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Catalytic Esterification of Alcohols, Carboxylic Acids and Transesterification Reactions with Cerium(IV) Triflate

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Esterification reactions of alcohols with acetic, chloroacetic, trifluoroacetic, propionic, stearic, and benzoic acids were catalyzed with $Ce(OTf)_4$ in a solvent or under solvent-free conditions with high yields. The formylation and acetylation of primary and secondary alcohols were also easily achieved in ethyl formate and ethyl acetate. A high retention of the configuration was observed in the acetylation and formylation of (−)-menthol.

The esterification of carboxylic acids and the acylation of alcohols are fundamental reactions in organic chemistry.[1,2] A direct reaction of carboxylic acids with alcohols is generally avoided because the equilibrium that is established between the reagents and the products requires the use of excess reagents or the elimination of water from the reaction mixture to lead the process to completion. Many useful methods for esterification have been reported in the literature.[3—5] Some of the recently developed methods involve the use of organic reagents, such as imidate esters,[6—8] inorganic[9] and organometallic reagents.[10] However, most of these methods suffer from one or more of the following disadvantages: long reaction times,[6—8] vigorous reaction conditions,[10] the occurrence of side reactions,[10] and unavailability of the reagent, as well as poor yields of the desired product in many cases. Lanthanides have found increasing use in organic synthesis.[11—14] Recently, the catalytic use of scandium(III) triflate has been described for the acylation of alcohols with acid anhydrides and carboxylic acids in the presence of excess *p*-nitrobenzoic anhydride.[12,13] Very recently, the use of scandium(III) triflate as a catalyst has also been reported for the acetylation of different alcohols only in acetic acid.[14] During the course of our studies on C–O bond-cleavage reactions with cerium(IV),[15—17a] we found that this reagent catalyzes the esterification of carboxylic acids with alcohols. In this paper we wish to report on the applicability of $Ce(OTf)_4$[17b] for efficient esterification of carboxylic acids and for the acetylation and formylation of alcohols. The acetylation of primary, secondary, and tertiary alcohols in the presence of catalytic amounts of $Ce(OTf)_4$ was performed in acetic acid to produce the desired esters in excellent yields (Table 1). Under these conditions, benzylic alcohols carrying both electron-donating and electron-withdrawing groups were also acetylated without the formation of any oxidative side products. The absence of an oxidative product in these reactions is expected, since 2.5 molar equivalents of this reagent have been reported to be required for the oxidation of benzylic alcohols.[17b] Although for the reaction of alcohols in acetic acid, 20—30 mol% of the reagent are usually used, this transformation for some alcohols with 5 mol% of the catalyst was also studied. Under this condition, although the reactions took a longer time, the yield of the obtained product was still high (Table 1). The acetylation of adamantan-1-ol (Table 1), Entries 13 and 14) as an example of bulky tertiary alcohol was also successfully performed very quickly in acetic acid at room temperature with 5 mol% of cerium(IV)

Table 1. Acetylation of Alcohols by Catalytic Amounts of $Ce(OTf)_4$ in Acetic Acid at Room Temperature

Entry	Alcohol	Mole ratio of $Ce(OTf)_4$/alcohol	Time h	Yield[a)] %
1	4-Chlorobenzyl alcohol	0.2	1	90
2	4-Chlorobenzyl alcohol	0.05	5	90
3	4-Nitrobenzyl alcohol	0.3	0.1	92
4	4-Nitrobenzyl alcohol	0.05	1	89
5	4-Bromobenzyl alcohol	0.3	0.1	93
6	4-Bromobenzyl alcohol	0.05	1	90
7	Benzyl alcohol	0.3	0.1	90
8	Benzyl alcohol	0.05	6	90
9	1-Buten-3-ol	0.2	0.1	92
10	1-Buten-3-ol	0.05	1	89
11	Cinnamyl alcohol	0.3	0.1	88
12	Cinnamyl alcohol	0.05	0.5	85
13	Adamantan-1-ol	0.2	0.1	92
14	Adamantan-1-ol	0.05	0.5	90
15	1-Octanol[b)]	0.3	1.5	85
16	1-Octadecanol	0.3	2	90
17	2-Octanol[b)]	0.3	3	80
18	Cyclohexanol[b)]	0.5	1	85
19	Cyclopentanol[b)]	0.5	1	88
20	2-Phenylethanol[b)]	0.3	2.5	85
21	3-Phenyl-1-propanol[b)]	0.5	3	90
22	(−)-Menthol[b,c)]	0.2	1.5	92

a) Yield refers to isolated product. b) The reaction was performed under reflux conditions. c) Optical rotation of the product $[\alpha]/CHCl_3 = -79.3°$ was compared with the rotation of the product $[\alpha]/CHCl_3 = -79.42°$.

