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Facile catalyzed acylation of alcohols, phenols, amines and thiols based on $ZrOCl_2 \cdot 8H_2O$ and acetyl chloride in solution and in solvent-free conditions

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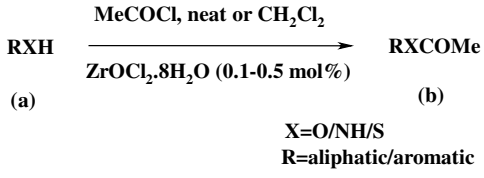
Abstract—Acylation of heteroatoms (O, N and S) with acetyl chloride based on the use of a catalytic amount of the moisture stable, inexpensive $ZrOCl_2 \cdot 8H_2O$, proceeds efficiently producing the corresponding acylated products in excellent yields.

Acetylation of hydroxy groups is an often used protection technique because of the ease of formation as well as mild conditions for deprotection.[1] Such acylations can be effected with acetic anhydride or acetyl chloride in the presence of bases like pyridine,[1] Et_3N,[1] DMAP,[2] Bu_3P,[3] etc. Acylations with acids,[4] acyl imidazoles[5] and acyl urea[6] are also known. Acid catalyzed acylations mainly use Brønsted acids[7] including polymeric acids[8] or Lewis acids. Metal chlorides,[9] metal triflates[4a,10] and metal perchlorates[11] have been utilized as Lewis acids for acetylation of heteroatoms. Recently, other reagents such as, I_2,[12] $La(O^iPr)_3$,[13] vanadyl(V) acetate,[14] distannoxane,[15] ionic liquids,[16] twisted amides,[17] solid supported reagents[18,19] or *lipase* enzymes[18] have also been employed for the same purpose. However, quite a few of the reported methods have limitations mainly in respect of stability, cost, availability, load and reusability of the catalyst or in terms of yields, cumbersome methodologies, flammability or risk of explosion of the reagents. Thus, the search for new reagents and methods is still of practical importance.

Due to their easy availability[20] and low toxicity[21] Zr(IV) salts have recently attracted much attention.[22] This has been reflected in their application, especially $ZrCl_4$, in several organic transformations.[4b,9e,23] Very recently, Chakraborty and co-workers reported $ZrCl_4$ catalyzed acetylations of heteroatoms by acetic anhydride.[9e] There have been only a few reports on the metal oxysalt-based organic reactions.[11b,24] In continuation of our systematic evaluation of the efficacy of metal salts/oxysalts as catalysts[25] or procatalysts,[24c] we report, herein, our results on acetylations of alcohols, phenols, aliphatic and aromatic amines, a thiol and a thiophenol with acetyl chloride using a catalytic amount of $ZrOCl_2 \cdot 8H_2O$ (Scheme 1, Tables 1 and 2).[26,27] To the best of our knowledge, this is the first demonstration of the $ZrOCl_2 \cdot 8H_2O$ based acetylation. $ZrOCl_2 \cdot 8H_2O$ is a moisture stable, readily available and inexpensive oxysalt of Zr and thus its handling is easier in comparison to that of the moisture sensitive $ZrCl_4$.



Scheme 1.

Table 1. Acetylation of β-naphthol based on $ZrOCl_2 \cdot 8H_2O$ (*x* mol%) and AcCl (2 equiv) in different solvents at room temperature

Entry	Mol%	Solvent	Time	Yield (%)
1	0.5	CH_3CN	1 h	91
2	0.5	THF	12 h	53
3	0.5	$PhCH_3$	12 h	85
4	0.1	CH_2Cl_2	2.5 h	85
5	0.5	CH_2Cl_2	45 min	95
6	2	CH_2Cl_2	30 min	97

Keywords: Acylation; Catalyzed; $ZrOCl_2 \cdot 8H_2O$; Acetyl chloride.
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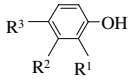
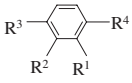
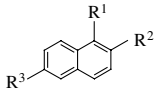
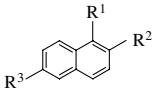
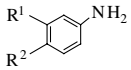
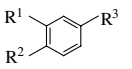
Table 2. Acetylation of heteroatoms based on $ZrOCl_2{\cdot}8H_2O$–acyl chloride

