

Kaolin-SO₃H as an efficient catalyst for one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles

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ABSTRACT

Kaolin-SO₃H as a new solid acid is prepared via reaction of kaolin and chlorosulfonic acid. This natural based catalyst is very inexpensive and easy available. A simple, highly versatile and efficient synthesis of 1,2,4,5-tetrasubstituted imidazoles is achieved using Kaolin-SO₃H as a catalyst at moderate temperature under solvent-free condition. The key advantages of this process are high yields with simple work-up using easy available inexpensive natural based catalyst.

Keywords: 1,2,4,5-tetrasubstituted imidazoles; Kaolin-SO₃H; Benzil; One-pot synthesis; Solvent-free conditions.

1. Introduction

Multicomponent reactions (MCRs) are one-pot processes bringing together three or more components and show high atom economy and selectivity [1]. Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes [2] such as anti-allergic [3], anti-inflammatory [4], analgesic, antifungal, antimycotic, antibiotic, antiulcerative, antibacterial and antitumor [5]. In addition, many of the substituted diarylimidazoles are known as potential inhibitors of the p38 MAP kinase [6]. Appropriately substituted imidazoles are extensively used as glucagon receptors [7] and CB1 cannabinoid receptor antagonists [8], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) [9] and antitumor [10] agents. The synthesis of 1,2,4,5-tetrasubstituted imidazoles have been carried out by four-component condensation of a 1,2-diketone, α -hydroxyketone or α -ketomonoxime with an aldehyde, primary amine and ammonium acetate using microwaves [11], heteropolyacid [12], BF₃·SiO₂ [13], silica gel/NaHSO₄ [14], HClO₄-SiO₂ [15], I₂ [16], K₅CoW₁₂O₄₀·3H₂O

[17], InCl₃·3H₂O [18], ZrCl₄ [19], DABCO [20], PEG-400 [21], silica-bonded propylpiperazine N-sulfamic acid (SBPPSA) [22], ionic liquids [23] and SBA-Pr-SO₃H [24].

In addition, they can also be synthesized by the cycloaddition reaction of mesoionic 1,3-oxazolium-5-olates with *N*-(arylmethylene)benzenesulfonamides [25], hetero-cope rearrangement [26], condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation [27]. Kaolinite (hydrated aluminum silicate) is a clay mineral, with chemical composition Al₂Si₂O₅(OH)₄. It is a layered silicate mineral, with one tetrahedral sheet linked through oxygen atoms to one octahedral sheet of alumina octahedral. Rocks that are rich in kaolinite are known as kaolin or china clay. Kaolin has been used commercially and medicinally for hundreds of years. It is currently found in the manufacture of pottery, bricks, cement, plastering material, color lakes (insoluble dyes) and insulators.

As a raw material, it is commonly found in paper, plastics, cosmetics and pharmaceuticals and it is also used in pharmaceutical preparations as a filtering agent to clarify liquids. Kaolin-SO₃H as a new solid acid was prepared via reaction of kaolin and chlorosulfonic acid. It could be an efficient solid acid catalyst for promotion of many organic reactions. In continuation of our previous works in application of heterogeneous catalysts in organic synthesis [28-30], in this work we

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have achieved 1,2,4,5-tetrasubstituted imidazoles from aromatic aldehydes, benzil, an amine and ammonium acetate in the presence of catalytic amount of kaolin-SO₃H in good to excellent yields.

2. Experimental

2.1. General

Chemicals were purchased from Sigma–Aldrich and Merck chemical companies and were used without any purification. All products were characterized by their FT-IR (ATR, attenuated total reflection), ¹HNMR and comparison of their physical properties with those reported in the literature. FT-IR (ATR) spectra were recorded on a Bruker, Eqinox 55 spectrometer. In all cases, the ¹HNMR spectra were recorded on a Bruker DRX-400 instrument. Melting points were determined by a Büchi melting point B-540 B.V.CHI apparatus. The X-ray diffraction (XRD) patterns of materials were prepared by employing a Philips Xpert MPD diffractometer equipped with a Cu K α anode ($\lambda=1.54 \text{ \AA}$) in the 2θ range from 5 to 80°. The thermal gravimetric analysis (TGA) was done with “NETZSCH TG 209 F1 Iris” instrument.

