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Article

Click Reactions as a Key Step for an Efficient and Selective Synthesis of D-Xylose-Based ILs

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Abstract: D-Xylose-based ionic liquids have been prepared from D-xylose following a five steps reaction sequence, the key step being a click cycloaddition. These ionic liquids (ILs) have been characterized through classical analytical methods (IR, NMR, mass spectroscopy, elemental analysis) and their stability constants, Tg and Tdec, were also determined. Considering their properties and their hydrophilicity, these compounds could be alternative solvents for chemical applications under mild conditions.

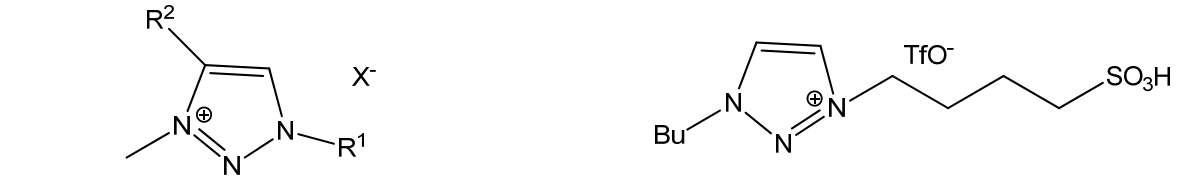
Keywords: ionic liquids; D-xylose; click chemistry

1. Introduction

In the last two decades, ionic liquids (ILs) have attracted considerable attention due to their unique properties (non-flammability, good electrolytic properties, unique solubility, negligible vapor pressure, good thermal stability, *etc*.) [1–3]. Due to the increasing growth of their applications as

alternative to volatile solvents in catalytic applications [1,4–6], biocatalysis [7,8], synthetic chemistry [9], electrochemistry [10–14], analytical applications [15–19], or for separations and extractions [20–26], the development of new IL structures is always being sought. Thanks to the click chemistry reaction, a large variety of 1,2,3-triazole structures can be obtained [27–29], but surprisingly, few ionic liquids derived from triazole have been reported (Figure 1) [30–34].

Figure 1. Triazolium based ionic liquids [13].



R^1 = Ph, Bn, Me, allyl; R^2 = H, Bu, Pn, Hex, *t*-Bu, Ph

X = OTf, Tos, I, BF_4, PF_6, NTf_2

Carbohydrates are among the most abundant and low-cost natural sources of chiral materials and represent building blocks of choice for the formation of various compounds with a broad spectrum of applications [35]. The use of ILs as solvents for the transformation of carbohydrates was first reviewed by Linhardt in 2005 [36]. Next, ILs have been shown to exhibit excellent solubilizing properties, facilitating a wide range of chemical transformations, including acetylation, ortho-esterification, benzylidenation and glycosylation reactions of carbohydrates [36–41]. Recently, Afonso and Tran discussed respectively the application of ILs in carbohydrate dissolution [42] and the recent developments of ionic liquids in oligosaccharide synthesis [43]. Therefore, sugar-based chiral ionic liquids (CILs) could be used as solvent or catalyst in asymmetric synthesis [44–48] or as chiral phases in gas chromatography [49].

Only a few examples of carbohydrates-based ILs were reported in the literature [50–57] (Figure 2). First, in 2003 Dickenson *et al*. published the preparation of ILs derived from fructose as a promising solvent for implementing fully "green chemistry" methods [50]. Glucose was also used as starting material for the elaboration of either a new class of chiral solvents from low-cost natural sources [51] or multiphase particles for cosmetic applications [52]. Next, isomanide or isosorbide-based ILs were prepared as solvents for chiral discrimination or asymmetric organic reactions [53–57].

For our part, we recently reported the preparation (and the use as solvent for catalysis) of biomass-derived ionic liquids from natural organic acids, among them osidic acids [58] (Figure 3). In this context, as we have been studying for many years the valuation of pentoses issued from hemicelluloses as surfactants [59–64] or glycodendrimers [65–67], we wish to report here a new way of valuation of these sugars as new ILs in which 1,2,3-triazolium salts [33,34,68–76] serve as the IL part and xyloside units are covalently tethered at the "4" position of the triazolium ring. To the best of our knowledge, no ionic liquid derived from D-xylose was previously described in the literature.

Figure 2. Carbohydrates-based ILs.

