Research Article

Silica Sulfuric Acid: An Eco-Friendly and Reusable Catalyst for Synthesis of Benzimidazole Derivatives

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Silica sulfuric acid ($\text{SiO}_2\text{-OSO}_3\text{H}$) as an eco-friendly, readily available, and reusable catalyst is applied to benzimidazole derivatives synthesis under reflux in ethanol. The procedure is very simple and the products are isolated with an easy workup in good-to-excellent yields.

1. Introduction

Benzimidazole derivatives are found in many biologically active compounds possessing antiviral, antihypertension, and anticancer properties [1, 2]. Compounds possessing the benzimidazole moiety exhibit significant activity against several viruses such as HIV [3, 4], herpes (HSV-1) [5], RNA [6], influenza [7], and human cytomegalovirus (HCMV) [3, 4]. Specifically, the 2-substituted analogs of benzimidazoles are known to be potent biologically active compounds [8]. There are several methods for benzimidazole synthesis; these compounds are conventionally prepared using condensation of *o*-phenylenediamine with carbonyl compounds in the presence of strong acids such as $\text{Me}_2\text{S}^+\text{BrBr}^{-7}$, P-TsOH [9], Alumina-methanesulfonic acid [10], $\text{BF}_3\cdot\text{OEt}_2$ [11], ceric(IV) ammonium nitrate [12]. However, many of the synthetic protocols reported so far suffer from disadvantages, such as a requirement for anhydrous conditions, use of organic solvents, harsh reaction conditions, expensive reagents, and low-to-moderate yields. Therefore, the development of a simple, mild, and efficient method is still needed.

Solid supported reagents have improved activity and selectivity than individual reagents, because the surface area of the reagent is increased manifold [14].

Silica sulfuric acid ($\text{SiO}_2\text{-OSO}_3\text{H}$), a solid acid, is a versatile catalyst that makes reaction processes more convenient, more economic, and environmentally benign. Owing

to the numerous advantages associated with this cheap and nonhazardous catalyst, under mild conditions, silica sulfuric acid has been explored as a powerful catalyst for various organic transformations [15, 16]. This solid acid has also been used in synthesis of oxazolines and imidazolines [17], synthesis of 2,3-dihydroquinazolin-4(1H)-ones [18], synthesis of substituted pyrroles [19], chemoselective detritylation of 5'-tritylated nucleosides [20], and deprotection of oxime to carbonyls [21]. In this paper, we wish to report an efficient and versatile procedure for the synthesis of 2-substituted benzimidazole derivatives in the presence of silica sulfuric acid.

We now wish to describe our efforts towards the synthesis of 2-substituted benzimidazole derivatives in the presence of solid acid catalyst see Scheme 1.

2. Experimental

The products were known and were characterized by IR and NMR and by comparing their physical properties with those reported in the literature. IR spectra were run on a Shimadzu IR-470 spectrometer. NMR was obtained using a Bruker Avans 400 MHz spectrometer. Melting points were determined with a Barnstead Electrothermal melting point apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer.

TABLE 1: Acid-catalyzed synthesis of 2-(phenyl)benzimidazole.

Entry	Catalyst	Condition/solvent	Time (min)/isolated yield (%)	Ref.
1	Me ₂ S ⁺ BrBr ⁻ (0.5 mmol) ^a	r.t./MeCN	10/85	[13]
2	P-TsOH (20 mol%) ^a	80°C/DMF	10/85	[9]
3	Alumina-methanesulfonic acid (0.33 g/0.39 g) ^b	MW	10/96	[10]
4	BF ₃ ·OEt ₂ (0.1 mmol) ^a	r.t./CH ₂ Cl ₂	30/90	[11]
5	Ceric(IV) ammonium nitrate ^a	Reflux/CH ₂ Cl ₂	45/75	[12]
6	SiO ₂ -OSO ₃ H (0.1 g)	80°C/EtOH	20/91	—
7	SiO ₂ -OSO ₃ H (0.1 g)	25°C/EtOH	60/30	—
8	SiO ₂ -OSO ₃ H (0.1 g)	45°C/—	30/65	—
9	SiO ₂ -OSO ₃ H (0.05 g)	80°C/EtOH	20/82	—
10	SiO ₂ -OSO ₃ H (0.15 g)	80°C/EtOH	20/92	—
11	SiO ₂ -OSO ₃ H (0.1 g) 2nd run	80°C/EtOH	20/85	—
12	SiO ₂ -OSO ₃ H (0.1 g) 3rd run	80°C/EtOH	20/82	—

SCHEME 1: Synthesis of benzimidazoles (4) using aldehydes (2) or benzonitriles (3) and *o*-phenylenediamine (1) in the presence of SiO₂-OSO₃H.

Benzonitrile or aldehyde (1 mmol), *o*-phenylenediamine (1 mmol), and ethanol in the presence of SiO₂-OSO₃H (0.1 g) were placed in a round bottom flask. The materials were mixed and heated at reflux for 20 min. The progress of the reaction was followed by TLC (3 : 1:n-hexane:ethylacetate). After the completion of the reaction, the mixture was filtered to remove the catalyst. By evaporation of the solvent, the crude product was recrystallized from hot aq. ethanol to obtain the pure compound. All products are known and were identified by comparison of their physical or spectral data with those of authentic samples.

