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ORIGINAL PAPER

Acetylation of alcohols and phenols with acetic anhydride under solvent-free conditions using an ionic liquid based on morpholine as a recoverable and reusable catalyst

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Abstract Rapid and efficient acetylation of alcohols and phenols with acetic anhydride is performed in the presence of economical Brønsted acidic ionic liquids that bear a propanesulfonic acid group on a morpholinium cation as catalysts under solvent-free conditions. [MMPPA][HSO_4] (*N*-methylmorpholinium propanesulfonic acid ammonium hydrogensulfate) was proven to be the most active catalyst, and after removal of water, it could be recycled and reused for up to four times without a noticeable decrease in catalytic activity.

Keywords Acetylation · Economical acidic ionic liquid · Catalyst · Acetic anhydride

Introduction

The acylation of alcohols and phenols is one of the most frequently used processes in organic chemistry. It provides an economical and efficient method for protecting hydroxyl groups during oxidation, peptide coupling, and glycosidation reactions. Furthermore, acetylation of alcohols and phenols with acetic anhydride is an important and preferable approach due to its ease of use, the formation and stability of products under mild basic or acidic conditions, and the ease of deprotection of acetates [1, 2]. However, the catalysts traditionally used are bases or acids, which have lots of disadvantages in the acetylation process. For example, some of the base catalysts are toxic, flammable, and possess offensive odors [3]. In addition, some of the traditional protic acid catalysts are not entirely satisfactory in terms of the stability of reactants or products under the reaction conditions and the time-consuming work-up procedures. Therefore, more attention has been focused on performing acylation catalyzed with some novel catalysts. In recent years a wide array of catalysts, such as metal triflates [4–6], metal perchlorates [7–9], solid acids [10–12], molecular iodine [13, 14], ionic liquids [15, 16], and others [17–20], have been employed. However, most of these catalysts suffer from limitations, such as expense, harsh reaction conditions, moisture sensitivity, long reaction times, and regulatory constraints. As a result, new kinds of catalysts and methodologies are still in demand.

With the increasing environmental concerns and regulatory constraints faced in industry, the development of environmentally benign catalysts has become a crucial and demanding area in many modern organic reactions [21]. Nowadays, room temperature ionic liquids, which have very low vapor pressure and are thermally stable, have been recognized as possible environmentally benign alternatives to volatile solvents in the chemical industry. However, as traditional task-specific ionic liquids with imidazole as the cation are rather expensive, which hinders their industrial applications, the synthesis and application of economical task-specific ionic liquids have become an attractive field [22, 23]. In our previous work, some relatively cheap ionic liquids were synthesized to extend the scope and decrease the cost of ionic liquids, and their catalytic activity was also investigated [24, 25]. Furthermore, solvent-free reactions are of great importance in organic synthesis as these reduce the environmental pollution, save energy, and bring down the handling costs due to simplification of work-up technique [26].

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Herein, we report an efficient and environmentally friendly acetylation of alcohols and phenols with acetic anhydride in the presence of 1 mol% economical ionic liquids based on morpholinium salts at room temperature under solvent-free conditions in short reaction time. To the best of our knowledge, acetylations with these ionic liquids as catalysts are unprecedented in the open literature.

