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Solid trichlorotitanium(IV) trifluoromethanesulfonate $TiCl_3(OTf)$ catalyzed efficient acylation of –OH and –SH: Direct esterification of alcohols with carboxylic acids and transesterification of alcohols with esters under neat conditions

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ABSTRACT

Solid $TiCl_3(OTf)$ catalyzed acetylation of alcohols, phenols and thiols with acetic anhydride in the absence of organic solvents at room temperature in a short reaction time. Benzoylation of alcohols, phenols and thiols also proceeded at higher temperature (~80 °C) under solvent-free conditions. Transesterification of alcohols with ethyl acetate and ethyl formate was also carried out efficiently in the presence of this catalyst. Direct esterification of different alcohols with different carboxylic acids also occurred readily in the presence of this catalyst and in the absence of any organic solvents.

1. Introduction

Protection of functional groups plays an important role in the synthesis of complex organic molecules such as natural products. Formylation and acetylation have found increasing attention as highly familiar protocols for protection of functional groups in this context.

Acetylation of alcohols, phenols and thiols is usually carried out by using acid anhydrides or acyl chlorides in the presence of protic acids [1], various Lewis acid catalysts or basic reagents such as 4-(dimethylamino)pyridine DMAP [2,3] and tributylphosphine [4]. Performing the reaction in the presence of acidic catalysts have found more attention and some of the recently reported methods include applying metal triflates such as cerium triflate [5], scandium triflate [6], bismuth triflate [7], copper triflate [8], gadolinium triflate [9] and aluminum triflate [10], metal halides such as tantalum chloride [11], zirconium(IV) chloride [12], indium chloride [13] and $ZrOCl_2{\cdot}8H_2O$ [14], and solid acid catalysts such as heteropoly acids [15], $Mg(NTf_2)_2$ [16] and alumina-supported MoO_3 [17].

Formylation of functional groups has the advantage of easy deprotection of the formyl group in the presence of the acetyl group and therefore, various formylating agents have also been reported [18]. Among formylating agents ethyl formate offers several advantages such as easy work-up, availability of the reagent and its relatively low cost. Some of the recently reported methods include formylation with ethyl formate in the presence of different reagents or catalysts, namely metal triflates such as $Ce(OTf)_4$ [19], heteropoly acids [20] and silphos $[PCl_{3-n}(SiO_2)_n]$ [21].

Direct esterification of alcohols with carboxylic acids is also very important transformation [22]. Along this line, articles published use Hf or $Sn[N_9SO_2C_8F_{17})_2]_4$ [23], Ph_2NH_2OTf [24] montmorilonite-enwrapped titanium [25], $CoCl_2{\cdot}6H_2O$ [26], I_2 [27], yttria–zirconia-based Lewis acid [28], $Sc(OTf)_3$ or lanthanide(III) triflates [29], hydrous zirconium oxide [30] and hafnium(IV) or zirconium(IV) salts [31]. Indirect esterification of alcohols in the presence of octamethylcyclotetrasiloxane catalyzed by $TiCl(OTf)_3$ [32] has been also reported. However, octamethylcyclotetrasiloxane is a dangerous compound for the environment and toxic for reproduction [33].

Titanium tetrachloride is extensively used in industrial processes as a catalyst especially for polymerization reactions. $TiCl_4$ is a watery liquid and a highly aggressive material whose major

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hazardous potential comes from the clouds of HCl and titanium compounds created when this substance is exposed to moisture. Therefore, its handling needs serious precautions.

Recently we have paid attention to a triflate analogue of $TiCl_4$; trichlorotitanium(IV) trifluoromethanesulfonate, $TiCl_3(OTf)$, which is a lemon yellow powder easier to handle than liquid $TiCl_4$. We have used $TiCl_3(OTf)$ as a catalyst for the conversion of epoxides to 1,3-dioxolanes [34a], aldol condensation of cycloalkanones with aromatic aldehydes [34b] and conversion of acetophenones to 1,3,5-triarylbenzenes [34c].

Esterification of alcohols with anhydrides or carboxylic acids is a fundamental process in organic chemistry. Esters are essential fine chemicals used widely in the manufacturing of flavors, pharmaceuticals and plastisizers, and as polymerization monomers, emulsifiers in the food and cosmetic industries and also environmentally benign solvents [35].

Recently direct condensation of carboxylic acids with alcohols in the presence of bulky diarylammonium arenesulfonates [36,37], hetropoly acids [38], fluorous ammonium triflate [39], surfactant combined catalysts [40] and polymer-supported sulfonamide [41] have also been reported.

Herein, we wish to report a new application of $TiCl_3(OTf)$ as an effective and solid catalyst in the acylation of alcohols, phenols and thiols with different anhydrides and introduce a simple and practical method for the formylation and acetylation of alcohols under neat conditions. Direct esterification of alcohols with carboxylic acids in the absence of any organic solvents has been achieved successfully using $TiCl_3(OTf)$ as a catalyst.

