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Ruthenium(III) chloride catalyzed acylation of alcohols, phenols, thiols, and amines

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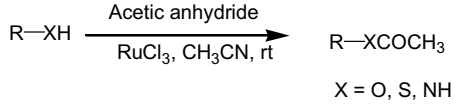
Abstract—Ruthenium(III) chloride catalyzes the acylation of a variety of phenols, alcohols, thiols, and amines under mild conditions. Some of the major advantages of this method are high yields, short reaction times, ease of operation, and compatibility with other protecting groups.

The acylation of alcohols, amines, and thiols is a common practice in organic synthesis.[1] In these reactions, acid chloride or anhydrides are often used as the acyl source in the presence of amine bases such as triethylamine, pyridine, or DMAP.[1] Most recently, some methods employing Bu_3P,[2] $Sc(OTf)_3$,[3] $Sc(NTf_2)_3$,[4] TMSOTf,[5] $Cu(OTf)_2$,[6] $InCl_3$,[7] $In(OTf)_3$,[8] $Bi(OTf)_3$,[9] $TaCl_5$,[10] zeolites,[11] clays,[12] and $LiClO_4$[13] have also been reported. However, many of these methods have some drawbacks such as low yields, long reaction times, harsh reaction conditions, use of hazardous materials (e.g., DMAP is highly toxic, Bu_3P is flammable and air sensitive), and the use of expensive[3–5,8,9] and not readily available reagents.[3,9] Some of the reported methods work well on primary or secondary alcohols only and fail to protect tertiary alcohols or less reactive phenols. A few of these methods also suffer from side reactions such as dehydration and rearrangement and might not be fully compatible for the acylation reactions with substrates bearing acid-sensitive groups. Thus, simple, efficient, and mild methods are still desirable.

In this communication, I wish to report a mild and efficient method for acylation of alcohols, phenols, thiols, and amines using a catalytic amount of ruthenium chloride in acetonitrile at room temperature.

The reaction of benzyl alcohol with acetic anhydride in the presence of 5 mol% $RuCl_3$ at room temperature afforded the desired compound in 10 min. Similarly, several primary and secondary alcohols underwent the acetylation reactions in excellent yields (Scheme 1). Interestingly, tertiary alcohols (entries 7, 8, and 13, in Table 4) are acetylated smoothly without any side products observed. Phenols are less reactive than alcohols toward acylation reactions and underwent acylation smoothly. Optically active substrates are efficiently acetylated without any detrimental effect on the optical purity (entries 6, 11, 12, and 14 in Table 4), illustrating the mildness of the acylation process.

To explore generality and scope further, the $RuCl_3$ catalyzed acylation was examined using other functionally and sterically diverse alcohols as depicted in Table 4. When 2,6-dimethylphenol (entry 5 in Table 3) was subjected to the present method, acylation took place smoothly in excellent yield. Similarly, sterically hindered substrates, (entries 3, 4 in Table 3, and entries 7, 8, and 13 in Table 4) were acetylated with a high yield of product. It is noteworthy that acid-sensitive functional groups such as allyloxy, *t*-Bu, and TBS ether can survive in the present method indicating mildness of reaction conditions. The 6-bromo-1-hexanol (Table 4, entry 18) underwent acetylation reaction smoothly, giving only acetylated product.[14] This compound should not be acetylated with any strong base condition, in which case a certain amount of elimination product



Scheme 1.

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might be observed. This method can be extended to thiols and amines for acetylation reactions. It should be mentioned that the ruthenium chloride catalyzed acetylation reactions are faster in acetonitrile than other solvents such as dichloromethane, chloroform, or tetrahydrofuran (Table 1). Interestingly, the reaction was very slow in tetrahydrofuran. The ruthenium chloride catalyzed acetylation of alcohols has little effect on solvent concentrations (0.5, 0.2, and 0.1 M are the best conditions, 0.05 M took longer time but gave almost the same yield). In case of primary alcohol, catalyst 0.1 mol % is sufficient for the acetylation. But secondary, tertiary, and aromatic alcohols need at least 5 mol % catalyst for the acetylation to give the comparable yields (Table 2). The acetylation reaction can be performed without using any solvent if substrates are liquid, thus making this method more environmentally acceptable.

