Nano silica phosphoric acid as an efficient catalyst for one-pot synthesis of 2,4,5-tri-substituted imidazoles under solvent free condition

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Nano silica phosphoric acid has been found to be an extremely efficient catalyst for the preparation of 2,4,5-trisubstituted imidazoles via three-component reactions of benzil, aldehydes and ammonium acetate under solvent free conditions. This process is simple and environmental benign in good to excellent yields. Furthermore, the catalyst can be recovered conveniently and reused for at least three times with a gradual decline in activity.

Keywords: 2,4,5-trisubstituted imidazole, nano-silica phosphoric acid, benzil, solvent-free conditions, heterogeneous catalyst.

INTRODUCTION

Compounds with an imidazole moiety have many pharmacological properties and play important roles in biochemical processes [1] Many of the substituted imidazoles are known as inhibitors of fungicides and herbicides, plant growth regulators and therapeutic agents [2] Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related N-heterocyclic carbenes [3]. The best reported route for synthesis of 2,4,5–trisubstituted imidazoles is presented by condensation of benzil, aldehydes and ammonium acetate in the presence of an acidic catalyst.

Recently some catalysts such as L-Proline [4], montmorrilonite K10 [5], zeolite [5], nano sulfated zirconia [5], [EMIM]OAc [6], Zr(acac)$_4$ [7], [HeMIM]BF$_4$ [8], HOAc [9], tetra- butyl ammonium bromide (TBAB) [10], polymer-supported zinc chloride [11] and potassium di-hydrogen phosphate [12] have been applied for the above mentioned route.

Some of the reported protocols have disadvantages such as harsh reaction conditions, poor yields, prolonged reaction times, use of hazardous and often expensive acid catalysts. Moreover, the synthesis of these heterocycle compounds has been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to uncomfortable isolation and recovery procedures. These processes also have generated wastes containing catalysts and solvents, which must 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 2,4,5-triaryl substituted imidazoles in the presence of nano-silica phosphoric acid (nano-SPA) under solvent free conditions.

EXPERIMENTAL
Material and methods

Chemicals were purchased from Sigma–Aldrich and Merck chemical companies and were used without any purification. All products were characterized by their FT-IR, ^{1}H-NMR and comparison of their physical properties with those reported in the literature. FT-IR spectra were recorded on a Bruker, Eqinox 55 spectrometer. In all cases, the ^{1}H-NMR spectra were recorded on a Bruker DRX-400 Avance instrument. Nano-SPA was synthesized according to SPA procedure [22]. The SEM photograph of nano particles was determined with VEGA/TESCAN scanning electron microscope. The TEM photograph was determined by Leo 912AB OMEGA microscope.

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles

Benzil (4 mmol), aldehyde (4 mmol), ammonium acetate (8 mmol) and nano-SPA (0.04 g) was heated with stirring at 140 °C for 3 h (Table 2). The progress of the reaction was followed by TLC on silica gel polygram SIL G /UV 254 plates.

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After completion of the reaction, the mixture was cooled to room temperature. CHCl₃ was added to the mixture and 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 products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

