

Copper *p*-toluenesulfonate/acetic acid: a recyclable synergistic catalytic system for the tetrahydropyranylation of alcohols and phenols

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Abstract Copper *p*-toluenesulfonate/acetic acid was found to be an efficient, chemoselective synergistic catalytic system, with catalyst loading as low as 0.3 mol% leading to clean, high-yielding tetrahydropyranylation of a variety of alcohols and phenols. By simple phase-separation, copper *p*-toluenesulfonate can be easily recovered and reused for several times without deterioration in catalytic activity.

Keywords Tetrahydropyranylation; Alcohols and phenols; Synergistic catalysis; Chemoselectivity; Reusability.

Introduction

Protection and deprotection strategy in organic synthesis is inevitable, owing to chemoselective transformations in the presence of various functional groups. Tetrahydropyran is an attractive protecting group that is often used for protection of alcohol moieties due to its stability and compatibility under various reaction conditions and reagents, such as metal hydrides, alkylolithiums, *Grignard* reagents, and catalytic hydrogenation [1]. There are several known catalysts for the tetrahydropyranylation of alcohols, the most commonly used are Li(OTf) [2], MgBr₂ [3], LiBF₄ [4], VO(OAc)₂ [5], CaCl₂ [6], *Ps*-AlCl₃ [7],

SAC-13 [8], PdCl₂(CH₃CN)₂ [9], Bi(NO₃)₃·5H₂O [10], and In(OTf)₃ [11], *etc.* However, these procedures have several drawbacks including elevated reaction temperature, long reaction times, harmful organic solvents, and expensive reagents. Despite a number of precedents, an efficient and practical method for tetrahydropyranylation is desired.

Over recent years, sulfonate mediated *Lewis* acid catalysis has attracted tremendous interest throughout scientific communities. The low toxicity, ease of handling, recyclable nature, and low cost make sulfonate species attractive alternatives to classical *Lewis* acids, particularly in large-scale industrial processes. During our endeavors to explore the utility of sulfonates, we have reported that the combination of copper methanesulfonate (*CMS*) and acetic acid was an efficient catalyst for diacetylation of aldehydes [12]. In further extension to our work, we discovered that copper *p*-toluenesulfonate (*CPTS*)/HOAc, which acts as synergistic catalytic system can catalyze tetrahydropyranylation efficiently at room temperature under solvent-free condition. It is important to mention that the procedure used only 0.3 mol% *CPTS* but reached the same yields as high as those provided by the procedure with 2 mol% *Lewis* acid catalyst reported recently [13]. After reaction, *CPTS* can be easily recovered by simple phase-separation and can be reused for many times. The details of our studies are presented herein.

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Results and discussion

A series of CuX or CuX/HOAc were used as catalysts in a model reaction of benzoic alcohol (15 mmol) and 3,4-dihydro-2H-pyran (*DHP*, 18 mmol) at room temperature, the results were shown in Table 1. As can be seen from Table 1, only 0.3 mol% CuX or 12 mmol HOAc used separately is poorly active. Some CuX combined with HOAc showed much higher catalytic activity than CuX used alone (entries 6–8). *CPTS*/HOAc showed the best results, which gave 96% yield of product within 0.5 h. A powerful synergistic effect was observed when *CPTS* was mixed with HOAc. Both *CPTS* and HOAc are indispensable for the rate acceleration of the reaction. It is an exothermic reaction and an increase of temperature indicates the reaction happened.

Encouraged by this result, we investigated the optimal conditions for tetrahydropyranylation of benzoic alcohol using *CPTS*/HOAc as catalyst. The amounts of *DHP* and HOAc were investigated in the presence of 15 mmol benzoic alcohol and 0.045 mmol

CPTS for 0.5 h in Table 2. As can be seen from Table 2, excess *DHP* facilitates the reaction (entries 1–3). The optimum molar ratio of *DHP* to benzoic alcohol was found to be 1.2:1. In the presence of 0.045 mmol *CPTS*, the increasing the amount of HOAc greatly increased the yields (entries 3–6). When 12 mmol HOAc was used, 96% yield of product was resulted. We believe what we were observing was a *Brønsted* assisted *Lewis* acid catalysis. In the complex, the copper cation and proton cooperatively act as a combined catalyst in the step of nucleophilic addition of alkoxy to *DHP*. It is impossible to form *p*-toluenesulfonic acid because the pK_a value of HOAc is higher than that of *p*-toluenesulfonic acid. We also determined that the yield of 2-phenylmethyl tetrahydropyranyl ether was only 45% in the presence of 0.045 mmol *p*-toluenesulfonic acid in this study. Similar examples closely relates to our situation were reported by *Deaton et al.* [14], *Aspinall et al.* [15], and *Mouhtady et al.* [16].

Under the optimal condition, a series of alcohols and phenols were subjected to tetrahydropyranylation in the presence of *CPTS*/HOAc at room temperature to give corresponding tetrahydropyranyl ethers in high yields (Table 3). All the reactions proceeded efficiently and smoothly. The procedure works with a variety of primary, secondary, tertiary alcohols, a cyclic saturated alcohol (entry 15), and phenols (entries 18–21). It is noteworthy that in the case of tertiary alcohols (entry 10) no dehydration products were observed (determined by GC). The recycling of *CPTS* was investigated in the model reaction of benzoic alcohol and *DHP* (entry 1). After reaction, the organic phase was extracted by CH_2Cl_2 . *CPTS* could be recovered by filtration and washed with CH_2Cl_2 , then reused for its next run. Compared with the fresh catalyst, no obvious decrease of catalytic activity was detected after four runs. The selectivity in protection of this process was demonstrated using equimolar benzoic alcohol and phenol (entry 22). Smooth conversion of the benzoic alcohol to the corresponding 2-phenylmethyl tetrahydropyranyl ether was observed while the phenol remained unaffected.

