COMMUNICATION / COMMUNICATION

Ruthenium(III) acetylacetonate [$Ru(acac)_3$] — An efficient recyclable catalyst for the acetylation of phenols, alcohols, and amines under neat conditions

Ravi Varala, Aayesha Nasreen, and Srinivas R. Adapa

Abstract: A catalytic amount of ruthenium(III) acetylacetonate (2 mol%) [$Ru(acac)_3$] enables solvent-free acetylation of phenols, alcohols, and amines at ambient temperature in good to excellent yields. Furthermore, the catalyst could be recovered and reused at least three times without a significant loss in yields.

Key words: acetylation, protecting groups, ruthenium(III) acetylacetonate, phenols, alcohols, amines.

Résumé : L'utilisation d'une quantité catalytique d'acétylacétonate de ruthénium(III) (2 mol %) [$Ru(acac)_3$] permet de réaliser l'acétylation, sans solvant, de phénols, d'alcools et d'amines à la température ambiante, avec des rendements allant de bons à excellents. De plus, il est possible de récupérer le catalyseur et de le réutiliser au moins trois fois sans diminution significative des rendements.

Mots-clés : acétylation, groupes protecteurs, acétylacétonate de ruthénium(III), phénols, alcools, amines.

[Traduit par la Rédaction]

Introduction

Acetylation of phenol, alcohol, and amine functionalities is one of the most frequently used transformations in organic synthesis (1). Among the various protecting groups used for the hydroxyl function, acetyl is the most common because it is easy to introduce, stable in acidic reaction conditions, and easily removable by mild alkaline hydrolysis. In general, this can be achieved by treating alcohols with acid anhydrides or acid chlorides in the presence of stoichiometric amounts of amine bases such as tertiary amines (2), 4-(dimethylamino)pyridine (DMAP), 4-(1-pyrrolidino)pyridine (PPY) (3), and Bu_3P (4). Acylation of alcohols can also be achieved under an acid-catalyzed condition by treating alcohols with acid anhydrides in presence of several protic acids (5) and by using various metal salts as Lewis acids (6).

Certain reported methodologies suffer from one or more of the following disadvantages (5, 6): (*i*) potential health hazard (DMAP is highly toxic (e.g., intravenous LD_{50} in the rat is 56 mg/kg), and Bu_3P is flammable (flash point is 37 °C)); (*ii*) difficult handling (Bu_3P undergoes aerial oxidation, and triflates are moisture sensitive); (*iii*) high cost of the catalysts (e.g., triflates); (*iv*) special efforts required to prepare the catalysts ($Bi(OTf)_3$, Nafion-H, yttria–zirconia, and $AlPW_{12}O_{40}$); (*v*) lack of atom economy (use of excess of acetylating agents); (*vi*) stringent reaction conditions and the requirement of prolonged reaction times; (*vii*) in many cases, the reported acylation methodologies are applicable to only alcohols and are not suitable for acid-sensitive substrates; and (*viii*) in addition, the metal triflates may involve competitive side reactions (e.g., dehydration and rearrangement) with acid-sensitive substrates because of the large negative $H_\circ$ value of TfOH. Furthermore, the use of large amounts of acylating agents and activators should be avoided to promote green chemistry and atom efficiency.

Despite a number of precedents, a catalytically efficient practical alternative that can be used under milder and cost-effective conditions for this very important transformation is highly desirable, and there is still scope for further improvement. Another promising approach to environment-friendly chemistry is to minimize or completely eliminate the use of harmful organic solvents in organic syntheses. This is because organic reactions run under solvent-free conditions are advantageous because of their enhanced selectivity, effi-