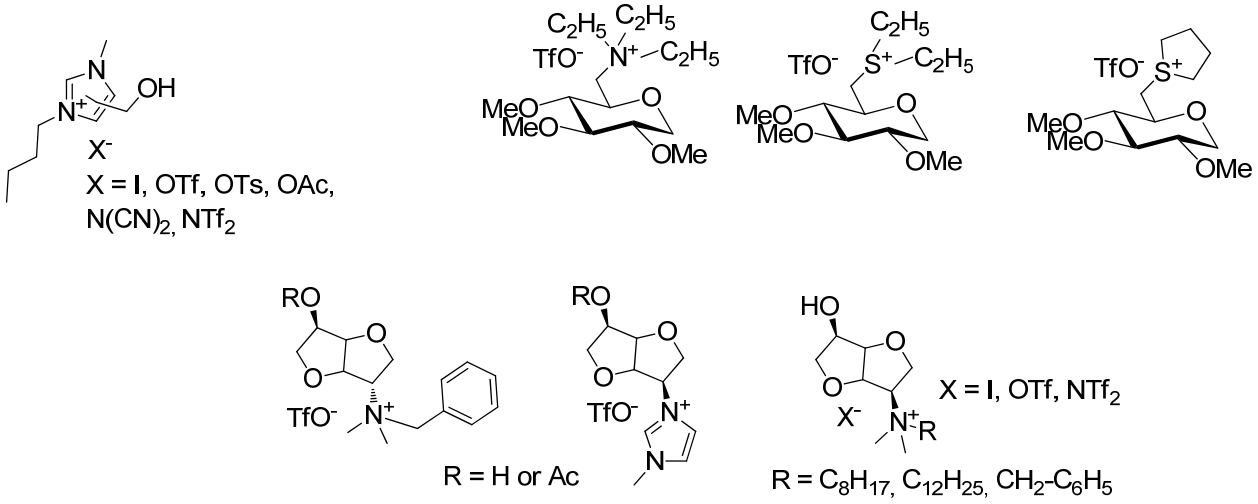
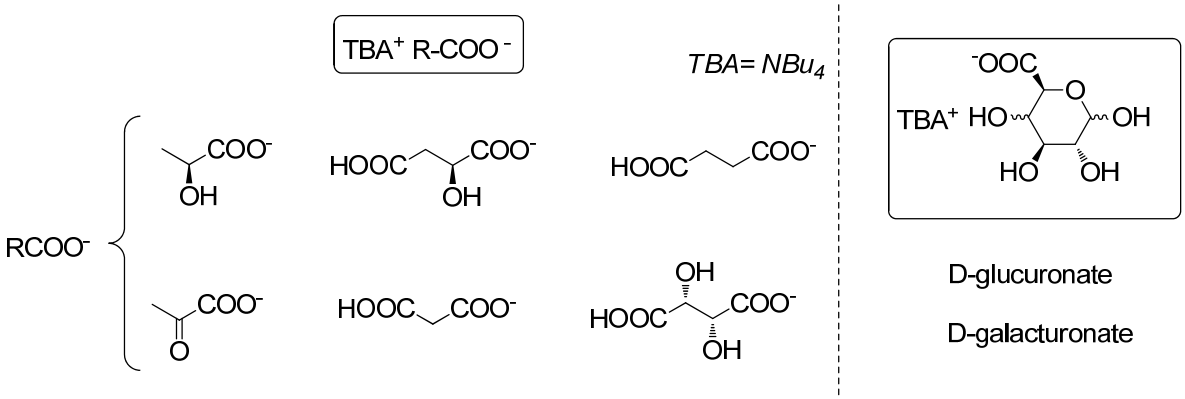


Figure 3. Biomass derived ILs.



