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Zinc oxide (ZnO) as a new, highly efficient, and reusable catalyst for acylation of alcohols, phenols and amines under solvent free conditions

Mona Hosseini Sarvari* and Hashem Sharghi*

Department of Chemistry, Faculty of Science, Shiraz University, Shiraz 71454, Islamic Republic of Iran

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Abstract—Zinc oxide (ZnO) is a highly efficient catalyst for the acylation of a variety of alcohols, phenols and amines with acid chlorides or acid anhydrides under solvent free conditions. Primary, secondary, tertiary, allylic and benzylic alcohols, diols and phenols with electron donating or withdrawing substituents can be easily acylated in good to excellent yield.

1. Introduction

The acylation of alcohols, phenols and amines is an important transformation in organic synthesis.[1] Acylation of such functional groups is often necessary during the course of various transformation in a synthetic sequence, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products. Various catalysts developed for acylation include DMAP,[2] $CoCl_2$,[3] Bu_3P,[4] Triflates,[5–10] $TaCl_5$,[11] zeolite,[12] clays,[13] Nafion-H,[14] Yttria-zirconia,[15] $LiClO_4$,[16] $Mg(ClO_4)_2$,[17] ionic liquids,[18] $InCl_3$,[19] $ZrCl_4$,[20] $Cu(BF_4)\cdot xH_2O$,[21] $RuCl_3$,[22] P_2O_5/SiO_2,[23] $ZrOCl_2\cdot 8H_2O$,[24] and alumina.[25] However, the reported methodologies suffer from various disadvantages, such as potential hazard associated with handling of the catalyst [e.g., the LD_{50} (intravenous in rat) value of 56 mg kg^{-1} of DMAP makes it highly toxic[26] and Bu_3P is flammable with a flash point of 37 °C and undergoes aerial oxidation],[27] expensive or commercially unavailable reagents, requirement of longer reaction times, harsh reaction conditions, use of halogenated solvents and excess acylating agents. Triflates are costly and moisture sensitive, and special efforts are required to prepare the catalyst [e.g., $Bi(OTf)_3$, Nafion-H, and yttria-zirconia]. In most of the cases the reported methods work well on primary or secondary alcohols only and failed to protect tertiary alcohols or less reactive phenols. A few of these methods also suffer from side reactions such as dehydration and rearrangement and might not be fully compatible for the acylation reactions with substrates bearing acid-sensitive groups.

Synthetic chemists continue to explore new methods to carry out chemical transformations. One of these new methods is to run reactions on the surface of solids. As the surfaces have properties that are not duplicated in the solution or gas phase, entirely new chemistry may occur. Even in the absence of new chemistry, a surface reaction may be more desirable than a solution counterpart, because the reaction is more convenient to run, or a high yield of product is attained. For these reasons, synthetic surface organic chemistry is a rapidly growing field of study. Experiments using these solid phase catalysts generally have the following features: (i) it is often easy to isolate the products and to separate the catalyst; (ii) comparing the reaction conditions with those of related homogeneous reactions, they are so mild that a high yield of specific products and suppression of by-product formation are expected; (iii) selectivity and activity of the catalysts are often comparable to those of enzymes.[28] Several classes of solids have commonly been used for surface organic chemistry including aluminas, silica gels, and clays. Zinc oxide (ZnO) is certainly one of the most interesting of these solids because it has surface properties that suggest that a very rich organic chemistry may occur there.[29,30d]

Although numerous methods to achieve acylation reactions are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. In continuation of our systematic evaluation of the efficacy of metal

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* Corresponding authors. Tel.: +98 711 2284822; fax: +98 711 2280926; e-mail addresses: hossaini@susc.ac.ir; shashem@susc.ac.ir

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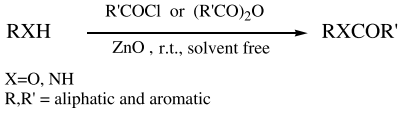
Table 1. Acetylation of phenol (1 mmol) based on ZnO and AcCl (1 mmol) in different reaction conditions