RESULTS AND DISCUSSION

Nano silica phosphoric acid (nano-SPA) as an efficient and reusable catalyst was prepared by reaction of nano-silica chloride with dry phosphoric acid. Nano silica chloride was prepared by reaction of commercial nano silicagel with thionyl chloride in reflux condition. The particle size of nano-SPA was measured by SEM and TEM phothography (Figure1). As it is shown in SEM and TEM photographs, the scale of nano-SPA particles are smaller than 100 nm.
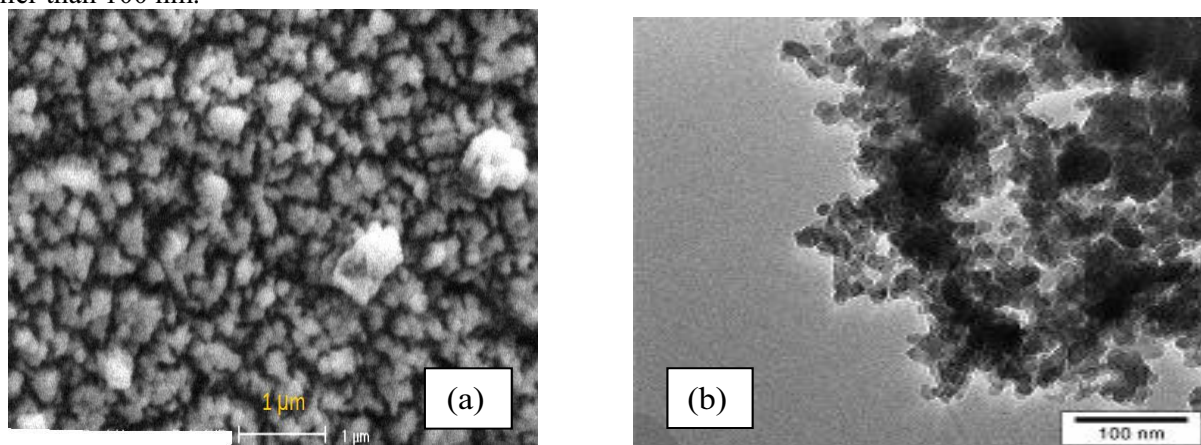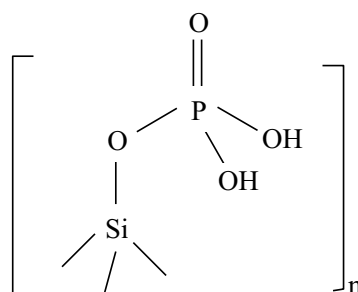
The acidic capacity of nano-SPA was presented 10.32 mmol. g^{-1}. It was determined *via* titration of 0.2 g of nano-SPA with standard solution of NaOH. The FT-IR (ATR) spectra of silica chloride, nano-SPA and $H_3PO_4.SiO_2$ were shown in Figure 2. In all ATR spectra, the Si-O-H and Si-O-Si stretching bands are appeared in the range of 900 to 1100 cm^{-1}. In silica chloride spectrum, the Si-Cl stretching band 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 bands are appeared in 910-1040, 1637 and 2400-2800 cm^{-1} respectively. According to above data, we have suggested the structure for nano-SPA with PO_3H_2 on silica gel (Scheme 1).

The X-ray diffraction (XRD) patterns of nano-SiO_2 and nano-SPA are shown in Figure 3. Nano-SiO_2 XRD pattern has a strong peak in 2θ value of 21.8024° and FWHM equal to 1.771 and nano-SPA XRD pattern has a strong broad peak in 21.718 and FWHM equal to 2.3616.
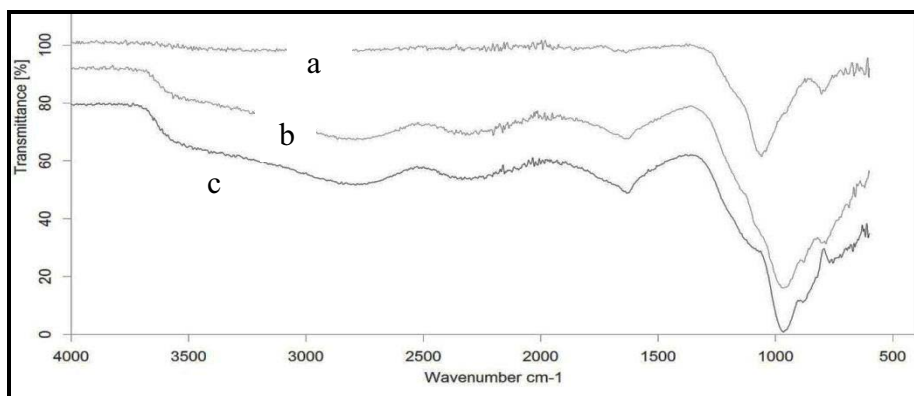

Fig. 1.. SEM (a) and TEM (b) photographs of nano SPA.

Scheme 1. A proposed structure for nano-SPA.