2. Results and Discussion

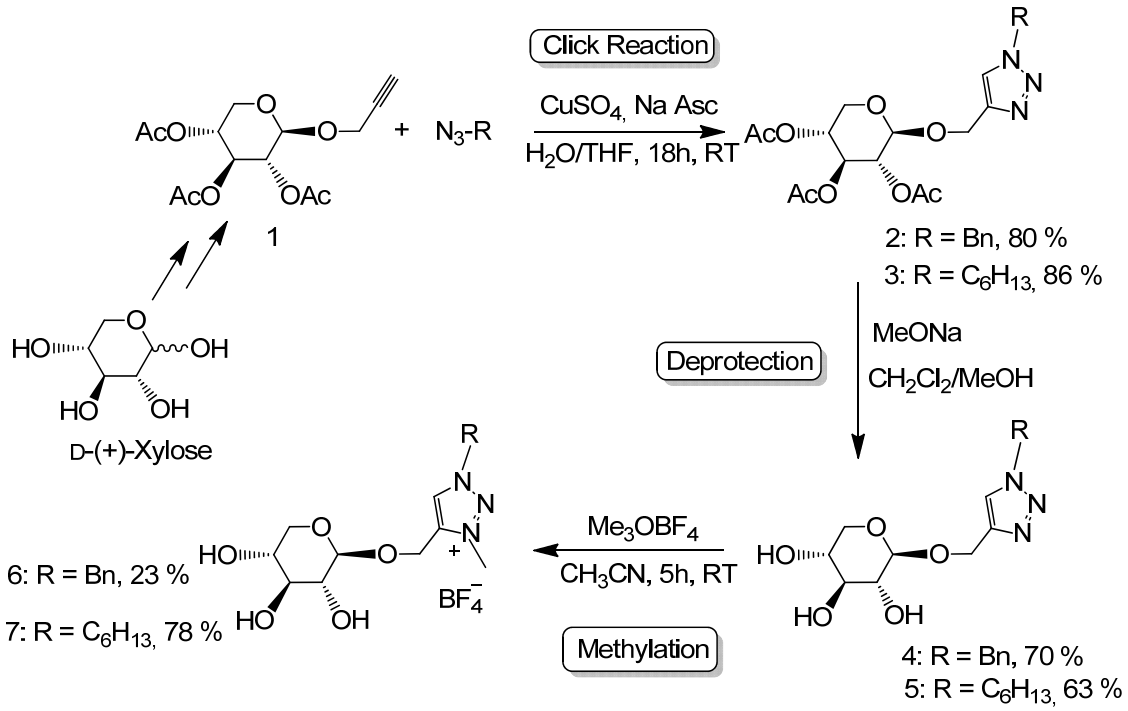
For the glycosylation step, treatment of peracetylated D-xylose with propargyl alcohol in the presence of $BF_3 \cdot Et_2O$ was used to access the β-propargyl xyloside **1** [77]. This method was preferred because previous trials on D-xylose using the Fisher method [78] with para-toluenesulfonyl acid as catalyst led to a mixture of anomers which are could not be separated, even after acetylation.

Cu^I-"catalyzed" Huisgen 1,3-dipolar cycloaddition reaction of the modified alkynyl sugar with phenyl or hexyl azide, was carried out in the presence of an excess of Cu^I in a homogeneous THF/water mixture (Scheme 1). Several reactions were performed with catalytic and stoichiometric amounts of copper, but led to very poor yields, a part of the copper salt probably being involved in the complexation of the acetate groups. The propargyl xyloside/azide ratio was also optimized after several trials to afford good yields for the cycloaddition adducts.

The excess of Cu salt was removed as $[Cu(NH_3)_2(H_2O)_2][SO_4]$ by washing with an ammonia solution. Purification by precipitation with CH_2Cl_2/petroleum ether in order to remove the excess of sugar provided compounds **2** and **3** in good yields. The presence of signals at 7.42 ppm and 7.49 ppm for **2** and **3**, respectively, in their ^{1}H-NMR spectrum, unambiguously proved the formation of the triazole ring. The composition of compounds **2** and **3** was further confirmed by ^{13}C-NMR and

elemental analysis. The acetylated benzyl and hexyl compounds **2** and **3** were then deprotected in the presence of sodium methanolate to give the corresponding derivatives **4** and **5** with free hydroxyl groups (Scheme 1). No signals were found for methyl groups or carbonyl carbons in the ^{1}H- and ^{13}C-NMR spectra, respectively. This set of derivatives was purified by precipitation.

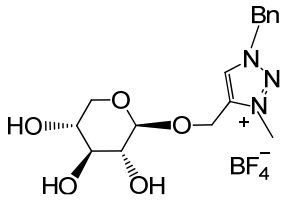
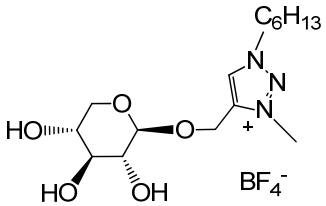
Scheme 1. Synthesis of ILs **6** and **7**.



In line with previous observations, trimethyloxonium tetrafluoroborate (Meerwein's salt) proved to be a very powerful methylating agent (29 equivalents used as described [79]), affording benzyl and hexyl triazolium salts **6** and **7** in good isolated yields in 5 h at room temperature in dry MeCN (Scheme 1). Alternative reaction conditions applied to the hexyl derivative, using methyl iodide (20 equivalents) in dry MeCN under reflux gave improved yields (95%) but required longer reaction times (85 h). The new ILs **6** and **7** were highly soluble in water and in methanol and insoluble in diethyl ether, therefore their purification was done by precipitation of the crude products from MeOH/Et_2O. The presence of signals around 4.32 ppm in their ^{1}H-NMR spectrum and at 38.7 ppm in their ^{13}C-NMR spectrum for the benzyl and hexyl derivatives, respectively, showed the quaternisation of the triazole ring.

