$FeCl_3 \cdot 6H_2O$ as a Versatile Catalyst for the Esterification of Steroid Alcohols with Fatty Acids

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Abstract: $FeCl_3 \cdot 6H_2O$ is an active catalyst for the esterification of some steroid alcohols with fatty acids under azeotropic reflux in mesitylene as solvent.

Key words: esterification, esters, steroids, multivalent metal salts, $FeCl_3 \cdot 6H_2O$, fatty acids, cholesterol

Fatty acid esters of steroid alcohols, such as cholesteryl stearate, are important chemicals for stabilizers of polymers, cosmetics, pharmceuticals, drug delivery, liquid-crystals, etc.[1–4] Generally, esters have been synthesized by using large amount of either acid or alcohol, and/or the removal of formed water during the reaction under azeotropic reflux, using a large amount of condensing agents, or using an acid chloride derivative.[5] However, these are less practical methods, because they often require tedious workup procedure to purify the desired products, particularly, products with large molecular weight. Thus, many efforts have been made to develop efficient methods with an environmentally benign chemical process. For example, direct esterification using an equimolar amount acid and alcohol, and heterogeneous modifications of catalyst by immobilization or support on matrix have been investigated.[6,7] Recently, we also described the efficient esterification and amidation reactions of long-chain fatty acids with long-chain aliphatic alcohols or amines over some multivalent metal salts, and found that ferric salts are active even when equimolar amounts of acids and alcohols or amines were used.[8] Here, we report the esterification of bulky alcohols such as cholesterol (**1**), ergosterol (**2**), and stigmasterol (**3**) (Figure 1) with long chain fatty acids over the multivalent metal salt hydrate, $FeCl_3 \cdot 6H_2O$.

Figure 2 shows the results of esterification of stearic acid and cholesterol over metal chlorides and its hydrates in mesitylene reflux condition by removing water azeotropically using Dean–Stark apparatus. Esterification did not occur in the absence of catalyst (1.3% yield), and no significant improvement of yield was observed even for 24 hours (13% yield). Among the metal salts used in this study, $FeCl_3 \cdot 6H_2O$ showed the highest catalytic activity to afford a cholesteryl stearate in 89% yield after 12 hours. Al^{3+}, Cr^{3+}, Mn^{2+}, Co^{2+}, Zn^{2+}, and Zr^{4+} also showed catalytic activities in 13–16% yields; however, other metal salts

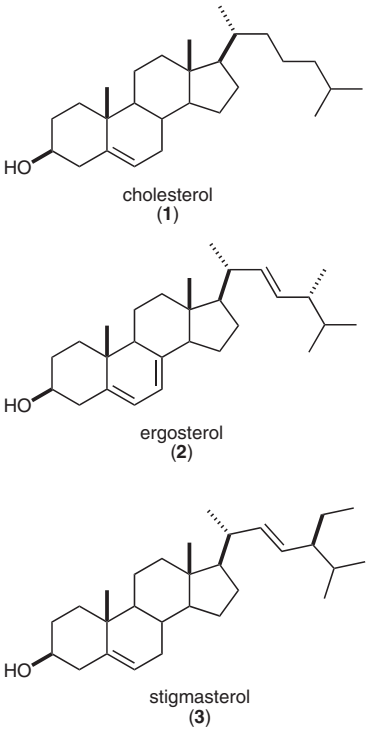

Figure 1 Cholesterol (**1**), ergosterol (**2**), and stigmasterol (**3**)

have only low activities. Typical acid catalysts, sulfuric acid and *p*-TsOH, moderately catalyzed the reaction in 42 and 71% yield, respectively. In our recent reports, aluminum, zirconyl, and ferric chlorides have been found as reliable catalysts for direct esterification of fatty acids and alcohols;[8] however, it was noted that $ZrOCl_2 \cdot 8H_2O$ and $HfOCl_2 \cdot 8H_2O$ were almost inert for the esterification of cholesterol. Anion moiety of ferric salts also affected the catalytic activity: ferric sulfate and nitrate gave the ester in 7.2 and 2.4% yield, respectively. Further, ferrous salts, $FeSO_4$ and $Fe(OAc)_2$, also had low catalytic activities: 9.9% yield for $FeSO_4$ and 1.7% yield for $Fe(OAc)_2$. These results mean that only $FeCl_3 \cdot 6H_2O$ is an active and promising catalyst for the esterification of cholesterol, and this is a specific feature compared to our recent results of esterification over multivalent metal salt catalysts.[8]