Entry	Equiv of ZnO	Solvent	Time	Yield (%)
1	0.5	CH_3CN	6 h	30
2	0.5	$PhCH_3$	10 h	10
3	0.5	CH_2Cl_2	5 h	30
4	0.5	No solvent	15 min	94
5	1	No solvent	20 min	87
6	0.1	No solvent	40 min	83
7	No catalyst	No solvent	10 h	Trace

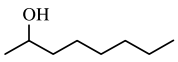
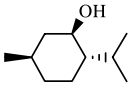
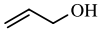
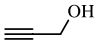
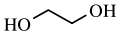
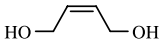
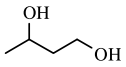
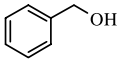
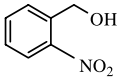
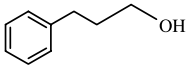
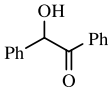
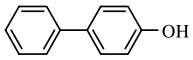
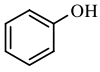
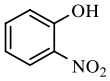
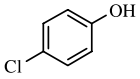
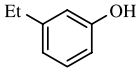
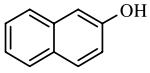
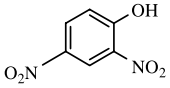
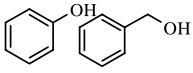
oxysalts as catalysts,[30] we report, herein, our results on acylation of alcohols, phenols, aliphatic and aromatic amines using ZnO at room temperature under solvent free conditions (Scheme 1, Tables 2 and 3). To the best of our knowledge, this is the first demonstration of the ZnO based acylation.



Scheme 1.

The reaction conditions were standardized after conducting the acylation of phenol in different reaction conditions using varying amounts of ZnO (Table 1). Thus, under optimum conditions, phenol (1 equiv) was acetylated at room temperature almost quantitatively with acetyl chloride (1 equiv) in the presence of 0.5 equiv ZnO without use of any solvents (Table 1, entry 4). Attempted acetylation of phenol with acetic anhydride in the presence of ZnO failed.

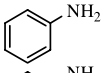
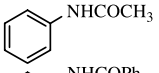
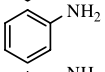
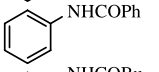
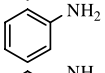
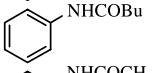
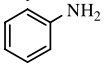
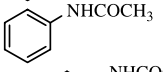
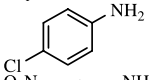
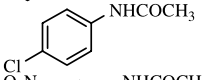
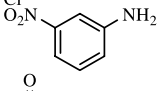
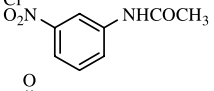
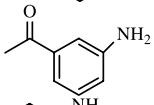
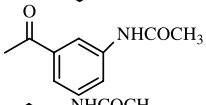
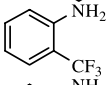
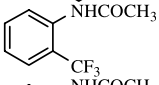
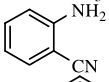
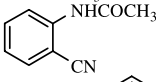
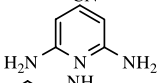
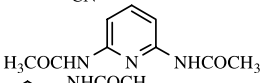
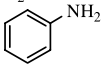
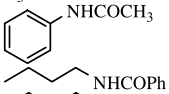
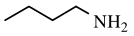
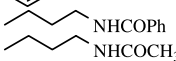
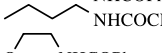
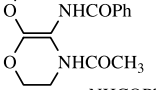
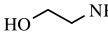
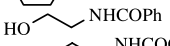
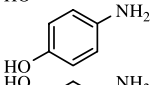
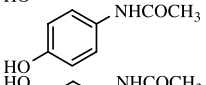
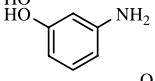
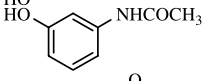
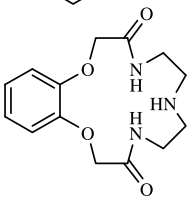
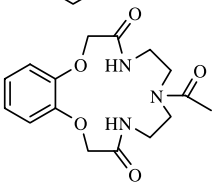
Table 2. ZnO (0.5 mmol) catalyzed acylation of alcohols and phenols (1 mmol) using acid chlorides (1 mmol)

