pTSA/[bmim][BF_4] Ionic Liquid: A Powerful Recyclable Catalytic System for the Synthesis of α-2-Deoxyglycosides

Gisela Díaz, Agustín Ponzinibbio & Rodolfo D. Bravo

Topics in Catalysis

ISSN 1022-5528
Volume 55
Combined 7-10

Top Catal (2012) 55:644-648
DOI 10.1007/s11244-012-9847-6

Springer

Top Catal (2012) 55:644–648
DOI 10.1007/s11244-012-9847-6

ORIGINAL PAPER

pTSA/[bmim][BF_4] Ionic Liquid: A Powerful Recyclable Catalytic System for the Synthesis of α-2-Deoxyglycosides

Gisela Díaz · Agustín Ponzinibbio · Rodolfo D. Bravo

Published online: 26 June 2012

Abstract α-2-Deoxyglycosides were synthesized in ionic liquid ([bmim]BF_4)by stereoselective glycosylation of *endo*-glycals with various *o*-nucleophiles in the presence of catalytic amount of pTSAin 71–95 % yield. High yields, easy recovery of the products, and reusable reaction medium (pTSA/IL couple) with consistent activity makes this protocol efficient and environmentally benign.

Keywords 2-Deoxyglycosides · Ionic liquid · *Endo*-Glycal · Glycosylation · *p*-Toluensulfonic acid

1 Introduction

Many biologically important natural products contain 2-deoxyglycosides in their scaffolds [1–4]. Furthermore, both 2-deoxy-*o*-glycosides and 1-hydroxy-2-deoxysugars are important building blocks in organic synthesis. Although these types of compounds have been obtained from glycals, only a few methodologies are selective for the direct addition of alcohols without a competing Ferrier rearrangement. For instance, they can be synthesized from 2-iodo-2-deoxyglycoside, followed by dehalogenation [5, 6]. The acid-catalyzed addition to glycals represents the most direct method that can be operated under various conditions, including hydrogen bromide [7], triphenylphosphine hydrogenbromide [8–12], Dowex-50 [H^+] [13], $CeCl_3$ and $LaCl_3$ hydrates in combination with NaI, [14, 15], TMSOTf-NEt_3 [16, 17], BCl_3 [18], ceric ammonium nitrate [19], $GaCl_3$ [20] and Rhenium(V) complexes [21]. However, these methods suffer from a number of problems, such as expensive and toxic reagents, tedious separation, filtration or neutralization of the catalyst. As a consequence, there is a constant need to develop an environmentally benign mild reaction condition for the preparation of 2-deoxyglycosides using less hazardous catalysts and reaction media. As part of our interests in the development of environmentally friendly reactions, we set out to explore the promising use of *p*-toluenesulfonic acid (pTSA) in ionic liquids (ILs) as a catalyst in the addition reaction to glycals.

ILs, described as one of the most promising green solvents, have attracted rising interest in the last decades due to their high thermal stability, non-volatility, non-flammability and recyclability [22, 23]. The ILs based on imidazolium cations are specially favorable for green synthetic applications. Because of their unique solubility properties, that is, miscibility gap between organic solvents, they have become interesting candidates for separation processes by simple liquid–liquid extraction with conventional organic solvents. Furthermore, ILs are found to be an efficient reaction media for the immobilization of transition metal-based catalysts, Lewis acids, and enzymes [24–26]. Due to their high polarity, reactions in ILs have kinetic and thermodynamic behavior different from classical solvents, which often leads to improved process performance. pTSA have been used to catalyze reactions in ILs [27]. Although the acidity of this acid in ILs has not been quantitated by a dissociation constant or an acidity function, it is clear from what is described in the literature that they are enough acidic to catalyze several very important organic reactions [28].

In view of our ongoing efforts in the development of environmentally friendly catalytic processes for the

G. Díaz · A. Ponzinibbio (✉) · R. D. Bravo
Laboratorio de Estudio de Compuestos Orgánicos (LADECOR), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, 47 y 115, 1900 La Plata, Argentina
e-mail: ponzinibbio@quimica.unlp.edu.ar

synthesis of biologically active carbohydrate derivatives [29–31], we decided to investigate the synthesis of 2-deoxyglycosides catalyzed by pTSA[32] immobilized in ILs as a powerful recyclable homogeneous catalytic system.