Although, recently metal triflates (Otera[9] type and other[3,5,6,8]) have been reported as a Lewis acid catalyst for the acetylation reaction. These catalysts are expensive and commercially not available (in some cases). The strong Lewis acid character of metal triflates makes them unsuitable in use with acid-sensitive substrates such as 1-ethynyl-1-cyclohexanol, 5-TBSO-pentanol, and 2-allyloxyethanol necessitating the requirement of the use of excess of acetic anhydride and/or low temperature (0 to −20 °C) to suppress the competitive side reactions. Therefore, the distinct advantages of $RuCl_3$

Table 1. Solvent effect on $RuCl_3$ catalyzed acetylation of benzyl alcohol with acetic anhydride at room temperature[a]

Entry	Solvent	Time	Conversion[b] (%)
1	THF (0.5 M)	24 h	10
2	THF (0.2 M)	24 h	14
3	THF (0.1 M)	24 h	15
4	CH_2Cl_2 (0.5 M)	24 h	60
5	CH_2Cl_2 (0.2 M)	24 h	65
6	CH_2Cl_2 (0.1 M)	24 h	64
7	$CHCl_3$ (0.2 M)	24 h	42
8	$CHCl_3$ (0.1 M)	24 h	38
7	CH_3CN (0.5 M)	10 min	>95
8	CH_3CN (0.2 M)	10 min	>95
9	CH_3CN (0.1 M)	10 min	>95
10	CH_3CN (0.05 M)	25 min	>90

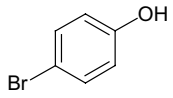
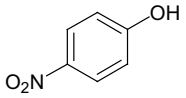
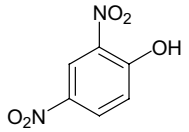
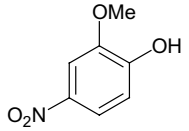
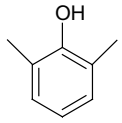
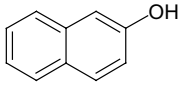
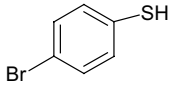
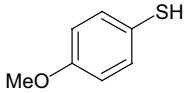
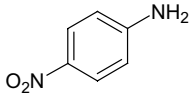
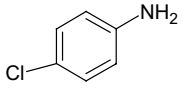
[a] 1 mmol benzyl alcohol, 1.2 mmol acetic anhydride, and 5 mol % catalyst were used.
[b] The conversion was determined by ^1H NMR analysis of the crude product.

Table 2. $RuCl_3$ catalyzed acetylation of alcohol at room temperature[a]

Entry	Alcohol	Catalyst/ mol %	Time	Yield (%)
1	$PhCH_2OH$	5	10 min	98
2	$PhCH_2OH$	1	30 min	91
3	$PhCH_2OH$	0.1	4 h	90
4	$PhCH_2OH$	0.01	7 h	66
5	$PhCH_2OH$	0.001	36 h	49
6	$PhCH(OH)CH_3$	5	3 h	92
7	$PhCH(OH)CH_3$	1	20 h	85
8	$PhCH(OH)CH_3$	0.1	54 h	65
9	*p*-Bromophenol	5	5 h	95
10	*p*-Bromophenol	1	19 h	61
11	*p*-Bromophenol	0.1	72 h	45
12	$PhCH_2C(OH)Me_2$	5	6 h	78
13	$PhCH_2C(OH)Me_2$	1	40 h	42
14	$PhCH_2C(OH)Me_2$	0.1	72 h	30

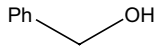
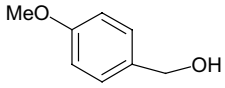
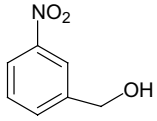
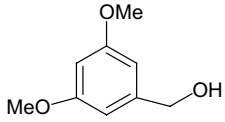
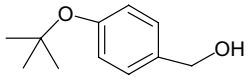
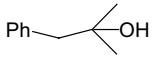
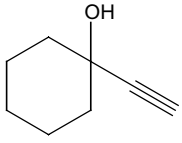
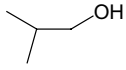
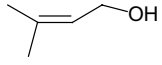
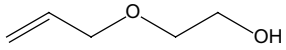
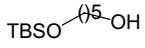
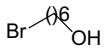
[a] 1 mmol alcohol (0.2 M CH_3CN), 1.2 mmol acetic anhydride were used.

