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Chemoselective tetrahydropyranylation of alcohols and phenols using polystyrene supported aluminium chloride as a catalyst

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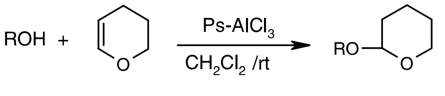
Abstract—A simple, efficient and highly chemoselective method for tetrahydropyranylation of alcohols and phenols has been developed by their reaction with 3,4-dihydro-2*H*-pyran at room temperature in the presence of a catalytic amount of polystyrene supported $AlCl_3$. The method is also highly selective for monoprotection of symmetrical diols.

A large number of polymer supported Lewis acids have been prepared by immobilization of the catalysts on polymers via coordination or covalent bonds.[1] Such polymeric catalysts are usually as active and selective as their homogeneous counterparts while having the advantages of being easily separable from the reaction media, recyclability and improved selectivity in various organic reactions. The most frequently used polymeric support is polystyrene; its hydrophobic nature protects water-sensitive Lewis acids from hydrolysis by atmospheric moisture until it is suspended in an appropriate solvent where it can be used in a chemical reaction.[2]

Tetrahydropyranylation is one of the most frequently used processes to protect hydroxyl groups due to the remarkable stability of tetrahydropyranyl ethers under a variety of conditions such as alkaline media, Grignard reagents, alkyl lithiums, metal hydrides, oxidative reagents and alkylating and acylating reagents.[3] A variety of catalysts that have been reported for this conversion include the use of protic acids,[4a] Lewis acids,[4b] ion-exchange resins,[4c] alumina impregnated with $ZnCl_2$,[4d] silica chloride,[4e] sulfuric acid on silica gel,[4f] heteropoly acids,[4g] dialkylimidazolium tetrachloroaluminates,[4h] K-10 clay[4i] and I_2.[4j] Also, monotetrahydropyranylation of diols has been well studied.[5] Although these methods are suitable for many synthetic conditions, many of these are associated with several drawbacks, which include long reaction times, refluxing conditions, the use of catalysts which may affect other functionalities present, harsh and acidic conditions, poor selectivity, formation of polymeric by-products of the dihydropyran and isomerization. In addition, some of these catalysts are not recyclable and require work-up of the reaction mixture. Thus, there is still a need for mild and selective methods, especially using heterogeneous catalysts for this purpose.

Neckers and co-workers used polystyrene supported $AlCl_3$, Ps–$AlCl_3$, as a catalyst in the condensation, esterification and acetalization of alcohols.[2b] In continuation of our recent work on the use of polymer supported reagents and catalysts, we found that Ps–$AlCl_3$ was a good catalyst for the synthesis of thiiranes from epoxides[6a] and for the highly chemoselective dithioacetalization of carbonyl compounds.[6b] Along this line, we now wish to report that Ps–$AlCl_3$ is also an effective and highly chemoselective catalyst for performing tetrahydropyranylation under mild conditions (Scheme 1).

Ps–$AlCl_3$ was prepared by addition of anhydrous aluminum chloride to polystyrene (8% divinylbenzene) in



Scheme 1.

Keywords: Protection; Terahydropyranylation; Aluminium chloride; Polymer supported Lewis acid.

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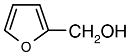
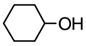
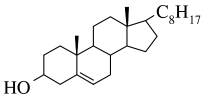
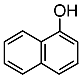
Table 1. Tetrahydropyranylation of alcohols and phenols using Ps–$AlCl_3$[a]

Entry	Hydroxy compound	Subst./DHP	Time (h)	Yield (%)[b]
1	Benzyl alcohol	1:1.2	0.7	97
2	*p*-Methoxy benzyl alcohol	1:1.2	0.5	97
3	*p*-Nitro benzyl alcohol	1:1.3	1.5	91
4	*n*-$CH_3(CH_2)_7$–OH	1:1.2	1.1	95
5	$CH_3CH(CH_3)CH_2OH$	1:1.2	1.2	93
6	Ph–$CH(CH_3)OH$	1:1.3	1.5	96
7		1:1.3	1.1	93
8	$(CH_3)_2CH$–OH	1:1.3	1.5	93
9		1:1.3	1.5	92
10	$Ph(CH_3)_2C$–OH	1:1.4	2.1	91
11	$CH_3CH_2C(CH_3)_2OH$	1:1.4	2.2	91
12	$CH_2{=}CH_2CH_2OH$	1:1.3	1.6	93
13	$CH\equiv CCH(OH)CH_2CH_2CH_3$	1:1.3	1.7	93
14		1:1.4	3.2	89
15	*p*-Methoxy phenol	1:1.3	0.9	93
16	Phenol	1:1.4	1	93
17		1:1.5	1.4	91

[a] All reactions were carried out in CH_2Cl_2 at room temperature except for the phenols (entries 15–17), which were performed in refluxing CH_2Cl_2.

