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Ruthenium(III) chloride-catalyzed chemoselective synthesis of acetals from aldehydes

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Abstract—A mild and chemoselective acetalization procedure for the protection of various aldehydes in the presence of ketones is described.

The protection of carbonyl compounds plays an important role during multistep syntheses in organic, medicinal, carbohydrate, and drug design chemistry. Among carbonyl protecting procedures, acetalization is one of the most widely used methods for protecting aldehydes and ketones.[1] Generally, they are prepared by the condensation of carbonyl compounds with the alcohols and/or the corresponding orthoformates in the presence of a protic or Lewis acid catalyst. Some methods employing dry HCl,[2] DCC–$SnCl_4$,[3] PTSA,[4] TMSOTf,[5] TMSOFs,[6] $PhSO_2NHOH$,[7] DDQ,[8] $ZrCl_4$,[9] $Sc(OTf)_3$,[10] $LaCl_3$,[11] $CeCl_3$,[12] $InCl_3$,[13] have been reported. A large number of these methods require long reaction times, high temperatures, and stoichiometric amount of catalyst and provide low yields in some cases. Interestingly, only a few of these methods have demonstrated chemoselective protection of aldehydes in the presence of ketones.[9,14] Therefore, there is still a need to develop a simple and efficient method for chemoselective protection of aldehydes in the presence of ketones.

In this letter we wish to report the chemoselective acetalization of aldehydes, without affecting ketones, using a catalytic amount of ruthenium chloride. Most recently, we have reported that $RuCl_3$ is a mild Lewis acid for acylation of alcohols, phenols, amines, and thiols.[15] The reaction of benzaldehyde with methanol in the presence of 5 mol% $RuCl_3$ at reflux temperature afforded the desired acetal in 85% yield. Similarly, benzaldehyde was treated with ethanol and 2-propanol in the presence of a catalytic amount of $RuCl_3$ yielding the corresponding acetals in good yields (Table 1). Several activated and deactivated aromatic aldehydes and aliphatic aldehydes underwent the protection reactions to give the corresponding carbonyl derivatives (Scheme 1). The use of cationic Ru(II) for acetal deprotection has been reported.[16] It is well known that acetalization and deacetalization reactions are reversible reactions. Therefore, we can use a higher proportion of $RuCl_3$ for acceleration of reaction but it can cause serious setbacks as well. Proper maintenance of the reaction time and conditions is necessary for the success of the reaction. Otherwise, a considerable amount of product can revert to the starting aldehydes.

The results have been summarized in Table 1, which clearly indicates the scope and generality of the reaction with respect to different aromatic, aliphatic, and unsaturated aldehydes. The experimental procedure[17] is very simple, convenient, and does not need any halogenated solvent or additive. It should be mentioned that addition of trimethylorthoformate accelerated the acetalization, but was not required for complete conversion (entry 2, Table 1). The method has the ability to tolerate a variety of other protecting groups such as acetyl, benzyl, benzoyl, allyl, and esters. Moreover, this procedure is highly chemoselective, providing selective acetalization of an aldehyde in the presence of a ketone. For instance, when an equimolar mixture of benzaldehyde and acetophenone was allowed to react with methanol in the presence of a catalytic amount of $RuCl_3$, only the acetal of

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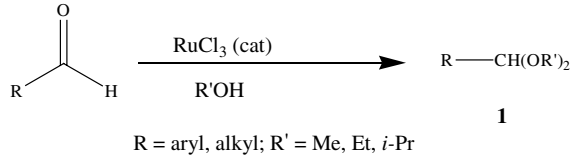
Table 1. Ruthenium(III) chloride catalyzed protection of aldehydes as acetals

Entry	Substrate	Alcohols	Time (h)	Yield[a] (%)
1	Benzaldehyde	MeOH	5	85
2	Benzaldehyde	MeOH	4	86[b]
3	4-Methoxybenzaldehyde	MeOH	5	84
4	4-Chlorobenzaldehyde	MeOH	5	80
5	4-Nitrobenzaldehyde	MeOH	9	71
6	Furfural	MeOH	4	80
7	4-Benzyloxybenzaldehyde	MeOH	5	81
8	Cinnamaldehyde	MeOH	3	82
9	2-Naphthaldehyde	MeOH	12	72
10	Thiophene 2-carboxaldehyde	MeOH	6	82
11	2-Nitrobenzaldehyde	MeOH	7	72
12	4-Carbomethoxybenzaldehyde	MeOH	8	85
13	4-Allyloxybenzaldehyde	MeOH	6	81
14	Hexanal	MeOH	8	76
15	Octanal	MeOH	9	70
16	Butanal	MeOH	8	73
17	Decanal	MeOH	8	70
18	4-Acetyloxybenzaldehyde	MeOH	8	83
19	4-Benzoyloxybenzaldehyde	MeOH	6	76
20	Benzaldehyde	EtOH	8	74
21	4-Methoxybenzaldehyde	EtOH	8	81
22	Hexanal	EtOH	14	65
23	4-Chlorobenzaldehyde	*i*-PrOH	12	71
24	4-Methoxybenzaldehyde	*i*-PrOH	12	68
25	Butanal	*i*-PrOH	16	62

