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Unrevealing transition metal-catalyzed terpenic alcohols esterification: a straightforward process for synthesis of fragrances

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Iron nitrate is a simple and available commercially Lewis acid and demonstrated to be able to catalyze the β-citronellol esterification with acetic acid, achieving high conversion and ester selectivity (*ca.* 80 and 70 %, respectively), within shorter reaction time than those reported in the literature. To the best of our knowledge, this is the first report of terpenic alcohol esterification reaction catalyzed by $Fe(NO_3)_3$. This process is an attractive alternative to the slow and expensive enzymatic processes, commonly used in terpenic alcohol esterification. Moreover, it avoids the undesirable steps of products neutralization, which are always required in mineral acid-catalyzed reactions. We have performing a study on activity of different metal Lewis acid catalysts, and find out that their efficiency is straightly linked to ability of metal cation generate H^+ ions from acetic acid ionization. The measurements of pH besides the conversions achieved on reactions allow obtain the following trend: $Fe(NO_3)_3$> $Al(NO_3)_3$> $Cu(NO_3)_2$> $Ni(NO_3)_2$ > $Zn(NO_3)_2$ > $Mn(NO_3)_2$ > $Co(NO_3)_2$ > $LiNO_3$. The three firsts are recognized as stronger Lewis acids and generate the more acid solutions. When we carried out reactions with different iron salts, it was possible realize that the type of anion affect the solubility of catalyst, as well as the conversion and selectivity of process. $Fe_2(SO_4)_3$ and $FeSO_4$ were insoluble and lees active. Conversely, though equally soluble, $Fe(NO_3)_3$ was most selective for the formation of β-citronelly acetate than $FeCl_3$. We assessed the effects of main reaction variables such as reactants stoichiometry, temperature, and catalyst concentration. In addition to citronellol, we investigate the efficiency of iron(III) catalyst on solvent free esterification of several terpenic alcohols (geraniol, nerol, linalool, α-terpineol) as well as other carboxylic acids.

Introduction

Terpenic alcohols are renewable and abundant feedstock employed as starting material to synthesizes chiral building blocks, agrochemicals, medicines and flavors [1-3]. In special, β-citronellyl acetate is an essentially important ingredient for production of perfumes [4]. The main process for synthesis of β-citronellyl acetate are enzymatic reactions, although Brønsted acid-catalyzed processes are also employed [5,6]. Arguably, β-citronellyl acetate synthesis may be much more attractive if carried out by Lewis acid catalyzed processes, which are less corrosive and avoid furthers steps of neutralization, minimizing the generation of salts and effluents [7].

Among Lewis acid used in esterification reactions, tin(II) halides catalysts are outstanding in the esters production from natural origin substrates such as glycerol, triglycerides and fatty acids [8,9]. Recently they have also demonstrated to be active on glycerol ketalization processes with acetone [10].

Currently, large efforts have been devoted to the development of enzymatic catalysts (i.e. lipases) for the terpenic alcohols esterification due to high selectivity [11,12]. Enzymatic catalysts commonly used in esterification require an adequate choice of solvent, besides rigid control of temperature and pH of reaction medium [13]. The immobilization processes of lipases have pivotal importance in the development of enzymatic reactions [14]. Nevertheless, its high cost, instability throughout reaction and difficulty of catalyst recovery are negative aspects of these processes and compromised its application in a large scale.

Metal acid Lewis are always an attractive alternative, due to the fact of it being are lees corrosive than Brønsted acids, more stables than enzymatic catalysts, available commercially and more easily supported onto solid matrixes. However, to develop heterogeneous catalysts based on supported Lewis acid metal is necessary an initial step where its activity should be evaluated in homogeneous catalysis conditions [15]. On this regard, iron(III) salt catalysts have been intensively used in organic synthesis reactions such as oxidative coupling, electrophilic or nucleophilic addition and/ or substitutions, oxidative esterification [16].

To develop selective functionalization processes for monoterpenes based on commercially available metal catalysts is a goal that has been pursued by our research group [17,18]. Iron(III)

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x nitrate, which is an inexpensive and easily handled solid catalyst was successfully used in alkoxylation reactions of monoterpenes [19]. Nevertheless, as far as we known, there is no work describing its use in the terpenic alcohols esterification until this moment.

Herein, we wish to describe a simple and efficient of $Fe(NO_3)_3$-catalyzed terpenic alcohols esterification process with HOAc in presence or absence of solvent. β-citronellol, an acyclic terpenic alcohol commonly present in essential oils was the model molecule selected. Initially, we carried out a screening to select the best metal Lewis acid catalyst. We paid special attention to assess the mechanism of action of metal catalyst. Afterward, we investigate effects of main reaction parameters (i.e. temperature, reactants stoichiometry, catalyst concentration) in the conversion and reactions selectivity.

Experimental

Chemicals

All chemicals are commercially available and utilized without prior handling. $Co(NO_3)_2{\cdot}6\ H_2O$ (98 wt. %), $Mn(NO_3)_2{\cdot}4\ H_2O$ (98 wt. %), $Cu(NO_3)_2{\cdot}3\ H_2O$ (98 wt. %) and $Ni(NO_3)_2{\cdot}6\ H_2O$ (98 wt %) were Dinamica Ltda (Brazil). $Fe(NO_3)_3{\cdot}9\ H_2O$ (98 wt. %), $FeCl_3{\cdot}6\ H_2O$ (98 wt %); $FeSO_4{\cdot}7\ H_2O$ (98 wt %); $Fe_2(SO_4)_3{\cdot}5\ H_2O$ (98 wt %), $Zn(NO_3)_2{\cdot}6\ H_2O$ (98 wt. %), $LiNO_3$ (99 wt. %), $Al(NO_3)_3{\cdot}6\ H_2O$ (99 wt. %) were acquired from Vetec (Brazil). β-citronellol (99 wt. %) and the solvents acetic acid (99.8 wt. %) and acetonitrile (99.7 wt. %) were purchased from Sigma-Aldrich.

Catalytic runs

Catalytic runs were performed in a glass reactor (50 mL) equipped with a magnetic stirrer and sampling septum. Typically, terpenic alcohol (i.e. β-citronellol; 4.75 mmol) and HOAc were dissolved in an adequate molar ratio (15 mL solution), and then the reaction was initiated by adding a metal catalyst (*ca*. 1 to 20 mol %). Solvent-free reactions were carried out by using of 1: 16 molar ratio between β-citronellol and HOAc.

