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V_2O_5/SiO_2 AS AN EFFICIENT CATALYST IN THE SYNTHESIS OF 5-AMINO-PYRAZOLE DERIVATIVES UNDER SOLVENT FREE CONDITION

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ABSTRACT. An efficient and facile approach for the synthesis of 5-aminopyrazoles from ketene *S,N*-acetal and hydrazine hydrate *via* catalytic reaction under solvent free condition has been described. V_2O_5/SiO_2 as a heterogeneous catalyst was prepared and characterized using X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) and scanning electron microscope (SEM).

KEY WORDS: One-pot synthesis, 5-Amino-1*H*-pyrazole, Hydrazine hydrate, Vanadium oxide, Silica

INTRODUCTION

Pyrazoles and their derivatives have attracted considerable interest during the last two decades due to their biological activities. For example, compound **A**, has been shown to exhibit antifungal activity [1]. Compound **B** is a potent inhibitors of neutrophil chemotactic responsiveness [2]. In addition, compound **C** showed antitumor activity by inhibition of cyclin-dependent kinases (CDK) [3] (Figure 1). Furthermore, pyrazole compounds used as intermediates in the synthesis of various bioactive compounds such as pyrazolopyrimidines, pyrazolotriazines, pyrazoloquinazolines and Schiff bases [4-9].

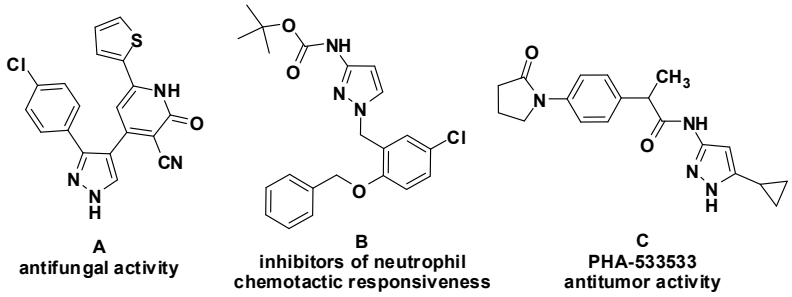

Figure 1. Structures of the biological activities of pyrazole derivatives A-C.

A recent review of 5-aminopyrazoles described the miscellaneous synthetic methods [10] as the condensation of β-ketonitriles [11] or malononitrile derivatives [12] with hydrazine hydrate. The literature survey describe that, the general method for the synthesis of 5-aminopyrazole was done by mixing the ketene *S,N*-acetal with hydrazine hydrate under reflux condition in ethanol [13].

A green chemistry characterized by more than one advantage safe, facile and free solvent reaction. Therefore, it is favorable for most researchers to use this technique. Basically for the

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reactions under heterogeneous catalytic condition, it is preferable than other catalytic conditions safe to store, insoluble in organic solvents, long lifetime, solid structure that avoids the conjunction of active catalyst and good thermal stability. Nowadays, solid acid catalysts play a significance role in organic synthesis under heterogeneous conditions [14]. Its constituents based on clay and silica [15].

The literature survey explained that a silica-based catalyst was widely applicable as presented in modern synthetic methods. In this work, we are trying to explore some significance and commonly used silica-based catalyst in organic synthesis. In addition, green organic reactions in solvent free conditions have attracted a great attention since it is eco-friendly, non-toxic, and economic cost compared to classical reactions in organic solvents.

From previously explained facts, we reported in this paper the synthesis of 5-aminopyrazole derivatives from the ketene acetal with hydrazine hydrate in solvent free condition by using catalysis for simple procedure optimum results than previous methods.

EXPERIMENTAL

Catalyst preparation

To a suspension of SiO_2 (for column chromatography, mesh 70-230, 0.06-0.2 mm, 2 g) in 50 mL $CHCl_3$, V_2O_5 (1 g) was added. The mixture stirred at room temperature for 90 min. The solvent was evaporated at room temperature to obtain a brown solid of 50% (w/w) V_2O_5/SiO_2. The catalyst was characterized by the following methods.

Catalyst characterization

X-Ray diffraction. X-Ray diffraction (XRD) pattern were recorded using PANalyticalX`Pert PRO XRD system occupied with Cu Kα of wavelength λ = 1.540 Å and tube operating voltage of 30 kV. Measured Bragg's angle (2θ) varied in between 5 to 60 degree.