Table 3. $RuCl_3$ catalyzed acylation of phenols, thiols, and amines with Ac_2O[a]

Entry	Substrate	Time	Yield[b] (%)
1		5 h	90
2		5 h	84
3		6 h	82
4		5 h	90
5		6 h	92
6		10 h	91
7		30 min	91
8		45 min	83
9	Butanethiol	1 h	87
10		1 h	95
11		1 h	93
12	Pentylamine	1 h	89

[a] 1.2 equiv of Ac_2O was used per OH/SH/NH groups.
[b] Yields refer to pure isolated products.

Table 4. $RuCl_3$ catalyzed acylation of alcohols at room temperature[a]

Entry	Substrate	Time	Yield[b]
1		10 min	95
2		10 min	94
3		30 min	89
4		25 min	95
5		50 min	82
6		2 h	85
7		6 h	87
8		7 h	92
9		25 min	91
10	4-Methyl-1-pentanol	40 min	92
11	*R*-(−)-2-Butanol	2 h	83
12	*R*-(−)-2-Hexanol	3 h	93
13	1-Adamantol	4 h	87
14	(1*R*,2*S*,2*R*)-(−)Menthol	2 h	82
15		35 min	91
16		1 h	95
17		1 h	81
18		2 h	89

[a] 1.2 equiv of acetic anhydride, 5 mol% catalyst were used.
[b] Yields refer to pure isolated products.

over the metal triflates may be explained through comparison of the results of a few representative examples of acid-sensitive substrates. Thus, 1-ethynyl-1-cyclohexanol was acetylated by $Sc(OTf)_3$ at −20 °C using 3 equiv of acetic anhydride, $Bi(OTf)_3$ catalyzed acetylation of the same compound required 10 equiv of acetic anhydride. The $RuCl_3$ catalyzed acetylation of the above mentioned compound requires only 1.2 equiv of acetic anhydride and it works at room temperature. The 5-TBSO-pentanol was acetylated in 72% yield in 4 h in the presence of $Bi(OTf)_3$ with 10 equiv of acetic anhydride, where as the same compound was acetylated in 81% yield in 1 h in the presence of $RuCl_3$ with 1.2 equiv of acetic anhydride.

In conclusion, a simple and efficient method for acetylation of all types of phenols, alcohols, thiols, and amines using a catalytic amount of ruthenium chloride has been developed. The method has advantages in terms of yields, short reaction times, ease of operation, and compatibility with other protecting groups and will make a useful and important addition to the present methodologies.

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14. Typical procedure: To a mixture of 6-bromo-1-hexanol (905 mg, 5 mmol) and acetic anhydride (610 mg, 6 mmol) in acetonitrile (10 mL) was added ruthenium chloride (53 mg, 5 mol%) at room temperature. After completion of reaction (TLC), then reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with satd NH_4Cl solution (30 mL), 1 N $NaHCO_3$ solution (25 mL), and brine

(40 mL), respectively. The organic layer dried over $MgSO_4$ and concentrated to give the pure product. When necessary, products were purified over silica gel chromatography (10–20% ethyl acetate in hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 1.35–1.48 (m, 4H), 1.64 (quintet, $J = 7$ Hz, 2H), 1.87 (quintet, $J = 6.8$ Hz, 2H), 2.01 (s, 3H), 3.41 (t, $J = 7$ Hz, 2H), and 4.06 (t, $J = 7$ Hz, 2H). The commercially available anhydrous ruthenium chloride (Aldrich) was used in all reactions. I have also observed that ruthenium chloride trihydrate can be used for the acetylation reaction but requires more catalyst and longer reaction times than anhydrous ruthenium chloride.