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Research Article

EFFICIENT SYNTHESIS OF PYRANOPYRAZOLE DERIVATIVES USING SILICA GRAFTED COPPER STANNATE CATALYST

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ABSTRACT

The $CuSnO_3$:SiO_2 catalyst was synthesized by hydrothermal method. The polycrystalline products were analyzed by using various physical investigative techniques including XRD, SEM, TEM and BET surface area. The present study deals with one-pot, four component reaction of aldehydes, malononitrile hydrazine hydrate and ethyl acetoacetate in the presence of catalytic amount of Silica grafted $CuSnO_3$ in ethanol at 70°C to prepare series of pyranopyrazoles. This method gives high yield of pyranopyrazoles in short reaction time with economic availability of the catalyst and easy purification.

Keywords: Pyranopyrazoles, Multicomponent reaction, Silica grafted $CuSnO_3$.

1. INTRODUCTION

The solvent-free synthesis is non-hazardous alternative to synthetic of organic molecules. Multicomponent reactions using reusable heterogeneous catalysts for the sustainable development of chemical enterprise has focused attention due to an increase in regulatory restrictions on the use, manufacture and disposal of organic solvents. These reactions are alternatives to traditional reactions using organic solvents, for example, the consumption of environmentally hazardous solvents is reduced due to solvent-free, multi-component reactions involving reusable heterogeneous catalysts and utilize scaled-down reaction vessels. In different areas of organic synthesis, the use of solid acids has received considerable attention as heterogeneous catalyst in recent years [1]. Heteropolyacids (HPAs) have many advantages such as experimental simplicity with high flexibility on modification of the acid strength, environmental compatibility, ease of handling and non-toxicity [2]. Conventionally catalyzing reactions using Lewis acids are efficiently catalyzed by heteropolyacids as they possess a strong purely Bronsted acidity. Thus, the process is convenient and eco-friendly using HPAs as a catalyst. The dehydration of diols, tetra-hydropyranylation of alcohols, rearrangements, Friedel-Craft alkylation, synthesis of dihydroquinolines and pyrimidine, Prins reaction, Dakin-West reaction Biginelli reaction are efficiently catalyzed by HPAs as a catalyst [3-11]. Pyranopyrazoles are reported to possess pharmacological properties including insecticidal, antimicrobial, anti-inflammatory, anticancer and molluscicidal activities, potential inhibitors of human Chk1 kinase. They are an important class of biologically active heterocycles [12] also having applications as pharmaceutical ingredients and biodegradable agro-chemicals [13]. Pyrazole derivatives have several biological activities as they represent the active classes of compounds [14-24]. In recent years, wide range of drugs like Fomepizole inhibits alcohol dehydrogenase; and Sildenafil inhibits phosphodiesterase Celecoxib; demonstrates anti-inflammatory effects and inhibits COX-2; Rimonabant utilized to treat obesity; are developed from pyrazole derivatives. Due to great importance of pyranopyrazoles, several methods for synthesis of 6-amino-5-cyanodihydro-pyrano- [2,3-c] pyrazoles have been reported. These compounds may be synthesized from the reaction of malononitrile, 4-arylmethylene-5- pyrazolone and or 2-pyrazolin-5-ones and benzylidenemalononitriles [25]. The first pyrano-pyrazole was synthesized from the reaction of

tetracyanoethylene and 3-methyl-1- phenylpyrazolin-5-one [26]. The reaction of arylidiene malononitrile with 3-methylpyrazoline-5-ones or by the condensation of 4- arylidienepyrazoline-5-one with malononitrile gives 6-amino-5-cyanodihydro-pyrano [2,3-c] pyrazoles derivatives [16]. Three-component reaction using malononitrile, an aldehyde and pyrazolone using triethylamine catalyst in ethanol was developed by Sharanin et al. [27]. The synthesis of pyranopyrazole derivatives by using an efficient four-component reaction in presence of bases such as piperidine, pyrrolidine, morpholine and triethylamine at ambient temperature was reported by Vasuki and coworkers [28]. Kappusami et al. use per-6-amino-β-cyclodextrin as a catalyst for solvent-free multicomponent synthesis of pyranopyrazoles. More, recently Myrboh et al. developed the reaction protocol for the synthesis of pyranopyrazoles using L-proline and γ-alumina as catalyst [29].

