

Synthesis of 1,2,4,5-tetrasubstituted imidazoles by a sequential one-pot reaction using tin tetrachloride supported on nanosilicagelas an efficient catalyst

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Abstract: An efficient and convenient synthesis of 1,2,4,5-tetrasubstituted imidazoles has been achieved by a one-pot, four-component reaction of benzil, an aromatic aldehyde, primary amine and ammonium acetate in the presence of tin tetrachloride supported on silica gel nanoparticles ($\text{SnCl}_4/\text{SiO}_2$ NPs) in improved yields. According to the obtained data, many of these protocols have one or more disadvantages, such as long reaction times, expensive catalysts, large amounts of catalysts and tedious procedure or work-up. For example sulfonated carbon/silica composit and cyclic phosphoric acid have more yields but have lasted longer (10 and 20 h). These results clearly show the advantages of our methodology over other protic or Lewis acid catalyzed 1,2,4,5-tetrasubstituted imidazole synthesis such as low consumption of catalyst, shorter reaction time and excellent yields. A mixture of aldehyde, benzil, aniline or benzyl amine, ammonium acetate and $\text{SnCl}_4/\text{SiO}_2$ NPs in ethanol was reacted at refluxing temperature. After the disappearance of the starting materials (monitored by TLC), 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.

Keywords: 1,2,4,5-tetrasubstituted imidazoles, $\text{SnCl}_4/\text{SiO}_2$ NPs, Solid acid, Benzil, One-pot synthesis

Introduction

Recently, multi-component, one-pot syntheses have become one of the most attractive reactions due to their vast applications. These reactions are widely applied in pharmaceutical chemistry for producing different structures and combinatorial libraries for drug discovery [1]. Compounds with an imidazole nucleus are fertile sources of biologically important molecules. Many of substituted imidazoles have many pharmacological properties and play important roles in biochemical processes. It is found in a large number of pharmacologically active compounds such as losartan [2], eprosartan [3], omeprazole [4] and candesartan [5]. Moreover, many of substituted imidazoles emerge as ionic liquid, organometallic catalysis [6] optical absorption [7] and ligands in coordination chemistry [8].

1,2,4,5-tetrasubstituted imidazoles are synthesized by four-component condensation of benzyl/benzoin with a wide variety of aldehydes, primary amines and ammonium acetate. Recently some catalysts such as sulfonated carbon/silica composit [9], nano- $\text{TiCl}_4.\text{SiO}_2$ [10], poly(AMPS-co-AA) [11], 1,3-disulfonic acid imidazolium hydrogen sulfate [12], zinc oxide [13], $\text{HBF}_4.\text{SiO}_2$ [14], FePO_4 [15], sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl]ester [16], SBA-15/2,2,2-trifluoroethanol [17], cyclic phosphoric acid [18] and clay-supported titanium [19] have been applied for the above mentioned route. Although many of the reported methods are effective, but, some of them suffer from disadvantages such as harsh reaction conditions, use of hazardous solvents, long reaction times, complex working and purification procedures, long volume of catalyst loading and moderate yields. Therefore, the development of a simple, mild and efficient method is still needed. In the present work, we used the tin

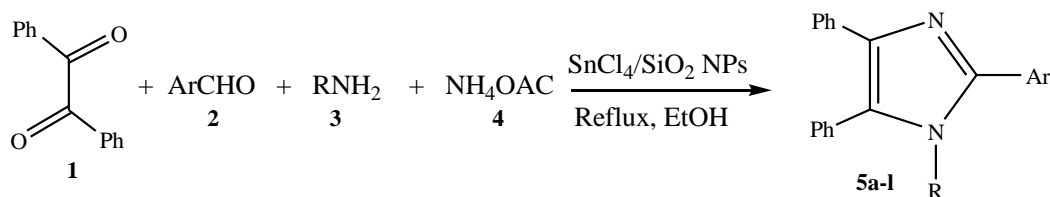
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tetrachloride supported on nanosilica gel as an efficient catalyst to contract these problems. Tin tetrachloride has been widely used as a Lewis acid catalyst in many organic transformations. SnCl_4 in protic solvents can also act as Brønsted acid. SnCl_4 supported on silicagel or alumina with high surface area results in better adsorption. It is believed that the surface species such as Al-O-SnCl_3 , Si-O-SnCl_3 , or the ion pair, $\text{Al-O-SnCl}_4\text{H}^+$ or $\text{Si-O-SnCl}_4\text{H}^+$ are involved in the adsorption process which make solid supported SnCl_4 to act as a solid super acid. Tin tetrachloride supported on silicagel or nanosilicagel has been used in the one-pot synthesis of β -acetamidoketones [20], 3-methylbut-3-en-1-ol [21] and 2,4,5-tri substituted imidazoles [22]. In this work, $\text{SnCl}_4/\text{SiO}_2$ nanoparticles were prepared via adsorption method. Since, tin tetrachloride is a liquid and reacts with the moisture to form HCl, The

supported form is preferable and used effectively as a catalyst. In here, we report a convenient and effective procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles by reacting benzil with aldehyde, primary amine and ammonium acetate using SnCl_4 supported on nanosilicagel as catalyst.

