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Synthesis and characterization of highly substituted pyrazoles using silica-phosphoric acid nanoparticles as a recoverable heterogeneous solid acid catalyst

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Highly substituted pyrazoles have been prepared by condensing 1,3-diketones and various hydrazine derivatives using silica-phosphoric acid nanoparticles (nano-SPA). This nano solid catalyst has been prepared by the reaction of nano silica chloride with dry phosphoric acid. This green methodology has advantages such as short reaction times, simple work-up, high efficiency, reusability of the catalyst and no use of any solvents.

Keywords: Highly substituted pyrazoles, Heterogeneous, Nano silica-phosphoric acid, Solid acid catalyst

Nowadays, researchers are working in a way which preserved the environment. They are developing procedures with the aim of minimization of pollution effects and reduction in energy and raw materials consumption that are environmentally and economically acceptable[1]. Among the most promising ways to reach this goal, solvent-free techniques are a strategic position because solvents are often very toxic, expensive, intruder to use and to remove. These approaches can also enable experiments to be run without strong mineral acids which caused corrosion, safety, manipulation and pollution problems as wastes[1]. These acids can be replaced advantageously by solid, recyclable acids such as clays[2-7]. Reactants are first impregnated as neat liquids onto solid supports such as alumina, silica and clays or via their solutions in an adequate organic solvent and further solvent removal in the case of solids[8-11].

In chemistry, heterogeneous catalysis is the process contrasts with homogeneous catalysis[12]. Heterogeneous catalysis makes faster and large-scale production and increases the selectivity[13]. 90% of chemicals (by volume) is produced by using the solid catalysts[14]. The chemical and energy industries rely heavily on heterogeneous catalysis[15]. To increase the surface area (spread the number of active sites) and provide stability, a solid catalyst is usually dispersed on a supporting material[14]. The catalyst supports are inert materials with high melting points. Most catalyst supports are porous (frequently carbon, silica, zeolite, or alumina-based) and chosen for their high surface area-to-volume ratio.

Pyrazole derivatives are chemical, biological and pharmacological active compounds[16-29]. Some of aryl pyrazoles have anti-HIV1 activity[30] and some of pyrazole-3-carboxamides have anti-CB1 cannabinoid ability[31-36]. Pyrazole derivatives have used in crop protection chemistry[37], design of new OLED materials[38] and as ligands for transition metal-catalyzed reactions[39]. A classical method for the synthesis of pyrazoles is the acid-catalyzed cyclocondensation of 1,3-diketones (**1**) with hydrazines (**2**)[40]. In this work, we have been synthesized some highly substituted pyrazoles (**3a-j**) in the presence of silica-phosphoric acid nanoparticles (nano-SPA) as a recoverable heterogeneous solid acid catalyst under thermal and solvent-free conditions.

Experimental Section

Materials and apparatus

Chemicals were purchased from Merck and Aldrich chemical companies. The products were characterized by their TLC, physical and spectral (IR, ^{13}C and ^{1}H NMR), data. TLC on commercial aluminium-backed plates of silicagel 60 F_{254} was used to monitor the progress of the reactions. Melting points of solid products were obtained with a micro melting point apparatus Electrothermal, Mk3. IR spectra were determined on a Nicolet Magna series FTIR 550 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded with a BRUKER (DRX- 400 MHz) in acetone-d_6 or DMSO-d_6 as the solvent and TMS as an internal reference. XRD patterns were collected on a Philips Xpert MPD diffractometer equipped with a

Cu-Kα anode (λ=1.54 Å) in the 2θ range from 10 to 80°. Average size of nanoparticles was analyzed by TEM using a Zeiss EM900 with a LaB6 cathode and accelerating voltage of 200 kV. The morphology and size of nanoparticles were characterized using MIRA3 TESCAN field emission scanning electron microscope (FESEM). Brunauer–Emmett–Teller (BET) surface area analysis of catalyst was done with Micromeritics, Tristar II 3020 analyzer.