2.2. Preparation of Kaolin-SO₃H

In a ventilated cabinet, a 100 ml suction flask containing 20 g of commercial Kaolin was equipped with a dropping funnel containing 10 ml of chlorosulfonic acid. A gas inlet tube was equipped for conducting of obtained HCl gas over a water vessel. Then, 50 ml of chloroform was added to suction flask and chlorosulfonic acid was added drop wise to mixture with variously mixing at room temperature till obtain a white solid. The solid was filtered and washed with chloroform and dried at room temperature. The kaolin-SO₃H was obtained with 90 % yield.

2.3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles (general procedure)

Benzil (1 mmol), amine (2 mmol), aldehyde (1.5 mmol), ammonium acetate (2 mmol) and Kaolin-SO₃H (0.05 g) were placed in a round bottom flask. The obtained mixture was stirred at 110 °C for 2.5 hours. The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature, dissolved in dichloromethane and filtered to separation of catalyst. A solid product was appeared by evaporation of filtrate solvent. The product was re-crystallized in hot ethanol. All the products were known and were identified by comparison of their physical and spectral data with those of authentic samples (Scheme 1).

Selected spectral data

Table 2, entry 2:

FT-IR (KBr): $\bar{\nu} = 3020, 1598, 1490-1435 \text{ cm}^{-1}$.
¹HNMR (400 MHz, CDCl₃): $\delta = 5.13$ (s, 2H), 6.82 (s br, 2H), 7.18-7.20 (m, 4H), 7.35-7.37 (m, 4H), 7.40-7.41 (m, 4H), 7.60 (d, $J = 8 \text{ Hz}$, 2H), 7.67-7.69 (m, 4H) ppm.

Table 2, entry 3:

FT-IR (KBr): $\bar{\nu} = 3053-2852, 1599, 1498-1440 \text{ cm}^{-1}$.
¹HNMR (400 MHz, CDCl₃): $\delta = 0.8$ (q br, $J = 12 \text{ Hz}$, 1H), 1.1 (q br, $J = 12 \text{ Hz}$, 2H), 1.60-1.62 (m, 6H), 1.9 (d br, $J = 12 \text{ Hz}$, 4.00 (t br, $J = 12 \text{ Hz}$, 1H), 7.10-7.11 (m, 3H), 7.45-7.48 (m, 10H), 7.65-7.67 (m, 2H) ppm.

Table 2, entry 4:

FT-IR (KBr): $\bar{\nu} = 1597, 1495-1410 \text{ cm}^{-1}$. ¹HNMR (400 MHz, CDCl₃): $\delta = 6.85$ (d br, $J = 6 \text{ Hz}$, 2H), 6.95 (d br, $J = 6 \text{ Hz}$, 2H), 7.05-7.09 (m, 11H), 7.20 (d, $J = 6 \text{ Hz}$, 2H), 7.41 (d, $J = 6 \text{ Hz}$, 2H) ppm.

Table 2, entry 5:

FT-IR (KBr): $\bar{\nu} = 3100-2900, 1601, 1497-1448 \text{ cm}^{-1}$.
¹HNMR (400 MHz, CDCl₃): $\delta = 5.11$ (s, 2H), 6.80-6.81 (m, 2H), 7.25-7.27 (m, 7H), 7.41-7.43 (m, 6H), 7.60-7.62 (m, 4H) ppm.