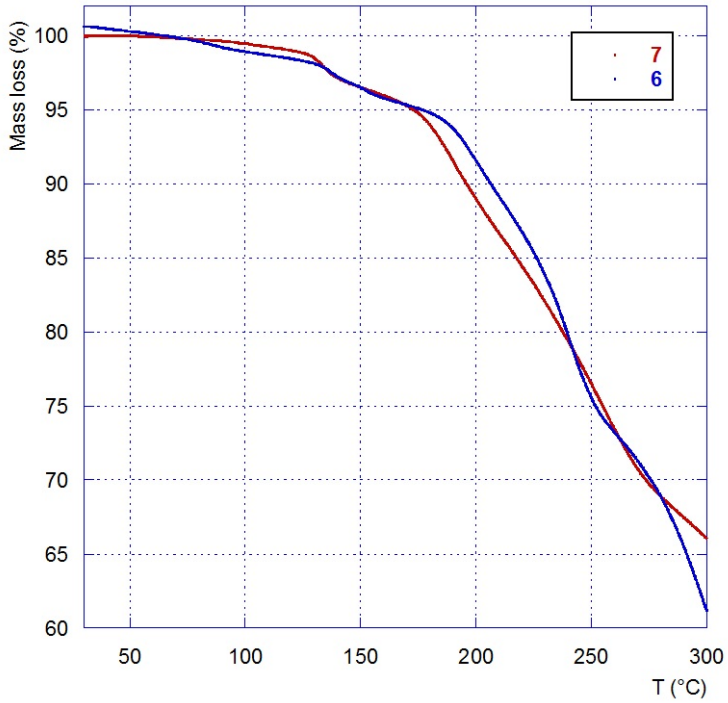
In addition of the IR, NMR, elemental analyses and mass spectroscopy, ILs **6** and **7** were characterized by DSC (Table 1) and TGA (Figure 4). Both compounds are stable until 120 °C and 150 °C, respectively, and showed a slight positive glass transition temperature (Tg). As previously described for tetrabutylammonium galacturonate and glucuronate [58], positive Tg and low decomposition temperature are observed what seems to be in relation with the presence of sugar moities. Considering these temperatures, **6** and **7** could be used only under mild conditions as solvents or chiral agents for chemical transformations or catalysis.

Table 1. Glass transition and decomposition temperatures of ILs **6** and **7**.

IL	Tg (°C) [a]	Tdec (°C) [b]
 **6**	4	150
 **7**	2.7	120

[a] Tg = Onset temperature measured at 10 K/min under argon; [b] Tdec = Onset temperature measured at 10 K/min under argon.

Figure 4. Thermogravimetric analysis of compounds **6** and **7**.



The thermal stability of **6** and 7 was determined by thermogravimetric analysis (TGA) under argon (Figure 4). The TG curve shows an initial weight loss of 1.33% and 0.76% of water respectively for **6** and **7** between room temperature and 110 °C followed by a second loss of water (3.20% and 3.01%). Such a noticeable mass loss corresponds to the hydroxyl groups. The thermal degradation (Tdec) occurring during the second step gives a loss of F (*m/z* = 19) fragments by mass spectrometry analysis originating from BF_4^- decomposition.