triflate. This reaction with 5 mol% of scandium(III) triflate under reflux conditions (30 min—18 h) does not complete, and gives 88% conversion and 81% of isolated yield; however, with $Ce(OTf)_4$, the reaction gives the corresponding ester in 90% isolated yield after 30 min at room temperature. The acetylation of optically active menthol in the presence of hydrous zirconium oxide[18] and zinc acetate[19] in acetic acid has been reported. In the former case, the formation of 43%, 10—42%, and 99% of the acetate has been reported in refluxing acetic acid, in refluxing acetic acid–toluene, and in autoclave at 250 °C, respectively, without any configuration assignment. In the latter reaction, complete inversion of configuration has been observed along with the formation of (+)-neomenthyl acetate in 80% yield. We have observed that cerium(IV) triflate can bring about this reaction with excellent yield and retention of the configuration in refluxing acetic acid (Table 1, Entry 22). In order to understand the possibility of using cerium(III) triflate[17c] for this transformation, the reaction of benzyl alcohol was performed in acetic acid with 10 mol% of cerium(III) triflate. It was observed that after 30 h, only 45% of the corresponding ester was obtained. A similar reaction with cerium(IV) triflate occurs in 1 h along with the quantitative formation of benzyl acetate. This observation rules out the possibility of the reduction of Ce(IV) to Ce(III) and a catalytic esterification reaction between alcohol with cerium(III). We extended the scope of this reaction by studying the possibility of doing this transformation in ethyl acetate. It was observed that $Ce(OTf)_4$ can catalyze the acetylation reactions of primary and secondary alcohols in refluxing EtOAc in high yields (Table 2). Under these conditions, adamantan-1-ol did not react with ethyl acetate, and recovered without change. These reactions in comparison with similar reactions which have been performed in an autoclave at 150—200 °C in the presence of hydrous zirconium oxide occur more efficiently and under milder reaction conditions. The acetylation of menthol has been performed in ethyl acetate with hydrous zirconium oxide[18] at 160 °C in an autoclave only in 4% and in the vapor phase at 200 °C in 43% yield. In comparison, with catalytic amounts of cerium(IV) triflate in refluxing ethyl acetate, menthyl acetate was obtained in 88% yield with a high retention of the configuration (Table 2, Entry 8). Similarly, the yield of the esterification of benzyl alcohol in ethyl acetate with hydrous zirconium oxide[18] was 32%, but with $Ce(OTf)_4$ it was 83%.

Although the application of formic acid esters for the protection of alcohols is well known in organic synthesis,[20] the procedure suffers from the difficult preparation of formates, which are generally obtained under drastic conditions (e.g. by heating the alcohol in 85% formic acid,[21] or *N*,*N*-diformyl acetamide[22]). However, due to the instability of the anhydride and the acid choloride of formic acid,[23—25] the formylation of alcohols by ethyl formate is an important synthetic reaction.

It was observed that in the presence of 30—50 mol% of $Ce(OTf)_4$, the formylation of primary, secondary, and tertiary alcohols in ethyl formate can be performed at room temperature (Table 3). These reactions in the presence of less than 30 mol% of $Ce(OTf)_4$ can not be completed. The formylation of (−)-menthol with this catalyst was also investigated in ethyl formate. A high retention of the configuration was observed for the product (Table 3, Entry 8). We expanded our studies with this reagent to the esterification of some other carboxylic acids with different alcohols. The esterification of carboxylic acids, such as chloroacetic, trifluoroacetic, propionic, stearic, and benzoic acids, with alcohols were performed in the presence of $Ce(OTf)_4$ as a catalyst under three different conditions: a) for low-boiling-point alcohols or acids, the reactions were performed under solvolytic conditions (Table 4, Entries 1—12), b) the reaction of high-boiling-point alcohols

Table 2. Acetylation of Alcohols by Catalytic Amounts of $Ce(OTf)_4$ in Ethyl Acetate Under Reflux Conditions