Fourier transform infrared. Fourier transform infrared (FTIR) measurement was recorded on a single beam spectrometer type Nicolet iS10 in the spectral range 4000-400 cm^{-1} at room temperature. KBr technique was used for measurements, 1/100 sample/KBr ratio with wavelength precision 0.01 cm^{-1} and spectral resolution 0.4 cm^{-1}.

Scanning electron microscopy (SEM). The morphology of prepared catalyst was characterized by scanning electron microscopy using (Jeol, Quanta FEG), operating at 200 V-30 kV accelerating voltage magnification 14 xup to 5000 x. Surfaces of the samples were coated with a thin layer of gold (3.5 nm) by the vacuum evaporation technique to minimize sample charging effects due to the electron beam.

Chemicals and apparatus

Melting points are uncorrected. NMR spectra were scanned in DMSO-d_6 on a Brucker NMR spectrophotometer at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts are expressed in δ-values (parts per million) relative to an internal standard (TMS at 0.0 ppm) and coupling constants (*J*) in Hz. Mass spectra were recorded on a Agilent LC-MS spectrometer (pump quarter nary 1200 Series, quadruple MSD 6110); LC column into multimode (ESI+APCI) ion source of MSD. Thin layer chromatography (TLC) was performed on Merck silica gel F_{254} plates and visualized by UV-light (254 nm) and all chemicals were purchased from Sigma-Aldrich.

General procedure and structure elucidation

The reaction was started by mixing ketene *S,N*-acetals (10 mmol) and hydrazine hydrate (20 mmol), the V_2O_5/SiO_2 (0.2 g, 20 mol %) was added and the mixture was allowed to stir at 70-80 ^oC. The reaction was monitored by TLC until reaction completion. Ethyl acetate (20 mL) was added to the reaction mixture. Then, the mixture was filtered off and the extract was vaporized. The remaining residue was recrystallized to give pure product.

5-Amino-3-(phenylamino)-1H-pyrazole-4-carboxamide ***(1)***. White, m.p. 178-180 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 5.79 (s, *br*, 2H, NH_2), 6.70 (s, 2H, NH_2), 7.13-7.31 (m, 5H, C_6H_5), 8.92 (s, *br*, NH), 10.95 (s, *br*, 1H, NH). MS (*m/z*): 217 (M^+) [16].

5-Amino-N-phenyl-3-(phenylamino)-1H-pyrazole-4-carboxamide ***(2)***. White, m.p. 247 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 6.01 (s, 2H, NH_2), 6.76-7.48 (m, 10H, $2C_6H_5$), 8.52 (s, 1H, NH), 8.73 (s, 1H, NH), 11.32 (s, 1H, NH). MS (*m/z*): 293 (M^+) [17].

5-Amino-3-(phenylamino)-N-(4-methylphenyl)-1H-pyrazole-4-carboxamide ***(3)***. White, m.p. 178 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 2.23 (s, 3H, CH_3), 5.98 (s, 2H, NH_2), 7.05-7.37 (m, 9H, C_6H_4 and C_6H_5), 8.54 (s, 1H, NH), 8.64 (s, 1H, NH), 11.29 (s, 1H, NH). MS (*m/z*): 308 (M^++1) [17].

5-Amino-N-(4-chlorophenyl)-3-(phenylamino)-1H-pyrazole-4-carboxamide ***(4)***. White, m.p. 115 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 6.02 (s, 2H, NH_2), 6.76-7.54 (m, 9H, C_6H_4 and C_6H_5), 8.51 (s, 1H, NH), 8.81 (s, 1H, NH), 11.29 (s, 1H, NH). MS (*m/z*): 327 (M^+) [17].

5-Amino-3-[(4-methoxyphenyl)amino]-1H-pyrazole-4-carboxamide ***(5)***. White crystals, m.p. 200 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 3.64 (s, 3H, OCH_3), 5.74 (s, 2H, NH_2, D_2O exchangeable), 6.60 (s, 2H, NH_2, D_2O exchangeable), 6.75 (d, 2H, aromatic, *AB-system*, J_{HH}=8.4 Hz), 7.24 (d, 2H, aromatic, *AB-system*, J_{HH}=8.4 Hz), 8.68 (s, 1H, NH, D_2O exchangeable), 10.82 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm) 55.6 (-OCH_3), 86.2 (C_4, pyrazole), 114.6 (2C, aromatic), 117.4 (2C, aromatic), 137.0 (C, aromatic), 148.2 (C_5, pyrazole), 152.2 (C_3, pyrazole), 152.8 (C, aromatic), 167.2 (C=O, amide). MS (*m/z*): 247 (M^+) [18].

