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Zinc triflate catalyzed acylation of alcohols, phenols, and thiophenols

N. Uday Kumar [a], B. Sudhakar Reddy [a], V. Prabhakar Reddy [b], Rakeshwar Bandichhor [a,*]

[a] Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupalli, Qutubullapur, R.R. Dist. 500072, Andhra Pradesh, India
[b] Department of Chemistry, Osmania University, Hyderabad 500007, India

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ABSTRACT

An expedient procedure for the acylation of alcohols, phenols, and thiophenols using catalytic amount of $Zn(OTf)_2$ is described. This procedure is highly suitable for industrial application due to use of less toxic metal as a part of catalyst, short reaction time at ambient temperature, without any racemization of chiral alcohols.

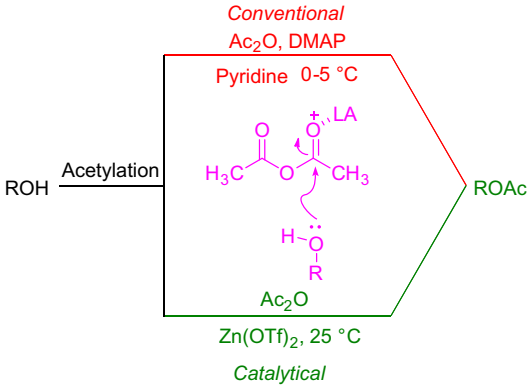
Acylation of an alcohol is an important transformation in organic synthesis. Although a myriad of literature evidence are available for acylation, the use of acyl chloride or acetic anhydride in the presence of pyridine[1] is the most commonly used procedure. Stoichiometric acylation is always considered to be inferior practice than the catalytic version of this reaction (Scheme 1).

Herein, we include hitherto known methods of acylation such as 4-(dimethyl amino)pyridine (DMAP),[2] $CoCl_2$,[3] $ZnCl_2$,[4a] ZnO,[4b,c] $CeCl_3$,[5] $ZrOCl_2{\cdot}8H_2O$,[6] molecular iodine,[7a,b] 3-nitro benzene boronic acid,[8] $La(NO_3)_3{\cdot}6H_2O$,[9] P_2O_5/Al_2O_3,[10] $NiCl_2$,[11] Co(II)salen-complex,[12] melamine trisulfonic acid,[13] $Sn(TPP)(BF_4)_2$,[14] alkylorthoformate–$ZnCl_2$–Ac_2O,[15] vanadium (IV) tetraphenylporphyrin,[16] [Ti^{IV}(salophen)$(OTf)_2$],[17] *N*-acyl 1,5-diazabicyclo [4.3.0] non-5-ene (DBN) tetraphenylborate salts,[18] iron(III) tosylate,[19] $Al(HSO_4)_3$,[20] and $NbCl_5$.[21]

As evident, a large number of methods for acylation are available, many of them suffer from limitations such as long reaction times, harsh reaction conditions, and use of expensive, moisture sensitive and toxic metal containing catalysts, formation of side products, and poor yields of desired products. In view of these limitations, there is still a need to develop mild and efficient catalytic protocol for the acetylation of alcohols.

Metal triflate catalyzed acylation procedures are well documented.[22] In most of the cases, the toxic metals as part of catalysts are not recommended for the synthesis of active pharmaceutical ingredients (APIs) due to stringent requirements by regulatory agencies as the traces of these need to be controlled in the order of ppms (parts per millions).[23,24] To accomplish this, a tedious work-up is required that becomes expensive due to material loss. Therefore, we attempted to develop non-or less toxic metal triflate catalyzed acylation and the catalyst is readily and cheaply available in the market. In comparison to other metals (Fig. 1), Zn is one of the most widely recommended due to its less toxic nature. $Zn(OTf)_2$, is very efficient and addresses the associated problems up to great extent. In general, such a catalytic process adds value to a better process efficiency as one can avoid purifications and thereby increase the isolated yield in comparison to hitherto known procedures.

In our endeavor, catalytic quantity of $Zn(OTf)_2$ was opted for acetylation of primary, secondary, benzylic and cyclic alcohols, phenols, and thiophenols using acetic anhydride, in excellent yields at room temperature using dichloromethane as solvent



Scheme 1. Conventional and catalytic acylation.

* Corresponding author.
E-mail address: rakeshwarb@drreddys.com (R. Bandichhor).

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medium or without solvent in a very short period of time. The reaction of alcohols **1** with Ac_2O proceeded smoothly in CH_2Cl_2. Gratifyingly, without solvent this protocol afforded product with excellent yields as shown in Scheme 2.

In most of cases, we obtained pure products hence there was no need to involve column chromatography.

In the absence of a catalyst, using same reaction conditions, the corresponding products were obtained in low yield even after prolonged reaction times (Table 2). The generality of this approach was established with the wide range of compounds as shown in Scheme 2.

When the chiral substrates were treated for acylation to obtain product **3g** & **3i** under these reaction conditions, racemization or epimerization was not observed in the acylated products. Furthermore, no Fries rearrangement products were obtained from **3c**, **3d**, **3e**, and **3f** substrates under these reaction conditions even after prolonged reaction time.

This strategy was extended not only to model substrates but it has found application in the synthesis of pharmaceutically relevant intermediates e.g. Abirterone (**3j**),[25,26] Ezetimibe (**3k**), and Eslicarbazapine acetate (**3t**).