Table 2, entry 11:

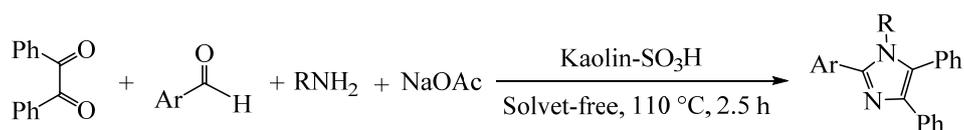
FT-IR (KBr): $\bar{\nu} = 3027-2900, 1601, 1481 \text{ cm}^{-1}$.
¹HNMR (400 MHz, CDCl₃): $\delta = 3.73$ (s, 3H), 5.12 (s, 2H), 6.84-6.86 (m, 2H), 6.97-6.98 (m, 1H), 7.20-7.23 (m, 10H), 7.35-7.37 (m, 4H), 7.61 (d, $J = 6 \text{ Hz}$, 2H) ppm.

Table 2, entry 14:

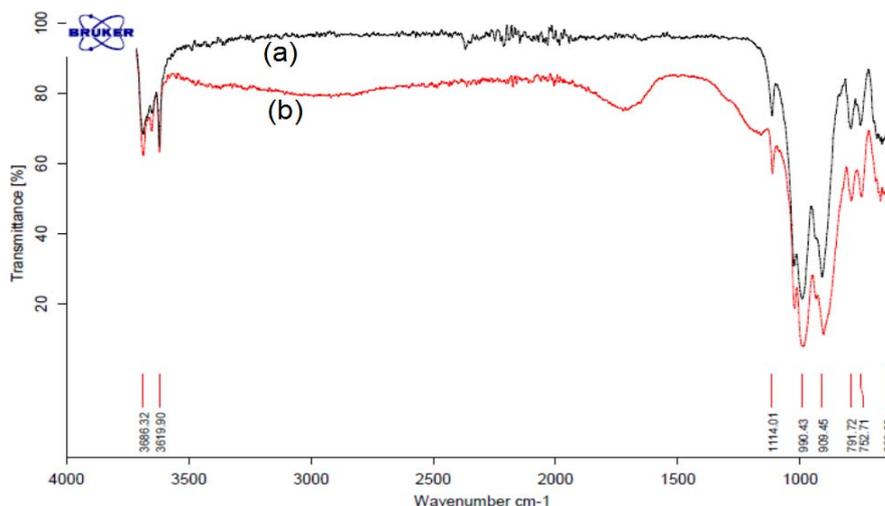
FT-IR (KBr): $\bar{\nu} = 3100-2965, 1601, 1496-1453 \text{ cm}^{-1}$.
¹HNMR (400 MHz, CDCl₃): $\delta = 1.20$ (d, $J = 6 \text{ Hz}$, 6H), 2.71 (m, 1H), 4.92 (s, 2H), 6.71 (d, $J = 5.8 \text{ Hz}$, 2H), 7.10-7.13 (m, 11H), 7.32 (d, $J = 5.8 \text{ Hz}$, 2H). ppm.

3. Results and discussion

For confirmation existence of SO₃H group on Kaolin, we have studied the FT-IR (ATR) spectra of Kaolin and Kaolin-SO₃H (Fig. 1). In Kaolin FT-IR spectrum, many bands at 3686, 3620, 1114, 990, 909, 791, 752 (cm⁻¹) were existed. In Kaolin-SO₃H, in addition to above mentioned bands, one band at 1160 (cm⁻¹) and a very broad band at 2700-3400 (cm⁻¹) were appeared. The peaks at 1114 (cm⁻¹) and 1160 (cm⁻¹) and a very broad peak at 2700-3400 (cm⁻¹) verify the -SO₃H group on Kaolin.

