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Short communication

Silica sulfuric acid as an efficient and recoverable catalyst for the synthesis of trisubstituted imidazoles

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Abstract

Trisubstituted imidazoles have been synthesized in high yields in the presence of silica sulfuric acid as a catalyst. The reaction is carried out in water, a very green solvent, under reflux conditions. The reaction work-up is simple and the catalyst is easily separated from the products by filtration.

Keywords: Imidazole; Silica sulfuric acid; One-pot condensation reaction; Solid acid catalyst; Water

1. Introduction

Multi-substituted imidazoles, an important class of pharmaceutical compounds, exhibit a wide spectrum of biological activity [1]. Because of this, numerous classical methods for their synthesis have been reported [2–7]. In these procedures, a 1,2-diketone, an aldehyde and ammonium acetate are condensed in the presence of a strong protic acid (such as H_3PO_4 [8], H_2SO_4 [9] and HOAc [10]) or other catalysts in HOAc [4], under reflux conditions. Isolation of the product is then achieved by neutralization of the reaction mixture. The solvent used for these syntheses has usually been a polar organic solvent, such as ethanol, methanol, acetic acid, DMF or DMSO, with the result that the isolation and recovery procedures are complicated. These processes also generate significant wastes containing catalysts, which have to be recovered, treated and disposed of in environmentally acceptable ways.

Recently, one-pot condensations of an aldehyde and ammonium acetate with an α-hydroxy ketone, an α-keto-oxime and a 1,2-diketone have been achieved by using solid supports under microwave irradiation [11–14]. Despite their potential utility, most of these methods are not environmentally friendly. They require a high temperature (180–200 °C), created by microwave irradiation, and the use of a solid support.

One important aspect of clean technology is the use of environmentally friendly catalysts—typically a solid catalyst that can be easily recovered when the reaction is complete. Employing such an approach results in minimal pollution and waste material production. The application of such catalysts to fine chemical manufacturing is likely to be increasingly important in the future.

The acidic sites of solid acids are usually poisoned by water. In fact, most solid acids loose their catalytic activities in aqueous solutions. Therefore, development of new water-tolerant solid acid catalysts could have a major impact in industrial applications.

During the course of our studies on the development of new routes for the syntheses of highly substituted hetrocycles using solid acid catalysts [15] in aqueous solutions [16], we have discovered an efficient and environmentally benign procedure for the preparation of substituted imidazoles. Herein we describe the synthesis of trisubstituted imidazoles by the one-pot condensation of benzil (**1**), benzoin (**2**) or benzylmonoxime (**3**) with a substituted benzaldehyde (**4**) and ammonium acetate in the presence of silica sulfuric acid (SSA) [17], as in Scheme 1, where the solvent is water.

2. Results and discussion

The results obtained form the silica sulfuric acid catalyzed synthesis of trisubstituted imidazoles are given in Table 1. These results were obtained by stirring a mixture of aldehyde

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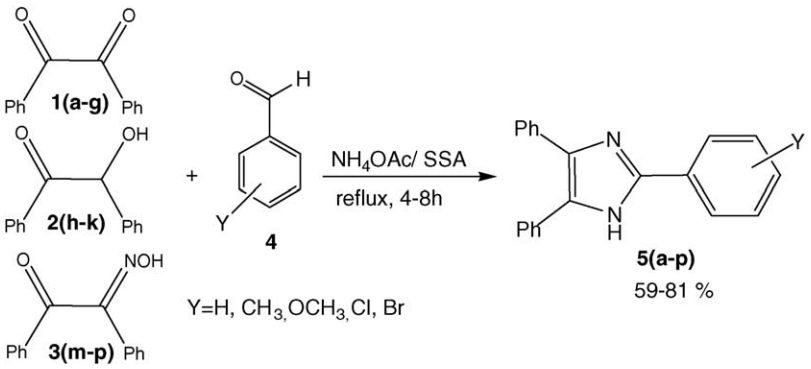

Scheme 1.

