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Acetylation of alcohol, phenols, thiols and amine promoted by succinimidinium hydrogensulfate ([H-Suc]HSO_4) in the absence of solvent

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ABSTRACT

Succinimidinium hydrogensulfate ([H-Suc]HSO_4), as a new and stable derivative of succinimide, is easily prepared by the reaction of succinimide with neat sulfuric acid. This ionic liquid can be used as an efficient catalyst for the acetylation of alcohols, phenols, thiols and amines at room temperature under mild and solvent free conditions. All the products are separated and identified using different types of methods including FT-IR, ^{1}HNMR and ^{13}CNMR spectroscopy. This new method consistently has the advantages of chemoselectivity, excellent yields of the products and short reaction times. Further, the catalyst can be reused and recovered for several times without any variations in the yield of the product.

***Keywords**: Succinimidinium hydrogensulfate ([H-Suc]HSO_4), Acetylation, Solvent free conditions, Reusability of the catalyst, Ionic liquid.*

1. Introduction

The improvement of environmentally friendly catalysts and solvents for organic reactions is an area of considerable significance. From both economic and environmental points of view, the use of non-volatile solvents and non-metallic catalysts is very promising. In latest decades, ionic liquids (ILs) have received considerable attention and been successfully used in numerous catalytic reactions as environmentally benign solvents and catalysts because of their attractive properties like their low vapor pressure, reusability, high thermal and chemical stability.

Use of Brönsted acidic ionic liquids has brought major sanitation as catalyst, they have been planned to replace traditional mineral liquid acids, such as sulfuric acid and hydrochloric acid [1]. Many organic reactions such as esterification [2-4], alkylation [5], alcoholysis [6], acylation [7], Claisen-Schmidt condensation [8], carbonylation [9], nitration [10], hydrolyzation [11], have been reported that can be accelerated in the presence of functionalized Brönsted acidic ILs.

The protection of alcohols, phenols, thiols and amines by the formation of esters, thioesters and amides is one are the most important and greatly used transformations in organic chemistry [12], also protection of such functional groups is often necessary during the course of various transformations in a synthetic sequence, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products [13, 14]. Some of the various procedures are routinely performed for the preparation of acetyl derivatives, including homogeneous or heterogeneous catalysts such as DMAP and 4-pyrolidinopyridine [15], TMEDA [16], Bu_3P [17] ,iodine [18], p-toluenesulfonic acid [19], alumina [20], zinc chloride [21], cobalt chloride [22], montmorillonit K-10 and KSF [23], zeolite HSZ-360 [24], zirconium sulfophenyl phosphonate [25], $Sc(OTf)_3$ [26], $TaCl_5$ [27], trimethylsilyltrifluoromethanesulfonate (TMSOTf) [28], $Cu(OTf)_2$ [29], $In(OTf)_3$ [30], magnesium bromide [31], bismuth(III) salts [32], ferric perchlorate adsorbed on silica-gel [33], $RuCl_3$ [34], $InCl_3$ [35], $Ce(OTf)_3$ [36], $Mg(ClO_4)_2$ [37], $ZrCl_4$ [38], Cp_2ZrCl_2 [39], and cerium polyoxometalate [40]. Although, some of them have been used for the acetylation with good to high yields, the majority of these methods feel pain at least from one of disadvantages such as: extended reaction times,

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reaction under oxidizing conditions, using of halogenated solvents and strong acids, low yields, harsh reaction conditions, difficulty in the preparation and moisture sensivity of the catalysts, high cost and high toxicity of the reagents. Hence, there is a need to develop an alternative method for the protection of alcohols, phenols, thiols and amines as their acetylated forms

2. Experimental

2.1. General procedure

All chemicals were purchased by Merck or Fluka Chemical Companies and used without further purification. All yields refer to the isolated products. Products were characterized by their physical constants and comparison with reliable samples. The purity determination of the substrates and reaction surveillance were accompanied by TLC using silica gel SILG/UV 254 plates.

