

Cobalt Sulfate-Acetic Acid as a Novel Synergistic Catalytic System for Tetrahydropyranylation of Alcohols and Phenols

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Abstract: Cobalt sulfate-acetic acid is found to catalyze the tetrahydropyranylation of alcohols and phenols efficiently at room temperature under solvent-free conditions. It is a synergistic catalytic system, and both cobalt sulphate and acetic acid are indispensable for the rate acceleration of the reaction. Compared with other conventional catalysts, cobalt sulphate-acetic acid proved to be the best. After reaction, cobalt sulphate can be easily recovered by simple phase-separation and re-used for many times without deterioration in catalytic activity. A probable reaction mechanism is proposed.

Key words: Tetrahydropyranylation; alcohol; phenol; cobalt sulphate; acetic acid

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The protection and deprotection strategies in organic synthesis are inevitable, owing to chemoselective transformations in the presence of various functional groups. The protection of 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 THP ethers under a variety of conditions such as strongly basic media, Grignard reagents, acylating agents, alkylolithiums, and metal hydrides^[1]. Some of the recently reported reagents that can catalyze tetrahydropyranylation are LiOTf^[2], polyaniline salt^[3], PdCl₂(CH₃CN)₂^[4], Fe(CIO₄)₃^[5], Bu₄NBr₃^[6], VO(OAc)₂^[7], CAN^[8], Fe(HSO₄)₃^[9], H₁₄[NaP₅W₃₀O₁₁₀]^[10], Bi(NO₃)₃·5H₂O^[11], NbCl₅^[12], Pyridinium chloride^[13], Ru(acac)₃^[14], Moβ^[15], activated carbon supported H₂SO₄^[16], 2, 4, 6-trichloro[1, 3, 5] triazine^[17], Dowex 50WX4-100^[18], and Fe₂(SO₄)₃·xH₂O^[19] etc. Most of these proved to be efficient for this reac-

tion. However, some of them have several drawbacks such as elevated temperature, long reaction time, harmful organic solvent, and expensive catalysts. In addition, some catalysts have to be prepared prior to use, and using large amounts of solid support that eventually results in the generation of large amounts of toxic waste, harsh and acidic conditions. Thus, there is still demand for the introduction of cheap, green and efficient methods for this transformation.

Recently, we reported CoSO₄·7H₂O-catalyzed chemoselective diacetylation of aldehydes^[20]. As part of our ongoing research on protection of functional groups in organic synthesis, we wish to report that CoSO₄·7H₂O is also an effective catalyst for the protection of hydroxyl groups. However, it was found that CoSO₄·7H₂O used alone was not an ideal catalyst for this transformation because the reactions completed after long time. Surprisingly, addition of small amount of acetic acid could enhance the efficiency greatly. Synergistic catalytic system that formed by mixing appropri-

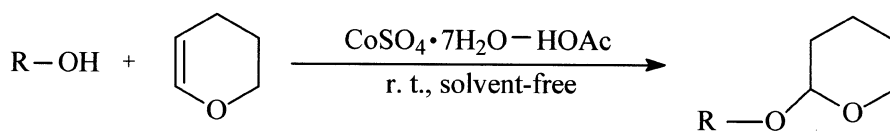
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ate Lewis and Brønsted acids has been used efficiently in many types of electrophilic substitutions. For example, Mouhtady and co-workers combined $\text{Sc}(\text{OTf})_3$ with $\text{CH}_3\text{SO}_3\text{H}$ in a 1: 2 ratio to produce a very active catalyst for the Fries rearrangement^[21]. Aspinall et al. reported a successful acceleration in a $\text{La}(\text{OTf})_3/\text{Ph-CO}_2\text{H}$ catalyzed allylation reaction^[22]. We also repor-

ted some extreme synergies between metal sulfonates or metal chlorides and acetic acid for the tetrahydropyranylation^[23–27]. In this communication, we report for the first time that $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ -HOAc is an excellent synergistic catalytic system for tetrahydropyranylation of alcohols and phenols at room temperature (Scheme 1).



Scheme 1 Tetrahydropyranylation of alcohols and phenols catalyzed by $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ -HOAc

1 Experimental

1.1 Instruments

Melting points were determined using RY-1 micro melting point apparatus. GC analysis was carried out on a PerkinElmer Auto System XL Gas Chromatograph. Infrared spectra were recorded on Spectrum GX series Fourier Transform instrument of PerkinElmer. ^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 (PerkinElmer) and agreed favorably with the calculated values.