Entry	Substrate (RXH) (a)	Method A[a] (CH_2Cl_2)		Method B[b] (Neat)		Product[c] (RXAc) (b)
		Time	Yield (%)	Time	Yield (%)	
1	R = $CH_3(CH_2)_3$, X = O	10 min	90	2 min	95	R = $CH_3(CH_2)_3$, X = O
2	R = $CH_3(CH_2)_5$, X = O	10 min	91	0.5 min	96	R = $CH_3(CH_2)_5$, X = O
3	R = $CH_3(CH_2)_5$, X = O	10 min	93[d]			R = $CH_3(CH_2)_5$, X = O
4	R = $CH_3(CH_2)_5$, X = O	10 min	92[d,e]			R = $CH_3(CH_2)_5$, X = O
5	R = $CH_3(CH_2)_7$, X = O	30 min	92	1 min	97	R = $CH_3(CH_2)_7$, X = O
6	R = $CH_3(CH_2)_7$, X = O	30 min	94[d]			R = $CH_3(CH_2)_7$, X = O
7	R = $CH_3(CH_2)_7$, X = O	30 min	94[d,e]			R = $CH_3(CH_2)_7$, X = O
8	R = $(CH_3)_3C$, X = O	15 min	94	4 min	96	R = $(CH_3)_3C$, X = O
9	R = $PhCH_2$, X = O	5 min	95	0.5 min	97	R = $PhCH_2$, X = O
10	R = $Ph(CH_2)_2$, X = O	5 min	94	0.5 min	98	R = $Ph(CH_2)_2$, X = O
11	D-Mannitol	1.5 d	93	4 h min	96	D-Mannitol hexaacetate
12	Cyclohexanol	5 min	95	2 min	93	Cyclohexyl acetate
13	Benzoin	2 h	97	20 min	97	Benzoin acetate
14	Cholesterol	2.5 h	97	15 min	97	Cholesteryl acetate
15	Methyl α-D-Glcp	3 h	95	1.5 h	95	Methyl-D-Glcp $(OAc)_4$
16	Allyl alcohol	3 min	89	—-	—	Allyl acetate
17	Propargyl alcohol	6 min	90	—	—	Propargyl acetate
						
18	$R^1 = CO_2Me$, $R^2 = R^3 = H$	12 h	96	1.5 h	95	$R^1 = CO_2Me$, $R^2 = R^3 = H$, $R^4 = OAc$
19	$R^1 = R^2 = H$, $R^3 = Br$	5 min	94	1 min	97	$R^1 = R^2 = H$, $R^3 = Br$, $R^4 = OAc$
20	$R^1 = R^2 = H$, $R^3 = Br$	5 min	96[d]			$R^1 = R^2 = H$, $R^3 = Br$, $R^4 = OAc$
21	$R^1 = R^2 = H$, $R^3 = Br$	5 min	94[d,e]			$R^1 = R^2 = H$, $R^3 = Br$, $R^4 = OAc$
22	$R^1 = R^3 = H$, $R^2 = Me$	2.5 h	87	5 min	98	$R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OAc$
23	$R^1 = OH$, $R^2 = R^3 = H$	1 h	86	15 min	97	$R^1 = OAc$, $R^2 = R^3 = H$, $R^4 = OAc$
24	$R^1 = R^3 = H$, $R^2 = OH$	2.5 h	92	5 min	97	$R^1 = R^3 = H$, $R^2 = OAc$, $R^4 = OAc$
25	$R^1 = R^2 = H$, $R^3 = OH$	30 min	94	5 min	98	$R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = OAc$
26	$R^1 = NO_2$, $R^2 = R^3 = H$	6 h	97[f]	12 h	94	$R^1 = NO_2$, $R^2 = R^3 = H$, $R^4 = OAc$
27	$R^1 = R^3 = H$, $R^2 = NO_2$	3 h	98	30 min	97	$R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = OAc$
28	$R^1 = R^2 = H$, $R^3 = NO_2$	5 h	97	30 min	94	$R^1 = R^2 = H$, $R^3 = NO_2$, $R^4 = OAc$
29	R^1=Ac, $R^2 = R^3 = H$	24 h	90	12 h	91	R^1 = Ac, $R^2 = R^3 = H$, $R^4 = OAc$
						