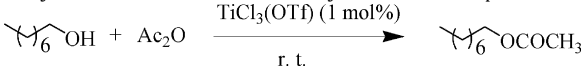
2. Results and discussion

2.1. Acetylation of –OH and –SH groups with acetic anhydride

Solid trichlorotitanium(IV) trifluoromethanesulfonate $TiCl_3(OTf)$ was prepared according to the literature [42]. First we investigated the catalytic activity of $TiCl_3(OTf)$ for acetylation of 1-octanol with acetic anhydride in the presence of 1.0 mol% of $TiCl_3(OTf)$ at room temperature in CH_2Cl_2 and or under solvent-free conditions. The reaction under solvent-free conditions was very clean and completed much more rapidly than the reaction using CH_2Cl_2 as solvent. The results of this study are summarized in Table 1.

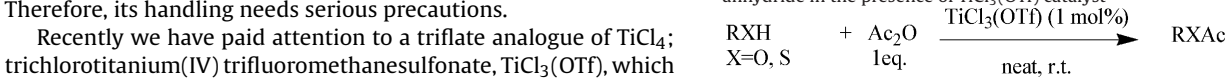
To explore the generality and scope of acetylation reaction catalyzed by $TiCl_3(OTf)$, the reaction was examined with structurally divers alcohols, phenols and thiols. From an atom-economical standpoint, most of the reactions were carried out with 1 equiv. of Ac_2O, unless otherwise stated, under solvent-free conditions at room temperature in the presence of 1 mol% of $TiCl_3(OTf)$. The results are summarized in Table 2. The reactions were clean and fast and the products were isolated mostly in excellent yields after simple work-up using a short pad of silica gel if necessary. No competitive fries rearrangement was observed for phenolic substrates (Table 2, entries 15–23). We have observed that acetylation of 1-hydroxynaphthaline required 2 molar equivalents of acetic anhydride for completion of the reaction and the desired ester was isolated in 84% yield after 10 min (Table 2, entry 21). Secondary alcohols (Table 2, entries 9–12) did not experience any competitive dehydration reaction; however, minor allylic rearrangement product (18%) was observed, when allyl alcohol (Table 2, entry 8) was acetylated under similar reaction conditions. *p*-Methoxybenzyl alcohol (Table 2, entry 5) produced a mixture of unidentified products. *p*-Methoxyphenol was acetylated smoothly and the –OMe group remained intact by this protocol. Acetylation of tertiary alcohols like *t*-BuOH and adamantanol proceeded smoothly with excellent yields (Table 2, entries 13 and 14). We have observed that acetylation of α-hydroxy phosphonates with acetic anhydride in

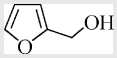
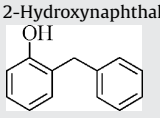
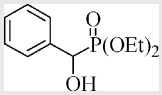
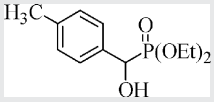
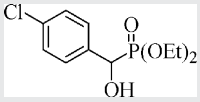
Table 1
Acetylation of 1-octanol with acetic anhydride at room temperature



Entry	Condition	Time	GC yield (%)
1	No solvent/Ac_2O (1 equiv.)	25 min	100
2	No solvent/Ac_2O (2 equiv.)	10 min	100
3	CH_2Cl_2/Ac_2O (1 equiv.)	7 h	100
4	CH_2Cl_2/Ac_2O (2 equiv.)	4 h	100

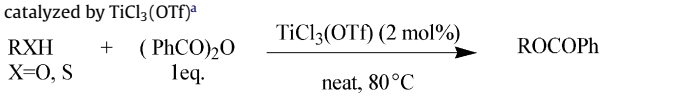
Table 2
Acetylation of alcohols, phenols, α-hydroxyphosphonates and thiols with acetic anhydride in the presence of $TiCl_3(OTf)$ catalyst[a]

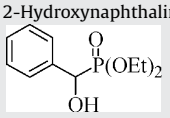
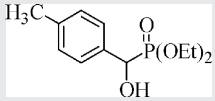
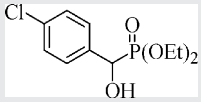


Entry	Substrate	Time (min)	Yield (%)[b]
1	1-Octanol	25	91
2	$PhCH_2CH_2OH$	10	91
3	$PhCH_2OH$	Immediately	96
4	*p*-NO_2-$C_6H_4CH_2OH$	2	96
5	*p*-MeO-$C_6H_4CH_2OH$	–	–[c]
6	Ph_2CHOH	1	92
7		5	100[d]
8	3-Methyl-2-butene-1-ol	5	77[e]
9	2-Octanol	120	87
10	Cyclohexanol	45	100[d]
11	Menthol	30	91
12	Cholesterol	60	94[f]
13	*t*-BuOH	60	99[d]
14	Adamantanol	45	94
15	PhOH	2	87
16	*o*-Me-C_6H_4OH	8	88
17	*p*-MeO-C_6H_4OH	1	87
18	*p*-NO_2-C_6H_4OH	60	85
19	*p*-Br-C_6H_4OH	6	95
20	Hydroquinone	5	92
21	1-Hydroxynaphthaline	10	84[g]
22	2-Hydroxynaphthaline	10	92
23		5	87
24		30	89[h]
25		30	92[h]
26		120	94[h]
27	PhSH	Immediately	91
28	$PhCH_2SH$	Immediately	93

