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## A green protocol for chemoselective *O*-acylation in the presence of zinc oxide as a heterogeneous, reusable and eco-friendly catalyst

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Abstract—The solvent-free acylation of alcohols and phenols with acyl chlorides using ZnO as a catalyst is described. The remarkable selectivity under mild and neutral conditions, and recyclability of the catalyst, are advantages. © 2005 Elsevier Ltd. All rights reserved.

The protection of hydroxyl groups by esterification constitutes the major backbone of many preparations of natural and synthetic products such as perfumes, flavors and food additives, cosmetics, pharmaceuticals, plastisizers and polymers.<sup>1</sup> Generally, esterification is carried out by acylation of alcohols and phenols with carboxylic acids and more conveniently anhydrides or acyl chlorides in the presence of basic catalysts, Brönsted or Lewis acids and metal salts.<sup>1b</sup> Amongst the catalysts used for activation of anhydrides and acyl chlorides, pyridine,<sup>1</sup> Et<sub>3</sub>N,<sup>1</sup> 4-(dimethylamino)pyridine (DMAP),<sup>2</sup> Bu<sub>3</sub>P,<sup>3</sup> MgBr<sub>2</sub>–Et<sub>3</sub>N<sup>4</sup> and KF–Al<sub>2</sub>O<sub>3</sub><sup>5</sup> are the most significant, whereas H<sub>2</sub>SO<sub>4</sub>,<sup>6</sup> *P*-TsOH<sup>7</sup> and NH<sub>2</sub>SO<sub>3</sub>H<sup>8</sup> are acidic catalysts. Recently, other reagents such as distannoxane,<sup>9</sup> metal triflates,<sup>10–13</sup> AlPW<sub>12</sub>O<sub>40</sub>,<sup>14</sup> ZrCl<sub>4</sub>,<sup>15</sup> Cu(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O,<sup>16</sup> LiClO<sub>4</sub>,<sup>17</sup> ZrOCl<sub>2</sub>·8H<sub>2</sub>O,<sup>18</sup> CeCl<sub>3</sub>,<sup>19</sup> BiOClO<sub>4</sub>·XH<sub>2</sub>O,<sup>20</sup> MgBr<sub>2</sub>,<sup>21</sup> LiCl,<sup>22</sup> I<sub>2</sub>,<sup>23a</sup> NBS,<sup>23b</sup> metal triflates in ionic liquids,<sup>13</sup> twisted amides,<sup>24</sup> solid supported reagents<sup>25</sup> and *Lipase* enzymes<sup>26</sup> have been applied for acylation of alcohols and phenols. However, there is always the need for better methods.

Recently, mineral oxides have proved to be useful to chemists in the laboratory and industry due to the good activation of adsorbed compounds and reaction rate enhancement, selectivity, easier work-up and recyclability of the supports and the eco-friendly, green, reaction conditions.<sup>27,28</sup> Herein, we wish to report acylation of hydroxyl groups with acyl chlorides using catalytic

 $\begin{array}{c} \text{RCOCl} + \text{R'OH} & \xrightarrow{\text{ZnO} (10 \text{ mol}\%)} \\ \hline \text{Solvent-free} \\ \text{R= CH}_3, \text{ Ph} \\ \text{R' = aryl, alkyl} \end{array} \xrightarrow{\text{RCO}_2 \text{R'}} \end{array}$ 

Scheme 1.

amounts of zinc oxide (ZnO) under solvent-free conditions (Scheme 1).

In the first set of experiments, the catalytic potential of some metal oxides was investigated for the benzoylation of ethanol with benzoyl chloride (1.1 equiv) under solvent-free conditions (Table 1). According to the results obtained, of the metal oxides tested, TiO<sub>2</sub>, SiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, Fe<sub>2</sub>O<sub>3</sub> and Ag<sub>2</sub>O were unable to promote benzoylation of ethanol while CaO and MgO gave large amounts of benzoic acid from the hydrolysis of the benzoyl chloride and the most efficient catalyst was ZnO. When a suspension of EtOH (10 mmol), ZnO (10 mol %) and benzoyl chloride (11 mmol) was stirred at ~40 °C, gas and heat were evolved resulting in a clear solution. Extraction of the reaction mixture with ethyl acetate afforded ethyl benzoate in excellent yield (Table 1, entry 8).

