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Selective Protection of Alcohols as 2-Tetrahydropyranyl Acetals Using Keggin $H_3PW_{12}O_{40}$ Effect of Different Reaction Parameters

REZA TAYEBEE* and BEHNAM MAHDAVI
Department of Chemistry, Sabzevar University, Sabzevar-397, Iran
E-mail: rtayebee@yahoo.com

Selective protection of some industrially and pharmaceutically important chemicals bearing primary and secondary hydroxyl groups were achieved using 3,4-dihydro-2*H*-pyran (DHP) as the protecting group by the presence of Keggin $H_3PW_{12}O_{40}$ as catalyst. Findings revealed only protection of the primary alcoholic group in good yields. Different reaction parameters affecting efficiency of the formation of 2-tetrahydropyranyl acetals from alcohols catalyzed by $H_3PW_{12}O_{40}$ were also studied. Characteristic reaction conditions include short times and room temperature.

Key Words: Selective tetrahydropyranylation, Heteropolyoxometalate, Reaction parameters.

INTRODUCTION

Selective protection of alcohols continues to receive wide attention from synthetic and industrial points of view. In this regard, protection of alcohols as a tetrahydropyranyl (THP) ether is often sought after as THP ethers are stable under basic conditions[1,2]. 3,4-Dihydro-2*H*-pyran (DHP) is a versatile and low cost reagent for the protection of hydroxyl groups giving tetrahydropyranyl ethers, which are robust protective groups and also useful intermediates for further functional transformations[3]. However, a wide range of well known protic and Lewis acids and other reagents and catalysts such as iodotrimethylsilane, triphenylphosphine hydrobromide, montmorillonite (an acidic clay) and of late, heteropoly acids, have been used to effect the tetrahydropyranylation of alcohols[4-7].

In continuation to our previous studies[8], herein a competitive protection of primary *vs.* secondary hydroxyl groups toward tetrahydropyranylation is presented. Moreover, different reaction parameters affecting efficiency of this protocol were also investigated. Obviously, alcohol concentration and $C_6H_{11}OH$:DHP molar ratio strongly affect selectivity and product formation.

EXPERIMENTAL

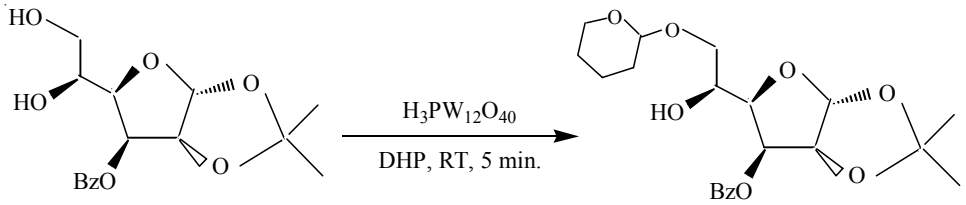
The solvents, reagents and other chemicals used in this study were of the highest grade available and were purchased commercially. Silica gel 60 (70-230 mesh, purchased from E-Merck A.G., Darmstadt, Germany) used for column chromato-

graphy. GLC analyses were performed on a Shimadzu GC-17A instrument equipped with a flame ionization detector using CPB 5-20. $H_3PW_{12}O_{40}$ was purchased commercially from Merck.

In a typical procedure $H_3PW_{12}O_{40}$ (0.01 mmol) was dissolved in acetone (5 mL) at room temperature for 5 min. Then 3,4-dihydro-2*H*-pyran (2 mmol) was added to the stirred solution. Then, cyclohexanol (1 mmol) was substantially added and the reaction mixture stirred for the required time. At the end of the reaction, the mixture was first filtered through a short column of silica gel, washed with a small amount of dichloromethane and concentrated to give impure tetrahydropyranyl acetal. The product was further purified by column chromatography to afford the corresponding THP-acetal.

RESULTS AND DISCUSSION

To investigate the acidic catalytic activity of $H_3PW_{12}O_{40}$, the chemoselective THP-protection of primary alcohols in the presence of secondary alcohols has been explored. In order to establish the nature of $H_3PW_{12}O_{40}$ in the chemoselective THP-protection of primary alcohols in the presence of secondary hydroxyl groups, 3,4-dihydro-2*H*-pyran with (**1**) at room temperature using 0.01 mmol of catalyst to produce the corresponding tetrahydropyranyl ether in 78 % yield (**Scheme-I**).



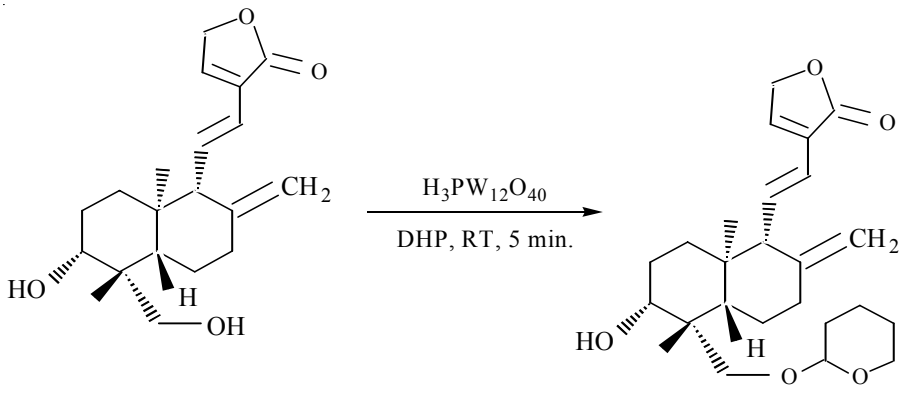
(**1**)