Entry	Substrate	Acylation reagent[a]	Time (min)	Yield (%)[b]
1	CH_3CH_2OH	PhCOCl	15	91
		CH_3COCl	10	95
		Ac_2O	180	—
		$(PhCO)_2O$	180	—
2	$CH_3(CH_2)_5CH_2OH$	PhCOCl	15	87
		CH_3COCl	10	90
3	$CH_3(CH_2)_2CH_2OH$	PhCOCl	15	84
		CH_3COCl	10	86
4	$CH_3(CH_2)_6CH_2OH$	PhCOCl	15	86
		CH_3COCl	10	78
5		PhCOCl	240	78
		CH_3COCl	30	80
6		PhCOCl	240	81
		CH_3COCl	30	70
7		PhCOCl	60	84
		CH_3COCl	20	86
8		PhCOCl	15	73
		CH_3COCl	8	70
9		PhCOCl	20	53
		CH_3COCl	8	58
10		PhCOCl	15	85[c]
		CH_3COCl	8	91[c]
11		PhCOCl	15	78[c]
		CH_3COCl	8	80[c]
12		PhCOCl	300	83[c]
		CH_3COCl	20	87[c]
13		PhCOCl	15	92
		CH_3COCl	10	90
14		PhCOCl	20	89
		CH_3COCl	10	92
15		PhCOCl	15	85
		CH_3COCl	10	90
16		PhCOCl	30	91[d]
		CH_3COCl	20	82[d]
17		PhCOCl	90	67[e]
		CH_3COCl	30	65[e]
18		PhCOCl	30	82[d]
		CH_3COCl	15	85[d]
19		PhCOCl	30	95
		CH_3COCl	15	94
20		PhCOCl	40	94
		CH_3COCl	20	90
21		PhCOCl	20	93
		CH_3COCl	15	90
22		PhCOCl	20	85
		CH_3COCl	15	92
23		PhCOCl	30	91
		CH_3COCl	20	90
24		PhCOCl	40	82[f]
		CH_3COCl	20	87[f]
25		PhCOCl	30	92[g]
26	CH_3CH_2OH	PhCOCl	30	90[h]

[a] Acylation reagent (1 equiv) for every OH function was used.
[b] Isolated yields.
[c] The corresponding dibenzoate and diacetate was prepared.
[d] The reaction was carried out in CH_2Cl_2.
[e] The reaction was carried out at <0 °C.
[f] The reaction was carried out at 90 °C.
[g] Only the aliphatic alcohol was benzoylated with the use of 1 equiv of acylating agent.
[h] The reaction was carried out on 100 mmol scale.

The results of the reactions of a diverse range of alcohols and phenols are summarized in Table 2. An acid chloride was preferred over the corresponding acid anhydride. The reaction with acid anhydride was too slow to have practical application. Both primary and secondary alcohols react very

Table 3. ZnO (0.5 mmol) catalyzed acylation of amines (1 mmol) using acid anhydrides (1 mmol)

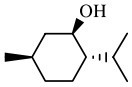
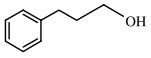
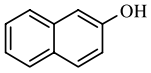
Entry	Substrate	Acylation reagent[a]	Products	Time (min)	Yield (%)[b]
1		$(CH_3CO)_2O$		10	96
2		$(PhCO)_2O$		10	92
3		$(BuCO)_2O$		15	94
4		CH_3COCl		15	94
5		$(CH_3CO)_2O$		15	95
6		$(CH_3CO)_2O$		20	95
7		$(CH_3CO)_2O$		15	95
8		$(CH_3CO)_2O$		20	87
9		$(CH_3CO)_2O$		20	82
10		$(CH_3CO)_2O$		40	58
11		$(CH_3CO)_2O$		40	96[c]
12		$(PhCO)_2O$ $(CH_3CO)_2O$	 	20 10	93 95
13		$(PhCO)_2O$ $(CH_3CO)_2O$	 	20 10	67 84
14		$(PhCO)_2O$		40	64
15		$(CH_3CO)_2O$		10	90
16		$(CH_3CO)_2O$		10	87
17		$(CH_3CO)_2O$		20	83