2.2. Characterization techniques

The IR spectra were recorded on a Perkin Elmer 283 B, 781 and 843 Spectrophotometers and FT-IR spectra were recorded a perkin-Elmer spectrum BX series and Thermo Nicolet Nexus 670 Spectrophotometers. In all the cases the ^{1}HNMR and ^{13}CNMR spectra were recorded with Varian Gemini 300, 200 and BrukerAvance 400, 300 MHz instruments. All chemical shifts are quoted in parts per million (ppm) relative to TMS using deuterated solvent.

2.3. Catalyst preparation

In a round-bottomed flask, 0.53 mL sulfuric acid (98%, d=1.84) was added drop-wise to a mixture of succinimide (0.99 g, 10 mmol) in 50 mL of dichloromethane on an ice bath. The reaction mixture was stirred at room temperature for 30 min, and then the solvent was evaporated under reduced pressure. The solid residue was washed with 2 × 5 mL ether and dried under vacuum. [H-Suc]HSO_4 was obtained as a cream solid (1.94 g, 97 %) (m.p. 78°C).

2.4. General procedure

The substrate (alcohol, phenol, thiol and amine; 1.0 mmol) was treated with Ac_2O (3.0 mmol) in the presence of [H-Suc]HSO_4 (2 mol%) at room temperature under solvent free conditions and magnetic stirring. The reaction was followed by TLC (n-Hexane: EtOAc, 70:30). Following completion of the reaction, the mixture was diluted with diethyl ether and filtered. The organic layer was washed with $NaHCO_3$ solution and water. Evaporation of the solvent under reduced pressure gave the highly pure product without further purification, identical to an authentic sample of the acetylated product (m.p., IR, ^{1}HNMR and ^{13}CNMR).

3. Results and Discussion

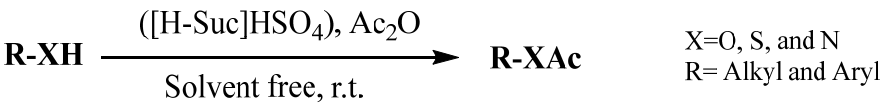
Very recently we have reported the preparation of succinimidinium hydrogen sulfate ([H-Suc]HSO_4) and its applicability in the acceleration of the *N*-Boc protection of amines [41]. The obtained results in this study clarified that this reagent can be used as an efficient catalyst for the promotion of the reactions which need the use of an acidic catalyst to speed-up. So we were interested to explore the applicability of this reagent in the acceleration of the acetylation of alcohols, phenols, thiols and amines using acetic anhydride.

At first and for optimization of the reaction conditions, different amounts of Ac_2O were used to get benzyl acetate from benzyl alcohol at room temperature under solvent free conditions, and the results are summarized in Table 1. The best result was observed with a 3:1 molar ratio of acetic anhydride to alcohol, whereas with lower amounts of Ac_2O, lower yields were obtained. The model reaction was also carried out with acetic acid and ethyl acetate as acylating agents, and only 40% and 28% of the corresponding acetate were produced, respectively. Finally the best result was obtained using 10 mg (2 mol%) of [H-Suc]HSO_4 at room temperature under solvent-free conditions (Scheme 1).

Table 1. Optimization of the Ac_2O amount in the acetylation of benzylalcohol.

Entry	Time (min)	Ac_2O (mmol)	Yield (%)[a,b]
1	6 h	-	trace
2	1	1	34
3	1	1.5	52
4	1	2	68
5	1	2.5	86
6	1	3	98

[a]Reaction conditions: alcohol (1 mmol), Ac_2O, ([H-Suc]HSO_4) (2 mol%), room temperature, solvent free condition.
[b]Isolated yield.



Scheme 1. The protection of alcohol, amine, phenol and thiols.

After these initially experiments, catalytic amounts of $[H\text{-}Suc]HSO_4$ (10 mg) was used to convert a variety of functionalized alcohols, phenols, thiols and amines with acetic anhydride into respective esters, thioesters and amides at room temperature under solvent free conditions and the results were presented in Table 2.

