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ORIGINAL PAPER

Copper nitrate/acetic acid as an efficient synergistic catalytic system for the chemoselective tetrahydropyranylation of alcohols and phenols

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Abstract Tetrahydropyranylation of alcohols and phenols was accomplished successfully using copper nitrate and acetic acid as a synergistic catalyst at room temperature under solvent-free condition. Compared with other synergistic catalytic systems, copper nitrate/acetic acid proved to be the most efficient. Both alcohols (primary, secondary, tertiary, benzylic, cyclic, allyl, cinnamyl, and furyl) and phenols reacted smoothly in high yields.

Keywords Tetrahydropyranylation · Alcohol · Phenol · Synergistic catalysis · Chemoselectivity

Introduction

Protection of alcohols and phenols in organic synthesis has been paid much attention [1]. In particular, protection as tetrahydropyranyl (THP) ether draws more attention due to its stability towards a variety of reaction conditions such as strongly basic media, Grignard reagents, acylating agents, alkyllithiums, and metal hydrides [2]. THP ethers can be synthesized from a variety of hydroxy-containing compounds by acid-catalyzed reaction with 3,4-dihydro-2H-pyran (DHP). Many catalysts, including H_2NSO_3H [3], *p*-TsOH [4], polyaniline salt [5], $PdCl_2(CH_3CN)_2$ [6], LiOTf [7], $Fe(ClO_4)_3$ [8], Bu_4NBr_3 [9], $VO(OAc)_2$ [10], CAN [11], $Fe(HSO_4)_3$ [12], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [13], $Bi(NO_3)_3{\cdot}5H_2O$ [14], Zeolite H-beta [15], and $Al(HSO_4)_3$ [16] have been reported. However, these procedures have several drawbacks, such as elevated temperature, long reaction time, inert atmosphere, harmful organic solvent, and expensive catalysts. Therefore, an efficient and practical method for the tetrahydropyranylation of alcohols and phenols under mild and economical reaction conditions is desired.

During our endeavours to explore the utility of “Brønsted assisted Lewis acid catalysis,” we earlier reported that the combinations of $Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$/HOAc and $CuCl_2{\cdot}2H_2O$/HOAc are efficient and mild catalysts for the tetrahydropyranylation [17, 18]. In further extension to our work, we discovered that $Cu(NO_3)_2{\cdot}3H_2O$/HOAc acts as a synergistic catalytic system was more efficient than the reports. In this paper, the details of the tetrahydropyranylation of alcohols and phenols in the presence of catalytic amounts of $Cu(NO_3)_2{\cdot}3H_2O$ and HOAc are presented (Scheme 1).

Results and discussion

The catalytic activity of several commonly used Lewis copper salts (CuX) and CuX/HOAc was examined in a model reaction of isopropyl alcohol (30 mmol) and DHP (36 mmol) at room temperature; the results are shown in Table 1. As can be seen from Table 1, CuX or HOAc used separately is poorly active, and the catalytic activity of CuX/HOAc is higher than that of CuX used alone. After several trials, we found a powerful synergistic effect when HOAc is mixed with $Cu(NO_3)_2{\cdot}3H_2O$, which gave 94%

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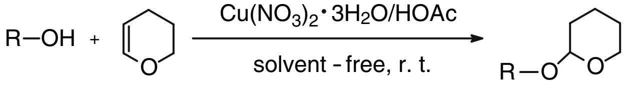

Scheme 1

Table 1 Screening of catalysts for the tetrahydropyranylation of isopropyl alcohol

CuX	Time (h)	Yield (%)[a]	
		CuX	CuX/HOAc[b]
None	10	–	3[c]
$CuSO_4·5H_2O$	7	1	13
$Cu(OAc)_2·H_2O$	8	0	3
$Cu(acac)_2$	7	0	2
$Cu(CH_3SO_3)_2·4H_2O$	5	9	87
$Cu(p\text{-}CH_3C_6H_4SO_3)_2·6H_2O$	0.5	2	72
$Cu(o\text{-}CH_3C_6H_4SO_3)_2·4H_2O$	0.5	3	75
$CuCl_2·2H_2O$	0.5	1	91
$Cu(NO_3)_2·3H_2O$	0.5	1	94

[a] Isolated yield

[b] 0.6 mmol CuX, 12 mmol HOAc

[c] Only 12 mmol HOAc was used

yield of the product within 0.5 h. The yields improved greatly when the amount of HOAc was increased, while a decrease of the amount of $Cu(NO_3)_2·3H_2O$ would retard the reaction. All the results stated above suggest that the copper cation and proton cooperatively act as a synergistic catalyst in the step of the nucleophilic addition of alkoxy to DHP.