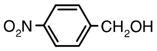
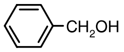
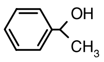
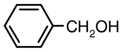
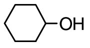
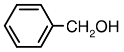
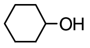
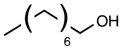
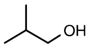
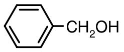
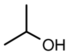
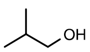
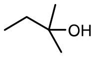
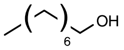
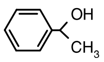
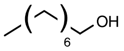
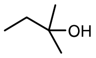
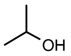
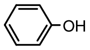
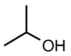
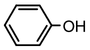
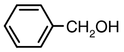
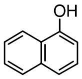
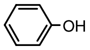
[b] Yields refer to pure isolated products. The tetrahydropyranyl ethers prepared are known compounds and were characterized by comparison of their physical and spectral data with those reported in the literature.[4c,d,i]

carbon disulfide under reflux conditions.[2b,7] Using this polymeric catalyst, different kinds of alcohols (primary, secondary, tertiary, benzylic and allylic) and phenols underwent tetrahydropyranylation in good to excellent yields[8] (Table 1). Reactions were carried out in methylene chloride, which proved to be the solvent of choice among other organic solvents. The optimum molar ratio of the polymeric catalyst to hydroxy compound was found to be 0.15:1. As shown in Table 1, tertiary and allylic alcohols were also converted to their corresponding tetrahydropyranyl ethers in high yields without formation of any elimination product or isomerization of C═C bonds (entries 10–13). Unlike strong acidic catalysts that produce polymeric by-products from the dihydropyran,[3,4c] no polymerization of the dihydropyran was observed when Ps–$AlCl_3$ was used probably due to its mild catalytic activity.

In order to examine the chemoselectivity of the present method, equimolar mixtures of alcohols and or phenols were allowed to react with DHP in the presence of Ps–$AlCl_3$. As shown in Table 2, Ps–$AlCl_3$. was able to discriminate between different types of alcohols and or phenols from each other, a transformation that is difficult to accomplish via conventional methods (Table 2, entries 1–12). Also, we found that symmetrical diols in the presence of a limited amount of DHP were protected as their monoethers, selectively (entries 13–16). It was noticed that diols with a higher number of carbon atoms showed more selectivity towards monoether formation (entries 15–16). Although, the reason for the observed chemoselectivity is not exactly clear it is possibly due to factors such as the mild catalytic activity of Ps–$AlCl_3$, its pore size and its hydrophobic nature, which affected the extent of penetration (that is the access to the active sites) of different hydroxy compounds in the swollen beads[2a] The present chemoselectivities can be suitable for protection of alcohols and phenols for the synthesis of complex molecules by multistep processes.

In conclusion, we have developed a simple, efficient and highly chemoselective process for tetrahydropyranylation of alcohols and phenols using Ps–$AlCl_3$. The mild reaction conditions, short reaction times, high to excellent yields, low cost and easy preparation and handling (as a bench top catalyst) of the polymeric catalyst are the obvious advantages of the present method. Most importantly, the work-up is reduced to a mere filtration and evaporation of the solvent. Finally, this polymeric catalyst can be recovered unchanged and used again at least six times with negligible loss in its activity. Ps–$AlCl_3$ is also efficient for deprotection of THP groups and this is currently under investigation and will be reported in due course.

Table 2. Chemoselective protection of alcohols and phenols in the presence of Ps–$AlCl_3$[a]

Entry	Subst. 1	Subst. 2	Subst. 1/Subst. 2/DHP	Time (h)	Yield (%)[b]	
					Ether 1	Ether 2
1			1:1:1.1	0.9	4	92
2			1:1:1.1	0.9	3	92
3			1:1:1.1	0.9	4	92
4			1:1:1.1	1.3	6	92
5			1:1:1.1	0.9	7	92
6			1:1:1.1	1.3	4	94
7			1:1:1.2	1.1	3	94
8			1:1:1.1	1.2	3	94
9			1:1:1.2	1.6	3	92
10			1:1:1.3	1.5	3	94
11			1:1:1.2	0.7	3	95
12			1:1:1.3	1.2	3	92
13	$HOCH_2CH_2OH$		1:1.1	1.6	9[c]	90[d]
14	$HOCH_2CH_2CH_2OH$		1:1.1	1.7	8[c]	90[d]
15	$HOCH_2(CH_2)_4CH_2OH$		1:1.1	1.7	3[c]	96[d]
16	$HOCH_2(CH_2)_6CH_2OH$		1:1.1	1.8	3[c]	96[d]

[a] All reactions were carried out in CH_2Cl_2 in the presence of Ps–$AlCl_3$ (0.15 mmol) at room temperature except for entry 12, which was performed in refluxing CH_2Cl_2.

[b] Conversion based on GC and NMR.

[c] Diether.

[d] Monoether.

Acknowledgements

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7. Preparation of Ps–$AlCl_3$:[2b] Anhydrous $AlCl_3$ (4.5 g) was added to polystyrene (8% divinyl benzene) (3.5 g) in carbon disulfide (25 mL). The mixture was stirred under reflux for 50 min, cooled and then water (20 mL) was cautiously added to hydrolyze the excess $AlCl_3$. The mixture was stirred until the deep orange color disappeared and the polymer became light yellow. The polymer beads were then filtered and washed with water (350 mL) and then with ether, acetone and ether. The polymer was dried in a vacuum oven overnight. Complex formation was demonstrated by a new bond at 1650 cm^{-1} in the IR spectrum of the polymer. The chloride content of Ps–$AlCl_3$ was 5.28%.[9]
8. A typical procedure is as follows: To a solution of the alcohol (1 mmol) and 3,4-dihydro-2*H*-pyran (1.2–1.5 mmol) in dry methylene chloride (10 mL), Ps–$AlCl_3$ (0.15 mmol) was added. The reaction was stirred at room temperature and monitored by TLC and GLC. After completion of the reaction, the catalyst was filtered off and washed with methylene chloride (2 × 15 mL) and the filtrate concentrated on a rotary evaporator under reduced pressure to give the pure product. The spent polymeric catalyst from different experiments was combined, washed with ether and dried overnight in a vacuum oven and reused.
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