JNS 2 (2012) 101-105

Journal of
NANOSTRUCTURES
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JNS.kashanu.ac.ir

Nano Silica Phosphoric Acid: An Efficient Catalyst for the One-Pot Synthesis of 1, 2, 4, 5-Tetrasubstituted Imidazoles

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Article history:
Received 2/ 2/2012
Accepted/14/5/2012
Published online 1/6/2012

Keywords:
Tetrasubstitutedimidazoles
Multi-component reactions
Nano silica
Phosphoric acid
Sonication condition

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Abstract

Two simple protocols for the synthesis of 1, 2, 4, 5-tetrasubstitutedimidazoles using nano-SPA as a reusable, eco-friendly, inexpensive, and efficient catalyst are reported. Short reaction times, high yields, scale-up and easy workup are the advantages of these protocols.

1. Introduction

Tetrasubstituted imidazole core present in many biological systems such as Losartan, Olmesartan, Trifenagrel and Eprosartane [1]. The presence of animidazole ring in natural products and pharmacologically active [2] compounds has instituted a diverse array of synthetic approaches to these heterocycles [3]. However, despite intensive efforts, only a handful of general methods exist for the construction of tetrasubstitutedimidazoles. Recently, the synthesis of 1, 2, 4, 5-tetrasubstitutedimidazoles has been catalyzed by silica gel or Zeolite HY [4], silica gel/$NaHSO_4$ [5], molecular iodine [6], $K_5CoW_{12}O_{40}.3H_2O$ [7], heteropolyacids [8], $HClO_4$-SiO_2 [9], $InCl_3.3H_2O$ [10], $ZrCl_4$ [11] and $BF_3.SiO_2$ [12]. Some of the

reported protocols have disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and often expensive acid catalysts. Moreover, the synthesis of these heterocycles has been usually carried out in polar solvents such as ethanol, methanol, acetic acid and DMSO leading to complex isolation and recovery procedures.These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off. During the course of our studies towards the development of new protocols to the synthesis of organic compounds, we wish to report a simple and efficient method for the synthesis of 1, 2, 4, 5-tetraaryl substituted imidazoles in the presence of nano-silica phosphoric acid.Nano silica phosphoric acid (nano-SPA) [13] as an efficient and reusable catalyst was prepared by reaction of nano-silica chloride [14] with dry phosphoric acid. Nano silica chloride was prepared by reaction of commercial nanosilicagel with thionyl chloride in reflux condition. The particle size of nano-silica gel and nano-SPA was measured by SEM photography (Fig. 1).

The acidic capacity of nano-SPA is 10.32 mmol.g-1 and was determined via titration of 0.2 g of catalyst with standard solution of NaOH.

The FT-IR (ATR) spectra of silica chloride, nano-SPA.and $H_3PO_4.SiO_2$ were shown in Fig 2. In all ATRspectrum, the Si-O-H and Si-O-Si stretching bonds are appeared in 900 until 1100 cm-1. In silica chloride spectrum, the Si-Cl stretching bond is appeared in 700 cm-1. In ATR spectra of nano-SPA and $H_3PO_4.SiO_2$, the P-O-H, P=O, P-O stretching bonds are appeared 910-1040, 1637 and 2400-2800 cm-1 respectively. According to above data, we suggested one structure for nano-SPA with PO_3H_2 on silica gel (scheme 1).

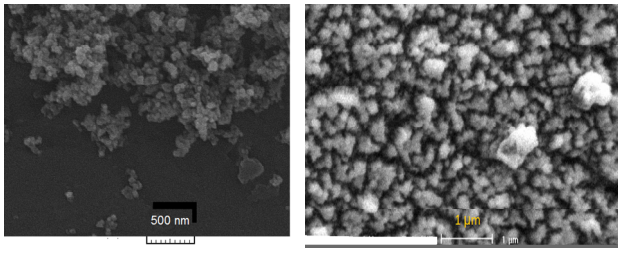


Fig. 1.SEM photograph of a) nano silica-gel and b) nano-SPA.