Results and discussion

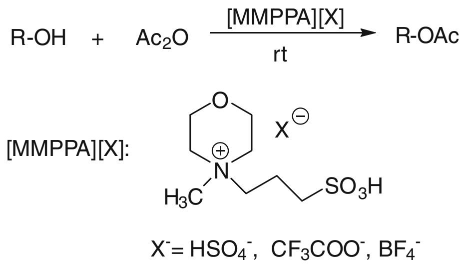
First, we investigated the miscibility of the morpholinium ionic liquids with other chemicals. All of the ionic liquids were miscible with acetic anhydride and water, but were immiscible with all products. Excess of acetic anhydride was necessary for the reaction to proceed at a reasonable rate and accelerated the solubility of solid substrates in the acetic anhydride. The reaction of benzyl alcohol with acetic anhydride was chosen as a model reaction to test the catalytic activity of these Brønsted acidic ionic liquids and no other solvents were added. The results are shown in Table 1. No appreciable amount of the corresponding product was detected even after prolonging the reaction time up to 30 min (entry 1, Table 1) in the absence of catalyst. The ionic liquid [MMPPA][HSO_4] (*N*-methylmorpholinium propanesulfonic acid ammonium hydrogensulfate) was demonstrated to be the best catalyst. We reasoned that [MMPPA][HSO_4], which has two catalytic groups (–SO_3H and HSO_4^-), possessed higher catalytic capacity than [MMPPA][BF_4] (*N*-methylmorpholinium propanesulfonic acid tetrafluoroborate) or [MMPPA][TFA] (*N*-methylmorpholinium propanesulfonic acid trifluoroacetate) both of which have a sole –SO_3H group. Th amount of [MMPPA][HSO_4] was then optimized. The experimental results showed that by increasing the amount of [MMPPA][HSO_4] catalyst, the acetylation was greatly accelerated. When 1 mol% of the catalyst was employed, the acetylation of benzyl alcohol with acetic anhydride was completed in 99% yield at room temperature (25 °C) under solvent-free conditions (Scheme 1).

On the basis of these results, we examined the acetylation of various alcohols and phenols with acetic anhydride using [MMPPA][HSO_4] as catalyst, and the results are summarized in Table 2**.** Good yields were obtained for a variety of primary, secondary, tertiary, cyclic, benzylic alcohols, and substituted phenols. Primary alcohols were acetylated faster than secondary and tertiary alcohols (entries 1, 4, and 5, Table 2). Furthermore, with the increasing of the length of alkyl chain of primary alcohols and the reaction time, the yields of acetylated products were decreased smoothly (entries 1, 2, and 3, Table 2). It was very interesting to note that tertiary alcohols such as *tert*-butyl alcohol can also be acetylated in 64% yield and there was no elimination product in the mixture through GC (entry 5, Table 2). Under similar conditions, the efficacy of the catalyst can be clearly visualized in the acetylation of diols and triols (entries 6 and 7, Table 2).

Table 1 Acetylation of benzyl alcohol with acetic anhydride catalyzed by Brønsted acidic ionic liquids at room temperature (25 °C) under solvent-free conditions

Entry	Catalyst	Time (min)	Yield[a] (%)
1	None	30	0
2	[MMPPA][BF_4]	2	78
3	[MMPPA][CF_3COO]	2	75
4	[MMPPA][HSO_4]	2	99

[a] Isolated yield of the acetylated product



Scheme 1

The structural properties of phenols were examined carefully and the results showed that the reactions were affected by electronic and steric factors. Table 2 shows that phenols with electron-donating groups were converted to the corresponding phenyl acetates in higher yields and shorter reaction time than those with electron-withdrawing groups. Furthermore the selectivity in the acetylation of diols was also high, as examined through HPLC.

The stability and reusability of the Brønsted acidic ionic liquid [MMPPA][HSO_4] were investigated in the acetylation of benzyl alcohol with acetic anhydride as a model reaction. The results listed in Table 3 show that [MMPPA][HSO_4] could be reused for four times without a noticeable decrease in the catalytic activity. Furthermore, no changes in the selectivity were observed. Comparing the IR spectra of the reused ionic liquid with that of fresh ionic liquid, small differences were observed. These results demonstrated that the structure of the catalyst did not change.

In conclusion, it was demonstrated that [MMPPA][HSO_4] was a highly efficient, chemoselective, and reusable catalyst for acetylation of alcohols and phenols with acetic anhydride under solvent-free conditions at room temperature. In terms of environmental and economical factors, [MMPPA][HSO_4] is also a promising alternative to the traditional catalysts. Therefore, we believe that the new synthesis method reported here would contribute greatly to

Table 2 Acetylation of alcohols and phenols with acetic anhydride catalyzed by [MMPPA][HSO_4] under solvent-free conditions

