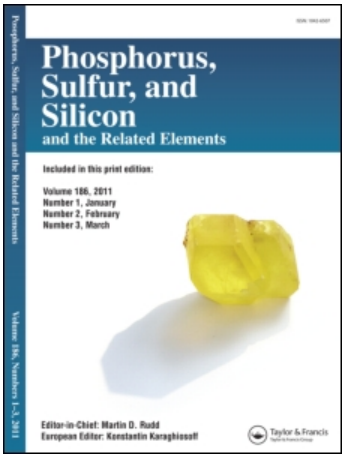

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Acetylation and Formylation of Alcohols in the Presence of Silica Sulfuric Acid

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ACETYLATION AND FORMYLATION OF ALCOHOLS IN THE PRESENCE OF SILICA SULFURIC ACID

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Alcohols are converted to esters in a mild, clean, and efficient reaction with acetic and formic acids in the presence of silica sulfuric acid. All reactions were performed under mild and completely heterogeneous conditions in refluxing n-hexane.

Keywords: Acetylation; alcohols; formylation; heterogeneous conditions; silica sulfuric acid

During the multistep synthesis of natural products, the efficiency of the synthetic protocol employed often depends largely on protection and deprotection of the functional groups involved. To this end, protecting groups have been playing a crucial role during the synthesis of complex natural products.[1] Among the various protecting groups used for hydroxyl function, acetyl is the most common group because of its easy introduction, stability to acidic reaction conditions, and ease of its removal by mild alkaline hydrolysis. Acetylation[2] is most commonly performed using,[3,4] reagents such as Ac_2O or AcCl in the presence of base procedures which are not environmentally friendly. The use of HOAc/mineral acid for acetylation suffer from the problem of reversability. Later modifications involving the use of Lewis acids,[5–10] in combination with Ac_2O, is inherently wasteful since half of every acid anhydride molecule is lost as a carboxylic acid and the use of HOAc (as solvent)-lanthanate trifilates,[11–13] while efficient, is expensive.

Formylation is a very important process in organic chemistry. Although various formylation reagents have been reported

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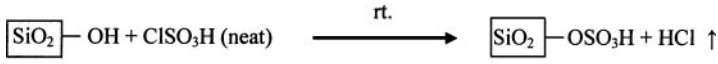
previously,[14–24] there are still serious limitations for the preparation of formates due to the drastic reaction conditions, the use of uncommon reagents, formation of undesirable or toxic by-products, the application of expensive catalysts for preparation of formylating agents and thermal instability of the reagents.

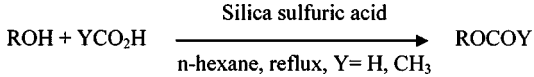
On the other hand, any reduction in the amount of sulfuric acid needed and/or any simplification in handling procedures are required for risk reduction, economic advantage, and environment protection.[25] In addition, there is current research and general interest in heterogeneous systems because of the importance such systems have in industry and in developing technologies.[26] In continuation of our studies on the application of inorganic acidic salts,[27] we found that silica gel reacts with chlorosulfonic acid to give silica sulfuric acid (I). It is interesting to note that the reaction is easy and clean without any work-up procedure because HCl gas is evolved from the reaction vessel immediately (Scheme 1).



I

SCHEME 1

We hoped that silica sulfuric acid (I) would be a superior proton source to all of the reported acidic solid supports or acidic resin such as polystyrene sulfonic acid and Nafion-H[28] for running reactions under heterogeneous conditions. Herein we report a mild, simple, and efficient method for the acetylation and formylation of alcohols with acetic and formic acids in the presence of silica sulfuric acid (Scheme 2).



SCHEME 2

As shown in Table I, this method can be used as an efficient method for acetylation and formylation of primary, allylic, benzylic, hindered, and unhindered secondary and sterically hindered tertiary alcohols. All reactions were performed under mild and completely heterogeneous conditions in n-hexane at reflux temperature and products were obtained in good to high yields.

