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CHEMOSELECTIVE ACYLATION AND BENZOYLATION OF ALCOHOLS, PHENOLS AND AMINES USING COPPER OXIDE UNDER SOLVENT FREE CONDITION

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ABSTRACT

Copper (II) oxide efficiently catalyzes chemoselective acylation and benzoylation of alcohols, phenols and amines with stoichiometric amount of acetyl chloride and benzoyl chloride under solvent free conditions and at room temperature. The remarkable selectivity under mild and neutral conditions, short reaction time, reusable, commercially available and inexpensive catalyst, are advantages.

Key words: Acylation, Benzoylation, CuO, Acetyl chloride, Benzoyl chloride, Solvent-free

INTRODUCTION

At the beginning of the new century, the green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a myriad of materials. [1] 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, plasticisers and polymers[2].

Generally, acetylation of alcohols and phenols is carried out with carboxylic acids and more conveniently anhydrides or acetyl chlorides in the presence of basic catalysts, Bronsted or Lewis acids and metals salts[2b]. Amongst the catalysts used for activation of anhydrides and acetyl chlorides are pyridine, Et_3N[2], ZnO[3], $ZrOCl_2\ 8H_2O$[4], $CeCl_3$[5], $ZrCl_4$[6], $[CuBF_4]\ 6H_2O$[7], metal triflates [8-11], $BiOClO_4$. H_2O[12], $AlPW_{12}O_{40}$[13], $LiClO_4$[14], KF-Al_2O_3[15], I_2[16a], NBS[16b], $MgBr_2$[17], distanoxane[18], LiCl[19], NH_2SO_3H[20], solid supported reagents[21], $MgBr_2$-Et_3N[22], twisted amides[23], Bu_3P[24], lipase enzymes[25], H_2SO_4[26], DMAP[27], p-TsOH[28]. Recently, acetylation of alcohols and phenols by HPAs in acetic anhydride has been reported[29]. However, some of the reported methods have limitations, mainly in respect of stability,

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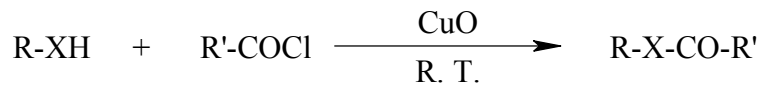
cost, availability, load and reusability of the catalyst or in terms of yields, cumbersome methodologies, flammability or risk of explosion of the reagents. Therefore, it is a demand of the time to introduce green catalyst for acetylation of alcohols, phenols and amines.

In this communication, copper oxide has been reported as an efficient and very mild catalyst for acylation and benzoylation of alcohols, phenols and amines using acetyl chlorides and benzoyl chloride under solvent free condition **Scheme 1.**



1 **2** **3**

X: O, -NH-

R: Alkyl, Phenyl

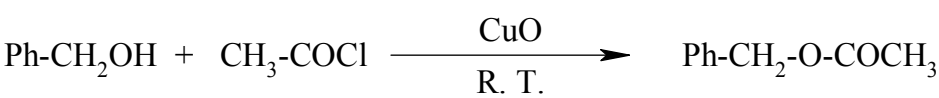
R': CH_3, Phenyl

Scheme 1

EXPERIMENTAL

In order to find out the most effective acylation, benzyl alcohol was chosen as a model substrate. It was treated with 1 equimolar amount of acetyl chloride in the presence of 0.1 mol% of CuO in different dry solvents at room temperature (Table 1). The reactions in the solvents such as CH_3CN, THF, CH_2Cl_2, $CHCI_3$ (Table 1, entries –1, 2, 3, 4) were found less effective. Since we have carried out the reaction under solvent free condition to get the excellent yield (98%, entries-5)

Table 1. Acylation of benzyl alcohol with acetyl chloride in the presence of copper oxide



Entry	CuO Mol (%)	Solvent	Time	Yield[a] (%)
1	0.1	CH_3CN	1 h	90
2	0.1	THF	6 h	65

Cont…

Entry	CuO Mol (%)	Solvent	Time	Yield[a] (%)
3	0.1	CH_2Cl_2	1 h	96
4	0.1	$CHCl_3$	7 h	70
5	0.1	Free	5 min	98[b]