Table 1 summarizes the influence of aromatic hydrocarbon as solvent in esterification of stearic acid with cholesterol over $FeCl_3 \cdot 6H_2O$ catalyst under reflux condition. A low yield of 17% was observed in *m*-xylene, although the yield was moderately improved to 37% by prolonged reaction time for 24 hours. The reaction occurred effectively

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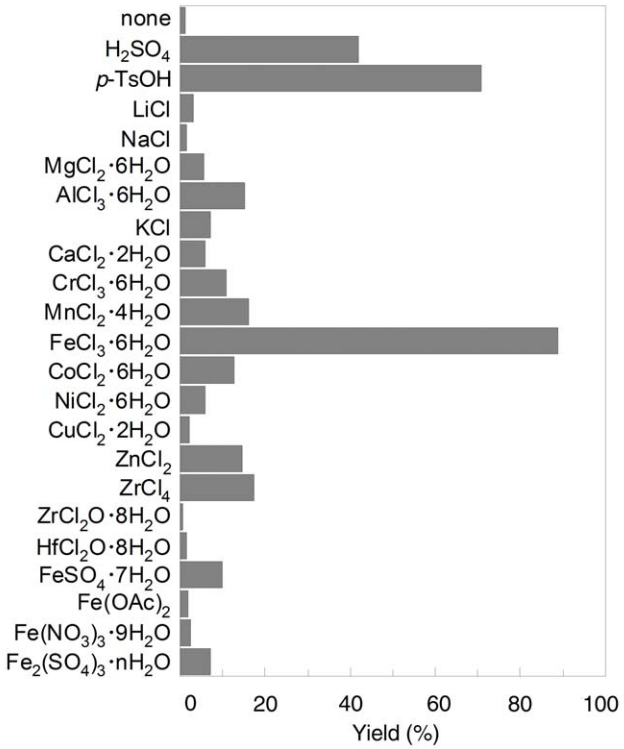

Figure 2 Esterification of cholesterol with stearic acid over metal chloride hydrates. *Reagents and conditions*: metal salt (0.06 mmol), stearic acid and cholesterol (6.0 mmol), solvent, mesitylene (40 mL), reflux, 12 h.

Table 1 The Influence of Solvent in the Esterification of Cholesterol with Stearic Acid Catalyzed by $FeCl_3 \cdot 6H_2O$[a]

Solvent	Bp (°C/760 Torr)	Yield (%)	
		12 h	24 h
benzene	80	0	4.4
toluene	110	1.5	9.9
m-xylene	140	17	37
mesitylene	160	89	100

[a] Reaction conditions: $FeCl_3 \cdot 6H_2O$ (0.06 mmol); stearic acid and cholesterol (6.0 mmol); solvent: mesitylene (40 mL). The reaction was carried out under reflux in mesitylene.

in 89% yield by the use of mesitylene as solvent. This means that catalytic activities depended on the temperature, and the reaction was enhanced with increasing boiling point of the solvent in the following order: benzene << toluene < *m*-xylene << mesitylene.

We attempted to carry out the solventless esterificationas follows: a mixture of cholesterol, stearic acid, and a catalytic amount of $FeCl_3 \cdot 6H_2O$ was stirred at 155 °C under N_2 flow (10 cm^3/min). The yield of ester increased gradually with reaction time: 47% for 6 hours and 77% for 12 hours, and the reaction was completed in 95% yield after 24 hours. These results indicate the possibility of a solventless esterification.

We also examined the catalyst amount required for the esterification of cholesterol with stearic acid over $FeCl_3 \cdot 6H_2O$. The yield of ester declined by increasing the cholesterol/catalyst (S/C, mol/mol) ratio over 100: 64% (S/C = 120) and 20% (S/C = 200). However, any significant improvement did not occur by using large amount of catalyst (93% yield at S/C = 50). From these results, it can be concluded that the amount of $FeCl_3 \cdot 6H_2O$ catalyst (S/C = 100) used is enough for a satisfactory yield of the ester.