Under the conditions of alcohol/phenol (30 mmol) and DHP (36 mmol), we then examined other substrates using 0.6 mmol $Cu(NO_3)_2·3H_2O$ and 12 mmol HOAc as catalysts to give corresponding THP ether at room temperature (Table 2). As evident from Table 2, all the reaction proceeded smoothly and efficiently. No polymeric by-product of DHP was observed, and the THP ether was isolated as the only product. It is worth mentioning that our procedure is more efficient than some of the recently reported procedures in terms of reaction times and yields. Most protections were completed within 0.1–1 h in almost quantitative yields. A wide range of hydroxy compounds, such as primary, secondary, tertiary alcohols, benzyl alcohol (entry 16), cyclic saturated alcohol (entry 18), allyl alcohol (entry 19), cinnamyl alcohol (entry 20), furyl alcohol (entry 21), and phenols (entries 22–28), could be protected by using the new synergistic catalytic system. In the case of tertiary alcohols (entry 7), no dehydration products were observed (as determined by GC). For linear chain aliphatic alcohols, the protection of short-chain alcohols proceeds faster than in case of the long-chain ones.

Table 2 Tetrahydropyranylation of alcohols and phenols catalyzed by $Cu(NO_3)_2·3H_2O$/HOAc

Entry	Alcohol/phenol	Time (h)	Yield (%)[a]	References[b]
1	CH_3OH	0.16	94	[19]
2	C_2H_5OH	0.3	97	[19]
3	$n\text{-}C_3H_7OH$	0.4	96	[19]
4	$i\text{-}C_3H_7OH$	0.5	92	[20]
5	$n\text{-}C_4H_9OH$	0.35	94	[19]
6	$s\text{-}C_4H_9OH$	1.5	90	[20]
7	$t\text{-}C_4H_9OH$	1.5	85	[21, 22]
8	$i\text{-}C_4H_9OH$	0.4	96	[20]
9	$n\text{-}C_5H_{11}OH$	0.5	93	[22]
10	$(CH_3)_2CHCH_2CH_2OH$	0.8	94	[20]
11	$n\text{-}C_7H_{15}OH$	1	96	[23]
12	$n\text{-}C_8H_{17}OH$	1	93	[20]
13	$i\text{-}C_8H_{17}OH$	1	92	[20]
14	$n\text{-}C_{12}H_{25}OH$	1.7	92	[20]
15	$n\text{-}C_{16}H_{33}OH$	5	90	[24]
16	$PhCH_2OH$	0.1	93	[19, 20]
17	$PhCH_2CH_2OH$	0.1	94	[14]
18	$c\text{-}C_6H_{11}OH$	0.7	96	[20]
19	$CH_2{=}CHCH_2OH$	0.8	91	[20]
20	$PhCH{=}CHCH_2OH$	1	89	[22]
21	Furfuryl alcohol	0.6	95	[19, 20]
22	PhOH	0.1	85	[19, 20]
23	$4\text{-}CH_3C_6H_4OH$	0.5	86	[22, 25]
24	$4\text{-}ClC_6H_4OH$	0.1	94	[25]
25	$4\text{-}BrC_6H_4OH$	0.1	95	[26]
26	$4\text{-}NO_2C_6H_4OH$	0.1	92	[20, 25]
27	1-Nathphol	5	44	[22]
28	2-Nathphol	5	62	[14]
29	$PhCH_2OH + PhOH$	0.2	99	–

[a] Isolated yield, the purity and the identity of the products were determined by GC, IR, ^1H NMR, and elemental analysis

[b] Reference for spectroscopic data of products

We were then interested in whether the same catalytic system could be employed for the tetrahydropyranylation of phenolic compounds. By following identical reaction conditions, various phenols except bulky phenols (entries 27 and 28) were converted into the corresponding THP ethers quickly in high yields (entries 22–26). Reactions of 1-nathphol and 2-nathphol were slow, and long reaction time was required. In addition to these results, we also investigated the selectivity in protection of this process using equimolar benzoic alcohol and phenol (entry 29). The results show that alcohol can be protected selectively and efficiently while the phenol remained unaffected.

In conclusion, tetrahydropyranylation of alcohols and phenols has been carried out successfully using the new synergistic catalyst system, $Cu(NO_3)_2·3H_2O$ and HOAc.

The significant advantages of this methodology are high yields, short reaction time, cheap and readily available catalysts, and mild reaction conditions. The most important is that the amount of HOAc of the new catalytic system was decreased to one half of the reported [17, 18]. This improvement can avoid environmental pollution especially in large-scale industrial processes. It can be predicted that this method will find useful application for tetrahydropyranylation in modern synthetic 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 PerkinElmer. ^{1}H 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 (PerkinElmer) and agreed favorably with the calculated values.

General procedure for the tetrahydropyranylation

To a mixture of 30 mmol alcohol or phenol and 3.028 g DHP (36 mmol) was added 0.145 g $Cu(NO_3)_2 \cdot 3H_2O$ (0.6 mmol) and 0.721 g HOAc (12 mmol) at room temperature. The mixture was stirred until completion of the reaction (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). Then the pure products were identified by comparing their m.p./b.p., IR, ^{1}H NMR, and elemental analysis with those reported for the authentic samples.

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