[a] All products were identified by their ^1H NMR and ^{13}C NMR spectra.
[b] Yields refer to isolated products unless otherwise stated.
[c] Mixture of unidentified products were obtained.
[d] GC yields.
[e] Rearranged product was obtained in 18% yield.
[f] The reaction was carried out with 2 equiv. of Ac_2O in THF as a solvent.
[g] The reaction was carried out with 2 equiv. of Ac_2O. When 1 equiv. of Ac_2O was used the reaction was not completed even after 4 h.
[h] The reaction was carried out at 70 °C in an oil bath.

Table 3
Benzoylation of alcohols, phenols, α-hydroxy phosphonates and thiols by $(PhCO)_2O$ catalyzed by $TiCl_3(OTf)$[a]



Entry	Alcohol or phenol	Time	Isolated yield (%)
1	$CH_3(CH_2)_6CH_2OH$	10 min	97
2	$PhCH_2CH_2OH$	15 min	89
3	$PhCH_2OH$	5 min	87
4	$CH_3(CH_2)_5CH(OH)CH_3$	15 min	92
5	$PhCH(OH)CH_3$	120 min	–[b]
6	PhOH	10 min	85
7	1-Hydroxynaphthaline	90 min	87
8	2-Hydroxynaphthaline	20 min	89
9		2 h	90
10		2 h	88
11		6 h	92
12	PhSH	5 min	92
13	$PhCH_2SH$	5 min	88

[a] All products were characterized with their ^1H NMR and ^{13}C NMR spectra.
[b] Mixture of products were obtained.

the presence of 1 mol% of $TiCl_3(OTf)$ required higher temperature and that the reaction proceeded with excellent yields at 70 °C in the absence of any solvents without C–P bond cleavage (Table 2, entries 24–26). Cholesterol was also acetylated by two equimolar acetic anhydride and catalyzed by 1 mol% of $TiCl_3(OTf)$ in solution of THF at room temperature with an excellent yield (Table 2, entry 12). Thiols were also acetylated in excellent yields (Table 2, entries 27 and 28) under solvent-free conditions using one molar equivalent of acetic anhydride in the presence of 1 mol% of $TiCl_3(OTf)$.

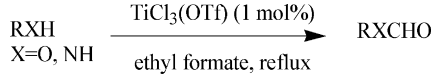
2.2. Benzoylation of –OH and –SH groups with benzoic anhydride

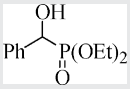
Reported benzoylation reactions of functional groups such as –OH and –SH are more limited in number than their corresponding acetates in the literature. The catalytic activity of $TiCl_3(OTf)$ for benzoylation of alcohols, phenols and thiols with benzoic anhydride was also studied. Different alcohols and phenols were treated with stoichiometric amounts of benzoic anhydride in an oil bath at 80 °C in the presence of 2 mol% of the catalyst under neat conditions. Benzoylation reaction of alcohols and phenols was cleanly completed after a short period of time (Table 3, entries 1–8) and yields of the desired benzoates were excellent, except in the case of 1-phenyl ethanol in which instead the expected benzoate a complex mixture of products were furnished (Table 3, entry 5). α-Hydroxy phosphonates (Table 3, entries 9–11) and thiols (Table 3, entries 12 and 13) were also benzoylated in short reaction times with excellent yields under similar reaction conditions.

2.3. Formylation of alcohols and amines using ethyl formate as a formylating agent

As we have mentioned in introduction, due to the easy deprotection of the formyl group, costs and the work-up, formylation has found much attention in protection of different functional groups. Therefore, we investigated the formylation of alcohols with ethyl

Table 4
Formylation of alcohols and amines using $TiCl_3(OTf)$ as a catalyst in refluxing ethyl formate[a]



Entry	Substrate	Time	Yield (%)[b]
1	$CH_3(CH_2)_6CH_2OH$	24 h	77[c]
2	$CH_3(CH_2)_6CH_2OH$	3 h	87
3	$PhCH_2CH_2OH$	1.5 h	89
4	$PhCH_2CH_2CH_2OH$	1.5 h	92
5	$PhCH_2OH$	4 h	83
6	p-NO_2-$C_6H_4CH_2OH$	14 h	75
7	p-MeO-$C_6H_4CH_2OH$	15 min	–[d]
8	Ph_2CHOH	3 h	92
9	3-Methyl-2-butene-1-ol	1 h	81
10	$CH_3(CH_2)_5CH(OH)CH_3$	5 h	88
11	Cholestrol	7	92
12	Menthol	12 h	90
13	Adamantanol	20 h	72
14	PhOH	4 h	NR
15		4 h	NR
16	2-Hydroxynaphthaline	4 h	NR
17	Aniline	12 h	91
18	Benzylamine	15 min	88
19	Dibenzylamine	1.5 h	93
20	*N*-Methyl benzylamine	20 min	89
21	*N*-Methyl cyclohexylamine	3 h	95
22	Octylamine	30 min	89
23	PhSH	4 h	NR
24	$PhCH_2SH$	4 h	NR

[a] All products were identified by their ^1H NMR and ^{13}C NMR spectra.
[b] Yields refer to isolated product.
[c] At room temperature, GC yield.
[d] A mixture of products were obtained.