Here, we report novel one pot four component simple, rapid and high yielding reaction for the synthesis of pyranopyrazole derivatives using eco- friendly $CuSnO_3$:SiO_2 as a catalyst (Scheme 1). It may contribute in ongoing program on the development of methods in organic synthesis [30].

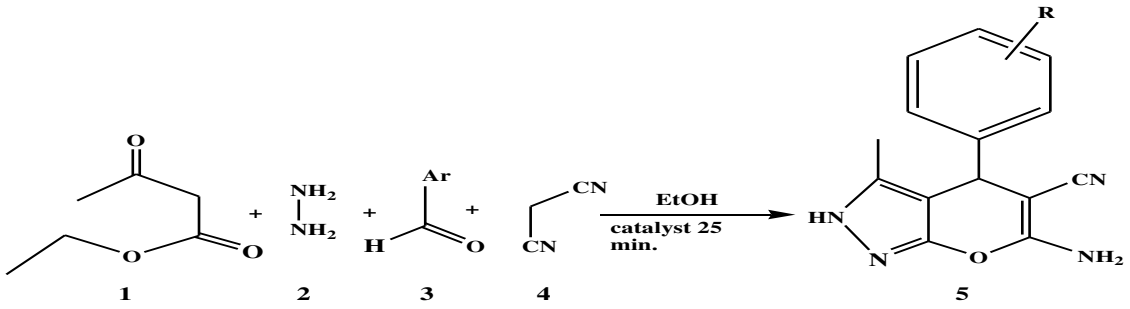
2. EXPERIMENTAL

2.1. Material and reagents

All the reagents, copper chloride ($CuCl_2$), Sigma-Aldrich, 99.99 %), tin chloride ($SnCl_4$, Sigma-Aldrich, 99.90 %) and sodium hydroxide (NaOH, Merck, 99 %) were purchased and used without further purification.

2.2. Synthesis of $CuSnO_3$

Equimolar mixture of analytical grade $CuCl_2$ (1 mol) and $SnCl_4$ (1 mol) was mixed with 1N NaOH and 0.5N sodium malonate surfactant. This reaction mixture was poured in Teflon autoclave which was kept in the oven at 120°C for 24 hrs. After 24 hrs, the product was cooled then filtered and washed with distilled water. The synthesized product was dried at 120°C for 12 hrs in the oven. Later on, the material was ground in morter and pestle and it was further calcined at 450°C for another 3 h. Finally, obtained polycrystalline $CuSnO_3$ powder was used for its characterization.



Scheme 1: Synthesis of pyranopyrazole derivatives using $CuSnO_3$:SiO_2 as a catalyst

2.3. Synthesis of silica grafted $CuSnO_3$

The silica grafted $CuSnO_3$ catalyst was prepared by mixing requisite amount of SiO_2 solution (1mol %) with synthesized $CuSnO_3$ powder (1 mol %) along with buffer solution. The solution obtained was then stirred for 1 h and transferred into steel lined Teflon autoclave. It was kept in the oven at 120°C for 24 h. The precipitate obtained was filtered and then washed with distilled water. Finally, it was dried at 100°C for 12 h in the oven. The brown polycrystalline product was directly placed in the furnace for calcination at 450°C for 4 h.

2.4. Characterization

Various analytical techniques were employed to characterize the synthesized pure $CuSnO_3$ powder. On a multipurpose X-ray diffractometer (Philips-1710 diffractometer with CuKα, λ=1.5406 Å), the XRD pattern was recorded at a scan rate of 0.17° 2θ S^{-1}. On a Hitachi SU 70 FESEM with a Scotty electron gun, electron micrograph images were taken. The Structure and particle size of the synthesized materials were studied using TEM with SAED on CM-200, Phillips's microscope. On Quantachrome Autosorb Automated Gas Sorption System Autosorb-1, NOVA-1200 and Mercury PorosimeterAutosorb-1c, the BET surface area was measured by N_2 adsorption–desorption isotherm.