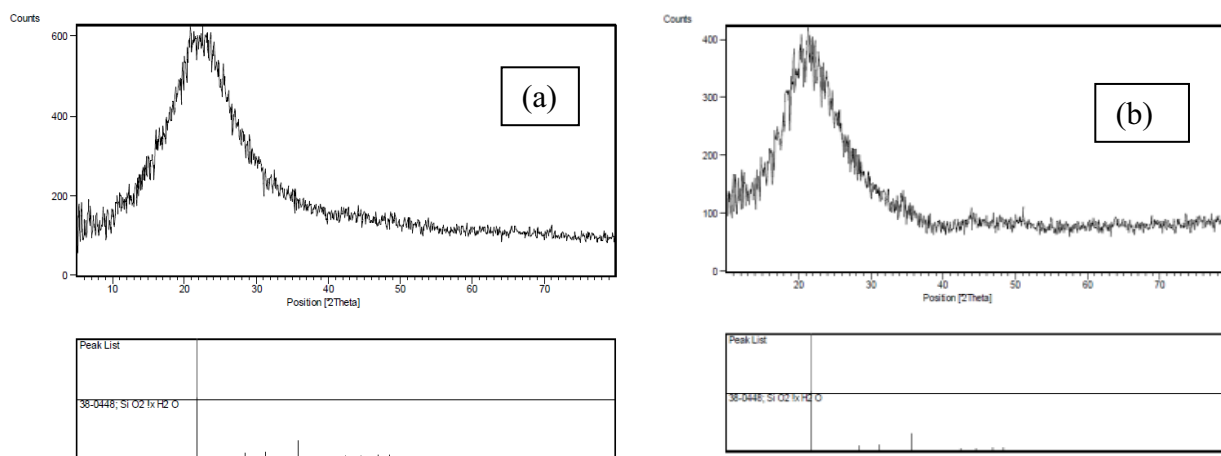**Fig. 2.** ATR of (a) silica chloride, (b) nano-SPA and c) $H_3PO_4.SiO_2$.

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

To find the optimum condition for the synthesis of 2,4,5-trisubstituted imidazoles in the presence of solid acid, we have synthesized 2, 4, 5-triphenyl imidazole in the presence of SPA and nano-SPA under various conditions (Table 1).

Reactions at different temperatures and various molar ratios of substrates in the presence of SPA and nano-SPA revealed that the best condition was presented as solvent-free at 140 °C and a ratio of aldehyde (mmol): benzil (mmol): ammonium acetate (mmol): nano-SPA (g) equal to 1:1:2:0.01. The reusability of the nano-SPA catalyst was also examined for three times. After each run, the product was filtered, the solvent was evaporated and the catalyst was washed with $CHCl_3$ and reused. Treatment with $CHCl_3$ removes tars more efficiently from the catalyst surface (table 1, entries 14 and 15). The catalyst was reusable, although a gradual decline in activity was observed. Therefore, various aldehydes were used as substrates for the synthesis of 2,4,5-tri-substituted imidazoles at 140°C under solvent-free condition (Scheme 1 and Table 2).

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Table 1. Synthesis of 2,4,5-triphenyl imidazole using SPA or nano-SPA under different conditions[a]
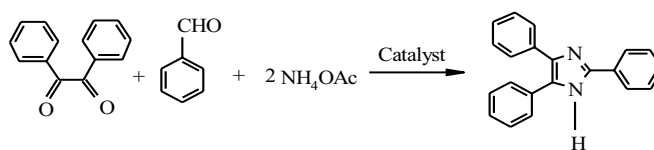
[a]The molar ratio of benzaldehyde: benzil: ammonium acetate is equal to 1:1:2

Entry	Catalyst, (g)	Solvent	Condition	Time, (h)	Yield, (%)	Ref.
1	SPA (0.05)	-	120 °C	3	60	-
2	SPA (0.06)	-	120°C	3	50	-
3	SPA (0.06)	-	140°C	3	92	-
4	SPA (0.06)	DMSO	110°C	3	86	-
5	SPA (0.06)	CH_2Cl_2	45 °C	24	20	-
6	SPA (0.06)	*n*-Hexane	50 °C	24	50	-
7	SPA (0.06)	EtOH	75°C	6	48	-
8	SPA (0.06)	HOAc	80°C	24	50	-
9	SPA (0.06)	MeOH	65 °C	6	46	-
10	SPA (0.06)	Isopropanol	82°C	6	45	-
11	SPA (0.06)	-	Ball mill	30 (min)	60	-
12	SPA (0.06)	Ethyl acetate	Ultrasound	30 (min)	70	-
13	nano-SPA (0.01)	-	140 °C	3	95	-
14	nano-SPA (0.01), 2nd run	-	140 °C	4	65	-
15	nano-SPA (0.01), 3rd run	-	140 °C	4	50	-
16	L-Proline	MeOH	60°C	9	90	[4]
17	Zeolite	EtOH	reflux	60 (min)	80	[5]
18	K10	EtOH	reflux	90 (min)	70	[5]
19	Nano –sulfated zirconia	EtOH	reflux	45 (min)	87	[5]
20	[EMIM]OAc	EtOH	Ultasound/r.t.	45 (min)	87	[6]
21	$Zr(acac)_4$	EtOH	Ultasound/r.t.	25 (min)	94	[7]
22	$Zr(acac)_4$	EtOH	reflux	2.5	90	[7]
23	$[HeMIM]BF_4$	-	MW	2 (min)	93	[8]
24	-	HOAc	MW	5 (min)	98	[9]
25	TBAB	Isopropanol	82°C	20 (min)	95	[10]
26	Polymer-$ZnCl_2$	EtOH	reflux	4	96	[11]
27	KH_2PO_4	EtOH	reflux	40 (min)	93	[12]
28	SSA	-	130 °C	50 (min)	83	[14]
29	SSA	-	mw	10 (min)	85	[14]
30	I_2	EtOH	75°C	15 (min)	99	[15]
31	[Hbim]BF4	-	100°C	25 (min)	93	[16]
32	$InCl_3.3H_2O$	MeOH	r.t	12	73	[17]
33	-	PEG-400	110°C	1/5	88	[18]
34	$Yb(OTf)_3$	HOAc	70°C	2	92	[19]

