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Selective conversion of alcohols and phenols to tetrahydropyranyl ethers catalyzed with *N*-chlorosaccharin under mild and solvent-free conditions

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ABSTRACT

An efficient method is described for the mild and rapid tetrahydropyranylation of alcohols and phenols using a catalytic amount of *N*-chlorosaccharin (1 mol %) and 3, 4-dihydro-2*H*-pyran under solvent-free condition at room temperature. Benzylic alcohols and phenols containing electron withdrawing or donating groups in various positions of phenyl ring, cinamyl alcohol, primary, secondary, tertiary as well as cyclic alcohols are converted to their corresponding tetrahydropyranyl ethers in short reaction times and in excellent yields *via* the present method. Primary benzylic alcohols in the presence of secondary ones and also primary or secondary aliphatic alcohols in the presence of tertiary ones can be efficiently tetrahydropyranylated with excellent selectivity *via* this method.

***Keywords**: Alcohol, Phenol, Tetrahydropyranylation, N-Chlorosaccharin.*

1. Introduction

An important and useful way for protection of alcohols and phenols in multistep organic synthesis is tetrahydropyranylation because of the products tetrahydropyranyl (THP) ethers are stable towards basic media, alkyl lithiums, Grignard reagent, metal hydrides and oxidative reagents [1] and easily reversed to alcohols and phenols at a later stage. This transformation has been carried out with a variety of catalysts such as iodine [2], anhydrous calcium chloride [3], $AlCl_3.6H_2O$ [4], $Bi(OTf)_3$. $4H_2O$ [5], $PdCl_2(CH_3CN)_2$ [6], imidazolium-based tetrachloroindate (III) under microwave irradiation [7], silica sulfuric acid [8], $CuSO_4.5H_2O$ [9], $HClO_4$-SiO_2 [10], $Fe(HSO_4)_3$ [11], Dowex 50WX4-100 [12], $Al(OTf)_3$ [13], SiO_2.*p*-TSA [14], trifluoroacetic acid (TFA) [15], aniline-terephthalaldehyde resin *p*-toluenesulfonic acid (ATRT) salt [16] and solid-supported sulfonic acid under continuous-flow conditions [17] in the presence of 3, 4-dihydro-2*H*-pyran (DHP).

However, many of these methods suffer from some disadvantages such as long reaction times, the use of unavailable catalyst, unsuitability for protection of phenols or tertiary alcohols, operation in a volatile solvent or under heating and high catalyst to substrate ratio and also do not provide selectivity or at least, selectivity of the method is ambiguous. Thus, there is a need for the development of new methods that are more convenient for this important synthetic transformation.

In this connection, in continuation of our previous works on the new applications of *N*-halo reagents in organic synthesis [18] including especially the silylation reaction using *N*-chlorosaccharin as a catalyst [18e], we now report an efficient conversion of different types of alcohols and phenols to their corresponding THP ethers using this catalyst (*N*-chlorosaccharin) and DHP under mild and solvent-free conditions at room temperature (Scheme 1).

2. Experimental

2.1. General

Solvents, reagents and chemicals were obtained from Merck, Fluka or Aldrich chemical companies. All the products are known compounds [2-5, 7, 10-13] and were characterized by comparison of their physical or spectral data with authentic samples. Fourier transform-infrared (FT-IR) spectra were recorded on a Perkin-Elmer RXI spectrophotometer.

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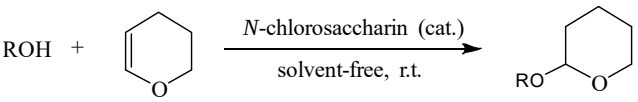


R= benzylic, primary, secondary, tertiary, allylic, cyclic and aryl

Scheme 1. Conversion of alcohols and phenols to THP ethers using N-chlorosaccharin as a catalyst.

Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker Avance 400 spectrometer. Thin-layer chromatography (TLC) was carried out on silica-gel 254 analytical sheets obtained from Fluka.

2.2. Typical procedure for tetrahydropyranylation of 4-chlorobenzyl alcohol using DHP catalyzed with N-chlorosaccharin:

N-Chlorosaccharin as finely powdered (0.01 mmol, 0.002 g) was added to a flask containing 4-chlorobenzyl alcohol (1 mmol, 0.143 g) and 3,4-dihydro-2*H*-pyran (DHP, 1.5 mmol, 0.126 g) under solvent-free conditions at room temperature. The reaction mixture was stirred until TLC showed the completion of the reaction (5 min).

4-Chlorobenzyl tetrahydro-2*H*-pyran-2-yl ether was obtained after short column chromatography of crude mixture on silica gel 60 using petroleum ether-ethyl acetate (40:1) as eluent in 96% yield (0.218 g).