[a] Acylation agent (1 equiv) for every NH_2 function was used.
[b] Isolated yields.
[c] The reaction was carried out on 100 mmol scale.

well (entries 1–16) and tertiary alcohol (entry 17) is also acylated smoothly without any side products observed. The conversion of ethanol into ethyl benzoate on a 100 mmol scale (entry 26) proceeded just as well as the 1 mmol reaction. Acylation of optically active substrate resulted in excellent yield (entry 7). Allyl and propargyl alcohols were also satisfactorily acylated under similar reaction conditions and no rearrangement was observed (entries 8 and 9). To extend the scope and generality of the use of the ZnO for this type process we have also investigated the acylation of diols. No selectivity between primary and secondary hydroxyl groups was observed.

Phenolic compounds containing both electron-withdrawing and donating groups (entries 18–24) reacted equally efficiently under the standard reaction conditions. Acylation of 2,4-dinitrophenol at room temperature was, however, sluggish; it could be completely acylated in an oil bath at 90 °C (entry 24). According to Table 2, the reaction of phenols with acid chlorides was slow in comparison to those aliphatic alcohols. Indeed, a mixture of benzyl alcohol and phenol furnished only the expected benzyl benzoate on reaction with 1 equiv of PhCOCl (entry 25). Finally, the reaction of benzoin and 4-hydroxybiphenyl (entries 16 and 18) were very slow under similar conditions. Even after

Table 4. Comparison of protocols for the acylation of alcohols and phenols

Entry	Substrate	Reagent/catalyst	Acylating agent	Time	Temperature (°C)	Yield (%)	References
1		ZnO	PhCOCl	60 min	25	84	[a]
		Al_2O_3	PhCOCl	120 min	25	96	25
		$Bi(OTf)_3$	$(PhCO)_2O$	60 min	Reflux	95	9e
		$ZrOCl_2 \cdot 8H_2O$	CH_3COCl	1.5 day	25	93	24
2		ZnO	PhCOCl	15 min	25	85	[a]
		Al_2O_3	PhCOCl	90 min	25	99	25
3		ZnO	PhCOCl	90 min	25	67	[a]
		Al_2O_3	PhCOCl	No reaction			25
		$Bi(OTf)_3$	$(PhCO)_2O$	80 min	Reflux	45	9e
		$ZrOCl_2 \cdot 8H_2O$	PhCOCl	No report			24
4		ZnO	PhCOCl	30 min	25	91	[a]
		Al_2O_3	PhCOCl	No reaction			25
		$Bi(OTf)_3$	$(PhCO)_2O$	45 min	Reflux	95	9e
		$ZrOCl_2 \cdot 8H_2O$	PhCOCl	21 h	25	98	24

[a] Present work.

vigorous stirring for 4 h at 25 °C, the reactions were incomplete. However, acylation was achived in 91 and 82% yields with benzoin and 4-hydroxybiphenyl, respectively, at 25 °C for 30 min in the presence of dichloromethane (CH_2Cl_2).

The experimental results of the acylation of amines are summarized in Table 3. It is significant to note that acid anhydrides were preferred to the acid chlorides. All the amines reacted very rapidly within 10–40 min The conversion of aniline into acetanilide on a 100 mmol scale (entry 11) proceeded just as well as the 1 mmol reaction. Other functional groups such as keto and cyano remained unaffected during the acylation reaction (entries 7 and 9).

The reactions of amines with Ac_2O were so fast in comparison to those of the aliphatic alcohols that the selective protection of an amine in the presence of aliphatic alcohols appeared to be a distinct possibility (entry 14). Also, the amino group in aminophenol was selectivity acylated (entries 15 and 16). It is noteworthy that, entry 17 can survive in the present method indicating mildness of reaction conditions.