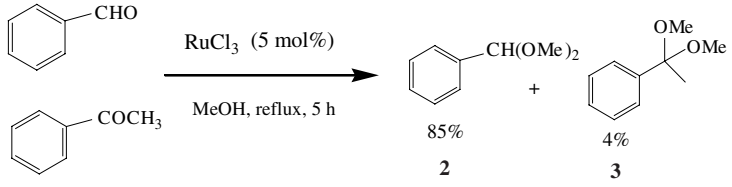
[a] Yields refer to pure isolated products,[27] characterized by IR, ^{1}H NMR, and MS.
[b] Trimethylorthoformate used (2 equiv).



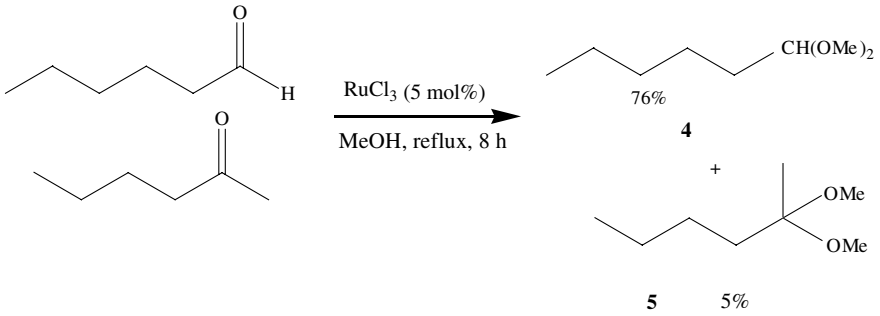
Scheme 1.

benzaldehyde was obtained,[18] while the ketone was completely recovered (Scheme 2). To explain this fact the electron density at the carbonyl carbon has been calculated using semi-empirical molecular orbital calculations by the AM1 method (Hyperchem, Inc, Grainsville, FL). The electron densities for benzaldehyde and acetophenone are 0.223 and 0.267, respectively. Due to the higher electron density of the aromatic ketone, acetophenone did not form a dialkyl ketal. Further, aliphatic aldehydes are selectively acetalized in the presence of aliphatic ketones[19] (Scheme 3). It is well known that ketones are less reactive than aldehydes due to the presence of alkyl groups that provide more electron density through the sigma bond. Moreover, the transition state of an aldehyde after its reaction has a lower energy than that of ketone due to steric crowding, and thus a ketone has a lower reactivity than aldehyde. The aldehyde functionality of a keto-aldehyde, was protected chemoselectively under identical condition[20] (Scheme 4). Interestingly, a highly reactive β-keto-aldehyde was selectively acetalized without affecting ketone functionality and in this case we did not observe any β-elimination product[21] (Scheme 5). These results illustrate the chemoselectivity[22] and mildness of the present method.

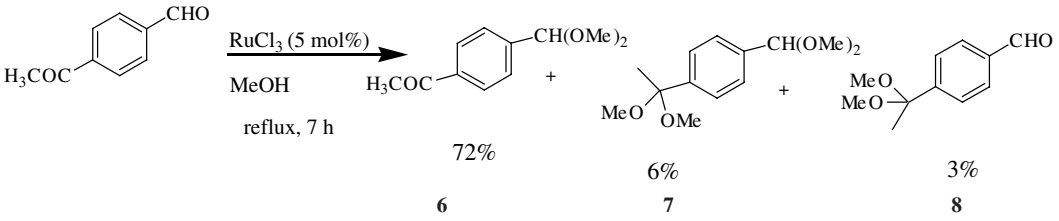
We propose the mechanism of ruthenium(III) chloride catalyzed acetalization of aldehyde as shown in Scheme 6. Like other Lewis acids catalyzed acetalizations,[23–25] ruthenium(III) first forms a reactive intermediate (A), after that methanol addition to carbonyl carbon occurs in concerted manner to form B. Finally, hemiacetal



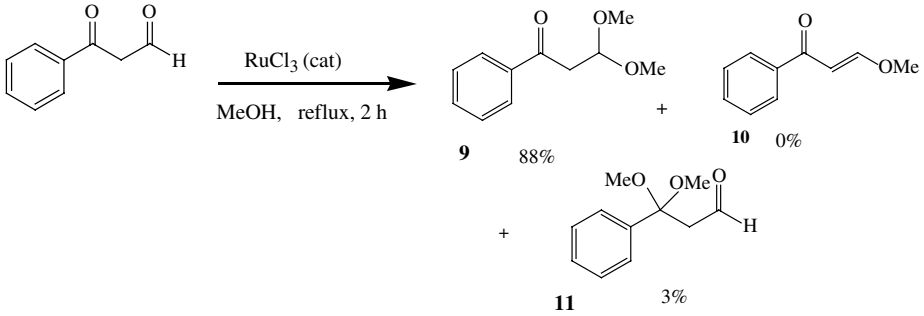
Scheme 2.