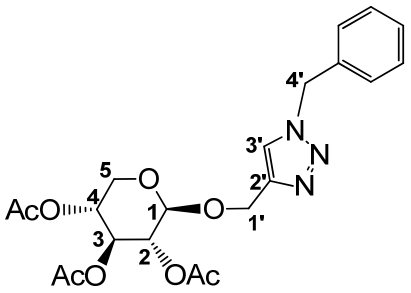
3. Experimental

3.1. General Procedures

All reagents were commercially available and used as received. CH_2Cl_2 was dried over CaH_2 and distilled under argon before use. CH_3CN was dried using a Pure Solv solvent drying system over aluminum oxide under an argon atmosphere before use. ^{1}H-NMR (250.1 MHz), ^{13}C-NMR (62.9 MHz) and ^{19}F-NMR (235.4 MHz) spectra were recorded on an AC 250 Bruker instrument in $CDCl_3$ or MeOD with TMS as reference for ^{1}H spectra and $CDCl_3$ (δ 77.0) or MeOD (δ 49.9) for ^{13}C spectra. IR spectra were recorded on a Nicolet AVATAR 320 FT-IR. C and H analyses were performed on a Perkin Elmer 2400 CHN equipment. Chromatographies were carried out on SDS Silica 60 (40–63 μm) or Silica 60 F_{254} (TLC plates). All experiments (MS and HRMS) were obtained on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operated in positive and negative mode. The electrospray potential was set to 3 kV in positive ion mode (flow of injection 5 μL/min.) and the extraction cone voltage was usually varied between 30 and 90 V. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Thermogravimetric analyses coupled with a mass spectrometer were performed between 30 °C and 300 °C under a constant flow of dry argon (50 mL·min^{-1}) using a Simultaneous Thermal Analyzer STA 449C Jupiter from Netzsch, and a heating rate of 10 K/min. The isothermal drift and sensitivity values are 0.6 μg/h and 0.1 μg, respectively. Alumina crucibles were loaded with 10–20 mg of sample. The DSC experiments were carried out on a Netzsch DSC 204F1 heat flux differential calorimeter at a heating rate of 10 K/min under a constant flow of dry argon (200 mL·min^{-1}). Aluminum crucibles were loaded with 10–15 mg of sample.

3.2. Synthetic Procedures

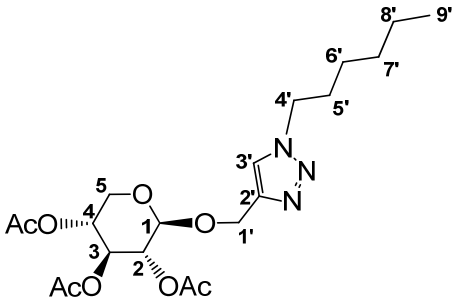
3.2.1. Preparation of 1-((1-Benzyl-1,2,3-triazol-4-yl)methoxy)2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (**2**)



To a solution of β-propargyl xyloside **1** (2.08 g, 6.3 mmol) in a THF/water 1:1 (v:v) (20 mL) mixture were added benzyl azide (560 mg, 4.2 mmol), $CuSO_4 \cdot 5H_2O$ (4.2 g, 16.9 mmol), and sodium ascorbate (3.3 g, 16.9 mmol). The mixture was stirred at room temperature under an argon atmosphere for 18 h. The mixture was concentrated and CH_2Cl_2 was added. The organic layer was washed with aqueous ammonium hydroxide (0.8 M) until a colorless aqueous layer was obtained, then with water to neutrality. The organic phase was concentrated to dryness *in vacuo*. The crude product was dissolved in a minimum of CH_2Cl_2 and precipitated with an excess of petroleum ether. Compound **2** was obtained as a white solid in 80% yield (2.25 g). IR (KBr) ν cm^{-1}: 2959, 2876, 1755, 1652, 1487, 1456,

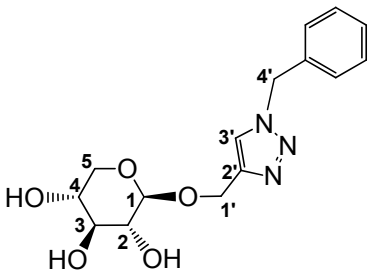
1371, 1224, 1172, 1123, 1046. ^{1}H-NMR ($CDCl_3$) 1.82, 1.91, 1.96 (3 × s, 9H, CH_{3Ac}), 3.37 (dd, J = 9 Hz, J = 11.7 Hz, 1H, H_5), 4.11 (dd, J = 5 Hz, J = 11.7 Hz, 1H, H_5), 4.61 (d, J = 5 Hz, 1H, $H_{1\beta}$), 4.73–4.97 (overlap, 2H + 1H + 1H, $H_{1'}$ + H_2 + H_4), 5.14 (t, J = 8.5 Hz, 1H, H_3), 5.52 (s, 2H, $H_{4'}$), 7.26–7.42 (overlapped, 5H, H_{arom}), 7.42 (s, 1H, $H_{3'}$). ^{13}C-NMR ($CDCl_3$) 20.4, 20.5, 20.6 (CH_{3Ac}), 54.0 ($C_{1'}$), 61.9, 62.3 (C_5, $C_{4'}$), 68.7, 70.5, 71.2 (C_2, C_3, C_4), 99.6 ($C_{1\beta}$), 122.6 ($C_{3'}$), 128.1, 128.7, 129.0 (CH_{arom}), 134.5 (Cq_{arom}), 144.5 ($C_{2'}$), 169.3, 169.7, 169.8 (C = O_{Ac}). Anal. Found (Calcd) for $C_{21}H_{25}N_3O_8$: C 56.39 (56.31), H 5.41 (5.62). $[\alpha]D^{20}$ = −71.9 (*c* 4.7, $CHCl_3$).

