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Solvent-free tetrahydropyranylation (THP) of alcohols and phenols and their regeneration by catalytic aluminum chloride hexahydrate

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Abstract—A catalytic amount of aluminum chloride hexahydrate enables solvent-free tetrahydropyranylation (THP) of alcohols and phenols at moderate temperatures. A simple addition of methanol helps to regenerate the corresponding alcohols and phenols, thus rendering these protection and deprotection sequences as very efficient transformations at high substrate to catalyst ratios. Published by Elsevier Science Ltd.

The protection and deprotection of alcohols is a common event in multi-step organic syntheses and tetrahydropyranylation (THP) is one of the most frequently employed methods.[1] The THP ethers are attractive because they are less expensive, easy to deprotect and are stable enough to strong basic media, oxidative conditions, reduction with hydrides, and reactions involving Grignard reagents, lithium alkyls and alkylating and acylating reagents. There are several reagents available for tetrahydropyranylation of alcohols, which include the use of Brønstead and Lewis acids,[2] iodine-microwave irradiation,[3] ion-exchange resins (Amberlyst H15[4] and Nafion-H[5]), zeolites,[6] montmorillonite K-10[7a] or sulfuric acid on silica gel,[7b] zinc chloride[8a] or $AlPO_4$[8b] on alumina, Envirocat EPZG,[9] tributylammonium bromide,[10] heteropoly acids,[11] *p*-toluenesulphonic acid, pyridinium *p*-sulphonate(PPTS) and triphenylphosphene hydrobromide in ionic liquids as catalysts,[12] cyclodextrin,[13] and lithium perchlorate–diethylether.[14] Although these methods are suitable for many synthetic conditions, they require a high catalyst to substrate ratio, have a long reaction time and involve the use of volatile organic solvents or large amounts of solid supports which eventually results in the generation of a large amount of toxic waste. Thus, there is a need for a solventless and catalytically efficient alternative for the protection and deprotection of hydroxyl functionality as THP ether. As a part of an ongoing research program to develop solventless chemical transformations,[15] herein, we report an efficient aluminum chloride hexahydrate-catalyzed solvent-free tetrahydropyranylation of alcohols and phenols.

In the present method, alcohol or phenol, 3,4-dihydro-2*H*-pyran (DHP) and aluminum chloride catalyst are mixed together to yield the corresponding THP ether. After the reaction, the product is purified by simple filtration through a silica gel pad and evaporation of the eluent, petroleum ether. A wide variety of hydroxylated compounds are converted to the corresponding THP ethers via this procedure and the results are shown in Table 1. The reactions are reasonably fast, even with a bulky molecule like benzhydrol (entry 7). It is important to note that an acid sensitive alcohol like *tert*-butanol (entry 8) undergoes protection as tetrahydropyranyl ether without the formation of a dehydration product. The study conducted with benzyl alcohol as the substrate for pyranylation shows that the rate of reaction decreases with the increase in substrate to catalyst ratio (Table 2). Increase in temperature with longer reaction time results in complete pyranylation even at higher substrate concentration. Higher temperatures are required in the case of substituted benzyl alcohols (high substrate to catalyst ratio) and with solid alcohols. An important feature of this method is the efficient monotetrahydropyranylation of 1,*n*-diols (entries 12 and 13), a transformation that is difficult to accomplish via conventional methods.

Keywords: tetrahydropyranylation; aluminum chloride; solvent-free.

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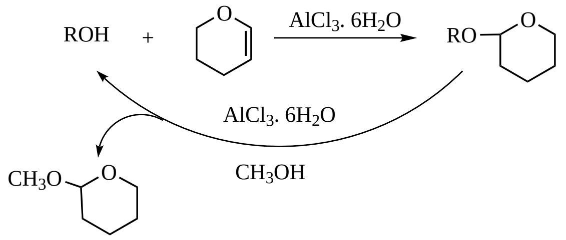
Table 1. Tetrahydropyranylation of alcohols[a,b]



Entry	Alcohol	Time (min)	Temperature (°C)	Yield (%) GC (isolated)
1	1-Hexanol	30	30	100 (95)[1]
2	3-Hexanol	30	30	100 (96)[17]
3	Cyclohexanol	30	30	93 (88)[5]
4	Phenol	30	60	96 (89)[13]
5	4-Chlorophenol	30	60	92 (85)[13]
6	2-Naphthol	30	80	96 (88)[6c]
7	Benzhydrol	30	80	85 (82)[16]
8	*tert*-Butanol	30	40	100 (95)[2c]
9	Geraniol	180	50	82 (81)[3b,4]
10	Allyl alcohol	30	30	100 (98)[3b]
11	3-Methyl-2-butene-1-ol	30	30	100 (98)[18]
12	1,2-Ethanediol	30	30	76 (74)[2a,b]
13	1,4-Butanediol	30	30	78 (75)[2a,b]
14	4-Chlorobenzyl alcohol	30	60	94 (90)[13,16]

[a] $AlCl_3·6H_2O$ (1 mmol) and 3,4-dihydropyran (110 mmol) and alcohol (100 mmol).

[b] For complete cleavage of tetrahydropyranyl ethers at room temperature: THP ether (100 mmol), aluminum chloride (1 mmol) and methanol (800 mmol), 30 min at 30°C.

