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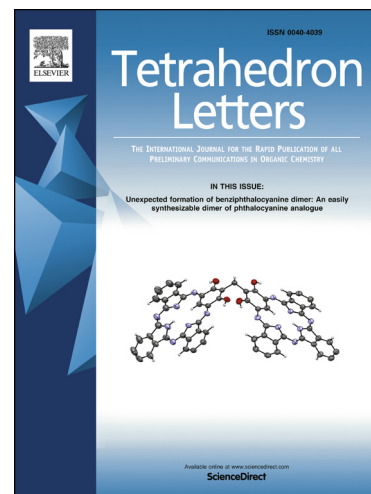
PII: S0040-4039(17)31031-6
DOI: <http://dx.doi.org/10.1016/j.tetlet.2017.08.033>
Reference: TETL 49223

To appear in: *Tetrahedron Letters*

Received Date: 12 July 2017
Revised Date: 11 August 2017
Accepted Date: 13 August 2017

Please cite this article as: Santiago, C.C., Lafuente, L., Bravo, R., Díaz, G., Ponzinibbio, A., Ionic liquids as phase transfer catalysts: enhancing the biphasic extractive epoxidation reaction for the selective synthesis of β -O-glycosides, *Tetrahedron Letters* (2017), doi: <http://dx.doi.org/10.1016/j.tetlet.2017.08.033>

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Tetrahedron Letters
journal homepage: www.elsevier.com

Ionic liquids as phase transfer catalysts: enhancing the biphasic extractive epoxidation reaction for the selective synthesis of β -O-glycosides

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ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

Ionic liquids
Phase transfer catalysis
 β -O-glycosides
Oxone
Epoxidation

ABSTRACT

Ionic liquids promoted the direct epoxidation of glycals acting as PTC. 1,2-anhydrosugars were prepared by the oxidation of glycals under biphasic conditions with dimethyldioxirane generated in situ from oxone/acetone and amphiphilic IL's as catalysts. β -O-glycosides were synthesized in good yields by the nucleophilic ring opening of epoxy carbohydrate derivatives. Also, 3, 4, 6-benzyl protected carbohydrates and β -N-glycosides could be prepared by this method.

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Epoxides are important organic intermediates due to their high reactivity. The nucleophilic ring opening reaction takes place with high stereocontrol leading selectively to pure products.¹⁻³ Commonly, the oxidation of alkenes to afford epoxides was achieved with organic peracids and peroxy acids, but lately dioxiranes have been used as new oxidizing agents.

Dimethyldioxirane (DMDO) is commercially available in low concentration and unstable solutions, nevertheless it can be prepared in situ by the oxidation of acetone with oxone.⁴⁻⁶ The complete epoxidation methodology often requires an efficient interchange of species between the organic phase where main substrates are dissolved and the aqueous media. Phase transfer catalysts (PTC) become irreplaceable reactants for the occurrence of biphasic reactions. Ionic liquids can be designed and synthesized on demand incorporating different active moieties. Molecules with amphiphilic structures are often used in organic synthesis to facilitate reactions between organic reactants and ionic inorganic salts, recently some IL's were tested as PTC.⁷⁻¹⁰

In the last years, there has been sustained interest in the selective synthesis of β -glycosides. The synthesis of 1,2-anhydrosugars and the subsequent nucleophilic ring opening reaction is a promising methodology to achieve this desired carbohydrate derivatives. Despite some techniques were developed and many synthetic efforts were made, there is still a demand for green methods in the selective synthesis of 2-hydroxy-glycosides.¹¹⁻¹³

For several years, we have been interested in the synthesis of carbohydrate derivatives. In our laboratory, different methods were applied to the synthesis of C-, O- and N-glycosides with promising biological activity as antiproliferative agents or enzymatic inhibitors.¹⁴ In view of our ongoing efforts to develop new environmentally friendly catalytic processes, we decided to investigate the use of ionic liquids as phase transfer catalyst for biphasic synthesis of 1,2-anhydrosugars and 2-hydroxy-glycosides.