The reaction progress was followed by GC analyses of aliquots taken at regular time intervals in a Shimadzu GC 2010 instrument, FID, fitted with Carbowax 20M capillary column. Toluene was the internal standard. The comparison of the corresponding GC peak areas of products and substrates with the corresponding calibrating curves allowed the reaction conversion. The dilution of aliquots with acetonitrile adjusted the concentration to the calibration curve.

Products identification

The products were isolated and analyzed as literature [25]. The ^1H and ^{13}C NMR spectra were recorded on the Mercury-300 Varian Spectrometer at 300 and 75 MHz respectively, in $CDCl_3$ solution using TMS as internal standard. FT-IR spectroscopy analyses were obtained in a Varian 660 FT-IR Spectrometer. Mass spectroscopy analysis on Shimadzu MS-QP 2010 ultra mass spectrometer instrument operating at 70 eV, coupled with a Shimadzu 2010 GC.

Results and discussion

General aspects

The use of metal salts as catalysts in esterification reactions is always desirable because these are commercially available reactants, water tolerant, less corrosive than Brønsted acids [20]. We have found that among tin catalysts investigated, $SnCl_2$ was always the most selective and active catalyst [21]. On the other hand, iron(II) nitrate was successfully used on the oxidation of monoterpenes[22].

Among numerous types of terpenic substrates, alcohols contains double bonds with different reactivity, besides primary, secondary, or tertiary hydroxyl groups, which make difficult the reactions selectivity control [23]. In general, commercial enzymes are ables to catalyze terpenic alcohol esterification reactions achieving high selective. However, they are expensive and generally requires long reaction times [24].

Recently, we described the use of $SnCl_2$ as catalyst on the β-citronellol esterification, which achieved high conversions and selectivity to β-citronellyl acetate [25]. However, this metal has high toxicity and less available compared to iron. Thus, inspired by these findings, we have investigates the activity iron catalysts on these reactions. β-citronellol was selected as the model molecule and initially the reactions were carried out in the presence of solvent (i.e. CH_3CN). At first, we compared iron(III) nitrate to other metal catalysts to try understand the role of the metal on these reactions.

Effect of Lewis acid catalyst nature on the β-citronellol esterification with HOAc

After assessing the effect of catalyst nature, the following kinetic curves were obtained as displayed in Figure 1.

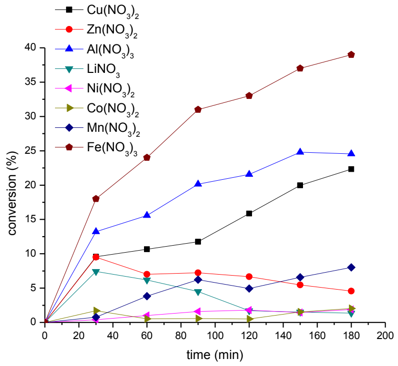
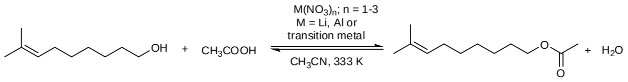


Figure 1. Effect of catalyst nature on β-citronellol esterification with HOAc[a]

[a]Reaction conditions: β-citronellol (4.79 mmol), HOAc (19.16 mmol), Lewis acid catalyst (10 mol % of M^{n+} in relation to β-citronellol); temperature (333 K); time (3 h).

It is important to note that the reactions conditions were selected aiming to highlight the most active catalyst, regardless of the maximum conversion being or not achieved. In all most of metal-catalyzed β-citronellol esterification reactions, the major product was β-citronellyl acetate (Scheme 1).



Scheme 1. Metal-catalyzed β-citronellol esterification[a] M(NO_3)$_n$ (10 mol %); 333 K; CH_3CN (15 mL); 3 h.
[a]Reaction conditions:β-citronellol: HOAc proportion 1:4.

Among catalysts evaluated, Fe(NO_3)$_3$·9 H_2O was the most active and selective. The selectivity data (Table 1) show that in addition to esterification reaction, the heating of terpenic alcohols in presence of HOAc and Lewis acids catalysts promote an undesirable transformation, the formation of oligomers, which are not detectable by GC analyses.

A comparing of GC peaks areas of formed products and consumed substrate allowed determine the amount of oligomers. Literature describe that Lewis acid can promoted the terpenes oligomerization, which was the major parallel reaction herein [26,27]. However, Lewis acid promotes also the conversion of β-citronellol to acetate. Therefore, these two concurrent transformations govern the process selectivity.

Table 1. Effects catalyst nature on the Lewis acid metal-catalyzed β-citronellol esterification with HOAc[a]

Exp.	Catalyst	Conversion (%)	Selectivity[b] (%)		
			(**1**)	ni	oligomers
1	-	3	10	0	90
2	LiNO$_3$	3	35	10	55
3	Al(NO$_3$)$_3$	27	50	14	36
4	Mn(NO$_3$)$_2$	8	18	10	72
5	Fe(NO$_3$)$_3$	38	70	15	15
6	Co(NO$_3$)$_2$	3	27	10	63
7	Ni(NO$_3$)$_2$	3	39	10	51
7	Cu(NO$_3$)$_2$	25	26	14	60
8	Zn(NO$_3$)$_2$	6	46	10	44
9[c]	**HNO$_3$**	**40**	**63**	**13**	**24**

[a]Reaction conditions: β-citronellol (4.79 mmol), HOAc (19.16 mmol), CH_3CN solution (15 mL), temperature (338 K); time (3 h).
[b](1) = β-citronellyl acetate; ni = complex mixture of non-identified products.
[c]It was used a HOAc: β-citronellol molar ratio equal to 1:16, 20 mol % H^+ cations

Brønsted or Lewis acids, each one through distinct mechanisms, catalyze esterification reactions. In the first one, the most known, proceeds via protonation of the carbonyl group of carboxylic acid, that favor its attack by hydroxyl group of the alcohol, generating an intermediate that after water elimination result in ester. On this regard, an essential point is that although the excess of acetic acid (i.e. alcohol: acid molar ratio was 1:4), the reaction proceeded slowly in catalyst absence, reaching only 3 % conversion.

To verify the efficiency of the Brønsted acid catalyst, we carried out experiments with HNO_3 catalyst aiming to achieve the same acetate selectivity obtained in reactions with Fe(NO_3)$_3$. The reactions were carry out with different reactant proportions; however, the maximum selectivity was reached (*ca*. 63 %) only when 1:16 molar ratio was used. Nonetheless, it reveals that HNO_3 catalyst was less effective than Fe(NO_3)$_3$, which achieved 70 % of selectivity to acetate using a lower excess of HOAc (*ca*. 1:4 molar ratio of reactants). Therefore, this resulted supports the crucial role of iron (III) catalyst on these reactions.