In conclusion, we have developed an efficient method for the acetylation and formylation of alcohols with acetic and formic acids under mild

TABLE I Acetylation and Formylation of Alcohols

Entry	Substrate	Product	Time (min)	Yield%[a,b]
1	2-$ClC_6H_4CH_2$ OH	2-$ClC_6H_4CH_2$ OAc	10	86
2	4-$ClC_6H_4CH_2$ OH	4-$ClC_6H_4CH_2$ OAc	10	90
3	2-$BrC_6H_4CH_2$ OH	2-$BrC_6H_4CH_2$ OAc	35	83
4	2-$MeC_6H_4CH_2$ OH	2-$MeC_6H_4CH_2$ OAc	5	85
5	4-$MeOC_6H_4CH_2$ OH	4-$MeOC_6H_4CH_2$ OAc	10	80
6	4-$(Me)_3CC_6H_4CH_2$ OH	4-$(Me)_3CC_6H_4CH_2$ OAc	10	85
7	3-$NO_2C_6H_4CH_2$ OH	3-$NO_2C_6H_4CH_2$ OAc	60	90
8	$C_6H_5CH(OH)C_6H_5$	$C_6H_5CH(OAc)C_6H_5$	5	93
9	$C_6H_5CH_2CH_2CH_2OH$	$C_6H_5CH_2CH_2CH_2$ OAc	45	85
10	$C_6H_5CH_2CH(OH)CH_3$	$C_6H_5CH_2CH(OAc)CH_3$	60	84
11	$C_6H_5CH(CH_3)CH_2$ OH	$C_6H_5CH(CH_3)CH_2$ OAc	40	90
12	$C_6H_5CH_2CH_2$ OH	$C_6H_5CH_2CH_2$ OAc	20	95
13	1-Methylcyclohexanol	1-Methylcyclohexyl acetate	60	85
14	Cyclohexanol	Cyclohexyl acetate	50	80
15	*tert*.Butyl alcohol	*tert*.Butyl acetate	50	82
16	$C_6H_5CH{=}CHCH_2$ OH	$C_6H_5CH{=}CHCH_2$ OAc	50	80
17	2-$ClC_6H_4CH_2$ OH	2-$ClC_6H_4CH_2$ OC(O)H	10	90
18	4-$ClC_6H_4CH_2$ OH	4-$ClC_6H_4CH_2$ OC(O)H	10	85
19	2-$BrC_6H_4CH_2$ OH	2-$BrC_6H_4CH_2$ OC(O)H	30	80
20	2-$MeC_6H_4CH_2$ OH	2-$MeC_6H_4CH_2$ OC(O)H	5	85
21	4-$MeOC_6H_4CH_2$ OH	4-$MeOC_6H_4CH_2$ OC(O)H	10	90
22	4-$(Me)_3CC_6H_4CH_2$ OH	4-$(Me)_3CC_6H_4CH_2$ OC(O)H	10	85
23	3-$NO_2C_6CH_4CH_2$ OH	3-$NO_2C_6H_4CH_2$ OC(O)H	60	83
24	$C_6H_5CH(OH)C_6H_5$	$C_6H_5CH[OC(O)H]C_6H_5$	5	92
25	$C_6H_5CH_2CH_2CH_2$ OH	$C_6H_5CH_2CH_2CH_2$ OC(O)H	55	87
26	$C_6H_5CH_2CH(OH)CH_3$	$C_6H_5CH_2CH[OC(O)H]CH_3$	15	85
27	$C_6H_5CH(CH_3)CH_2$ OH	$C_6H_5CH(CH_3)CH_2$ OC(O)H	50	85
28	$C_6H_5CH_2CH_2$ OH	$C_6H_5CH_2CH_2$ OC(O)H	30	90
29	1-Methylcyclohexanol	1-Methylcyclohexyl formate	75	95
30	Cyclohexanol	Cyclohexyl formate	60	90
31	*tert*.Butyl alcohol	*tert*.Butyl formate	35	85
32	$C_6H_5CH{=}CHCH_2$ OH	$C_6H_5CH{=}CHCH_2$ OC(O)H	40	90

[a] Products were characterized by their physical constants, comparison with authentic samples and IR and NMR spectroscopy.

[b] Isolated yield.

reaction conditions. The reactions are clean and the products yields are good to high and the procedure is easy.

Experimental Section

Preparation of Silica Sulfuric Acid

A 500 mL suction flask equipped with a constant-pressure dropping funnel and a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water) was used. It was charged with silica gel (60.0 g).

Chlorosulfonic acid (23.3 g, 0.2 mmol) was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 1). After the addition was complete the mixture was shaken 30 min. A white solid (silica sulfuric acid, 76.0 g) was obtained.

General Procedure for Acetylation and Formylation of Alcohols in the Presence of Silica Sulfuric Acid. A mixture of the substrate (1 mmol), acid (1 mmol), and silica sulfuric acid (0.05 g) in n-hexane (3 mL) was refluxed for the specified time (Table I). The reaction was monitored by TLC or GC. After completion of the reaction, the mixture was filtered and the solid residue was washed with dichloromethane (10 mL). Evaporation of the solvent followed by column chromatography on silica gel gave the corresponding esters in good to high yields.

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