In conclusion, we present an efficient catalytic system under which tetrahydropyranylation of alcohols and phenols can be carried out in good to high yields. The *Lewis* acid catalyst can be easily recovered and recycled providing an atom economic procedure. A series of experiments confirmed that the *Brønsted* acid or *Lewis* acid was not simply regen-

Table 1 Tetrahydropyranylation of benzoic alcohol and *DHP* catalyzed by CuX or CuX/HOAc

Entry	CuX	Time/h	Yield/% ^a	
			CuX	CuX/HOAc
1	–	10	–	0 ^b
2	Cu(OAc) ₂ · H ₂ O	1	0	0
3	Cu(acac) ₂	1	0	0
4	CuSO ₄ · 5H ₂ O	0.5	0	0
5	Cu(NO ₃) ₂ · 3H ₂ O	0.6	0	7
6	CuCl ₂ · 2H ₂ O	0.7	6	44
7	CMS	0.5	0	45
8	CPTS	0.5	5	96

^a Isolated yields

^b Only 12 mmol HOAc was used

Table 2 Tetrahydropyranylation of benzoic alcohol and *DHP* under different condition^a

Entry	$n_{\text{benzoic alcohol}}:n_{\text{DHP}}$	$n_{\text{HOAc}}/\text{mmol}$	Yield/% ^b
1	1:1	12	84
2	1:1.1	12	92
3	1:1.2	12	96
4	1:1.2	9	91
5	1:1.2	6	79
6	1:1.2	3	17
7	1:1.2	0	5

^a Benzoic alcohol 15 mmol, *CPTS* 0.045 mmol, 0.5 h

^b Isolated yields

Table 3 Tetrahydropyranylation of alcohols and phenols using a catalytic amount of *CPTS* and *HOAc*

$R-OH + \text{DHP} \xrightarrow[\text{rt, solvent-free}]{\text{CPTS (0.045 mmol) + HOAc (12 mmol)}} R-O\text{-DHP}$				
Entry	Alcohol	Time/h	Yield/% ^a	Refs. ^b
1	<i>Ph</i> CH ₂ OH	0.5	96, 94, 93, 89	[17, 18]
2	<i>Ph</i> CH ₂ CH ₂ OH	1	93	[17, 18]
3	CH ₃ OH	0.5	96	[17, 18]
4	C ₂ H ₅ OH	0.5	92	[17, 18]
5	<i>n</i> -C ₃ H ₇ OH	0.5	91	[17, 18]
6	<i>i</i> -C ₃ H ₇ OH	1.5	94	[17, 18]
7	<i>n</i> -C ₄ H ₉ OH	1	92	[17, 18]
8	<i>i</i> -C ₄ H ₉ OH	3	93	[17, 18]
9	<i>s</i> -C ₄ H ₉ OH	3	85	[17, 18]
10	<i>t</i> -C ₄ H ₉ OH	3	77	[17, 18]
11	(CH ₃) ₂ CHCH ₂ CH ₂ OH	2.5	91	[17, 18]
12	<i>n</i> -C ₈ H ₁₇ OH	4	91	[17, 18]
13	<i>i</i> -C ₈ H ₁₇ OH	3	89	[17, 18]
14	<i>n</i> -C ₁₂ H ₂₅ OH	6	87	[17, 18]
15	<i>c</i> -C ₆ H ₁₁ OH	2	96	[17, 18]
16	CH ₂ =CHCH ₂ OH	2	91	[17, 18]
17	<i>n</i> -BuOCH ₂ CH ₂ OH	5	90	[13]
18	<i>Ph</i> OH	0.5	91	[17, 18]
19	4-CH ₃ C ₆ H ₄ OH	0.5	94	[17, 18]
20	4-CH ₃ OC ₆ H ₄ OH	0.7	93	[17, 18]
21	4-ClC ₆ H ₄ OH	2	76	[17, 18]
22	<i>Ph</i> CH ₂ OH + <i>Ph</i> OH	4	96 + 0	[17, 18]

^a Isolated yields, the purity, and the identity of the products were determined by ¹H NMR and GC^b Reference for spectroscopic data of products

erating the catalyst and that the *Brønsted* acid and *Lewis* acid were acting together as a combined catalyst for the reaction. A number of synthetic applications about synergistic catalysis are currently under study, and further results in this area will be described in due course.

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 CDCl₃ 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 alcohol or phenol 15 mmol, *DHP* 18 mmol, *CPTS* 0.045 mmol, and *HOAc* 12 mmol was stirred at ambient

temperature for an appropriate time (monitored by GC). After reaction, the organic layer was washed twice with 10 cm³ saturated NaHCO₃ solution, dried (Na₂SO₄), 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 tetrahydropyranyl ethers were characterized by IR, ¹H NMR, and elemental analysis.

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