In the second mechanism (i.e. when Lewis acids are the catalysts), who activate the carbonyl group is the metal, that may coordinate to the carbonylic oxygen, resulting in its polarization that also favor an attack by the alcohol hydroxyl. In this case, the acidity strength is determining for the activity of Lewis acid catalysts. It is related to ability to accept one pair of electrons, a property that straightly depend of the existence of empty orbitals with symmetry and energy adequate [28,29].

$$CH_3COOH \xrightleftharpoons[CH_3CN,\ 333\ K]{M(NO_3)_n} CH_3COO^- + H^+$$

Scheme 2. Ionization of acetic acid catalyzed by M(NO_3)$_n$ salts (i.e. “acetolyisis”)

However, it is possible that the reactions studied herein will proceed by a third way; the simple addition of Lewis acid metal to the reaction solution trigger a decreasing on pH value, meaning that ionization of acetic acid was favored by the presence of Lewis acid metal (Scheme 2). To verify this hypothesis, we carried out measurements of pH values of reaction solutions in presence of the different metal catalysts.

Effect of metal-catalyzed acetolysis in the β-citronellol esterification with HOAc

Table 2 show this effect produced when 20 mol % of catalyst was added to the reaction solution. The trends in terms of acidity decreasing was as follow: Fe(NO_3)$_3$ > Al(NO_3)$_3$ > Cu(NO_3)$_2$ > Ni(NO_3)$_3$ > Zn(NO_3)$_2$ > Mn(NO_3)$_2$ > Co(NO_3)$_3$ > Li(NO_3)$_3$.

Table 2. Effect of Lewis acid metal catalyst on initial pH values of reaction solutions[a]

Exp.	Catalyst	pH	Exp.	Catalyst	pH
1	-	2.73	-	-	
2	$LiNO_3$	1.90	6	$Co(NO_3)_2$	1.28
3	$Al(NO_3)_3$	-0.73	7	$Ni(NO_3)_2$	1.43
4	$Mn(NO_3)_2$	0.80	8	$Cu(NO_3)_2$	0.04
5	$Fe(NO_3)_3$	-1.81	9	$Zn(NO_3)_2$	0.38

[a]Conditions: β-citronellol (4.79 mmol), HOAc (19.16 mmol), catalyst (20 mol %); CH_3CN solution (15 mL)

It was almost the same tendency verified in terms of the most effective catalysts; $Fe(NO_3)_3$ > $Al(NO_3)_3$ > $Cu(NO_3)_2$ In addition, the three highest pH values (i.e. $Co(NO_3)_3$ > $Ni(NO_3)_3$ > $Li(NO_3)_3$) were measured in the reactions where the three lowest conversions were reached.

We suppose that β-citronellol esterification with HOAc in presence of nitrate salts proceed through of two mechanisms (i.e. Lewis or Brønsted acid catalysis). As proposed in the Equations of 1 to 4, the metal has pivotal participation in three steps of esterification process of β-citronellol. It is important to note that even though HOAc is a weak acid (i.e. p*Ka* = 4.75), its dissociation in absence of metal catalyst does not provide H^+ ions in sufficient amount to catalyze the reaction, as suggest the poor conversion achieved in these reaction conditions (Run 1, Table 1). Conversely, when metal-catalyzed, the releasing of the H^+ ions in solution is much more significant, as show the pH values measured in presence of different metals (Table 2).

Therefore, we are proposing a similar mechanism to that which occur throughout the acid hydrolysis of metal cations, where metal cation is coordinated to number of water molecules, and furthermore promotes liberation of H^+ cations, resulting in the H_3O^+ species (Scheme 3) [30].

$$M^+ + nCH_3COOH \rightleftharpoons [M^+(CH_3COOH)_n] \quad (Eq.1)$$

$$[M^+(CH_3COOH)_n] + CH_3COOH \rightleftharpoons [M^+(CH_3COOH)_{n-1}(CH_3COO^-)] + CH_3COOH_2^+ \quad (Eq.2)$$

$$CH_3COOH_2^+ + ROH \rightleftharpoons CH_3COOR + H_2O + H^+ \quad (Eq.3)$$

$$[M^+(CH_3COOH)_{n-1}(CH_3COO^-)] + H^+ \rightleftharpoons M^+ + nCH_3COOH \quad (Eq.4)$$

Scheme 3. Equations involved on the metal-catalyzed ROH esterification with CH_3COOH

Herein, acetic acid coordinate to the metallic cation (Eq. 1) giving an intermediate that posteriorly transfer a proton to other acetic acid molecule, resulting in the protonated specie and metallic intermediate coordinated to acetate anion (Eq. 2). The Lewis acidity strength of metal plays a key-role. The acetic acid coordination to the metal depends on its Lewis acid character in accept pair electrons of carbonylic oxygen.

Contrariwise, the third step proceeded without the participation metal; only protonated acetic acid and alcohol (i.e. β-citronellol) are involved. After nucleophilic attack of the alcohol hydroxyl group on the carbonylic carbon of protonated acetic acid, the reaction resulted in water, H^+ ions and terpenic ester (Eq.3). This means that reaction occur typically as in the Brønsted acid-catalyzed processes.

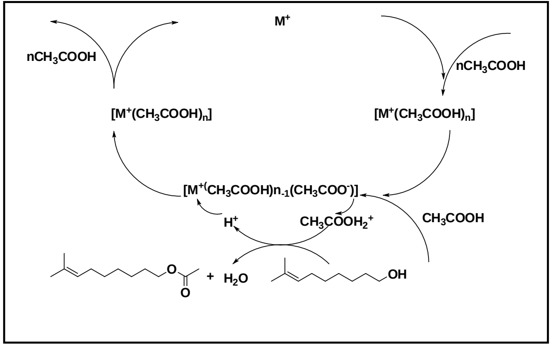


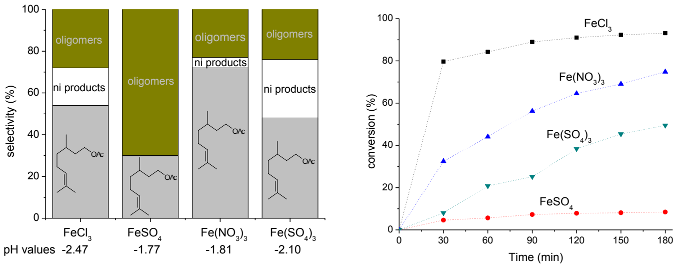
Figure 2. Catalytic cycle of M^{n+}-catalyzed β-citronellol esterification with CH_3COOH

In the fourth step, intermediate containing metal the coordinate to acetate anion trapped H^+ ion, regenerating an acetic acid molecule and metal cation, closing a catalytic cycle depicted in Figure 2.