Table 2. Catalytic effect of $AlCl_3$ on tetrahydropyranylation of benzyl alcohol[a]

Benzyl alcohol (mmol)	3,4-Dihydropyran (mmol)	Time (min)	Temperature (°C)	Yield (%) GC
1	1.1	5	30	100
100	110	30	30	100
500	550	60	30	79
1000	1100	60	30	64
1000	1100	30	55	100
2500	2750	60	80	100
5000	5500	90	80	100[b]

[a] $AlCl_3·6H_2O$ (1 mmol).

[b] For complete cleavage of tetrahydropyranyl ether at high substrate to catalyst ratio: THP ether (5000 mmol), aluminum chloride (1 mmol) and methanol (20,000 mmol), 1 h at 80°C.

These reactions catalyzed by aluminum chloride do not require any solvent or solid support and consequently assist in minimizing the generation of toxic wastes to the environment. While most of the existing protocols require distilled and/or dry reagents, the present method tolerates the presence of moisture although the reaction rate decreases with increase in water concentration as shown in Fig. 1. It is significant that the present method is suitable for the preparation of THP–ether even at higher water content (Fig. 1).

The capability of aluminum chloride to cleave the THP protective group is also investigated to establish the regenerative potential of catalyst. To this end, the THP ether (100 mmol), aluminum chloride (1 mmol) and excess methanol (800 mmol) are mixed together at room temperature affording a complete conversion in 30 min. The deprotection is conveniently followed via GC–MS when a complete disappearance of the THP ether occurs with the regeneration of the alcohol and the formation of tetrahydro-2-(methoxy)-2*H*-pyran. At a relatively higher temperature of 80°C, this catalyst is able to deprotect THP ethers using excess methanol at high substrate to catalyst ratio (5000 mmol:1 mmol) in 1 h.

Preparative procedure for THP ethers: Aluminum chloride hexahydrate (1 mmol), DHP (110 mmol) and benzyl alcohol (100 mmol) were mixed in a 50 ml round bottomed flask and stirred at 30°C and the progress of the reaction was monitored by TLC and GC–MS (Table 1). The complete protection was ascertained by the disappearance of the alcohol signal in the GC. For solid substrates (entries 6, 7, and 14), moderate heating was required. The product was purified by filtering the reaction mixture through a short column of silica gel (2

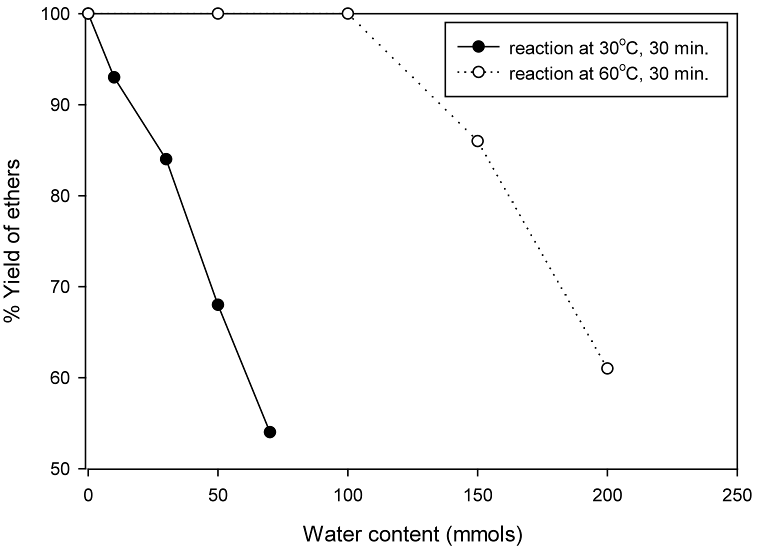


Figure 1. Yield versus water content. Effect of water content on the reaction of benzyl alcohol (100 mmol) with DHP (110 mmol) in the presence of $AlCl_3\cdot6H_2O$ catalyst (1 mmol).

cm length, 0.5 cm diameter) with petroleum ether (~4 ml) to obtain pure THP ether (99%).[4]

All the THP ethers are known compounds and were characterized by spectral analyses, comparison with authentic samples (GC and NMR), and also by regeneration of the corresponding alcohols or phenols. The regeneration experiments also reaffirmed that there were no other side reactions occurring during THP ether formation.

Deprotection of THP ethers: THP ether (100 mmol), aluminum chloride (1 mmol) and excess methanol (800 mmol) were mixed together at room temperature for 30 min affording complete regeneration of the alcohol. The cleavage of THP ethers and regeneration of alcohols was similarly followed by GC. The reaction mixture was filtered through a short silica column (eluted with petroleum ether). Isolated yield of benzyl alcohol after deprotection was 96%.

In conclusion, the present method describes an efficient and practical alternative to the protection and deprotection of alcohols and phenols as tetrahydropyranyl ethers. The significant advantages of this methodology are mild reaction conditions, absence of volatile solvent, faster reaction rates, high substrate to catalyst ratios, and ease of protection and deprotection with the same catalyst. We predict that this method will find useful application for the protection and deprotection of the alcohols in modern synthetic chemistry.

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