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Bismuth Triflate Catalyzed Prins-Type Cyclization in Ionic Liquid: Synthesis of 4-Tetrahydropyranol Derivatives

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ABSTRACT: *The reaction of aldehydes with homoallylic alcohols in the presence of catalytic amount of bismuth triflate in [bmim]PF$_6$generates 4-tetrahydropyranol derivatives in excellent yield and with high diastereoselectivity.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:104–106, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20403

INTRODUCTION

The acid-catalyzed olefin-aldehyde condensation, known as the Prins reaction, is an important carbon–carbon bond forming reaction in organic synthesis. Substituted tetrahydropyrans are the common structural motif of many natural products [1], such as avermectins, aplysiatoxin, oscillatoxins, latrunculins, talaromycins, acutiphycins, and apicularens. Especially, tetrahydropyrans hydroxylated at the 4-position are having more synthetic value [2]. Although many synthetic methods have been reported [3], there is still the scope to find potential alternate approaches and the development of ecofriendly and good yield procedures would be more useful. In recent years, bismuth compounds have been attracted as ecofriendly reagents in organic synthesis [4]. The ionic liquids are attracting growing interest as an alternative to organic solvents for various chemical and biotransformations [5]. Because of the high polarity and ability to solubilize both inorganic and organic compounds, ionic liquids are finding increasing applications in organic synthesis [6]. In this report, we describe the synthesis of tetrahydropyranol derivatives through the Prins-type cyclization reaction of homoallylic alcohols with aldehydes using bismuth triflate in [bmim]PF$_6$ solvent system.

RESULTS AND DISCUSSION

The reaction was carried out by adding benzaldehyde and 3-buten-1-ol to a mixture of bismuth triflate and [bmim]PF$_6$. After the mixture was stirred at room temperature for 15 min, the TLC observation showed the disappearance of starting materials. The product was obtained after simple extraction with ether. Furthermore, the crude product was purified over silica gel, providing the product in 80% yield. By ^{1}H NMR spectrum and NOE studies, the product was confirmed as cis-diastereoisomer and compared with the literature data [3] (Scheme 1). The remaining ionic liquid was washed with ether and recycled in subsequent runs with gradual decrease in the activity (Table 1).

Similarly, various aldehydes reacted smoothly with homoallylic alcohols to give the corresponding tetrahydropyran derivatives in good yield (Table 2). It should be noted that the nature of substituents

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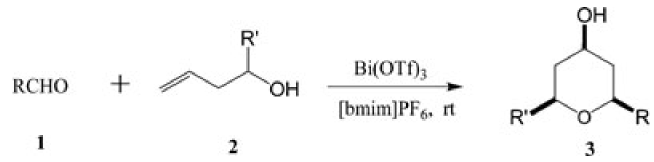
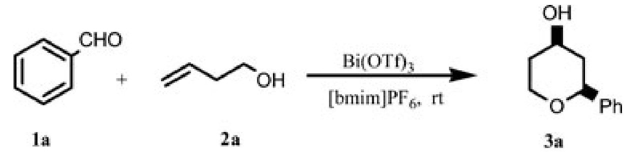


SCHEME 1

TABLE 1 Recovery and Reuse of the Ionic Liquid Phase Containing $Bi(OTf)_3$[a]



Run	1	2	3
Yield(%)[b]	80	72	68

[a] Reaction conditions: 2 mmol of benzaldehyde, 2 mmol of 3-buten-1-ol, 5 mol% of $Bi(OTf)_3$, 1 mL of $[bmim]PF_6$, rt, 15 min.
[b] Isolated yield after column chromatography.

shows some effect on the yields. The aliphatic, simple aromatic, and moderately activated aldehydes such as chloro and methyl gave high yields of products when compared with deactivated nitro-substituted aldehydes.

We have also carried out the reaction in organic solvent, such as chloroform, and found the formation of a mixture of tetrahydropyranol and the corresponding ether after refluxing for 2 h. This may be due to the hydrophilic nature of ionic liquid, which solubilize the water and provides the OH^- nucleophile for the tetrahydropyran carbonium ion.