2.5. General Procedure for the Synthesis of the Pyranopyrazoles (3a-j)

In a 25 ml R.B. flask, ethyl acetoacetate (0.26 g, 1mmol), hydrazine hydrate 96% (0.107 g, 1mmol), 3-nitro benzaldehyde (0.30 g, 2 mmol), malononitrile (0.13 g, 1mmol) and Silica grafted $CuSnO_3$ (2 mol)

were taken. Under solvent free conditions, the reaction mixture was heated for 10 mins at 60°C. On completion of reaction, it was cooled to room temperature, acetonitrile was added and then shaken well for 5 min and, then poured over crushed ice, stirred for 10 min. The precipitate of product was obtained which is filtered and then washed with water, dried and recrystallized by using methanol as a solvent.

3. RESULTS AND DISCUSSION

3.1. Spectral and analytical data of some representative compounds

3.1.1. 6-Amino-3-methyl-4-phenyl-2,4-dihydro-pyrano[2,3-c]-pyrazole-5-carbonitrile (3a)

FT-IR (KBr) (cm^{-1}): 1045, 2193, 3172, 3311 ,3374, ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.77 (s, 3H), 4.58 (s, 1H), 6.85 (s, 2H), 7.15-7.23 (m, 3H), 7.29-7.33 (m, 2H), 12.08 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 9.69, 36.19, 57.15, 97.60, 120.74, 126.69, 127.42, 128.39, 135.53, 144.40, 154.73, 160.83.

3.1.2. 6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]-pyrazole-5- carbonitrile (3b)

FT-IR (KBr) (cm^{-1}): 768, 1087, 2221, 3241, ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.09 (s, 3H), 4.23 (s, 1H), 6.37 (s, 2H), 7.32-7.45 (m, 3H), 7.65-7.79 (m, 2H), 9.08 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.54, 32.78, 62.43, 102.43, 112.87, 120.74, 122.76, 124.56, 131.21, 142.28, 144.12, 156.21.

3.1.3. 6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5 carbonitrile (3c)

FT-IR (KBr) ν(cm^{-1}): 1029, 2195, 2981, 3220, 3274, 3328, 3412, 3490. 1 H-NMR (400 MHz, DMSO-d6) δ: 1.81 (s, 3H), 3.70 (s, 3H), 4.49 (s, 1H), 6.52-6.55 (m, 1H), 6.69-6.71 (m, 2H), 6.77 (s, 2H), 8.83 (s, 1H), 12.04 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 9.79, 35.79, 55.57, 57.59, 97.85, 111.57, 115.37, 119.72, 120.87, 135.34, 135.55, 145.19, 147.29, 154.68, 160.64.

3.1.4. 6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5- carbonitrile (3d)

FT-IR (KBr) νmax (cm^{-1}): 1024, 2176, 2898, 3276, 3310, 3387, 3421. 1 H-NMR (400 MHz, DMSO-d_6) δ: 1.54 (s, 3H), 3.65 (s, 3H), 6.78-7.09 (m, 1H), 7.15-7.38 (m, 2H), 6.86 (s, 2H), 8.34 (s, 1H), 10.15 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 16.26, 38.56, 61.12, 62.34, 102.12, 112.18, 116.65, 120.47, 122. 91, 136.21, 138.12, 148.54, 149.12, 152.32, 158.12.

