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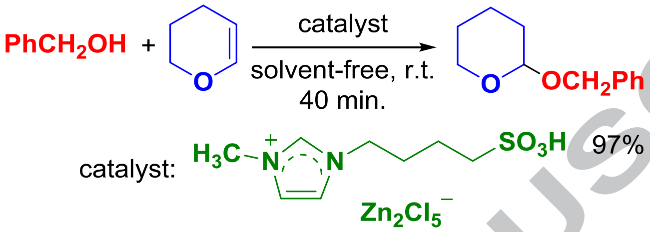

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An efficient Brønsted–Lewis acidic ionic liquid catalyzed tetrahydropyranylation of alcohols

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ABSTRACT

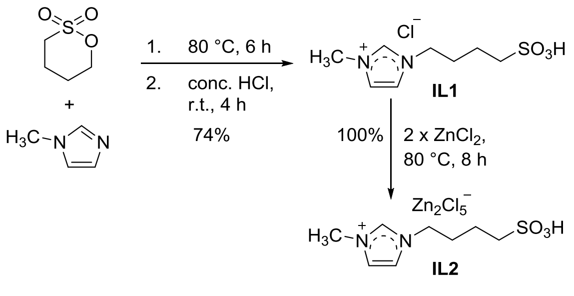
An imidazolium based Brønsted–Lewis acidic ionic liquid has been shown to be an excellent catalyst and reaction medium for the tetrahydropyranylation of various alcohols in good to excellent yields with short reaction times. Selective protection of benzyl alcohol in the presence of phenol was achieved. The novel ionic liquid was prepared from readily available starting materials and could be easily recovered and reused several times without significant deterioration in catalytic activity.

Protecting groups play a pivotal role in the multi-step synthesis of structurally complicated natural products.[1] Among the protecting groups, the tetrahydropyranyl (THP) protection of hydroxy compounds with 3,4-dihydro-2*H*-pyran (DHP) is attractive due to its low cost, ease of deprotection and stability under a variety of reaction conditions such as strongly basic media, oxidative conditions and reducing agents.[2] Tetrahydropyranylation has generally been achieved using both Brønsted acid and Lewis acid catalysts.[3,4] However, some of these methods have drawbacks such as elevated temperatures, long reaction times and the use of harmful organic solvents.

Green chemistry has emerged as a new research area in the chemical sciences as well as industry.[5] Volatile organic solvents, especially halogenated solvents, as well as industrial catalysts that are used in large quantities are significant sources of pollution.[6] Ionic liquids (IL) are molten salts with melting points below 100 °C, that came into the spotlight during the last decade, based on their possible use as alternatives to conventional organic solvents due to their unique properties, such as low vapor pressure, high thermal stability, recyclability, and non-flammability.[7] The characteristics of IL can be controlled through various combinations of cations and anions, allowing the design of IL with unique properties. Additionally, by incorporating functional groups, it is possible to form task-specific IL that have dual properties.[8] In this context, the introduction of acidic functional groups may offer a convenient solution to both the problem of solvent use and recycling. Furthermore, acidic IL possess the advantages of both liquid and solid acid catalysts such as water solubility, recyclablity, high acid density and easy separation.[9]

Herein, we report the convenient tetrahydropyranylation of alcohols using a Brønsted–Lewis acidic IL as an environmentally-friendly catalyst and reaction medium.

The Brønsted–Lewis acidic IL was prepared by treatment of the known sulfonic acid-functionalized Brønsted acidic IL HSO_3-pmim]$^+Cl^-$ [10] with 2 eq. of $ZnCl_2$ at 80 °C. After water removal under vacuum the Brønsted–Lewis acidic IL was obtained (Scheme 1).



Scheme 1. Synthesis of the acidic IL.

To explore the feasibility of using the acidic IL for tetrahydropyranylation, the model reaction of benzyl alcohol with DHP was selected (Table 1, entry 1). The reaction was carried out at room temperature under solvent-free conditions with low catalyst loading (0.5 mol%) to give the corresponding THP ether

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∗ Corresponding author. Tel.: +98-21-44787775; fax: ++98-21-44787775; e-mail: azizi@ccerci.ac.ir in 97% isolated yield. Under identical conditions, **IL1** and **IL1** with one equivalent of $ZnCl_2$ showed low catalytic activity (Table 1, entry 1) in comparison to **IL2**. Furthermore, compared with the commercial Lewis acid $ZnCl_2$ as well as Brønsted acids *p*-toluenesulfonic acid (*p*-TsOH) and methanesulfonic acid (MsOH), **IL2** produced the THP product with a better result (Table 1, entry 1).

Next, we examined the protection of a variety of commercially available alcohols using this methodology (Table 1). Primary, secondary, tertiary, allylic, furyl and benzylic alcohols underwent facile tetrahydropyranylation to afford the corresponding ethers. Acid-sensitive alcohols, such as *tert*-butanol, benzhydrol and menthol, which are sterically hindered, underwent tetrahydropyranylation with no dehydration being observed (Table 1, entries 9, 11, 12).

Furthermore, we examined the acidic IL for the selective protection of hydroxyl groups, and excellent chemoselectivity was observed for benzyl alcohol in the presence of phenol (Scheme 2).

Further investigation involved examining the reusability of the Brønsted-Lewis acidic IL for the tetrahydropyranylation of benzyl alcohol on a 5 mmol scale in the presence of 3 mol% catalyst (Fig. 1). After reaction completion, the product was extracted with Et_2O and the remaining catalyst left in the reaction vessel washed with Et_2O and dried under vacuum. The catalyst was used directly without further treatment for the next run after being charged with fresh starting materials. Using this procedure, the Brønsted-Lewis acidic IL could be reused up to four times without significant loss of the initial catalytic activity (Fig. 1).