30	$R^1 = R^3 = H$, $R^2 = OH$	30 min	95	3 min	94	$R^1 = R^3 = H$, $R^2 = OAc$
31	$R^1 = R^3 = H$, $R^2 = OH$	30 min	93[d] (94)	3 min	92[d] (95)	$R^1 = R^3 = H$, $R^2 = OAc$
32	$R^1 = R^3 = H$, $R^2 = OH$	30 min	94[d,e]	3 min	94[d,e]	$R^1 = R^3 = H$, $R^2 = OAc$
33	$R^1 = OH$, $R^2 = R^3 = H$	12 h	96	5 min	94	$R^2 = R^3 = H$, $R^1 = OAc$
34	$R^1 = H$, $R^2 = R^3 = OH$	12 h	97	7 h	95	$R^2 = R^3 = OAc$, $R^1 = H$
						
35	$R^1 = H$, $R^2 = Cl$	10 min	94[g]	5 min	94	$R^1 = H$, $R^2 = Cl$, $R^3 = NHAc$
36	$R^1 = NO_2$, $R^2 = H$	5 min	90[g]	—	—	$R^1 = NO_2$, $R^2 = H$, $R^3 = NHAc$
37	$R^1 = H$, $R^2 = NO_2$	5 min	94[g]	3 min	93	$R^1 = H$, $R^2 = NO_2$, $R^3 = NHAc$
38	$R^1 = OH$, $R^2 = H$	12 h	94[g]	8 h	94	$R^1 = OAc$, $R^2 = H$, $R^3 = NHAc$
39	$PhCH_2NH_2$	30 min	98[g]	—	—	$PhCH_2NHAc$
40	CH_3CH_2SH	30 min	95	4 min	96	CH_3CH_2SAc
41		40 min	95	5 min	95	

[a] Using 0.5 mol% $ZrOCl_2{\cdot}8H_2O$.
[b] Using 0.1 mol% $ZrOCl_2{\cdot}8H_2O$.
[c] All products were characterized by IR, NMR and also by comparing the physical data with those of known compounds.
[d] Scale-up (~10-fold) experiment, value in parenthesis (entry 31) is based on ~30-fold substrate.
[e] With recovered catalyst.
[f] In refluxing $(CH_2Cl)_2$.
[g] In CH_3CN.

The reaction conditions were standardized after conducting the acetylation of β-naphthol in different solvents using varying amounts of $ZrOCl_2{\cdot}8H_2O$ (Table 1). Thus, under optimum conditions, β-naphthol (~1 equiv) was acetylated at room temperature almost quantitatively with acetyl chloride (~2 equiv) in the presence of 0.5 mol% $ZrOCl_2{\cdot}8H_2O$ in dichloromethane (Table 1, entry 5). Attempted acetylation of β-naphthol with acetic anhydride in the presence of $ZrOCl_2{\cdot}8H_2O$ failed.

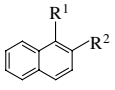
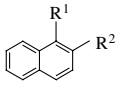
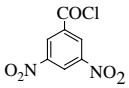
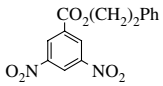
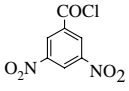
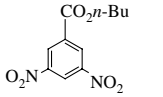
Phenolic compounds containing both electron-withdrawing (Table 2, entries 18, 27–29) and -donating groups (Table 2, entries 19, 22–25) reacted equally efficiently under the standard reaction conditions (method A). Acetylation of *o*-nitrophenol at room temperature was, however, sluggish; it could be completely acetylated in refluxing dichloroethane (entry 26). Similarly, α-naphthol (entry 33) and 2,6-dihydroxynaphthalene (entry 34) were also converted into the corresponding acetates in excellent yields. Compounds containing primary (Table 2, entries 1, 2, 5, 9 and 10), secondary (entries 12–14) and tertiary (entry 8) hydroxy groups were all readily acetylated under similar reaction conditions without any side reactions of the secondary and tertiary alcohols. Allyl and propargyl alcohols were also satisfactorily acetylated generating the corresponding acetates in 89% and 90% respective yields (entries 16 and 17). D-Mannitol (entry 11) and methyl α-D-glucopyranoside (entry 15) could be fully acetylated in excellent yields without any competitive acetylation of the anomeric methoxy group[28] in the latter case. The present method is equally applicable to acetylation of cholesterol (entry 14) in almost quantitative yield and optical purity.