Table 2 shows the typical results of the esterification of steroid alcohols such as cholesterol (**1**), ergosterol (**2**), and stigmasterol (**3**) with fatty acids using $FeCl_3 \cdot 6H_2O$ as a catalyst. The esterification occurred efficiently for all fatty acids, resulting in the formation of corresponding fatty acid esters of steroid alcohols in high yields. $FeCl_3 \cdot 6H_2O$ gave esters in high yields irrespective of chain length. These tendencies are different from our recent reports that catalytic activity of metal salts increased with the decrease of chain-length of used substrate.[8] The esterification of cholesterol with an unsaturated fatty acid, oleic acid, pro-

Table 2 The Influence of Chain Length of Fatty acid in the Steroid Alcohols Catalyzed by $FeCl_3 \cdot 6H_2O$[a]

Alcohol	Acid	Yield (%)
	octanoic acid (C8)	>88 (97)
	decanoic acid (C10)	>99
	lauric acid (C12)	>99
Cholesterol (**1**)	myristic acid (C14)	94
	palmitic acid (C16)	77 (96)
	stearic acid (C18)	89 (>99)
	oleic acid	69 (>99)
	octanoic acid	>99
	decanoic acid	>99
Ergosterol (**2**)	lauric acid	84 (>99)
	myristic acid	>99
	palmitic acid	86 (>99)
	stearic acid	57 (>99)
	octanoic acid	90
	decanoic acid	97
Stigmasterol (**3**)	lauric acid	>99
	myristic acid	96
	palmitic acid	90
	stearic acid	80 (97)

[a] Reaction conditions: $FeCl_3 \cdot 6H_2O$ (0.06 mmol); acid and alcohol (6.0 mmol); solvent: mesitylene (40 mL); time: 12 h. Number in parentheses refers to the yield after 24 h. The reaction was carried out under reflux in mesitylene.

ceeded in 90% yield in 24 hours without isomerization of the double bond moiety.

In summary, multivalent metal chlorides, especially, $FeCl_3 \cdot 6H_2O$ is a versatile catalyst for esterification of steroid alcohols with long-chain fatty acids.

Metal salts, stearic acid, palmitic acid, myristic acid, lauric acid, decanoic acid, octanoic acid, oleic acid, cholesterol, ergosterol, and stigmasterol are commercially available and used without further purification. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a JEOL ECA-500 NMR spectrometer. IR spectra of solids were recorded on a Nexus 470 (Thermo Nicolet) FT-IR spectrometer as KBr discs. Elemental analyses of all amides were entrusted to measure at Center for Organic Elemental Microanalysis, Kyoto University.

Esterification of Steroid Alcohols with Fatty Acids; General Procedure

The esterification of steroid alcohols with fatty acids was carried out in a single-necked round-bottomed flask (100 mL) equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted with a reflux condenser. An equimolar amount of each substrate, steroid alcohol and the fatty acid (6 mmol each), and $FeCl_3 \cdot 6H_2O$ (16.2 mg, 0.06 mmol) in mesitylene (40 mL) were charged into the round-bottomed flask. The mixture was heated to reflux temperature with continuous removal of H_2O. After 24 h, the resulting mixture was cooled to r.t. The solvent was removed in vacuo, and the crude solid was purified by column chromatography using $CHCl_3$ as an eluent (Table 2).

Cholesteryl Palmitate

Mp 80–81 °C.

IR (KBr): 1742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.67 (3 H, s), 0.82–0.92 (12 H, m), 0.92–0.99 (2 H, m), 1.00 (3 H, s), 1.02–1.18 (6 H, m), 1.2 (28 H, br s), 1.28–1.38 (6 H, m), 1.40–1.61 (10 H, m), 1.83 (3 H, m), 1.94–2.04 (2 H, m), 2.25 (2 H, t, *J* = 7.6 Hz), 2.36 (2 H, m), 4.6 (1 H, m), 5.4 (1 H, br d).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.9, 14.2, 18.8, 19.4, 21.1, 22.6, 22.8, 22.9, 23.9, 24.4, 25.2, 27.9, 28.1, 28.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 32.0, 34.8, 35.9, 36.3, 36.7, 37.1, 38.2, 39.6, 39.8, 42.4, 50.1, 56.2, 56.8, 73.7, 122.7, 139.8, 173.4.