The results incorporated in Table 2 exhibit the generality and scope of $[H\text{-}Suc]HSO_4$ during the acetylation of structurally diverse alcohols and phenols. The reaction could be carried out with 3.0 equiv. of Ac_2O at room temperature in 2-15 min. The compounds containing both electron-withdrawing and electron-donating groups react in an equal manner efficiently under the standard reaction conditions to give the acetylated products to extraordinary yields. The reaction conditions are mild enough not to bring about any damage to moieties like methoxyl group (Table 2, entry 9) which often undergo cleavage in the presence of strong acids or certain *Lewis* acids. Indeed hindered and electron deficient alcohols (Table 2, entries 5, 6 and 13-16) are also efficiently acetylated under solvent free conditions. Excellent selectivity was obtained in that secondary and tertiary alcohols do not experience any competitive dehydration (Table 2, entries 9-16). In order to clarify the mildness and stereospecificity of the $[H\text{-}Suc]HSO_4$ catalyzed acetylation of alcohols, the reaction of optically active L(-)-Menthol and R(+)-Borneol were studied (Table 2, entries 12 and 16). We observed that L(-)-Menthol ($[\alpha]_D$ = -49.0º, c =10 in 95% ethanol, 99% e.e.) and R(+)-Borneol ($[\alpha]_D$ = +37.9º, c =5 in ethanol, 99% e.e.) are enantioselective with retention of configuration on the chiral center to provide L-(-)-Menthyl acetate ($[\alpha]_D$ = -73.0º, neat, 98% e.e.) and (+)-Bornyl acetate ($[\alpha]_D$ = +41.8º, neat, 98% e.e.). The highest optical purity was observed in an enantiopure form in high yield and under high regioselectivity by using $[H\text{-}Suc]HSO_4$ at room temperature under solvent free conditions. The optical rotation of the product was determined and compared with that reported from Aldrich.

Also, we extended the use of $[H\text{-}Suc]HSO_4$ for direct acetylation of amines (Table 2, entries 24-28) and thiols (Table 2, entries 33-35) with Ac_2O. The superiority of ($[H\text{-}Suc]HSO_4$) is further established in the fact that direct acetylation of amines and thiols with 3.0 equiv. Ac_2O could be achieved in 2-5 min at room temperature (89-98% yields) under the catalytic influence of 10 mg $[H\text{-}Suc]HSO_4$. Our protocol has some advantages because the two groups were acetylated during the reaction conditions (Table 2, entries 29-32, 35) and furylmercaptane was transformed smoothly to the corresponding acetate derivative (Table 2, entry 36).

We have also found that $[H\text{-}Suc]HSO_4$ can be easily recovered by filtration, washing with EtOAc and drying at 65 °C under vacuum for 2 h. The reusability of this reagent is exemplified by the acetylation of benzylalcohol in the presence of recycled ionic liquid, which gave the requested product in 98, 98, 98, 96 and 96% yields after five runs. The average time for five consecutive runs was 2.5 min and 100% conversion for all, which clearly demonstrates the practical recyclability of this catalyst.

In order to show the merit of the presented method in the acetylation reactions, we have compared the obtained results in the acetylation of benzyl alcohol with acetic anhydride catalyzed by $[H\text{-}Suc]HSO_4$ with some of those reported in the literature (Table 3). It is clear that the presented method is superior in terms of reaction time, catalyst amount or product yield.

The plausible mechanism is that acetic anhydride is first activated by $[H\text{-}Suc]HSO_4$ to afford **(I)**. Alcohol, phenol, thiol and amine attacks **I** which in turn converts to the final product and releases $[H\text{-}Suc]HSO_4$ for the next catalytic cycle (Scheme 2).

The selectivity of this method was examined by competitive acetylation of benzyl alcohol, phenol, aniline and thiophenol with together. Our results showed that aniline was acetylated selectively in the presence of phenol and thiophenol (Table 4, entries 2, 5). This may be measured as a useful practical achievement in the acetylation of amines in the presence of alcohols, phenols and thiols. In addition, benzyl alcohol was acetylated in the presence of phenol and thiophenol in 82:18% and 86:14% yields, respectively (Table 4, entry 1, 4). Lastly, phenol was acetylated in the presence of thiophenol in 64:36% yield (Table 4, entry 3).