Therefore, as Li(I) cations are poor receptor of electronic density it was less efficient on activation of carbonyl group of acetic acid, an obligatory step on two reactions. The same did not occur with Al^{3+} cations, which recognized are strong Lewis acid and were the second most active catalyst assessed herein. Al(III) cations have vacancy on the "s" and "p" valence orbitals, which usually accept electronic density of carbonylic oxygen atoms in different reactions, confirming that these groups have compatible energies [28].

Conversely, the Lewis acidity of the metals belonging to the same transition series depends on the energy and the filling level of their valence d orbitals. Another pivotal aspect is the charge density that depends on the ionic radius. It was found that Zn(II), Mn(II) cations have a very poor activity. They have totally filled d^{10} orbital (i.e. Zn (II)), or semi-filled d^5 orbital (i.e. Mn(II)), which are highly stable. Whereas, Fe(III) cations (i.e. $Fe(NO_3)_3$) were the most effective transition metal catalysts, followed by the Cu(II) cations. These cations are those with the lowest ionic radium, respectively. These results are in agreement with literature [31].

On the other hand, steric or electronic factors of anionic ligands may change the catalytic activity of Lewis acid (i.e. Fe(III) cations salts). Therefore, we have also assessed the activity of Fe(III) cations coordinated with other anionic ligands (Figure 3).



(a) Reaction selectivity

(b) Kinetic curves

Figure 3. Effect of iron catalyst nature on selectivity (a) and kinetic curves (b) of the esterification reaction of citronellol with acetic acid in acetonitrile solutions[a]

[a]Reaction conditions: β-citronellol (4.79 mmol); HOAc (76.64 mmol);

$Fe(NO_3)_3$ (20 mol %); CH_3CN solution (15 mL); time (3 h).

Previously, Sugi et al have assessed the esterification of long chain acids with cetyl alcohol in presence of various metal nitrates, chlorides and acetates; they found that $FeCl_3$ was the most active catalyst [32,33]. Those authors proposed that cationic cluster formed by hydrolysis of the ferric cation is probably the catalytically active species.

Kinetic curves of the Figure 3b show that conversions reached on the iron-catalyzed reactions followed the trend: $FeSO_4$ <$Fe_2(SO_4)_3$ <$Fe(NO_3)_3$ <$FeCl_3$. Conversely, the acetate selectivity achieved in the reactions had another behavior, that was similar to that observed on measurement of the solutions acidity: $FeSO_4$ <$Fe_2(SO_4)_3$ <$FeCl_3$ <$Fe(NO_3)_3$; decreasing of the pH values (Figure 3a).

Before comparing these tendencies, it is outstanding to note that among catalysts investigated, iron(II) and mainly iron(III) sulfates were less soluble. It can be meaning that despites $Fe_2(SO_4)_3$ catalyst generate higher H^+ concentration than $Fe(NO_3)_3$, its lower solubility compromised its activity. In according with the trend shown in Tables 1 and 2, it could be expected that high acidity (i.e. $Fe_2(SO_4)_3$) should result in higher conversion. Nonetheless, the conversion attained was lower than that reached in $Fe(NO_3)_3$ catalyzed reactions. We may suggest a possible explanation analyzing the selectivity of these reactions. Meanwhile $Fe_2(SO_4)_3$-catalyzed reactions gave 54 and 27 % of selectivity for citronellyl acetate and oligomers, respectively, the $Fe(NO_3)_3$-catalyzed reactions achieved 73 and 23 % of selectivity for these same products. It is suggestive that these two concurrent reactions (i.e. oligomerization and esterification) are differently depending of the Fe^{3+} and H^+ cations concentration.

Effect of reactants molar ratio in the $Fe(NO_3)_3$-catalyzed β-citronellol esterification

We have investigate the effect of reactants stoichiometry on reaction rates ranging proportion of 1:1 to 1:16 (Figure 4).

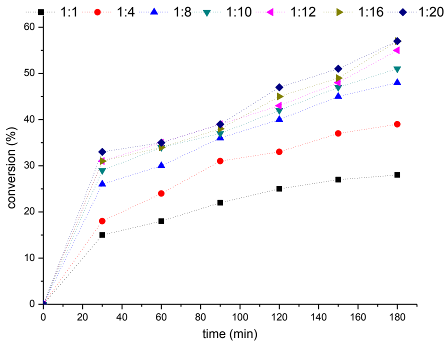


Figure 4. Effect of stoichiometry of reactants on kinetic curves of $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc[a]

[a]Reaction conditions: β-citronellol (4.79 mmol), $Fe(NO_3)_3$ (10 mol %); CH_3CN (15 mL); 3 h.

An increase on molar ratio of HOAc to citronellol resulted in an increase of both reactions initial rates, as well as on final conversion. However, the oligomers formation and of unidentified products was favored, compromising the β-citronellyl acetate selectivity (Table 3).

Table 3. Effects of reactants stoichiometry on the conversion and selectivity of $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc[a]

Run	Molar ratio β-citronellol: HOAc	Conversion (%)	Selectivity[b] (%)		
			(**1**)	ni	Oligomers
1	1:1	28	93	1	6
2[c]	1:1	0	0	0	0
3	1:4	38	70	15	15
4	1:8	48	72	6	22
5	1:10	51	73	9	18
6	1:12	55	68	14	18
7	1:16	57	64	15	21
8	1:20	57	59	19	22
9[c]	1:16	5	51	0	49

[a]Reaction conditions: β-citronellol (4.79 mmol); $Fe(NO_3)_3$ (10 mol %); CH_3CN solution (15 mL), temperature (333 K); time (3 h).
[b](1) = β-citronellyl acetate; ni = complex mixture of non-identified products.
[c]Blank-reactions carried without catalyst.

The usage of molar ratio higher than 1:16 does not resulted in a benefit effect on the reaction within period of the reaction studied. It was meaning that the reaction rate depends lesser of the acetic acid concentration than β-citronellol concentration, as suggested in the mechanism proposed in Scheme 2, where at least two HOAc molecules are straightly involved in the formation of the β-citronellyl acetate.

Effect of temperature on the $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc: A kinetic study to determining of activation energy

The $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOA was accomplished at range of temperatures between 298 to 333 K, in presence or absence of catalyst (Table 4). However, for simplification we report only results of blank-reaction carried out to 333 K.