^{1}HNMR ($CDCl_3$, 400 MHz): δ= 1.50-1.68 (m, 4H), 1.70-1.77 (m, 1H), 1.82-1.87 (m, 1H), 3.51-3.57 (m, 1H), 3.86-3.92 (m, 1H), 4.44-4.47 (d, 1H, *J*= 12 Hz), 4.68-4.70 (t, 1H, *J*= 3.6 Hz), 4.72-4.75 (d, 1H, *J*= 12 Hz), 7.29 (br s, 4H) ppm. ^{13}CNMR ($CDCl_3$, 100 MHz): δ= 19.31, 25.44, 30.51, 62.09, 67.99, 97.77, 128.45, 129.06, 133.18, 136.87 ppm; IR (KBr): $\bar{\nu}$ = 3048 (w), 2944 (s), 2871 (s), 1600 (w), 1492 (s), 1122 (s), 1035 (s), 906 (m), 870 (m), 811 (s) cm^{-1}.

3. Results and Discussion

First we selected 4-chlorobenzyl alcohol as a model and optimized reaction conditions for its solvent-free conversion to 4-chlorobenzyl tetrahydro-2*H*-pyran-2-yl ether using a catalytic amount of *N*-chlorosaccharin and DHP at room temperature. The results of this study are shown in Table 1.

As shown in this table, this transformation was completely unsuccessful in the absence of *N*-chlorosaccharin even using two equivalents of DHP after 2 h (Table 1, entry 1). Surprisingly, this reaction was successfully carried out in the presence of merely 1 mol% of *N*-chlorosaccharin so that the desired product was produced in quantitative yield after only 4 min (Table 1, entry 2).

However, decreasing of the amount of the catalyst caused an increase in the reaction time and decrease of the yield of the desired product (Table 1, entries 3 and 4). In addition, decreasing the DHP to 1.5 equivalent, though slightly caused an increase in the time of this reaction, did not change the yield of the desired product. This condition was selected as the optimized conditions for this transformation (Table 1, entry 5). However, the rate and the yield of this reaction were decreased with additional decreasing of the amount of DHP to 1.2 and 1 equivalent (Table 1, entries 6 and 7 respectively). Finally, we observed that application of *N*-bromosaccharin [19] as a catalyst instead of *N*-chlorosaccharin caused a decrease in both the rate and the yield of this reaction (Table 1, entry 8). Then, the determined optimized reaction conditions (Table 1, entry 5) was used for the conversion of other alcohols and also phenols to their corresponding THP ethers. The results are shown in Table 2.

Table 1. Solvent-free conversion of 4-chlorobenzyl alcohol to 4-chlorobenzyl tetrahydro-2*H*-pyran-2-yl ether using a catalytic amount of *N*-chlorosaccharin and DHP at room temperature under various conditions.

Entry	Molar ratio of (alc.:cat.:DHP)	Time (min)	Yield (%)
1	1:0:2	120	0
2	1:0.01:2	4	100
3	1:0.005:2	15	95
4	1:0.0025:2	60	90
5	1:0.01:1.5	5	100
6	1:0.01:1.2	15	90
7	1:0.01:1	45	80
8	1:0.01:1.5	30	60[a]

[a]In this case, *N*-bromosaccharin [19] was used as a catalyst instead of *N*-chlorosaccharin.

Table 2. Conversion of alcohols and phenols to THP ethers using DHP and *N*-chlorosaccharin as a catalyst under solvent-free condition at room temperature.