Result and Discussion

On our ongoing program to study the application of solid supported catalysts in organic reactions [24-26] the synthesis of 1,2,4,5-tetrasubstituted imidazoles **5** have investigated by condensation of benzil **1**, an aromatic aldehyde **2**, primary amine **3** and ammonium acetate **4** in the presence of tin tetrachloride supported on silica gel nanoparticles ($\text{SnCl}_4/\text{SiO}_2$ NPs) as a catalyst (Scheme 1).



Scheme 1. Synthesis of 1,2,4,5-tetrasubstituted imidazoles by condensation of an aldehyde, benzil, primary amine and ammonium acetate using $\text{SnCl}_4/\text{SiO}_2$ NPs as catalyst

To optimize the reaction conditions, the reaction of benzil, benzaldehyde, benzyl amine and ammonium acetate was used as a model reaction. The efficiency of $\text{SnCl}_4/\text{SiO}_2$ nanoparticles is comparable with other catalysts such as sulfonated carbon/silica composite, nano- $\text{TiCl}_4.\text{SiO}_2$, poly(AMPS-co-AA), 1,3-disulfonic acid imidazolium hydrogen sulfate, SBA-15/2,2,2-trifluoroethanol and cyclic phosphoric acid. According to the obtained data, many of these protocols have one or more disadvantages, such as long reaction times, expensive catalysts, large amounts of catalysts and tedious procedure or work-up. For example sulfonated carbon/silica composite and cyclic phosphoric acid have more yields but have lasted longer (10 and 20 h). These results clearly show the advantages of our methodology over other protic or Lewis acid catalyzed 1,2,4,5-tetrasubstituted imidazole synthesis such as low

consumption of catalyst, shorter reaction time and excellent yields. (Table 1, entry 1-6). Different solvents and amount of catalyst were screened in the model reaction, and the results are collected in Table 1. Different solvents, for example, CH_2Cl_2 , EtOH, CH_3CN and n-Hexan were tested under reflux in the presence of $\text{SnCl}_4/\text{SiO}_2$ NPs as catalyst. The best results were obtained when EtOH was used as a solvent under reflux condition. (Table 1, entry 10). Decreasing the catalyst loading from 0.03 to 0.02 g, lowered the yield of the reaction significantly (Table 1, entries 10, 11). The yields of **5a** were not further improved with increased amount of the catalyst (Table 1, entry 12). Thus, it is clear from the experiments that the best condition for **5a** could be entry 10, employing $\text{SnCl}_4/\text{SiO}_2$ NPs (0.03 g) as solid acid and reflux in EtOH.

Table 1: Comparison of the efficiency of SnCl₄/SiO₂ NPs with reported catalysts for the synthesis of 5a and optimization of the reaction condition

Entry	Catalyst (amount)	Cond./Sol.	Time (h)	Yield ^a (%)	Ref.
1	Sulfonated carbon/silica composite (0.2g)	80°C/ EtOH	10	94	10
2	Nano-TiCl ₄ .SiO ₂ (0.1g)	110°C/-	0.5	84	11
3	Poly(AMPS-co-AA) (0.03g)	110°C/-	0.5	87	12
4	1,3-disulfonic acid imidazolium hydrogen sulfate(1mol%)	90°C/-	0.16	87	13
5	SBA-15(0.1g)	90°C/TFE	3	90	19
6	Cyclic phosphoric acid (0.09g)	78°C/EtOH	20	93	20
7	SnCl ₄ /SiO ₂ NPs (0.03)	40°C/CH ₂ Cl ₂	0.5	10	-
8	SnCl ₄ /SiO ₂ NPs (0.03)	82°C/CH ₃ CN	0.5	20	-
9	SnCl ₄ /SiO ₂ NPs (0.03)	68°C/n-Hexan	0.5	35	-
10	SnCl ₄ /SiO ₂ NPs (0.03)	78°C/EtOH	0.5	95	-
11	SnCl ₄ /SiO ₂ NPs (0.02)	78°C/EtOH	0.5	80	-
12	SnCl ₄ /SiO ₂ NPs (0.04)	78°C/EtOH	0.5	96	-

^a Isolated yields.

To study the scope of the reaction, a series of aromatic aldehydes with benzil, aniline or benzyl amine, ammonium acetate catalyzed by SnCl₄/SiO₂ NPs were examined (Scheme 1). The results are shown in Table 2.

In all cases, aromatic aldehyde substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields.

