Facile Acetylation of Alcohols, Ethers and Ketals with Catalytic $FeCl_3$ in AcOH#

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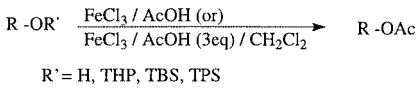
Abstract: A simple and efficient protocol for the conversion of alcohols, ethers and ketals to acetates using catalytic $FeCl_3$(5mol%) in AcOH, or AcOH (3eq) in CH_2Cl_2 in very high yield is reported. A variety of other acids such as CF_3CO_2H, HCO_2H, CH_2=$CHCO_2H$, $CH_3CH_2CO_2H$, $CH_3(CH_2)_2CO_2H$ have also been utilised for the acylation of alcohols successfully.

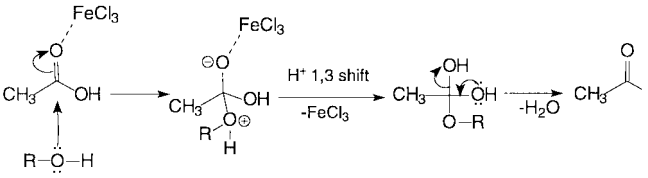
Key words: esterification, acetylation, catalyst

Functional group protection and deprotection is important in synthetic organic chemistry.[1] Amongst protecting groups for alcohols, the esters are the most important with acetate being the simplest and easiest of all. Acetylation[2] is most commonly performed using[3,4] reagents such as Ac_2O or AcCl in the presence of base, procedures which are not environmentally friendly. The use of HOAc/mineral acid for acetylation suffers from the problem of reversibility. Later modifications involving the use of Lewis acids[5-10] in combination with Ac_2O is inherently wasteful since half of the every acid anhydride molecule is lost as a carboxylic acid and the use of HOAc (as solvent)-lanthanide triflates[11-13] whilst efficient, is expensive. Herein, we report efficient $FeCl_3$ (5mol%) catalysed conversion of alcohols, ethers and ketals, by using either HOAc as solvent or CH_2Cl_2-AcOH (3 equiv) into acetates (Scheme 1) in very high yields.



Scheme 1

Initially, 4-phenyl butanol (entry 1, 1.0 mmol) in AcOH (5 mL) was treated with different mol% of $FeCl_3$(commercial) and 5 mol% was found to be optimal, giving (at room temperature) the acetate[14] in >95% yield in 1h. Having established the reaction conditions, a wide variety of alcohols as shown in Table-I were subjected to acetylation to give the desired acetates in 81-99% yield. The plausible role of the $FeCl_3$ may be the activation of acyl moiety by coordination, triggering the acylation process with concomitant regeneration of $FeCl_3$, followed by the loss of water (Scheme 2).



Scheme 2

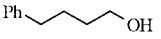
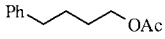
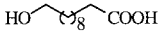
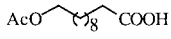
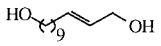
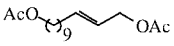
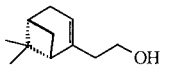
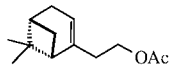
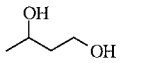
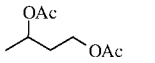
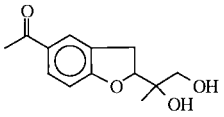
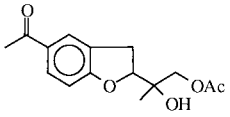
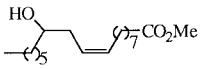
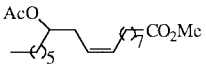
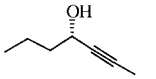
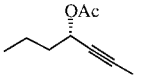
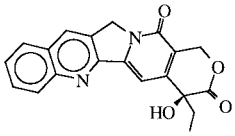
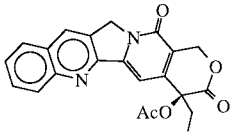
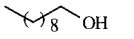
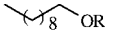
Generally primary alcohols underwent very fast acetylation, but in case of entries 6,7 and 8, longer reaction times were required. This aspect could be partly attributed to bidentate complexation of the catalyst. The secondary alcohols both in allylic, propargylic as well as steroid and terpenoid substrates required longer reaction timings. In the present reagent system, the tertiary alcohols (entries 8 and 14), were found unreacted. Under the similar reaction conditions the acylation of decanol was also effected with a variety of acids such as trifluoroacetic acid, formic acid, acrylic acid, propionic acid and butyric acid (Table 1, entry 15) in good yields.