Entry	Alcohol	THP ether	Time (min)	Yield (%)[a]
1	$C_6H_5CH_2OH$	$C_6H_5CH_2OTHP$	3	97
2	*p*-Cl-$C_6H_4CH_2OH$	*P*-Cl-$C_6H_4CH_2OTHP$	5	96
3	*o*-Cl-$C_6H_4CH_2OH$	*o*-Cl-$C_6H_4CH_2OTHP$	5	94
4	*p*-O_2N-$C_6H_4CH_2OH$	*p*-O_2N-$C_6H_4CH_2OTHP$	6	98
5	*m*-O_2N-$C_6H_4CH_2OH$	*m*-O_2N-$C_6H_4CH_2OTHP$	5	96
6	*p*-CH_3O-$C_6H_4CH_2OH$	*p*-CH_3O-$C_6H_4CH_2OTHP$	10	96
7	*o*-Br-$C_6H_4CH_2OH$	*o*-Br-$C_6H_4CH_2OTHP$	8	93
8	$C_6H_5CH(OH)CH_3$	$C_6H_5CH(OTHP)CH_3$	8	95
9	$C_6H_5CH=CHCH_2OH$	$C_6H_5CH=CHCH_2OTHP$	5	98
10	$C_6H_5(CH_2)_2OH$	$C_6H_5(CH_2)_2OTHP$	30	88
11	$C_6H_5(CH_2)_3OH$	$C_6H_5(CH_2)_3OTHP$	35	90
12	$PhCH_2CH(OH)CH_3$	$PhCH_2CH(OTHP)CH_3$	30	84
13	$(CH_3)_3COH$	$(CH_3)_3COTHP$	30	89[b]
14	Cholesterol	Cholesterol THP ether	15	90[c,d]
15	Cyclohexanol	Cyclohexyl-OTHP	30	91
16	C_6H_5OH	C_6H_5OTHP	3	98
17	*p*-Cl-C_6H_4OH	*p*-Cl-C_6H_4OTHP	3	94[e]
18	*m*-CH_3-C_6H_4OH	*m*-CH_3-C_6H_4OTHP	3	97[f]
19	*p*-Br-C_6H_4OH	*p*-Br-C_6H_4OTHP	3	96[g]
20	*p*-CH_3O-C_6H_4OH	*p*-CH_3O-C_6H_4OTHP	5	92
21	α-Naphthol	α- Naphthyl THP ether	5	98
22	β-Naphthol	β- Naphthyl THP ether	5	95

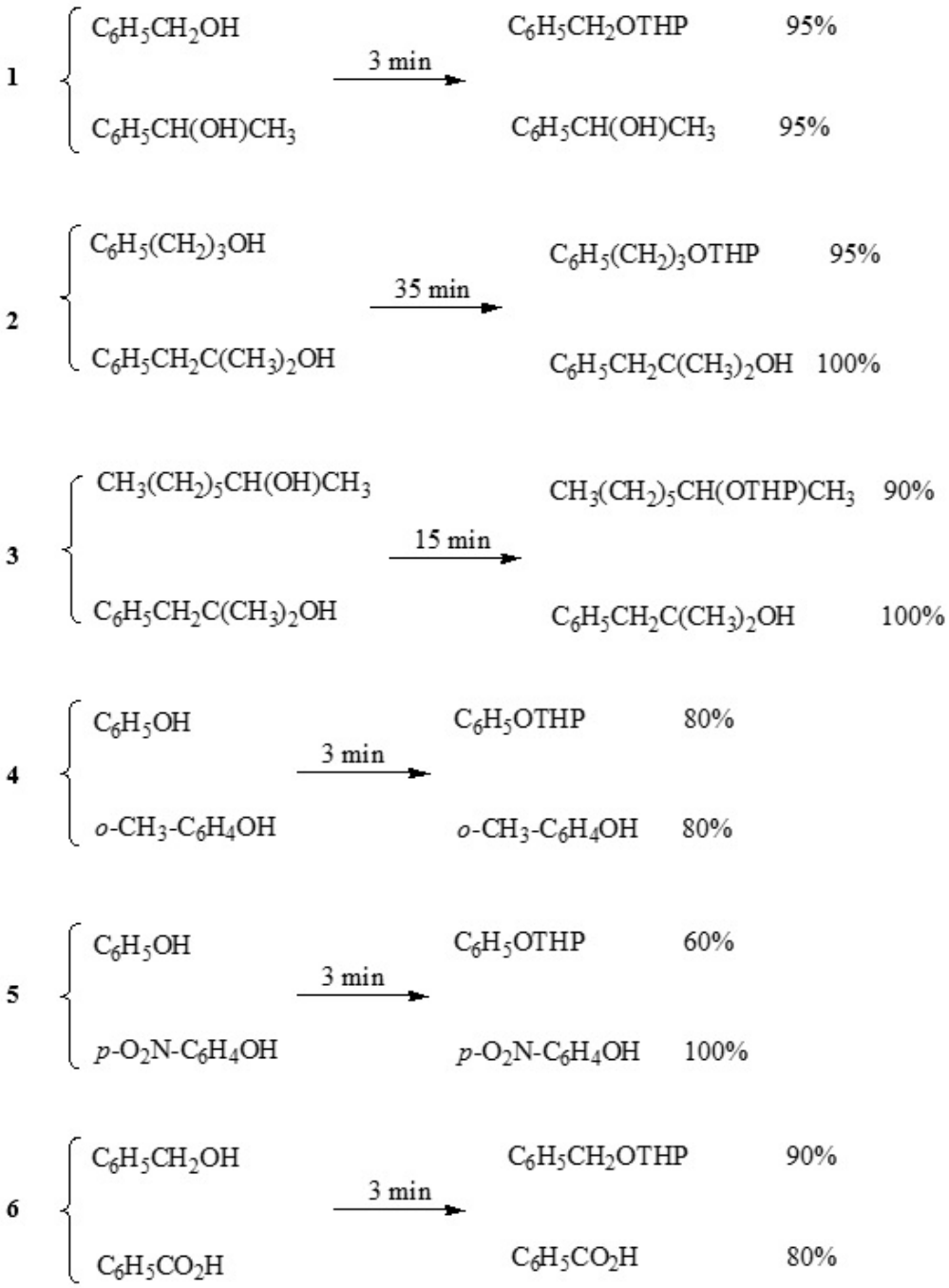
[a]Isolated yield.
[b]In this case, *N*-chlorosaccharin was used in 2 mol% as catalyst.
[c]In this case, *N*-chlorosaccharin was used in 2 mol% as catalyst in CH_2Cl_2 (0.5 mL for 1 mmol of alcohol).
[d]m.p.= 144-146°C (lit. [20] m.p.= 144-146°C).
[e]m.p.= 48-50°C (lit. [21] m.p.= 48-49°C).
[f]m.p.= 36-38°C (lit. [13] m.p.= 35-37°C).
[g]m.p.= 57-59°C (lit. [13] m.p.= 57-58°C).