Preparation of nano-SPA particles

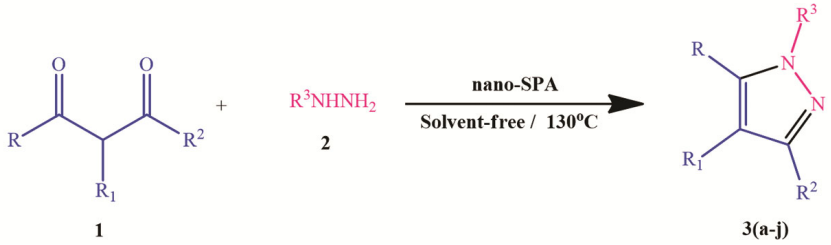
Nano silica chloride (nano-SC) was prepared by the reaction of commercial nano silicagel (nano-SG, 8 g) with thionyl chloride (15 mL) under reflux conditions for 48 h. 10 mL dry phosphoric acid was added to 5 g of prepared nano-SC to produce nano-SPA in 96% yield (Scheme 1). The acidic capacity of nanocatalyst was determined via titration of 0.2 g of nano-SPA with standard solution of NaOH. It was 10.32 mmol g^{-1}.

Preparation of highly substituted pyrazoles

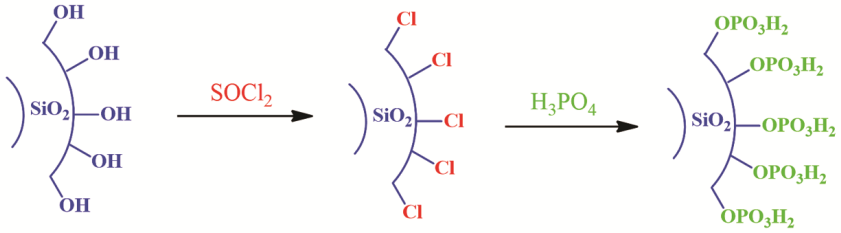
In a general procedure, a mixture of 1,3-diketone (**1**, 1 mmol) and a hydrazine derivative (**2**, 1 mmol) was stirred in the presence of an optimized amount of nano-SPA, for an appropriate time under thermal and solvent-free conditions. After completion the reaction monitored via TLC, the reaction mixture was cooled and then, washed with acetone. Product was separated from the nanoparticles by simple filtration and after removing the solvent, the pure product was obtained . The synthesis of highly substituted pyrazoles in the presence of nano-SPA scheme is shown in Scheme 2 and the results are summarized in Table 1.

Spectroscopic data of some products

3,5-diphenyl pyrazole-1-carbaldehyde (2): Brown oil. $\bar{\upsilon}_{max}$ (KBr)/cm^{-1}: 3060 (=C-H), 1600-1400 (C=C and C=N), 750 and 690 (=C-H bending OOP of monosubstituted phenyl rings). ^{1}H NMR (Acetone-d_6)/ppm: δ_H= 8.06 (1H, s, COH), 7.81 (4H, d, $^3J_{HH}$ =



Scheme 1 — Preparation of nano-SPA



Scheme 2 — Synthesis of highly substituted pyrazoles in the presence of nano-SPA

Table 1 — Synthesis of highly substituted pyrazoles using nano-SPA

Entry	1,3-diketone			Hydrazine	Product	Time (min)	Yeild (%)	MP (°C) [Ref.]
	R	R^1	R^2	R^3				
1	Ph	H	Ph	H	3a	120	91	199-200 [41]
2	Ph	H	Ph	CHO	3b	125	86	Oil
3	Ph	H	Ph	4-Br-C_6H_4	3c	95	90	120-122 [42]
4	Ph	H	Ph	4-Me-$C_6H_4SO_2$	3d	90	92	100-102 [42]
5	Me	H	Me	4-Br-C_6H_4	3e	87	91	89-91 [42]
6	Me	H	Me	2,4-NO_2-C_6H_3	3f	150	84	165-167 [42]
7	Me	H	Me	4-OMe-C_6H_4	3g	80	92	Oil
8	-$CH_2CH_2CH_2$-		Me	2,4-NO_2-C_6H_3	3h	135	82	Oil
9	-$CH_2CH_2CH_2$-		Me	2-Br-C_6H_4	3i	105	90	Oil
10	Me	H	Me	2,4-NO_2-C_6H_3	3j	150	88	119-121 [42]