CONCLUSION

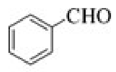
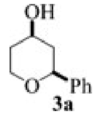
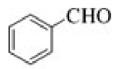
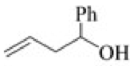
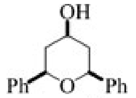
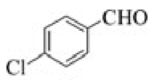
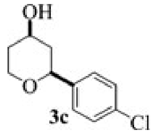
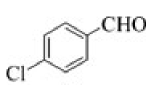
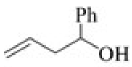
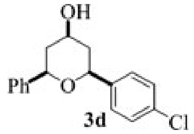
In summary, we have described a green protocol for the preparation of tetrahydropyran derivatives through the Prins-type cyclization using bismuth triflate and $[bmim]PF_6$ system. The attractive features of this process are the recyclability, mild reaction conditions, ecofriendly reagent, and cleaner reactions with good yields, which make it a useful process for the synthesis of tetrahydropyran core structure.

EXPERIMENTAL

General Procedure

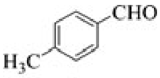
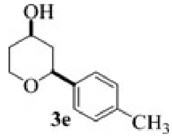
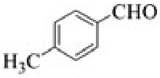
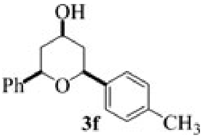
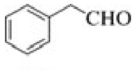
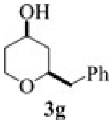
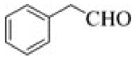
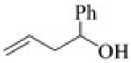
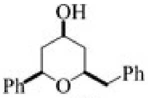
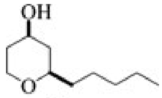
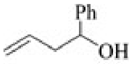
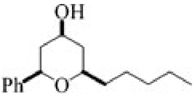
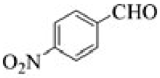
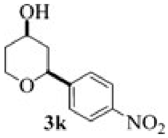
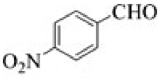
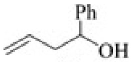
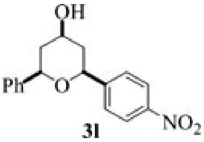
Bismuth triflate (5 mol%) was added in one portion to 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL). Benzaldehyde (212 mg, 2 mmol) was then added followed by water (0.1 mL) and 3-buten-1-ol (144 mg, 2 mmol) at room temperature. The mixture was allowed to stir for 15 min and then washed with diethyl ether (3 × 5 mL). The combined ether extracts were concentrated in vacuo, and the resulting product was separated by column chromatography over silica gel (ethyl acetate: hexane, 1:2). The product **3a** was obtained in 80% yield. The rest of the ionic liquid was further washed with

TABLE 2 Bismuth Triflate Catalyzed Synthesis of 4-Tetrahydropyranols

Entry	*Aldehyde*	*Alcohol*	*Products*[a]	*Yield (%)*[b]
1	 **1a**	 **2a**	 **3a**	80
2	 **1a**	 **2b**	 **3b**	78
3	 **1b**	 **2a**		80
4	 **1b**	 **2b**		76

Continued

TABLE 2 Continued

Entry	*Aldehyde*	*Alcohol*	*Products*[a]	*Yield (%)*[b]
5	 **1c**	 **2a**	 **3e**	74
6	 **1c**	 **2b**	 **3f**	70
7	 **1d**	 **2a**	 **3g**	68
8	 **1d**	 **2b**	 **3h**	72
9	 **1e**	 **2a**	 **3i**	70
10	 **1e**	 **2b**	 **3j**	66
11	 **1f**	 **2a**	 **3k**	62
12	 **1f**	 **2b**	 **3l**	60

[a] All the products were characterized by ^{1}H NMR, IR, and mass spectroscopy and compared with previously reported data.
[b] Yields are isolated after column chromatography.

ether and recycled, and the activity was retained until three runs.

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