Remarkably, we have noticed that the conversion of 4-chlorobenzylalcohol to the respective acetate product can be carried out even in a larger scale (10 mmol) in 92% yield within 5 min without any difficulty by using 10 mg of $[H\text{-}Suc]HSO_4$. Hence, it indicates that a large-scale reaction is possible using a same amount of the catalyst. It is significant to point out that the present method is much cleaner, does not involve any chromatographic separation for a large-scale reaction.

Table 2. ([H-Suc]HSO_4) catalyzed acetylation of alcohols, phenols, thiols and amines.[a,b]

Entry	Substrate	Time (min)	Yield (%)
1	Benzylalcohol (a)	2	98
2	2-Mehtyl-benzylalcohol (b)	2	96
3	2-Chloro-benzylalcohol (c)	2	96
4	2-Bromo-benzylalcohol (d)	2	96
5	2-Nitro-benzylalcohol (e)	2	94
6	3-Nitro-benzylalcohol (f)	15	94
7	4-Chloro-benzylalcohol (g)	3	98
8	4-Methoxy-benzylalcohol (h)	4	98
9	Cyclopentanol (i)	2	96
10	Cyclohexanol (j)	2	96
11	Cycloheptanol (k)	2	96
12	L(-)-Menthol (l)	8	90
13	2-Adamantanol (m)	4	91
14	Benzoin (n)	6	98
15	1-Adamantanol (o)	6	93
16	R(+)-Borneol (p)	5	98
17	Phenol (q)	6	97
18	1-Naphthalenol (r)	9	95
19	2-Naphthalenol(s)	9	95
20	Catechol (t)	15	88[c]
21	Resorcinol (u)	10	89[c]
22	Hydroquinone (v)	1	96[c]
23	Pyrogallol (w)	15	96[d]
24	Aniline (x)	2	98
25	2-Methylaniline (y)	2	98
26	4-Bromoaniline (z)	2	93
27	4-Nitroaniline (aa)	4	97
28	1-Naphthylamine (bb)	2	94
29	1-Phenyl-ethane-1,2-diol (cc)	5	96[c]
30	2-(Hydroxymethyl) phenol (dd)	3	98[c]
31	2-Benzylamino-ethanol (ee)	4	98[c]
32	2-Amino-phenol (ff)	2	98[c]
33	Benzenethiol (hh)	5	92
34	Phenylmethanethiol (ii)	4	93
35	2-Mercapto-phenol (jj)	10	90
36	Furan-2-thiol (kk)	8	89

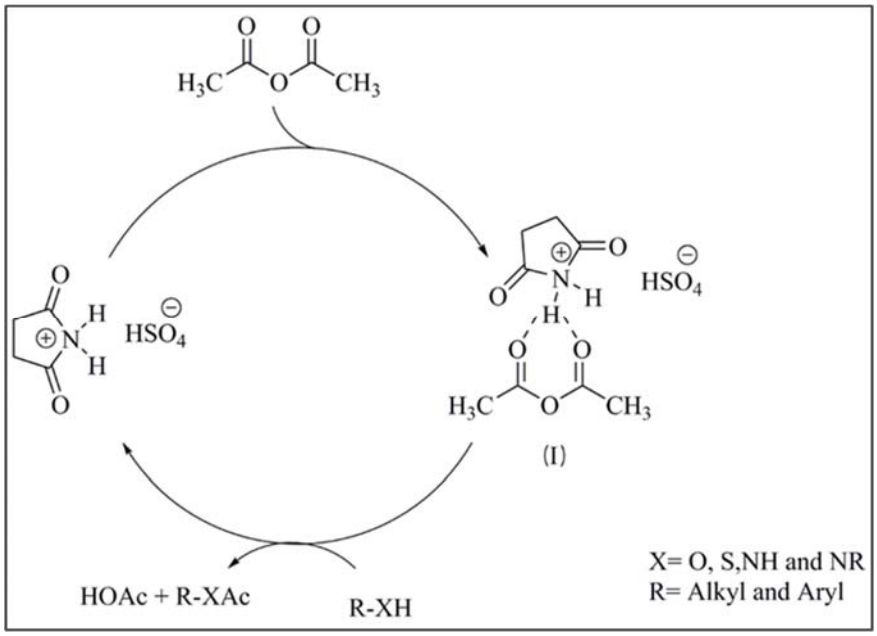
[a]Reaction conditions:substrate, 1.0 mmol; Ac_2O, 3.0 equiv.; ([H-Suc]HSO_4) (2 mol%).
[b]Isolated yield of the corresponding acetylated product.
[c]Isolated yield of the di-acetate.
[d]Isolated yield of the tri-acetate.

