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A convenient and highly efficient method for the protection of aldehydes using very low loading hydrous ruthenium(III) trichloride as catalyst

Jian-Ying Qi,[a] Jian-Xin Ji,[a] Chi-Hung Yueng,[a,*] Hoi-Lun Kwong[b] and Albert S. C. Chan[a,*]

[a] *Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China*

[b] *Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drugs Discovery and Synthesis and Department of Biology and Chemistry, City University of Hong Kong, Hong Kong, China*

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Abstract—A convenient method for the chemoselective protections of both aliphatic and aromatic aldehydes has been developed. Ruthenium(III) trichloride (0.1 mol%) has found to be an highly efficient catalyst in the acetalizations of aldehydes with various simple alcohols such as methanol, ethanol, or diols such as 1,2-ethylanediol and 1,3-propanediol under mild reaction conditions.

The efficient and selective protection of carbonyl compounds is an important subject in organic synthesis.[1] Up to now, many methods have been developed for this purpose by using various catalysts,[2–13] such as protic or Lewis acids ($FeCl_3$, NH_4NO_3, BF_3, $ZnCl_2$, rare earth metal chloride), alumina, and other organometallic compounds. However, very few[5,6] of them were reported for the chemoselective protection of aldehydes in the present of keto functionalities. Although Yadav et al.[14] recently developed a new method for the selective acetalization of aldehydes by using 10% $LiBF_4$ as catalyst and 2-mercaptoethanol as an acetal reagent in acetonitrile, some ketones such as cyclohexanone and tetralone were still acetalized in this catalytic system. Besides, 2-mercaptoethanol and its corresponding acetal products possess an unpleasant odor.[9,15]

Herein, we wish to report a convenient method for the highly chemoselective acetalization of aldehydes with different alcohols or diols using ruthenium(III) trichloride as catalyst under mild reaction conditions. Ruthenium(III) trichloride has been widely used to catalyze oxidation,[16] reduction,[17] or polymerization[18] of organic compounds. In this study, we investigated the acetalizations catalyzed by ruthenium(III) trichloride and found that a series of aliphatic and aromatic aldehydes including acid-sensitive 2-furylaldehyde as well as aldehydes containing keto functionalities such as 4-acetylbenzaldehyde could be efficiently converted to the corresponding acetals in high yields by using only 0.1 mol% $RuCl_3\cdot 3H_2O$ as catalyst.

Initially, the acetalizations employing simple alcohols as protective reagents were tested and the results[19] were listed in Table 1. Isobutyraldehyde was chosen as a model substrate to react with methanol, ethanol, *n*-propanol, or *n*-butanol, respectively (entries 1–4). Methanol, the simplest alcohol, was preferred to other alcohols and gave the best yield of 91%. Similarly, the acetalizations of other aliphatic aldehydes with methanol, such as *n*-butyraldehyde, *n*-heptaldehyde, *n*-nonylaldehyde, and 3-phenylpropionaldehyde, were carried out successfully and gave 84–90% yields (entries 5–8). Compared with aliphatic aldehydes, benzaldehyde gave a rather low yield of 45% (entry 9). Various ketones, whether cyclic or acyclic ones, did not react under identical reaction conditions (entries 10–13).

In the subsequent investigation, the acetalizations using 1,2-ethanediol or 1,3-propanediol as protective reagents were examined. The results[19] summarized in Table 2

Keywords: Protection; Aldehydes; Ruthenium; Chemoselective.

* Corresponding authors. Tel.: +852 2766 5607; fax: +852 2364 9932; e-mail: bcachan@polyu.edu.hk

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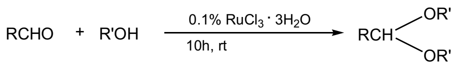
Table 1. Acetalization of aliphatic aldehydes with simple alcohols[a]

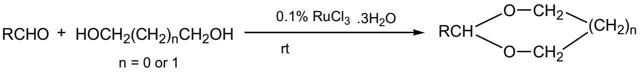


Entry	RCHO (or ketone)	R′OH	Yield[b] (%)
1	*i*-PrCHO	EtOH	85
2	*i*-PrCHO	*n*-PrOH	83
3	*i*-PrCHO	*n*-BuOH	81
4	*i*-PrCHO	MeOH	91
5	*n*-PrCHO	MeOH	90
6	*n*-$C_6H_{13}CHO$	MeOH	84
7	*n*-$C_8H_{17}CHO$	MeOH	87
8	$PhCH_2CH_2CHO$	MeOH	85
9	PhCHO	MeOH	45
10	Acetone	MeOH	0
11	2-Pentanone	MeOH	0
12	Acetophenone	MeOH	0
13	Cyclohexanone	MeOH	0

[a] The reactions were carried out according to the typical procedure.[19]

[b] Isolated yields.

