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Direct formation of tetrahydropyranols via catalysis in ionic liquid

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Abstract—Utilizing a simple homoallyl alcohol and an aldehyde in the presence of a catalytic amount of cerium triflate, the direct stereoselective formation of tetrahydropyranol derivatives in ionic liquid is reported. © 2002 Elsevier Science Ltd. All rights reserved.

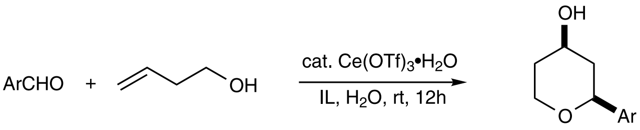
Tetrahydropyrans are prevalent subunits in an assortment of natural products including carbohydrates, polyether antibiotics and marine toxins.[1] The Prins cyclization, which entails the formation of a C–C bond,[2] is a notable method in the formation of tetrahydropyran derivatives. Initially discovered in 1899, it consisted of the condensation of olefins with aldehydes under strongly acidic conditions (e.g. sulfuric acid) and high reaction temperatures which limited its potential as an effectual synthetic methodology. Currently there has been an actualization of the potentiality in the utilization of the Prins cyclization for the formation of tetrahydropyran derivatives in a stereocontrolled manner.[3]

In our laboratories,[4] we had investigated the efficacy of the Prins cyclization utilizing $InCl_3$ which is a mild Lewis acid, relative to the stronger Lewis acid catalysts (e.g. $TiCl_4$, $SnCl_4$) previously developed. The usage of a Lewis acid with a nucleophilic anion resulted in the formation of 4-halotetrahydropyran derivatives,[5] which are not as synthetically useful as the 4-tetrahydropyranol derivatives. Recently, we have found that the usage of a catalytic amount of scandium triflate,[6] a Lewis acid with a non-nucleophilic anion, allowed for the formation of oxygenated tetrahydropyran derivatives in refluxing chloroform.[7]

However, one of the primary and fundamental objectives in our methodology development, has always been to incorporate effective methodology with the principles of green chemistry.[8] Therefore, this objective led us to the development of the direct formation of tetrahydropyranols in ionic liquid,[9] specifically butylmethylimidazolium hexafluorophosphate, [bmim]-$[PF_6]$.[10] This direct formation of the desired and synthetically valuable derivative is in accordance with our green chemistry objective in two ways: 1) usage of an environmentally benign solvent and 2) elimination of an additional step required to convert from the halogenated to the oxygenated derivative.

Room temperature ionic liquids are presently being used in numerous applications such as an alternative environmentally friendly media for organic synthesis[9,11] and separations.[12] On account of the fact that these room temperature liquids are composed of ions (organic cations and organic or inorganic anions), they lack measurable partial pressure. They are also recyclable and tolerate repetitious use without evaporation into the environment.

Our method for the direct formation of tetrahydropyranol derivatives involves taking a simple homoallyl alcohol and an aldehyde and reacting it in the presence of a catalytic amount of cerium triflate hydrate in ionic liquid (Scheme 1).



Scheme 1.

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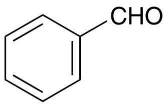
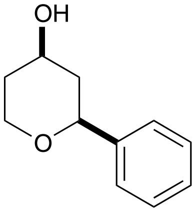
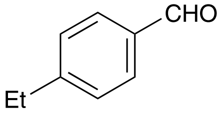
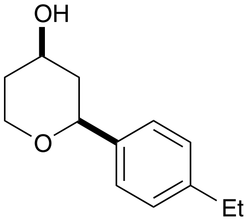
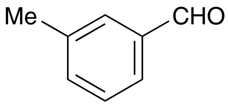
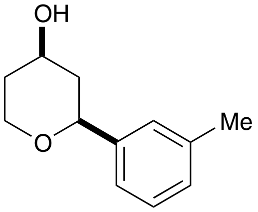
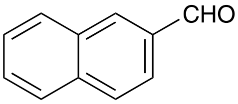
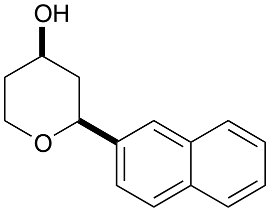
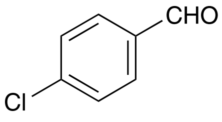
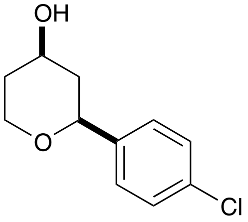
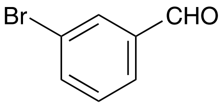
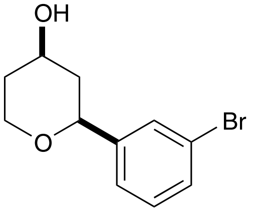
Table 1. Direct formation of tetrahydropyranols in ionic liquid

Entry	Aldehdye	Conditions	Product[a]	Isolated Yield (%)
1		$Ce(OTf)_3.H_2O/IL/H_2O/rt/12h$		50
2		$Ce(OTf)_3.H_2O/PhCO_2H/IL/H_2O/rt/12h$		69
3		$Ce(OTf)_3.H_2O/IL/H_2O/rt/12h$		42
4		$Ce(OTf)_3.H_2O/PhCO_2H/IL/H_2O/rt/12h$		59
5		$Ce(OTf)_3.H_2O/IL/H_2O/rt/12h$		45
6		$Ce(OTf)_3.H_2O/PhCO_2H/IL/H_2O/rt/12h$		55
7		$Ce(OTf)_3.H_2O/IL/H_2O/rt/12h$		47
8		$Ce(OTf)_3.H_2O/PhCO_2H/IL/H_2O/rt/12h$		53
9		$Ce(OTf)_3.H_2O/IL/H_2O/rt/12h$		47
10		$Ce(OTf)_3.H_2O/PhCO_2H/IL/H_2O/rt/12h$		55
11		$Ce(OTf)_3.H_2O/IL/H_2O/rt/12h$		47
12		$Ce(OTf)_3.H_2O/PhCO_2H/IL/H_2O/rt/12h$		56

a: ^1H NMR of the crude reaction mixture showed <3% of the trans diastereomers.