Entry	Alcohol	Mole ratio of $Ce(OTf)_4$/alcohol	Time h	Yield[a] %
1	1-Octanol[b]	0.3	3	90
2	1-Octadecanol[b]	0.5	1	75
3	2-Octanol	1	24	10
4	Cyclohexanol	0.5	1.5	85
5	Cyclopentanol	0.5	1.5	80
6	2-Phenylethanol	0.5	4	90
7	3-Phenyl-1-propanol	0.5	5	90
8	(−)-Menthol[c]	0.5	3	88
9	4-Chlorobenzyl alcohol	0.5	3.5	85
10	4-Nitrobenzyl alcohol	0.5	4	90
11	4-Bromobenzyl alcohol	0.5	2	93
12	Benzyl alcohol	0.5	4	83
13	1-Buten-3-ol	0.5	5	80

a) Yield refers to isolated product. b) The reaction was performed at room temperature. c) Optical rotation of the product $[\alpha]/CHCl_3 = -77.4°$ was compared with the rotation of the product $[\alpha]/CHCl_3 = -79.42°$.

Table 3. Formylation of Alcohols in the Presence of $Ce(OTf)_4$ in Ethyl Formate at Room Temperature

Entry	Alcohol	Mole ratio of $Ce(OTf)_4$/alcohol	Time h	Yield[a] %
1	1-Octanol	0.3	1/4	90
2	1-Octadecanol	0.3	1/6	65
3	2-Octanol	0.3	1/4	80
4	Cyclohexanol	0.3	1/2	60
5	Cyclopentanol	0.3	2	75
6	2-Phenylethanol	0.5	1	70
7	3-Phenyl-1-propanol	0.5	1/2	65
8	(−)-Menthol[b]	0.5	1/2	50
9	4-Chlorobenzyl alcohol	0.3	2	60
10	4-Nitrobenzyl alcohol	0.5	4	60
11	4-Bromobenzyl alcohol	0.5	2	65
12	Benzyl alcohol	0.5	3	70
13	1-Buten-3-ol	0.5	2	70
15	Cinnamyl alcohol	0.3	4	60
16	Adamantan-1-ol	0.3	2	60

a) Yield refers to isolated product. b) Optical rotation of the product $[\alpha]/CHCl_3 = -75.3°$ was compared with the rotation of the product $[\alpha]/CHCl_3 = -79.1°$.

Table 4. Esterification of Carboxylic Acids with Catalytic Amounts of $Ce(OTf)_4$

Entry	Alcohol	Acid	Mole ratio of $Ce(OTf)_4$/alcohol	Time h	Temp °C	Yield[a)] %
1	1-Octanol	Propionic	0.2	1/4	25	80
2	2-Octanol	Propionic	0.2	1/4	25	87
3	(−)-Menthol	Propionic	0.2	1/2	25	87
4	Benzyl alcohol	Propionic	0.3	1/4	25	80
5	Benzyl alcohol	Propionic	0.1	1.5	25	80
6	Cinnamyl alcohol	Propionic	0.2	1/2	25	90
7	MeOH	Stearic	0.2	8	Reflux	88
8	EtOH	Stearic	0.2	14	Reflux	87
9	1-PrOH	Stearic	0.3	20	Reflux	90
10	MeOH	Benzoic	0.2	10	Reflux	75
11	EtOH	Benzoic	0.2	14	Reflux	72
12	1-PrOH	Benzoic	0.2	24	Reflux	78
13	1-Octanol[b)]	Benzoic	0.2	24	Reflux	75
14	Benzyl alcohol[b)]	Benzoic	0.2	20	Reflux	73
15	Benzyl alcohol[b)]	Stearic	0.3	3	Reflux	95
16	*t*-Butanol[b)]	$ClCH_2CO_2H$	0.5	8	25	90
17	1-Octanol[b)]	$ClCH_2CO_2H$	0.3	8	25	80

a) Yield refers to isolated product. b) The reaction was performed with equimolar amount of alcohol and carboxylic acid in CCl_4.

can be performed in CCl_4 (Table 4, Entries 13—17) or c) under solvent free-conditions (Table 5).

As examples, the reaction of stearic, benzonic or chloroacetic acid with 1-octanol in CCl_4 or in the absence of a solvent could proceed in high yields with this catalyst (Tables 4 and 5). The esterification of the same carboxylic acids under solvolytic conditions also proceeded efficiently in different alcohols (Table 4). A comparison of our results obtained from the esterification of carboxylic acids with those reported for hydrous zirconium oxide[18)] shows the efficiency of $Ce(OTf)_4$ for this transformation. As an example, from the reaction of benzoic acid with ethanol in the presence of hydrous zirconium oxide[18)] or $Ce(OTf)_4$, ethyl benzoate was obtained in 29 and 72%, respectively. The results obtained for the esterification of different carboxylic acids with alcohols in the absence of a solvent are given in Table 5.

