Highly Efficient Solvent-Free Condensation of Carboxylic Acids with Alcohols Catalysed by Zinc Perchlorate Hexahydrate, $Zn(ClO_4)_2 \cdot 6\,H_2O$

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Abstract: Zinc perchlorate hexahydrate, $Zn(ClO_4)_2 \cdot 6\,H_2O$, efficiently catalyses the esterification between nearly equimolar amounts of carboxylic acids and alcohols. The reaction works under solvent-free conditions at relatively low temperatures. Excellent results were obtained with a wide range of substrates.

Keywords: atom economy; esterification; esters; heterogeneous catalysis; solvent-free; zinc perchlorate

The reaction between a carboxylic acid and an alcohol is the most straightforward way for the preparation of esters, and constitutes a transformation of primary importance in both laboratory and industrial processes.[1] Since esterification is an equilibrium process, the full conversion into the products is usually performed by carrying out the reaction with a large excess of one of the two reactants. Recently, the growing interest towards green chemistry led to the development of a new generation of protocols which aimed at a 1:1 stoichiometry between the acid and the alcohol,[2] according to the atom economy concept.[3] In this context, Otera[4] recently indicated the requirements to be pursued in a modern practical esterification: the reaction should be run with a 1:1 ratio of the reactants, under mild and almost neutral conditions, and without the use of elaborate dehydrating systems. The employment of a non-sophisticated and recyclable catalyst undoubtedly represents an additional important goal.

Given the intrinsic difficulty of such a challenge, only few methodologies have been proposed recently which represent a significant step forward along this line. Therefore, there is an actual demand for a new general, efficient and environmentally benign protocol.

Recently, we reported that $Zn(ClO_4)_2 \cdot 6\,H_2O$[5] acts as a powerful catalyst in the acylation of alcohols with anhydrides,[6] and in the conversion of β-keto esters into β-enamino esters.[7] Since $Zn(ClO_4)_2 \cdot 6\,H_2O$ is inexpensive, non-toxic, stable to air and moisture, it could represent a very attractive choice for other Lewis acid-promoted transformations. Therefore we decided to investigate its catalytic activity in a challenging Fischer condensation with nearly equimolar amounts of reactants.

Preliminary experiments, reported in Table 1, disclosed the ability of $Zn(ClO_4)_2 \cdot 6\,H_2O$ to catalyse the esterification of 3-phenylpropionic acid (1.1 equivs.) with 1-octanol (1 equiv.). Solvent-free conditions,[8] besides allowing a green procedure, gave the best results compared to various solvents, such as toluene and dichloromethane (entries 2 and 7). Although the reaction at 80 °C proceeded very well even in the absence of any dehydrating agent (entry 5), we noticed a slight rate increase when a stoichiometric amount of $MgSO_4$ was introduced (entry 4). Such a recoverable dehydrating additive represents a practical and economical choice. On the other hand, $MgSO_4$ alone was not able to promote the condensation, thus confirming the role of $Zn(ClO_4)_2 \cdot 6\,H_2O$ as the effective catalyst (entry 6). We found that under the best reaction conditions, namely in the presence of 5 mol % of $Zn(ClO_4)_2 \cdot 6\,H_2O$ and 1 equivalent of $MgSO_4$, without solvent at 80 °C, the reaction resulted in full conversion into the ester in 8 h.

Upon completion of the esterification, the catalyst and $MgSO_4$ could be recovered by filtration from the reaction mixture diluted in CH_2Cl_2, and heating in an oven at 60 °C overnight. The reactivated catalyst was reused without an appreciable loss of its catalytic activity. The recycling process was repeated successfully for 4 times, with 95%, 93%, 93%, 91% yields, respectively.

We tested the scope and limitations of our methodology by analysing the reactivity of a variety of RCOOH/ROH systems (Table 2). As depicted in Table 2, our methodology gives excellent results in the condensation of various carboxylic acids with several alcohols. It is noteworthy that the esterification could be run successfully at relatively low temperatures (80–100 °C). Solvent-free conditions were in all cases adopted, even when both reagents were solid at room temperature (entry 6).[9]

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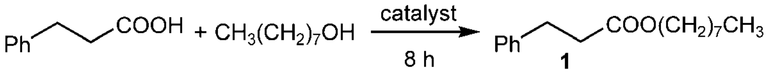
Table 1. Esterification of 3-phenylpropionic acid (1.1 equivs.) with 1-octanol (1 equiv.), under different conditions, after 8 h.