[a]Isolated yield

[b]The solvent free reaction is more effective

Table 2. Acylation of benzyl alcohol with acetyl chloride in the presence of various copper salts as a catalyst

$$Ph\text{-}CH_2OH + CH_3\text{-}COCl \xrightarrow[R.\ T.]{Cu\ salts} Ph\text{-}CH_2\text{-}O\text{-}COCH_3$$

Entry	Copper salts (0.1 mol %)	Time	Yield[a] (%)
1	CuCl	12 h	45
2	$CuCl_2$	6 h	65
3	$CuCO_3$	1 h	20
4	$CuSO_4.5H_2O$	30 min	45
5	$Cu(OAc)_2.H_2O$	30 min	75
6	CuO	5 min	98

[a]Isolated yield

In order to find out the most effective catalyst for acylation, we have employed various copper salts during acylation of benzyl alcohol with acetyl chloride (1 : 1 equimolar) under solvent free conditions (Table 2). According to the results obtained, copper oxide was found to be the most efficient catalyst. However, other copper salts such as CuCl, $CuCl_2$, $CuSO_4.5H_2O$, $CuCO_3$, $Cu(OAc)_2.H_2O$ exhibit less significant catalytic property in the acylation of benzyl alcohol with acetyl chloride.

General experimental procedure

A mixture of alcohol or phenol or amine (1 m mol), benzoyl chloride or acetyl

chloride and CuO (0.1 mol %) was stirred for an appropriate time under neat conditions and at r. t. The progress of reaction was followed by TLC. After completion of the reaction, mixture was quenched with H_2O (10 mL) and extracted with $CHCl_3$ (2 10 mL). The organic layer was washed with 10% Na_2CO_3 and water, dried with Na_2SO_4 and concentrated to dryness. The crude products were purified by silica column. All products (Table 3) are known and gave the same spectral data as authentic samples.

Table 3. Spectral data of the compounds

Compd.	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, ppm)
1	1766 (-OCO-), 1595 (Ar), 1197 (-$OCOCH_3$)	6.9 (s, 5H, Ar-H); 1.8 (s, 3 H, -$COCH_3$); 4.7 (s, 2 H, -CH_2-)
2	1741 (-OCO-), 1613 (Ar), 1176 (-$OCOCH_3$), 1234 (-OCH3)	2.08 (s, 3 H, $COCH_3$), 3.81 (s, 3H, OCH_3), 5.04 (s, 2 H, Ar-CH2O), 6.92 (d, 2 H, J = 6, Ar-H), 7.32 (d, 2 H, J = 6, Ar-H)
5	1732(-OCO-), 1611(Ar), 1096(-$OCOCH_3$)	0.95 (t, 6H, 2x CH_3); 2.2 (q, 4H, 2 x NCH_2), 2.02 (s, 3H, $COCH_3$); 2.8 (d, 2H, CH_2, J 7); 3.2 (d, 2H, CH_2, J7).
7	1725(-OCO-), 1618(Ar), 1215 (-$OCOCH_3$)	2.03 (s, 3H, $COCH_3$); 4.03 (s, 1H, O CH); 7.15 (m, 10H, 2 x Ar-H).
13	1710(-OCO-), 1605(Ar), 1197 (-$OCOCH_3$)	7.15 (m, 7H, Ar-H); 2.5 (s, 3H, $COCH_3$)
14	1720 (-OCO-), 1593 (Ar), 1198 (-$OCOCH_3$)	7.04 (s, 5H, Ar-H); 2.2 (s, 3H, $COCH_3$)
20	1698 (-CO-NH-), 1614 (Ar), 1275 (-$COCH_3$)	2.2(s, 3H, CH_3), 6.5 (m, 5H, Ar-H); 7.2 (s, NH).
23	1702(-CO-NH-), 1605(Ar), 1259 (-$COCH_3$)	5.7 (s, 1H, NH); 7.1 (d, 1H, Ar-H); 7.2 (d, 1H, Ar-H); 7.3 (d, 1H, Ar-H); 2.1 (s, 3H, CH_3).

