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Vanadyl(IV) acetate: a mild and efficient heterogeneous catalyst for the tetrahydropyranylation of alcohols, thiols and phenols☆

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Abstract

A variety of alcohols, thiols and phenols readily add to 3,4-dihydro 2H-pyran under mild conditions in the presence of catalytic amount of vanadyl(IV) acetate to afford the corresponding tetrahydropyranyl ethers in good to excellent yields at a faster rate for the first time in a novel heterogeneous medium. This methodology marks the first report of catalytic tetrahydropyranylation of thiols. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Vanadyl(IV) acetate; Tetrahydropyranylation; Alcohols; Thiols and phenols

1. Introduction

The protection of thiols and alcohols has found widespread applications especially in steroids, sugars, glycerides and natural products [1,2]. The tetrahydropyranylation is one of the most frequently used processes to protect hydroxyl group [3] of alcohols and phenol. Due to the remarkable stability of tetrahydropyranyl ether towards a variety of conditions such as strongly basic media, reactions involving Grignard reagents and lithium alkyls, reduction with hydride, oxidation, oxidative alkylation and acylation reactions, and due to its low cost and ease with which it can be removed, often makes dihydropyran, the reagent of choice for hydroxyl group protection in multi-step organic synthesis [4]. A variety of reagents have been developed for tetrahydropyranylation which include mainly protic acids, hydrochloric acid [5] and *p*-toluenesulfonic acid [6], Lewis acids (BF_3–OEt_2) [7], aluminum sulfate on silica gel [8], pyridinium *p*-toluenesulfonate [9] and bis(trimethylsilylsulfate) [10], ion-exchange resins [11,12], $MgBr_2{\cdot}Et_2O/NaHCO_3$ [13], 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) [14], transition metal catalysts [15–20] and heterogeneous catalysts, K-10 clay [3], H-Y zeolite [21], alumina/$ZnCl_2$ [22], Envirocat EPZG [23], natural kaolinite-clay [24], zeolite HSZ [25]. Although these methods are satisfactory for many molecules, some have limitations such as use of strongly acidic media, expensive reagents, tedious and time-consuming work-up procedure, high temperature, long reaction times and non-reusability. Although many transition metal based catalysts that mediate the process have been reported, none of them have enjoyed widespread use as they suffer from one or more disadvantages, including poor functional group tolerance, slow rates with bulky molecules and tertiary alcohols and the lack of a commercial source for the catalyst.

On the other hand, the role of THP thioethers as protective groups in biochemical processes [26] and their high reactivity with various electrophiles has made

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them attractive synthetic intermediates in a variety of chemical transformations [27]. A comprehensive literature search has revealed that tetrahydropyranylation of thiols is not reported so far using transition metal complexes and heterogeneous catalysts. Further, the protection of thiols as THP and THF ethers require hazardous reagents (HCl gas, SO_2Cl_2) and drastic reaction conditions [28,29]. Thus, there is a need for mild and efficient alternative method for protection of alcohols and thiols as THP ethers. Based on simple insolubility principle, we have recently designed a heterogeneous catalytic system, vanadyl(IV) acetate for acylation of alcohols [30] and transesterification of β-ketoesters [31]. The simple preparation, low cost and easy handling of this catalyst prompted us to study its application for tetrahydropyranylation, an important reaction for the protection of hydroxyl group.

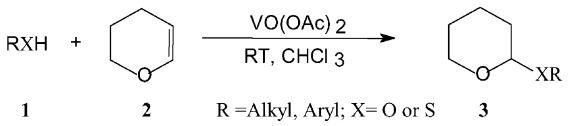
2. Experimental

2.1. Preparation of the vanadyl(IV) acetate

Vanadyl(IV) acetate was prepared according to the literature procedure [30].