Entry	Catalyst	Solvent	Temp. [°C]	Yield [%]
1	$Zn(ClO_4)_2 \cdot 6\,H_2O$ (20 mol %), $MgSO_4$ (1 equiv.)	None	25	20
2	$Zn(ClO_4)_2 \cdot 6\,H_2O$ (5 mol %), $MgSO_4$ (1 equiv.)	CH_2Cl_2	reflux	15
3	$Zn(ClO_4)_2 \cdot 6\,H_2O$ (5 mol %), $MgSO_4$ (1 equiv.)	None	60	60
4	$Zn(ClO_4)_2 \cdot 6\,H_2O$ (5 mol %), $MgSO_4$ (1 equiv.)	None	80	95
5	$Zn(ClO_4)_2 \cdot 6\,H_2O$ (5 mol %)	None	80	85
6	$MgSO_4$ (1 equiv.)	None	80	10
7	$Zn(ClO_4)_2 \cdot 6\,H_2O$ (5 mol %), molecular sieves	Toluene	80	30

The esterification process worked well with primary, secondary, benzylic and homoallylic alcohols (entries 1–6), and neither isomerisation of the substrate (entries 4 and 5) nor racemisation (entry 6) were observed.

It is well known that the reactivity of alcohols and carboxylic acids towards esterification primarily depends on the steric hindrance of both the reactants. We found that acids bearing at the α position a bulky cyclohexyl (entries 13–14) or adamantyl group (entry 15) gave the desired ester, although a higher temperature or a higher catalyst loading was needed to reach good yields. Nevertheless, the reactions were carried out at 100 °C at the most, since at higher temperatures some decomposition processes occurred.[10] Very good results were obtained in the case of low reactive carboxylic acids (entries 16 and 17), and long-chain substrates as well (entry 24). Unfortunately, tertiary alcohols failed to give the desired ester,[11] since the dehydration process largely prevailed over the condensation.

The reaction is highly chemoselective. In fact, other functionalities present in the carboxylic acid or in the alcohol, such as a carbonyl, a cyano and a nitro group, a carbon-carbon double bond or a bromide were unaffected under the adopted reaction conditions. The compatibility of some typical protecting groups with the reaction conditions was also evaluated. Regarding the alcohol functionality, only the benzyl derivative was almost completely unaffected (entry 7). Among the *O*-silyl derivatives, the *t*-$BuMe_2Si$ group (TBDMS) does not survive under the reaction conditions, in fact after 6 h we recovered 60% of the hydroxy ester **8**, together with 25% of diester **9**, meaning that the alcohol deprotection is faster than the esterification process (entry 8). On the contrary, the (*i*-Pr)$_3$Si group (TIPS) is more resistant than TBDMS, in fact we could recover 55% of the desired protected ester **10**, together with the deprotected one (**11**, 35%), meaning that the deprotection step occurs after the esterification reaction (entry 9).

Moreover, the acetonide moiety does not survive under the adopted conditions, in fact only a small amount of the desired ester **12** (15%) was recovered, within a mixture of tri- and diesters of glycerol (entry 10). Finally, the presence of an ester in the starting materials was not tolerated owing to the occurrence of transesterification phenomena. In fact, the reaction of ethyl 2-hydroxypropionate with 3-phenylpropanoic acid gave the appropriate ester **13** only in 10% yield, together with ethyl 3-phenyl propionate and starting materials (entry 11).

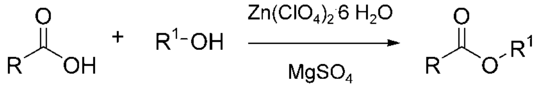
Concerning the amine function, amide and BOC derivatives are compatible with the reaction conditions, in fact the expected protected amino esters were obtained in high yield (entries 19 and 20). The protected amino moiety only considerably reduces the reaction rate with respect to non-functionalised substrates (entry 1), probably as a consequence of its competitive coordination to the catalyst.

In order to evaluate the possibility of applying our methodology in a large-scale esterification, we carried out the reaction of 1-octanol with 3-phenylpropanoic acid starting from 13 g (100 mmol) of alcohol. The yield in the ester **1** (93%) was almost the same as that of the small-scale (1 mmol) run.

In conclusion, we have found a benign protocol which proceeds efficiently at moderate temperatures, in the presence of a non-sophisticated catalytic system, which can be recovered and recycled. In addition, the reaction is carried out under solvent-free conditions, which implies a simple work-up and a low waste procedure.