5-Amino-3-[(4-methoxyphenyl)amino]-N-phenyl-1H-pyrazole-4-carboxamide (6). White crystals, m.p. 175-177 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 3.63 (s, 3H, OCH_3), 5.98 (s, 2H, NH_2, D_2O exchangeable), 6.76 (d, 2H, aromatic, J_{HH}=7.7 Hz), 6.98 (t, 1H, aromatic, J_{HH}=7.7 Hz), 7.18 (t, 2H, aromatic, J_{HH}=8.4 Hz), 7.25 (d, 2H, aromatic, J_{HH}=7.7 Hz), 7.45 (d, 2H, aromatic, J_{HH}=7.7 Hz), 8.30 (s, 1H, NH, D_2O exchangeable), 8.74 (s, 1H, NH, D_2O exchangeable), 11.22 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm) 55.6 (-OCH_3), 88.3 (C_4, pyrazole), 114.7, 117.5, 120.3, 123.3, 129.1, 137.6, 139.4 (11C, aromatic), 149.1 (C_5, pyrazole), 150.9 (C_3, pyrazole), 153.1 (C, aromatic), 163.6 (C=O) [19].

5-Amino-3-[(4-methoxyphenyl)amino]-N-(4-methylphenyl)-1H-pyrazole-4-carboxamide ***(7)***. White crystals, m.p. 198-200 ^oC. ^1H-NMR (DMSO-d_6, δ ppm) 2.21 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 5.95 (s, 2H, NH_2, D_2O exchangeable), 6.76 (d, 2H, aromatic, J_{HH}=8.4 Hz), 7.04 (d, 2H, aromatic, J_{HH}=8.4 Hz), 7.16 (d, 2H, aromatic, J_{HH}=8.4 Hz), 7.33 (d, 2H, aromatic, J_{HH}=8.4 Hz), 8.30 (s, 1H, NH, D_2O exchangeable), 8.66 (s, 1H, NH, D_2O exchangeable), 11.21 (s, 1H, NH, D_2O exchangeable) [19].

5-Amino-N-(4-chlorophenyl)-3-[(4-methoxyphenyl)amino]-1H-pyrazole-4-carboxamide ***(8)***. White crystals, m.p. 190-192 ^oC. ^1H NMR (DMSO-d_6, δ ppm) 3.64 (s, 3H, OCH_3), 6.00 (s, 2H, NH_2, D_2O exchangeable), 6.77-7.51 (m, 8H, aromatic), 8.30 (s, 1H, NH, D_2O exchangeable),

8.82 (s, 1H, NH, D_2O exchangeable), 11.20 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, δ ppm) 55.7 (-OCH_3), 87.9 (C_4, pyrazole), 114.7, 117.7, 121.9, 126.8, 128.9, 137.4, 138.4 (11C, aromatic), 149.1 (C_5, pyrazole), 151.1 (C_3, pyrazole), 153.2 (C, aromatic), 163.6 (C=O). MS (*m/z*): 358 (M^+) [19]. X-ray crystal structure is shown in Figure 3.

RESULTS AND DISCUSSION

Catalyst preparation and characterization

Catalyst was prepared and characterized before using XRD, FTIR spectra and SEM [20]. X-Ray diffraction pattern for SiO_2 and prepared V_2O_5/SiO_2. XRD of SiO_2 show the amorphous nature