A comparison of the catalytic efficiency of ZnO with selected previously known catalysts is collected in Table 4 to demonstrate that the present protocol is indeed superior to several of the other protocols. Menthol is completely benzoylated in less than 60 min at 25 °C in 84% isolated yield using the present protocol. Most of the other protocols listed take either longer time for completion or use high temperature. Benzoylation of *t*-butanol with 1 equiv of PhCOCl afforded 67% yields in 270 min under solvent free conditions in the presence of ZnO but Al_2O_3 and $ZrOCl_2.\cdot 8H_2O$ did not catalyze the same reaction. The ZnO catalyzed benzoylation of 2-naphthol with stoichiometric amount of PhCOCl afforded 94% yield at room temperature for 30 min while the 2-naphthol and other phenols did not react at all in the presence of Al_2O_3. The use of $ZrOCl_2 \cdot 8H_2O$ is equally effective, however, it requires long times to completion. This is in contrast to the use of ZnO that was very effective for acylation of phenols.

Another interesting behaviour of zinc oxide (ZnO) lies in the fact that it can be re-used after simple washing with CH_2Cl_2, rendering thus process more economic. The yields of acetanilide (a model compound for amines) and phenyl benzoate (a model compound for phenols) in the 2nd, 3rd, 4th and 5th uses of the ZnO were almost as high as in the first use.

In conclusion, we have presented a simple, solvent free, and efficient protocol for the acylation of alcohols, phenols, and amines. Furthermore, an alcohol can be acylated in the presence of phenols with very high selectivity. No competitive Fries rearrangement was observed for phenolic substrates. Secondary and tertiary alcohols did not experience any competitive dehydration. Also, the advantages include the low cost of the catalyst, operation at room temperature, large scale treatment, high yields, and excellent chemoselectivity.

2. Experimental

2.1. General procedure

To a mixture of ZnO (dry powder, 0.04 g, 0.5 mmol) and an acid chloride or anhydride (1 mmol), alcohol, phenol or amine (1 mmol) was added. The reaction mixture was stirred with a mechanical stirrer for a certain period of time (Tables 2 and 3) as required to complete the reaction (monitored by TLC) at room temperature. The solid mass (ZnO) was then eluted with CH_2Cl_2 (20 mL), and the CH_2Cl_2 extract was then washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of solvent furnished, practically pure, the corresponding product. The identity of these compounds was easily established by comparison of their ^1H NMR spectra with those of authentic samples.[31]

2.1.1. 7-Acetyl-5,6,7,8,9,10-hexahydro-2*H*,1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (entry 17, Table 3). To a mixture of ZnO (dry powder, 0.04 g, 0.5 mmol) and an acetic anhydride (1 mmol, 0.094 mL), 5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (1 mmol

0.29 g) was added. The reaction mixture was stirred with a mechanical stirrer for 20 min as required to complete the reaction (monitored by TLC) at room temperature. The solid mass (ZnO) was then eluted with CH_2Cl_2 (20 mL), and the CH_2Cl_2 extract was then washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of solvent furnished practically pure the corresponding product. This was further purified by recrystallization with suitable solvent (ether or $CHCl_3$) gave the title compound as a white solid, mp 218–220 °C. [Found: C 57.21; H, 6.22. $C_{16}H_{21}N_3O_5$ requires C, 57.30; H, 6.31%]; δ_H (250 MHz, $CDCl_3$) 7.85 (2H, s, –N*H*), 7.00–7.08 (4H, m, Ph), 4.50 (4H, s, CH_2CO), 3.53 (8H, s, NHCH_2-CH_2N), 3.00 (3H, s, *Me*CO); δ_C (62.9 MHz, $CDCl_3$) 16.2, 41.1, 45.7, 77.6, 112.1, 120.8, 147.9, 165.8, 169.3; *m*/*z* 335 (100 MH^+).

Acknowledgements

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