3.2. General

Hydrothermally synthesized products were calcined at 450°C for 3 h to remove organic matter and then analysed by X-ray diffraction method. The pure $CuSnO_3$ shows XRD pattern with 2θ values along with (hkl) planes at 25.6 (100), 28.4 (110), 33.5 (200), 34.5 (200), 50.1 (101). These peaks in the XRD profile well matches with JCPDS data (Card No. 270997) and confirm that crystals are cubic in nature. Fig. 1b gives XRD pattern for $CuSnO_3$:SiO_2 having 2θ values with (hkl) plane are 25.9 (110), 28.7 (111), 34.5 (111), 35.5 (002), 42.4 (100), 50.3 (202) 56.3 (220), 62.4 (211), 67.85 (111), 76.54 (200). The recorded XRD pattern shows there is no any amorphous phase found and it reveals that product is highly polycrystalline with cubic in nature.

SEM images along with EDAX pattern were obtained for synthesized nanocrystalline products. Using SEM technique, it was found that, the $CuSnO_3$, $CuSnO_3$:SiO_2 shows that few particles are big, some of the short and most of them are agglomerated. The EDAX analysis confirms the stoichiometric composition taken during analysis and also confirmed the presence of Cu, Sn, Si, and O elements in catalyst with stoichiometric composition.

TEM images along with SAED pattern were obtained for synthesized three nanocrystalline products. It was observed that most of the $CuSnO_3$ crystals are cubic in nature. The particle size obtained by TEM for $CuSnO_3$ is found to be 104.5 nm. The particle size for $CuSnO_3$: SiO_2 by TEM is 98.72 nm. TEM analysis clearly reveals that crystals are cubic in nature and well matches with XRD analysis.

In catalysis, surface area of material plays an important role. In the present investigation, the typical N_2 adsorption/desorption isotherm and BJH pore distribution of prepared $CuSnO_3$ and $CuSnO_3$:SiO_2 are nearly same in curve shape which is depicted in Fig. 1a-b. N_2-adsorption/desorption isotherm method gives detailed information about surface area (BET), the mesoporous volume and pore size distribution. This method leads to the identification of mesoporous material as it shows the isotherm profile as type IV in the BDDT system. All the samples have narrow pore diameter range indicated by the BJH pore size

distribution. The BET surface area (S_{BET}), pore volume (Vp), pore diameter (Dp) and other parameters are recorded in table 1. This clearly gives evidence that the grafting of SiO_2 with $CuSnO_3$ shows increase in large surface area (Table 1). A careful inspection of Table 1 shows that the surface area was found to be highest for $CuSnO_3$:SiO_2 is 110.10 m^2/g, the average pore volume and diameter are 0.04565cc/g and 82.29Å. For $CuSnO_3$, the surface area is 89.439m^2/g, the average pore volume (Vp) and pore diameter (dp) are 0.0428cc/g and 90.68Å respectively.

