Metal Benzenesulfonates/Acetic Acid Mixtures as Novel Catalytic Systems: Application to the Protection of a Hydroxyl Group

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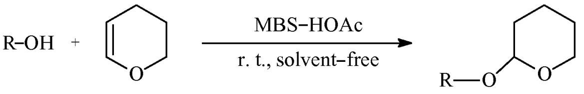
A surprising synergistic effect has been discovered in mixtures of metal benzenesulfonates (Co, Al, Ni, Zn, Cd, Pr, La, Cu, Mn) and acetic acid, leading to active catalytic systems for the tetrahydropyranylation of alcohols and phenols to produce tetrahydropyranyl ethers. All reactions proceed mildly and efficiently with moderate to high yields at room temperature without solvent. After the reaction, the metal benzenesulfonate can be easily recovered and reused many times. The efficiency of these systems might result from the "double activation" by Brønsted and Lewis acid catalysis.

Key words: Tetrahydropyranylation, Metal Benzenesulfonate, Alcohol, Phenol, Protection

Introduction

The protection of a hydroxyl group is a common process in multistep organic synthesis. The tetrahydropyranyl (THP) group is frequently used for the protection of alcohols and phenols due to the remarkable stability of the resulting acetals (THP ethers) under a variety of conditions such as strongly basic media, or the presence of Grignard reagents, acylating agents, lithium alkyls, and metal hydrides [1]. Some of the recently reported reagents that can catalyze tetrahydropyranylation are LiOTf [2], polyaniline salts [3], $PdCl_2(CH_3CN)_2$ [4], $Fe(HSO_4)_3$ [5], $H_{14}[NaP_5W_{30}O_{110}]$ [6], $Bi(NO_3)_3{\cdot}5H_2O$ [7], $NbCl_5$ [8], pyridinium chloride [9], $Ru(acac)_3$ [10], Moβ zeolite [11], activated carbon-supported H_2SO_4 [12], 2,4,6-trichloro-[1,3,5]triazine [13], Dowex 50WX4-100 [14], *etc.* Most of them proved to be efficient for this reaction. However, some of these have several drawbacks such as elevated temperature, long reaction time, harmful organic solvents, and expensive catalysts. In addition, some catalysts have to be prepared prior to use, and/or require by using large amounts of solid support that eventually results in the generation of large amounts of toxic waste, under harsh and acidic conditions. Thus, there is still a demand for the introduction of cheap, green and efficient methods for this transformation.

Recently, the synthesis, characterization, and use of metal sulfonates in organic synthesis have received much attention [15 – 17]. Properties such as low toxicity, moisture tolerance, and reusability make them attractive alternatives to conventional Lewis acids. In addition, a most remarkable characteristic of metal sulfonates is the ability to form superacidic systems by mixing an appropriate metal sulfonate and a Brønsted acid. Such complexation (ideally between an inactive Lewis acid and an inactive organic acid toward a specific reaction) has been used efficiently in many types of electrophilic substitutions. For example, Mouhtady and co-workers combined $Sc(OTf)_3$ with CH_3SO_3H in a 1 : 2 ratio to produce a very active catalyst for the Fries rearrangement [18]. Aspinall *et al.* reported a successful acceleration in a $La(OTf)_3$-$PhCO_2H$-catalyzed allylation reaction [19]. We also reported that $Cu(CH_3SO_3)_2{\cdot}4H_2O$/HOAc can efficiently catalyze the diacetylation of aldehydes and the tetrahydropyranylation of alcohols and phenols [20, 21]. Both Lewis acid and Brønsted acid are indispensable for these conversions. For protecting functional groups, 2 mol-% of $Cu(CH_3SO_3)_2{\cdot}4H_2O$ and 12 mmol of HOAc were used as catalysts. During our further endeavors to explore the utility of metal sulfonates, we found that the combination of a metal benzenesulfonate (MBS) and HOAc, acting as a synergistic catalytic system, can catalyze efficiently the tetrahydropyranylation of alcohols or phenols with 3,4-dihydro-2*H*-pyran (DHP) (Scheme 1). The amount of MBS is only 1 mol-%, and benzenesulfonates are significantly cheaper than methanesulfonates. The new catalytic system enlarges



Scheme 1. Tetrahydropyranylation of alcohol or phenol catalyzed by a metal benzenesulfonate (MBS) and HOAc.

the scope of reactants. After reaction, the MBS can be easily recovered by simple phase-separation and can be reused many times. The details of our studies are presented herein.