7.6 Hz), 7.40 (4H, "t", $^{3}J_{HH}$ = 7.6 Hz), 7.35 (2H, "t", $^{3}J_{HH}$ = 7.6 Hz), 7.20 (1H, s).

1-[(4-methylphenyl)-sulfonyl]-3,5-diphenyl pyrazole (4): White solid. mp/°C: 100-102 (Lit. 101-103[42]). $\bar{\upsilon}_{max}$ (KBr)/cm^{-1}: 3058 (=C-H), 2929 (-C-H), 1600-1400 (C=C and C=N), 1375 (CH_3, bending), 850 (=C-H bending OOP of para disubstituted phenyl ring), 753 and 684 (=C-H bending OOP of monosubstituted phenyl rings). ^{1}H NMR (Acetone-d_6)/ppm: δ_H= 8.14 (2H, d, $^{3}J_{HH}$ = 7.6 Hz), 7.90 (2H, d, $^{3}J_{HH}$ = 7.2 Hz), 7.64 (2H, "t", $^{3}J_{HH}$ = 7.2 Hz), 7.59 (2H, "t", $^{3}J_{HH}$ = 6.8 Hz), 7.46 (4H, m), 7.38 (2H, m), 7.13 (1H, s), 2.03 (3H, s). ^{13}C NMR (Acetone-d_6)/ppm: δ_H= 183.9, 149.13, 136.31, 132.71, 132.05, 128.93, 127.96, 126.99, 125.10, 99.57, 10.00. 20.20.

1-(2,4-dinitrophenyl)-3,5-diphenyl-3-methyl-4,5,-cyclopentapyrazole (8): Yellow oil. λ_{max} (Acetone)/nm: 327 ($\pi\rightarrow\pi^{*}$). $\bar{\upsilon}_{max}$ (KBr)/cm^{-1}: 3059 (=C-H), 2922 (-C-H), 1600-1400 (C=C and C=N), 1387 (CH_3, bending), 1349 and 1549 (N=O). ^{1}H NMR (DMSO-d_6)/ppm: δ_H= 8.78 (1H, s), 8.50 (1H, d, $^{3}J_{HH}$ = 8.8 Hz), 7.93 (1H, d, $^{3}J_{HH}$ = 8.8 Hz), 2.96 (2H, m), 2.55 (4H, m), 2.10 (3H, s). ^{13}C NMR (Acetone-d_6)/ppm: δ_H= 151.81, 147.07, 144.55, 142.57, 137.01, 130.72, 127.50, 124.05, 121.16, 30.85, 25.51, 22.10, 11.73.

Results and Discussion

Characterization of nanoparticles

FT-IR spectra of nano-SC and nano-SPA are presented in Fig. 1. The Si-O-H and Si-O-Si stretching bands for these structures are detected at the range of 900 to 1100 cm^{-1}. In addition, for nano-SC, the Si-Cl stretching band is appeared at 700 cm^{-1}. The P-O-H, P=O and P-O stretching bands for nano-SPA are recorded at 910-1040, 1637 and 2400-2800 cm^{-1}, respectively.

In order to survey the surface morphology of nanoparticles and their size and porosity, the FESEM images were obtained (Figs 2a-c). According to these images, nano-SC and nano-SPA particles are amorphous as their parent silica gel. Nano-SC and nano-SPA particles are more porous than nano-SG while nano SG particles are more uniform. The average size distribution of these nanoparticles is 20, 60 and 30 nm for nano-SG, nano-SC and nano-SPA, respectively.

TEM images of nano-SG, nano-SC and nano-SPA have been also obtained in scale 80 nm (Figs 3a-c). These figures clearly show the amorphous nature of the non-uniform big particles which formed via the condensation of nearly spherical small particles with the average size of 20-35 nm.

