$InCl_3$ immobilized in ionic liquids: a novel and recyclable catalytic system for tetrahydropyranylation and furanylation of alcohols

Letter

Jhillu Singh Yadav,* Basi. V. Subba Reddy and Dughani Gnaneshwar

Division of Organic Chemistry, Indian Institute of Chemical Technology,
Hyderabad 500 007, India. E-mail: yadav@iict.ap.nic.in; Fax: +91 40 716 0512

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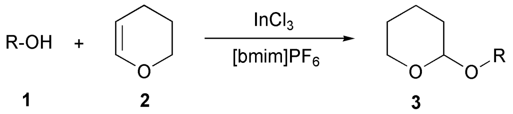
A mild and highly efficient method has been developed for the protection of hydroxyl compounds as tetrahydropyranyl and furanyl ethers using a catalytic amount of indium trichloride immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid under mild conditions. A wide range of functional and protecting groups such as THP, TBDMS, TBDPS, PMB, MOM ethers, acetonides, olefins and epoxides are compatible with ionic liquids. Monoprotection of diols has also been achieved using this novel procedure.

Environmental protection laws and corporate pressure to minimize the amount of toxic waste arising from chemical processes have motivated the development of innovative and environmentally friendly chemical technologies. As a result, enviro-economics has become the focused theme for the development of new processes for existing products or new products. The fact is that recently discovered room temperature ionic liquids are emerging as a set of green solvents, mainly as a replacement for conventional organic solvents, especially those that are volatile and difficult to handle.[1] Ionic liquids, especially those based on the 1-*n*-alkyl-3-methylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents. They are non-volatile, recyclable, non-explosive, easy to handle, thermally robust, and in addition they are compatible with various organic compounds and organometallic reagents.[2] The unique property of ionic liquids is that they have essentially no vapor pressure, which makes them optimal replacements for volatile organic solvents. A nice feature of ionic liquids is that yields can be optimized by changing anions or properties of the cation. These ionic liquids show enhancement in reaction rates and selectivity, compared to molecular organic solvents. The use of room temperature ionic liquids has led to significant advances in the development of clean chemical processes in organic synthesis targeted to avoid or at least minimize the use of toxic or waste generating reagents or solvents. Because of the distinct advantages of ionic liquids, they can make an important contribution to green chemistry.

Protective groups play an important role in the multi-step synthesis of complex natural products; hence there is always a demand for selective reagents. Tetrahydropyranylation is one of the most widely used processes for the protection of alcohols and phenols.[3] Due to the remarkable stability of tetrahydropyranyl ethers toward a variety of reaction conditions such as strong basic media, oxidative conditions, reduction with metal hydrides, reactions involving Grignard reagents, lithium alkyls and alkylating and acylating reagents, *etc.*, tetrahydropyranylation is one of the methods of choice to protect a hydroxyl group in a multi-step organic synthesis.[4] Consequently, a variety of reagents have been developed for the tetrahydropyranyl protection of alcohols, which include mainly protic acids,[5] Lewis acids,[6] solid acids,[7] solid supported reagents,[8] catalysts immobilized in ionic liquids,[9] and many others.[10] However, in spite of their potential utility in the protection of simple hydroxyl compounds, many of these methods have limitations when applied to complex molecules containing acid-sensitive functional groups and polyhydroxyl compounds bearing acid-labile protecting groups. Thus, there is a need for the development of a more general and efficient alternative for the pyranylation of alcohols. In recent years, $InCl_3$ has evolved as a versatile Lewis acid for a variety of organic transformations, such as the Diels–Alder reaction, Mukaiyama-aldol reactions, Mannich reaction, Michael additions, Prins cyclization, glycosylation reactions and Sakurai allylation reactions under mild conditions.[11] Compared to conventional Lewis acids, indium trichloride has the advantages of low catalyst loading, moisture stability and catalyst recycling. However, there are no examples of the tetrahydropyranylation of alcohols using indium halides. The unique catalytic features of indium trichloride prompted us to explore further applications of $InCl_3$ as a catalyst in other carbon-carbon and carbon-heteroatom bond forming reactions.[12]

In view of the emerging importance of ionic liquids as novel reaction media, we wish to report a mild and highly efficient method for the tetrahydropyranylation of alcohols using a catalytic amount of indium trichloride in ionic liquids (Scheme 1).