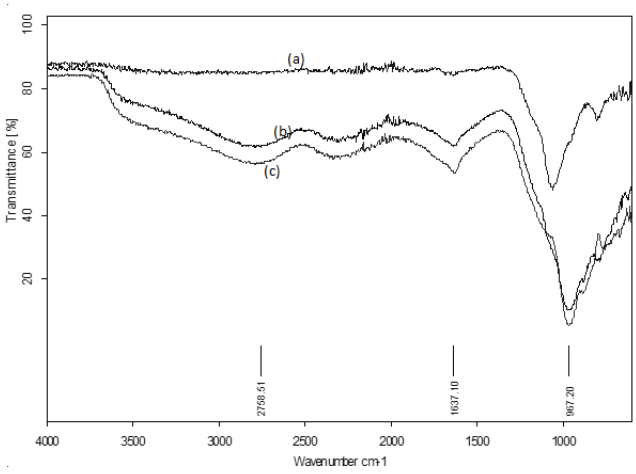
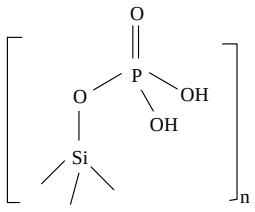


Fig. 2.ATR of a) silica chloride, b) nano-SPA and c) $H_3PO_4.SiO_2$



Scheme 1

The X-ray diffraction (XRD) patterns of nano-$SiO_2$and nano-SPA are shown in figure 3. Nano-SiO_2XRD pattern has a strong peak in 2θ value of 21.8024° and FWHM equal to 1771 and nano- SPA XRD pattern has a strong broad peak in 21.718 and FWHM equal to 2.3616.