We have extended this method to the one pot conversion of ethers and ketals to acetates (Table 2). Compounds having acid sensitive groups such as THP, TBS and TPS ethers as well as ketal (entries 1, 2 and 3) underwent deprotection with concomitant acetylation in the presence of 0.3 equiv of $FeCl_3$ in AcOH in 84-96% yields. In the case of entry 3, with 0.3 equiv $FeCl_3$, debenzylation was not observed as reported.[15]

After the above general study, next it was aimed at the use of equimolar quantity of AcOH for acetylation which not only is cost effective but also simplifies the work up procedure. Accordingly, 4-phenyl butanol (entry 1, 1.0 mmol) in CH_2Cl_2 (5 mL) containing HOAc (3 equiv)-$FeCl_3$ (0.3 equiv) was efficiently converted into acetate in 90% yield over a period of 6h. Under the modified reaction conditions, the acetylation was smooth and good yielding, however duration of reaction was found to be longer. The results of this study are summerised in Table 3.

Thus, in conclusion the present protocol offers a) mild reaction conditions using cheaper catalyst such as $FeCl_3$ (5 mol%)-AcOH for the efficient conversion of a wide variety of alcohols to acetates, b) acylation with other acids such as trifluoroacetic acid, formic acid, acrylic acid, propionic acid and butyric acid in good yields under the

Table 1 Conversion of alcohols to acetates

Entry No.	Starting Material	Product	Time(h)	Yield(%)
1.			1	99
2.			1	95
3.			1	88
4.	4-Nitrobenzyl alcohol	4-Nitrobenzyl acetate	6	95
5.			1	95†
6.	Tetrahydrofurfuryl alcohol	Tetrahydrofurfuryl acetate	9	85
7.			10	95
8.			8	87
9.			12	95
10.			8	95†
11.	Cholesterol	Cholesteryl acetate	13	86†
12.	3-Methoxy-17β-estrol	3-Methoxy-17β-estryl acetate	12	81†
13.	(-) Menthol	(-) Menthyl acetate	3	90†
14.			No reaction	
15			R = $COCH_3$	1	94
			R = CHO	1	88
			R = $COCF_3$	2	92
			R = $COCH{=}CH_2$	1	85
			R = $COCH_2CH_3$	3	92
			R = $CO(CH_2)_2CH_3$	3	90

† The optical purity of these compounds remained unaffected (based on optical rotation)

Table 2 Conversion of ethers and ketal to acetates

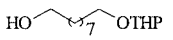
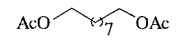
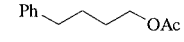
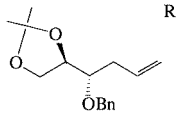
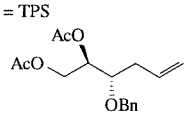
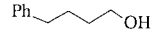
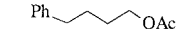
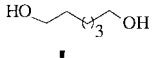
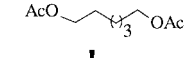
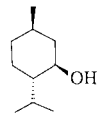
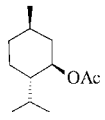
Entry	Starting Material	Product	Time(h)	Yield(%)
1.			1	96
2.				
		R = TBS	1.5	90
		R = TPS	2	84
3.			12	85

Table 3 Conversion of alcohols to acetates under modified condition

Entry	Starting Material	Product	Time(h)	Yield(%)
1.			6	90
2.			8	90
3.			24	80

above reaction conditions, c) the direct conversion of several acid sensitive groups into acetates in a one pot procedure and d) modified reaction conditions whereby the reaction could be carried out in CH_2Cl_2 using 3 equiv of HOAc instead using the later as solvent. Thus, this protocol is an efficient alternate to the existing methods for the preparation of acetates and other acylated products.

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References and Notes

[#]IICT communication No. 4201.

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