2.2. Typical procedure

In a typical experiment, a solution of 3,4 dihydro-2H pyran (100 mg, 1.2 mmol) in chloroform (2 ml) was added drop-wise to a stirred mixture of benzyl alcohol (0.1 ml, 1 mmol) and vanadyl(IV) acetate (50 mg, 0.27 mmol) at room temperature. The progress of the reaction was monitored by TLC. After 1 h, the reaction mixture was filtered and the residue was washed with chloroform (5 ml). The organic layer was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, eluant; hexane/ethyl acetate, 98/2, v/v) to afford tetrahydropyranyl ether of benzyl alcohol (Yield 95%, 168 mg). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4–1.8 (m, 6H, $3CH_2$), 3.3–4.1 (m, 2H, CH_2O), 4.6 (dd, 2H, $PhCH_2O$), 4.7 (m, 1H, O–CH–O), 7.3 (s, 5H, C_6H_4); IR (KBr): 3062, 3029, 2940, 2868, 1450, 1350, 1262, 1183, 1120, 1078, 1057, 1026, 976, 906, 870, 810, 736, 699 cm^{-1}; *m/z* 192 (M^+), 146 $(M–C_2H_6O)^+$, 101 $(C_5H_9O_2)^+$, 91 $(C_7H_7)^+$ and 85 $(C_5H_9O)^+$.



Scheme 1. Tetrahydropyranylation catalysed by vanadyl(IV) acetate.

3. Results and discussion

We deliberately devised and report herein a heterogeneous system, in which vanadyl(IV) acetate, a powerful Lewis acid catalyst almost practically insoluble in the chosen solvent medium, chloroform, for tetrahydropyranylation of alcohols, thiols and phenols in good to excellent yields (Scheme 1, Table 1) and consistently active for several cycles by simple

Table 1
Tetrahydropyranylation of alcohols, thiols and phenols catalysed by vanadyl(IV) acetate

Entry	Alcohol or thiol	Time (h)	Yield (%)[a]
1	1-Octanol	0.5	95
2	2-Pentanol	0.5	92
3	*tert*-Butanol	1.0	84[b]
4	Allyl alcohol	0.5	88
5	Propargyl alcohol	0.5	97
6	2-Methoxy ethanol	1.0	87
7	Cyclohexanol	1.5	88
8	4-Methyl cyclohexanol	1.5	94
9	Phenol	1.0	95
10	2-Chloro phenol	2.0	78
11	4-Nitro phenol	2.0	70
12	Catechol	1.5	70
13	Benzyl alcohol	1.0	95[b], 90[c]
14	2-Hydroxy benzyl alcohol	1.0	92
15	*sec*-Phenethyl alcohol	1.0	90
16	(-) Menthol	1.5	94
17	Cholesterol	1.5	92
18	1,3-Propane diol	0.5	80[b]
19	1,4 -Butane diol	0.5	75[b]
20	1-Butane thiol	1.5	96
21	Dodecane thiol	2.0	92
22	Cyclohexane thiol	1.5	95
23	4-Chloro thiophenol	4.0	48
24	4-Methoxy thiophenol	4.0	54

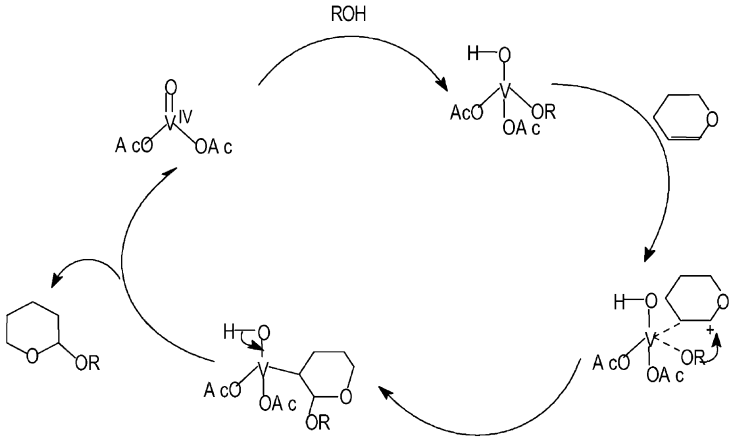
[a] Yields determined by ^{1}H NMR.
[b] Isolated yield.
[c] Yield after 5th cycle.

filtration. Incidentally, it happens to be the first report for tetrahydropyranylation of thiols catalysed by a transition metal catalyst.

