Iranian Journal of Catalysis 4(3), 2014, 213-218

IRANIAN JOURNAL OF CATALYSIS

Mild and efficient solvent-free tetrahydropyranylation (THP) of alcohols catalyzed by reusable acidic ionic liquid $[Et_3N(CH_2)_4SO_3H][OTs]$

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Received 9 November 2013; received in revised form 21 December 2013; accepted 26 July 2014

ABSTRACT

A variety of alcohols readily add to 3,4-dihydro-2*H*-pyran under solvent free conditions in the presence of catalytic amount of acidic ionic liquid $[Et_3N(CH_2)_4SO_3H][OTs]$ to afford the corresponding tetrahydropyranyl ethers in good to excellent yields at room temperature. The use of this procedure allows easy separation of the desired products from ionic liquid and recycling the ionic liquid. Some of the major advantages of this procedure are nonaqueous work-up, very good yields, catalytic amount of catalyst and reusability of ionic liquid.

***Keywords**: Solvent-free reaction, Tetrahydropyranylation, Reusable acidic ionic liquid, Protection.*

1. Introduction

A common requirement in synthesis is that a hydroxyl group be masked as a derivative lacking active hydrogen. An example of this requirement is in reactions involving Grignard or other organometallic reagents. Conversion to alkyl or silyl ethers is the most common means of protecting hydroxyl group. An important method that is applicable when mildly acidic hydrolysis is an appropriate method for deprotection is to form a tetrahydropyranyl ether (THP group). The tetrahydropyranyl group is often the protective group of choice for peptides [1], nucleotides [2], carbohydrates [3] and steroids [4]. The THP group is a versatile protecting group for alcohols and phenols in organic synthesis owing to its stability under strongly alkaline conditions, to Grignard and alkyllithium reagents, to reduction with inorganic hydrides, and to alkylating and acylating agents. In addition to the well known protic and Lewis acids [5], other reagents and catalysts such as pyridinium *p*-toluenesulfonate [6], the hydrochloride salt of poly(4-vinylpyridine) [7], iodotrimethylsilane [8], triphenylphosphene hydrobromide [9], montmorillonite K-10 [10], bis(trimethylsilyl) sulfate [11], Nafion-H [12], NH_4Cl [13], I_2 [14], $ZrCl_4$ [15], $[t\text{-}BuNH_4]Br$ [16], $Fe(ClO_4)_3$ [17], $K_5CoW_{12}O_{40}.3H_2O$ [18], $PdCl_2(CH_3CN)_2$ [19], $Bi(NO_3)_3.5H_2O$ [20], $In(OTf)_3$ [21], $La(NO_3)_3.6H_2O$ [22] and *etc.* have been used to effect the tetrahydropyranylation of alcohols.

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2. Experimental

2.1. Preparation of ionic liquid

The acidic ionic liquid has been synthesised previously in our laboratory [23].

2.2. General procedure for tetrahydropyranylation

A mixture of benzyl alcohol (110 mg, 1 mmol), DHP (92 mg, 1.1 mmol), and ionic liquid (10 mg, 0.02 mmol) were mixed in a 10 ml round bottomed flask and stirred at room temperature until the reaction was finished as indicated by thin-layer chromatography (TLC). The reaction mixture was diluted with cyclohexane and decantated. IL was not dissolve in cyclohexane and adhered to the wall of the flask (The ionic liquid adhered to the flask was washed with cyclohaxane and chareged with alcohol and DHP for second run.). After removal of cyclohexane under reduced pressure and drying (Na_2SO_4), the crude product was purified by column chromatography on silica gel with AcOEt/cyclohexane (1:4) as eluent to afford 230 mg of the corresponding THP ether in 96% yield as colorless oil.

^{1}HNMR (300 MHz, $CDCl_3$): δ= 7.45 (5H, arom. H), 4.8 (1H, d, *J*= 11.7 Hz), 4.65 (1H, t, *J*= 3.7 Hz), 4.45 (1H, d, *J*= 11.7 Hz), 3.9 (1H, m), 3.5 (1H, m) ppm. IR

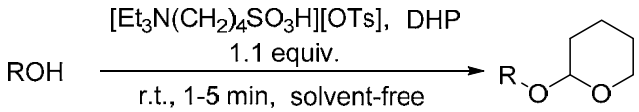
(Neat): $\bar{\nu}$ = 2942 (s, br), 2869 (s), 1600 (w), 1465 (w), 1357 (w), 1127 (s), 1038 (s) cm^{-1}.