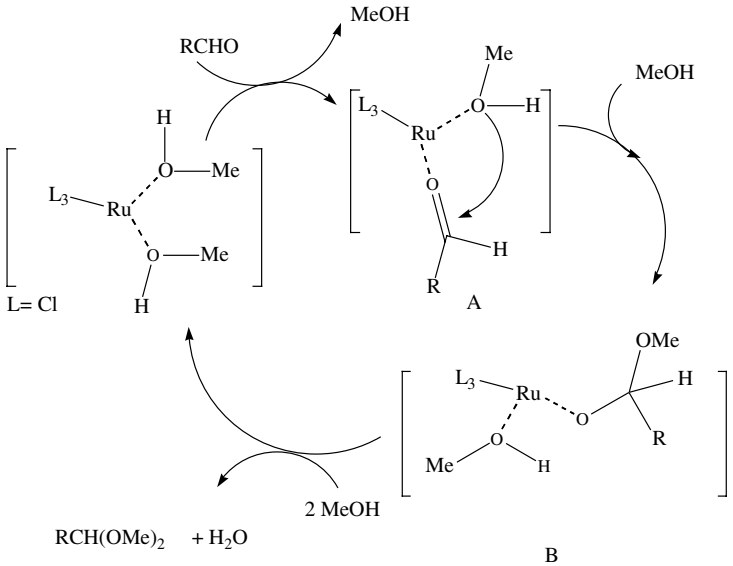
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

complex B probably converts to acetal via prior formation of an oxocarbenium ion[26] and subsequent addition of methanol.

In conclusion, a very simple, efficient, and eco-friendly method has been developed for the protection of aldehydes as acetals in the presence of a number of protecting groups using a catalytic amount of $RuCl_3$. Moreover, the high chemoselectivity, good to high yields, and non-aqueous work-up are the main advantages of this new method and will make a useful and important addition to the present methodologies.

Acknowledgements

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17. General acetalization procedure: A mixture of aldehyde (1 mmol) and $RuCl_3$ (5 mol%, anhydrous available from Aldrich) in dry alcohol (10 mL) was refluxed for the specified time (Table 1). After completion of reaction (TLC monitoring), the reaction mixture was concentrated in vacuo. The residue was chromatographed over silica gel (10% ethyl acetate in hexane) to afford the pure product in good to excellent yields.
18. Experimental procedure: A mixture of benzaldehyde (1 mmol), acetophenone (1 mmol), and $RuCl_3$ (5 mol%) in methanol (10 mL) was refluxed for 5 h. After usual work-up, the crude mixture showed primarily the acetal of benzaldehyde. In the same reaction after 12 h, the ratio of **2** and **3** was 91:13, was determined by ^1H NMR of crude mixture.
19. Reaction condition: A mixture of hexaldehyde (1 mmol), 2-hexanone (1 mmol), and $RuCl_3$ (5 mol%) in methanol was refluxed for 8 h. The ratio of **4** and **5** after 12 h was 82: 8.
20. Experimental condition: A mixture of 4-acetylbenzaldehyde (1 mmol) and $RuCl_3$ (5 mol%) in methanol (10 mL) was refluxed. After 12 h, the ratio of **6** and **7** was 78: 9.
21. Reaction condition: A mixture of keto-aldehyde (1 mol) and $RuCl_3$ (5 mol%) in methanol (10 mL) was refluxed for 2 h.
22. All yields for the competition study were determined by ^1H NMR analysis of crude mixture.
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27. Selected spectral data: *4-Nitrobenzaldehyde dimethyl acetal* (entry 4) ^1H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 6H), 5.46 (s, 1H), 7.64 (d, J = 8.2 Hz, 2H), 8.21 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.8, 101.7, 123.4, 127.8, 145.1, 148.1; MS *m/z* 197 (M^+); *2-Thiophenecarboxaldehyde dimethyl acetal* (entry 9) ^1H NMR (300 MHz. $CDCl_3$) δ 3.35 (s, 6H), 5.64 (s, 1H), 7.01 (dd, J = 3.9, 4.9 Hz, 1H), 7.09 (d, J = 3.9 Hz, 1H), 7.32 (d, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.5, 100.1, 125.5, 125.7, 126.8, 141.6; *1-[4-(Dimethoxymethyl)phenyl]ethanone* (compound **6**, Scheme 4) ^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.34 (s, 6H), 5.45 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.2Hz, 2H); 13C NMR (75 MHz, $CDCl_3$) δ 26.8, 52.7, 102.4, 127.1, 128.4, 137.1, 143.2, 197.8; MS *m/z* 194 (M^+), 163, 75, 43; *3,3-Dimethoxy-1-phenylpropan-1-one* (compound **9**, Scheme 5) ^1H NMR (300 MHz, $CDCl_3$) δ 3.31 (d, J = 5.2 Hz, 2H), 3.46 (s, 6H), 5.03 (t, J = 5.2 Hz, 1H), 7.40–7.62 (m, 3H), 7.92–8.01 (m, 2H); MS *m/z* 194 (M^+), 163, 136, 105, 85, 77, 51.