Table 4. Temperature effects on the conversion and selectivity of $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc[a]

Exp.	Temperature	Conversion	Selectivity[b]

	(K)	(%)	(%)		
			(1)	ni	Oligomer
1	298	11	51	0	49
2	308	18	57	6	37
3	318	29	57	7	36
4	328	43	65	7	28
5	338	48	72	6	22
6^c	338	5	10	0	90

[a] Reaction conditions: β-citronellol (4.79 mmol), HOAc (38.32 mmol), $Fe(NO_3)_3$ (10 mol%); CH_3CN solution (15 mL), 3 h.

[b] (1) = β-citronellyl acetate; ni = complex mixture of unidentified products.

[c] Reaction carried out in absence of $Fe(NO_3)_3$ catalyst.

We would to note that the reaction conditions (catalyst concentration, reactant stoichiometry (HOAc/ β-citronellol molar ratio) are not optimized to provide high conversions within short reaction times. We verified that an increase of temperature increased the reaction conversions. Nonetheless, the selectivity shifted towards the β-citronellyl acetate, due to diminishing of oligomers. Indeed, the undesirable formation of oligomers was much more noteworthy in absence of catalyst (*ca*. 90 % selectivity, entry 6, Table 4). After the reaction solution cooling, the oligomers were precipitated as a white solid and analyzed by FT-IR spectroscopy.

The higher conversion rates reached in the reaction heated to high temperatures suggests an endothermic character for this process (Figure 2). Esterification reactions involving alcohols and fatty acids also have endothermic behavior [34]. Kinetic data of reaction studied herein are scarce on literature. We carried out a kinetic study aiming determining activation energy and kinetic constants of reaction at each temperature.

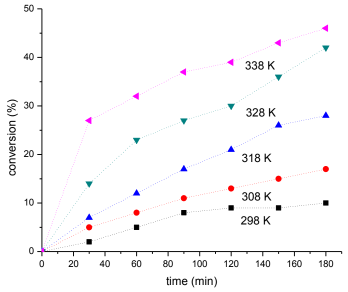


Figure 5. Effect of temperature on $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc

[a] Reaction conditions: β-citronellol (4.79 mmol); HOAc (38.32 mmol); $Fe(NO_3)_3$ (10 mol %); CH_3CN solution (15 mL); time (3 h).

Table 5. Rate constants and linearity coefficient of first-order plots in relation to β-citronellol concentration measured in the esterification reactions at different temperatures[a]

T (K)	Rate $10^{-5}(s^{-1})$	Linearity coefficient (R^2)	1/T (x 10^{-3})	ln k
298	1.62	0.987	3.36	10.85
308	2.95	0.981	3.25	10.62
318	2.42	0.993	3.14	10.43
328	3.39	0.982	3.05	10.29
338	3.59	0.998	2.96	10.15

[a] Reaction conditions: β-citronellol (4.79 mmol); HOAc (38.32 mmol); $Fe(NO_3)_3$ (10 mol %); CH_3CN solution (15 mL); time (3 h).

The dependence of the reaction rate in relation to substrate concentration was determined from plots of ln [β-citronellol] versus reaction time, which were thus built for each $Fe(NO_3)_3$-catalyzed reaction at different temperatures (Figure 6). However, we have calculate the ln$[\beta\text{-citronellol}]_{t=ti}/[\beta\text{-citronellol}]_{t=0}$ only for three first points, established in the first 90 minutes of reaction. Within this initial period, we assume that the reaction has pseudo-zero order in relation to acetic acid concentration, which is in large excess at reaction beginning.

From the curves presented in Figure 6, the rate constants (k) for each process were obtained (Table 5). As displayed in the Figure 6 and Table 5, the resulting linear equations had high linear correlation coefficients (R^2), thus indicating that the reactions have pseudo-first-order rate law in relation to β-citronellol concentration [35].

The *"k"* values measured to different temperatures allow built the Arrhenius plot. Employing a linear regression method, the angular coefficient of Arrhenius curve (-E/ R) of the obtained curve gave the activation energy of this reaction, which was equal to 17.39 kJ mol^{-1}. As can be observed in Figure 7, the high R^2 value (*ca*. R^2 = 0.99) achieved clearly indicate the efficiency of the method employed.

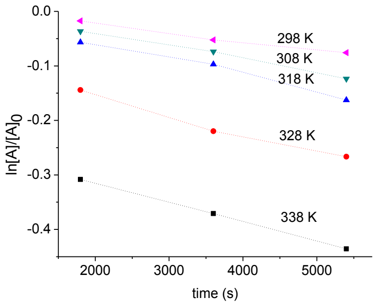


Figure 6. First-order plot of $Fe(NO_3)_3$-catalyzed citronellol esterification with HOAc

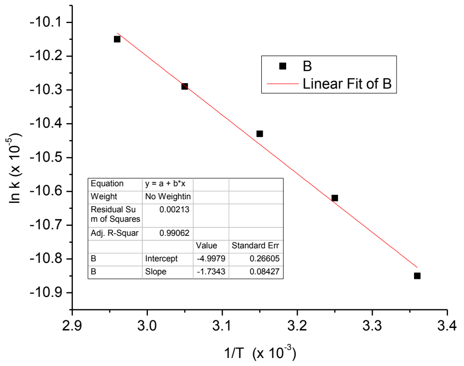


Figure 7. Arrhenius plot of $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc

Effect of catalyst concentration on the $Fe(NO_3)_3$-catalyzed β-citronellol esterification with HOAc

In all runs, an increase of catalyst concentration positively affected the reaction initial rate of the β-citronellol esterification (Figure 8). It is in agreement with experimental observation that a high amount of metal catalyst provide a high H^+ ions concentration, which are to protonate the acetic acid carbonyl and favor the formation of β- citronellyl acetate (Scheme 3).

Conversely, in terms of acetate selectivity, an increase on catalyst amount has benefitted only to concentration of 10 mol %; values higher than it resulted in higher conversion without significantly favor the acetate formation (Table 6).

It is important highlight that this was the best reaction condition for synthesis of citronellyl acetate; 20 mol % of $Fe(NO_3)_3$, and 1: 8 molar ratio of alcohol to acid giving 80 % of conversion and 70 % of β-citronellyl acetate selectivity, after 3 h of reaction.

Table 6. Effect of $Fe(NO_3)_3$ $9{\cdot}H_2O$ concentration on the conversion and selectivity of β-citronellol esterification[a]

Exp.	$Fe(NO_3)_3{\cdot}$ 9 H_2O (mol %)	Conversion (%)	Products selectivity[b] (%)		
			(1)	ni	Oligomer
1	-	<3	0	0	100
2	1.0	10	30	0	70
3	2.5	16	42	0	38
4	5.0	21	65	3	32
5	7.5	33	68	5	27
6	10.0	48	72	6	22
7	15.0	67	68	9	23
8	20.0	80	70	7	23

[a] Reaction conditions: β-citronellol (4.79 mmol), HOAc (38.32 mmol), reactants molar ratio (1:8); CH_3CN solution (15 mL); temperature (333 K); time (3 h).
[b] (1) = β-citronellyl acetate; ni = complex mixture of non-identified products.