As shown in this Table, benzylic alcohols containing electron withdrawing or donating groups in various positions of phenyl ring, cinamyl alcohol, primary, secondary, tertiary as well as cyclic alcohols are converted to their corresponding THP ethers in short reaction times and in excellent yields *via* the present method (Table 2, entries 1-15).

Also, phenols containing electron withdrawing or donating groups as well as naphthols are *rapidly* tetrahydropyranylated in excellent yields using the present method (Table 2, entries 16-22). In addition, as shown in this Table, it seems that the reactivity of benzylic and allylic alcohols as well as phenols and naphthols is more than the other types of alcohols mentioned in this table in the present method.

However, application of the present procedure on the tetrahydropyranylation of 2-methylphenol and 4-nitrophenol was unsuccessful so that in these cases the related products were formed in only 15 and 5% yield respectively due to steric hindrance of methyl and high electron withdrawing effect of nitro group respectively on phenolic OH.

In addition, for obtaining deeper insight into the applicability, selectivity, and limitations of the present method, we examined the possibility of the tetrahydropyranylation of different types of alcohols and phenols in binary mixtures. For this purpose, a binary mixture of two different types of alcohols or phenols (1:1) was treated with *N*-chlorosaccharin (1 mol %) and DHP (1.5 equiv.) at room temperature under solvent-free conditions. The conversion yields obtained for these selective reactions of different binary mixtures are shown in Scheme 2. Although simple primary and secondary aliphatic alcohols are not distinguishable by the present method but as shown in the Scheme 2, primary benzylic alcohols in the presence of secondary ones and also primary or secondary aliphatic alcohols in the presence of tertiary ones can be efficiently converted to their corresponding THP ethers with excellent selectivity *via*



Scheme 2. Various selectivities in the tetrahydropyranylation of alcohols using DHP (1.5 eq.) and *N*-chlorosaccharin (1 mol %) as a catalyst at room temperature under solvent-free conditions.

this method (Scheme 2, entries 1-3). Also, unsubstituted phenol can be tetrahydropyranylated in the presence of ortho substituted phenols or phenols containing a powerful electron withdrawing group with good to excellent selectivity using the present method (Scheme 2, entries 4-5). Finally, this method distinguishes between alcohols and carboxylic acids so that alcohols are selected for tetrahydropyranylation reaction (Scheme 2, entry 6).

4. Conclusion

In conclusion, the present investigation has demonstrated that the use of *N*-chlorosaccharin as a catalyst and DHP offers a simple, novel and efficient method for the conversion of different types of alcohols and phenols to their corresponding THP ethers.

It must be noted that many previous reported methods suffer from some disadvantages such as long reaction times [3,5,13,15,16], the use of unavailable catalysts [7,10,12,13,16], unsuitability for protection of phenols or tertiary alcohols [6,8,13,14], operation in a volatile solvent [3,8,12,13,15] or under heating [7] and high catalysts to substrate ratio [2,3,7,9,15] and also do not provide selectivity or at least, selectivity of the method is ambiguous. But, the present method shows excellent selectivity between different types of alcohols and phenols and does not contain the above-mentioned disadvantages.

Finally, excellent yields, easy work up, operation in mild and solvent-free conditions and at room temperature, the use of DHP in a low molar ratio, very low catalyst to substrate ratio, availability and ease of handling of the catalyst, and short reaction times can be considered as other advantages of this method in comparison with some previous reported methods.

Acknowledgments

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