Table 3. The superiority of ([H-Suc]HSO_4) for the acetylation of benzylalcohol over those obtained by the recently reported catalysts at room temperature under solvent free conditions.

Entry	Catalyst	Catalyst (mol%)	Time (min)	Yield (%)[a]	Ref.
1	$CoCl_2$	0.5	240	98	[22]
2	montmorillonit KSF	20 mg	60	90	[23]
3	zeolite HSZ-360	20 mg	60	84	[24]
4	$Cu(OTf)_2$	2	30	97	[29]
5	$RuCl_3$	5	60	96	[34]
6	$InCl_3$	0.1	30	85	[35]
7	$Ce(OTf)_3$	1	12	98	[36]
8	$Mg(ClO_4)_2$	1	15	100	[37]
9	Cp_2ZrCl_2	1	600	93	[39]
10	SuSA	2.8	2	98	[41]
11	[Hmim]HSO_4	20	20	87	[42]
12	([H-Suc]HSO_4)	2	1	98	This work

[a]Isolated yield.

[b]Temperature= 60ºC.

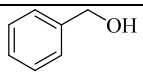
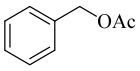
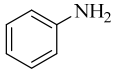
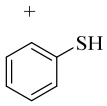
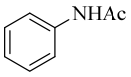
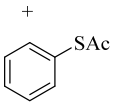
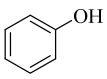
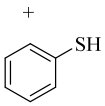
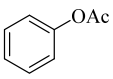
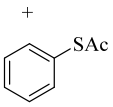
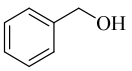
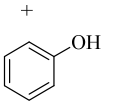
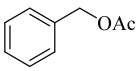
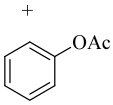
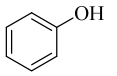
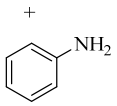
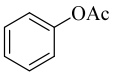
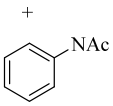


Scheme 2. The plausible mechanism of the reaction.

4. Conclusions

In conclusion, we have developed a simple, efficient and chemoselective protocol for the acetylation of various alcohols, phenols, thiols and amines using [H-Suc]HSO_4 as a newly reported solid acid catalyst. The protocol is highly chemoselective offering potential in different applications. The methodology also has several other advantages such as: high reaction rates and excellent yields, no side reactions, ease of preparation and handling of the catalyst, cost efficiency and effective reusability of the catalyst, use of inexpensive catalyst with lower loading and simple experimental procedure. Further work to explore this novel catalyst in other organic transformations is in progress.

Table 4. Competitive acetylation of benzyl alcohol, phenol, thiophenol and aniline.

Entry	Substrate	Product	Time (min)	Yield (%)[a,b]
1			5	86 14
2	 + 	 + 	5	100 0
3	 + 	 + 	5	66 34
4	 + 	 + 	5	82 18
5	 + 	 + 	5	0 100

[a]Reaction conditions:substarte, 1.0 mmol; Ac_2O, 3.0equiv; catalyst (2 mol%).
[b]Determined by GC-MS of the corresponding acetylated product.

Acknowledgements

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