2 Experimental Section

2.1 Instruments and Reagents

All purchased chemicals (reagent grade) were obtained from Sigma-Aldrich de Argentina S.A. Column chromatography purifications were carried out with silica gel 60 (70–230 mesh). Commercially available reagents were directly used without further purification unless otherwise noted. All sugar derivatives were prepared and carefully purified by known methods and fully characterized by ^{1}H and ^{13}C NMR. All the reactions were carried out at room temperature with magnetic stirring of 600 rpm. Reaction progress was monitored by thin layer chromatography (TLC) on precoated plates of silica gel 60 F_{254} in hexane:ethyl acetate (AcOEt) (7:3).

^{1}H NMR spectra were recorded at a Varian spectrometer (200 MHz) in CDCl3 (δ_H 7.26), Acetone-d_6 (δ_H 2.05) or DMSO-d_6 (δ_H 2.50); ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ (δ_H 77.16 (central line of a triplet)). Splitting patterns are shown by the abbreviations, such as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

The IL: 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) was obtained by quaternisation of 1-methylimidazole with alkyl bromide and $NaBF_4$ in solvent free conditions according to [33]. The structure was determined by NMR spectroscopy. ^{1}H NMR (200 MHz, acetone-d_6): δ 9.51 (s, 1H, CH), 7.89 (s, 1H, CH), 7.83 (s, 1H, CH), 4.42 (t, 2H, CH_2), 4.09 (s, 3H, CH_3), 1.92 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 0.93 (t, 3H, CH_3). ^{13}C NMR (50 MHz, acetone-d_6): δ 137.44, 124.34, 122.98, 49.72, 36.53, 32.48, 19.62, 13.37.

2.2 Glycosylation Procedure

Typical experimental procedure: a solution of glycal (0.5 mmol) and nucleophile (0.75 mmol) in 0.5 ml of [bmim][BF_4] containing 5 mol% of pTSA was stirred at room temperature, until the complete disappearance of the starting materials as judged by TLC. The reaction mixture was extracted by diethyl ether (4 × 1 ml). The combined ether phase were concentrated under reduced pressure. The residue was purified by CC on silica gel (eluent hexane:AcOEt) to afford the corresponding product. All sugar derivatives were fully characterized by ^{1}H and ^{13}C NMR. Compound: Isopropyl-2-deoxy-3,4,6-tri-*o*-benzyl-α-D-lyxo-hexopyranoside. Pale yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.20 (15H, m, ArH), 5.11 (1H, d, H1), 4.97 (1H, d, $PhCH_2$), 4.71 (1H, d, $PhCH_2$), 4.62 (2H, br s, CH_2Ph), 4.57 (1H, d, $PhCH_2$), 4.39 (1H, d, $PhCH_2$), 4.15–4.05 (3H, m, H3, H4, H5), 3.99–3.89 (1H, m, H1), 3.59 (1H, dd, H6a), 3.54 (1H, dd, H6b), 2.40–2.29 (1H, m, H2a), 2.03–1.95 (1H, m, H2b), 1.24 (3H, d, CH_3), 1.11 (3H, d, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.9, 138.6, 138.1, 128.5–127.2, 95.6, 75.0, 73.9, 73.2, 73.1, 70.44, 69.8, 69.5, 67.3, 31.6, 23.1, 21.2.

2.3 IL Recycling

The residue (IL/pTSA) 0.5 ml obtained after extraction of the products with diethyl ether, was dried in vacuum resulting in recycled pTSA/IL couple.

3 Results and Discussion

One of the most important contributions that ILs makes to homogeneous catalysis is the possibility of catalyst recycling by immobilization in the IL-phase. Firstly we studied the solubility behavior of pTSA in [bmim][BF_4] and the subsequent liquid–liquid extraction by diethyl ether. A solution of pTSA (15 mg) in [bmim][BF_4] (0.5 ml) was extracted by vigorous stirring with diethyl ether (4 × 1 ml). The combined ether phase was analyzed and no pTSAwas detected. The results showed that the pTSA can be excellently distributed in the ionic liquid.

Then we have investigated the use of pTSA/[bmim][BF4] as a catalytic system for the acid-catalyzed addition reactions to glycals, in which two-pathways products may be generated, associated to either protonation or allylic rearrangement routes (Fig. 1).