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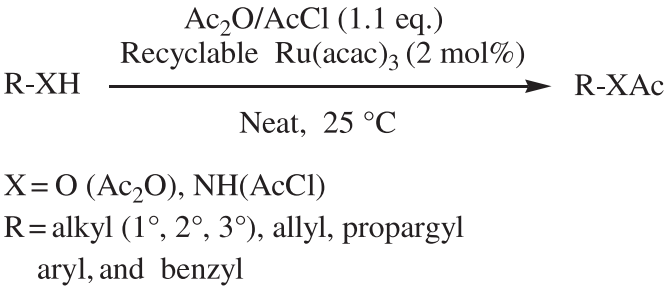
Scheme 1.



ciency, ease of manipulation, cleaner product formation, and the avoidance of toxic or volatile solvents (7). Thus, a paradigm shift from using solvents toward solvent-free reactions not only simplifies organic synthesis but also improves process conditions for large-scale synthesis.[2]

Recently, we have reported [$Ru(acac)_3$] as an efficient Lewis acid (LA) catalyst for chemoselective tetrahydropyranylation (THP) of alcohols and phenols under solvent-free conditions (8).

Results and discussion

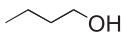
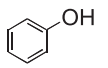
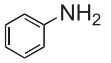
In a continuation of our recent efforts to develop new synthetic routes for carbon–carbon and carbon–heteroatom bond formation and heterocycles (9), we herein present our preliminary results using an efficient recyclable [$Ru(acac)_3$]-catalyzed solvent-free acetylation of hydroxy and amine functions (Scheme 1). The procedure, based on the Lewis acid catalytic activity of the [$Ru(acac)_3$], represents an environmentally benign alternative to current chemical processes that use water-intolerant Lewis acids.

Initially, we have screened a few available acetylacetonates, such as [$VO(acac)_2$], [$Pd(acac)_2$], [$Ru(acac)_3$], and [$Co(acac)_3$], for the model reaction between aniline (1 mmol) and acetyl chloride (1.1 mmol) under neat conditions at ambient temperature. Among the catalysts tested, [$Ru(acac)_3$] proved to be the most efficient LA catalyst in terms of yields and reaction time (the corresponding acetylated product was obtained in 5 min with quantitative isolated yield >99%). An optimum concentration of 2 mol% of [$Ru(acac)_3$] is sufficient to afford the acetylated product in an excellent yield. While optimizing the acylating agent, several features that deserved comment are shown in Table 1.

In case of alcohols and phenols (Table 1, entries 1 and 2), acetic anhydride was preferred over the corresponding acid chloride or acetic acid. It is significant to note that acetyl chloride was preferred over acetic anhydride with the acetylation reaction of amines (Table 1, entry 3). This is in complete contrast with the observations reported by Yadav et al. (6*c*). This clearly demonstrates that the acetylation reaction behaviour is completely dependent on the chosen catalyst. Acetylation of amines, using acetic acid at ambient temperature, with our catalyst did not give acetylated product.

The direct condensation of acetic acid with alcohols is generally avoided because the equilibrium between the substrates and the products require the elimination of water from the reaction mixture, using a dehydrant or azeotropically, to shift the equilibrium in favor of the product.

Table 1. Effect of acylating agent in [$Ru(acac)_3$]-catalyzed acetylation of phenols, alcohols, and amines.

Entry	Substrate	Acylating agent[a]	Time(h)	Yield (%)[b]
1		**A**	0.5	60
		B	0.5	82
		C	0.5	90
2		**A**	2.0	71
		B	2.0	78
		C	2.0	91
3		**A**	5 min	>99
		B	0.5	NR[c]
		C	0.5	62

[a] **A** = CH_3COCl; **B** = CH_3COOH; **C** = $(CH_3CO)_2O$.
[b] Isolated yields.
[c] NR = No reaction.

Table 2. Results of the recycling and reuse of [$Ru(acac)_3$] in the acetylation of aniline, as a model substrate.

Cycle	Yield (%)[a]
1	99
2	99
3	97
4	96

[a]Isolated yields with reused catalyst (recovered catalyst 99%, 99%, and 98% respectively).

Intrigued by the observations in hand, we have studied the scope and the generality of this process for a wide range of aromatic and aliphatic phenols, alcohols and amines.