With respect to literature data, the present method is comparable or in some cases superior to the recently reported procedures. The highly atom-efficient protocol based on fluoroalkyldistannoxane catalysts was found to be limited to unhindered substrates,[2a] whereas those employing $HfCl_4 \cdot THF$[2b] and DPAT[2c] poorly tolerated the presence of other functionalities. In an analogous manner, powerful heterogeneous systems, such as $NaHSO_4 \cdot H_2O$[2d] and montmorillonite-enwrapped titanium[2e] catalysts, were applied to a limited range of substrates. Elegant but uneconomical was the choice of BOC_2O/DMAP combination proposed by Gooßen.[2f] Finally, our protocol can be considered as an alternative and is competitive with the method proposed

Table 2. Esterification of nearly equimolar amounts of carboxylic acids and alcohols catalysed by $Zn(ClO_4)_2 \cdot 6\,H_2O$.



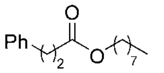
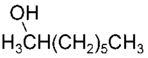
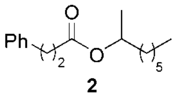
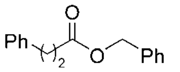
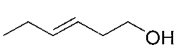
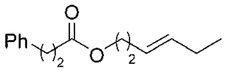
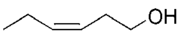
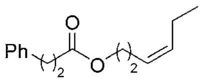
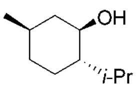
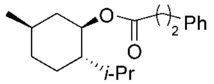
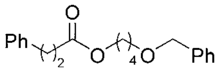
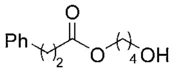
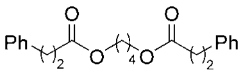
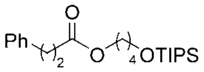
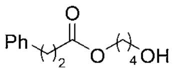
Entry	R in RCOOH	R^1-OH	Time [h]	Temp. [°C]	Product	Yield [%]
1	$PhCH_2CH_2$-	$CH_3(CH_2)_7$-OH	8	80	 **1**	95
2	$PhCH_2CH_2$-	 $CH_3\overset{OH}{C}H(CH_2)_5CH_3$	22	80	 **2**	95
3[a]	$PhCH_2CH_2$-	$PhCH_2$-OH	8	80	 **3**	75
4	$PhCH_2CH_2$-		8	80	 **4**	90
5	$PhCH_2CH_2$-		8	80	 **5**	90
6[b]	$PhCH_2CH_2$-		40	80	 **6**	85
7[c]	$PhCH_2CH_2$-	$PhCH_2$-O-$(CH_2)_4$-OH	8	80	 **7**	82
8	$PhCH_2CH_2$-	TBDMSO-$(CH_2)_4$-OH	6	80	 **8**	60
					 **9**	25
9	$PhCH_2CH_2$-	TIPSO-$(CH_2)_4$-OH	6	80	 **10**	55
					 **11**	35

Table 2 (cont.)

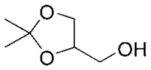
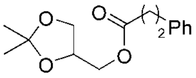
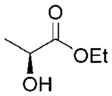
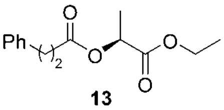
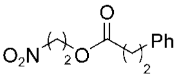
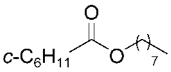
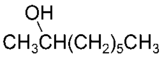
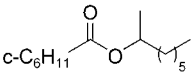
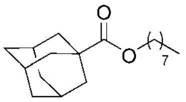
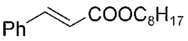
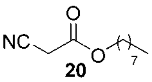
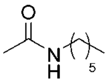
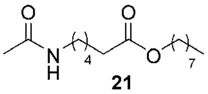
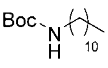
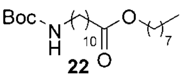
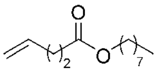
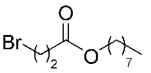
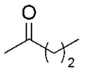
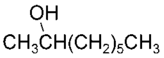
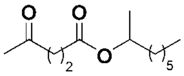
Entry	R in RCOOH	R^1-OH	Time [h]	Temp. [°C]	Product	Yield [%]
10[d]	$PhCH_2CH_2$-		12	80	 **12**	15
11[e]	$PhCH_2CH_2$-		10	80	 **13**	10
12	$PhCH_2CH_2$-	O_2N-CH_2CH_2-OH	48	80	 **14**	94
13	*c*-C_6H_{11}-	$CH_3(CH_2)_7$-OH	26	80	 **15**	93
14[b]	*c*-C_6H_{11}-	 $\overset{OH}{CH_3CH}(CH_2)_5CH_3$	40	80	 **16**	70
15	1-adamantyl	$CH_3(CH_2)_7$-OH	40	100	 **17**	82
16	Ph-	$CH_3(CH_2)_7$-OH	26	100	$PhCOO(CH_2)_7CH_3$ **18**	89
17	*E*-PhCH=CH-	$CH_3(CH_2)_7$-OH	40	80	 **19**	88
18	N≡C-CH_2-	$CH_3(CH_2)_7$-OH	40	80	 **20**	95
19[f]		$CH_3(CH_2)_7$-OH	26	80	 **21**	65
20		$CH_3(CH_2)_7$-OH	24	80	 **22**	90
21	CH_2=CH$(CH_2)_2$-	$CH_3(CH_2)_7$-OH	13	80	 **23**	96
22	$BrCH_2CH_2$-	$CH_3(CH_2)_7$-OH	8	80	 **24**	90

Table 2 (cont.)