3. Results and Discussion

There are several processes available in the literature for the preparation of THP-ethers but majority of them involve the use of volatile organic solvents or large amounts of solid supports, which eventually leads to generation of a large amount of toxic waste. Therefore, there is a need for a solvent-free and efficient alternative for the protection of hydroxyl compounds.

The discovery of ionic liquids has widened the horizons for newer synthetic strategies in the area of organic chemistry. These innovative fluids are organic salts, whose cation, anion and the alkyl chain attached to organic cation can be varied virtually at will, to change their chemical and physical properties as per the needs of the chemical process. A key feature of these liquids is their intrinsic ability to solvate a wide array of organic and inorganic substrates. They are blessed with qualities such as incredibly large liquidus ranges, negligible vapor pressure and recyclability. In short, these ionic liquids have enlightened the way to complete environmentally benign procedures. In view of environmental mandates, there is a global effort to replace conventional catalysts by eco-friendly catalysts. Due to their intriguing properties, these liquids have fascinated us. We have studied the applicability of ionic liquid in synthetically useful transformation of alcohols to tetrahydropyranyl ethers.

In this letter we report a mild and efficient method for the tetrahydropyranylation of alcohols using catalytic amount of acidic ionic liquid (IL) as a promoter in the presence of 3,4-dihydro-2*H*-pyran (1.1 mmol) without solvent at room temperature (Scheme 1). The tetrahydropyranylation of various alcohols was carried out using 0.02 mmol of acidic ionic liquid and as evident from table 1, the protection methodology was successful over a range of functional groups furnishing the protected alcohols in good yields. The results are summarized in Table 1. All of the products were purified by column chromatography, and the corresponding ethers were obtained in good yields. However, phenol (entry 21) yielded the product in only 52% yield. The possible reason ascribed to this observation could be the resonance electron-withdrawing effect of the phenyl moiety. Tetrahydropyranylation did not occur when the blank runs were performed in the absence of IL.



Scheme 1. Tetrahydropyranylation of alcohols catalyzed by reusable acidic ionic liquid.

Table 1. Tetrahydropyranylation of alcohols in the presence of a catalytic amount of acidic ionic liquid under optimized conditions.

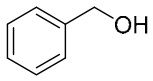
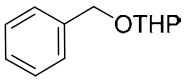
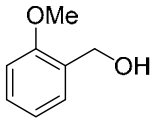
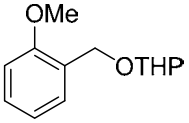
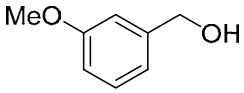
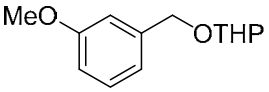
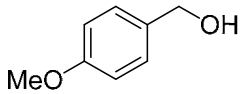
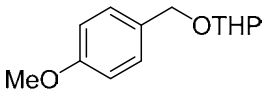
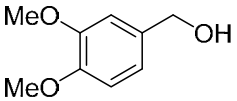
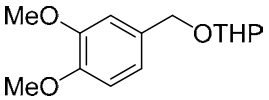
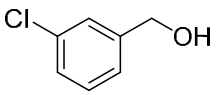
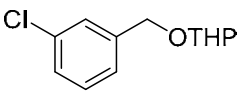
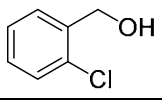
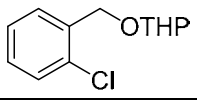
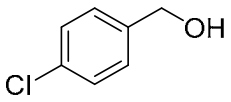
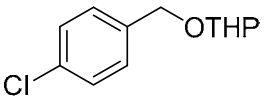
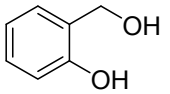
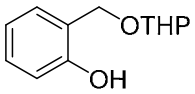
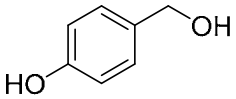
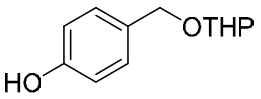
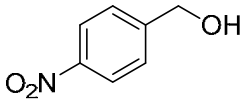
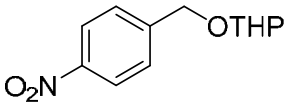
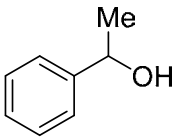
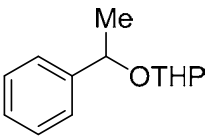
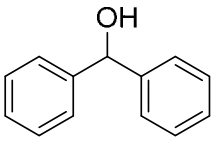
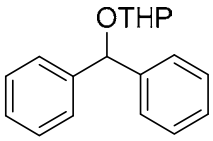
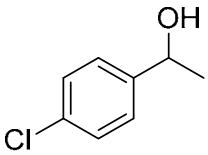
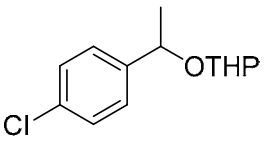
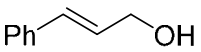
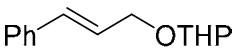
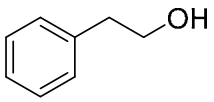
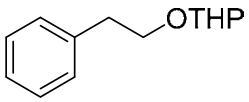
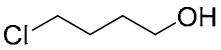
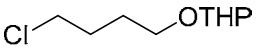
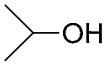
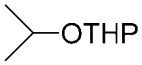
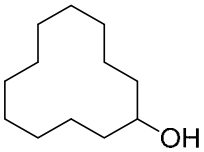
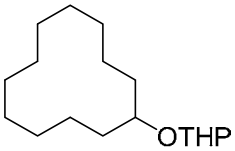
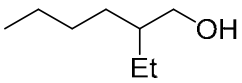
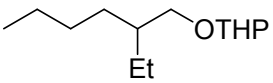
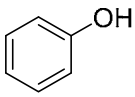
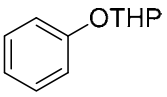
Entry	Alcohol	Product	Reaction Time (min)	Yield (%)[a]
1			3	90
2			2	95
3			2	94
4			2	96
5			1	96
6			3	92
7			3	90