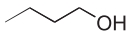
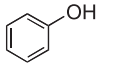
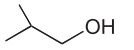
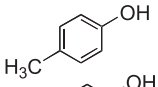
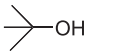
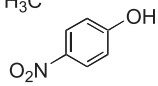
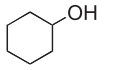
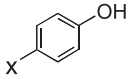
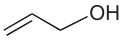
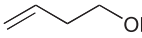
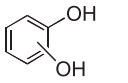
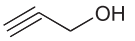
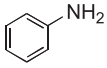
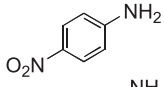
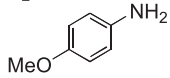
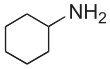
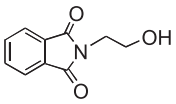
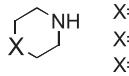
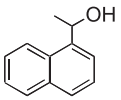
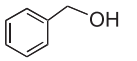
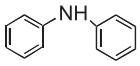
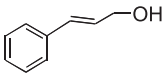
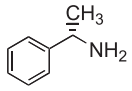
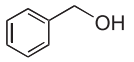
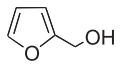
One of the important features of the present developed protocol for the formation of acetylated products is that absolute anhydrous conditions are not required. The reactions are clean and devoid of unwanted products and gave the corresponding acetylated products in moderate to excellent yields. Very importantly, this protocol allowed us to adopt a simple work-up procedure by employing ether to dissolve the organic material not the catalyst, which could be easily removed by filtration. The recovered catalyst is oven dried at 60 °C for 2 h and then reused for the model reaction without significant loss of yield for at least three cycles (Table 2; Table 3, entry 27).

As evident from Table 3, the described methodology illustrates a fine acetylation procedure that has wide applicability, extending the scope to alkyl (1°, 2°, and 3°), allyl, propargylic, aryl, and benzylic alcohols (Table 3, entries 1–36).

Under optimized reaction conditions, secondary and tertiary alcohols do not experience any competitive dehydration (Table 3, entries 3, 4, and 12). Acid-sensitive functionalities, such as allylic and propargylic substrates (Table 3, entries 5–8 and 14), are tolerated, and no rearrangement took place for those substrates. Chiral alcohols and amines (Table 3, entries 9 and 36) were easily acetylated with complete retention of

[2] Exothermicity of a large-scale reaction should be controlled by maintaining the temperature and using an appropriate solvent, if necessary.

Table 3. Ruthenium(III) acetylacetonate-catalyzed acetylation of phenols, alcohols, and amines.

Entry	Substrate	Time (h)/ Acylating agent	Yield (%)[a]	Entry	Substrate	Time (h)/ Acylating agent	Yield (%)[a]
1		0.5/**C**	90	17		2.0/**C**	91
2		5.5/**C**	80	18		8.0/C	80
3		12/**C**	65	19		12/C	65
4		4.0/**C**	92	20 21 22		x =F x =Br x =Cl	3.0/C 2.5/C 4.0/C	95 90 87
5		10/**C**	89	23		15.0/C	62
6		8.0/**C**	78	24 25 26		o- = *m*-= *p*- =	12/C 8.0/C 6.5/C	72 85 88
7		6.5/**C**	87	27		5 min/A	99
8		5.0/**C**	91	28		1.0/A	85
9	(R)-Menthol	6.5/**C**	82	29		5.5/A	92
10	Geraniol	8.0/**C**	85	30		6/A	82
11		15/**C**	90	31 32 33		X=CH_2 X=O X=S	10 min/A 10 min/A 30 min/A	95 98 90
12		10/**C**	78	34	$(PhCH_2)_2NH$	18/A	78
13		5.0/**C**	90	35		24/A	65
14		7.5/**C**	72	36		8.0/A	88
15		6.0/**C**	88				
16		5.5/**C**	75				

[a] All isolated products were characterized by IR, ^{1}H NMR, and mass spectral analyses.

the optical purity. Steric factors played vital role in affecting acetylation (Table 3, entries 34 and 35), and the reaction completion took longer times with moderate yields.

