H), 1.57–1.62 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.68, 164.95, 164.39, 137.68, 135.51, 133.49, 133.32, 132.80, 129.98, 129.85, 129.68, 129.69, 129.46, 129.14, 129.03, 128.46, 128.33, 128.19, 128.10, 126.28, 121.19, 120.02, 114.97, 97.42, 72.08, 69.23, 68.48, 67.42, 63.89, 63.29, 30.10, 28.60.
(b) **3,4,6-Tri-*O*-benzoyl Galactopyranosyl Allyl Orthoester**:
R_f = 0.2954 (25% EtOAc–hexane). IR (neat): ν_{max} = 2917, 2366, 1721, 1452, 1263, 1086, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.97 (m, 20 H), 6.21 (d, 1 H, *J* = 5.03 Hz), 5.92–5.80 (m, 1 H), 5.56 (dd, 1 H, *J* = 4.26, 5.06 Hz), 5.12 (d, 2 H, *J* = 10.45 Hz), 4.79 (dd, 1 H, *J* = 7.14, 12.35 Hz), 4.64–4.50 (m, 1 H), 4.38 (dd, 1 H, *J* = 4.93, 10.60 Hz), 3.93 (d, 2 H, *J* = 4.87 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.18, 164.91, 164.28, 136.29, 133.78, 133.51, 133.35, 133.13, 129.81, 129.78, 129.73, 129.63, 129.42, 129.11, 128.92, 128.49, 128.35, 128.31, 126.09, 125.98, 120.31, 116.70, 98.55, 98.21, 73.41, 70.09, 68.88, 66.47, 64.96, 62.35, 29.68.
(c) **3,4,6-Tri-*O*-benzoyl Mannopyranosyl Isopropyl Orthoester**:
R_f = 0.2973 (25% EtOAc–hexane). IR (neat): ν_{max} = 2917, 2849, 2356, 1716, 1458, 1269, 1086 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–8.01 (m, 20 H), 5.74 (d, 1 H, *J* = 2.98 Hz), 5.62 (dd, 1 H, *J* = 3.64, 9.97 Hz), 5.04 (t, 1 H, *J* = 3.4 Hz), 4.47 (dd, 1 H, *J* = 3.40, 11.99 Hz), 4.31 (dd, 1 H, *J* = 4.84, 11.97 Hz), 3.73 (m, 1 H), 1.07 (d, 3 H, *J* = 6.12 Hz), 1.03 (d, 3 H, *J* = 6.12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.78, 165.70, 165.03, 145.37, 137.35, 133.36, 133.26, 132.79, 130.11, 129.91, 129.82, 129.23, 129.18, 128.44, 128.41, 128.23, 128.07, 126.61, 124.29, 123.57, 123.03, 119.16, 97.90, 75.73, 72.41, 71.18, 67.35, 66.77, 63.28, 23.51, 23.43.