As previously stated, eco-friendly ionic liquids as promoters and catalyst represent an interesting alternative in organic synthesis developments. To study in detail the use of ILs in epoxidation reactions, we tested a series of ILs

with alkyl substituents on the quaternary cation. The ILs were prepared with excellent yields using a one-pot solventless methodology.¹⁵

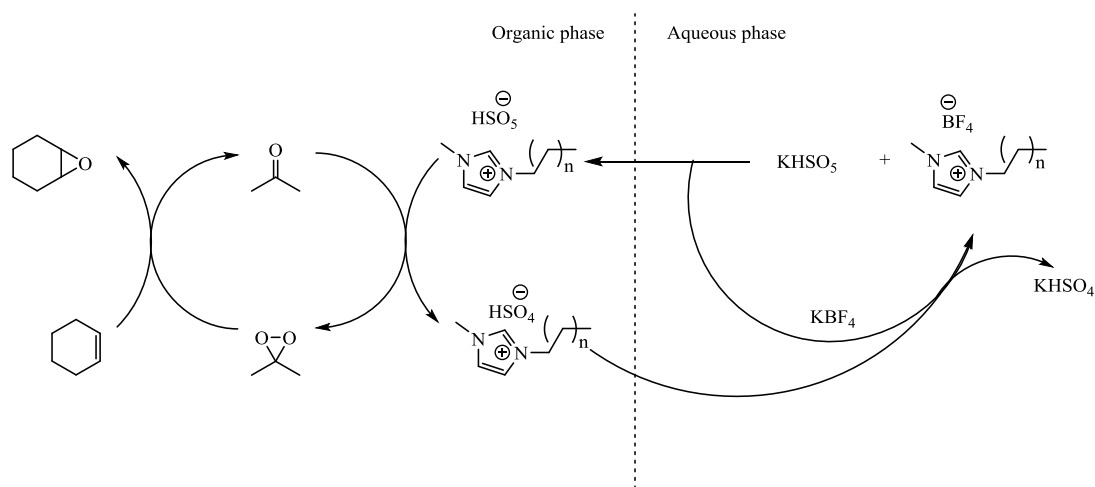
At first, we studied the cyclohexene oxidation in different ways to optimize the reaction conditions. The method includes a ketone -acetone-, and a peracid -potassium peroxydisulphate (KHSO_5)- commercially available as Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$). The well known mechanism indicates that KHSO_5 is the oxidizing agent and acetone acts as catalyst.⁴ Despite many applications have been reported, major problems are, low conversions and yields of the corresponding dioxirane and their subsequent alkene oxidation. To compile accurate information, we divided the preliminary experiments in three different systems: 1) epoxidation with KHSO_5 and acetone in aqueous media, 2) epoxidation with KHSO_5 , acetone and biphasic media (water/dichloromethane), 3) epoxidation with KHSO_5 , acetone, biphasic media and a IL as a phase transfer catalyst (1-butyl-3-methylimidazolium tetrafluoroborate, BMImBF_4).

Table 1. Epoxidation of cyclohexene in three different media.

| System | % Conversion |
|--------|--------------|
| 1 | 50 |
| 2 | 69 |
| 3 | 91 |

By comparing the results obtained, it could be concluded that the use of PTC is essential to enhance the reaction performance. In system 1, KHSO_5 was used as an aqueous solution, dimethyldioxirane (DMDO) produced from acetone and the peracid in the basic aqueous phase reacts with cyclohexene in the organic media and at the interface of cyclohexene/ KHSO_5 . When a solvent is added to the system (case 2), acetone can be dissolved in both aqueous and dichloromethane phases, for this reason DMDO can be formed in the aqueous solution and in the interface. The presence of CH_2Cl_2 facilitates the migration of DMDO to the organic phase where cyclohexene was oxidized, so the yields are higher. It's a typical extractive reaction process. Finally, system 3 is also an extractive process but with better efficiency. The DMDO could be formed and transfer to the organic phase easily and faster. The peracid forms a salt with the organic cation of PTC. This salt moves to the dichloromethane phase and oxidized the acetone to produce the desired DMDO. (Figure 1)

Figure 1. Oxidation of cyclohexene by DMDO in biphasic media.



Then we screened imidazolium ILs with different alkyl substituents and anions. As expected ILs with BF_4^- anion acts more efficiently in the interchange of peracid ($-\text{HSO}_5^-$) between the phases. It's well known that ILs with PF_6^- anions are barely soluble in water, therefore their capacity to transfer ions from the aqueous to the organic phase is lower. Increasing the length of the N-alkyl substituent in the imidazolium cation represents an improvement in the amphiphilic character of the molecule. Therefore, 1-dodecyl-3-methylimidazolium tetrafluoroborate (DodMImBF_4) represents the best choice to enhance the formation and reactivity of DMDO in the dichloromethane phase.

Considering the promising results obtained we tried to extrapolate this methodology to the biphasic epoxidation of endo-glycals since the nucleophilic ring opening of the 1,2-anhydrosugars leads to biologically relevant β -glycosides.