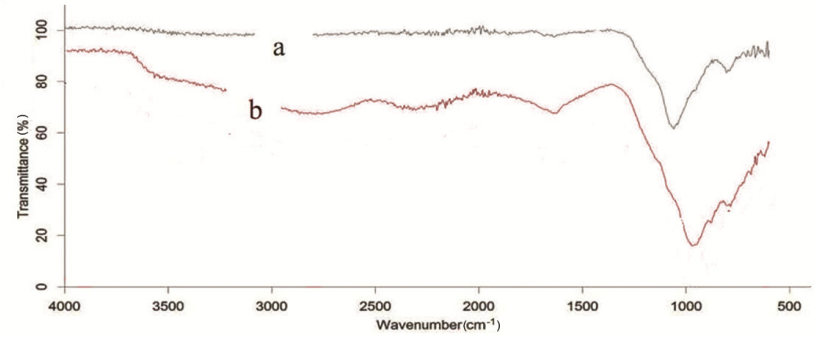


Fig. 1 — ATR spectra of (a) nano-SC and (b) nano-SPA

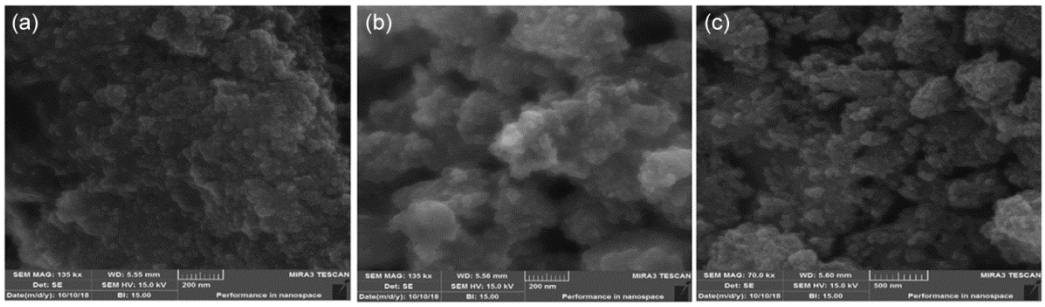


Fig. 2 —FESEM images of (a) nano-SG, (b) nano-SC and (c) nano-SPA

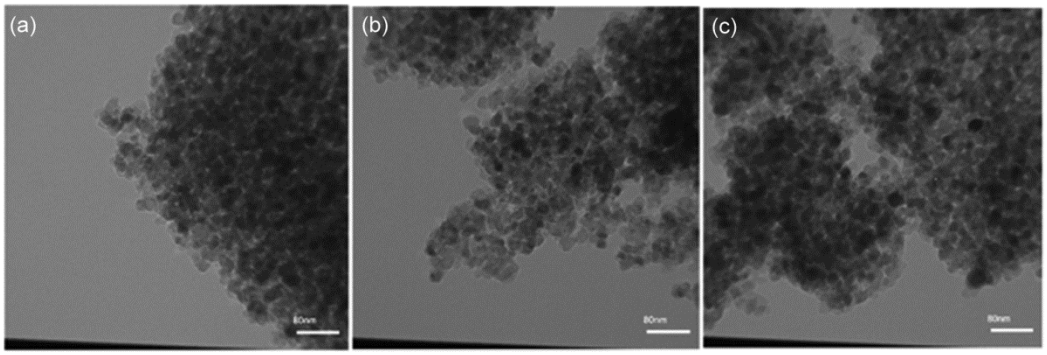


Fig. 3 — TEM images of (a) nano-SG, (b) nano-SC and (c) nano-SPA

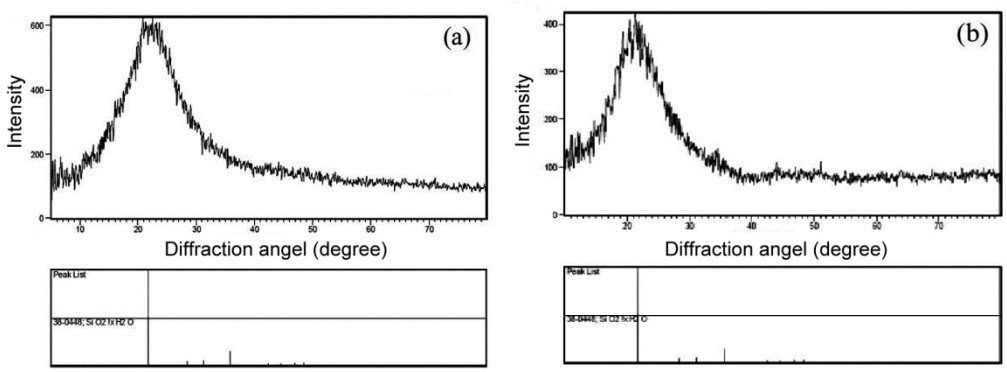


Fig. 4 — XRD pattern of (a) nano SC and (b) nano-SPA

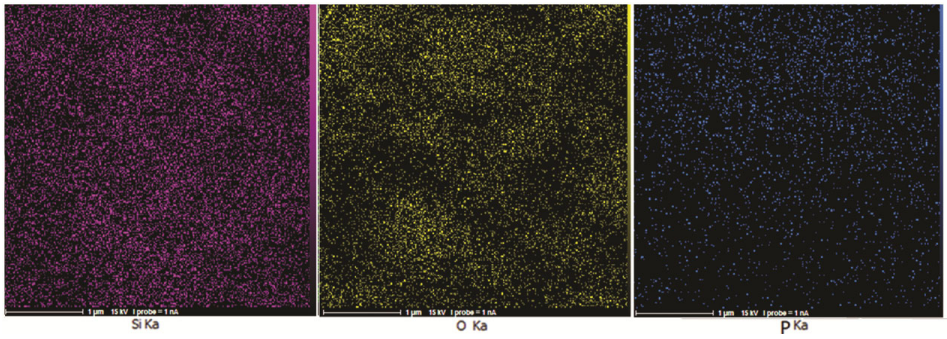


Fig. 5 — EDS mapping images of nano- SPA

XRD difractograms of nano-SG and nano-SPA are shown in Fig. 4. For each nanocatalyst, a strong broad peak is detected (2θ=21.8024° for nano-SG and 2θ=21.718 for nano-SPA).We suggest an amorphous and non-crystalline structures for nanoparticles because there are no peaks that would show a symmetrical structure[43].

The spatial distribution of Si, O and P in nano-SPA particles is confirmed by the EDS mapping images obtained for the catalyst (Fig. 5).

Specific surface area of nano-SPA was measured by BET analysis. The values of single point surface area, average pore diameter and the total pore volume at P/P_0=0.986 are 87/063 m²/g, 8/2172 nm and 0/1789 cm^3g^{-1}, respectively. The N_2 adsorption isotherm of catalyst is shown in Fig. 6.