Next, the scope of the present methodology was extended to other anhydrides and acid chlorides to test the efficacy of the catalyst, and the results are quite satisfactory. From Table 4, solid anhydrides, such as benzoic, maleic, succinic, and phthalic anhydrides, also reacted well in the acylation reaction with the model substrates chosen.

The present [Ru(acac)$_3$]-catalyzed acetylation may probably follow the mechanism depicted in Scheme 2: For alcohols and phenols, initially, electrophilic activation by [Ru(acac)$_3$] for possible coordination to both carbonyl oxygen atoms of the anhydride **2** to form a six-membered transition state, and then nucleophilic attack by the alcohol **1** to give the desired acetylated product **3**. For amines, [Ru(acac)$_3$] first activates the acyl halide **4** and then polarizes it on the nucleophilic amine **5** to form the corresponding acetylated product **6** and regenerates back.

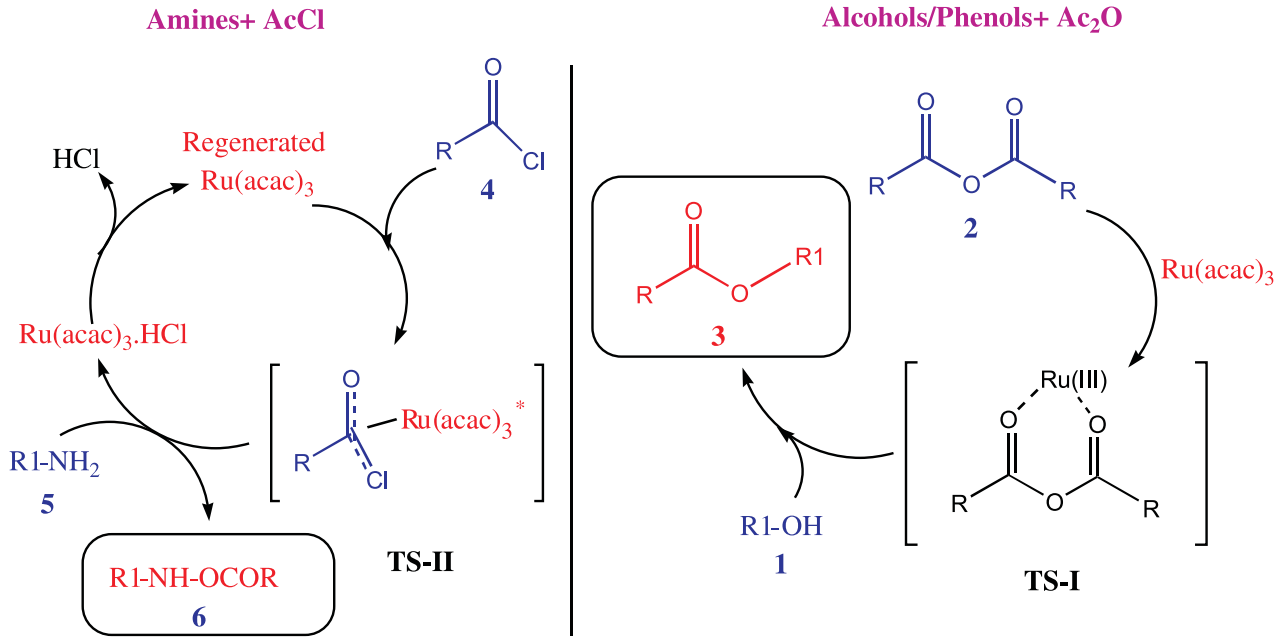
The efficiency and generality of the present [Ru(acac)$_3$]-catalyzed protocol can be realized at a glance by comparing our results for the chosen model substrates with those of

Table 4. Acylation of *n*-butanol, aniline, and piperidine with different anhydrides and acyl chlorides.