Results and Discussion

First, nine MBSs including Co, Al, Ni, Zn, Cd, Pr, La, Cu, and Mn benzenesulfonates were screened for their ability to catalyze the protection of a hydroxyl group using benzyl alcohol as a model hydroxyl compound for 1 h (Table 1). It appeared that all MBSs used alone were inactive or poorly active. However, powerful synergistic effects were observed when the MBS was mixed with HOAc. In the investigation of various catalysts, the combination of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ with HOAc was the most efficient and gave the corresponding THP ether in 98 % yield. The recycling of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ was realized easily. It could be recovered by simple phase-separation because it was slightly soluble in the reaction system. After being washed with acetone and dried at ambient temperature, $Co(C_6H_5SO_3)_2\cdot 6H_2O$ was reused for the next reaction run. It could be recycled four times without significant loss of catalytic activity (entry 1).

Next, the optimization of the amount of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ and HOAc was investigated in a model reaction of benzyl alcohol with DHP (Table 2). The control experiment showed that no product was obtained in the absence of catalyst even after one day (entry 1). $Co(C_6H_5SO_3)_2\cdot 6H_2O$ or HOAc, when applied alone, did not catalyze the conversion either (entries 2 and 8). A surprising synergistic effect occurred when $Co(C_6H_5SO_3)_2\cdot 6H_2O$ was mixed with HOAc. The yields improved greatly when the amount of HOAc increased from 3 mmol to 12 mmol (entries 3–5). When 2 mol-% of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ and 12 mmol of HOAc were used together, a 98 % yield of the product resulted. Moreover, it was found that 1 mol-% of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ was also efficient to drive the transformation (entry 6). However, the reaction proceeded incompletely when the amount of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ was less than 1 mol-% (entry 7). Therefore, the optimal catalyst consists of 1 mol-% of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ and 12 mmol of HOAc.

Table 1. Screening of MBSs for the tetrahydropyranylation of benzyl alcohol.

Entry	MBS	Yield (%)[a]	
		MBS	MBS-HOAc[b]
1	$Co(C_6H_5SO_3)_2\cdot 6H_2O$	0	98, 95, 91, 85[c]
2	$Al(C_6H_5SO_3)_2\cdot 6H_2O$	2	91
3	$Ni(C_6H_5SO_3)_2\cdot 6H_2O$	33	83
4	$Zn(C_6H_5SO_3)_2\cdot 6H_2O$	0	83
5	$Cd(C_6H_5SO_3)_2\cdot 5H_2O$	0	80
6	$Pr(C_6H_5SO_3)_3\cdot 2H_2O$	9	66
7	$La(C_6H_5SO_3)_3\cdot 2H_2O$	5	56
8	$Cu(C_6H_5SO_3)_2\cdot 6H_2O$	7	41
9	$Mn(C_6H_5SO_3)_2\cdot 6H_2O$	0	36

[a] Isolated yield; [b] 2 mol-% of MBS and 12 mmol of HOAc; [c] $Co(C_6H_5SO_3)_2\cdot 6H_2O$ was reused four times.

Table 2. Effect of the amounts of $Co(C_6H_5SO_3)_2\cdot 6H_2O$ and HOAc on the yields.

Entry	$Co(C_6H_5SO_3)_2\cdot 6H_2O$ (mol-%)	HOAc (mmol)	Time (h)	Yield[a] (%)
1	0	0	24	0
2	2	0	1	0
3	2	3	1	31
4	2	6	1	72
5	2	12	1	98
6	1	12	1	97
7	0.5	12	1	84
8	0	12	1	0

[a] Isolated yields.

Table 3. Tetrahydropyranylation of alcohols and phenols catalyzed by $Co(C_6H_5SO_3)_2\cdot 6H_2O$-HOAc.