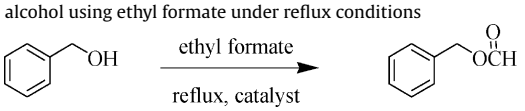
formate in the presence of $TiCl_3(OTf)$ as a catalyst. First, 1-octanol (1 mmol) was treated with ethyl formate (2 mL) in the presence of 1.0 mol% of $TiCl_3(OTf)$ at room temperature. The reaction was not completed even after 24 h (Table 4, entry 1). However, when the reaction was conducted under reflux condition the reaction proceeded well and after 3 h the desired ester was isolated in 87% (Table 4, entry 2). Formylation of other alcohols has also been accomplished successfully with ethyl formate under reflux condition. We have also found that this protocol is applicable for formylation of structurally different amines as well to produce the corresponding amides in excellent yields (Table 4, entries 17–22). However, α-hydroxy phosphonates, thiols and phenols did not react and the substrates were isolated intactly after the appropriate reaction times (Table 4, entries 14–16, 23, 24).

In order to show advantage of $TiCl_3(OTf)$ in catalytic activity, we have studied the reaction of benzyl alcohol with ethyl formate in the presence of different acids and have compared the results as presented in Table 5. The results show that $TiCl_3(OTf)$ is much more effective than HCl which may be liberated by the reaction of ROH with $TiCl_3(OTf)$ during the reaction. The catalytic activity of $TiCl_3(OTf)$ is also more pronounced than either $AlCl_3$ or $FeCl_3$. The reaction in the presence of HOTf which is a strong protic acid proceeded well but took longer reaction time (6 h).

2.4. Acetylation of alcohols by ethyl acetate as an acetylating agent

Acetylation of alcohols via transesterification reaction using ethyl acetate as solvent and the reagent is a useful and practical protocol. $TiCl_3(OTf)$ has proved to be a highly efficient catalyst

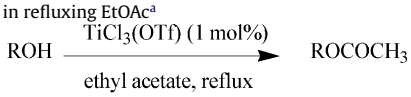
Table 5
Comparison between different acid catalysts and $TiCl_3(OTf)$ for formylation of benzyl alcohol using ethyl formate under reflux conditions

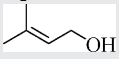
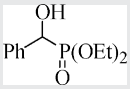


Entry	Catalyst	Time (h)	GC yield (%)
1	$TiCl_3(OTf)$ (1 mol%)	4	100
2	aq. HCl (3 mol%)	10	30
3	$AlCl_3$ (1 mol%)	8	85
4	$FeCl_3$ (1 mol%)	8	80
5	TfOH	6	100

(1.0 mol%) for this purpose under reflux conditions. By this method, structurally diverse alcohols were esterified easily and their corresponding acetates were isolated in good to excellent yields (Table 6). The reaction of primary alcohols in refluxing ethyl acetate in the presence of 1.0 mol% of $TiCl_3(OTf)$ provided the desired acetates in 87–92% yields (Table 6, entries 1–3). Benzyl and allyl alcohols reacted faster than the other types of alcohol (Table 6, entries 4 and 8). However, acetylation of *p*-nitrobenzyl alcohol was sluggish and the corresponding ester was isolated in only 60% yield after 24 h (Table 6, entry 5). We have observed by GC that *p*-methoxybenzyl alcohol produced its acetyl ester and dibenzyl ether in 40 and 30% yields, respectively (Table 6, entry 6). Acetylation of cholesterol and menthol by this transesterification method did not proceed well and the corresponding esters were isolated in poor yields (Table 6, entries 10 and 11). Adamantanol did not undergo esterification and was isolated intactly after 8 h (Table 6, entry 12). Amines, thiols, phenols and α-hydroxy phosphonates were quite inactive towards esterification by ethyl acetate in the presence of this catalyst.

Table 6
Transesterification of alcohols in the presence of $TiCl_3(OTf)$ (1.0 mol%) as a catalyst in refluxing EtOAc[a]



Entry	Substrate	Time (h)	Isolated yield (%)
1	$CH_3(CH_2)_6CH_2OH$	6	87
2	$PhCH_2CH_2OH$	5	89
3	$PhCH_2CH_2CH_2OH$	5	92
4	$PhCH_2OH$	2	83
5	*p*-NO_2-$C_6H_4CH_2OH$	24	60[b]
6	*p*-OMe-$C_6H_4CH_2OH$	1	–[c]
7	Ph_2CHOH	10	92
8		1	81
9	$CH_3(CH_2)_5CH(OH)CH_3$	12	88
10	Cholestrol	20	<50
11	Menthol	20	<10
12	Adamantanol	8	NR
13		8	NR
14	$PhCH_2NH_2$	8	NR
15	phenol	8	NR
16	$PhCH_2SH$	8	NR

[a] All products were identified by their ^1H NMR and ^{13}C NMR spectra.
[b] The reaction did not complete even after 48 h.
[c] The desired acetate was obtained in 40% and the yield of the corresponding ether was 30%.