Table 1. *(Continued).*

8			3	91
9			2	87
10			2	93
11			4	83
12			3	92
13			4	88
14			3	91
15			3	65
16			2	94
17			2	96
18			3	89
19			5	85
20			5	87
21			9	52

[a]Isolated yield after purification by column chromatography on silica gel.
[b]Conditions: 1.1 equiv. DHP, 2 mol% acidic IL, r.t., solvent-free.

In order to compare this method with solution condition for the tetrahydropyranylation of alcohols, several solvents were examined under the same reaction conditions. Cyclohexane, dichloromethane, diethyl ether, acetonitrile and ethyl acetate were used as solvents, but longer reaction times were needed to complete tetrahydropyranylation reaction. In the solvent free condition, both the time and yield of reaction is favor (Table 2, Fig 1). It is because in the neat condition the reacting molecules are more closely rather than solution.

In order to optimize the amount of IL, we were used different amount of it (Table 3). Fig. 2 demonstrates the correlation between time, yield and amount of IL in the reaction between benzyl alcohol and DHP. The high yield associated to a short reaction time was obtained in the presence of 0.02 mmol (2 mol %) of IL. Higher amount of IL decrease the yield of reaction.

It is noteworthy that IL did not dissolve to the non-polar solvents such as cyclohexane because of its ionic nature. On the other hand, the tetrahydropyranyl ether products simply dissolved to this solvent. This result prompted us to recycle it in the presence of cyclohexane. We choose cyclohexane for extracting the product from reaction mixture for two reasons: 1) nonpolar nature or this solvent that dissolve the product but no IL, 2) less toxicity of cyclohexane rather than other formal solvents such as dichloromethane, chloroform, CCl_4, EtOAc and toluene. As shown in Table 4, LD50 Oral Rat for cyclohexane is 12705 that mean less toxicity of this solvent compared with other solvents in Table 4.

To investigate the possibility of recycling the catalyst, the IL is recovered for further use by simply extracting the products with cyclohexane, which can be conveniently decanted off, followed by fresh charge of reactants in the same reaction vessel. The recycling study reveals that the catalyst can be recycled several times without much loss of its reactivity. To show the efficiency of this method with reported methods in Table 5, we compared the reaction time for tetrahydropyranylation of benzyl alcohol as a model alcohol. As demonstrated in Table 5, our reaction times are shorter than that of the reported methods.

4. Conclusions

In conclusion, a solvent-free protocol is developed for the synthesis of tetrahydropyranyl ethers from alcohols. The use of this ionic liquid in protection of alcohols is demonstrated in this reaction that precludes the use of volatile organic solvents in the reaction mixture. Furthermore, this ionic liquid catalyst can be effectively recycled, thus rendering this expeditious protection protocol more efficient and eco-friendly.

Table 2. Conversion of benzyl alcohol under different conditions using 2 mol % of IL and 1.1 mmol DHP.

Reaction Conditions	Dichloromethane	Cyclohexane	Solvent-free (neat)	Diethyl ether	acetonitrile	Ethyl acetate
Time (min)	30	23	3	15	45	40
Yield (%) [a]	90	92	89	85	80	78

[a]Isolated yield after puification by column chromatography on silica gel.