3.2.2. Preparation of 1-((1-Hexyl-1,2,3-triazol-4-yl)methoxy)2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (**3**)



Same procedure as described for compound **2** was followed with a solution of β-propargyl xyloside **1** (3 g, 9.5 mmol) in a THF/water 1:1 (v:v) (20 mL) mixture, hexyl azide (809 mg, 6.4 mmol), $CuSO_4 \cdot 5H_2O$ (6.5 g, 26.0 mmol), and sodium ascorbate (5.1 g, 26.0 mmol). Compound **3** was obtained as a white solid in 86% yield (2.34 g). IR (KBr) ν cm^{-1}: 2957, 2870, 1758, 1637, 1464, 1435, 1228, 1122, 1046. ^{1}H-NMR ($CDCl_3$) 0.85 (m, 3H, $H_{9'}$), 1.30 (overlapped, 6H, $H_{6'}$ + $H_{7'}$ + $H_{8'}$), 1.90 (m, 2H, $H_{5'}$), 2.01, 2.03, 2.05 (3 × s, 9H, CH_{3Ac}), 3.40 (dd, J = 9 Hz, J = 11.2 Hz, 1H, H_5), 4.15 (dd, J = 5 Hz, J = 11.7 Hz, 1H, H_5), 4.35 (t, J = 7.5 Hz, $H_{4'}$), 4.64 (d, J = 6.5 Hz, 1H, $H_{1\beta}$), 4.89–4.97 (overlapped, 2H + 1H + 1H, $H_{1'}$ + H_2 + H_4), 5.17 (t, J = 10 Hz, 1H, H_3), 7.49 (s, 1H, $H_{3'}$). NMR ^{13}C (62.9 MHz, $CDCl_3$) 13.8 ($C_{9'}$), 20.5 (CH_{3Ac}), 22.9, 26.0, 30.1, 30.9 ($C_{5'}$, $C_{6'}$, $C_{7'}$, $C_{8'}$), 50.2 ($C_{1'}$), 61.9, 62.4 (C_5, $C_{4'}$), 68.7, 70.6, 71.2 (C_2, C_3, C_4), 99.6 ($C_{1\beta}$), 122.3 ($C_{3'}$), 144.0 ($C_{2'}$), 169.3, 169.7, 169.8 (C = O_{Ac}). Anal. Found (Calcd) for $C_{20}H_{31}N_3O_8$: C 54.34 (54.41), H 7.01 (7.08). $[\alpha]_D^{20}$ = −67.0 (*c* 4.2, $CHCl_3$).

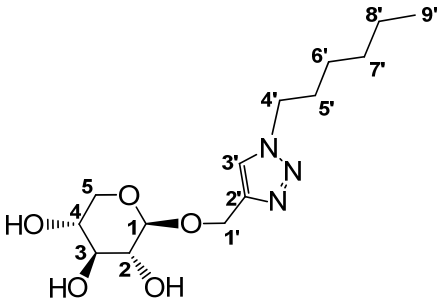
3.2.3. Preparation of 1-((1-Benzyl-1,2,3-triazol-4-yl)methoxy)β-D-xylopyranoside (**4**)



The acetylated compound **2** (170 mg, 0.38 mmol) was dissolved in CH_2Cl_2/MeOH 1:1 (v:v) (5 mL) under Ar and NaOMe (61.8 mg, 1.14 mmol) was then added. After stirring for 24 h at room temperature, the mixture was neutralized with Amberlite IR120 and filtered. The organic phase was concentrated to dryness *in vacuo*. The crude product was dissolved in a minimum of MeOH and precipitated with an excess of diethylether. Compound **4** was obtained as a white solid in 70% yield