Entry	Substrate	Product	Mole ratio (substrate/acetic anhydride)	Time (min)	Yield[a] (%)
1	*n*-BuOH	*n*-BuOAc	1:1.1	2	99
2	*n*-PentOH	*n*-PentOAc	1:1.1	3	98
3	*n*-OctOH	*n*-OctOAc	1:1.1	5	96
4	*i*-BuOH	*i*-BuOAc	1:1.1	5	94
5	*t*-BuOH	*t*-BuOAc	1:1.1	8	64
6	$HO(CH_2)_2OH$	$AcO(CH_2)_2OAc$	1:2.2	10	97[b]
7	$HOCH_2(CHOH)CH_2OH$	$AcOCH_2(CHOAc)CH_2OAc$	1:3.3	5	95[c]
8	$PhCH_2OH$	$PhCH_2OAc$	1:1.1	2	99
9	Cyclohexanol	Cyclohexyl acetate	1:1.1	5	95
10	PhOH	PhOAc	1:1.5	2	96
11	*o*-Methyl-PhOH	*o*-Methyl-PhOAc	1:1.5	3	95
12	*m*-Methyl-PhOH	*m*-Methyl-PhOAc	1:1.5	2	97
13	*p*-Methyl-PhOH	*p*-Methyl-PhOAc	1:1.5	3	99
14	*p*-Methoxy-PhOH	*p*-Methoxy-PhOAc	1:1.5	2	99
15	*p*-Nitro-PhOH	*p*-Nitro-PhOAc	1:1.5	10	95
16	*o*-Hydroxy-PhOH	*o*-Acetoxyl-PhOAc	1:4.0	3	97[b]
17	*m*-Hydroxy-PhOH	*m*-Acetoxyl-PhOAc	1:4.0	5	97[b]
18	*p*-Hydroxy-PhOH	*p*-Acetoxyl-PhOAc	1:4.0	5	98[b]

[a] Yields of the corresponding acetylated products refer to isolated yields. All products were identified by their ^1H NMR spectra and/or by comparison of their b.p. with authentic samples [29–33]

[b] Yield of the diacetate

[c] Yield of the triacetate

Table 3 Catalyst recycling of ionic liquid for acetylation of benzyl alcohol with acetic anhydride

Entry	Catalyst	Time (min)	Yield (%)
1	Fresh	2	99
2	First recycle	2	98
3	Second recycle	2	95
4	Third recycle	2	96
5	Fourth recycle	2	95

Reaction conditions: benzyl alcohol/acetic anhydride 1:1.1 (molar ratio), ionic liquid [MMPPA][HSO_4] (1%), 25 °C

environmentally greener methodology and be suitable for industrial applications.

Experimental

^1H NMR was measured on a Bruker DRX (300 or 500 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. The IR spectra were run on a Nicolet spectrometer. HPLC (Waters 2487, mobile phase CH_3OH/H_2O = 50:50, column 4.6 × 250 mm, detection at 254 nm) and GC were used to analyze the purity of products of acetylation. All yields refer to isolated products after chromatographic purification. All chemicals (AR grade) were commercially available. Acetic anhydride was distilled before use. The Brønsted acidic ionic liquids [MMPPA][HSO_4], [MMPPA][TFA], and [MMPPA][BF_4] were prepared according to Refs. [27, 28].

Typical procedure for acetylation of alcohols or phenols with acetic anhydride

To a mixture of 32 mg [MMPPA][HSO_4] (0.1 mmol) and 1,120 mg acetic anhydride (11 mmol) was added 10 mmol alcohol or phenol and the resulting mixture was stirred under dry N_2 atmosphere at room temperature for 2 h. Completion of the reaction was monitored by TLC (eluent: petroleum ether/ethyl acetate = 4:1). After the reaction, 5 cm^3 water was added, and the (upper) organic phase was washed with 10% aqueous solution of sodium bicarbonate (3 × 5 cm^3), dried, filtered, and purified by silica chromatography (eluent: petroleum ether/ethyl acetate = 4:1). The ionic liquid was recovered by concentrating the (bottom) water phase to remove acetic acid and water and reused in the next reaction.

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