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COMMUNICATION

An extremely efficient and green method for the acylation of secondary alcohols, phenols and naphthols with deep eutectic solvent as catalyst

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The typical deep eutectic solvent [CholineCl][$ZnCl_2$]$_3$ easily prepared from choline chloride and zinc chloride is green and useful for the acylation of secondary alcohols, phenols, and naphthols with acid anhydrides. Its efficiency allows the acylation of sterically hindered secondary alcohols and acid anhydrides to proceed in high yield under mild condition. The catalyst is cheap, easy to handle, conveniently synthesized in a single step, and recyclable for several times without significant loss of the catalytic activity.

The acylation of alcohols with acid anhydrides is a valuable tool in the synthesis of biologically active compounds and pharmaceutical products.[1-3] This reaction is commonly catalysed by acid or base catalysts which are only efficient for highly reactive primary alcohols.[4-6] Although there have been advances in acylation methods,[7-10] highly efficient, low-cost and green catalysts are still in strong demand for the acylation of sterically-hindered secondary alcohols and phenols. Up to now, 4-(dimethylamino)pyridine (DMAP) has been the most widely used nucleophile base catalyst for the acylation of sterically-hindered alcohols even though it is known to have acute toxicity.[11] Other catalysts that have been shown to be efficient for acylation of sterically-hindered alcohols are metal triflates, such as scandium triflate,[12] trimethylsilyl triflate,[13] indium triflate,[14] bismuth triflate.[15] Amongst these, scandium triflate and bismuth triflate demonstrated highly catalytic activity. However, these catalysts required the use of donor solvents such as dichloromethane, THF, or acetonitrile and the excess of acid anhydrides (3-5 equiv.). Furthermore, despite being classified as strong, efficient and stable Lewis acidic catalysts, metal triflates are expensive, and the recycling of catalyst involving the recrystallization from the toxic organic solvent such as acetonitrile is required. Consequently, they are not convenient to apply on a large scale. Bartoli and co-workers reported the use of $Mg(ClO_4)_2$ and $Zn(ClO_4)_2.6H_2O$ as the better alternatives to metal triflates. This research showed that the $Zn(ClO_4)_2.6H_2O$ is able to act as a powerful catalyst which can be potentially applied in industrial processes.[16] However, this catalyst cannot be recovered and reused after the aqueous work-up. Recently, Li and co-workers developed DMAP saccharin-catalysed acylation of alcohols with an almost equimolar amount of anhydrides under solvent-free and base-free conditions.[17] More recently, Collado and co-workers reported the uses of titanium(III) species as a reductant for O-acylation of alcohols and phenol.[18] Although these methods are efficient, many of them involve high-cost catalyst, large amounts of volatile organic solvents and/or long reaction times.

The development of green and sustainable chemistry has led to the search for an efficient and environmentally benign catalyst.[19] The deep eutectic solvents which are composed of two or three components to form an eutectic mixture with lower melting point than individual components were first prepared by Abbott's group in 2001.[20] Up to now, they have been used as catalysts for many organic transformations including C-C, C-O, C-N bonding formation.[21-25] Deep eutectic solvents possessing the excellent catalytic activity and stability can be comfortably handle due to low toxic, non-corrosive properties. Moreover, these catalyst are easily recovered and reused without the significant loss of reactivity.[26] Consequently, deep eutectic solvents are suitable for industrial applications.[27-32]

In our previous work, we found the Friedel–Crafts acylation of aromatic compounds proceeded smoothly in the presence of [CholineCl][$ZnCl_2$]$_3$ as dual solvent–catalyst.[25] Herein, we report that [CholineCl][$ZnCl_2$]$_3$ demonstrates efficient catalytic activity for the acylation of sterically-hindered secondary alcohols and phenols under mild condition. Until now, its use as a catalyst for acylation of alcohols and phenols has remained unreported. The Lewis acidity of [CholineCl][$ZnCl_2$]$_3$ is

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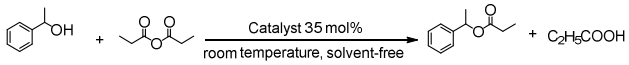
robust enough to promote the acylation of sterically-hindered secondary alcohols to afford the acylated products in quantitative yields. Moreover, [CholineCl][$ZnCl_2$]$_3$ is easily prepared, stable to air and moisture, low-cost, and recyclable without loss of catalytic activity.