The scope of this methodology was further extended by esterification of different alcohols or phenols with a variety of other acid chlorides. Thus, benzoylation of α-naphthol, β-naphthol and octanol proceeded efficiently with benzoyl chloride (Table 3, entries 1, 2 and 4), although, ~5 equiv of benzoyl chloride were required for the optimum yields of the products. Similarly, β-naphthol could also be converted to the corresponding acylated derivative in quantitative yield with phenylacetyl chloride (Table 3, entry 3). Esterification of β-phenyl ethanol and *n*-butanol with 3,5-dinitrobenzoyl chloride (~2 equiv) resulted in the desired products in almost quantitative yields (Table 3, entries 5 and 6) and that of methanol with myristoyl chloride (~2 equiv) also furnished, efficiently, methyl myristoate in excellent yield (Table 3, entry 7).

The generality of the reagents $ZrOCl_2{\cdot}8H_2O$–acetyl chloride was established by efficient acetylation of aliphatic (Table 2, entry 39) and aromatic amines containing both electron withdrawing (entries 36 and 37) and donating groups (entries 35 and 38) in the aromatic ring leading to the corresponding acetamides in excellent yields. However, the best results were obtained by conducting the acetylation of amines in acetonitrile solution at ~50 °C. A thiol (entry 40) and a thiophenol (entry 41) were also acetylated satisfactorily under the standard reaction conditions. The acetylations, in general, were chemoselective with respect to the following functionalities: C=C, C≡C, CO_2R, COR and NO_2.

Most of the above substrates were acetylated in excellent yields in the presence of $ZrOCl_2{\cdot}8H_2O$ (0.1 mol%) and acetyl chloride (~3 equiv) under solventless conditions (Table 2, method B). Moreover, in all these cases, the reactions were faster requiring less $ZrOCl_2{\cdot}8H_2O$ than those conversions in solution. The preparative efficacy of the present procedure was established through scale-up (~10-fold) experiments in solvent using smaller amounts of acetyl chloride (~1.5 equiv) (Table 2, entries 3, 6, 20 and 31, method A). This reagent system was also amenable to further scale-up (~30-fold) in solvent as well as under neat conditions (Table 2, entry 31, values in parentheses, methods A and B). The hydrated zirconium oxychloride was separately recovered from the aqueous solutions of the above experiments and reused

Table 3. Acylation of alcohols and phenols with acyl chlorides in the presence of $ZrOCl_2{\cdot}8H_2O$ (0.5 mol%) in CH_2Cl_2

Entry	Substrate (ROH)	R′COCl	Time	Yield (%)	Product (ROCOR′)
					
1	R^1 = OH, R^2 = H	PhCOCl	2.5 d	97[a]	R^1 = OBz, R^2 = H
2	R^1 = H, R^2 = OH	PhCOCl	21 h	98[a]	R^1 = H, R^2 = OBz
3	R^1 = H, R^2 = OH	$PhCH_2COCl$	12 h	95[a]	R^1 = H, R^2 = $OCOCH_2Ph$
4	$Me(CH_2)_7OH$	PhCOCl	1.5 d	93[a]	$PhCO_2(CH_2)_7Me$
5	$Ph(CH_2)_2OH$		18 h	97[b]	
6	$Me(CH_2)_3OH$		15 h	96[b]	
7	MeOH	$Me(CH_2)_{12}COCl$	10 h	83[b]	$Me(CH_2)_{12}CO_2Me$

[a] Using ~5 equiv of acid chloride.
[b] Using ~2 equiv of acid chloride.

without any loss of its efficacy as a catalyst (Table 2, entries 4, 7 and 21, methods A and entry 32, method A and B), however, the composition of the recovered zirconium complex ($ZrOCl_2{\cdot}xH_2O$) may vary with respect to the water content.