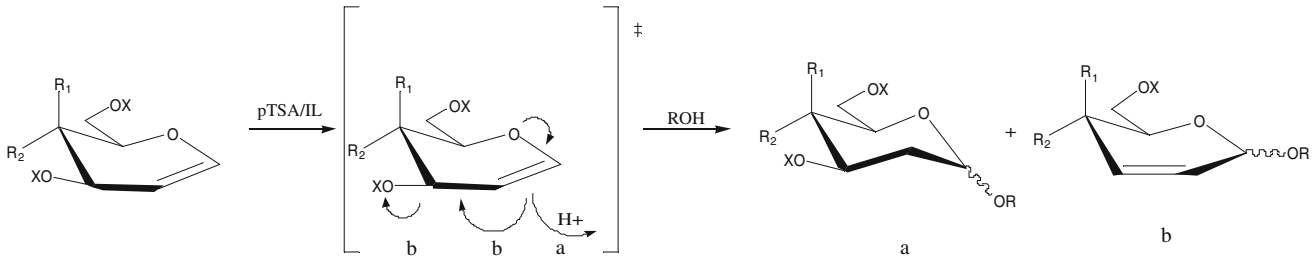


Fig. 1 Possible pathways proposed to explain the formation of 2-deoxyglycosides (*a*) and 2,3-unsaturated glycopyranosides (*b*)

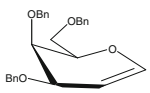
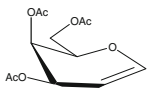
Initially, acid-catalyzed glycosylation was investigated on 3,4,6-tri-*o*-benzyl-D-galactal (**1**), prepared from 3,4,6-tri-*o*-acetyl-D-galactal based on a reported procedure [34], with dry methanol in 0.5 ml of [bmim][BF_4] containing 5 mol% of pTSA. The progress of the reaction was monitored by TLC which showed gradual disappearance of the substrate and the appearance of a more polar product. Complete consumption of the starting material was noticed after 1.5 h assuming 100 % of glycal conversion in all cases. These reaction conditions lead to exclusive formation of 2-deoxygalactosides via the protonation pathway.

Encouraged by the initial results, the reaction was then carried out with a variety of alcohols, and using either perbenzyl or peracetyl galactal (**2**) as substrates, which in all cases underwent the protonation route smoothly to afford the corresponding 2-deoxygalactosides in high yields (Table 1).

Having successfully accomplished the direct *o*-glycosylation of peracetyl and perbenzyl-D-galactals with a few alcohols, we next focused our attention with great emphasis on similar reactions with the glucose derivatives. From the literature [35], it has been reported that perbenzyl glucal undergo addition reactions to afford 2-deoxy-*o*-glycosides upon treatment with alcohols in the presence of acid catalysts. It is noteworthy that under the present conditions, the reaction of 3,4,6-tri-*o*-benzyl glucal (**3**) proceeded without difficulties leading to the complete conversion in high yield and α-selectivity. The exclusive formation of 2-deoxy-D-glucosides was still observed when the reaction was carried out with a set of alcohols. However the reaction of peracetyl glucal generated both the desired product in low yields and the major rearranged product (Table 2). It is well known that the protecting groups of glycosyl donors have influence on the glycosylation rate, depending on if they stabilize the cationic transition state or not, electron-donating groups (benzyl ethers) facilitate the protonation route. On the contrary, electron-withdrawing groups (acetates) make the oxonium ion relatively less stable so that Ferrier rearrangement has the advantage to form a more stable α,β-conjugated oxonium ion [36].

The reactions all displayed high α-stereoselectivity so the nucleophiles attacked from the bottom face of the

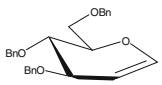
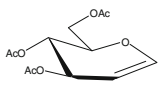
Table 1 Glycosylation of protected-D-galactals in [bmim][BF_4]/pTSA

Glycal	Acceptor (ROH)	Time (h)	Yield%[a]	Ratio (α:β)[b]
	Methanol	1.5	91 + 0	4:1
1	Benzyl alcohol	1.5	86 + 0	6:1
1	Isopropanol	4	75 + 0	8:1
1	*n*-Dodecylalcohol	1.5	94 + 0	6:1
	Methanol	1.5	90 + 0	4:1
2	Benzyl alcohol	1.5	89 + 0	5:1
2	Isopropanol	4	78 + 0	8:1
2	*n*-Dodecylalcohol	1.5	92 + 0	6:1