Typical procedure for the preparation of 1-(2,4-dinitro phenyl) -3,5-dimethyl pyrazole (3j)

Various conditions for the synthesis of 1-(2,4-dinitro phenyl)-3,5-dimethyl pyrazole (**3j**) in the presence of nano-SPA were optimized. The results are summarized in Table 2. The best conditions were presented by using 0.07 g of nanocatalyst at 130°C under solvent free conditions (Entry 14).

Table 2 — Optimization of reaction conditions for preparation 1-(2,4-dinitro phenyl) -3,5-dimethyl pyrazole (3j)

Entry	Solvent	Catalyst (g)	Temperature (°C)	Time (min)	Yield (%)
1	EtOH	0.03	rt	720	10
2	MeOH	0.03	rt	720	5
3	CH_3CN	0.03	70	650	15
4	Solvent-free	0.03	70	600	25
5	Solvent-free	0.03	80	580	34
6	Solvent-free	0.03	100	500	43
7	Solvent-free	0.03	110	470	48
8	Solvent-free	0.03	120	450	55
9	Solvent-free	0.03	130	420	60
10	Solvent-free	0.03	140	420	60
11	Solvent-free	0.04	130	360	68
12	Solvent-free	0.05	130	300	73
13	Solvent-free	0.06	130	260	81
14	Solvent-free	0.07	130	150	88
15	Solvent-free	0.08	130	150	88

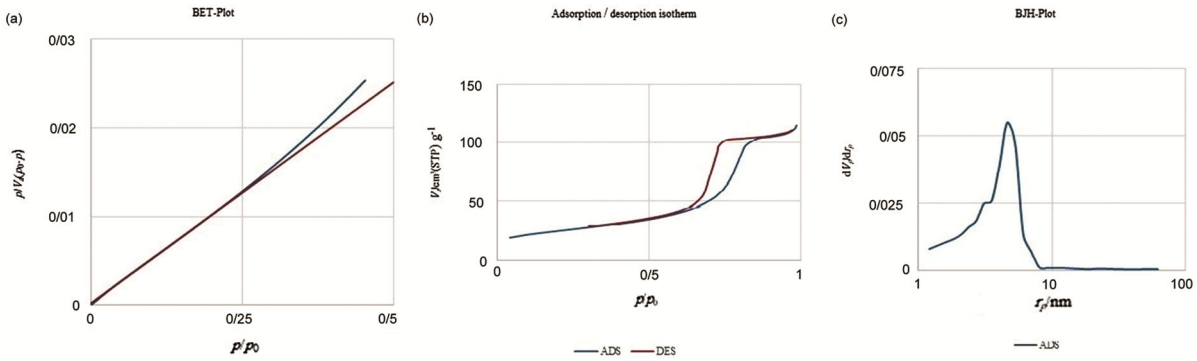


Fig. 6 — (a) BET plot, (b) adsorption desorption isotherm and (c) BJH (Barrett-Joyner-Halenda) plots of nano-SPA