1.2 General procedure for tetrahydropyranylation of alcohols and phenols

A mixture of alcohol or phenol (15 mmol), 3,4-dihydro-2H-pyran (DHP, 18 mmol), $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$

(0.3 mmol), and HOAc (12 mmol) was stirred magnetically at ambient temperature for an appropriate time (monitored by GC). After 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 IR, ^1H NMR, and elemental analysis. The data were compared with literature ones and found to be identical with the authentic samples.

2 Results and Discussion

First, our effects focused on achieving the optimum amounts of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ and HOAc using benzyl alcohol as a model hydroxyl compound. The results were summarized in Table 1. From the results obtain-

Table 1 Effect of the amounts of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ and HOAc on the yields^a

Entry	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ (mmol)	HOAc (mmol)	Time (h)	Yield (%)
1	0	0	24	0
2	0	12	1	0
3	0.075	12	1	11
4	0.15	12	1	46
5	0.3	12	1	98
6	0.3	9	1	90
7	0.3	6	1	88
8	0.3	3	1	43
9	0.3	0	1	28

^a Reaction conditions: benzyl alcohol 15 mmol, DHP 18 mmol, rt

ed, we noted that 0.3 mmol $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ and 12 mmol HOAc were the appropriate amounts for the reaction (entry 5). The yields decreased greatly when the amount of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ or HOAc reduced, and HOAc or $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ used separately is inactive or poorly active (entries 2 and 9). These results emerge that the combination of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ with HOAc leads to an extremely synergistic effect, which is very

favorable for the protection of hydroxyl groups. However, no reaction occurred in the absence of catalyst even after one day (entry 1).

In order to choose the best catalyst, several commonly used Lewis acids and Lewis acid-HOAc were screened in a model reaction of benzyl alcohol and DHP at room temperature for 1 h. The results were shown in Table 2. As can be seen from Table 2, Lewis

Table 2 Screening of different catalysts for tetrahydropyranylation of benzyl alcohol^a

Entry	Lewis acid catalyst	Yield (%)	
		Lewis acid	Lewis acid-HOAc ^b
1	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$	37	98, 96, 97, 95, 93, 90 ^c
2	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	2	97
3	$\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$	53	90
4	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	9	86
5	$\text{Co}(\text{CH}_3\text{SO}_3)_2 \cdot 4\text{H}_2\text{O}$	3	66
6	$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$	7	65
7	$\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$	0	12
8	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	0	8
9	$\text{MnSO}_4 \cdot \text{H}_2\text{O}$	0	2
10	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	18	0
11	$\text{Cu}(\text{acac})_2$	0	0
12	$\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	0	0

a. Reaction conditions: benzyl alcohol 15 mmol, DHP 18 mmol, rt

b. Lewis acids 0.3 mmol and HOAc 12 mmol

c. $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ was reused for six times.

acid used alone is poorly active. The yields of most products catalyzed by Lewis acid-HOAc were higher than those catalyzed by Lewis acids. After several trials, $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ -HOAc proved to be the most efficient synergistic catalyst, which give 98% yield of the product. After reaction, $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ can be recovered conveniently by filtration because it was insoluble in the reaction system. Then, $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ was washed with CH_2Cl_2 , and reused for its next run. Before reused, the recovered catalyst was determined by IR, which testified it was $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ exclusively.

The recycled results listed in entry 1 show the successive reused catalyst gave the product with yields almost as high as that on the first run. Even in the sixth round, the recovered catalyst can afford the corresponding product with a yield of 90%. In addition, some important experimental phenomena must be mentioned. One is $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ can not be recovered quantitatively at the end of the reaction for its solubility in the reaction mixture (entry 2). Another is that polymerization of DHP occurred in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (entry 10).

Under optimized experimental conditions, tetrahydropyranylation of a wide range of alcohols and phenols was investigated in Table 3. With a catalytic amount of $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ -HOAc, various alcohols including

Table 3 Tetrahydropyranylation of alcohols and phenols catalyzed by $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ -HOAc^a