[a] Mol% protonation + rearrangement products. Isolated yield after column chromatography

[b] Anomeric ratios were obtained from ^{1}H NMR spectra

Table 2 Glycosylation of protected-D-glucals in [bmim][BF_4]/pTSA

Glycal	Acceptor (ROH)	Time (h)	Yield%[a]	Ratio (α:β)[b]
	Methanol	1.5	95 + 0	3:1
3	Benzyl alcohol	1.5	83 + 0	4:1
3	Isopropanol	4	71 + 0	5:1
3	*n*-Dodecylalcohol	1.5	90 + 0	4:1
	Methanol	1.5	10 + 82	2:1
4	Benzyl alcohol	1.5	15 + 80	4:1
4	Isopropanol	4	12 + 71	4:1
4	*n*-Dodecylalcohol	1.5	9 + 84	3:1

[a] Mol% protonation + rearrangement products. Isolated yield after column chromatography

[b] Anomeric ratios were obtained from ^{1}H NMR spectra

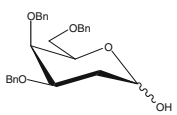
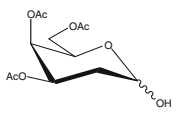
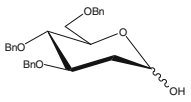
carbohydrate ring. This result is not only consistent with the anomeric effect, but also favorable by the less steric hindrance (i.e., the axial hydroxyl group at C4-position prefers α-stereoselectivity). In contrast, the reactions of tri-*o*-benzyl-D-glucal with alcohols offered similar reactivity and yield, but lower stereoselectivity. To gain further insight into the acid catalyzed reaction mechanism in ILs, we will perform a systematic quantitative study by NMR spectroscopy. Investigations along this line are in progress.

Several methodologies have been developed to synthesize 1-hydroxy-2-deoxysugars from glycals, but none are without drawbacks. The direct acid-catalyzed hydration requires rather drastic conditions that may affect many protecting groups, the reduction of phenylthio derivatives requires high temperature (refluxing toluene) [37], the hydration via oxymercuration-demercuration using $Hg(OAc)_2$/$NaBH_4$ is effective but not ideal since mercury salts are toxic in nature [38]. In order to broaden the scope of the pTSA/IL couple glycosylation protocol, we decided to explore the direct hydration of *endo*-glycals.

Screening several reaction conditions indicated that a mixture of glycal (0.5 mmol) and water (0.75 mmol) in 0.5 ml of [bmim][BF_4] containing 5 mol% of pTSA at room temperature was ideal for the optimum hydration without the Ferrier rearrangement products. Both acetyl and benzyl protected glycals gave the hydrated products in good to excellent yields. Our results are summarised in Table 3.

The advantage of using ILs is that the products of the reaction can be extracted into the organic solvent leaving the ionic liquid behind which can be successfully recycled. The recycling performance of pTSA immobilized in [bmim][BF_4] was studied in the reaction of 3,4,6-tri-*o*-benzyl-D-galactal with MeOH. The data listed in Table 4 show that could be reused four times with consistent activity. After five cycles, a slight drop in yields by about 10–15 % was found with the recycled IL after dried in vacuum. It is possible that this decrease values could be due to partial decomposition of the IL during the reaction as in NMR spectra appeared some minor unknown peaks.

Table 3 Direct hydration of glycals in [bmim][BF_4]/pTSA

Glycal	Product	Time (h)	Yield%[a]
1		2.5	91
2		5	71
3		2.5	85

[a] Isolated yield (2-deoxyglycoside mol%) after column chromatography

[b] Spectral data are consistent with literature values [21]

Table 4 Recyclability of ionic liquid [bmim][BF_4]/pTSA

Run	Yield%[a]
1	91
2	91
3	89
4	86

[a] Isolated yields (2-deoxyglycoside mol%)

4 Conclusions

We have developed a quick, selective and green method for synthesizing α-2-deoxyglycosides by glycosyl addition of *endo*-glycals with several alcohols. Addition of water to benzyl-protected glycals, is also a significant advantage of the protocol presented here. The obtained results are very useful since carbohydrate derivatives are products of interest as key intermediates for the synthesis of a number of biologically active compounds. We believe that the methodology reported here is synthetically quite attractive and would spur on further interests toward the synthesis of complex glycosides. Moreover, the simple experimental procedure being combined with ease of recovery and reuse of pTSA is expected to contribute to the development of green strategies for other acid-catalyzed reactions. Further studies on the pTSA/[bmim][BF_4] recyclable catalytic system are now in progress.