Thus, we performed and analyzed the model tandem reaction of biphasic oxidation of 3,4,6-tri-O-benzyl-D-glucal with DMDO, generated in situ, using several ILs as PTC, and the subsequent MeOH addition to generate more stable 2-hydroxy-OMe- glycosides. The experiments to test the efficiency of ILs as PTC are shown in Table 2.

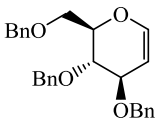
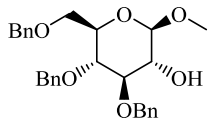
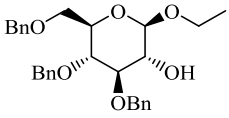
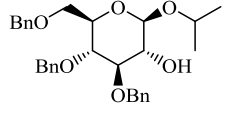
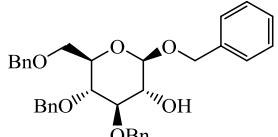
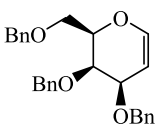
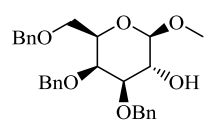
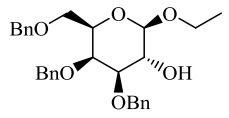
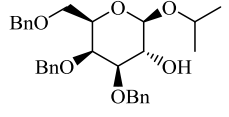
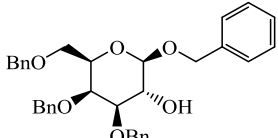
Table 2. Epoxidation of TOBnGlu using different IL as PTC.

| Entry | PTC | Time of epoxidation step (h) | Yield (%) |
|-------|------------------------|------------------------------|-----------|
| 1 | BMIImBF ₄ | 12 | 5% |
| 2 | BMIImPF ₆ | 12 | 5% |
| 3 | HMIImBF ₄ | 12 | 40% |
| 4 | HMIImPF ₆ | 12 | 10% |
| 5 | DodMIImBF ₄ | 3 | 70% |
| 6 | DodMIImPF ₆ | 12 | 15% |

Room temperature, slightly basic aqueous solution, dichloromethane, intense magnetic stirring (700 rpm) and IL as PTC to accelerate the exchange of reactive species between phases conforms the method proposed as described in detail in the experimental section. Very good yields and high β selective products were obtained, after column chromatography purification, as confirmed by NMR analysis.¹⁶

With the method optimized a variety of nucleophilic alcohols were tested for the scope and specificity of the system (Table 3). With less hindered alcohols the yields were better than ones bearing a secondary or tertiary -OH group. Comparing the substrate influence, glycals derived from D-glucose and D-galactose were tested, the yields obtained were similar, regardless of the C4 configuration.

Table 3. Reactions of 1,2-anhydro-3,4,6-tri-O-benzyl- β -D-glucopyranoside with several nucleophiles.^a

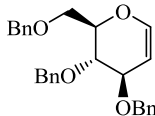
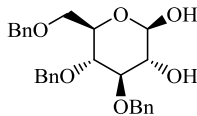
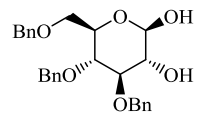
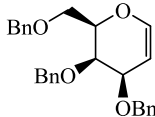
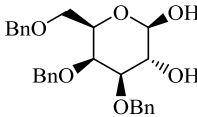
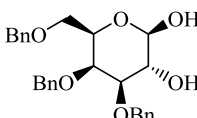
| Entry | Glycal | Alcohol | Product | Yield (%) ^b |
|-------|---|---------|--|------------------------|
| 1 |  | MeOH |  | 70 |
| 2 | | EtOH |  | 75 |
| 3 | | iPrOH |  | 64 |
| 4 | | BnOH |  | 60 |
| 5 |  | MeOH |  | 77 |
| 6 | | EtOH |  | 73 |
| 7 | | iPrOH |  | 65 |
| 8 | | BnOH |  | 60 |

^a Reagents and conditions: i) Oxone (2 equiv.), acetone, DodMImBF₄ (0.1 equiv.), NaHCO₃, H₂O, CH₂Cl₂ ii) Alcohol, rt^b Yields calculated after purification by column chromatography.

In all cases, excellent to very good yields were obtained. The anomeric selectivity was studied by the analysis of ¹H NMR spectra. As expected, due to the *anti* nucleophilic opening of the α -epoxide generated by oxidation of TOBnGlu by DMDO, all β - configuration products were obtained, deduced by the chemical shifts and coupling constants of the anomeric proton.