Zinc oxide is an inexpensive, moisture stable, reusable, commercially available and environmentally benign catalyst used in Beckmann rearrangements,<sup>27b</sup> Friedel–Crafts acylation,<sup>27c</sup> the synthesis of cyclic ureas,<sup>29</sup> dehydration of aldoximes<sup>30</sup> and oxidation of alcohols.<sup>31</sup>

The ZnO-catalyzed benzoylation of benzylic, primary and secondary alcohols proceeded efficiently with high

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 Table 1. Benzoylation of ethanol with benzoyl chloride in the presence of metal oxides<sup>a</sup>

Entry	Metal oxide (mol%)	Time/temp. (h)/(°C)	Yield <sup>a</sup>
1	Al <sub>2</sub> O <sub>3</sub> (10)	5/rt	60
2	SiO <sub>2</sub> (10)	5/40	52
3	$Fe_2O_3$ (10)	5/40	37
4	MgO (10)	5/40	50 <sup>b</sup>
5	CaO (10)	5/40	63 <sup>b</sup>
6	TiO <sub>2</sub> (10)	5/40	24
7	Ag <sub>2</sub> O (10)	5/40	$40^{\mathrm{b}}$
8	ZnO <sup>c,d</sup> (10)	0.5/40	93
9	ZnO (20)	0.5/40	94
10	ZnO(5)	0.5/40	85
11	None	12/40	35
12	Pyridine (1 mL)	12/80	48

 $PhCOCl + EtOH \xrightarrow{Cat.} PhCO_2Et$ 

<sup>a</sup> Isolated yield.

<sup>b</sup>A large amount of PhCO<sub>2</sub>H was isolated from hydrolysis of the PhCOCl.

<sup>c</sup> The reaction also occurred at room temperature but needed a longer reaction time.

<sup>d</sup> The reactions in CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, CH<sub>3</sub>CN and toluene were not effective.

isolated yields under solvent-free conditions after short reaction times (Table 2). Similarly, cinnamyl and allyl alcohol (Table 2, entries 7 and 8) underwent benzoylation to afford the corresponding esters in 89% and 90% yields, respectively. In the case of alcohols, primary alcohols were benzoylated faster than secondary ones. Sterically hindered alcohols, such as triphenylmethanol (entry 13) remained unchanged and *tert*-butyl alcohol (entry 14) was benzoylated in only 40% yield under similar conditions. Phenols were

Table 2. Zn	O catalyzed	benzoylation	of alcohols	and	phenols
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 $PhCOCl + R'OH \xrightarrow[Solvent-free, 40 \ \circ C]{} PhCO_2R'$ 

Entry	Substrate	Product <sup>c</sup>	Time/yield <sup>b</sup> (min)/(%)
1	Methanol	Methyl benzoate	30/93
2	Ethanol	Ethyl benzoate	35/93
3	Benzyl alcohol	Benzyl benzoate	35/92
4	1-Butanol	1-Butyl benzoate	35/95
5	1-Octanol	1-Octyl benzoate	40/97
6	1-Decanol	1-Decyl benzoate	40/95
7	Cinnamyl alcohol	Cinnamyl benzoate	60/89
8	Allyl alcohol	Allyl benzoate	35/90
9	2-Propanol	2-Propyl benzoate	60/94
10	2-Butanol	2-Butyl benzoate	60/91
11	2-Octanol	2-Octyl benzoate	60/92
12	Cyclohexanol	Cyclohexyl benzoate	60/95
13	Triphenylmethanol	Triphenylmethyl benzoate	120/0
14	tert-Butyl alcohol	tert-Butyl benzoate	120/45
15	Phenol <sup>d</sup>	Phenyl benzoate	120/70
16	α-Naphthol <sup>d</sup>	α-Naphthyl benzoate	120/86
17	β-Naphthol <sup>d</sup>	β-Naphthyl benzoate	120/91

<sup>a</sup> The substrate was treated with PhCOCl (1.1 equiv per OH group) in the presence of 10 mol % ZnO under neat conditions at ~40 °C. <sup>b</sup> Isolated vield.

<sup>c</sup> All products were characterized satisfactorily (IR and <sup>1</sup>H NMR).

<sup>d</sup> The reaction was carried out at 60 °C.

also satisfactorily benzoylated generating the corresponding benzoates in 70-91% yields (Table 2, entries 15-17).