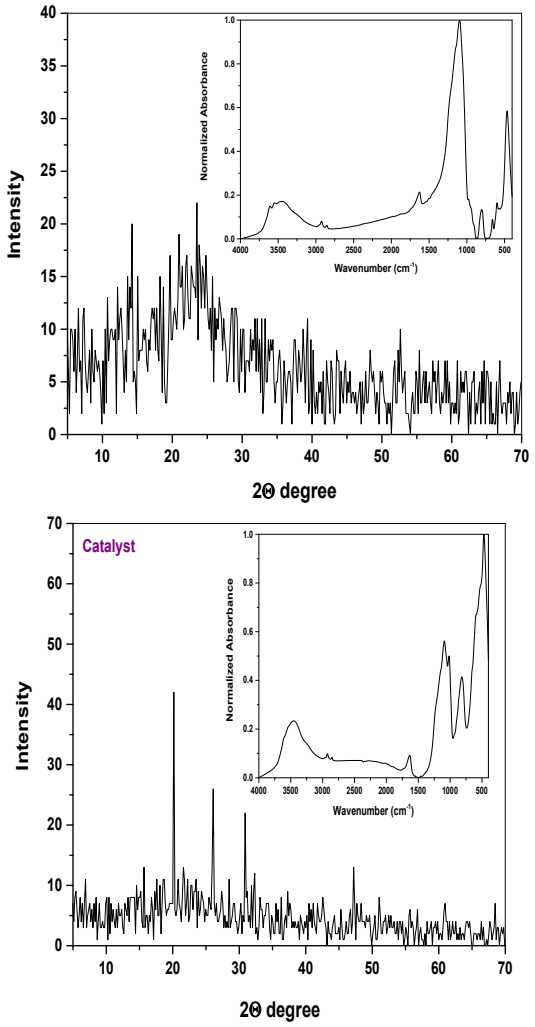
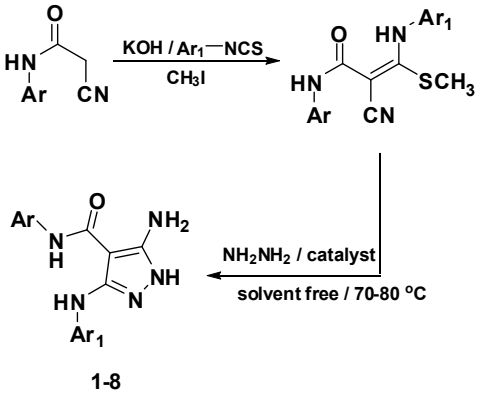


Figure 2. XRD diffraction scans and collective FTIR spectra of received silica and vanadium dioxide before the catalyst preparation and after interaction.

with no sharp peaks and the prepared V_2O_5/SiO_2 explains sharp intense peaks at about (20.2, 26.1, 31.0 and 47.3°) and less intense sharp peaks at about (14.8, 24 and 53.5°) explaining the formation of crystalline phase with orthorhombic geometry. The partially hydrated silanols (Si–OH residue) and bonded hydrogen bands were reported in the range from 3500 to 3055 cm^{-1} band [21-23]. A detected band at 1030-1230 cm^{-1} overlapped with another broad band recognized to Si–OH and Si–O–Si vibrations observed. The FTIR spectra of the catalyst band presented at 990 cm^{-1} for V\O as a vibration-stretching band. Also, it was observed a various functional groups at 3400 cm^{-1} for OH stretching and at 1571 cm^{-1} for bending OH vibration, this result is due to wide specific surface area of silica and water molecules that trapped by the obtained catalyst (Figure 2).

Organic synthesis

Catalysts contain silicon element attracted our attention and play an important role in our group [24-26], and we forward are the aim of investigation new methods for design and synthesis of heterocyclic compounds by efficient and simple reaction. This work presented the synthesis of 5-aminopyrazole derivatives using V_2O_5/SiO_2 as a heterogeneous catalyst under solvent free condition. The reaction was done *via* mixing one mol of ketene *S*,*N*-acetals and two moles of hydrazine hydrate (80%) in the presence of selected catalyst under solvent free condition and in the way to prove the effectiveness of our mixed catalyst (Scheme 1).

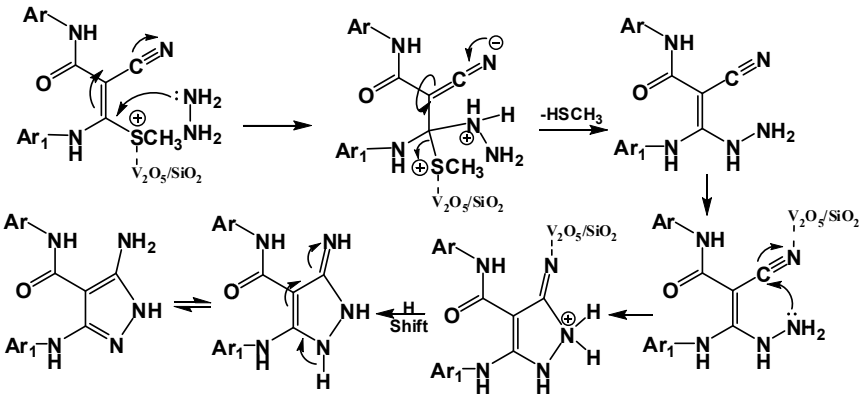


	Ar	Ar_1
1	H	C_6H_5
2	C_6H_5	C_6H_5
3	4-CH_3-C_6H_4	C_6H_5
4	4-Cl-C_6H_4	C_6H_5
5	H	4-CH_3O-C_6H_4
6	C_6H_5	4-CH_3O-C_6H_4
7	4-CH_3-C_6H_4	4-CH_3O-C_6H_4
8	4-Cl-C_6H_4	4-CH_3O-C_6H_4