Table 3. Effect of various amount of acidic IL $[Et_3N(CH_2)_4SO_3H]^+[OTS]^-$ in tetrahydropyranylation of benzyl alcohol (solvent-free condition).

Entry	mmol of IL	Time (min)	Yield (%)[a]
1	0.01 (0.005 gr)	4	40
2	0.02 (0.01 gr)	3	90
3	0.1	3	90
4	0.2	4	85
5	0.5	4	80
6	1	5	85
7	1.5	5	75

[a]Isolated yield after purification by column chromatography on silica gel.

Table 4. LD50 Oral Rat for some formal solvents (The higher value associated to less toxicity).

Solvent	Cyclohexane	Dichloromethane	Chloroform	CCl_4	EtOAc	Toluene
LD50 Oral Rat (mg/Kg)	12705	1600	908	1770	5620	636

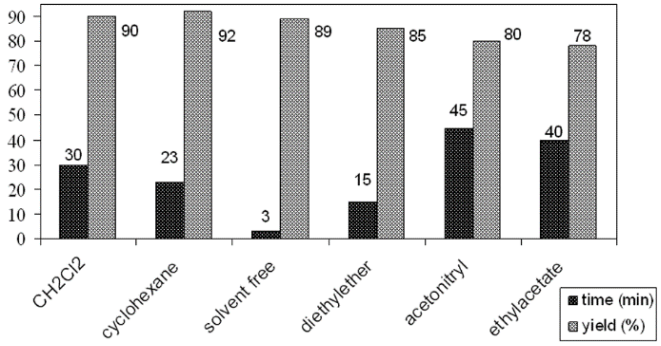


Fig. 1. Optimization of solvent in the reaction of benzyl alcohol using 2 mmol % of IL and 1.1 mmol DHP under solvent-free conditions.

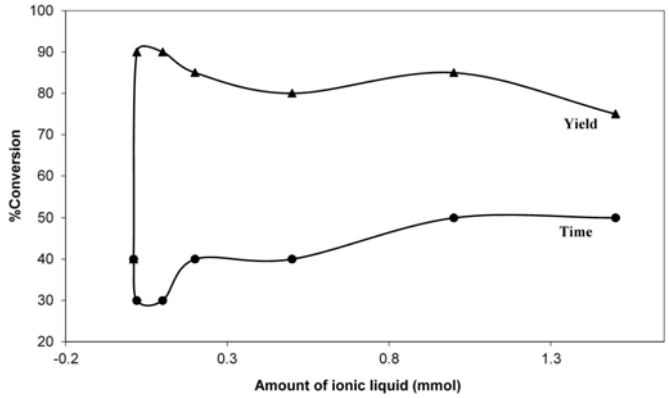


Fig. 2. Influence of the IL amount on the reaction time and yield for the reaction of benzyl alcohol and DHP.

Table 5. Comparison of some reports on tetrahydropyranylation of benzyl alcohol as the model alcohol.

Entry	Time (h)	Yield (%)	Conditions	Ref.
1	1.5	89	$CuCl_2$, CH_2Cl_2, r.t.	[24]
2	1.83	89	BNBBS, CH_2Cl_2, r.t.	[25]
3	1	85	Bu_4NBr_3, CH_2Cl_2, r.t.	[16]
4	0.5	85	$In(OTf)_3$, CH_2Cl_2, 0 °C	[26]
5	2.5	93	$La(NO_3)_2.6H_2O$, r.t.	[22]
6	0.7	72	$PdCl_2(MeCN)_2$, THF, r.t.	[19]
7	<5 min	97	ATPB	[27]
8	0.7	97	PS-$ALCl_3$, CH_2Cl_2, r.t.	[28]
9	0.7	90	$CuSO_4.5H_2O$, MeCN, r.t.	[29]
10	2	99	Well-Dawson acid, $PhCH_3$, r.t.	[30]
11	8	59	polyaniline sulfate, 50 °C	[31]
12	4	28	[bmim]PF_6, TsOH, r.t.	[32]
13	2.5	96	LiOTf, $ClCH_2CH_2Cl$, reflux	[33]
14	0.25	98	$[C_4MIM]AlCl_4$, r.t.	[34]
15	1	95	$VO(OAc)_2$, $CHCl_3$, r.t.	[35]
16	3 min	90	Acidic IL	This work

Acknowledgment

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran (A.R.H.) and Grant GM 33138 (A.E.R.) from the National Institutes of Health, USA. Further financial support from Center of Excellency in Chemistry Research (IUT) is gratefully acknowledged.

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