Table 2: Synthesis of 1,2,4,5-tetrasubstituted imidazoles

Entry	Ar	R	Product ^a	Yield ^b %	m.p.°C	
					Found	Reported ^[Ref]
1	C ₆ H ₅	C ₆ H ₅ CH ₂	5a	95	159-162	162-165 ^[11]
2	C ₆ H ₅	C ₆ H ₅	5b	90	216-218	217-218 ^[11]
3	4-CH ₃ OC ₆ H ₄	C ₆ H ₅ CH ₂	5c	89	162-164	162-163 ^[10]
4	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	5d	91	184-186	183-185 ^[20]
5	4-CH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂	5e	90	165-166	165-168 ^[11]
6	4-CH ₃ C ₆ H ₄	C ₆ H ₅	5f	89	185-187	185-188 ^[11]
7	2-NO ₂ C ₆ H ₄	C ₆ H ₅ CH ₂	5g	93	156-158	154-155 ^[11]
8	4-NO ₂ C ₆ H ₄	C ₆ H ₅	5h	92	188-190	190-191 ^[10]
9	4-ClC ₆ H ₄	C ₆ H ₅ CH ₂	5i	85	164-165	162-163 ^[11]
10	4-ClC ₆ H ₄	C ₆ H ₅	5j	87	148-150	148-151 ^[11]

11	4-OHC ₆ H ₄	C ₆ H ₅ CH ₂	5k	82	258-260	257-259 ^[12]
12	2-Naphthyl	C ₆ H ₅	5l	92	244-246	241-243 ^[20]

^a All the products were identified by ¹H NMR and ¹³C NMR spectra and also by comparing of melting point and ¹H NMR spectra with those of authentic samples reported in the literature.

^bYields refer to isolated products.

Conclusion

In conclusion, an efficient, environmentally benign, atom-economical, and simple methodology for the preparation of 1,2,4,5-tetrasubstituted imidazoles in four-component reaction under reflux in EtOH is reported. Prominent among the advantages of this method are operational simplicity, mild reaction condition and higher yields.

Experimental

Material and instrumentation

Melting points were determined with an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H NMR and ¹³C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-*d*₆ solutions. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Science and Research Unite of Islamic Azad University. The morphologies of the nanoparticles were observed using SEM of a VEGA//TESCAN microscope with an accelerating voltage of 15 kV. The chemicals for this work were purchased from Fluka and were used without further purification.

The stable silicagel nanoparticles is prepared ^[23] and used for preparation of catalyst (SnCl₄/SiO₂NPs). The dimensions of nano-SiO₂ were observed with SEM (Figure 1).

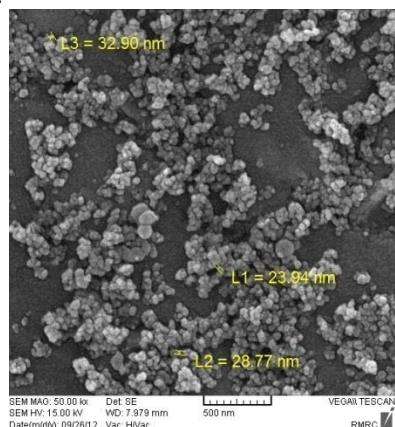


Figure 1. The SEM image of SiO₂ nanoparticles

Synthesis of tin tetrachloridesupported on silicagel nanoparticles

The reagent was prepared by stirring a mixture of SnCl₄ (0.16 ml, 1.34 mmol) and 0.65 g of nanosilica gel in 5 ml of chloroform for 1 h at room temperature. The slurry was filtered and washed with chloroform. The obtained solid (35% w/w SnCl₄/SiO₂ NPs) was dried at an ambient temperature for 2 h and then stored in a dry container. The dimensions of nanoparticles were observed with SEM (Figure 2). The size of particles is between 28-36nm.

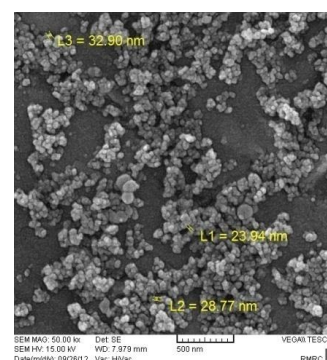


Figure 2: The SEM image of SnCl₄/SiO₂ NPs

General Procedure for the Synthesis of 1,2,4,5-tetrasubstituted imidazoles

A mixture of aldehyde (1mmol),benzil(1mmol), aniline or benzyl amine (1 mmol), ammonium acetate (1.5mmol)and SnCl₄/SiO₂ NPs (0.03g) in ethanol (5 mL) was reacted at refluxing temperature. After the disappearance of the starting materials (monitored by TLC), 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.

The selected spectral data:

1-Benzyl-4,5-diphenyl-2-(4-methoxyphenyl)-imidazole (5d):

White powder; m.p.: 162–164°C; IR(ν_{\max} , cm^{-1}): 3052, 1596, 1477; ^1H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H), 5.12 (s, 2H), 6.81–6.93 (m, 4H), 7.15–7.40 (m, 11H), 7.57–7.62 (d, $J = 7.5$ Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 48.1, 55.2, 113.9, 122.7, 125.9, 126.2, 126.7, 127.2, 127.9, 128.5, 128.7, 129.0, 129.7, 130.3, 130.9, 131.0, 134.5, 137.6, 147.9, 159.9; Anal. Calcd. for $\text{C}_{29}\text{H}_{24}\text{N}_2\text{O}$: C, 83.63; H, 5.81; N, 6.73. Found: C, 83.67; H, 5.86; N, 6.69.

Acknowledgements

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