Entry	Substrate	Acylating agent	Conditions	Time	Yield (%)[a]
1	*n*-butanol	Benzoic anhydride	RT	3.0 h	90
		Maleic anhydride		3.0 h	80
		Succinic anhydride		3.0 h	82
		Phthalic anhydride		3.5 h	78
		Boc anhydride		1.0 h	92
		Propionic anhydride		1.0 h	95
		Butyric anhydride		1.0 h	98
2	2-Naphthol	Benzoic anhydride		3.5 h	88
		Succinic anhydride	RT	4.0 h	62
		Boc anhydride		2.5 h	85
3	Aniline	Benzoyl chloride	RT	20 min	95
		CH_2=CHCOCl		30 min	78
4	Piperidine	Benzoyl chloride	RT	10 min	92
		CH_2=CHCOCl		15 min	88

[a]Isolated yields.

Scheme 2. Proposed mechanism for the [Ru(acac)$_3$]-catalyzed acetylation of phenols, alcohols, and amines.



some recently developed procedures (as shown in Table 5). The reactions have been compared with respect to the reaction times, mol% of the catalyst used, and the yields.

Conclusion

In summary, we have developed a mild, efficient, and highly selective methodology for the acetylation of alcohols using [Ru(acac)$_3$] as LA catalyst (2 mol%). Notable features of the protocol are clean and simple solvent-free reaction conditions, non-aqueous workup, and the use of recyclable and environmentally benign catalyst. This work widens the scope of using transition-metal salts and complexes in organic synthesis because of the nontoxic nature of the catalyst. We believe that this protocol will be a valuable addition to acetylation-related modern synthetic methodologies.

Typical experimental procedure

The hydroxy or amine compound (Table 3, entries 1–36; 1.0 mmol), acylating agent (1.1 mmol), [Ru(acac)$_3$] (2 mol%) were placed, successively, in a flask under neat conditions at room temperature. After stirring, the reaction mixture was treated with Et_2O (2 × 5 mL), and the catalyst was removed by filtration. The filtrate extracts were concentrated under reduced pressure, and the crude product was then purified by silica-gel chromatography (hexane – ethyl acetate). All the obtained acylated products were characterized by IR,

Table 5. Comparison of the catalytic efficiency of $[Ru(acac)_3]$ with some recently reported catalysts.

Entry	Catalyst	mol%	AA[a]	Time (min)	Yield (%)[b]
For the reaction of aniline with an acylating agent					
1	**$[Ru(acac)_3]$ (neat)**	2	A	5	99
2	$AlPW_{12}O_{40}$ (neat)	0.5	C	1	96
3	I_2	10	C	105	77
4	$NbCl_5$	20	C	60	95
5	Zeolite	5	B	30	73
6	Fe^{+3}-Montmorillonite	20	B	180	98
7	$Gd(OTf)_3$–$[bmim][BF_4]$	0.2	C	120	96
For the reaction of *n*-butanol with an acylating agent					
1	**$[Ru(acac)_3]$ (neat)**	2	C	30	90
2	$CuSO_4 \cdot 5H_2O$ (neat)	10	C	1440	93
3	$Sn(tpp)(OTf)_2$	1	C	60	87
For the reaction of phenol with an acylating agent					
1	**$[Ru(acac)_3]$ (neat)**	2	C	120	91
2	$CuSO_4 \cdot 5H_2O$ (neat)	10	C	90	92
3	$H_{14}[NaP_5W_{30}O_{110}]$	0.1	C	60	95
4	$Gd(OTf)_3$–$[bmim][BF_4]$	0.2	C	120	88
5	I_2	10	C	30	90
6	K-10–DCM	100[c]	C	120	83

[a]Acylating agent.
[b]Isolated yields.
[c]mg/1 mmol.

^{1}H NMR spectroscopy, and mass spectrometry, and their structures are consistent with their published physical data (6).

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