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Research Paper

Synthesis of 2,4,5-Triaryl-1*H*-imidazoles Using Silica Sulfuric Acid is an Inexpensive, Efficient and Mild Catalyst Under Microwave Irradiation

Chemistry

KEYWORDS : Benzil, aldehydes, silica sulphuric acid, 2,4,5-triaryl-1H-imidazoles, microwave

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ABSTRACT

Silica sulphuric acid was found to be an efficient catalyst for the green synthesis of 2,4,5-Triaryl-1H-Imidazoles by the coupling of Benzil/Benzoin, aldehyde and ammonium acetate under microwave-irradiation at ambient temperature for appropriate time to furnish the desired product in good to excellent yield. The catalyst provides clean conversion; greater selectivity and easy workup make this protocol practical and economically attractive.

Imidazole derivatives are a very interesting class of heterocyclic compounds because they are found in many natural products and pharmacologically active compounds such as antiulcerative agent cimetidine[1], the proton pump inhibitor omeprazole[2] and the benzodiazepine antagonist flumazenil[3] are imidazole derivatives. Many of the substituted imidazoles are known as inhibitors of p38 MAP kinase, fungicides, herbicides, plant growth regulators and therapeutic agents[4–7].

Owing to the wide range of pharmacological and biological activities, the synthesis of imidazoles has become an important target in current years. Methods for the synthesis of imidazoles include a four-component condensation using Wang's in refluxing acetic acid[8], condensation of 1,2-diketones, aldehydes, primary amines and ammonium acetate in phosphoric acid[9], acetic acid[10], using an organocatalyst in acetic acid[11], as well as in H_2SO_4[12] and dimethyl sulfoxide (DMSO)[13].

The three component condensation of benzil/benzoin, aldehydes and ammonium acetate in a variety of catalysts, such as ionic liquid[14], iodine[15], zeolite HY/silica gel[16], $ZrCl_4$[17], acidic Al_2O_3[18], AcOH[19], NH_4OAc[20], $Yb(OTf)_3$[21], scolecite[22], PEG-400[23], L-proline[24], boric acid[25] and CAN[26]. However many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields, use of hazardous and expensive catalysts. So the development of clean, high-yielding and environmentally friendly approaches is still desirable and much in demand.

The use of a catalyst has significant practical advantages since it is inexpensive and nontoxic. In particular, the chemistry of organic synthesis has recently received increasing attention over its companion reagents owing to its stability in water and air actively utilized as a catalyst for various types of organic syntheses[27-30]. In addition, the growing concern for the influence of the chemical reagents on the environment as well as on human body, recovery and reusability of the chemical reagents have attracted the attention of synthetic organic chemists. Notably pharmaceutical industry has given more importance toward recovery and reuse of chemical reagents to reduce the cost of a product as well as the environmental burden. As part of continuing effort in our laboratory[31-34] toward the development of new methods in organic synthesis.

The application of microwaves (MWs), as an efficient heating source for organic reactions and it has been reported in the literature[35]. The main advantages of MW irradiation usage were: very short reaction time and the solvent less procedures which are eco-friendly[36,37]. To the best of our knowledge MW irradiation has been mostly reported as a heating technique particularly for low molecular weight compound chemical modifications.

Experimental:

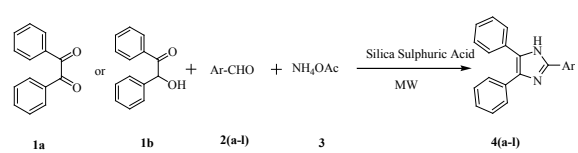
Melting points were determined in open capillaries in a paraffin bath and are uncorrected. IR spectra were recorded on a Bruker spectrophotometer using KBr discs, and the absorption bands are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are expressed in Hertz (Hz). Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES).

A typical experimental procedure

A mixture of aldehydes **2** (1 mmol), Benzil **1a** or Benzion **1b**, (1 mmol) and ammonium acetate **3** (1.5 mmol) and silica sulphuric acid (10 mol%) in acetonitrile (500 ml) was irradiated under microwave irradiation for an appropriate time. The reaction progress was monitored by TLC (EtOAc:Hexane, 10-25% mixture in Hexane) and HPLC, respectively. After complete conversion the heterogeneous mass was filtered and the catalyst was washed with acetonitrile. The solid was filtered and dried in an oven in vacuum to afford the pure product (Yield: 94%).

Results & Discussion

In continuation of our research work of developing methods in various organic transformations[38-42], we have developed a methodology for the synthesis of 2,4,5-triaryl-1*H*-imidazoles using silica sulphuric acid, which makes use of mild catalyst under microwave-irradiation.