2.5. Selective protection of different functional groups with acid anhydrides and ethyl formate

The competitive reaction between different functional groups in formylation, acetylation and benzoylation reactions is also notable in the presence of this catalyst (Table 7). Formylation of a molecule carrying both –SH and –OH groups led to *O*-formylation as a sole product with a strong stingy odor (Table 7, entry 1). A similar reaction with a substrate carrying both $–NH_2$ and –OH groups resulted in *N*-formylation reaction (Table 7, entry 2). The above-mentioned competitive reactions were also investigated in the acylation reactions (Table 7, entries 3–8). Our results in Table 6 explain that nitrogen nucleophile reacts more rapidly than oxygen nucleophile and the oxygen nucleophile reacts more easily than sulfur nucleophile. The competitive reactions between primary and secondary alcohols and between alcohols and phenols were also investigated. Selective acetylation and formylation of benzyl alcohol proceeded smoothly in the presence of phenol (Table 7, entries 9 and 10). Formylation of 1-octanol in the presence of phenol proceeded with high selectivity (Table 7, entries 11) whereas acetylation and benzoylation of similar substrates proceeded with low selectivity (Table 7, entries 12 and 13). This method is not suitable for selective acetylation, benzoylation and formylation of primary, secondary and benzylic alcohols in the presence of each other (Table 7, entries 14–18). We have also tried monoacetylation of diols such as 1,4-butanediol with Ac_2O (1 equiv.) in the presence of $TiCl_3(OTf)$ (1.0 mol%) in solvent and under solvent-free conditions. Unfortunately a mixture of mono- and diacetylated products was observed (Table 7, entries 19 and 20).

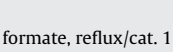
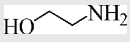
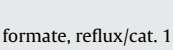
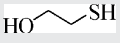
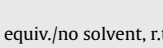
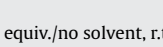
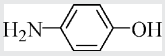
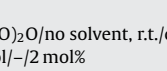
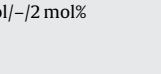
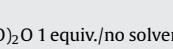
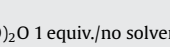
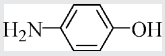
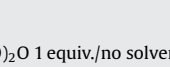
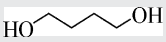
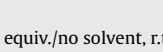
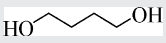
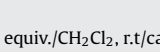
2.6. Direct esterification of alcohols with carboxylic acids

Finally, we have examined direct esterification of alcohols with carboxylic acids. First we tried the reaction of 1-octanol and benzyl alcohol with acetic acid as model reactions under different reaction conditions. Acetylation of benzyl alcohol with 1 equiv. of HOAc in the presence of 1 mol% of $TiCl_3(OTf)$ at 115 °C resulted in an insoluble polymeric material (Table 8, entry 1). However, esterification of 1-octanol with 1.0 and 1.5 equiv. of HOAc under similar reaction conditions proceeded well to produce the corresponding ester in 84 and 89% yield, respectively plus 4–8% of the corresponding aldehyde (Table 8, entries 2 and 3). When the reaction of benzyl alcohol and 1-octanol were carried out with 2 equiv. of HOAc the corresponding esters were produced as the sole products in quantitative yields (Table 8, entries 4 and 5). When the reaction was carried out at lower temperature, the reaction was accomplished more slowly (Table 8, entry 6). In the absence of the catalyst the reaction between benzyl alcohol and acetic acid was not completed even after 24 h at 115 °C and only 75% of the desired ester was detected by GC analysis (Table 8, entries 7 and 8).

In order to show the general applicability of the method we have employed the above reaction conditions for esterification of different alcohols with 2 equiv. of HOAc in the presence of $TiCl_3(OTf)$ (1.0 mol%). Primary, secondary, allylic and benzylic alcohols reacted smoothly and the desired acetates were obtained in short reaction times (Table 9, entries 1–9). Reaction of adamantanol and menthol proceeded with lower yields at longer reaction times (Table 9, entries 10 and 11). Other carboxylic acids such as propionic acid, chloroacetic acid, trichloroacetic acid, phenylacetic acid, cinnamic acid, lauric acid, stearic acid and benzoic acid also reacted with 1-octanol under similar conditions producing the corresponding esters in high yields (Table 9, entries 12–19).