Scheme-I

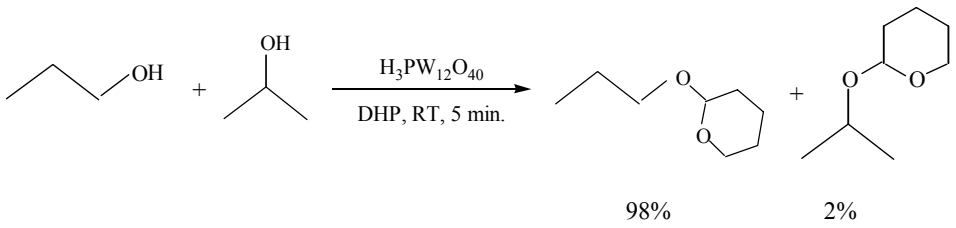
Moreover, when the diterpene andrographolide (**2**) containing a lactone ring, primary and secondary hydroxyl groups was reacted with 3,4-dihydro-2*H*-pyran, only the primary alcoholic group was protected in 73 % yield (**Scheme-II**).

In order to check the versatility of $H_3PW_{12}O_{40}$, a mixture of 1-propanol and 2-propanol with the same molar ratio was reacted with dihydropyran in the presence of catalyst to give exclusively, THP-protected 1-propanol (**Scheme-III**).

Effect of alcohol concentration on the efficiency of the tetrahydropyranylation protocol: The effect of different concentration of alcohol is presented in Table-1. As is expected, conversion decreases by enhancing alcohol concentration at short reaction times. For example, cyclohexanol led to 65, 50 and 45 % of conversions with 0.1, 0.5 and 1 mmol of cyclohexanol after 0.5 min, respectively. Moreover, selectivity is sharply decreased with lowering concentration of alcohol.



Scheme-II



Scheme-III

TABLE-1
EFFECT OF CYCLOHEXANOL CONCENTRATION ON THE TETRAHYDROPYRANYLATION CATALYZED BY $H_3PW_{12}O_{40}$

Entry	Cyclohexanol (mmol)	Yield (%)			
		0.5 min	5 min	15 min	30 min
1[b]	0.1	65	33	32	32
2[c]	0.5	50	57	52	44
3[d]	1.0	45	80	86	77
4	3.0	27	27	27	29
5	5.0	25	21	19	18

[a]$H_3PW_{12}O_{40}$ (0.01 mmol) was dissolved in acetone (5 mL) at ambient temperature. Then DHP (2 mmol) was added to the stirred solution. Finally, cyclohexanol (0.1-5.0 mmol) was substantially added and the reaction medium stirred for the required time. [b]In this run, selectivity is clearly decrease from 98 to < 45 %. [c]In this run, selectivity is *ca.* 90 %. [d]Selectivity is > 98 %.

In the presence of 1 and 0.5 and 0.1 mmol of cyclohexanol, the observed selectivities were > 98, ~ 90 and < 45 %, respectively. Higher concentrations of alcohol, above 1 mmol, leading to low conversion at short and long reaction times. Conclusively, the best results were obtained in the presence of 1 mmol of cyclohexanol at short and long reaction times.

Effect of $C_6H_{11}OH$:DHP molar ratio on the tetrahydropyranylation of cyclohexanol catalyzed by $H_3PW_{12}O_{40}$: Table-2 shows the effect of different molar ratio of $C_6H_{11}OH$:DHP on the progress of tetrahydropyranylation of cyclohexanol catalyzed by $H_3PW_{12}O_{40}$. According to the findings, tetrahydropyranylation increases with enhancing DHP concentration from 1:0.5 to 1:2. With 1:0.5 molar ratio of $C_6H_{11}OH$:DHP, 17 % conversion was achieved after 0.5 min; whereas, with 1:1 and 1:2 molar ratios 45 % of conversion was reached during the same time. It should be noted that 1:2 ratio is better than 1:1, leading to higher conversion at longer reaction times. With the former ratio, 86 % of conversion achieved after 15 min; whereas, with 1:1 molar ratio only 39 % of the protected alcohol required the same time. Higher increase in DHP concentration (1:4) resulted in a clearly distinct decrease in conversion and selectivity of the protection. With 1:4 molar ratio of $C_6H_{11}OH$:DHP, 27 % yield with < 70 % selectivity was obtained after 0.5 min.

TABLE-2
EFFECT OF $C_6H_{11}OH$:DHP MOLAR RATIO ON THE TETRAHYDRO-PYRANYLATION OF CYCLOHEXANOL CATALYZED BY $H_3PW_{12}O_{40}$

Entry	$C_6H_{11}OH$:DHP	Yield (%)			
		0.5 min	5 min	15 min	30 min
6	1:0.5	17	23	23	22
7	1:1.0	45	45	39	38
8	1:2.0	45	80	86	77
9*	1:4.0	27	24	20	18

Reactions were run with > 98 % selectivity as described below Table-1, with different values of DHP (0.5-4.0 mmol) against 1 mmol of cyclohexanol; *Select. < 70 %.

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