Entry	Alcohol/phenol	Time (h)	Yield (%)[a]	Refs.[b]
1	$PhCH_2OH$	1	97	[22, 23]
2	$PhCH_2CH_2OH$	5	90	[7]
3	CH_3OH	1.0	97	[22]
4	C_2H_5OH	1.5	97	[22]
5	n-C_3H_7OH	2.0	92	[22]
6	i-C_3H_7OH	2.5	95	[23]
7	n-C_4H_9OH	2.5	93	[22]
8	i-C_4H_9OH	1.5	98	[23]
9	s-C_4H_9OH	5	60	[23]
10	t-C_4H_9OH	9	0	–
11	n-$C_5H_{11}OH$	3.5	91	[24]
12	i-$C_5H_{11}OH$	6	84	[23]
13	n-$C_8H_{17}OH$	4	92	[23]
14	n-$C_{12}H_{25}OH$	6	74	[23]
15	c-$C_6H_{11}OH$	6	24	[23]
16	PhOH	1	85	[22, 23]
17	4-$CH_3C_6H_4OH$	1	95	[24, 25]
18	4-ClC_6H_4OH	2.5	90	[25]
19	4-$NO_2C_6H_4OH$	2	73	[23, 25]
20	2-naphthol	5.5	57	[7]
21	$PhCH_2OH$+PhOH	1	95+0	–

[a] Isolated yield; the purity and the identity of the products were determined by GC, IR, ^1H NMR, and elemental analysis; [b] references for spectroscopic data of products.

From a mechanistic point of view, we can speculate that the observed catalytic effects arise as follows: (i) a pure Lewis acid or Brønsted acid catalysis could be ruled out according to the results in entries 2 and 8; (ii) a ligand exchange between MBS and HOAc, generating acetate and benzene sulfonic acid, is impossible because the pK_a value of benzene sulfonic acid is lower than that of HOAc. Moreover, the peak of benzenesulfonic acid was not detected through GC; (iii) a Brønsted-Lewis acid catalysis resulting in the double activation of reactants. Based on the above results and previous reports, it seems that the real catalyst might be HOAc-assisted $Co(C_6H_5SO_3)_2 \cdot 6H_2O$, which produces a "double activation" of DHP. Then, nucleophilic attack of alcohol to DHP occurs, followed by proton transfer and formation of the final product. A similar example of Brønsted-assisted Lewis acid catalysis was reported by Mouhtady [18] and Aspinall [19] *et al.*

In order to ascertain the scope and limitation of this catalyzed tetrahydropyranylation, the use of the catalytic system was extended to the reaction of various alcohols and phenols (Table 3). Under the optimized experimental conditions, benzylic, primary, isomerical, secondary alcohols as well as phenols undergo tetrahydropyranylation in moderate to excellent yields. In the case of linear-chain aliphatic alcohols, the protection of short-chain alcohols proceeds faster than in case of the long-chain ones. However, the catalyst system appears to show no catalytic activity for the protection of acid-sensitive and sterically hindered alcohols such as *tert*-butyl alcohol (entry 10). In addition, cyclohexanol gave generally very low yields (entry 15).

With the present methodology, tetrahydropyranylation of phenolic hydroxyl groups was also investigated. Phenol was conveniently protected as the corresponding THP ether no matter whether the benzene ring was substituted with electron-donating or -withdrawing substituents (entries 16 – 19). A bulky phenol like 2-naphthol was also smoothly tetrahydropyranylated in moderate yield when reacted with DHP (entry 20). Furthermore, chemoselective protection of an alcohol in the presence of phenol was explored under similar reaction conditions. The results show that an alcohol can be protected selectively and efficiently while the phenol remains unaffected (entry 21).

Conclusion

In conclusion, we have demonstrated that mixing an appropriate MBS with HOAc leads to a strong synergistic effect, which can be employed in a new set of active catalysts for the protection of a hydroxyl group. This method has notable advantages over the existing ones owing to its features of environmental friendliness, low cost, and easy operation. On the other hand, this protocol supplies a good further example of catalytic applications of metal sulfonates towards organic synthesis. The extension of this work to other reactions is currently under investigation in our laboratory.

Experimental Section

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

General procedure for the tetrahydropyranylation of alcohols and phenols

A mixture of alcohol or phenol (15 mmol), DHP (18 mmol, 1.514 g), $Co(C_6H_5SO_3)_2 \cdot 6H_2O$ (0.15 mmol, 0.072 g), and HOAc (12 mmol, 0.721 g) was stirred magnetically at ambient temperature for an appropriate time (monitored by GC). After the reaction, the organic layer was washed twice with saturated $NaHCO_3$ solution (10 mL), dried (Na_2SO_4), and evaporated to yield the almost pure product. The products were purified further by column chromatography on silica gel (ethyl acetate-*n*-hexane 1 : 9 as the eluent). All the THP ethers were characterized by m. p./b. p., IR, ^{1}H NMR, and elemental analysis. The data were compared with literature data and found to be identical with those of authentic samples.

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