In conclusion, this method could be useful for the esterification and transesterification reactions which are often required in complex synthetic schemes. The possibility of performing the reactions in a solvent or under solvent-free conditions as well as in ethyl acetate or ethyl formate, high stereospecificity of the reaction of (−)-menthol in both acetylation and formylation reactions and easy procedure and work up make this method a useful addition to the present methodologies.

Experimental

All yields refer to isolated products after column chromatography. All of the products were characterized by a comparison of their spectral and physical data with those of known samples. IR spectra were run on a Perkin–Elmer 781 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The purity of the substances and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates or by a Shimadzu

Table 5. Esterification of Carboxylic Acids in the Absence of Solvent with $Ce(OTf)_4$

Entry	Alcohol	Acid	Mole ratio of $Ce(OTf)_4$/alcohol	Time h	Temp °C	Yield[a)] %
1	1-Octanol	Stearic	0.1	3	70	85
2	(−)-Menthol	Stearic	0.2	2	70	92
3	Benzyl alcohol	Stearic	0.2	3	70	90
4	1-Octanol	Benzoic	0.2	24	70	70
5	1-Butanol	$ClCH_2CO_2H$	0.2	3	80	93
6	*t*-Butanol	$ClCH_2CO_2H$	0.2	3	80	90
7	Benzyl alcohol	$ClCH_2CO_2H$	0.1	3	70	85
8	1-Octanol	$ClCH_2CO_2H$	0.2	3	80	85
9	1-Adamantanol	$ClCH_2CO_2H$	0.05	1	70	87
10	Benzyl alcohol	CF_3CO_2H	0.1	3	70	87
11	1-Pentanol	CF_3CO_2H	0.2	2	70	82

a) Yield refers to isolated product.

Gas Chromatograph GC-10A instrument with a flame-ionization detector using a column of 15% carbowax 20M chromosorb-w acid washed 60—80 mesh.

Acetylation of 1-Octanol with $Ce(OTf)_4$ in Acetic Acid as Typical Procedure: To a solution of 1-octanol (1 mmol) in acetic acid (2 ml) was added $Ce(OTf)_4$ (0.3 mmol). The reaction mixture was stirred for 1.5 h at room temperature. The progress of the reaction was monitored by GLC. Acetic acid was removed under reduced pressure and ether (50 ml) was added. The reaction mixture was washed with a 10% aqueous solution of $NaHCO_3$, then washed with water, and dried with Na_2SO_4. Evaporation of the organic solution was followed by column chromatography on a short column of silica-gel using petroleum ether as an eluent. 1-Octyl acetate was obtained as a colorless liquid in 85% yield; bp 198—199 °C/760 mmHg (1 mmHg = 133.322 Pa), Lit,[26] 199 °C/760 mmHg.

Formylation of 1-Octanol with $Ce(OTf)_4$ in Ethyl Formate as Typical Procedure: 1-Octanol (1 mmol) and $Ce(OTf)_4$ (0.3 mmol) were mixed together in ethyl formate (2 ml). The reaction mixture was stirred for 15 min at room temperature. The solvent was evaporated and ether was added (50 ml). The mixture was washed with water and dried with Na_2SO_4. Evaporation of the organic solution was followed by column chromatography on a short column of silica-gel using petroleum ether as eluent. 1-Octyl formate was obtained as a colorless liquid in 90% yield; bp 197—198 °C/760 mmHg, Lit,[27] 198 °C/760 mmHg.

Trifluoroacetylation of 1-Pentanol with $Ce(OTf)_4$ at 70 °C in the Absence of Solvent as Typical Procedure: 1-Pentanol (1 mmol), trifluoroacetic acid (1 mmol), and $Ce(OTf)_4$ (0.3 mmol) were mixed together. The mixture was heated for 2 h in an oil bath at 70 °C. Ether (20 ml) was added. The mixture was washed with water and dried with Na_2SO_4. Evaporation of the organic solution was followed by column chromatography on a short column of silica-gel using petroleum ether as an eluent. 1-Pentyl trifluroacetate was obtained as a colorless liquid in 82% yield; bp 120—123 °C/760 mmHg, Lit,[28] 123—125 °C/760 mmHg.

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