The treatment of cinnamyl alcohol with 3,4-dihydro-2*H*-pyran in the presence of 5 mol % $InCl_3$ in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquid afforded the tetrahydropyranyl derivative in 92% yield. Similarly, a wide range of hydroxy compounds were converted to the corresponding THP ethers in excellent yields by using this procedure. The reactions proceeded efficiently at ambient temperature with high chemoselectivity. The reaction conditions are mild enough not to induce isomerization of multiple bonds during pyranylation of allylic and propargylic systems and are selective for the protection of hydroxyl groups in the presence of other acid-sensitive protecting groups, which is difficult to achieve under conventional conditions. Furthermore, the reactions of alcohols with 2,3-dihydrofuran under the influence of indium trichloride in [bmim]PF_6 ionic liquid afforded the corresponding tetrahydrofuranyl ethers in high yields (Scheme 2). The reaction proceeds smoothly at ambient temperature with high chemoselectivity. The products were isolated in high yields after 3–6 h.



Scheme 1

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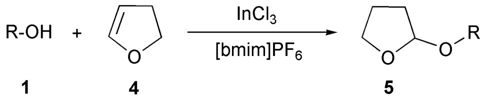
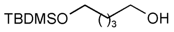
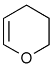
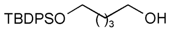
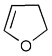
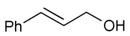
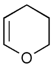
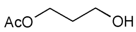
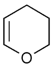
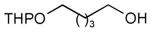
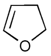
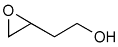
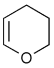
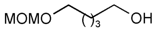
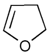
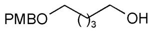
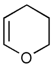
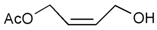
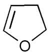
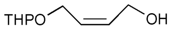
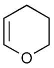
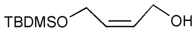
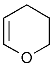
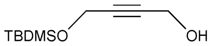
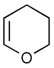
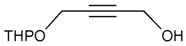
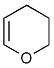
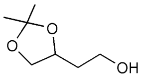
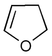
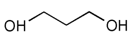
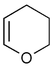
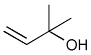
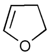
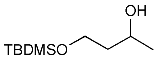
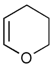


Scheme 2

This method is highly chemoselective to protect hydroxyl groups as THP and THF ethers. Enhanced reaction rates, improved yields and high functional group compatibility are the features obtained in these ionic liquids. Another advantage of the use of ionic liquids as a novel reaction medium as well as promoters for this transformation is that these ionic solvents can be easily recovered after completion of the reaction and can be reused in subsequent reactions. As the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and dried at 80 °C under reduced pressure and recycled in five runs without any loss of activity. The products obtained were of the same purity as in the first run and no decrease in yields was obtained in runs carried out using recycled ionic liquid. For example, the treatment of cinnamyl alcohol with 3,4-dihydro-2*H*-pyran in the presence of 5 mol % $InCl_3$in $[bmim]BF_4$ afforded 92%, 91%, 92%, 91% and 90% yields over five cycles. Another advantage of this method is in the selective protection of alcohols in the presence of highly acid-sensitive epoxides, silyl ethers and acetals. As evident from Table 1, the acid-sensitive protecting groups such as THP, TBDMS, TBDPS, PMB, MOM ethers, acetonides and epoxides survived under these reaction conditions. Thus, the present method is mild enough to tolerate a wide range of functional groups present in the substrate. Monoprotection of diols was also achieved by this procedure (entry o). This method is equally effective for the protection of primary, secondary and tertiary alcohols (entries p, q). In the absence of indium trichloride, the reactions proceeded smoothly in 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim]BF_4$), but longer reaction periods (8–12 h) are required to achieve comparable yields to those obtained with indium trichloride in 1-butyl-3-methylimidazolium