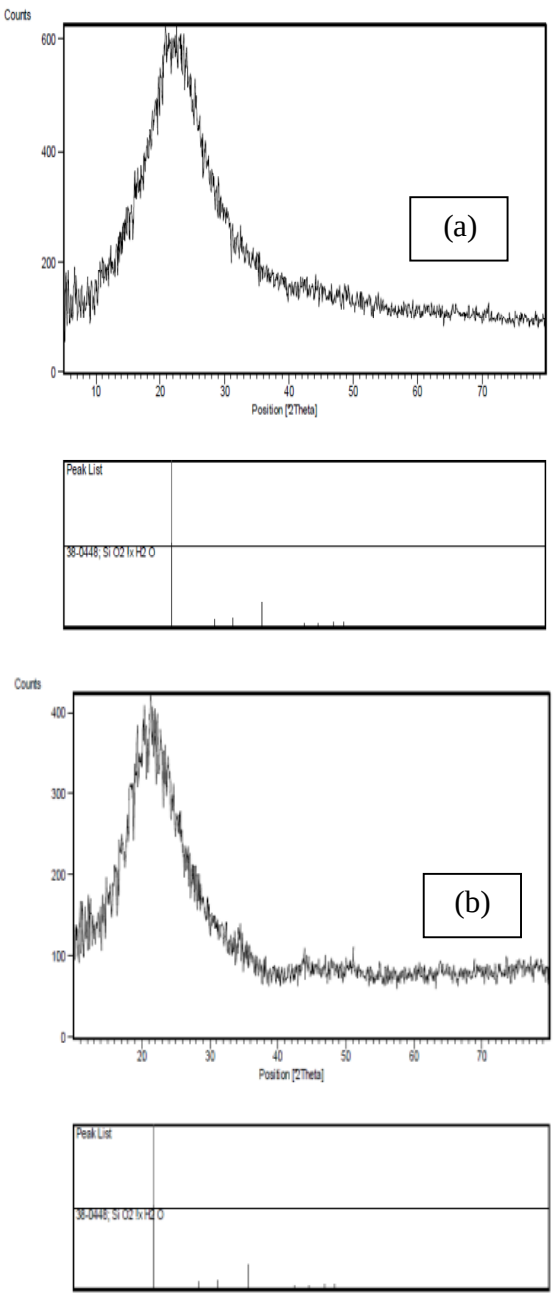


Fig. 3. X-ray diffraction (XRD) pattern of a) nano SiO_2 and b) nano-SPA

2. Experimental procedure

2.1. General. The materials were purchased from Merck Company and were used without any additional purification. Products were characterized by FT-IR, 1H-NMR and comparison of their physical properties with those reported in the literature. FT-IR (ATR) spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the 1HNMR spectra. The SEM of nano particles determined with VEGA/TESCAN scanning electron microscope. A BANDELIN Sonopulse HD 3200 ultrasonic apparatus was used for sonication. The X-ray diffraction (XRD) patterns of materials were recorded by employing a Philips XpertMPDdiffractometer equipped with a Cu Kα anode (λ = 1.54 A°) in the 2θ range from 5 to 80◦.

2.2. General procedure for the synthesis of 1, 2, 4, 5-tetrasubstitutedimidazoles:

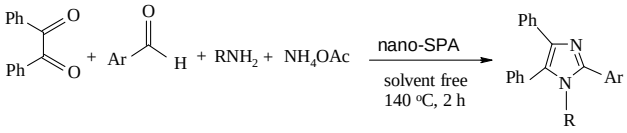
Benzil (4 mmol), amine (4 mmol), aldehyde (4 mmol), ammonium acetate (4 mmol) and nano-SPA (0.08 g) was heated with stirring at 140 ℃ for 2 h (Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature. Chloroform was added to the mixture which was filtered to remove the catalyst. After evaporation of the solvent, an oily residue or an impure solid was obtained. By adding ethanol and water to the residue, a milky to yellow solid was obtained. The solid was then crystallized from ethanol. All the products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

3. Results and discussion

In continuation of our investigation on application of solid acids in organic synthesis [15-19], we have used nano-SPA for the synthesis of 1, 2, 4, 5-tetrasubstitutedimidazoles. We have synthesized 1, 2, 4, 5-tetrasubstitutedimidazolesin the presence of SPA under various conditions (table 1).Reaction at

different temperatures and various molar ratios of substrates in the presence of SPA revealed that the best conditions were solvent-free at 140 °C and a ratio of aldehyde (mmol) / amine (mmol) / benzyl (mmol) / ammoniumacetate (mmol) / SPA (g) equal to 1:1:1:0.06.The ultrasonic assisted synthesis of the present reaction was studied by using SPA or nano-SPA in ethyl acetate under reflux conditions (Table 1, entries 15). It was found that under sonication conditions, the reaction time decreased to 40 minutes.

The reusability of the SPA catalyst was also examined. After each run, the product was filtered, the solvent was evaporated. The catalyst residue was washed with $CHCl_3$ and reused. Treatment with $CHCl_3$ removes tars more efficiently from the catalyst surface (Table 1, entries 13 and 14). The catalyst was reusable, although a gradual decline in activity was observed. Therefore, various amine and various aldehydes were used as substrates for the synthesis of 1, 2, 4, 5-tetrasubstitutedImidazoles derivatives at 140 °C under solvent-free condition (Scheme 2 and Table 2).

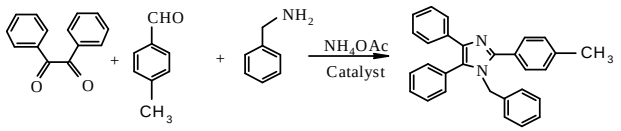


Scheme 2

4. Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of 1, 2, 4, 5-tetrasubstitutedImidazoles using Nano-SPA as a reusable, eco-friendly, inexpensive, and efficient catalyst. Short reaction times, High yield, simplicity of operation and easy work-up are some advantages of this method.

Table 1. Synthesis of 1-benzyl-4, 5-diphenyl-2-*p*-tolyl-1*H*-imidazole under different conditions.