It should be noted that unlike that of the BiOCl–acetyl chloride combination, which has been shown to generate $BiCl_3$ in situ,[24c,29b] a similar combination of $ZrOCl_2{\cdot}8H_2O$–acetyl chloride does not generate $ZrCl_4$ in situ as evidenced by the ^{13}C NMR spectra of $ZrOCl_2{\cdot}8H_2O$–acetyl chloride and $ZrCl_4$–acetyl chloride in $CDCl_3$ and by the GLC of the reaction mixture.[30]

In summary, we have demonstrated the efficiency of $ZrOCl_2{\cdot}8H_2O$, towards the acetylation of alcohols, phenols, amines and thiols with acetyl chloride. The notable special features of this methodology are the simple reaction procedure, excellent yields of products, moderate Lewis acidity of $ZrOCl_2{\cdot}8H_2O$, low cost, ready availability,[20] low toxicity (LD_{50} oral in rat: 1688 mg/kg),[21] and moisture compatibility and recyclability of the catalyst both in solution and under neat conditions. Thus, this methodology represents a better, eco-friendly alternative to many existing procedures and is also suitable for industrial application. This is the first report of $ZrOCl_2{\cdot}8H_2O$-based organic transformations.

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26. General procedure for acetylation: (a) Method A (in solution) to a mixture of substrate (~1 equiv) and $ZrOCl_2{\cdot}8H_2O$ (0.5 mol%) in CH_2Cl_2 (or in CH_3CN for amines, 4 mL) was added acetyl chloride (~2 equiv) and the reaction mixture was stirred at room temperature. After completion of the reaction (by TLC) the mixture was diluted with CH_2Cl_2 (5 mL) and then washed subsequently with brine (20 mL), saturated aqueous $NaHCO_3$ (2×15 mL) and H_2O (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude product was filtered through a silica column or crystallized before taking spectral data.
(b) Method B (under neat conditions) to a mixture of substrate (~1 equiv) and $ZrOCl_2{\cdot}8H_2O$ (0.1 mol%) was added acetyl chloride (~1.5 equiv) with stirring at room temperature. After completion of the reaction, the mixture was processed as described in method A.
Recovery of $ZrOCl_2{\cdot}xH_2O$—After completion of the reaction, the mixture was diluted with CH_2Cl_2 and washed with water (7×3 mL). The pooled aqueous layer was evaporated to dryness by repeated co-distillation with toluene and finally dried under high vacuum (4 h) at ~60 °C to a powdery mass.
27. All products were characterized by NMR, IR and by comparing the physical data with those in the literature.[1–18]
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30. ^{13}C NMR (75 MHz, $CDCl_3$) of $ZrOCl_2{\cdot}8H_2O$–MeCOCl: δ 20.5, 21.7 (trace), 33.2, 167.0 (trace), 170.1 and 179.7. ^{13}C NMR (75 MHz, $CDCl_3$) of $ZrCl_4$–MeCOCl: δ 21.3, 33.4, 170.4 and 183.3. ^{13}C NMR (75 MHz, $CDCl_3$) of MeCOCl: δ 33.5 and 170.5.
The peaks at δ 20.5 (Me) and 179.7 (CO) indicate that acetic acid is generated from $ZrOCl_2{\cdot}8H_2O$–acetyl chloride mixture, which is also evidenced from the GLC of the mixture (retention time for acetic acid: 1.94 min) on a 10% SE-30 column (programming: 80 °C, 2 min to 150 °C at an increase of temperature by 10 °C/min). It seems that acetyl chloride is first hydrolyzed to acetic acid by the loosely bound water of crystallization of the zirconium salt. A trace amount of the acetic acid is converted to acetic anhydride (as evidenced by very small peaks at δ 21.7 and 167.0 in the ^{13}C NMR), however, the fact that this acetic acid played no role in the acetylation was established from a separate experiment where no β-naphthyl acetate could be isolated from a mixture of β-naphthol, acetic acid and $ZrOCl_2{\cdot}8H_2O$ (0.5 mol%) in dichloromethane even after 48 h. Thus, acetylation under the present protocol seems to proceed following a similar mechanistic pathway as in other reported Lewis acid–acid chloride reagent systems.