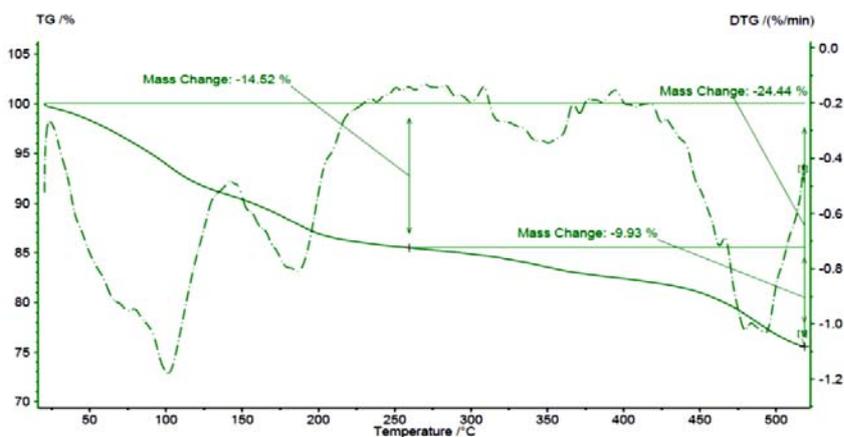


Scheme 1. Synthesis of 1,2,4,5-tetrasubstituted imidazoles.

Fig. 1. FT-IR (ATR) spectrum of (a) Kaolin and (b) Kaolin-SO₃H.

Thermal gravimetric analysis (TGA) pattern of Kaolin-SO₃H was detected from 20 to 510 °C (Fig. 2). The catalyst is stable until 80 °C and only 4.16% of its weight was reduced in 80 °C. By heating of catalyst between 80 to 150 °C, the reducing amount of its weight is 5.51%. Only 2.84% of the catalyst weight was reduced between 150-190 °C. Between 190-330 °C, its weight is nearly constant and only 3.37% of mass was reduced. Two processes between 330-460 °C and 460-510 °C caused mass changed equal to 3.77% and 4.4%, respectively. According to TGA diagram of Kaolin-SO₃H, this catalyst is stable until 80 °C. This initial reducing mass (4.16%) of catalyst is related to removal of catalyst moisture.

Powder X-ray diffraction studies were performed for Kaolin-SO₃H and the obtained diffractogram is displayed in Fig. 3. As shown in this figure, incorporation of -SO₃H leads to some changes in the diffractogram of Kaolin. In the diffractogram of kaolin in 2θ from 62 to 74, nine peaks but in Kaolin-SO₃H, only three peaks (at 70.60, 72.67 and 74.08) are existed. In Kaolin-SO₃H, three peaks in 2θ from 20 to 25 were disappeared. Other peaks in Kaolin and Kaolin-SO₃H diffractograms are in same position. The sharpness of peaks in the Kaolin-SO₃H diffractogram shows crystallite form for this catalyst. The acidity of the catalyst was compared with Kaolin. The pH of 0.05 g of commercial Kaolin or Kaolin-SO₃H in 5 ml

Fig. 2. Thermal gravimetric analysis (TGA) pattern of Kaolin-SO₃H.

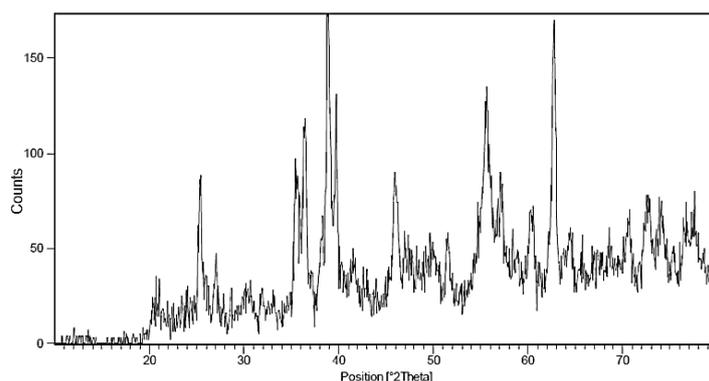


Fig. 3. X-ray diffraction (XRD) pattern of kaolin-SO₃H.

of distilled water is 6 and 3.4, respectively. The acidic capacity of catalyst was determined via titration of 0.05 g of it with 12.16 ml of 0.009 N of NaOH and was 2.268 meq/g H⁺. In continuation of our studies on the application of solid acids in organic synthesis, we have investigated the synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of kaolin-SO₃H. Kaolin-SO₃H combines the properties of a Lewis acid (Al³⁺) and a Brønsted acid (SO₃H) which an efficient catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and is comparable with other catalysts such as DABCO, I₂, InCl₃.3H₂O and K₅CoW₁₂O₄₀.3H₂O.