During preliminary studies, it was detected in some cases that 1,2 diols were obtained, presumably due to the nucleophilic attack of H₂O after the oxidation reaction. Especially for non-imidazolium IL's such as BPyBF₄ and trihexyl(tetradecyl)phosphonium dicyanamide (Cyphos 105). An endeavor to expand the scope was done to synthesize sugar derived 1,2 diols. Carbohydrate derivatives with selective protection of their multiple -OH groups are useful intermediates in glycoside synthetic chemistry.¹⁷ As seen in Table 4, BuPyBF₄ and Cyphos 105 are effective catalyst for the transformation of protected glycals into their corresponded 1,2 diols in moderate yields. NMR analysis indicates that the stereochemistry at C2 is equatorial in every case, nevertheless anomeric mixtures of the diols were obtained (anomeric ratio α/β 1.5:1 in all cases).¹⁸

Table 4. Synthesis of 1,2 diols from glycols via DMDO oxidation.^a

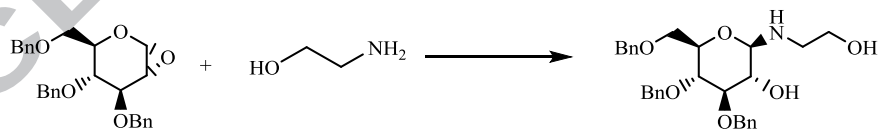
| Entry | Glycol | IL | Product | Yield (%) ^b |
|-------|---|---------------------|--|------------------------|
| 1 |  | BuPyBF ₄ |  | 70 |
| 2 | | Cyphos 105 |  | 75 |
| 3 |  | BuPyBF ₄ |  | 77 |
| 4 | | Cyphos 105 |  | 45 |

^a Reagents and conditions: i) Oxone (2 equiv.), acetone, IL (0.1 equiv.), NaHCO₃, H₂O, CH₂Cl₂ 0° C to rt

^b Yields calculated after purification by column chromatography.

Finally, we studied the selectivity towards different nucleophilic moieties in the reagents. An interesting result was achieved when ethanolamine was used as nucleophile. A β-N-glycoside was obtained after 6 hours through a regio- and stereoselective ring opening reaction in good yields and enantiopure form (Figure 2).

Figure 2. Nucleophilic attack of 1,2-anhydroglycol with ethanolamine.



The complete analysis by ¹H, ¹³C NMR and gHSQC, gCOSY and NOESY experiments confirm the selectivity of the product formed.¹⁹

In summary, the use of amphiphilic IL's as PTC in the oxidation of benzyl protected glycols conforms a simple, rapid and efficient method to the synthesis of β-O-2-hydroxyglycosides, current building blocks of biologically active molecules. Moreover, under certain reaction conditions 1,2 unprotected carbohydrates could be prepared. Further work expanding on the scope of the substrates and on the suitability of the protocol to prepare β-N-glycosides are under way in our laboratory.

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.