Although reactions proceed at higher temperature than lipase-catalysed processes (*ca*. 333 K against 303 K), the iron catalyzed reactions achieved much higher selectivity, within shorter reaction time (*ca.* 3 h herein, versus 48 h reported on literature) [36]. Recently, Badgujar et al summarized the main synthesis methods of β-citronellyl acetate [38].

They emphasized that due to high sensibility of enzymes in relation to acetic acid, the most of processes proceed in hydrocarbon solvent, by using of other acyl donation group [38]. In terms of metal-catalyzed process, we recently described the use of tin(II) halides in β-citronellol esterification process [25].

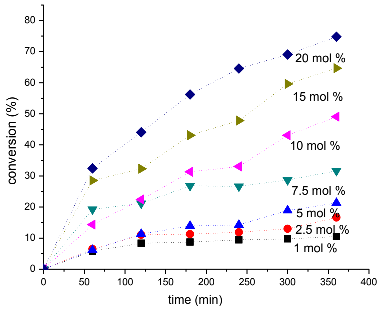


Figure 8. Effect of $Fe(NO_3)_3{\cdot}9H_2O$ concentration in the β-citronellol esterification with HOAc in acetonitrile solutions.[a]

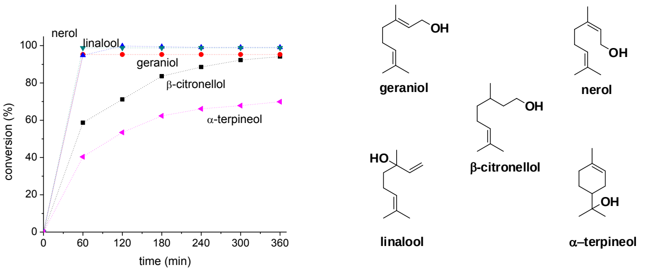
[a] Reaction conditions: β-citronellol (4.79 mmol); HOAc (38.32 mmol); CH_3CN solution (15 mL); temperature (333 K)

Nonetheless, due to high toxicity of the tin, its replacement by a metal catalyst as iron nitrate seems more environmentally desirable.

Solventless $Fe(NO_3)_3$-catalyzed terpenic alcohols esterification with HOAc

Due to economic and environmental reasons, even that possible, it should be avoid the use of solvent in liquid phase reactions. In addition, it is possible that the presence of solvent as acetonitrile may have an inhibitory effect on ionization of acetic acid and thus reduce the conversion and selectivity of $Fe(NO_3)_3$-catalyzed esterification reactions.

The great challenge in perform reactions with terpenes in pure acetic acid, comprise in to avoid the undesirable formation of oligomers, that is favored mainly if the terpenic substrates have more than one double bond and or tertiary carbon atoms. In this case, they are more susceptible to undergo carbon skeletal rearrangement that can compromise the selectivity of esterification reaction.



(a) kinetic curves

(b) alcohols structure

Figure 9. $Fe(NO_3)_3$-catalyzed esterification kinetic curves of terpenic alcohols with HOAc (a) and their structures [a]

[a]Reaction conditions: terpenic alcohol (4.79 mmol), HOAc (76.74 mmol), reactants molar ratio (1:16), $Fe(NO_3)_3$ catalyst (20 mol %), temperature (333 K); time (3 h).

To investigate these effects, we carried out the terpenic alcohols esterification in acetic acid solutions containing catalytic amount of iron(III) nitrate, without presence of acetonitrile. Figure 9a show kinetic curves obtained in the reactions with $Fe(NO_3)_3$ (*ca*. 20 mol %) and molar ratio of 1:16 between HOAc and terpenic alcohol.

Terpenic alcohols have hydroxyl groups with different reactivity and carbon skeletal containing di- or trisubstituted double bonds, consequently, the conversion and selectivity provide by them were completely distinct (Figure 9b).

In general, except for the α-terpineol, all the terpenes were virtually consumed after 4 h of $Fe(NO_3)_3$-catalyzed reactions. Nerol and linalool were consumed within the first hour of reaction (Figure 8a). Nevertheless, the conversion it is not the only aspect to be taking in account on these reactions. To better evaluate these reactions, it is also require analyze two other fundamental aspects; the first one, the behavior of the reactions without or with catalyst (Figures 10 and 11).

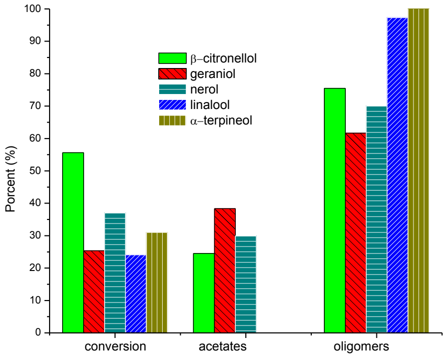


Figure 10. Conversion and selectivity of terpenic alcohol esterification reactions in absence of solvent and catalyst[a]

[a]Reaction conditions: terpenic alcohol (4.79 mmol), HOAc (76.74 mmol), reactants molar ratio (1:16), temperature (333 K); time (3 h).

The second reason, the different selectivity of products (Figures 10 and 11)). We have addressed these two points and the main results showed that, expectedly, due to different structures, to control the selectivity of reactions was the major obstacle. Nonetheless, the β-citronellol was the substrate that provide the highest selectivity for acetate.

We establish that reactions carried out in acetic acid were less efficient than those in acetonitrile. This different behavior occurred either in presence or absence of $Fe(NO_3)_3$ catalyst. For instance, while the blank-reactions performed in acetonitrile achieved a poor conversion of β-citronellol (*ca*. 5 %, 51 % acetate selectivity) (entry 9[c], Table 3), in catalyst-free reactions carried without CH_3CN in pure acetic acid, the conversion was 55 % (*ca.* 28 % selectivity acetate). These two blank-reactions gave oligomers in significant amount; in acetonitrile, the selectivity was 49 % (see entry 9[c], Table 3). When in pure HOAc, they were major product (ca. 75 %, Figure 11).