[a]s, singlet; d, doublet; m, multiplet

RESULTS AND DISCUSSION

In order to extend the scope of this acylation and benzoylation reaction, it was

carried out on a variety of substrates such as primary, benzylic, hindered and unhindered secondary and sterically hindered tertiary alcohols, phenols and amines. The results are summarized in the Table 4.

Table 4.

Entry	Substrate	Product[b]	Time (min.)	Yield[c] (%)
Alcohols				
1	Benzyl alcohol	Benzyl acetate	5	98
2	4-Methoxy benzyl alcohol	4-Methoxy benzyl acetate	5	92
3	Ethanol	Ethyl benzoate	5	94
4	2-Butanol	2-Butyl acetate	5	93
5	N, N-Diethyl ethanol	N, N-Diethyl ethyl acetate	5	92
6	t-Butyl alcohol	t-Butyl acetate	10	95
7	Diphenyl methanol	Diphenyl methyl acetate	30	95
8	Triphenyl methanol	Triphenyl methyl acetate	40	50
9	Benzyl alcohol	Benzyl benzoate	30	97
Phenols				
10	p-Nitrophenol	p-Nitrophenyl benzoate	5	93
11	m-Dihydroxybenzene	m-(O-Diacetyl) benzene	5	97
12	p-Nitrophenol	p-Nitrophenyl acetate	5	97
13	β-Naphthol	β-Naphthyl acetate	10	90
14	Phenol	Phenyl acetate	20	95
15	p-Bromophenol	p-Bromophenyl acetate	30	85
16	p-Hydroxylphenol	1, 4-(O-Diacetyl benzene)	30	96
17	1-Naphthol	1-Naphthyl benzoate	45	98
18	Salicylic acid	Acetyl salicylic acid	180	85

Cont…

Entry	Substrate	Product[b]	Time (min.)	Yield[c] (%)
19	o-Nitrophenol	O-Nitrophenyl acetate	240	90
Amines				
20	Aniline	Acetanilide	1	95
21	Aniline	N-phenylbenzamide	5	95
22	m-Nitroaniline	m-Nitroacetanilide	5	94
23	3, 4-Dinitro aniline	3, 4-Dinitroacatanilide	5	95
24	m-Bromo aniline	m-Bromophenyl acetate	5	90
25	o-Chloro aniline	2-Chlorophenyl acetamide	30	90

[a] The substrate was treated with CH_3COCl or PhCOCl (1 equiv. per –OH group) in the presence of 0.1 mol % of CuO under neat condition at room temperature and solvent free.

[b] All products were identified by their IR and ^1H NMR spectra

[c] Isolated yields.