A wide range of hydroxyl compounds, thiols and phenols are converted to the corresponding THP ethers in high yields using catalytic amount of vanadyl(IV) acetate. The results are presented in Table 1. In addition to being effective for primary, secondary and tertiary alcohols alike (entries 1–3), the reaction is tolerant of a wide variety of functional groups including C=C, C≡C, –Cl, –OMe and $–NO_2$. It is noteworthy that all the reactions mentioned above are complete in a short time at room temperature. The reactions are reasonably fast, even the bulky molecules like l-menthol (entry 16) and cholesterol (entry 17) which require days for complete conversion by many conventional methods are found to give satisfactory yields in a short time at room temperature. The low acid strength of the catalyst and mild reaction conditions have not affected double or triple bonds during tetrahydropyranylation of allylic and propargylic alcohols (entries 4, 5). It is important to note that acid sensitive alcohol such as *t*-butanol undergoes protection as tetrahydropyranyl ether without the formation of a dehydration product (entry 3). Labile benzylic alcohols (entries 13, 15) and allylic alcohol (entry 4) are converted into their THP ethers in good yields. Of particular interest is the selective protection of alcoholic –OH group in the presence of a phenolic group (entry 14) and selective mono tetrahydropyranylation of symmetric diols (entries 18, 19) yielding 80% of monoether and 10–20% of diether. Of the various phenols studied, only phenol is converted to the tetrahydropyranyl ether in high yield (entry 9) where as substituted phenols reacted slowly to give products in moderate yields (entries 10–12). The catalyst was also found to be highly active for tetrahydropyranylation of thiols in quantitative yields (entries 20–22) except for substituted thiophenols where THP thioethers are obtained in low yields (entries 23, 24). The most significant achievement is the reusability of the deliberately chosen heterogeneous salt of transition metal catalyst for several cycles with almost consistent activity.

It is important to introduce sulfur effectively into organic compounds, as many biologically active compounds contain sulfur functional groups. Although there is no report of thiol additions to dihydropyran employing Lewis acid as catalyst or reagent as discussed above, the addition of thiols to other enol ethers takes place to give a mixture of O/S- and S/S-acetals using Lewis acids such as $AlCl_3$ [32], $ZnCl_2$, $HgCl_2$. Stronger acid catalysts like $TiCl_4$ [33] leads to complete formation of ring opened S/S-acetals. Therefore, our method is mild, selective, convenient and simple to protect thiols as THP thioethers effectively.

The plausible mechanism for the tetrahydropyranylation of alcohols with 3,4-dihydropyran is illustrated in Scheme 2. The vanadyl(IV) acetate reacts with alcohol to form vanadium(IV) alkoxide species. The alkoxide anion further reacts with dihydropyran to



Scheme 2. Plausible mechanism for tetrahydropyranylation reactions catalysed by vanadyl(IV) acetate.

form 2-alkoxytetrahydropyranyl anion, which on interaction with H^+ forms 2-tetrahydropyranyl ether by regenerating the original catalyst.

4. Conclusion

In conclusion, we have demonstrated that vanadyl-(IV) acetate acts as an efficient, convenient and reusable catalyst for the tetrahydropyranylation of alcohols, thiols and phenols in high yields and selectivities. The advantages are high catalytic activity under very mild liquid phase conditions, easy separation of the catalyst by simple filtration, tolerance to a wide range of functionalities, selectivity for symmetric diols, involvement of non-toxic and inexpensive materials. The superiority and flexibility of our method over the existing methods coupled with the ease of operation, simplicity and recyclability provide an useful alternative to the preparation of tetrahydropyranyl ethers from alcohols, phenols or thiols. The work widens the scope of using transition metal salts and complexes as such as heterogeneous catalysts invoking insolubility principle.

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