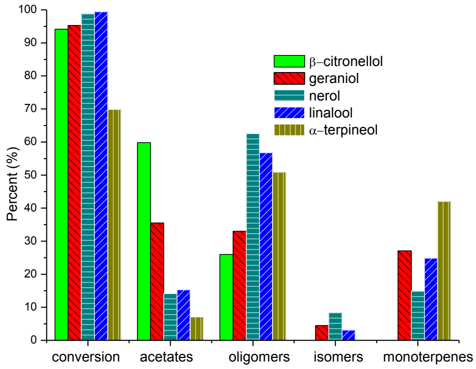


Figure 11. Conversion and selectivity of $Fe(NO_3)_3$-catalyzed terpenic alcohol esterification reactions in absence of solvent [a]

[a]Reaction conditions: terpenic alcohol (4.79 mmol), HOAc (76.74 mmol), reactants molar ratio (1:16), $Fe(NO_3)_3$ catalyst (20 mol %), temperature (333 K); time (3 h)

Indeed, by inspection of Figure 10, we can concluded that regardless terpenic alcohol the oligomers were always main product formed in catalyst-free reactions. It meaning that to drive the selectivity toward acetates formation, it always require the presence of $Fe(NO_3)_3$ catalyst. Moreover, the use of solvent improved reaction selectivity.

In general, the addition of $Fe(NO_3)_3$ catalyst had an positive effect in terms of acetate formation in the reactions with terpenic alcohols, nonetheless, it also resulted in the formation of isomers (i.e. others terpenic alcohols), and or dehydration or cyclization products (i.e. monoterpenes).

We could expect that substrates containing primary or allylic hydroxyl groups could react with acetic acid faster than tertiary alcohols. Geraniol and nerol (i.e. allylic alcohols) reacted quickly if compared to the β-citronellol (i.e. primary alcohol), (Figure 9a).

Nevertheless, the tertiary alcohols had different performance; while the reaction quickly consumed linalool within first thirty minutes, the reactions with α-terpineol were slower. The different selectivities obtained in the reactions of each terpenic alcohol explains these observations (Figure 9a).

In either presence or absence of the catalyst, acetates were obtained only when terpenic substrate was a primary alcohol (i.e. β-citronellol, geraniol, nerol). The data shown in Figures 9 and 10 show the following order of reactivity for acetate selectivity: β-citronellol > geraniol > nerol.

However, in addition to esterification, allylic alcohols (i.e. geraniol, nerol) suffered also isomerization, giving isomers, which afterwards, were converted to their respective acetates. By simplification, Figure 11 show only the total percent of isomers obtained in reaction with each substrate. It means that we did not included the acetates obtained after isomerization process. Indeed, this point have minimum impact on overall resulted.

In presence of iron nitrate catalyst, geraniol underwent isomerization to α-terpineol (*ca*. 7 %); similarly, in another run, nerol also isomerized to α-terpineol (*ca*. 12 %). Moreover, GC-MS analyses revealed that geraniol and nerol undergo also dehydration followed by cyclization, resulting in the equimolar mixture of monoterpenes (i.e. limonene, δ-terpinolene, *ca*. 34 % selectivity).

Tertiary alcohols such as α-terpineol and linalool did not gave esters as products. In this case, although linalool isomerization reactions gave α-terpineol (*ca*. < 5 %), major products were limonene and δ-terpinolene (i.e. trough dehydration/ cyclization process), in proportion of 3:1, respectively (ca. 28 % selectivity). Conversely, α-terpineol, the only cyclic alcohol studied herein, suffered mainly dehydration reactions, resulted in the formation of monoterpenes limonene and δ-terpinolene in 1:1 proportions (*ca*. 50 % selectivity).

Effect of nature of carboxylic acid on $Fe(NO_3)_3$-catalyzed β-citronellol esterification in CH_3CN solutions

We have investigate the effect of nature of carboxylic acid on esterification of β-citronellol in CH_3CN solutions. The reactions were carried out with an alcohol to acid molar ratio equal to 1:4 and 20 mol % of $Fe(NO_3)_3$ catalyst (Table 7, Figure 12).

Table 7. Conversion of β-citronellol and products selectivity obtained on $Fe(NO_3)_3$-catalyzed esterification reactions with different carboxylic acids in CH_3CN solutions[a]

Run	Carboxylic acid	Conversion (%)	Selectivity (%)		
			ester[b]	other[c]	olig[d]
1	acetic acid	80	70	7	24
2	propanoic acid	97	52	28	20
3	cyclobutane carboxylic acid	87	52	24	24
4	pentanoic acid	77	41	30	29
5[e]	benzoic acid	21	0	68	32

[a] Reaction conditions: β-citronellol (4.79 mmol), carboxylic acid (38.32 mmol), reactants molar ratio (1:8); CH_3CN solution (15 mL); temperature (333 K); time (3 h).
[b] ester = β-citronellyl ester of carboxylic acid.
[c] other = different products identified by GC-MS analysis (it will be discussed in the text) and complex mixture of minority non-identified products.
[d] oligom = determined through mass balance.
[e] No aromatic product was detected.

In most of reactions, it was detected a variable amount of dihydromyrcenol, an isomerization product of β-citronellol and their respective ester (i.e. both included in the Table 7 as "other"). Conversely, the reaction with benzoic acid not gave any aromatic ester; only a complex mixture of minority products was detected. This experimental data is in agreement with literature, which describes that conjugation with the aromatic ring compromises the carboxyl group reactivity of the benzoic acid [40]. In addition, the effect of steric hindrance hampers the nucleophilic attack of alcohol on carbocation intermediate.

The conversion rate of β-citronellol obtained in the $Fe(NO_3)_3$-catalyzed esterification reactions with different carboxylic acids followed the trend: acetic acid> propionic acid > cyclobutane carboxylic acid> benzoic acid (Figure 12). Nonetheless, the selectivity to β-citronellyl ester obtained on these reactions was completely distinct.

The esterification of propionic acid with β-citronellol gave β-citronellyl propionate with selectivity of *ca*. 52 %. The only secondary product was dihydromyrcenyl propionate.

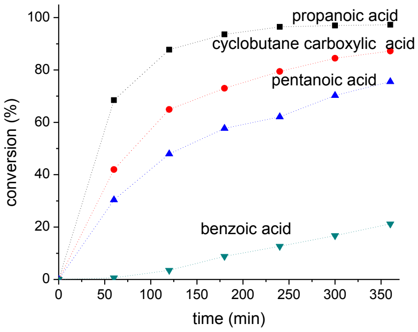


Figure 12. Conversion of β-citronellol on $Fe(NO_3)_3$-catalyzed esterification reactions with different acids in CH_3CN solutions[a]

Conversely, the cyclobutane carboxylic acid apparently underwent a ring opening reaction followed by carbon skeletal rearrangement, resulting in 2-methyl-2buten-carboxylic acid. This intermediate product was esterified with β-citronellol, and gave a product identified by GC-MS analysis as β-citronellyl 2-methyl-2-butenolate (i.e. 2-butenoic acid, 2-methyl-, 3,7-dimethyl-6-octenyl ester) (Figure 13).