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15. *1-dodecyl-3-methylimidazolium tetrafluoroborate*. Anhydrous sodium tetrafluoroborate (15.30 g, 0.14 mol), 1-methylimidazole (11.5 ml, 0.14 mol) and 1-bromododecane (33.55 ml, 0.14 mol) were placed in a round bottom flask equipped with a reflux condenser. The mixture was stirred at 80°C for 4 hs, under inert atmosphere. The resultant suspension was diluted with 25.0 ml of acetonitrile and then filtered. After the solvent was removed under reduce pressure, the ionic liquid was dried at 80°C in vacuo (0.02 torr) for 6 hs to obtained a light yellow semi-solid product (yield=97%). ¹H NMR (500 MHz, CDCl₃): δ 8.97 (s, 1 H, H-2), 7.42 (s, 1 H, H-4), 7.34 (s, 1 H, H-3), 4.14 (t, J = 7.78 Hz, 2 H, H-5), 3.91 (s, 3 H, H-1), 1.81 (broad t, 2 H, H-6), 1.25-1.18 (m, 18 H, H7-15), 0.81 (t, J = 7.28 Hz, 3 H, H-16). ¹³C NMR (125 MHz, CDCl₃): δ 136.20 (C2), 123.79 (C3), 122.13 (C4), 49.96 (C5), 36.22 (C1), 31.83 (C6), 30.07, 29.55, 29.53, 29.47, 29.26, 28.93, 26.16, 22.60 (C7-C15), 14.04 (C16).
16. Ionic liquid (10% mmol) and 3,4,6-tri-O-benzyl-D-glucal (200 mg, 0.48 mmol) were placed in a round-bottomed flask and dissolved in 2.0 ml of dichloromethane, then were added acetone (0.8 ml) and saturated NaHCO₃ aqueous solution (1.5 ml). To this vigorously stirred biphasic mixture was added dropwise a solution of oxone (600 mg, 0.9760 mmol in 2.5 ml of water) at 0°C for 15 minutes, maintaining the temperature 20 minutes more. After completion of the reaction, the mixture was extracted with dichloromethane (5 x 2.0 ml) and the combined organic phases were dried over sodium sulphate (Na₂SO₄). After filtration, the solvent was evaporated and the residue was immediately dissolved in anhydrous methanol (5.0 ml) and stirred for 12 hs at room temperature. This solution was concentrated under reduced pressure and the residue was purified by column chromatography to obtain pure methyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside. ¹H NMR (300 MHz, CCl₃D): δ 7.38-7.15 (m, 15 H, 3 C₆H₅), 4.94-4.81 y 4.64-4.52 (m, 6 H, CH₂Ph), 4.19 y 4.16 (d, 1 H, J=7.26 Hz, H-1), 3.74 (m, 2 H, H-6), 3.60-3.58 (m, 3 H, H-3, H-4, H-5), 3.55 (s, 3 H, OCH₃), 3.53 (broad s, 1 H, H-2), 2.46 (broad s, 1 H, OH). ¹³C NMR (75 MHz, CCl₃D): δ 138.65, 138.16, 138.11, 128.56-128.27, 127.99-127.61 (3 C₆H₅), 103.74 (C1), 84.54 (C3), 77.68 (C4), 75.22 (C10), 75.17 (C9), 75.03 (C8), 74.66 (C2), 73.56 (C5), 68.90 (C6); 57.17 (C22).
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18. Ionic liquid (10% mmol) and 3,4,6-tri-O-benzyl-D-glucal (200 mg, 0.48 mmol) were placed in a round-bottomed flask and dissolved in 2.0 ml of dichloromethane, then were added acetone (0.8 ml) and saturated NaHCO₃ aqueous solution (1.5 ml). To this vigorously stirred biphasic mixture was added dropwise a solution of oxone (600 mg, 0.9760 mmol in 2.5 ml of water) at 0°C for 15 minutes, maintaining this temperature 20 minutes more. The reaction was controlled by TLC, until no further progress was observed. The mixture was extracted with dichloromethane (5 x 2.0 ml) and the combined organic phases were dried over sodium sulphate (Na₂SO₄). This solution was concentrated under reduced pressure and the residue was purified by column chromatography. ¹H NMR (500 MHz, CCl₃D): δ 7.43-7.27 (m, 15 H, 3 C₆H₅), 5.43 (d, 1 H, J=3.16 Hz, H-1), 4.92-4.73 (m, 1 H, H-2), 4.66-4.43 (m, 6 H, CH₂Ph), 4.30 (d, 1H, J=7.55 Hz, H-C5), 4.01 (d, 1H, H-4), 3.59-3.47 (m, 2 H, H-C6), 1.86 and 1.38 (m, 2H, OH C2 and C3). ¹³C NMR (125 MHz, CCl₃D): δ 138.15-136.01, 128.50-127.94 (C₆H₅), 93.38 (C1), 82.73 (C4), 78.39 (C3), 75.22 (C2), 74.87-73.58 (CH₂Ph), 73.23 (C5), 69.21 (C6). Minor β anomer: δ 4.82 and 97.39 (H-1 and C1).
19. ¹H NMR (600 MHz, CCl₃D): δ 7.42-7.18 (m, 15 H, 3 C₆H₅), 5.00 (d, 1 H, 11.37 Hz, H-5), 4.88-4.53 (m, 6 H, CH₂Ph), 3.90 (d, 1 H, J=8.83 Hz, H-1), 3.73-3.71 (dd, 1 H, H-6), 3.66-3.53 (m, 5 H, H-3, H-4, H-6 and CH₂OH), 3.38-3.35 (t, 1 H, 8.91 Hz, H-2), 3.03-3.00 (m, 2 H, CH₂N). ¹³C NMR (150 MHz, CCl₃D): δ 138.71, 138.08, 137.86, 128.61-127.72 (C₆H₅), 90.91 (C1), 85.54 (C3), 77.67 (C4), 75.87 (C5), 75.09 (C2), 75.02, 74.58, 73.52 (CH₂Ph), 68.98 (C6), 62.99 (CH₂OH), 49.48 (NCH₂).

Highlights

- + DMDO generated in situ oxidize endo-glycals under biphasic conditions.
- + DodMImBF₄ ionic liquid promoted the direct epoxidation of glycals acting as PTC.
- + β -O-glycosides were synthesized in good yields and high stereoselectivity.

Graphical abstract

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