Entry	Alcohol/phenol	Time/h	Yield/%	Refs. ^b
1	PhCH ₂ OH	1	98	[28 , 29]
2	PhCH ₂ CH ₂ OH	6	93	[11]
3	CH ₃ OH	4. 5	91	[28]
4	C ₂ H ₅ OH	5	90	[28]
5	<i>n</i> -C ₃ H ₇ OH	6	89	[28]
6	<i>i</i> -C ₃ H ₇ OH	5	91	[29]
7	<i>n</i> -C ₄ H ₉ OH	7	92	[28]
8	<i>s</i> -C ₄ H ₉ OH	8	67	[29]
9	<i>i</i> -C ₄ H ₉ OH	7	93	[29]
10	<i>t</i> -C ₄ H ₉ OH	6	trace	—
11	<i>n</i> -C ₅ H ₁₁ OH	8	94	[30]
12	<i>i</i> -C ₅ H ₁₁ OH	7	82	[29]
13	<i>n</i> -C ₈ H ₁₇ OH	9	93	[29]
14	<i>i</i> -C ₈ H ₁₇ OH	9	59	[29]
15	<i>n</i> -C ₁₂ H ₂₅ OH	10	74	[29]
16	<i>c</i> -C ₆ H ₁₁ OH	9	87	[29]
17	CH ₂ = CHCH ₂ OH	2. 5	84	[29]
18	Furfuryl alcohol	2	88	[28 , 29]
19	PhOH	3	83	[28 , 29]
20	4-CH ₃ C ₆ H ₄ OH	2	68	[30 , 31]
21	4-ClC ₆ H ₄ OH	1. 1	70	[31]
22	4-NO ₂ C ₆ H ₄ OH	1. 3	75	[29 , 31]
23	2-Nathphol	5	91	[11]
24	PhCH ₂ OH + PhOH	1	96	—

a. Reaction conditions: alcohol or phenol 15 mmol, DHP 18 mmol, $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ 0.3 mmol, HOAc 12 mmol, rt. 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.

benzylic, primary, isomeric, secondary, cyclic, allyl, and furyl alcohols as well as phenol undergo tetra-

hydropyranlation in moderate to excellent yields. The sterically hindered alcohols (e. g. tert-butyl alcohol) proved resistant to tetrahydropyranlation with this reagent (entry 10). For linear chain aliphatic alcohols, the protection of short-chain alcohols proceeds faster than in case of the long-chain ones, so proceed isomeric aliphatic alcohols. Phenol groups were also protected in shorter reaction time whether the benzene ring was substituted with electron donating or withdrawing substituent (entries 19 – 22). In addition, protection of a bulky phenol like 2-naphthol was also achieved at room temperature in good yield (entry 23).

Chemoselective protection of alcohol in the presence of phenol was also studied under similar reaction conditions. The reaction was carried out by stirring benzyl alcohol (15 mmol), phenol (15 mmol), DHP (18 mmol), $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ (0.3 mmol), and HOAc (12 mmol), and the process was monitored by GC. GC analysis indicated an almost complete disappearance of benzyl alcohol, whereas, phenol was still intact. The results show that alcohol can be protected selectively and efficiently while the phenol remained unaffected (entry 24).

The authors consider that a ligand exchange between $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ and HOAc generating cobalt acetate and sulfuric acid is impossible. One reason is the pK_a value of sulfuric acid is lower than that of HOAc. The other reason is that the polymerization of DHP should occur in presence of little sulfuric acid. However, polymerization did not proceed (determined by GC). Furthermore, $\text{Cu}(\text{acac})_2$ was inert for this transformation (see data in Table 2). A series of experiments confirmed that the Brønsted acid was not simply regenerating the catalyst and that the Brønsted and Lewis acids were acting together as a combined catalyst for the reaction. Acetic acid combines with the Lewis acid to produce a “double activation” of the DHP. Then, nucleophilic attack of alcohol to DHP, which upon proton transfer produces final product and releases the catalyst for the next run. A similar example of Brønsted-assisted Lewis acid catalysis was reported by Mouhtady^[21] and Aspinall^[22] et al.

3 Conclusion

In conclusion, we have demonstrated a combined catalyst, $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ -HOAc, as an effective catalyst for protecting structurally varied alcohols and phenols to produce tetrahydropyranyl ethers. The $\text{CoSO}_4 \cdot 7\text{H}_2\text{O}$ was easily recovered and reused following the reaction, thus providing an atom economic reaction. HOAc is a cheap protonic acid, environmentally benign, commercially available, and easy to handle. The novel combined catalyst overcomes the problems encountered with the classical catalyst. We believe that this work will find useful application for the protection of alcohols and phenols in modern synthetic methodologies.

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硫酸钴-乙酸协同催化醇和酚的四氢吡喃化反应

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摘 要:报道了硫酸钴-乙酸在室温、无溶剂条件下催化醇和酚的四氢吡喃化反应。硫酸钴-乙酸作为协同催化体系,二者缺一不可。与传统催化剂相比,新催化体系的催化活性最好。反应结束后,硫酸钴经简单相分离可回收,重复使用多次催化活性无明显下降。提出了可能的催化反应机理。

关 键 词:四氢吡喃化; 醇; 酚; 硫酸钴; 乙酸