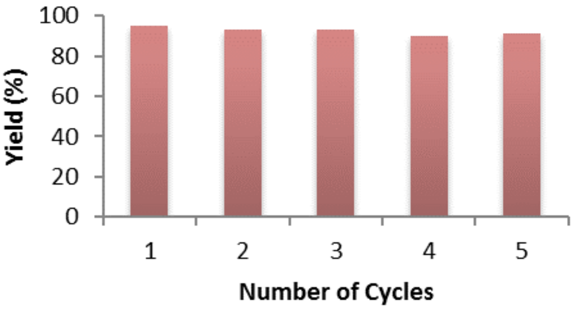
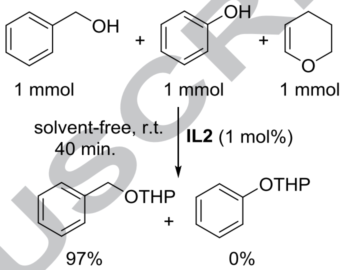
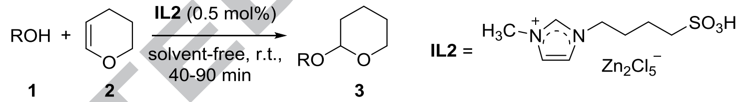


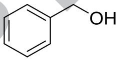
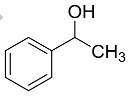
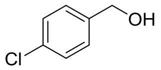
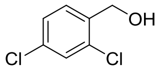
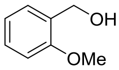
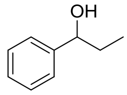
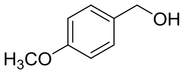
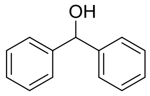
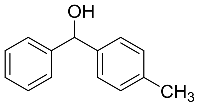
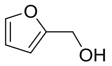
Figure 1. Recycling of the Brønsted-Lewis acidic **IL2**

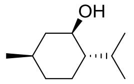
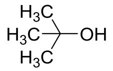


Scheme 2. Chemoselective protection of benzyl alcohol in the presence of phenol

Table 1. Tetrahydropyranylation of various alcohols in the presence of **IL2**



Entry	Alcohol	Product	Time (min.)	Yield **3** (%)^{a,b}
1		**3a**	40	97 (80, 88, 72, 84, 68)^{c}
2		**3b**	45	97
3		**3c**	60	90
4		**3d**	80	82
5		**3e**	45	92
6		**3f**	45	92
7		**3g**	45	90
8		**3h**	60	97
9		**3i**	60	95
10		**3j**	80	70

11		**3k**	90	74
12	 $(\mathrm{H_3C})_3\mathrm{C{-}OH}$	**3l**	80	72

[a]Reaction conditions: alcohol (5 mmol), DHP (5 mmol), catalyst (0.5 mol%), rt. [b]Isolated yield. [c]Yields refer to the use of 2 mol% **IL1**, **IL1** with $ZnCl_2$ (1 equiv.), $ZnCl_2$, $MeSO_3H$ and *p*-TSOH.

In summary, a novel Brønsted-Lewis acidic IL was investigated as a reusable catalyst for the tetrahydropyranylation of various alcohols in good to high yields with short reaction times. The advantages are high catalytic activity under mild reaction conditions, low cost and a readily available IL, easy separation of the catalyst by simple extraction, and selectivity for alcohols over phenols.[11]

Acknowledgments

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11. ***Preparation of catalyst:*** The acidic IL was synthesized using a modified literature method.[10] 1-Methylimidazole (1.57 mL, 20 mmol) was added to a 50 mL round-bottom flask. Under vigorous magnetic stirring, 1,4-butane sultone (2.04 mL, 20 mmol) was added dropwise at room temperature. The mixture was continuously stirred at 80 °C for 6 h to afford the white solid zwitterion after repeated washing with Et_2O which was further converted into the acidic IL upon acidification with HCl (37%) at r.t. for 4 h. The mixture was distilled under vacuum for 4 hours to remove residual water and acid to give **IL1** (3.78 g, 74%, 14.8 mmol). ^1H NMR: (500 MHz; D_2O): 1.59-1.62 (m, 2H), 1.84-1.91 (m, 2H), 2.82 (t, 2H), 3.77 (s, 3H), 4.10 (t, J = 7.01 Hz, 2H), 7.34-7.36 (m, 2H), 8.58 (s, 1H). ^{13}C NMR: (125 MHz; D_2O): 20.8, 27.9, 35.5, 48.6, 49.9, 121.0, 123.5, 135.8. Anhydrous $ZnCl_2$ (28 mmol) was added to the reaction mixture and heated at 80

°C for 8 h to give **IL2** (7.82 g, 14.0 mmol, M = 527.37 g/mol) as a dark honey like viscous oil (Scheme 1).

12. ***General procedure:*** A test tube, equipped with a magnetic stirrer bar, was charged with benzyl alcohol (0.51 mL, 5.0 mmol), DHP (0.45 mL, 5.0 mmol), and catalyst (15 mg, 0.5 mol%, M = 527 g/mol). The resulting mixture was stirred at room temperature until reaction completion (40-90 min, GC and TLC). The crude product was dissolved in Et_2O (for compounds **8**, **9**, **11**, EtOAc was used) and purified by passing through a short column of silica gel using hexane–ethyl acetate as eluent or recrystallized from EtOH or Et_2O to give pure products. All products are known compounds and identical to literature reports.[3]

Highlights

► Tetrahydropyranylation of alcohols in excellent yields and short reaction times

► The method used a mild and efficient Brønsted–Lewis acidic ionic liquid catalyst.

► Selective protection of benzyl alcohol in the presence of a phenol was achieved.