In order to show the advantage of $TiCl_3(OTf)$ over other catalysts used for direct condensation of benzyl alcohol with acetic acid, we have tabulated some of the results in Table 10. As evident from

Table 7
$TiCl_3(OTf)$ used for selective protection of different functional groups with acid anhydrides and ethyl formate

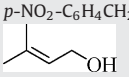
Run	Substrate	Reaction condition	Products	Time	Yield (%)[a]
1		Ethyl formate, reflux/cat. 1 mol%	 	4 h	95[b] 0
2		Ethyl formate, reflux/cat. 1 mol%	 	10 min	100 0
3		Ac_2O 1 equiv./no solvent, r.t/cat. 1 mol%	 	1 h	100 0
4		Ac_2O 1 equiv./no solvent, r.t/cat. 1 mol%	 	1 min	100 0
5		$(CH_3CO)_2O$/no solvent, r.t./cat. 1mmol/–/2 mol%	 	1 min	100 0
6		$((PhCO)_2O$ 1 equiv./no solvent, 70 °C/cat. 2 mol%	 	30 min	100 0
7		$(PhCO)_2O$ 1 equiv./no solvent, 70 °C/cat. 2 mol%	 	2 min	100 0
8		$(PhCO)_2O$ 1 equiv./no solvent, 70 °C/cat. 2 mol%	 	10 min	100 0
9	$PhCH_2OH$ (1 mmol) + PhOH (1 mmol)	Ac_2O 1 equiv./no solvent, r.t/cat. 1 mol%	$PhCH_2OAc$ PhOAc	10 min	100 0
10	$PhCH_2OH$ (1 mmol) + PhOH (14 mmol)	Ethyl formate, reflux/cat. 1 mol%	$PhCH_2OCOH$ PhOCOH	4 h	100 0
11	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + PhOH (1 mmol)	Ac_2O 1 equiv./no solvent, r.t/cat. 1 mol%	$CH_3(CH_2)_6CH_2OAc$ PhOAc	1 h	88 12
12	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + PhOH (1 mmol)	Ethyl formate, reflux/cat. 1 mol%	$CH_3(CH_2)_6CH_2OCOH$ PhOCOH	4 h	100 0
13	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + PhOH (1 mmol)	$(PhCO)_2O$ 1 equiv./no solvent, 70 °C/cat. 2 mol%	$CH_3(CH_2)_6CH_2OCOPh$ PhOCOPh	15 min	50 50
14	$PhCH_2OH$ (1 mmol) + $CH_3(CH_2)_6CH_2OH$ (1 mmol)	Ethyl formate, reflux/cat. 1 mol%	$PhCH_2OCOH$ $CH_3(CH_2)_6CH_2OCOH$	5 h	100 100
15	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + $CH_3(CH_2)_5CH(OH)CH_3$ (1 mmol)	Ac_2O 1 equiv./no solvent, r.t/cat. 1 mol%	$CH_3(CH_2)_6CH_2OAc$ $CH_3(CH_2)_5CH(OAc)CH_3$	1 h	80 20
16	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + $CH_3(CH_2)_5CH(OH)CH_3$ (1 mmol)	Ac_2O 1 equiv./CH_2Cl_2, r.t/cat. 1 mol%	$CH_3(CH_2)_6CH_2OAc$ $CH_3(CH_2)_5CH(OAc)CH_3$	8 h	75 25
17	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + $CH_3(CH_2)_5CH(OH)CH_3$ (1 mmol)	$(PhCO)_2O$ 1 equiv./no solvent, 70 °C/cat. 2 mol%	$CH_3(CH_2)_6CH_2OCOPh$ $CH_3(CH_2)_5CH(OCOPh)CH_3$	1 h	80 20
18	$CH_3(CH_2)_6CH_2OH$ (1 mmol) + $CH_3(CH_2)_5CH(OH)CH_3$ (1 mmol)	Ethyl formate, reflux/cat. 1 mol%	$CH_3(CH_2)_6CH_2OCOH$ $CH_3(CH_2)_5CH(OCOH)CH_3$	4 h	100 90
19		Ac_2O 1 equiv./no solvent, r.t/cat. 1 mol%	 	5 h	40 30
20		Ac_2O 1 equiv./CH_2Cl_2, r.t/cat. 1 mol%	 	5 h	40 30

[a] The percentage of the products in the reaction mixture was determined by GC analysis.
[b] Trace of unreacted substrate was remained after 4 h.

Table 8
Optimization of reaction conditions for direct esterification of alcohols with acetic acid in the presence of $TiCl_3(OTf)$ (1.0 mol%) as catalyst

Entry	Alcohol	Alcohol (mmol):acetic acid (mmol)	Condition temperature/time	GC yield (%)
1	$PhCH_2OH$	1:1	115 °C/10 min	Polymeric compounds
2	$CH_3(CH_2)_6CH_2OH$	1:1	115 °C/6 h	84 + aldehyde 8%
3	$CH_3(CH_2)_6CH_2OH$	1:1.5	115 °C/6 h	87 + aldehyde 4%
4	$CH_3(CH_2)_6CH_2OH$	1:2	115 °C/30 min	100
5	$PhCH_2OH$	1:2	115 °C/20 min	100
6	$PhCH_2OH$	1:2	94 °C/6 h	96
7	$CH_3(CH_2)_6CH_2OH$	1:2 without catalyst	115 °C/24 h	40
8	$PhCH_2OH$	1:2 without catalyst	115 °C/24 h	75

Table 9
Direct esterification of different alcohols with different 2.0 molar ratios of carboxylic acids

