

Protection of aldehydes and hydroxy compounds with acetic anhydride in presence of sulfonic acid functionalized ionic liquid

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Abstract: Functionalized ionic liquids (FILs) are efficient ILs for the protection of various functionalities such as aldehydes, phenol, and alcohols with acetic anhydride under neat conditions. The attracted rising interest and the subject of active research in the field of catalysis is the variety of expanded applications and yet reports on ILs are still quickly increasing. This work reports a sulfonic acid functionalized ionic liquid is an environmentally friendly, easy handling, and reusable ionic liquid catalyst for the protection of aldehydes and phenols. The catalyst was characterized with different spectroscopic techniques which indicates the fabricated IL is matching with the reported methods. The catalyst can be recycled up to eight times without substantial loss in activity. Furthermore, no chromatographic separations were needed to obtain the desired products.

Keywords: Ionic liquid; acetylation; room temperature; short reaction time. ©2024 ACG Publication. All rights reserved.

1. Introduction

The production of library molecules in multistep synthesis is prominent for the development of drug candidates. During this, protection of the functional group is necessary for the synthesis of carbohydrates, dendrons, natural products, and nucleosides¹. Eco-friendly neat protection procedure has arisen as part of vast interest in point of environmentally friendly and cost-effective aspects². Although various substances are employed for the protection of functionalities such as amines, thiols, phenols, alcohols, and aldehydes with various reagents such as acetic anhydride, acetyl chloride, acetyl acetone, and carboxylic acids are used for amine functionalities³, trialkyl orthoformate, 2-mercaptoethanol, acetic anhydride, ethane dithiol, alcohols for aldehydic functionalities⁴. Among all these protected reagents, common one is acetic anhydride due to its cheap and quick availability and easier deprotection.

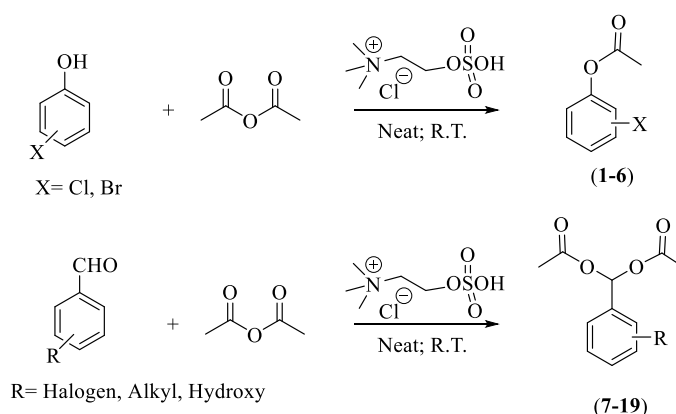
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Protection of aldehydes, hydroxy compounds

Frequently the protection reactions were accomplished in the presence of either basic or acidic nature catalysts^{5,6}. Still, the majority of the reports to date possess important disadvantages including long reaction times, harsh conditions with the use of harmful organic solvents, and requiring deadly work-up procedures^{7,8}.

Ionic liquids (ILs) are effective interesting reagents that acts as solvent, catalysts, tunable, soluble in various solvents, and are reusable. Moreover, it produces no harmful emissions, rendering them safer and more appropriate than traditional mineral acids⁹. Functionalized indentations (ILs) are noteworthy novel materials that possess the advantages of solid-state acids, such as negligible vapor pressure and recyclable nature^{10,11}. Their adaptability is another advantage: an infinite number of ILs were created using different cations, anions, and functional groups¹². The quaternary ammonium salt choline chloride (ChCl) is biocompatible, non-flammable, inexpensive, and safe for the environment¹³. These fundamental characteristics have allowed researchers to create some choline-based ILs and deep eutectic solvents using just the reagent ChCl^{14,15}. These ILs have recently attracted a lot of attention due to their exceptional catalytic, polymerization, and green solvent properties.

The performance of reactions under neat method is simple, effective synthetic approaches for the target product. Furthermore, sustainable methodologies for the fabrication of various organic transformations are also being developed. The most vital goals of “green chemistry” include the prevention of organic solvents, and toxic reagents, and the reduction of costs. For these reasons in mind, and our continued interest in conducting the reaction under water-ethanol mixture without catalyst¹⁶ solvent-free¹⁷, sonochemical¹⁸, grindstone⁴ methodologies were used for the targeted compounds. We here report the use of sulfated choline ionic liquid (SCIL) as an environmentally benign and recyclable IL for protection of aldehydes, and hydroxy compounds (Scheme 1).



