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Tetrahydropyranylation of Alcohols and Phenols Using the Synergistic Catalyst System, Copper(II) Chloride-Acetic Acid

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Summary. Copper(II) chloride-acetic acid was found to be an efficient synergistic catalytic system for the tetraphydropyranylation of various alcohols and phenols in high yields at room temperature in short reaction times.

Keywords. Tetrahydropyranylation; Alcohols and phenols; Synergistic catalysis; Copper chloride; Acetic acid.

Introduction

Protection and deprotection of functional groups is an important step in synthesizing biologically active natural products. Among these functional groups, hydroxyl is very familiar and its protection as tetrahydropyranyl (*THP*) ether is frequently used in organic synthesis. *THP* ethers are inexpensive and stable under a variety of reaction conditions such as strongly basic media, *Grignard* reagents, acylating agents, alkyllithiums, and metal hydrides [1]. Several reagents have been developed as catalysts for the formation of *THP* ethers from alcohols and 3,4-dihydro-2*H*-pyran (*DHP*). These include *p*-*Ts*OH [2], $Fe(ClO_4)_3$ [3], $La(NO_3)_3 \cdot 6H_2O$ [4], $MgBr_2$ [5], $CuSO_4 \cdot 5H_2O$ [6], $AlCl_3 \cdot 6H_2O$ [7], VCl_3 [8], $CaCl_2$ [9], $Al(HSO_4)_3$ [10], $LiBF_4$ [11], In(O*Tf*)$_3$ [12], Nafion-H [13], SO_4^{2-}/ZrO_2 [14], heteropolyacids [15], and lithium perchlorate-diethyl ether [16]. However, these procedures have several drawbacks including long reaction time, elevated temperature, harmful organic solvents, moisture sensitive catalysts, and the formation of polymeric byproducts of *DHP* and isomerization. Thus, there is a need for a greener, efficient method that might work under mild and cheaper conditions.

As a part of our ongoing research to develop new synergistic catalytic methodology [17], we perceived that $CuCl_2 \cdot 2H_2O$–HO*Ac*, thus readily available reagents, might be a useful catalyst system for tetrahydropyranylation in solvent-free media. In this paper, an improved synthesis of the *THP* ethers catalysed by this $CuCl_2 \cdot 2H_2O$–HO*Ac* combination catalyst system at room temperature in high yields is reported.

Results and Discussion

A model tetrahydropyranylation of *n*-butyl alcohol (30 mmol) with *DHP* (36 mmol) was performed at room temperature, no reaction occurred after 1 day (Table 1). After 0.6 mmol $CuCl_2 \cdot 2H_2O$ were added, the reaction progressed sluggishly for 10 h. However, addition of small amount of acetic acid at the start greatly enhanced the efficiency of $CuCl_2 \cdot 2H_2O$. The yield was greatly improved when the amount of HO*Ac* was increased. Benzyl alcohol reached 90% completion only after 0.5 h using 0.6 mmol $CuCl_2 \cdot 2H_2O$ and 24 mmol HO*Ac* as catalysts, while much lower yields were obtained in the presence of $CuCl_2 \cdot 2H_2O$ or HO*Ac* only. These results indicate

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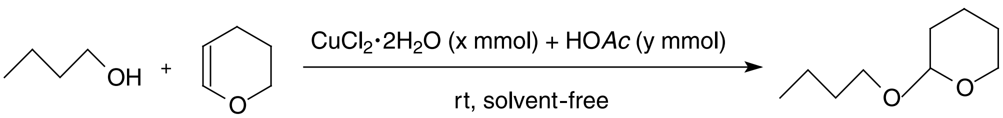
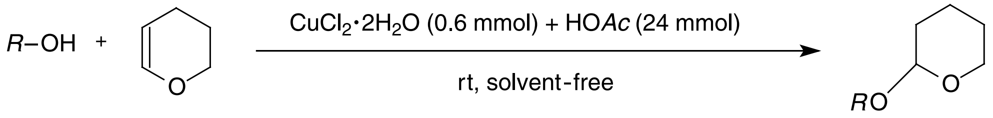
Table 1. Effect of the amounts of $CuCl_2 \cdot 2H_2O$ and HO*Ac*