The scope of this methodology was further extended by esterification of alcohols or phenols with acetyl chloride, which is more reactive than benzoyl chloride. In short reaction times at room temperature, different acetate esters were prepared in excellent yields by reacting the alcohols or phenols with acetyl chloride (12 mol) in the presence of 10 mol % ZnO under solvent-free conditions (Table 3).

Further, we investigated the possible chemoselectivity of ZnO-mediated *O*-acylation reactions by running the competitive acetylation and benzoylation of alcohols and phenols or primary and secondary alcohols over 30 min. It is found that alcohols were acylated selectively in the presence of phenols and primary alcohols in the presence of secondary ones. The reaction temperature is an important factor for chemoselectivity and the best temperature was around room temperature (Scheme 2).

Additionally, the catalytic activity of reused ZnO, which was readily recovered by filtration of the reaction mixture and consequent washing with ethyl acetate and  $H_2O$ , was investigated. Acetylation and/or benzoylation of benzyl alcohol with twice or three times recycled zinc oxide gave the corresponding esters, in comparable yields to the fresh catalyst (95% benzyl acetate and 90% benzyl benzoate).

Although the mechanism of the reaction has not been clarified, it seems that coordination of the C=O bond of the acyl chloride to the zinc ion activates the C=O

Table 3. ZnO catalyzed acetylation of alcohols and phenols<sup>a</sup>

Entry	Substrate	Product <sup>b</sup>	Time/yield <sup>c</sup> (min)/(%)
1	Methanol	Methyl acetate	10/94
2	Ethanol	Ethyl acetate	10/96
3	Benzyl alcohol	Benzyl acetate	10/93
4	1-Butanol	Butyl acetate	15/95
5	1-Octanol	1-Octyl acetate	15/95
6	1-Decahol	1-Decyl acetate	20/94
7	Cinnamyl alcohol	Cinnamyl acetate	25/90
8	Allyl alcohol	Allyl acetate	20/91
9	2-Propanol	2-Propyl acetate	30/95
10	2-Butanol	2-Butyl acetate	30/91
11	2-Octanol	2-Octyl acetate	30/91
12	Cyclohexanol	Cyclohexyl acetate	25/98
13	Triphenyl methanol	Triphenyl methyl acetate	120/20
14	tert-Butyl alcohol	tert-Butyl acetate	120/65
15	Phenol	Phenyl acetate	60/90
16	α-Naphthol	α-Naphthyl acetate	60/88
17	β-Naphthol	β-Naphthyl acetate	60/86

 $CH_{3}COCl + R'OH \xrightarrow[Solvent-free, rt]{In O(10 mol \%)} CH_{3}CO_{2}R'$ 

<sup>a</sup> The substrate was treated with CH<sub>3</sub>COCl (1.2 equiv per OH group) in the presence of 10 mol % of ZnO under neat conditions at room temperature.  $^{\rm b}\,All$  products were identified by their IR and  $^1{\rm H}$  NMR spectra.

<sup>c</sup> Isolated yields.



## Scheme 2.

group and enhances the leaving ability of the chloride. It is noteworthy that acylation of alcohols does not occur using anhydrides or acids.

This protocol benefits from short reaction times, operational simplicity, neutral reaction conditions, reusability of the catalyst, avoidance of solvents, reduced environmental and economic impacts and chemoselectivity. In conclusion, the present results on the acylation of alcohols demonstrate the efficiency of ZnO as an inexpensive reusable green catalyst and constitutes a useful alternative to commonly accepted procedures.

General experimental procedure for benzoylation: To a mixture of alcohol or phenol (10 mmol) and ZnO (10 mol %) was added benzoyl chloride (11 mmol) with stirring at ~40 °C. The progress of the reaction was followed by TLC. After completion of the reaction (Table 2), the resulting mixture was extracted with EtOAc ( $2 \times 5$  ml) and filtered to remove ZnO. The organic layer was washed with 10% NaHCO<sub>3</sub> and water, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give the product. All of the benzoate esters are known and were characterized by comparison of their spectral and physical data with those of authentic samples.

General experimental procedures for acetylation: To a mixture of alcohol or phenol (10 mmol) and ZnO (10 mol %) was added acetyl chloride (12 mmol) with stirring at room temperature. The progress of the reaction was followed by GC. After completion of the reaction (Table 3), the products were isolated either as described above or by the addition of NaHCO<sub>3</sub> (10%) and water, separation of the organic layer and drying it with Na<sub>2</sub>SO<sub>4</sub>. All of the acetate esters are known and gave the same spectral data as authentic samples.

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