Table 1 Ionic-liquids-promoted protection of alcohols as THP and THF ethers[a]

			5% $InCl_3$–$[bmim]PF_6$		$[bmim]BF_4$	
Entry	Alcohol	Enol ether	Time/h	% Yield[b]	Time/h	% Yield[b]
a			3.0	90	8.0	84
b			4.5	87	9.0	81
c			3.5	92	10.0	85
d			4.0	90	9.5	80
e			3.5	91	8.0	83
f			4.0	82	12.0	71
g			5.0	90	8.0	85
h			4.0	88	11.0	81
i			4.5	85	10.0	78
j			4.0	91	8.0	87
k			4.5	90	7.5	83
l			5.0	87	12.0	79
m			4.0	85	9.0	80
n			3.0	87	12.0	75
o			6.0	85[c]	9.5	80[c]
p			3.5	81	8.0	70
q			5.5	89	8.5	

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy. [b] Isolated and unoptimized yields after purification. [c] Monoprotection of diol was obtained.

hexafluorophosphate ([bmim]PF_6) ionic liquid. In the absence of catalyst, low conversions (25–55%) were obtained in [bmim]PF_6 ionic liquid. No significant differences in reaction rates and yields were observed with either the [bmim]BF_4–$InCl_3$ or [bmim]PF_6–$InCl_3$ catalytic systems.

Finally, the catalytic performance of various quaternary ammonium salts was studied for this conversion. The tetrahydropyranylation was not successful when *n*-tetrabutyl ammonium chloride (*n*-Bu_4NCl) or 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl) was used as the reaction media. Similar results were obtained even in the *n*-Bu_4NCl–$InCl_3$ or [bmim]Cl–$InCl_3$catalytic systems. This indicates that both cation and anion play an important role as the solvent in this transformation. Furthermore, the recovery and reuse of indium trichloride is especially simple in ionic liquids compared to organic solvents.

In summary, this paper describes a method for the chemoselective conversion of alcohols to tetrahydropyranyl and furanyl ethers using a catalytic amount of indium trichloride in ionic liquids that operates under mild conditions, thereby leaving acid- and base-labile protecting groups intact. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of a green strategy for the tetrahydropyranylation and furanylation of alcohols in protective group chemistry. Furthermore, the use of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) ionic liquid as promoter for this transformation avoids the use of toxic or corrosive and moisture-sensitive reagents.

Experimental

1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids were prepared according to the procedures reported in the literature.[13]

Experimental procedure. A mixture of alcohol (1 mmol), DHP or DHF (1.5 mmol), in 1-butyl-3-methylimidazolium tetrafluoroborate (1 mL) or 5 mol % $InCl_3$ in 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL) was stirred at ambient temperature for an appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate–*n*-hexane (1:9) to afford pure ether. The rest of the viscous ionic liquid was further washed with ether and recycled in subsequent reactions. Spectral data for selected products: **3d**: ^{1}H NMR ($CDCl_3$) δ: 1.45–1.80 (m, 6H), 1.85–1.95 (m, 2H), 2.05 (s, 3H), 3.35–3.50 (m, 2H), 3.75–3.85 (m, 2H), 4.15 (t, 2H, $J = 6.0$ Hz), 4.55 (br s, 1H). **3k**: ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 6H), 0.85 (s, 9H), 1.45–1.90 (m, 6H), 3.40–3.48 (m, 1H), 3.78–3.90 (m, 1H), 4.05 (dd, 1H, $J = 6.0$, 11.7 Hz), 4.18–4.28 (m, 3H), 4.60 (br s, 1H), 5.55–5.70 (m, 2H). **3j**: ^{1}H NMR ($CDCl_3$) δ: 1.45–1.80 (m, 12H), 3.40–3.57 (m, 2H), 3.75–3.85 (m, 2H), 4.0–4.15 (m, 2H), 4.18–4.28 (m, 1H), 4.60 (br s, 2H), 5.63–5.70 (m, 2H).

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