Entry	Alcohol	Acid	Time	Isolated yields (%)
1	$CH_3(CH_2)_6CH_2OH$	CH_3CO_2H	30 min	94
2	$CH_3(CH_2)_5CH(OH)CH_3$	CH_3CO_2H	45 min	92
3	$PhCH_2OH$	CH_3CO_2H	20 min	89
4	*p*-OMe-$C_6H_4CH_2OH$	CH_3CO_2H	2 min	85
5	*p*-NO_2-$C_6H_4CH_2OH$	CH_3CO_2H	1 h	91
6		CH_3CO_2H	2 min	78
7	Ph_2CHOH	CH_3CO_2H	1 h	85[a]
8	$PhCH_2CH_2OH$	CH_3CO_2H	20 min	88
9	$PhCH_2CH_2CH_2OH$	CH_3CO_2H	20 min	90
10	Adamantanol	CH_3CO_2H	6 h	75
11	Menthol	CH_3CO_2H	4 h	77
12	$CH_3(CH_2)_6CH_2OH$	$CH_3CH_2CO_2H$	30 min	91
13	$CH_3(CH_2)_6CH_2OH$	$PhCH_2CO_2H$	25 min	87
14	$CH_3(CH_2)_6CH_2OH$	$ClCH_2CO_2H$	25 min	89
15	$CH_3(CH_2)_6CH_2OH$	Cl_3CCO_2H	5 min	86
16	$CH_3(CH_2)_6CH_2OH$	$PhCO_2H$	4 h	90
17	$CH_3(CH_2)_6CH_2OH$	Cinnamic acid	1.5 h	92
18	$CH_3(CH_2)_6CH_2OH$	Lauric acid	25 min	95
19	$CH_3(CH_2)_6CH_2OH$	Stearic acid	25 min	94

[a] The reaction was carried out in the presence of 5.0 equiv. of acid.

Table 10
Reaction of benzyl alcohol with acetic acid in the presence of different catalysts

Entry	Catalyst/solvent/condition	Catalyst	Time (h)	Yield (%)	Reference
1	$CoCl_2{\cdot}6H_2O$/AcOH/60 °C	2 mol%	1	98	[26]
2	ZrO_2/toluene/reflux (alcohol/acid: 10/1)	1 g	1	100	[30]
3	Yttria–zirconia-based Lewis acid/–/110 °C (alcohol/acid: 1/5)	20% (w/w with respect to the substrate)	4	94	[28]
4	$Ce(OTf)_4$/AcOH/r.t.	5 mol%	6	90	[19]
5	$K_5CoW_{12}O_{40}{\cdot}3H_2O$/AcOH/reflux	1 mol%	1	90	[20]

the results, the required ratio for the most catalysts used for this purpose is >1.0 mol% and also the required reaction times are much longer than what we have observed using $TiCl_3(OTf)$ (1–6 h), and also excess amounts of AcOH need to be used.

3. Experimental

3.1. General remarks

Chemicals were either prepared in our laboratories or were purchased from Fluka or Merck. The purity of the products was determined by GC on a Shimadzu model GC-14A instrument or by TLC on silica gel polygram SIL G/UV 254 plates. The IR spectra were recorded on a PerkinElmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker avance DPX 250 MHz spectrometer.

3.2. Typical procedure for acetylation of 2-benzyl phenol with acetic anhydride

To a mixture of 2-benzylphenol (184 mg, 1 mmol) and freshly distilled acetic anhydride (102 mg, 1 mmol), $TiCl_3(OTf)$ (3 mg, 1 mol%) was added at room temperature. After the mixture was stirred at room temperature for 5 min, 15 mL diethyl ether was added and washed with 15 mL of 10% solution of sodium hydrogen carbonate, and the product was extracted with ether. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude product. Further purification of 2-benzyl phenyl acetate was done by column chromatography on silica gel (194 mg, 87%); ^{1}H NMR δ (ppm): 2.18 (s, 3H), 3.88 (s, 2H), 6.95–7.48 (m, 9H); ^{13}C NMR δ (ppm): 20.8, 36.4, 115.2, 121.5, 126.2, 127.5, 128.5, 128.6, 131.0, 139.8, 149.6, 169.6.

3.3. Typical procedure for benzoylation of 2-hydroxynaphthaline with benzoic anhydride

In a round-bottom flask, 2-hydroxynaphthaline (144 mg, 1 mmol) was treated with benzoic anhydride (226 mg, 1 mmol) in the presence of $TiCl_3(OTf)$ (6 mg, 2 mol%). The temperature was kept at 80 °C by soaking the flask in an oil bath. The reaction was completed after 20 min. Then Et_2O and $NaHCO_3$ aq. was added, and organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O three times, and the organic layers were

combined and dried over Na_2SO_4 and filtrated. Evaporation of solvent followed by column chromatography on silica gel afforded 2-naphthyl benzoate (220 mg, 89%) which was identified with its spectral data. ^{1}H NMR δ (ppm): 7.49 (d, J = 11 Hz, 1H), 7.59–7.60 (m, 4H), 7.68 (d, J = 6 Hz, 1H), 7.78 (s, 1H), 7.91–7.97 (m, 3H), 8.34 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ (ppm): 118.8, 121.3, 125.8, 126.6, 127.9, 129.0, 129.5, 129.6, 131.6, 133.3, 133.7, 133.9, 148.7, 165.4.