In addition, Kaolin-SO₃H is a natural based catalyst and is inexpensive. To optimize the reaction conditions, the reaction of benzaldehyde, benzyl amine, benzil and ammonium acetate was used as a model reaction. To support this idea, the condensation was carried out separately in the presence of the same amount of Kaolin and Kaolin-SO₃H under various conditions (Table 1).

Reactions at different temperatures and various conditions in the presence of Kaolin-SO₃H revealed that the best conditions were solvent-free at 110 °C and a molar ratio of aldehyde/amine/benzil/ammonium acetate / Kaolin-SO₃H (g) of 1.5:2:2:1:0.05. Next, various aldehydes and amines were used as substrates for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Table 2).

All of the products were known and characterized by FT-IR, ¹H-NMR, and the physical properties of those reported in the literature. A mechanism for the catalytic activity of Kaolin-SO₃H in the synthesis of tetrasubstituted imidazoles may be postulated as shown in Scheme 2. Initially, the H⁺ from Kaolin-SO₃H can protonated the carbonyl groups of aldehyde and benzil to activate of them for nucleophilic addition. Then nucleophilic attack of the nitrogen of ammonia and amine on the protonated carbonyl group of aldehyde

resulted in the formation of diamine intermediate. This intermediate in the presence of catalyst, condenses with protonated benzil to form a new cyclic intermediate which dehydrated to the tetrasubstituted imidazoles. The reusability of the catalyst was also investigated and we concluded that kaolin-SO₃H is not reusable in this protocol.

4. Conclusions

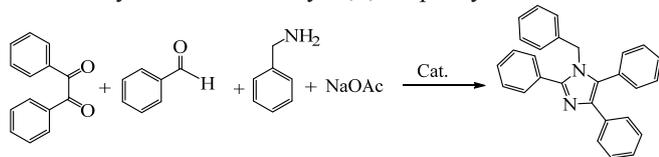
We have demonstrated a simple method for the synthesis of 1,2,4,5-tetra-substituted imidazoles using Kaolin-SO₃H as eco-friendly, inexpensive and efficient reagent. Short reaction times, high yield, scale-up, simplicity of operation and easy work-up are some advantages of this method.

Acknowledgments

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Table 1. Synthesis of 1-benzyl-2,4,5-triphenyl- imidazole under various conditions. ^a

Entry	Catalyst (g)	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ref.
1	Kaolin-SO ₃ H (0.05)	Ethanol	Reflux	4.5	12	This work
2	Kaolin-SO ₃ H (0.05)	ClCH ₂ CH ₂ Cl	Reflux	4.5	15	This work
3	Kaolin-SO ₃ H (0.05)	Ethylacetate	Reflux	4.5	10	This work
4	Kaolin-SO ₃ H (0.05)	H ₂ O	80 °C	2.5	10	This work
5	Kaolin-SO ₃ H (0.05)	Solvent-free	140 °C	2.5	90	This work
6	Kaolin-SO ₃ H (0.05)	Solvent-free	125 °C	2.5	91	This work
7	Kaolin-SO ₃ H (0.05)	Solvent-free	110 °C	2.5	91	This work
8	Kaolin-SO ₃ H (0.05)	Solvent-free	110 °C	1	75	This work
9	Kaolin-SO ₃ H (0.05)	Solvent-free	90 °C	2.5	64	This work
10	Kaolin-SO ₃ H (0.02)	Solvent-free	110 °C	1	75	This work
11	Kaolin-SO ₃ H (0.1)	Solvent-free	110 °C	2.5	90	This work
12	Kaolin-SO ₃ H (0.05)	MW	-	5 min	-	This work
13	Kaolin (0.05)	Solvent-free	110 °C	2.5	40	This work
14	I ₂ (5 mol %)	Ethanol	75 °C	15 min	9	[16]
15	K ₅ CoW ₁₂ O ₄₀ .3H ₂ O (0.1 mol %)	CH ₂ Cl ₂	140 °C	2	95	[17]
16	PEG-400 (1.5 g)	Solvent-free	110 °C	6	86	[22]
17	DABCO (0.7 mol %),	t-BuOH	60–65 °C	12-15	92	[21]
18	InCl ₃ .3H ₂ O (10 mol %)	Methanol	r.t	8.3	82	[18]
19	BF ₃ /SiO ₂ (21 mol %)	Solvent-free	140 °C	2	92	[13]
20	SBPPSA (0.25 g, 0.31 mmol of H ⁺)	Solvent-free	140 °C	1	95	[22]
21 ^b	SBA-Pr-SO ₃ H	Solvent-free	140 °C	0.1	100	[24]