Entry	$CuCl_2 \cdot 2H_2O$/x mmol	HO*Ac*/y mmol	Time/h	Yield/%[a]
1	0	0	24	0
2	0.6	0	10	47
3	0.6	3	3	52
4	0.6	6	3	70
5	0.6	12	3	84
6	0.6	24	0.5	90
7	0	24	10	5

[a] Isolated yields

Table 2. Protection of various alcohols and phenols giving the corresponding *THP* ethers using a catalytic amount of $CuCl_2 \cdot 2H_2O$ and HO*Ac*



Entry	Alcohol	Time/h	Product	Yield/%[a]	Refs.[b]
1	$PhCH_2OH$	1	$PhCH_2OTHP$	86	[18, 19]
2	$PhCH_2CH_2OH$	1.5	$PhCH_2CH_2OTHP$	92	[18, 19]
3	$PhCH(CH_3)OH$	2.0	$PhCH(CH_3)OTHP$	91	[18, 19]
4	$n\text{-}C_3H_7OH$	0.5	$n\text{-}C_3H_7OTHP$	93	[18, 19]
5	$i\text{-}C_3H_7OH$	0.15	$i\text{-}C_3H_7OTHP$	92	[18, 19]
6	$n\text{-}C_4H_9OH$	0.5	$n\text{-}C_4H_9OTHP$	90	[18, 19]
7	$i\text{-}C_4H_9OH$	3	$i\text{-}C_4H_9OTHP$	90	[18, 19]
8	$s\text{-}C_4H_9OH$	7	$s\text{-}C_4H_9OTHP$	90	[18, 19]
9	$t\text{-}C_4H_9OH$	2	$t\text{-}C_4H_9OTHP$	62	[18, 19]
10	$(CH_3)_2CHCH_2CH_2OH$	2.5	$(CH_3)_2CHCH_2CH_2OTHP$	90	[18, 19]
11	$CH_3(CH_2)_3CH(C_2H_5)CH_2OH$	4	$CH_3(CH_2)_3CH(C_2H_5)CH_2OTHP$	84	[18, 19]
12	$n\text{-}C_8H_{17}OH$	1.0	$n\text{-}C_8H_{17}OTHP$	77	[18, 19]
13	$n\text{-}C_{12}H_{25}OH$	6	$n\text{-}C_{12}H_{25}OTHP$	75	[18, 19]
14	$c\text{-}C_6H_{11}OH$	3	$c\text{-}C_6H_{11}OTHP$	92	[18, 19]
15	$n\text{-}BuOCH_2CH_2OH$	3.5	$n\text{-}BuOCH_2CH_2OTHP$	81	–
16	Furfuryl alcohol	1.5	Furfuryl alcohol*THP*	88	[18, 19]
17	$CH_2{=}CHCH_2OH$	2	$CH_2{=}CHCH_2OTHP$	83	[18, 19]
18	$PhCH{=}CHCH_2OH$	3	$PhCH{=}CHCH_2OTHP$	87	[18, 19]
19	$PhOH$	0.15	$PhOTHP$	93	[18, 19]
20	$4\text{-}CH_3C_6H_4OH$	0.15	$4\text{-}CH_3C_6H_4OTHP$	94	[18, 19]
21	$4\text{-}CH_3OC_6H_4OH$	0.2	$4\text{-}CH_3OC_6H_4OTHP$	91	[18, 19]
22	$4\text{-}ClC_6H_4OH$	0.15	$4\text{-}ClC_6H_4OTHP$	95	[18, 19]
23	$4\text{-}O_2NC_6H_4OH$	0.1	$4\text{-}O_2NC_6H_4OTHP$	92	[18, 19]
24	2-Naphthol	0.1	2-Naphthol*THP*	90	[18, 19]
25	Ph_2CHOH	0.5	$Ph_2CHOTHP$	84	–

[a] Isolated yields, the purity, and the identity of the products were determined by ^{1}H NMR and GC; [b] reference for spectroscopic data of products

that incorporation of $CuCl_2 \cdot 2H_2O$ and HO*Ac* as a catalyst system was a key to the development of the new process: both $CuCl_2 \cdot 2H_2O$ and HO*Ac* are indispensable for the rate acceleration of the reaction.