Table 2. Acetalization of aldehydes with diols



Entry	RCHO	*n*	Yield[a] (%)
1	*n*-PrCHO	0	81
2	*i*-PrCHO	0	91
3	*n*-$C_6H_{13}CHO$	0	81
4	$PhCH_2CH_2CHO$	0	82
5	*n*-PrCHO	1	94
6	*i*-PrCHO	1	95
7	*n*-$C_8H_{17}CHO$	1	83
8	*n*-$C_8H_{17}CHO$	1	85[b]
9	$PhCH_2CH_2CHO$	1	81
10	$PhCH_2CH_2CHO$	1	81[b]
11	PhCHO	1	51
12	PhCHO	1	91[b]
13	*p*-MeO–PhCHO	1	72
14	*p*-MeO–PhCHO	1	82[b]
15	*o*-MeO–PhCHO	1	91[b]
16	*p*-F–PhCHO	1	93[b]
17	*o*-F–PhCHO	1	85[b]
18	*p*-Br–PhCHO	1	86[b]
19	*o*-Br–PhCHO	1	81[b]
20	2-Furylaldehyde	1	90[b]
21	*p*-MeCO–PhCHO	1	95[b,c]

[a] Isolated yields.

[b] The reactions were carried out in the presence of 10mmol of anhydrous Na_2SO_4 and other conditions were according to the typical procedure.[19]

[c] Mono protection of aldehyde was observed.

showed the scope and generality of the acetalizations of various aliphatic and aromatic aldehydes with these two kinds of diols. In most cases, the reactions of aldehydes with 1,3-propanediols gave slightly higher yields than those with 1,2-ethanediol or methanol. For example, the yields of isobutyraldehyde with 1,3-propanediol, 1,2-ethanediol, and methanol were 95%, 91%, and 91%, respectively.

Since water was a concomitant by-product in the acetalizations, it was estimated that adding a dehydration reagent might increase the yield of acetal products. In this study, the addition of anhydrous Na_2SO_4 to the reaction system did not show any improvement of the yield of the acetals of aliphatic aldehydes (entries 7–10). In contrast, the acetal products of aromatic aldehydes increase significantly in the presence of anhydrous Na_2SO_4. For example, the acetal yield of benzaldehyde with 1,3-propanediol was only 51% in the absence of Na_2SO_4 (entry 11). After adding anhydrous Na_2SO_4, the yield was increased to 91%. The reactions of other aromatic aldehydes with 1,3-propanediol also gave high yields in the presence of anhydrous Na_2SO_4 (entries 14–21). In addition, the properties of the substituent groups in the aromatic ring, whether electron-donating groups (*p*-MeO and *o*-MeO) or electron-withdrawing groups (*p*-F, *o*-F, *p*-Br, and *p*-Br), had no obvious effect on the acetalization under the reaction conditions. Furthermore, the acid-sensitive substrate 2-furylaldehyde was also efficiently protected in excellent yield without the formation of any by-products, which were normally encountered under acidic conditions (entry 20). It was noteworthy that the mono protection of aldehyde was observed when using multifunctional 4-acetylbenzaldehyde as substrate (entry 21). This result clearly showed that the method is particularly useful for the chemoselectivity protection of aldehydes in the presence of keto groups.

In summary, ruthenium(III) trichloride has been found to be a highly efficient catalyst in the chemoselective protection of aldehydes including acid-sensitive 2-furylaldehyde and multifunctional 4-acetylbenzaldehyde. Various alcohols such as methanol, ethanol, and diols such as 1,2-ethanediol, 1,3-propanediol can be used as acetalating reagents at ambient temperature. This new protective method for aldehydes is attractive for its high chemoselectivity, low catalyst loading, operational simplicity, high yields, and mild reaction conditions.

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19. Typical procedure. A solution of an aldehyde (10 mmol), alcohol (2 ml), and hydrate $RuCl_3$ (10^{-2} mmol) was stirred at ambient temperature for 10 h. The reaction mixture was diluted with water and extracted twice with dichloromethane (2×10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by distillation or column chromatography on silicon gel (Merck, 70–230 mesh, ethyl ether–hexane = 1:20) to give a pure acetal.