Acknowledgments Authors wish to thank Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CICPBA), UNLP and CONICET for their financial support to the present work. G.D. thanks CONICET for providing a doctoral research fellowship.

References

1. He X, Agnihotri G, Liu H-W (2000) Chem Rev 100:4615
2. He XM, Liu HW (2002) Curr Opin Chem Biol 6:590
3. Rohr J, Thiericke P (1992) Nat Prod Rep 9:103
4. Weymouth-Wilson AC (1997) Nat Prod Rep 14:99
5. Costantino V, Imperatore C, Fattorusso E, Mangoni A (2000) Tetrahedron Lett 41:9177
6. Costantino V, Fattorusso E, Imperatore C, Mangoni A (2002) Tetrahedron Lett 43:9047
7. Lam SN, Gervay-Hague J (2003) Org Lett 5:4219
8. Bolitt V, Mioskowski C (1990) J Org Chem 55:5812
9. Colinas P, Bravo RD (2003) Org Lett 5:4509
10. Wandzik I, Bieg T (2006) Carbohydr Res 341:2702
11. Jaunzems J, Kashin D, Schonberger A, Kirschning A (2004) Eur J Org Chem :3435

12. Hou D, Lowary TL (2009) Carbohydr Res 344:1911
13. Sabesan S, Neira S (1991) J Org Chem 56:5468
14. Yadav JS, Reddy BVS, Reddy KB, Satyanarayana M (2002) Tetrahedron Lett 43:7009
15. Rani S, Agarwal A, Vankar YD (2003) Tetrahedron Lett 44:5001
16. Kolar C, Kneissl G (1990) Angew Chem Int Ed Engl 29:809
17. Kaila N, Blumenstein M, Bielawska H, Franck RW (1992) J Org Chem 57:4576
18. Toshima K, Nagai H, Ushiski Y, Matsumura S (1998) Synlett :1007
19. Pachamuthu K, Vankar YD (2001) J Org Chem 66:7511
20. Yadav JS, Subba Reddy BV, Vijaya Bhasker E, Raghavendra S, Narsaiah A (2007) Tetrahedron Lett 48:677
21. Sherry BD, Loy RN, Toste FD (2004) J Am Chem Soc 126:4510
22. Olivier-Bourbigou H, Magna L, Morvan D (2010) Appl Catal A Gen 373:1
23. Hallett JP, Welton T (2011) Chem Rev 111:3508
24. Sheldon RJ (2001) Chem Soc, Chem Commun 23:2399
25. Gordon CM (2001) Appl Catal A 222:101
26. Zimmermann HE, Wang PA (1993) J Am Chem Soc 115:2205
27. Rosatella AA, Frade RFM, Afonso CAM (2011) Curr Org Synth 8:840
28. Johnson KE, Pagni RM, Bartmess J (2007) Monatsh Chem 138:1077
29. Tasca JE, Ponzinibbio A, Díaz G, Bravo RD, Lavat A, González MG (2010) Top Catal 53:1087
30. Ponzinibbio A, Colinas PA, Lieberknecht A, Bravo RD (2006) Lett Org Chem 3:459
31. Colinas PA, Ponzinibbio A, Lieberknecht A, Bravo RD (2003) Tetrahedron Lett 44:7985
32. Baghernejad B (2011) pTSA was selected as the Brønsted acid for these experiments, envisioned as a robust, non-volatile, easy to manipulate and inexpensive solid. Curr Org Chem 15:3091
33. Fang D, Cheng J, Gong K, Shi Q-R, Zhou X-L, Liu Z-L (2008) J Fluor Chem 129:108
34. Szeje W, Fockt I (1989) Recl Trav Chim Pays-Bas 108:224
35. Hotha S, Tripathi A (2005) Tetrahedron Lett 46:4555
36. Agarwal A, Rani S, Vankar YD (2004) J Org Chem 69:6137
37. Wild R, Schmidt R (1995) Liebigs Ann 5:755
38. Bettelli E, Cherubini P, D'Andrea P, Passacantilli P, Piancatelli G (1998) Tetrahedron 54:6011