Ent.	Catalyst (g)	Solvent	Cond.	Time (h)/ Yield (%)[ref.]
1	SPA (0.05)	-	140 °C	2/58
2	SPA (0.06)	-	140°C	2/94
3	SPA (0.06)	-	r.t.	15/60
4	SPA (0.06)	CH_2Cl_2	140°C	15/86
5	SPA (0.06)	H_2O	140 °C	15/80
6	SPA (0.06)	DMSO	110°C	3/90
7	SPA (0.06)	n-Hexan	140 °C	15/60
8	SPA (0.06)	EtOH	140 °C	15/70
9	SPA (0.06)	HOAc	140 °C	15/75
10	SPA (0.06)	MeOH	140 °C	15/86
11	SPA (0.06)	Acetone	140 °C	15/87
12	nano-SPA (0.02)	-	140 °C	2/90
13	nano-SPA (0.02), 2nd run	-	140 °C	2/65
14	nano-SPA (0.02), 3rd run	-	140 °C	2/50
15	Nano-SPA (0.02)	EtOAc	Ultra.	0.6/80
16	Zeolite HY (1 g)	-	MW	0.1/85[4]
17	SiO_2\$NaHSO_4$ (0.4 g)	-	140 °C	2/92[5]
18	SiO_2\$NaHSO_4$ (0.4 g)	-	MW	0.25/96[5]
19	I_2(10 mol%)	EtOH	45°C	0.6/98[6]
20	$K_5CoW_{12}O_{40}.3H_2O$ (0.1 mol%)	-	140°C	2/95[7]
21	$K_5CoW_{12}O_{40}.3H_2O$ (0.1 mol%)	-	MW	0.05/95[7]
22	$H_4[PMo11VO_{40}]$ (1 mol%)	EtOH	78°C	0.25/90[8]
23	$SiO_2/HClO_4$ (1 mol%)	-	140°C	0.1/90[9]
24	$InCl_3.3H_2O$	MeOH	r.t.	6/83[10]
25	$ZrCl_4$	CH_3CN	r.t.	1/86[11]
26	37%$BF_3.SiO_2$	-	140°C	2/80[12]

Acknowledgment

The authors are grateful to University of Kashanfor supporting this work by Grant No (159189-90/12/14).

Table 2: Nano-SPA (0.01 g) catalyzed synthesis of 1, 2, 4, 5-tetrasubstitutedImidazoles at 140 °C for 2 hours.

Ent.	Ar	R	Yield (%) heating[a]/ sonication[b]	M.P./ °C[ref.]
1	C_6H_5	C_6H_5	79/70	216[9]
2	C_6H_5	$C_6H_5CH_2$	87/82	163[7]
3	C_6H_5	Cyclohexyl	56/50	167[4]
4	C_6H_5	CH_3CH_2	60/55	115[4]
5	4-ClC_6H_4	C_6H_5	78/70	149[6]
6	4-ClC_6H_4	$C_6H_5CH_2$	79/65	162[7]
7	2-ClC_6H_4	$C_6H_5CH_2$	80/84	140[7]
8	4-OHC_6H_4	$C_6H_5CH_2$	62/60	134[7]
9	4-$CH_3C_6H_4$	C_6H_5	75/70	185[8]
10	4-$CH_3C_6H_4$	$C_6H_5CH_2$	90/80	165[4]
11	4-$CH_3C_6H_4$	Cyclohexyl	70/60	162[4]
12	3-$OMeC_6H_4$	$C_6H_5CH_2$	90/80	128[9]
13	2-$NO_2C_6H_4$	$C_6H_5CH_2$	89/80	152[9]
14	$(CH_3)_2CH$	$C_6H_5CH_2$	55/50	129[9]

[a]Molar ratio of benzil:aldehyde :amine :ammonium acetate: is 1:1: 1:1: heated in 140 °C for 120 minutes.

[b] Molar ratio of benzil:aldehyde :amine :ammonium acetate: is 1:1: 1:1: in ethyl acetate was sonicated under power 100 for 45 minutes.

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