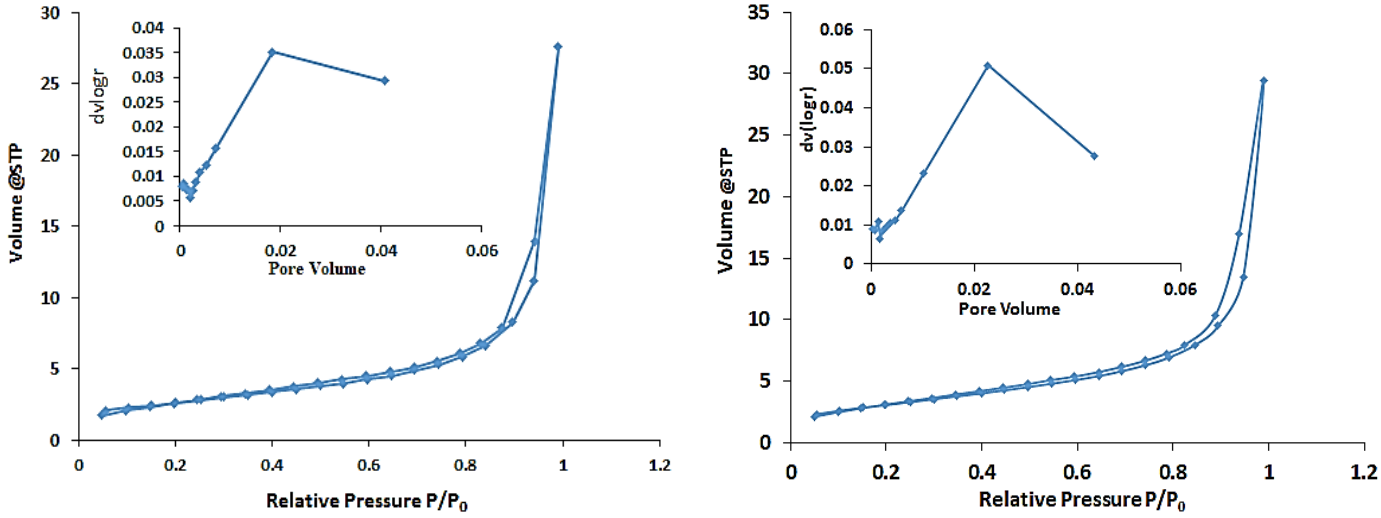


Fig. 1: BET analysis of a) $CuSnO_3$, b) $CuSnO_3$:SiO_2

Table 1: BET surface area, pore diameter and pore volume of $CuSnO_3$ and $CuSnO_3$:SiO_2

Synthesized compound	Surface area (m^2/g)	Pore volume (cc/g)	Pore diameter (Å)
$CuSnO_3$	89.439	0.0428	90.68
$CuSnO_3$: SiO_2	110.10	0.04565	82.29

The n-propylamine; a strong base, was used to measure acidity of the catalysts by potentiometric titration. On sites of different acid strengths adsorption of n-propyl amine could be expected. Without distinguishing the type of acidity, the total solid acidity is titrated. The potentiometric titration curves obtained for $CuSnO_3$ and $CuSnO_3$:SiO_2 during the titration with n-propylamine are shown in Fig. 2. Total number of acid sites is evaluated by this technique (meq amine/gm catalyst) as well as their strength (E_i) on the catalyst surface. The acid sites strength classified by using following scale: E_i> 100 mV (very strong sites), 0<E_i< 100 mV (strong sites), -100 <E_i<0 mV (weak sites), and E_i< -100 mV (very weak sites) [21]. Fig. 2 shows the titration curves of $CuSnO_3$ and $CuSnO_3$:SiO_2 acid catalysts. According to this scale, $CuSnO_3$ and $CuSnO_3$:SiO_2 show total number of acidic sites at 0.56, 0.67, 0.92 and 1.25 mmol gm^{-1} respectively along with strong acid sites at E_i = 76, 80 mV. It is observed that the strength of acid sites of $CuSnO_3$:SiO_2 is stronger than the others.

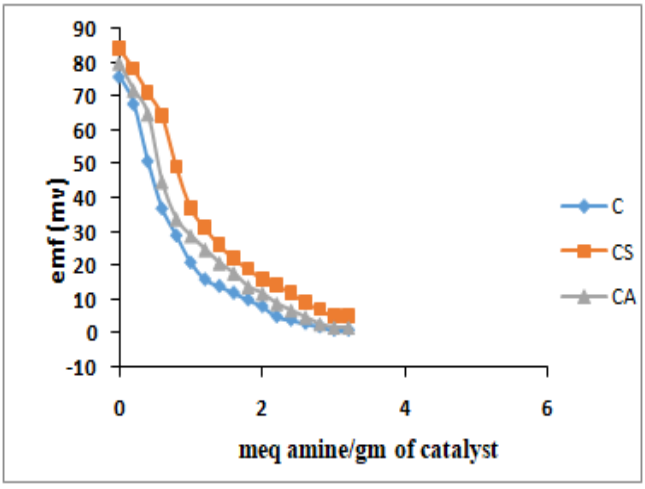


Fig. 2: Potentiometric titration curves for $CuSnO_3$(C), and $CuSnO_3$:SiO_2 (CS) catalysts

We initially focused on the one pot, four component solvent free reactions of malononitrile, ethyl acetoacetate, hydrazine hydrate and 3-Nitrobenzal-dehyde by using different catalyststs, and the results obtained are listed in Table 2.