The reaction of benzil **1a** benzaldehyde **2a** and ammonium acetate **3** using 10 mol% silica sulphuric acid under microwave-irradiation, has been considered as a standard model reaction.

Initially, we have screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of Indion 130, p-TsOH, Dowex 50, Sulphamic acid, amberlyst 15, under microwave-irradiation it gave lower yield of product even after prolonged reaction time. However, when the same reaction was conducted under microwave-irradiation using silica sulphuric acid as a catalyst it gave excellent yields of product in short reaction time (Table 1, entry 5).

After optimizing the conditions, we have carried out the same cyclocondensation reaction with various aromatic/heteroaromatic aldehydes containing electron donating or electron withdrawing functional groups at different positions worked well and did not show remarkable differences in the yields of product and reaction time and the results are shown in Table 2. Under similar reaction conditions, we have carried out the cyclocondensation of benzoin **1b** with aromatic/heteroaromatic aldehydes and ammonium acetate in presence of silica sulphu-

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ric acid, resulted into the corresponding triaryl imidazoles in good yields but the reaction requires more time as compared to benzil (Table 2). The formation of triaryl imidazoles have been confirmed by physical and spectroscopic data and is in full agreement with reported data. Also, the present method was found to be effective for benzil compared to benzoin in terms of time and yield.

Our attention was then directed towards the possibility of recycling the reaction media since the recovery and reuse of catalyst is highly preferable for greener process. The recyclability of the catalyst in the model reaction was checked as shown in (Table 3). The separated catalyst can be reused after washing with acetonitrile and drying at 110ºC. The catalyst was removed in excellent yields and catalyst was used in mentioned reaction for five times it shows the same activity such as fresh catalyst without any loss of its activity.

Conclusions

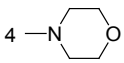
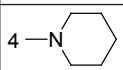
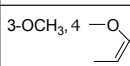
In conclusion, we have demonstrated that silica sulphuric acid is an excellent catalyst for the synthesis of 2,4,5-Triaryl-1*H*-Imidazoles. The catalyst has high activity and can be handling very easily in large scale synthesis. The procedure has the advantages of mild reaction conditions, higher yield of the products, short reaction time & ease of product isolation. We believe that this method is a useful addition to the present methodology for the synthesis of 2,4,5-Triaryl-1*H*-Imidazoles.

Table 1. Screening of catalysts on the model reaction[a]

Entry	Catalysts	Time (min)	Yield[b] (%)
1	Indion 130	15	64
2	p-TsOH	15	55
3	Dowex 50	15	68
4	Sulphamic acid	15	47
5	Amberlyst-15	15	71
6	Silica Sulphuric acid	15	94

[a]Reaction of benzil, benzaldehyde and ammonium acetate in presence of silica sulphuric acid under microwave-irradiation. [b]Isolated yield.

Table 2. Synthesis of 2,4,5-Triaryl-1*H*-Imidazoles 4(a-l) Using silica sulphuric acid as a catalyst[a]

Entry	Comp	R	1	Time (min)	Yield (%)[b]	m.p (ºC)
1	4a	H	Benzil	15	94	276-278
2	4b	4-Cl	Benzil	20	92	261-263
3	4c	2-Cl	Benzil	17	90	195-196
2	4d	4-OMe	Benzil	18	94	227-229
5	4e	4-NO_2	Benzil	20	89	230-232
6	4f	4-F	Benzil	18	94	188-189
7	4g	2-Thienyl	Benzil	20	89	261-262
8	4h	2-Furyl	Benzil	22	92	198-200
9	4i	4-OH	Benzil	17	88	270-272
10	4j		Benzil	28	75	280-282
11	4k		Benzil	30	79	271-273
12	4l		Benzil	27	70	291-293
13	4a	H	Benzoin	35	90	_
14	4b	4-Cl	Benzoin	32	89	_
15	4h	2-Furyl	Benzoin	34	87	_
16	4d	4-OMe	Benzoin	34	88	_
17	4g	2-Thienyl	Benzoin	35	85	_

[a]Reaction conditions: benzil/benzoin (1 mmol), aldehydes (1 mmol), ammonium acetate (1.5 mmol), Silica sulphuric acid (10 mol%)under microwave irradition. [c]Isolated yields.

Table 3: Recyclability of catalyst for the synthesis of (4a)

Cycle	Fresh	First	Second	Third	Fourth
Yield (%)[a]	94	93	93	90	89

[a]Isolated Yields

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