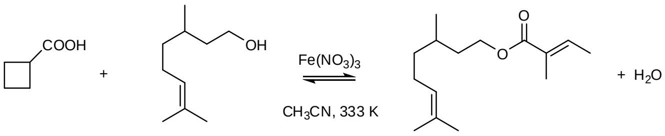


Figure 13. Carbon skeletal rearrangement followed by esterification with β-citronellol of cyclobutane carboxylic acid in presence $Fe(NO_3)_3$catalyst.

Previously, we had found that iron(III) cations are able to provoke rearrangement of carbon skeletal in cyclic compounds (i.e. monoterpenes), where carbon-carbon bounds are initially broken to originate more stable compounds [19]. Herein, iron (III) nitrate promoted the ring opening of cyclobutane carboxylic acid providing an unsaturated carboxylic acid, which was converted to ester in presence of β-citronellol in CH_3CN solutions (Figure 13).

The $Fe(NO_3)_3$-catalyzed esterification of pentanoic acid (i.e. valeric acid) with β-citronellol provided mainly β-citronellyl valerate (ca. 41 % selectivity). As secondary products were formed dihydromyrcenyl valerate besides a mixture of minority products (i.e. combined selectivity *ca*. 30 %).

Benzoic acid was the only carboxylic acid that did not converted to ester in $Fe(NO_3)_3$-catalyst esterification reactions with β-citronellol. We can be explain this observation if we analyze the rate-determining step (i.e. rds) of esterification reactions. After the protonation of carboxylic acid carbonyl group, it require that alcohol hydroxyl attacks the carbonylic carbon atom, which should have an electrophilic character [39,40]. Nonetheless, the group attached to the carbon atom can increase or decrease these electrophilicity, through the withdrawing or donating electron effect, respectively. Because ethyl group has higher electron donating capacity than methyl group, the esterification of acetic acid was more effective than that propionic acid.

When we analyze the actuation of benzyl group, we realize that besides steric hindering, which hamper the attack of alcohol hydroxyl group on carbonylic carbon atom, the π-system provide electron density to the carbocation, make it less electrophilic, hampering that alcohol attack [40].

Conclusion

A novel study of metal-catalyzed reactions for synthesize terpenic acetates was developed. Iron (III) nitrate hydrate, an inexpensive and commercially available catalyst was used in absence or presence of solvent. Among metal nitrate catalysts assessed, $Fe(NO_3)_3$ was the most selective towards formation of acetate products. The comparison with others tin catalyst provided the following order in terms of activity: $Fe(NO_3)_3 > Al(NO_3)_3 > Cu(NO_3)_2 > Ni(NO_3)_3 > Zn(NO_3)_2 > Mn(NO_3)_2 > Co(NO_3)_3 > Li(NO_3)_3$. We find out that nitrate metal salts promoted ionization of acetic acid, increasing the H^+ ions concentration in solution. We suppose that the reaction proceeded through two acid catalysis mechanisms (i.e Lewis and mainly Brønsted acid catalysis). When we have investigated the activity of others irons salts, we found that the solubility of salts show to be another important point on this reaction. Insoluble iron salts in acetonitrile ($FeSO_4$ and $Fe_2(SO_4)_3$ were much less active than iron nitrate. Conversely, the totally soluble catalyst $FeCl_3$ was more active than $Fe(NO_3)_3$. However, it was less selective because of higher formation of oligomers. The following order of reactivity for acetate selectivity was found: β-citronellol > geraniol > nerol. The tertiary terpenic alcohols (i.e. α-terpineol and linalool) did not underwent esterification. We verified that in absence of solvent, the formation of oligomers compromise significantly the reaction selectivity. Although two processes depending of H^+ ions to occur, oligomerization is notably lower when we have iron(III) nitrate catalyst in solution. The reaction scope was extended to the other carboxylic acids. We have found that $Fe(NO_3)_3$ catalyst was able to esterify alkyl acids with β-citronellol. However, it failed on benzoic acid esterification, a resulted attributed to lowering of electrophilicity of carbocation intermediate, due to electron donating effect of aromatic ring. Finally, we carried out reactions with alone HNO_3 acid, and we could verify that this Brønsted acid was less active and selective than iron(III) catalyst.

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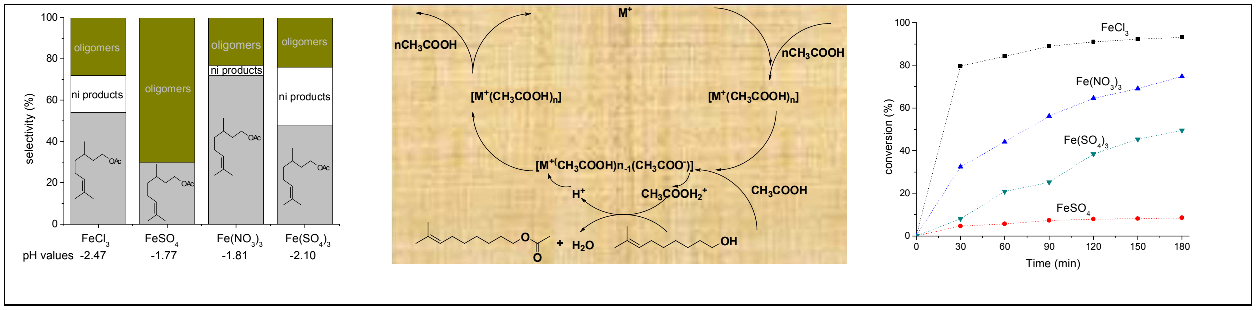
selectivity (%)
100
80
60
40
20
0
oligomers
ni products
OAc
FeCl$_3$
FeSO$_4$
Fe(NO$_3$)$_3$
Fe(SO$_4$)$_3$
pH values -2.47 -1.77 -1.81 -2.10
M$^+$
nCH$_3$COOH
nCH$_3$COOH
[M$^+$(CH$_3$COOH)$_n$]
[M$^+$(CH$_3$COOH)$_n$]
[M$^+$(CH$_3$COOH)n$_{-1}$(CH$_3$COO$^-$)]
H$^+$
CH$_3$COOH$_2^+$
CH$_3$COOH
O
O
+ H$_2$O
OH
conversion (%)
Time (min)
0
30
60
90
120
150
180
FeCl$_3$
Fe(NO$_3$)$_3$
Fe(SO$_4$)$_3$
FeSO$_4$