(1 mmol), benzil, benzoin or benzilmonoxime (1 mmol), ammonium acetate (6 mmol) and silica sulfuric acid (0.5 g) under reflux in water (30 ml) for 4–8 h. After completion of the reaction, the mixture was cooled to room temperature. The solid materials were filtered off and washed with cold water. Then, the product was separated from the catalyst by washing with acetone. After evaporating the solvent, pure product was obtained.

To illustrate the need of catalysts for these reactions, experiments were conducted in which the reaction of *p*-methylbenzaldehyde and NH_4OAc with benzil, benzoin or benzilmonoxime was studied in the absence of silica sulfuric acid. The yield of product with benzil was only 10%, while no reaction occurred with the other two reactants, even after 24 h. Obviously, the catalyst is an essential component of the reaction.

To explore the scope and limitations of this reaction, we studied the reactions of benzil, benzoin and benzilmonoxime with benzaldehydes bearing either electron-releasing or electron-withdrawing substituents in the *ortho*, *meta* or *para* positions. The reaction proceeded very efficiently in all cases, except with 4-nitrobenzaldehyde. No reaction took place when the aldehyde had this very electron-withdrawing substituent.

As indicated in Table 1, we have repeated the reaction numerous times with good success each time. In fact, we observed that the catalyst can be recycled and reused at least four times (entry **5b**).

In conclusion, we have been able to introduce an efficient and environmentally friendly approach for the synthesis of biologically active trisubstituted imidazoles via condensation of a representative 1,2-diketone, α-hydroxyketone and α-ketooxime with various aromatic aldehydes and ammonium acetate, using SSA as a recyclable solid acid catalyst in water. The reactions are characterized by non-corrosiveness, safety, low waste, ease of separation and high yields. Replacement of liquid acids (that were often used for these reaction in the past) with a solid acid catalyst is a desirable feature of the reactions that may be important for their industrial manufacture. It is a green chemistry approach to the preparation of these compounds.

Table 1
One-pot synthesis of trisubstituted imidazoles in water in the presence of silica sulfuric acid as a solid acid catalyst

Entry	Y	Time (h)	Yield (%)	mp (°C)	
				Found	Reported
5a	4-H	4	73	>300	–
5b	4-CH_3	4	81 (79, 75, 74, 68)[a]	226–228	232–235[b]
5c	4-OCH_3	4.5	71	228–231	230–232[c]
5d	4-Cl	5	69	259–261	262–264[c]
5e	4-Br	4.5	72	252–254	261.5–263.5[c]
5f	2-Me	5	69	198–202	205–207[c]
5g	3-Cl	5	64	282–286	285–287[c]
5h	4-H	6	71	>300	–
5i	4-CH_3	4	76	227–229	232–235[b]
5j	4-OCH_3	6	69	226–230	230–232[c]
5k	4-Cl	6.5	65	256–258	262–264[c]
5l	3-Cl	8	59	280–283	285–287[c]
5m	4-H	4	72	>300	–
5n	4-CH_3	4	78	226–229	232–235[b]
5o	4-OCH_3	4.5	71	228–230	230–232[c]
5p	4-Cl	4.15	70	257–260	262–264[c]

[a] The same catalyst was used for each of the four runs.
[b] Ref. [1].
[c] Ref. [18].

3. Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. NMR spectra were obtained in DMSO-d_6 solutions.

In a typical procedure, a mixture of ammonium acetate (0.462 g, 6 mmol), silica sulfuric acid (0.5 g), 4-methylbenzaldehyde (0.122 ml, 1 mmol) and benzil, benzoin or benzilmonoxime (1 mmol) was refluxed in water (30 ml) with stirring for 4 h. After cooling, the reaction mixture was filtrated and washed with cold water. The solid residue was then washed with acetone and the solvent evaporated to give crude product. For further purification this product was crystallized from a 9:1 acetone–water solution. Pure products were obtained in good yields, as summarized in Table 1.

All the products are known compounds; they were characterized by IR, ^{1}H NMR and mass spectral data. All melting points compared satisfactorily with those reported in the literature.

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