Scheme 1. Acetylation of Phenols and Aldehydes

2. Experimental

2.1. General

We bought choline from a local company and aldehydes, hydroxy compounds, acetic anhydride, and chlorosulfonic acid from Merck. NMR (¹H & ¹³C, 400 & 100 MHz) spectra were checked at 25 °C using a Varian INOVA 400 MHz spectrometer. FT-IR spectra were recorded at 25 °C using a Shimadzu IR Prestige 21 spectrometer using KBr disk in the range of 4500 to 500 cm⁻¹.

2.2. Synthesis and Characterization of SCIL

Choline chloride (ChCl 4 mmol) was added to the 50 mL reaction flask and was fitted with a dropping funnel. To this ClSO₃H (4 mmol) acid in acetonitrile (20 mL) was added drop-wise over a period of 20 min at R.T. and the reaction was continued stirring for 3 h. After that, the white color solid was filtered and washed with acetonitrile with 30 ml for 3 times. The obtained solid was in good agreement with the reported one⁴.

2.3. General Procedure for Acetylation Reaction

15 mL reaction flask equipped on a magnetic stirrer, after that aldehyde/hydroxy compound (1 mmol), acetic anhydride (1 mmol), and 10 mol% SCIL were added and the reaction was stirred at room temperature for an appropriate time. After that, the reaction was checked by thin-layer chromatography (TLC). There is no aldehyde/hydroxy compound in TLC assumed, as the reaction was completed. Later the reaction mixture was dissolved with ethyl acetate (15 mL), insoluble catalyst was separated and the residue was concentrated by a Rota-evaporator and the crude product was recrystallized by ethanol to obtain the pure product. The products of chemical compounds were characterized by IR, ^1H , and ^{13}C NMR spectra. Detailed spectral data is provided in Supporting information.

3. Results and Discussion

3.1. Chemistry

Aldehydes, hydroxy compounds protection is very significant during multistep synthesis and it does not protect with acetic anhydride without promoter. Protection of functional groups commonly needs long reaction times, high catalyst loadings, and exotic reagents to promote the formation of the desired product. To avoid these problems for the protection of aldehydes, hydroxy compounds were carried out with suitable promoters, readily available which are inexpensive, easy to prepare, and recyclable SCIL.

Different hydrogen donor (isopropanol (IPA), ethanol, and formic acid) and nonhydrogen donor (Acetone, methylethylketone, and Ethyl acetate) liquids were used for the acylation, follow-on it gives unsatisfactory yields (50–70%) after 3 h of reaction (see entries 1–6 in Table 1). The acylation of aldehyde was then conducted under a solvent-free method. Entry 7 in Table 1 the formation of targeted product with high yields (94%) in a short reaction time (15 min) under a solvent-free method. The amount of catalytic agent is reduced from 10 mg to 5 mg and the rate of the reaction time increased and product yield decreased (82%) (entry 8 in Table 1). Whereas the catalyst amount was increased from 10 to 15 mol % the rate of the reaction was the same and the product yield was slightly increased with no much difference (entry 9 in Table 1). Furthermore, the SCIL was increased from 15 mol% to 20 mol %, the reaction rate was decreased from 15 min to 10 min and the product yield remained constant (entry 10 in Table 1). Hence 15 mol% of catalyst is sufficient to complete the reaction.

Table 1. Acylation of Phenols and aldehydes in the presence of SCIL^a

Entry	Solvent	Catalyst amount (mol %)	Time (min)	Yield (%) ^[b]
1	IPA	10	180	63
2	EtOH	10	180	58
3	Formic acid	10	180	50
4	Acetone	10	140	70
5	Methylethylketone	10	180	65
6	Ethyl acetate	10	180	64
7	Neat	10	15	94
8	Neat	5	32	82
9	Neat	15	15	96
10	Neat	20	10	96

^aReaction conditions: phenol (1 mmol), aldehyde (1 mmol), acetic anhydride (1 mmol), and catalyst (15mol%).