Anal. Calcd for $C_{43}H_{76}O_2$: C, 82.63; H, 12.26. Found: C, 82.73; H, 12.18.

Ergosteryl Stearate

Mp 108–109 °C.

IR (KBr): 1742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.62 (3 H, s), 0.78–0.92 (14 H, m), 0.92 (2 H, s), 1.02 (3 H, br d), 1.24 (40 H, s), 1.46 (1 H, m), 1.58 (4 H, m), 1.64–1.78 (2 H, m), 1.82–1.94 (4 H, m), 1.96–2.08 (2 H, m), 2.25–2.95 (2 H, m), 2.30–2.38 (1 H, m), 2.40–2.52 (1 H, m), 4.7 (1 H, m), 5.20–5.50 (2 H, m), 5.3 (1 H, br s), 5.5 (1 H, br s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 14.2, 16.3, 17.7, 19.7, 20.0, 21.1, 21.2, 22.8, 23.1, 25.1, 28.2, 28.4, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 32.0, 33.2, 35.0, 36.8, 37.2, 38.0, 39.1, 40.5, 42.9, 46.1, 54.6, 55.7, 72.5, 116.4, 120.2, 132.1, 135.6, 138.7, 141.5, 173.4.

Anal. Calcd for $C_{46}H_{78}O_2$: C, 83.32; H, 11.86. Found: C, 83.57; H, 12.13.

Stigmasteryl Palmitate

Mp 106–107 °C.

IR (KBr): 1741 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.67 (3 H, s), 0.7–0.9 (14 H, m), 1.0 (9 H, m), 1.1–1.2 (3 H, m), 1.3 (28 H, br s), 1.38–1.74 (14 H, m), 1.83 (2 H, m), 1.92–2.08 (2 H, m), 1.92–2.08 (2 H, m), 2.27 (2 H, d, *J* = 7.2 Hz), 2.30 (2 H, br d), 4.6 (1 H, m), 5.0 (1 H, dd, *J* = 9.0, 15.2 Hz), 5.1 (1 H, dd, *J* = 8.3, 11.0 Hz), 5.3 (1 H, br d).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 2.1, 12.3, 14.2, 19.1, 19.4, 21.1, 21.2, 21.3, 22.8, 24.4, 25.2, 25.5, 27.9, 29.0, 29.2, 29.3, 29.4, 29.5, 29.7, 29.8, 31.9, 32.0, 34.8, 36.7, 37.1, 38.2, 39.7, 40.6, 42.3, 50.1, 51.3, 56.0, 56.9, 73.7, 122.6, 129.4, 138.4, 139.8, 173.4.

Anal. Calcd for $C_{45}H_{78}O_2$: C, 83.01; H, 12.07. Found: C, 82.76; H, 11.94.

Cholesteryl Oleate

IR (KBr): 1741 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.67 (3 H, s), 0.80–0.94 (12 H, m), 0.94–1.21 (12 H, m), 1.21–1.40 (30 H, m), 1.40–1.66 (12 H, m), 1.78–1.88 (3 H, m), 1.93–2.05 (6 H, m), 2.23–2.34 (8 H, m), 4.56–4.65 (1 H, m), 5.29–5.40 (3 H, m), 6.81 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.9, 14.2, 18.8, 19.4, 21.1, 21.3, 22.6, 22.8, 22.9, 23.9, 24.4, 25.1, 27.3, 27.4, 27.9, 28.1, 28.3, 29.2, 29.3, 29.4, 29.6, 29.8, 29.9, 31.9, 32.0, 34.8, 35.9, 36.3, 36.9, 37.1, 38.3, 39.6, 39.8, 42.4, 50.1, 56.2, 56.8, 73.8, 122.7, 127.0, 129.8, 130.1, 137.8, 139.8, 173.4.

Anal. Calcd for $C_{45}H_{78}O_2$: C, 83.01; H, 12.07. Found: C, 82.76; H, 12.06.

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