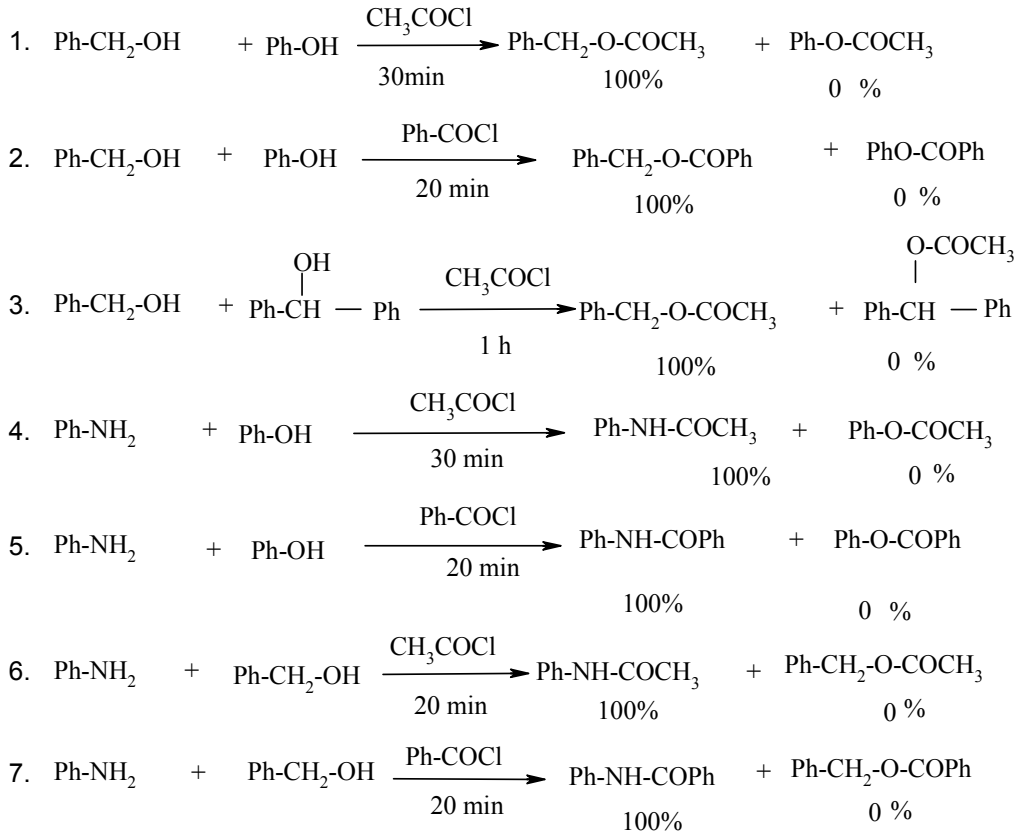
[d] The substrate was treated with CH_3COCl (2 equiv. per –OH group)

Compounds containing primary (Table 4, Entries 1, 2, 3, 5), secondary (Table 4, Entries 4, 7), Tertiary (Table 4, Entries 6, 8) hydroxy groups were readily acetylated with acetyl chloride under similar conditions without any side reactions. Phenolic compounds containing electron withdrawing (Table 4, Entries 12, 19) and donating groups (Table 4, Entries 15, 18) were also acetylated with considerable yields. Acylation of dihydroxy phenols (Table 4 Entries 11, 16) proceeds by using 2 mol of acetyl chloride with excellent yield. Similarly, primary alcohols were bezoylated faster than secondary ones (Table 4 Entries 3, 9). Sterically hindered alcohols (Table 4 Entries 7, 8) acetylated in excellent yields within a specific time.

The generality of the reagents CuO, acetyl chloride was established by efficient acylation of amines containing both; electron withdrawing (Table 4 Entries 22, 23) and donating groups (Table 4 Entries 24, 25) in the aromatic ring leading to the corresponding amides in excellent yields.

The scope of this methodology was further extended for investigation of chemo-selective acylation and benzoylation of alcohols, phenols and amines. The acylation and

benzoylation, in general, were chemoselective with respect to alcohols, phenols and amines **(Scheme 2).**



Scheme 2

Most of the above substrates were acetylated in the excellent yields in the presence of CuO (0.1 mol %) and acetyl chloride (1 equiv.) under solvent free conditions and proceed with faster reaction rates. This protocol benefits for short reaction time, operational simplicity, neutral reaction conditions, reusability of the catalyst, avoidance of solvents, reduced environmental and economic impacts and chemoselectivity

Chemoselectivity of acylation and benzoylation in presence of (0.1 mol %) CuO with solvent free condition

In conclusion, we have demonstrated the efficiency of CuO, towards the acylation or benzoylation of alcohols, phenols and amines with acetyl and benzoyl chlorides using a catalytic amount of CuO under solvent free conditions. The notable special features of this

methodology are the simple reaction procedure, excellent yields of the products, mild reaction conditions, short reaction time, ready availability and compatibility of the catalyst under neat conditions. Thus, this methodology represents a better, eco-friendly alternative to many existing procedures and is also suitable for industrial applications.

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