Table 2. Synthesis of 2,4,5-trisubstituted imidazoles in the presence of nano-SPA at 140 °C and solvent free condition in 3 hours.[a]
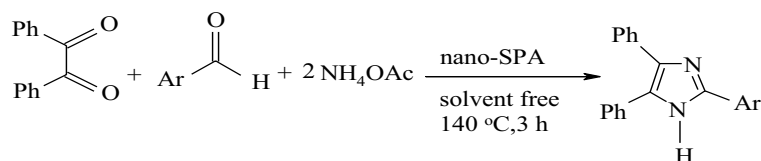
[a]The molar ratio of aldehyde: benzil: ammonium acetate is equal to 1:1:2

Entry	Ar	Yield, (%)[b]	M.P., °C (lit.)	Ref.
1	C_6H_5	90	274(274-275)	[6]
2	$4\text{-}CH_3C_6H_4$	87	236(227-229)	[14]
3	$4\text{-}NO_2C_6H_4$	78	240(239-242)	[6]
4	$4\text{-}ClC_6H_4$	85	261(260-262)	[5]
5	$2\text{-}OMeC_6H_4$	93	210(210-211)	[4]
6	$4\text{-}OMeC_6H_4$	94	230 (230–231)	[7]
7	$2\text{-}ClC_6H_4$	80	186(188)	[16]
8	$2,4\text{-}DiClC_6H_3$	88	175(174-175)	[7]
9	$4\text{-}BrC_6H_4$	80	254(254-256)	[5]
10	$2\text{-}NO_2C_6H_4$	88	230 (230–231)	[4]
11	$3\text{-}NO_2C_6H_4$	89	>300 (>300)[	[18]
12	$4\text{-}OH\ C_6H_4$	90	267 (265–267)	[18]
13	$2\text{-}BrC_6H_4$	80	201 (201-202)	[6]

CONCLUSION

In this article, we have synthesized nano silica phosphoric acid and studied its structure with FT-IR, XRD, SEM and TEM. A simple method for the synthesis of 2,4,5-trisubstituted imidazoles using nano-silica phosphoric acid as a reusable, eco-friendly, inexpensive and efficient catalyst was demonstrated. Short reaction times, high yields, simplicity of operation and easy work-up are some advantages of this method.

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НАНО-СИЛИЦИЕВО-ФОСФОРНА КИСЕЛИНА КАТО ЕФЕКТИВЕН КАТАЛИЗАТОР ПРИ ЕДНОСТЕПЕННАТА СИНТЕЗА НА 2,4,5-ТРИ-ЗАМЕСТЕНИ ИМИДАЗОЛИ В ОТСЪСТВИЕ НА РАЗТВОРИТЕЛ

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(Резюме)

Установено е, че нано-силициево-фосфорната киселина е изключително ефективен катализатор за получаването на 2,4,5-тризаместени имидазоли чрез три-компонентна реакция на бензил, алдехиди и амониеш ацетат в отсъствие на разтворител. Процесът е прост и съвместим с опазването на околната среда, като дава високи добиви. Освен това катализатирът лесно се регенерира и мове да се използва трикратно с постепенно спадане наактивността му.