The results listed in Table 1 demonstrate the powerfully catalytic activity of [CholineCl][$ZnCl_2$]$_3$ in the propionylation of 1-phenyletanol at room temperature for 30 min under solvent-free condition. The reactions were carried out with propionic anhydride (1.05 equiv.) in the presence of 35 mol% of the catalyst. The propionylation of sterically-hindered 1-phenyletanol did not proceed in the presence of traditional Brønsted acid (Table 1, entry 2). Bismuth triflate was not reactive under the present method (Table 1, entry 3). As previously reported, bismuth triflate-catalyzed acylation of 1-phenyletanol proceeded quantitatively but required the excess of acylating reagent (10 equiv) and took a longer reaction time (2 h).[15] The excellent yield was noted under catalytic influence of [CholineCl][$ZnCl_2$]$_3$ (Table 1, entry 10). The reaction was also carried out on a 10 mmol scale, and the yield is almost the same as on 1 mmol scale (94% vs 96%, entry 10). The control experiments were investigated by employing individual components such as choline chloride (entry 4) or $ZnCl_2$ (entry 5). $ZnCl_2$ displayed good catalytic activity but it cannot be recovered after aqueous workup. The search for other deep eutectic solvents was conducted but the lower yields of products (Table 1, entries 6-9) were noted in comparison with [CholineCl][$ZnCl_2$]$_3$.

Table 1 The solvent-free propionylation of 1-phenyletanol with



propionic anhydride at room temperature.

Entry	Catalyst	Yield[a] (%)
1	None	0
2	H_2SO_4	0
3	$Bi(OTf)_3$	7[b]
4	Choline chloride	6
5	$ZnCl_2$	80
6	[CholineCl][urea]$_2$	0
7	[CholineCl][Malonic acid]	7
8	[CholineCl][Oxalic acid]	38
9	[Urea]$_7$[$ZnCl_2$]$_2$	5
10	[CholineCl][$ZnCl_2$]$_3$	96 (94)[c]

[a] Isolated yield. [b] 10 mol% of $Bi(OTf)_3$ was used. [c] 10 mmol scale reaction.

Under the optimal condition, the scope of acylating reagents was investigated by treating 1-phenyletanol with acetic, butyric and benzoic anhydride in the presence of 35 mol% of [CholineCl][$ZnCl_2$]$_3$. The desired products were obtained in good to excellent yields at room temperature for 30 min (Table 2, entries 1-3). The benzoic anhydride afforded the lowest yield due to its least reactivity (Table 2, entry 4). The benzoylation of 1-phenyletanol taken place for 30 min afforded only 55% yield while prolonging the reaction time to 180 min produced 80% yield under the present method. As previously reported, the acylation of alcohols proceeded with complete retention of configuration at the hydroxyl-bearing carbon.[10, 13, 15, 18]

Table 2 The solvent-free acylation of 1-phenyletanol with acid anhydrides at room temperature.

Entry	Acid anhydride	Yield[a] (%)
1	Acetic anhydride	81
2	Propionic anhydride	96
3	Butyric anhydride	86
4	Benzoic anhydride	55

[a] Isolated yield

After these preliminary results, the propionylation of secondary alcohols and phenols was conducted in the presence of 35 mol% of [CholineCl][$ZnCl_2$]$_3$ at room temperature (Table 3). The aliphatic acyclic secondary alcohols containing 3–7 carbon atoms, cyclohexanol, and menthol were propionylated in excellent yields, and no olefin was detected (Table 3, entries 1-7). The [CholineCl][$ZnCl_2$]$_3$-catalysed propionylation of isoborneol proceeded smoothly at room temperature for only 30 min under solvent-free (Table 3, entry 8). The use of bismuth triflate, in this case, was reported with co-solvent (THF or toluene) and with longer reaction time (3 h to 7 h).[33] In addition, no side-product was detected under the present method. Moreover, it is noteworthy that the desired products obtained after the workup attained the sufficient purity for NMR analysis without further purification.

Remarkably, the propionylation of diphenylmethanol bearing more sterically hindered substituents afforded the desired benzhydryl propionate in 83% yield along with 17% yield of dibenzhydryl ether as a side product (Table 3, entry 10). In the previous report, only moderate yield was obtained for the same reaction.[34] Per-*O*-acylation is one of the most useful techniques for the protection of hydroxyl groups in carbohydrates.[35] In the current method, per-*O*-propionylation of α-D-glucose with the stoichiometric quantity of propionic anhydride afforded in excellent yield (Table 3, entry 11). As previously reported, a similar yield was obtained in the presence of pyridine derivative and excess of acylating reagent or organic solvent.[17] *Myo*-inositol and phosphorylated myo-inositol derivatives are useful precursors which play an important role in calcium mobilization, insulin stimulation, exocytosis, cytoskeletal regulation.[36] Myo-inositol was propionylated in 95% isolated yield of the per-*O*-propionylated product at room temperature for 120 min. Phenols and naphthols were also reactive under the current method (Table 3, entries 13-15). Tertiary alcohols were unreactive under any investigated conditions (Table 3, entries 16, 17). As reported by Procopiou, no acetylation of tertiary alcohols by acetic anhydride was observed in the presence of TMSOTf as a catalyst. The reaction only proceeded in a slow rate with the addition of DMAP.[13] It has also been known that 1,1-diphenyletanol was not acetylated by acetic anhydride in the presence of $Zn(ClO_4)_2.6H_2O$.[16]

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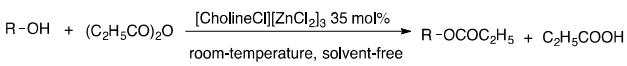
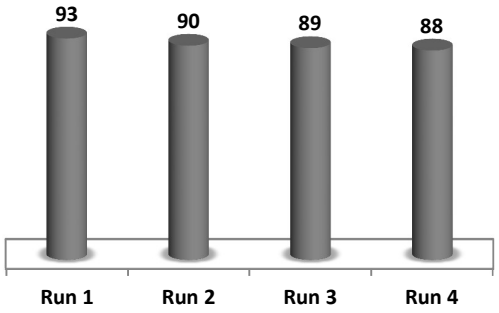
Table 3 The solvent-free propionylation of secondary alcohols and phenols at room temperature.