3. Results and Discussion

In continuation of our investigation about application of solid acids in organic synthesis [22, 23], we herein report a simple and efficient protocol for benzimidazole synthesis using a cheap and readily available SiO₂-OSO₃H catalyst. The efficiency of this acid is comparable with some other catalysts such as Me₂S⁺BrBr⁻, P-TsOH, alumina-methanesulfonic acid, and BF₃·OEt₂. Most of these methods have limitations such as organic solvents, fuming catalyst, and harsh reaction condition. To optimize the catalytic system, the synthesis of 2-(phenyl)benzimidazole was used as a model reaction. The catalytic activity and efficiency of this method can be influenced by various parameters such as the employed catalyst, catalyst amount, and temperature.

Silica sulfuric acid, owing to the numerous advantages such as solid acid, nonhazardous, and available was selected for this protocol.

It is worthwhile to mention that the minimum amount of the catalyst was optimized to be 0.1 g.

The effect of temperature was studied by carrying out the model reaction in the presence of silica sulfuric acid (0.1 g) in ethanol (10 mL) and solvent-free at different temperatures (room temperature, 45 and 80°C). It was observed (Table 1, entries 6, 7, and 8) that the yield was increased as the reaction temperature was raised. From these results, 80°C is selected as the best temperature for all future studies.

The reusability of the SiO₂-OSO₃H catalyst was also examined. After each run, CHCl₃ was added and the product was filtered, the solvent evaporated and the residue (catalyst) was washed with CHCl₃ and reused. Apparently, treatment with CHCl₃ removes tars more efficiently from the catalyst surface (Table 1, entries 11 and 12). This catalyst was reusable, although a gradual decline in activity was observed.

TABLE 2: Synthesis of benzimidazoles catalyzed by silica sulfuric acid^a.

Entry	R ¹	R ²	Product ^b	Yield/% ^c	M.P./°C	Ref.
1	C ₆ H ₅ 2a	—	4a	91	289–291	[9]
2	4-ClC ₆ H ₄ 2b	—	4b	87	288–291	[9]
3	2-ClC ₆ H ₄ 2c	—	4c	89	230–231	[9]
4	4-CH ₃ C ₆ H ₄ 2d	—	4d	82	262–264	[9]
5	2-OMeC ₆ H ₄ 2e	—	4e	84	224–227	[10]
6	3,4-OMeC ₆ H ₃ 2f	—	4f	80	228–230	[13]
7	3-NO ₂ C ₆ H ₄ 2g	—	4g	85	202–204	[9]
8	4-NO ₂ C ₆ H ₄ 2h	—	4h	86	308–310	[9]
9	CH ₃ CH ₂ 2i	—	4i	74	172–174	[10]
10	4-OMeC ₆ H ₄ 2j	—	4j	89	224–226	[12]
11	C ₆ H ₅ CH=CH 2k	—	4k	90	199–202	[11]
12	C ₄ H ₃ S 2l	—	4l	78	327–329	[12]
13	C ₅ H ₄ N 2m	—	4m	81	218–220	[12]
14	—	4-BrC ₆ H ₄ 3a	4n	86	283–285	[10]

TABLE 2: Continued.

Entry	R ¹	R ²	Product ^b	Yield/% ^c	M.P./°C	Ref.
15	—	C ₆ H ₅ 3b	4a	85	289–291	[9]
16	—	4-NH ₂ C ₆ H ₄ 3c	4o	82	202–204	[10]

^a Molar ratio of aldehyde or benzonitrile: 2-amino aniline: SiO₂-OSO₃H(g) was 1: 1: 0.1. ^b Isolated yield. ^c All products are known and were identified by their melting points, IR, ¹H NMR, and ¹³C NMR spectra.

We also tried to use benzonitrile instead of benzaldehyde in the model reaction (Table 2, entry 15). We can mention fortunately, that our attempts to carry out the reaction in the presence of benzonitrile were successful.

To show the generality of this method, the optimized conditions used for the synthesis of other benzimidazoles and all results are summarized in Table 2. As shown in Table 2, this method is effective for the preparation of benzimidazoles from both benzonitrile derivatives as well as benzaldehydes.

The work-up procedure of this reaction is very simple. After completion of reaction the mixture was filtered off to separate the catalyst and then the solvent was evaporated to dryness under reduced pressure. The pure products were obtained by recrystallization from a mixture of ethanol and water.

4. Conclusion

In summary, silica sulfuric acid is an efficient catalyst for the synthesis of benzimidazoles. In addition, as a water stable solid acid, reusable, and green catalyst, the handling of this catalyst is easy, it makes this catalyst suitable for the large-scale operation. The reaction appears to be heterogeneously catalyzed. High yields, relatively short reaction times, simplicity of operation, and easy work-up procedure are some other advantages of this protocol.

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