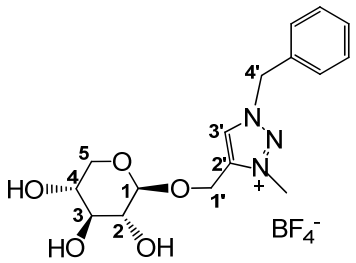
(m = 85 mg). ^{1}H-NMR (CD_3OD). 3.13–3.28 (overlapped, 1H + 1H + 1H, H_2 + H_3 + H_5), 3.44 (m, 1H, H_4), 3.82 (dd, J = 5 Hz, J = 11.2 Hz, H_5), 4.26 (d, J = 7.5 Hz, 1H, $H_{1\beta}$), 4.67 (d, J = 12.5 Hz, $H_{1'}$), 4.87 (overlap, 3H + 1H, OH + $H_{1'}$), 5.56 (s, 2H, $H_{4'}$), 7.30 (m, 5H, H_{arom}), 7.94 (s, 1H, $H_{3'}$). ^{13}C-NMR (CD_3OD) 54.7 ($C_{1'}$), 62.8 ($C_{4'}$), 66.7 (C_5), 70.9, 74.5, 77.3 (C_2, C_3, C_4), 104.0 ($C_{1\beta}$), 125.1 ($C_{3'}$), 128.9, 129.4, 129.8 (CH_{arom}), 136.5 (Cq_{arom}), 145.7 ($C_{2'}$). Anal. Found (Calcd) for $C_{15}H_{19}N_3O_5$: C 55.97 (56.03), H 5.94 (5.92). $[\alpha]_D^{20}$ = −36.7 (*c* 6.0, H_2O).

3.2.4. Preparation of 1-((1-Hexyl-1,2,3-triazol-4-yl)methoxy)β-D-xylopyranoside (**5**)



The same procedure as described for compound **4** was followed with compound **3** (2.34 g, 5.5 mmol) dissolved in CH_2Cl_2/MeOH 1:1 (v:v) (40 mL) and NaOMe (887 mg, 16.4 mmol). The compound **5** was obtained as a white solid in 63% yield (m = 1.09 g). ^{1}H-NMR (CD_3OD) 0.88 (m, 3H, $H_{9'}$), 1.32 (overlapped, 6H, $H_{6'}$ + $H_{7'}$ + $H_{8'}$), 1.88 (m, 2H, $H_{5'}$), 3.18–3.31 (overlapped, 1H + 1H + 1H, H_2 + H_3 + H_5), 3.48 (m, 1H, H_4), 3.87 (dd, J = 5 Hz, J = 11.2 Hz, 1H, H_5), 4.30 (d, J = 7.5 Hz, 1H, $H_{1\beta}$), 4.38 (t, J = 7.5 Hz, 1H, $H_{4'}$), 4.70 (d, J = 12.5 Hz, 1H, $H_{1'}$), 4.87 (overlapped, 3H + 1H, OH + $H_{1'}$), 7.97 (s, 1H, $H_{3'}$). ^{13}C-NMR (CD_3OD) 13.9 ($C_{9'}$), 22.0, 25.5, 29.7, 30.6 ($C_{5'}$, $C_{6'}$, $C_{7'}$, $C_{8'}$), 49.3 ($C_{1'}$), 61.5 ($C_{4'}$), 65.8 (C_5), 69.6, 73.2, 76.6 (C_2, C_3, C_4), 102.8 ($C_{1\beta}$), 124.0 ($C_{3'}$), 143.6 ($C_{2'}$). Anal. Found (Calcd) for $C_{14}H_{25}N_3O_5$: C 53.28 (53.32), H 7.88 (7.99). $[\alpha]_D^{20}$ = −40.0 (*c* 2.4, H_2O).

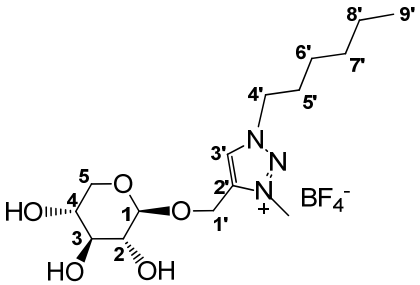
3.2.5. Preparation of 1-((1-Benzyl-3-methyl-1,2,3-triazol-4-yl)methoxy)β-D-xylopyranoside tetrafluoroborate (**6**)



The corresponding triazole **4** (936 mg, 2.9 mmol) and Me_3OBF_4 (517 mg, 3.5 mmol) were stirred in dry acetonitrile (40 mL) for 5 h at room temperature. The reaction was quenched with MeOH (10 mL), and the solvent was removed under reduced pressure to give the crude product, which was in a minimum of MeOH and precipitated with excess of diethyl ether. Compound **6** was obtained as a white wax in 23% yield (m = 291 mg). IR: ν cm^{-1}: 3363, 2891, 1737, 1635, 1589, 1456, 1348, 1286, 1244, 1155, 1035. ^{1}H-NMR (CD_3OD) 3.13–3.29 (overlapped, 1H + 1H + 1H, H_2 + H_3 + H_5), 3.36 (m, 1H, H_4), 3.85 (dd, J = 5 Hz, J = 11.2 Hz, H_5), 4.35 (s, CH_{3Tr}), 4.41 (d, J = 7.5 Hz, 1H, $H_{1\beta}$), 4.87 (sl,