3.4. Typical procedure for benzoylation of benzyl mercaptane with benzoic anhydride

In a round-bottom flask, benzyl mercaptane (0.12 mL, 1 mmol) was treated with benzoic anhydride (226 mg, 1 mmol) in the presence of $TiCl_3(OTf)$ (6 mg, 2 mol%). The temperature was kept at 80 °C by soaking the flask in an oil bath. The reaction was completed after 5 min. Then Et_2O and NaOH aq. was added, and organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O three times, and the organic layers were combined and dried over Na_2SO_4 and filtrated. By using short column chromatography, pure thiobenzyl benzoate was obtained (201 mg, 88%) which was identified by comparison of its spectral data with those of an authentic sample. ^{1}H NMR δ (ppm): 4.29 (s, 2H), 7.23–7.41 (m, 8H), 7.94 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ (ppm): 32.2, 127.0, 128.1, 128.5, 128.7, 133.4, 136.8, 137.5, 191.2.

3.5. Typical procedure for formylation of 3-phenyl-1-propanol in refluxing ethyl formate

$TiCl_3(OTf)$ (3 mg, 1 mol%) was added to a mixture of 3-phenyl-1-propanol (136 mg, 1 mmol) in 4.0 mL of ethyl formate. The reaction mixture was stirred under reflux condition and monitored by TLC. After completion of the reaction (1.5 h), the reaction mixture was washed with water and extracted with ether (20 mL), and then the organic layer was dried over Na_2SO_4 and filtered. The solvent was removed and pure 3-phenyl-1-propyl formate was obtained after a short pad of column chromatography in 151 mg, 92% yield; ^{1}H NMR δ (ppm): 1.88–2.02 (m, 2H), 2.64 (t, J = 5Hz, 2H), 4.13 (t, J = 7.5 Hz, 2H), 7.15–7.30 (m, 5H), 8.03 (s, 1H); ^{13}C NMR δ (ppm): 30.1, 32.0, 63.2, 126.1, 128.4, 128.5, 140.9, 161.0.

3.6. Typical procedure for acetylation of benzhydrol in refluxing ethyl acetate

$TiCl_3(OTf)$ (3 mg, 1 mol%) was added to a mixture of benzhydrol (184 mg, 1.0 mmol) in 4.0 mL of ethyl acetate. The reaction mixture was stirred under reflux condition and monitored by TLC. After 10 h, the reaction was completed. The resulting reaction mixture was washed with water and extracted with ether (20 mL). The organic layer was separated and dried over Na_2SO_4 and filtered. Evaporation of the solvent followed by column chromatography using a short pad of silica gel afforded benzhydryl acetate (208 mg, 92%); ^{1}H NMR δ (ppm): 2.01 (s, 3H), 6.88 (s, 1H), 7.18–7.33 (m, 10H); ^{13}C NMR δ (ppm): 21.2, 77.9, 127.5, 128.4, 129.2, 140.4, 170.0.

3.7. Typical procedure for esterification of 1-octanol with benzoic acid

In a round-bottom flask, 1-octanol (130 mg, 1 mmol) was treated with benzoic acid (244 mg, 2 mmol) in the presence of $TiCl_3(OTf)$ (3 mg, 1 mol%). The temperature was kept at 115 °C by soaking the flask in an oil bath. The reaction was completed after 4 h. Upon addition of Et_2O and NaOH aq. to the reaction mixture, organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O (3 mL × 15 mL), and the combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvent followed by column chromatography on silica gel afforded 1-octyl benzoate (210 mg, 90%); ^{1}H NMR δ (ppm): 0.80 (t, J = 6.4 Hz, 3H), 1.18–1.39 (m, 10H), 1.60–1.69 (m, 2H), 4.18 (t, J = 6.6 Hz, 2H), 7.35–7.46 (m, 3H), 7.93 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ (ppm): 14.0, 22.6, 26.2, 28.7, 29.2, 29.7, 31.7, 65.0, 128.5, 129.5, 130.5, 133.2, 166.6.

4. Conclusion

In this study we have introduced solid $TiCl_3(OTf)$ as an active catalyst for highly useful reactions such as acylation of phenols, alcohols and thiols. In the presence of this catalyst only stoichiometric amounts of acylating agents are necessary for both acetylation and benzoylation reactions. Moreover, this catalyst offers mild reaction condition with short reaction times, performing the acylation reactions under neat condition.

The catalytic activity of $TiCl_3(OTf)$ for selective formylation of alcohols and amines in the presence of other functional groups is worthy of mentioning. The advantage of $TiCl_3(OTf)$ catalyst over some other catalysts for formylation of alcohols has also been shown. Direct esterification of carboxylic acids and alcohols has been also conducted in the presence of this catalyst with high to excellent yields.

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