Besides, we screened several other copper salts, such as $CuSO_4 \cdot 5H_2O$, $Cu(OAc)_2 \cdot H_2O$, and $Cu(acac)_2$ using *n*-butyl alcohol and *DHP* as substrates. As we expected, all of them showed no catalytic activities even if they were used with HO*Ac*. All the yields were less than 30% after 6 h. The system of $CuCl_2 \cdot 2H_2O$–HO*Ac* provides the highest yield under the same conditions.

Results obtained from several representative substrates under the same conditions are summarized in Table 2. The tetrahydropyranylation of various alcohols and phenols with *DHP* was performed in the presence of catalytic amounts of $CuCl_2 \cdot 2H_2O$–HO*Ac* at room temperature. Not only do these improvements allow a reduction of $CuCl_2 \cdot 2H_2O$ loading to just 2 mol% but total conversion is achieved in shorter reaction time (0.1–7 h). In all cases, the reactions proceeded very cleanly (checked by GC) and no side reaction products were observed. Good to excellent yields of *THP* products were obtained for a broad selection of aliphatic, aromatic, and α,β-unsaturated alcohols. Primary, secondary, and tertiary alcohols were protected without forming any other side products. Tertiary alcohol gave poor yield under the same condition (Entry 9). Both short and long chain aliphatic alcohols gave good yields. In comparison to the conventional catalysts, the new system tolerates acid sensitive functional groups, such as furyl (Entry 16), allyl (Entry 17), and cinnamyl (Entry 18). Phenol groups were also protected in shorter reaction times whether the benzene ring was substituted with electron withdrawing or donating substituents (Entries 19–24). All the results suggest that the copper cation and proton cooperatively act as a combined catalyst in the step of the nucleophilic addition of alkoxy to *DHP*.

In conclusion, a new catalytic system employing readily available and greener $CuCl_2 \cdot 2H_2O$–HO*Ac* provides a simple and mild way for protection of hydroxyl groups. This catalyst system is quite effective for both alcohols and phenols. While work is in progress to study detailed reaction mechanism of this new catalytic system, the simplicity and availability of the catalyst system should encourage the use of this catalytic system in synthetic organic chemistry.

Experimental

Melting points were determined using RY-1 micromelting point apparatus. GC analysis was carried out on a Perkin Elmer Auto System XL Gas Chromatograph. Infrared spectra were recorded on Spectrum GX series *Fourier* Transform instrument of Perkin Elmer. ^1H NMR spectra were recorded on Bruker ARX-300 spectrometer in $CDCl_3$ using *TMS* as an internal standard. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin-Elmer) and agreed favorably with the calculated values.

General Procedure for Tetrahydropyranylation

A mixture of 30 mmol alcohol or phenol, 36 mmol *DHP*, 0.6 mmol $CuCl_2 \cdot 2H_2O$, and 24 mmol HO*Ac* were magnetic stirred at ambient temperature for an appropriate time (monitored by GC). After reaction, the organic layer was washed twice with 20 cm^3 saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to yield the almost pure product. The product was purified further by column chromatography on silica gel (ethyl acetate/*n*-hexane, 1/9, as the eluent). All the *THP* ethers were characterized by IR, ^1H NMR, and elemental analysis.

2-(n-Butoxyethyl) tetrahydropyranyl ether (**15**, $C_{11}H_{22}O_3$)
Colorless oil, IR (KBr): $\bar{\nu} = 1517, 1452, 1360, 1209, 1173, 1063, 1026, 991, 817, 740\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.69$ (t, $J = 3.1$ Hz, 1H), 3.73–3.89 (m, 2H), 3.44–3.59 (m, 6H), 1.83–1.96 (m, 1H), 1.50–1.72 (m, 7H), 1.31–1.44 (m, 2H), 0.89 (t, $J = 7.0$ Hz, 3H) ppm.

2-Diphenylmethyl tetrahydropyranyl ether (**25**, $C_{18}H_{20}O_2$)
White solid, mp 50–52°C; IR (KBr): $\bar{\nu} = 2941, 2903, 2877, 1491, 1201, 1121, 1024, 976, 914\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$–7.35 (m, 10H), 5.78–5.91 (s, 1H), 4.65–4.83 (t, $J = 2.9$ Hz, 1H), 3.84–3.90 (m, 1H), 3.47–3.53 (m, 1H), 1.51–1.98 (m, 6H) ppm.

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