Entry	R in RCOOH	R^1-OH	Time [h]	Temp. [°C]	Product	Yield [%]
23		 $CH_3\overset{OH}{CH}(CH_2)_5CH_3$	18	80	 **25**	92
24	$CH_3(CH_2)_7$-	$CH_3(CH_2)_{21}$-OH	12	80	n-$C_8H_{17}COOC_{22}H_{45}$ **26**	95

Reaction conditions: 1 mmol of alcohol, 1.1 mmol of carboxylic acid, 0.05 mmol of $Zn(ClO_4)_2 \cdot 6\,H_2O$, 1 mmol of $MgSO_4$; the yields reported refer to isolated products.

[a] 10% of dibenzyl ether was obtained.

[b] 10 mol % of catalyst were used.

[c] 10% of deprotected product was observed.

[d] A mixture of tri- and diesters of glycerol was recovered.

[e] 10% of ethyl 3-phenylpropionate was observed.

[f] 15 mol % of catalyst were used.

by Ishihara, Yamamoto et al.,[12] which appeared during the revision of the present manuscript.

We can assert that the present protocol for the $Zn(ClO_4)_2 \cdot 6\,H_2O$-catalysed esterification joins the practical and environmental advantages of heterogeneous catalysis with a fair applicability to several substrates, typical of a homogeneous Lewis acid catalysis.

Experimental Section

Typical Experimental Procedure

An oven-dried Schlenk tube was charged with $Zn(ClO_4)_2 \cdot 6\,H_2O$ (18.6 mg, 0.05 mmol), $MgSO_4$ (120 mg, 1 mmol), 1-octanol (157 μL, 1 mmol), 3-phenylpropionic acid (165 mg, 1.1 mmol), and immersed up to the top in an oil bath at 80 °C. The mixture was stirred for 8 hours, then cooled to room temperature, and diluted with CH_2Cl_2. The catalyst was filtered off, and the organic layer was washed with water, then aqueous $NaHCO_3$. After drying with $MgSO_4$ and evaporation of the solvent, the crude product was purified by flash chromatography on a silica gel column (petroleum ether:diethyl ether, 4:1) to give the desired carboxylic ester; yield: 249 mg (95%).

The filtered catalyst was reactivated by heating in oven at 60 °C overnight and reused.

Spectroscopic data of two representative unknown products are as follows:

(Z)-3-Hexenyl 3-phenylpropanoate (5): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (t, 3H, $J_{H,H} = 7.5$ Hz), 2.00–2.05 (m, 2H), 2.15–2.20 (m, 2H), 2.61 (t, 2H, $J_{H,H} = 7.8$ Hz), 2.94 (t, 2H, $J_{H,H} = 7.8$ Hz), 4.06 (t, 2H, $J_{H,H} = 6.0$ Hz), 5.10–5.15 (m, 1H), 5.20–5.25 (m, 1H), 7.05–7.10 (m, 3H), 7.10–7.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 20.4 (CH_2), 26.8 (CH_2), 30.8 (CH_2), 35.8 (CH_2), 63.5 (CH_2), 123.7 (CH), 126.3 (CH), 128.2 (CH), 128.4 (CH), 134.5 (C), 140.5 (C), 172.9 (C).

2-Methylheptyl 4-oxopentanoate (14): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, 3H, $J_{H,H} = 6.8$ Hz), 1.21 (d, 3H, $J = 6.0$ Hz), 1.20–1.35 (m, 8H), 1.35–1.45 (m, 1H), 1.50–1.60 (m, 1H), 2.20 (s, 3H), 2.55 (t, 2H, $J_{H,H} = 6.5$ Hz), 2.74 (t, 2H, $J_{H,H} = 6.5$ Hz), 4.80–4.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 19.8 (CH_3), 22.5 (CH_2), 25.2 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 29.9 (CH_3), 31.7 (CH_2), 36.0 (CH_2), 38.1 (CH_2), 71.7 (CH), 172.3 (C), 206.6 (C).

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