^[b] Isolated Yields

The optimized protocol is in hand, and was further extended for the acylation of various aldehydes and hydroxy (Phenols and Benzylic alcohols). Based on the obtained results, aldehydes protection with acetic anhydride is underwent smoothly compared with hydroxy compounds. The aldehydes having

Protection of aldehydes, hydroxy compounds

electron-donating groups resulted in good yields compared to electron-withdrawing group due to some steric hindrance. Acylation of hydroxy compounds reaction rate and product yields were low compared to aldehydes owing to the rate of reactivity. In hydroxy compounds also, the substitution of functional groups plays a key role for completion and yield of the correspond derivatives. Electron releasing groups and less steric hindrance compounds are giving better yields and fast reaction rate compared to electron withdrawing compounds the results are presented in Table 2.

Table 2. Acetylation of phenols, and aldehydes with acetic anhydride under neat conditions in presence of SCIL^a

Compound	Substrate	Time (min)	Yield (%) ^b
1	C ₆ H ₅ OH	20	97
2	C ₆ H ₅ CH ₂ OH	14	95
3	4-Br-C ₆ H ₄ CH ₂ OH	10	96
4	4-Cl-C ₆ H ₄ CH ₂ OH	12	93
5	C ₆ H ₅ (CH ₂) ₂ OH	15	92
6	C ₁₀ H ₇ OH	16	93
7	C ₆ H ₅ CHO	4	97
8	2-Cl-C ₆ H ₄ CHO	4	98
9	2-Br-C ₆ H ₄ CHO	3	97
10	3-Br-C ₆ H ₄ CHO	4	98
11	4-Br-C ₆ H ₄ CHO	3	98
12	4-NO ₂ -C ₆ H ₄ CHO	6	96
13	4-Me-C ₆ H ₄ CHO	4	95
14	2-OH-5-Br-C ₆ H ₃ CHO	4	96
15	2-OH-3,5-Cl-C ₆ H ₂ CHO	5	98
16	2-Furfural(C ₄ H ₃ O)	4	97
17	C ₁₄ H ₉ CHO	4	98
18	CH(CH ₃) ₂ CHO	6	75
19	C ₅ H ₁₃ CHO	8	79

^aReaction conditions: substrate (1 mmol), acetic anhydride (1mmol) and catalyst (15mol%) at 25 °C under neat conditions.

^bIsolated yields.

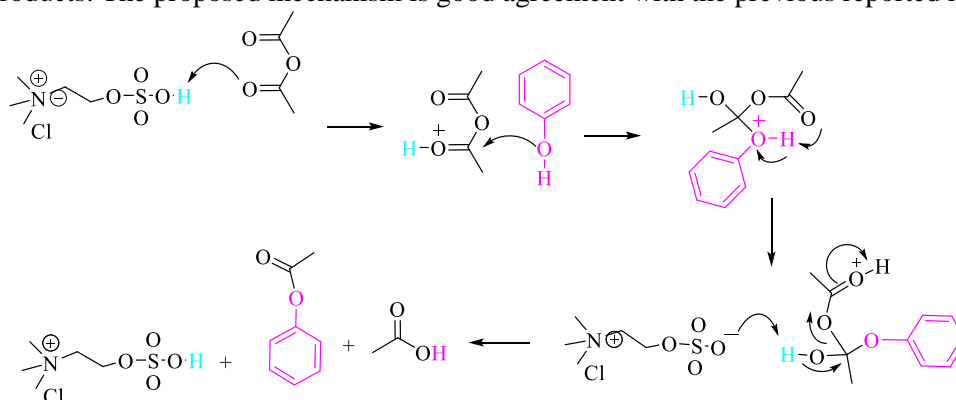
Comparison study was done between reported catalyst and SCIL for the acetylation of aldehydes and hydroxy compounds. The results were represented in Table 3. In 2018 Bazi et al., hydroxyapatite and fluorapatite catalyst was synthesized, the catalyst is not active even after 48 h the yield was only 11-15%. The catalyst was mixed with metal halides and the reaction time was reduced from 48 h to 1.5h where the yield was extremely enhanced from 15 to 96 %. The hydroxyapatite and fluorapatites are required supported metal halides for enhancing the catalytic activity. Review study on metal-based ILs as catalysts for the synthesis of acylals was reported by Ramazani et al., in 2020. The metals are toxic to the environment and are not completely recyclable taking tedious workup procedures, whereas the reported ILs are expensive and it takes long reaction time. Dhakshinamoorthy et al., have been reported for the protection of hydroxy compounds without any catalyst and solvent. The targeted products were obtained at 60 °C and completion of the reaction took 7 h. Recently Sabuzi et al., have been reported for the protection of hydroxy compounds with acetic anhydride in presence of VOSO₄·5H₂O under solvent free condition, for which the completion of reaction took 24 h. This procedure requires long reaction times and tedious work-up procedures. Hence, new IL catalyst for the protection of aldehydes, and hydroxy compounds without any solvent were used. Compared to the existing methods, the current proposed method is cheaper, easier to handle that too with faster reaction rates.