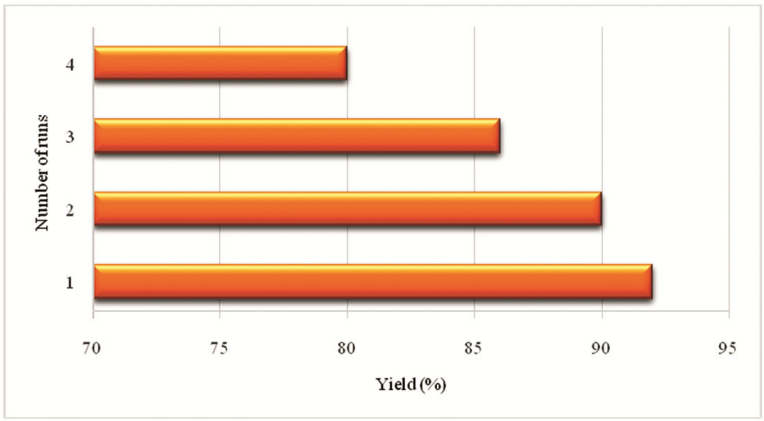


Fig. 7 — Reusability of nano-SPA

Reusability of the catalyst

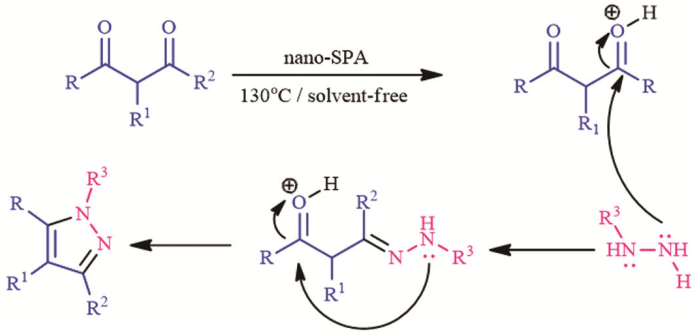
Reusability of nano-SPA was examined. After completion of the model reaction (Table 2, entry 7), nano-SPA was separated, washed with dichloromethane (3×5 mL) and dried to use for the next run. It was found that the nanocatalyst could be reused for four times without any considerable loss of its activity (Fig. 7).

Comparison of present method with previous reports

We compared this work with several previous reports. The results are summarized in Table 3 .As can be seen from this table, this catalyst is

Table 3 — The effect of various catalysts on the synthesis of pyrazoles under thermal and solvent-free conditions

Entry	Catalyst	Solvent	Conditions	Time (h)	Yield (%)	Ref.
1	37% $P_2O_5{\cdot}SiO_2$ (0.08g)	Solvent-free	100ºC	2	74	[44]
2	48% nano-$P_2O_5{\cdot}SiO_2$ (0.02g)	Solvent-free	120ºC	2	84	[44]
3	Y-Zeolite (1g)	CH_2Cl_2	rt	2	84	[45]
4	H_2SO_4 (0.1 drop)	Solvent-free	rt	1	86	[46]
5	20% PSSA (0.1 ml)	Solvent-free	rt	0.04	92	[47]
6	$Sc(OTf)_3$ (2 mol%)	Solvent-free	rt	0.35	94	[48]
7	$[a\text{-}Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}]$ (0.025)	Solvent-free	40ºC	2	95	[49]
8	Nano-SSA(0.014)	Solvent-free	60ºC	0.5	95	[50]
9	nano-SPA (0.07g)	Solvent-free	130ºC	2.5	92	This work



Scheme 3 — Proposed mechanism for one-pot synthesis of pyrazole derivatives in the presence of nano-SPA

considerably efficient for the synthesis of pyrazoles under thermal and solvent-free conditions.

Mechanism of the reaction

A possible mechanism for the condensation reaction of hydrazine derivatives with various 1,3-diketones in the presence of nano-SPA is shown in Scheme 3. According to the suggested mechanism, at first, nano-SPA activates the carbonyl groups of 1,3-diketone and then the nucleophilic attack from nitrogen of hydrazine occurs at the activated carbonyl of aldehyde and a molecule of water is removed. The process is repeated again and the product formed after a cycloaddition reaction.

Conclusion

In this work, we have introduced a green procedure for the synthesis of highly substituted pyrazoles via condensation of 1,3-diketones and hydrazine derivatives in the presence of nano-SPA as a recyclable solid acid catalyst. This procedure is solvent- free with remarkable advantages such as easy and clean work up, high yields, reusability of catalyst and heterogeneous conditions.

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