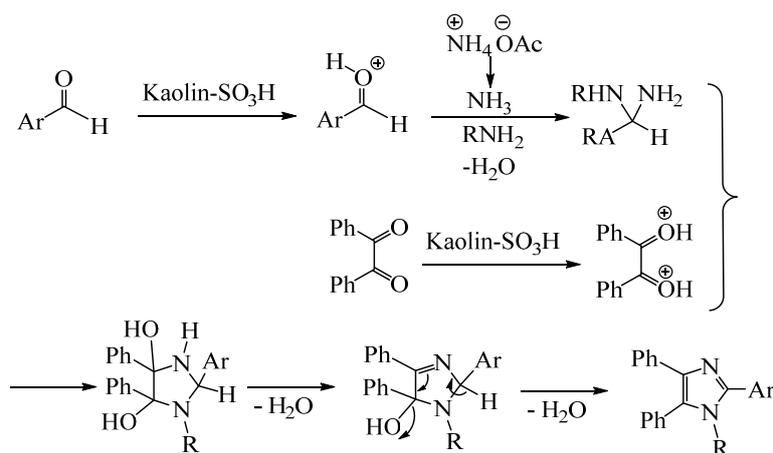
^aThe used amount of benzil, benzaldehyde, benzyl amine, benzil and ammonium acetate is 1.5:2:1:2 mmol.

^b4-chlorobenzaldehyde was used as aldehyde.

Table 2. Kaolin-SO₃H catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles^a.

Entry	Ar	R	Yield (%)	m.p (°C)	Ref.
1	C ₆ H ₅	C ₆ H ₅	85	217-219	[18]
2	C ₆ H ₅	C ₆ H ₅ CH ₂	90	164-165	[12]
3	C ₆ H ₅	Cyclohexyl	62	166-168	[14]
4	4-ClC ₆ H ₄	C ₆ H ₅	85	148-149	[17]
5	4-ClC ₆ H ₄	C ₆ H ₅ CH ₂	88	161-163	[18]
6	2-ClC ₆ H ₄	C ₆ H ₅ CH ₂	80	140-142	[18]
7	4-OHC ₆ H ₄	C ₆ H ₅ CH ₂	60	134-136	[18]
8	4-CH ₃ C ₆ H ₄	C ₆ H ₅	75	186-188	[15]
9	4-CH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂	85	165-167	[14]
10	4-CH ₃ C ₆ H ₄	Cyclohexyl	70	162-164	[14]
11	3-OMeC ₆ H ₄	C ₆ H ₅ CH ₂	88	129-131	[18]
12	2-NO ₂ C ₆ H ₄	C ₆ H ₅ CH ₂	83	153-156	[18]
13	4-NO ₂ C ₆ H ₄	C ₆ H ₅	83	191-192	[31]
14	(CH ₃) ₂ CH	C ₆ H ₅ CH ₂	65	131-133	[18]

^aThe ratio of benzil (mmol): aldehydes (mmol): amine (mmol): ammonium acetate (mmol): Kaolin-SO₃H (g) is 1:1.5:2.2:0.05.



Scheme 2. Proposed mechanism for synthesis of tetrasubstituted imidazoles by Kaolin-SO₃H.

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