Entry	Substrate	Time (min)	Yield[a] (%)
1	Propan-2-ol	30	88
2	Butan-2-ol	35	89
3	Pentan-2-ol	30	91
4	Hexan-2-ol	40	89
5	Heptan-2-ol	40	94
6	Cyclohexanol	45	92
7	Menthol	30	89
8	Isoborneol	30	93
9	1-Phenyletanol	60	96
10	Diphenylmetanol	60	83[b]
11	α-D-Glucose	100	94[c]
12	*myo*-Inositol	120	95[d]
13	4-Methoxyphenol	60	95
14	[1,1'-Biphenyl]-2-ol	100	90
15	2-Naphthol	110	92
16	2-Phenylpropan-2-ol	150	trace[e]
17	1,1-Diphenylethanol	150	trace[e]

[a] Isolated yield.
[b] Side product is (oxybis(methanetriyl))tetrabenzene.
[c] per-*O*-propionylated in the presence of a stoichiometric quantity of propionic anhydride (5 mmol).
[d] per-*O*-propionylated in the presence of a stoichiometric quantity of propionic anhydride (6 mmol).
[e] The major alkene products were obtained by the dehydration of tertiary alcohols.

The recycling ability of [CholineCl][$ZnCl_2$]$_3$ was investigated under optimized condition by using 1-phenyletanol as substrate (Scheme 1).[37] After completion of the reaction, the crude product was extracted with diethyl ether. The recovered [CholineCl][$ZnCl_2$]$_3$ was dried under reduced pressure in 6 h and reused without further purification. The [CholineCl][$ZnCl_2$]$_3$ could be successfully reused four times without significant loss of catalytic activity.



Scheme 1 Recycling ability of [CholineCl][$ZnCl_2$]$_3$ in the propionylation of 1-phenyletanol. Conditions: 1-phenyletanol (1.00 mmol), propionic anhydride (1.05 mmol), [CholineCl][$ZnCl_2$]$_3$ (0.35 mmol) at room temperature for 30 min. Yields are isolated yields after aqueous workup.

In conclusion, we have developed [CholineCl][$ZnCl_2$]$_3$ as a recyclable and highly efficient catalyst for the acylation of sterically-hindered alcohols and phenols. This is the first time that the acylation of secondary alcohols and phenols using deep eutectic solvent as a catalyst has been reported. Moreover, the present method demonstrates several merits, including a cheap and highly stable catalyst, mild reaction conditions, operational simplicity and no need for volatile organic solvents or inert atmosphere condition. The fact that [CholineCl][$ZnCl_2$]$_3$ can be easily prepared from commercially available cheap reactants makes it more favorable than formerly investigated catalysts for acylation of alcohols such as DMAP or metal triflates (2–10 mol%) even though an uncommon large catalytic quantity of DES (35 mol%) was required for a complete conversion. Besides, the high efficiency of [CholineCl][$ZnCl_2$]$_3$ allows for the acylation of poorly reactive secondary alcohols under milder condition. Even a challenging substrate for acylation as diphenylmethanol can be also propionylated in good yield at room temperature. Moreover, the [CholineCl][$ZnCl_2$]$_3$ is efficient, easily recovered and reused without significant loss of catalytic activity for four consecutive cycles, making it ideal for industrial processes.

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37. *General procedure*: 1-Phenyletanol (122 mg, 1.0 mmol) was treated with propionic anhydride (136 mg,1.05 mmol) in the presence of $[CholineCl][ZnCl_2]_3$ (191 mg, 0.35 mmol) for 30 min at room temperature under solvent-free magnetic stirring. The mixture was diluted with diethyl ether (10 x 5 ml). The ether solution was decanted, washed with H_2O (10 mL), aqueous $NaHCO_3$ (2 x 20 mL), and brine (10 mL), and dried over $MgSO_4$. The solvent was removed on a rotary evaporator to afford the desired product (432 mg, 96%). The product was characterized by ^1H and ^{13}C NMR, and MS. The recovered catalyst was activated by heating under reduced vacuum at 80 ^oC for 6 h and reused for consecutive cycles.

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An efficient and green method was developed for the acylation of secondary alcohols, phenols and naphthols using deep eutectic solvent [CholineCl][$ZnCl_2$]$_3$ as a catalyst at room temperature under solvent-free condition.