We compared the experimental data obtained with or without solvent which revealed that there is no role of solvent as shown in Table 1. Moreover, efficient acylation was only obtained in the presence of $Zn(OTf)_2$ as shown in Table 2. Thus, our approach allowed us to gain quick access of the products as the rate of the reaction was found to be very fast in comparison to the non-catalytic reactions.

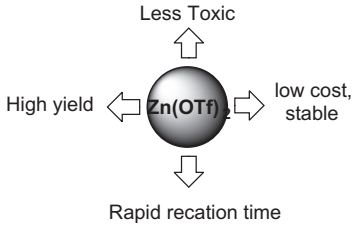
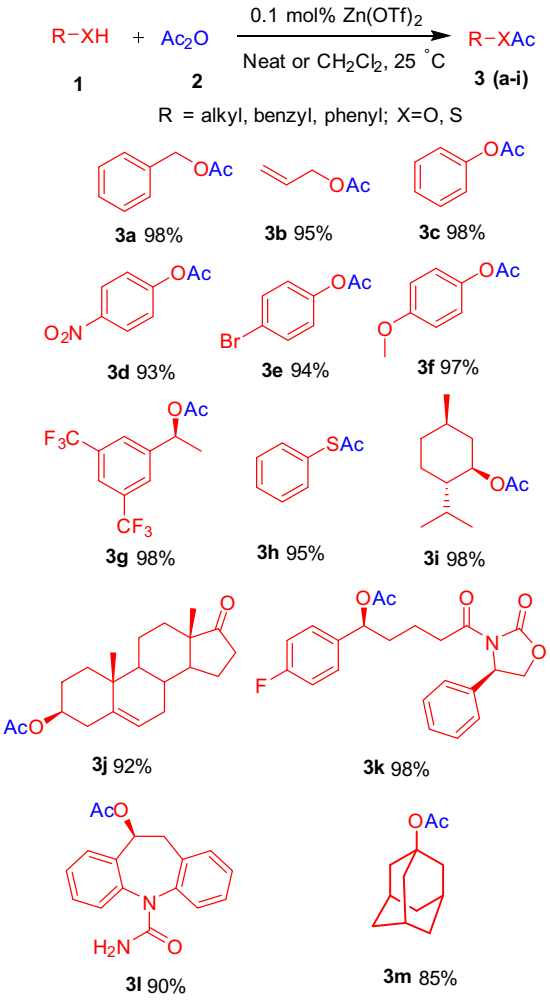


Figure 1. Industrial suitability of zinc triflate.



Scheme 2. $Zn(OTf)_2$ catalyzed acylation of various alcohols.

Table 1
Acetylation efficacy of various acyl donors catalyzed by 0.1 mol % $Zn(OTf)_2$ under solvent and solvent-free conditions

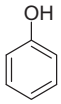
Acyl donor	Substrate	Solvents	Time	Yield
Acetic acid		DCM	2 (h)	—
Acetic anhydride		DCM	60 (s)	98
Acetic anhydride		—	10 (s)	98
Acyl chloride		DCM	10 (s)	98
Acyl chloride		—	10 (s)	97
Vinyl acetate	**2c**	DCM	2 (h)	—

Table 2
Acylation reaction time of various alcohols using acetic anhydride in the presence and absence of $Zn(OTf)_2$

Entry	$Zn(OTf)_2$ mediated		Without catalyst	
	Time (s)	% Conversion[a]	Time (h)	% Conversion[b]
3a	10	98	12	5
3b	15	95	12	3
3c	10	98	12	10
3d	10	93	12	5
3e	10	94	12	5
3f	10	97	12	4
3g	10	98	12	1
3h	15	95	12	4
3i	13	98	12	2
3k	18	98	—	—
3m	15	85	—	—

[a] >95% pure material without column.
[b] Tentative% conversion is based on the TLC which corresponds to material balance.

Table 3
Reuse of recovered catalyst

Substrate	Catalyst loading	Recycle times	Time[a] (s)
2f	0.1 mol %	0	10
	0.1 mol %	1	60
	0.1 mol %	2	180

[a] Conversion time up to completion of reaction by TLC.

Table 4
Comparison of pyridine (Py)/AC_2O mediated acylation with $Zn(OTf)_2$ catalyzed acylation

Substrate	Reagent/catalyst	Conditions	Time	Yield (%)
2l	Cat. DMAP, Py/Ac_2O[41]	CH_2Cl_2, reflux	2 h	90
	$Zn(OTf)_2$ (0.1 mol %)/Ac_2O	25–25 °C	60 s	90
2j	Py/Ac_2O	25–25 °C	3 h	87
	$Zn(OTf)_2$ (0.1 mol %)/Ac_2O	25–25 °C	30 s	92

We examined acylation by using recovered catalyst, and the results are presented in Table 3. It was observed that the potency of the catalyst decreases as the iterative application for the same increases.

Acylation of abiraterone intermediate **2j** lasted for 3 h using pyridine and acetic anhydride at 25–35 °C whereas our method offered the same product in less than a minute as shown in Table 4.

A typical procedure[27,28] was adopted to synthesize all the products which were found to be pure without column purification and characterized by comparison of their spectral data and physical prosperities with those of authentic samples.

We have developed and demonstrated a novel method by involving catalytic quantity of zinc triflate which can be considered as synthetically useful reagent system for acylation of alcohols and phenols.

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Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.039.

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