When an organic solvent such as chloroform was employed, we found that there was a mixture of the desired tetrahydropyranol and the less desired ether derivative (as the major product).[7] However, in ionic liquid, there is the exclusive formation of the desired tetrahydropyranol. Even though the yields are moderate, this is the first relatively facile and direct formation of the synthetically useful pyranol derivative. The additional desirability of this methodology is that, so far it is only effective in the environmentally benign ionic liquid.

In our optimization of the reaction yields, we noticed inconsistencies when benzaldehyde was used and this motivated us to further examine the reaction. We propose that the benzoic acid impurity found in the readily oxidizable benzaldehyde is possibly assisting in the reaction. This is similar to what Aspinal et al.[13] have reported in their allylation reactions in which they used lanthanide triflates and benzoic acid to accelerate the reaction in what they term a 'double activation' of the aldehyde.

When 1 equiv. of benzoic acid was added to the reaction together with catalytic amount of Lewis acid, there was a slight increase in the isolated yield of the desired tetrahydropyranol (Table 1). However, we are currently uncertain as to whether the Brønsted acid is accelerating the reaction by an enhanced activation of the aldehyde or whether it is simply regenerating the Lewis acid. When only 1 equiv. of benzoic acid was used with no Lewis acid, there was no reaction. Due to the decomposition of the ionic liquid when 1 equiv. of the Lewis acid is used under our conditions, we have not yet been able to measure for any true quantitative differences in rate enhancement.

In summary, we have developed a promising green method for the relatively facile and direct formation of tetrahydropyranols in ionic liquid. Additional investigation into the role of the Brønsted acid in the rate enhancement will be investigated along with the further optimization of the reaction in ionic liquid and other alternative media.

Typical procedure: Cerium triflate (41 mg, 0.069 mmol, 10 mol%) was added in one portion to the ionic liquid (1 mL). Benzaldehyde (110 mg, 0.104 mol) was then added and allowed to stir for 10 min. A solution of homoallyl alcohol (50 mg, 0.69 mmol) and water (0.3 mL) was then added and allowed to stir at room temperature. The reaction was monitored by TLC and upon completion, the ionic liquid was extracted with diethyl ether (8×3 mL) and concentrated in vacuo. The product (yield 60 mg, 50%) was isolated through column chromatography on silica gel (eluent: 2:1 hexane:ethyl acetate).

Acknowledgements

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References

1. (a) *Polyether Antibiotics*; Westly, J. W., Ed.; Marcel Dekker: New York, 1983; Vol. I and II; (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.
2. For reviews of the Prins reaction, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505; (b) Adams, D. R.; Bhatnagar, S. R. *Synthesis* **1977**, 661; (c) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp. 527–561.
3. For representative recent examples, see: (a) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899; (b) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022; (c) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271; (d) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092; (e) Chen, C.; Marino, P. S. *J. Org. Chem.* **2000**, *65*, 3252; (f) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420; (g) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679; (h) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.
4. (a) Yang, X. F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739; (b) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627; (c) Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993.
5. For other examples for the formation of 4-halo derivatives, see: (a) Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441; (b) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973; (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913; (d) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768.
6. (a) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590; (b) Kobayashi, S. In *Organic Synthesis in Water*; Greico, P. A., Ed.; Thomson Science: Glasgow, 1998.
7. (a) Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun.* **1999**, 291; (b) Zhang, W. C.; Li, C. J. *Tetrahedron* **2000**, *56*, 2403.
8. Anastas, P. T.; Warner, J. C. *Green Chemistry*; Oxford: New York, 1998.
9. (a) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351; (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (c) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (d) Varma, R.; Namboodiri, V. V. *Pure Appl. Chem.* **2001**, *73*, 1309.
10. Suarez, P. A. Z.; Einloft, S.; Dullius, J. E.; de Souza, R. F.; Dupont, J. *J. Chim. Phys.* **1998**, *95*, 1626.
11. For representative recent examples, see: (a) Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 403; (b) Ren, R. X.; Zueva, L. D.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8441; (c) Lee, S.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, 1698; (d) Wasserscheid, P.; Gordon, C.

M.; Hilgers, C.; Muldoon, M. J.; Dunkin, I. R. *Chem. Commun*. **2001**, 1186.

12. (a) Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commun*. **1998**, 1765; (b) Blanchard, L.; Nancu, D.; Bechman, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28; (c) Schäfer, T.; Rodrigues, C. M.; Alfonso, C. A. M.; Crespo, J. G. *Chem. Commun*. **2001**, 1622.
13. (a) Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett*. **1998**, *39*, 9283; (b) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett*. **2002**, *43*, 319.