Table 2: Catalytic activities of various catalysts

Entry	Catalyst	Time (min)	Yield (%)
1	No catalyst	60	8
2	$CuSnO_3$	55	76
3	$CuSnO_3$:SiO_2	46	82

Table 3: Synthesis of dihydropyrano [2,3-*c*] pyrazole derivatives (3a-j)

Entry	Compound	Ar	Time (min)	Yield (%)	M.P.
1	**3a**	-C_6H_5	35	91	241-243
2	**3b**	4-ClC_6H_4	32	92	231-233
3	**3c**	4-OHC_6H_4	30	93	221-224
4	**3d**	4-$OCH_3C_6H_4$	25	98	207-210
5	**3e**	3-$NO_2C_6H_4$	26	91	192-195
6	**3f**	4-$NO_2C_6H_4$	30	90	250-252
7	**3g**	4-$CH_3C_6H_4$	31	93	207-210
8	**3h**	4-BrC_6H_4	29	89	175-177
9	**3i**	4-$N(CH_3)_2C_6H_4$	26	90	165-168
10	**3j**	4-F C_6H_4	29	91	

It was found that $CuSnO_3$:SiO_2 showed better catalytic activity than $CuSnO_3$ and reaction without catalyst. The reaction proceeded smoothly and gave the 93 % yield of product 3c (Table 3, entry 3) by using1 mol of $CuSnO_3$:SiO_2. We observed that the yields of products were affected by the amount of $CuSnO_3$:SiO_2 catalyst used to carry out reaction. When 0.1, 0.2, 0.3, 0.4 and 0.5 mol, of silica grafted $CuSnO_3$ were used, the yields were 69%, 81%, 87%, 92% and 91%, respectively (Table 4, entries 1-5). Thus, we found that 0.4 mol of $CuSnO_3$:SiO_2 was sufficient to give the highest yield, and further increase in the amount of $CuSnO_3$:SiO_2 did not increase the yield of product. In the absence of the catalyst, no desired product was detected (Table 2, entry 1). It was observed that $CuSnO_3$:SiO_2 was essential in the reaction. The reaction carried out with 0.4 mol of $CuSnO_3$:SiO_2 at 70°C in ethanol gives the best result. Then, we studied the effect of change of solvents for above reaction. The results obtained are shown in Table 5 and it indicates that by changing the solvent, efficiency of the reaction was affected. Poor yield was obtained in acetonitrile, DMF, water as a solvent and in solvent free condition also (Table 5, entries 1-5). We obtained highest yield in ethanol (Table 5, entry 4).

The generality of this protocol was studied, by preparing a series of pyranopyrazoles (3a-j, Table 3) with different aromatic aldehydes. Products were obtained in good to excellent yield with aromatic aldehyde. All the synthesized pyranopyrazoles derivatives were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and LCMS. The presence of product 3a was indicated by ^{1}H NMR and ^{13}C NMR spectra obtained.

Table 4: Effect of amount of catalyst on reaction

Entry	Catalyst (mol)	Time (min)	Yield (%)
1	0.1	50	69
2	0.2	40	81
3	0.3	28	87
4	0.4	20	92
5	0.5	15	91

Table 5: Optimization of solvent

Entry	Solvent	Time (min)	Yield (%)
1	No solvent	120	40
2	MeCN	90	60
3	DMF	85	56
4	EtOH	35	84
5	H_2O	75	62

4. CONCLUSION

The combination of multicomponent reactions (MCRs) and $CuSnO_3$:SiO_2 as a catalyst has become a new research direction. The present protocol representing a new methodology for pyranopyrazoles synthesis by combination of the advantages of multi-component reactions (MCRs) with silica grafted $CuSnO_3$ catalyst. This catalyst can also be used as an alternative catalyst for various acidic mediated reactions.

5. ACKNOWLEDGEMENT

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Conflicts of interest

None declared

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