3H, O*H*), 5.05 (dd, *J* = 15 Hz, *J* = 20 Hz, 2H, $H_{1'}$), 5.85 (s, 2H, $H_{4'}$), 7.50 (m, 5H, H_{arom}), 8.72 (s, 1H, $H_{3'}$). ^{13}C-NMR (CD_3OD) 38.7 (CH_{3Tr}), 58.0, 59.5 ($C_{1'}$, $C_{4'}$), 66.9 (C_5), 70.8, 74.6, 77.5 (C_2, C_3, C_4), 104.6 ($C_{1\beta}$), 129.5 ($C_{3'}$), 129.8, 130.0, 130.5 (CH_{arom}), 133.4 (Cq_{arom}), 142.2 ($C_{2'}$). ^{19}F-NMR (CD_3OD) 154.8 (s, BF_4). Anal. Found (Calcd) for $C_{15}H_{19}N_3O_5$ + 1 H_2O: C 43.96 (43.56), H 5.18 (5.48). $[\alpha]_D^{20} = -13.1$ (*c* 4.1 MeOH). HRMS calcd. for $C_{16}H_{22}N_3O_5^+$: 336.1559, found 336.1555

3.2.6. Preparation of 1-((1-Hexyl-3-methyl-1,2,3-triazol-4-yl)methoxy)β-D-xylopyranoside tetrafluoroborate (**7**)



The same procedure as described for compound **6** was followed with the triazole **5** (900 mg, 2.8 mmol) and Me_3OBF_4 (506 mg, 3.4 mmol) in dry acetonitrile (40 mL). Compound **7** was obtained as as a white wax in 78% (m = 896 mg). IR: ν cm^{-1}: 3392, 3140, 2956, 2929, 2872, 2494, 1589, 1460, 1356, 1323, 1286, 1247, 1038. ^{1}H-NMR (250 MHz, CD_3OD) 0.93 (m, 3H, $H_{9'}$), 1.37 (overlap, 6H, $H_{6'} + H_{7'} + H_{8'}$), 2.01 (m, 2H, $H_{5'}$), 3.17–3.34 (overlap, 1H + 1H + 1H, $H_2 + H_3 + H_5$), 3.49 (m, 1H, H_4), 3.85 (dd, *J* = 5 Hz, *J* = 11.2 Hz, 1H, H_5), 4.32 (s, 3H, CH_{3Tr}), 4.37 (d, *J* = 7.5 Hz, 1H, $H_{1\beta}$), 4.61 (t, *J* = 7.5 Hz, 1H, $H_{4'}$), 4.87 (sl, 3H, O*H* sugar), 5.03 (dd, *J* = 7.5 Hz, *J* = 22.5 Hz, 2H, $H_{1'}$), 8.71 (s, 1H, $H_{3'}$). ^{13}C-NMR (CD_3OD) 14.3 ($C_{9'}$), 23.4, 26.7, 30.1, 32.1 ($C_{5'}$, $C_{6'}$, $C_{7'}$, $C_{8'}$), 38.9 (CH_{3Tr}), 54.9 ($C_{4'}$), 59.6 ($C_{1'}$), 67.0 (C_5), 70.9, 74.5, 77.4 (C_2, C_3, C_4), 104.8 ($C_{1\beta}$), 130.7 ($C_{3'}$), 142.0 ($C_{2'}$). NMR ^{19}F (235.4 MHz, CD_3OD) 155.1 (s, BF_4). Anal. Found (Calcd) for $C_{14}H_{25}N_3O_5$ + 1.5 H_2O: C 40.11 (40.56), H 6.67 (7.03). $[\alpha]^{20}_D = -20.4$ (*c* 4.4 MeOH). HRMS calcd. for $C_{15}H_{28}N_3O_5^+$: 330.2029, found 330.2033.

4. Conclusions

D-Xylose-based ILs have been prepared from D-xylose following an original pathway, the key step being a click cycloaddition. These ILs have been fully characterized and are hydrophilic. After determination of their ecotoxicity and their biodegradability in a near future, these solvents could be used as alternative solvents or chiral agents for synthesis or catalysis in water under mild conditions.

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Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **2**–**7** are available from the authors.