Scheme 1. Synthesis of 5-aminopyrazole derivatives **1-8**

The suggested mechanism for the V_2O_5/SiO_2-catalyzed synthesis of 5-aminopyrazole is presented in Scheme 2. The initial step involves improve the leaving power of (-SCH_3) by the catalyst and then nucleophilic substitution occurs by hydrazine hydrate and in the second step the catalyst activate the nitrile group towards nucleophlic attack from (NH_2). Ultimately, the reaction ended by H-rearrangement to obtain more stable structure.

The proposed reaction mechanism was confirmed by the single crystal X-ray structure analysis of compound **8** (Figure 3) [The crystallographic data was deposited to the Cambridge Crystallographic Data Center (CCDC 1528985)].



Scheme 2. The proposed reaction mechanism.

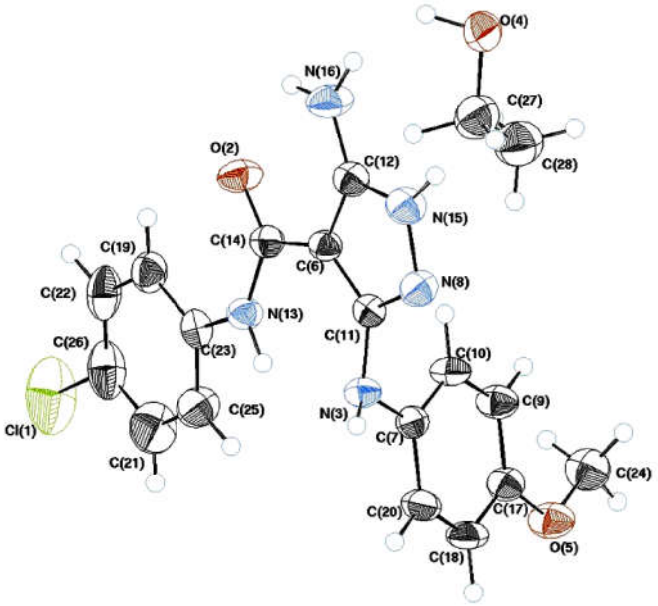


Figure 3. X-ray structure of compound **8**.

These results prompted us to explore the potential of this protocol for the synthesis of various 5-aminopyrazole **1-8** in excellent yield. The results summarized in Table 1. From the data presented in the Table 1, we noticed that when (Ar_1) equal (C_6H_5) the reaction gives more yield and less reaction time. In addition, the presence of halogen in *para* position of aromatic ring at (Ar) gives more yields and less reaction time rather than the presence of methyl group in *para* position.

Table 1. Synthesis of 5-aminopyrazole **1-8** derivatives from ketene *S,N*-acetals and hydrazine hydrate.

Entry	Ar	Ar_1	Traditional method		Ref.	Catalysis method	
			Yield (%)	Time (min)		Yield (%)	Time (min)
1	H	C_6H_5	85	120	[16]	93	20
2	C_6H_5	C_6H_5	75	120-180	[17]	92	20
3	4-CH_3-C_6H_4-	C_6H_5	77	120-180	[17]	90	25
4	4-Cl-C_6H_4-	C_6H_5	78	120-180	[17]	95	15
5	H	4-CH_3O-C_6H_4-	82	240	[18]	91	30
6	C_6H_5	4-CH_3O-C_6H_4-	79	240	[19]	92	25
7	4-CH_3-C_6H_4-	4-CH_3O-C_6H_4-	82	240	[19]	88	25
8	4-Cl-C_6H_4-	4-CH_3O-C_6H_4-	80	240	[19]	93	20

CONCLUSION

In conclusion, we have prepared and characterized V_2O_5/SiO_2 as a heterogeneous catalyst, which has been successful used as effective catalyst for the synthesis of various 5-aminopyrazoles **1-8**. This procedure has many advantages compared with common reported methods in terms of high yield, mild reaction condition, simple procedure, green catalyst, low cost, lack of toxicity and simplicity of workup.

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