Table 3. Comparison of various catalysts used for the synthesis of targeted compound 1^a

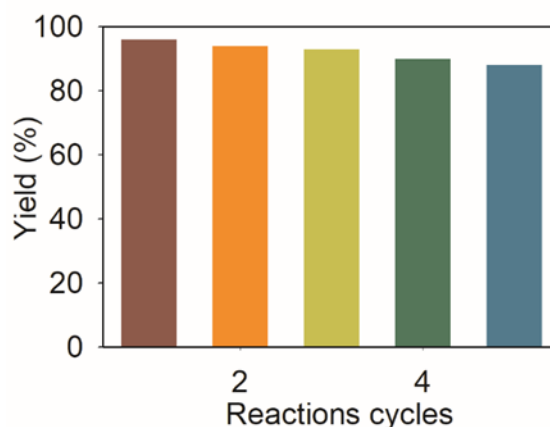
Entry	Catalyst	Medium	Time (min)	Yield (%)	Ref.
1	ZnCl ₂ /Hydroxyapatite	Neat (MW)	120	96	19
2	Metal based Catalysts/ILs	Neat	10	96	20
3	Catalyst Free	Neat	420	98	21
4	VOSO ₄ .5H ₂ O	Neat	1440	97	22
5	SCIL (3.5 mol%)	Neat	20	96	This work

^aReaction conditions: Aldehyde and Phenol = 1 mmol and acetic anhydride = 1 mmol.

The resulting reaction mechanism was planned for the acetylation of aldehydes and hydroxy compounds in presence of SCIL (Scheme 2). In hydroxy compounds, the SCIL synchronizes to the acetic anhydride carbonyl group to make easily nucleophilic addition by taking hydroxy compounds to form the targeted products. Whereas in case of aldehydes it reacts with SCIL which contains acidic hydrogen to form an intermediate benzylideneoxonium ion which reacts with acetic anhydride to give oxonium ion. The intramolecular rearrangement and the hydrogen is rearranged to SCIL to reach targeted products. The proposed mechanism is good agreement with the previous reported method²³.

**Scheme 2.** Anticipated mechanism for the SCIL-catalyzed acetylation of phenols

The recyclability of SCIL was finally investigated in relation to the synthesis of acetylated derivatives 3 and 7, which are products of the reaction between 4-bromo benzyl alcohol and Benzaldehyde and acetic anhydride. After completion of the reaction, the catalyst was isolated by simple filtration by using diethyl ether solvent. The catalyst displays good catalytic activity up to 5 cycles without loss of its activity as shown in Figure 1.

**Figure 1.** Effect of recycled SCIL on the yield of acetylated derivatives 3 and 7

Protection of aldehydes, hydroxy compounds

The manufactured derivatives were identified using infrared (IR) spectroscopy, and ^1H and ^{13}C NMR spectroscopy. The obtained spectral data is in good agreement with the reported one with our earlier reports^{3,23}

4. Conclusion

Readily available and cheap choline chloride was functionalized with sulfonic acid, it shows good acidic property. Based on this, it was used as an acidic catalyst for the protection of aldehydes and hydroxy compounds under solvent free method which gives reduces the chemicals usage in laboratories. The catalyst gives good catalytic activity in both aldehydes and hydroxy compounds. Furthermore, the catalyst can recycle up to 5 cycles without loss of its catalytic activity. Henceforth, Functionalized ionic liquids (FILs) would be so efficient ILs for the protection of various functionalities such as aldehydes, phenol, and alcohols with acetic anhydride under neat conditions.

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