Composite SiO_2:$PbCrO_4$ catalyst as an efficient heterogeneous catalyst for one pot four component synthesis of 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives

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Abstract

An efficient one pot four component 1H-pyrazolo [1,2-b] phthalazine-5,10-dione derivatives was synthesized by using benzaldehyde, phthalic anhydride, hydrazine hydrate and malononitrile in presence of SiO_2 composite $PbCrO_4$ as a catalyst. The composite SiO_2:$PbCrO_4$ catalyst was prepared by using hydrothermal process. The XRD, TEM and BET measurement techniques were used for characterization of catalyst.

The present method offers several advantages such as use of an inexpensive catalyst, high product yield, short reaction time, mild reaction condition and reusability of the catalyst.

Keywords: SiO_2 composite $PbCrO_4$ as a catalyst, 1H-pyrazolo [1,2-b] phthalazine-5,10-dione, phthalic anhydride, hydrazine monohydrate, malononitrile.

Introduction

Strecker[21] discovered multicomponent reactions (MCRs) in 1850 and they are becoming more important in the synthesis of various heterocyclic compounds, as well as having great potential for the synthesis of drug-like heterocyclic molecules. MCRs are a type of multicomponent reaction that may be utilized to make physiologically active molecules and they have become a contentious issue in organic and pharmaceutical chemistry.

Further research in the synthesis of heterocyclic compounds via MCR technique and environmentally friendly methodologies is essential in the drug development process. The synthesis of novel heterocyclic compounds has attracted researchers' attention in recent decades due to their large variety of applications. Heterocyclic compounds are abundant in nature and are necessary for life to exist.

Among a wide range of heterocyclic compounds, nitrogen-containing heterocyclic compounds are abundant in nature and their use in medicines, agricultural chemicals and biomaterials is gaining significant attention[4,8,10-12]. 1H-pyrazolo[1,2-b] phthalazine-5,10-diones are nitrogen-containing heterocycles with anticancer, antibacterial, antifungal, anti-inflammatory, anticonvulsant, cytotoxic, antiviral, antitumor, anticoagulant, antibiotic and antihypoglycemic properties[5,9,14,16,18,20,22,23].

Cardiotonic[14] and vasorelaxant[22] properties have also been discovered in phenazine derivatives. As a result, it is essential to design a simple approach for 1H-pyrazolo [1,2-b]phthalazine-5,10-diones.

The following conditions were used to synthesise 1H-pyrazolo [1,2-b]phthalazine-5,10-diones from one-pot three-component condensation of phthalhydrazide, malononitrile/ethyl cyanoacetate and benzaldehyde: [Bmim]OH under microwave irradiation at 100 W power and 45°C[17], triethylamine in ethanol at 50°C for 1 hour and ultrasonication at 50 KHz and 350 W output power[15] and p-TSA in ionic liquid [Bmim]Br as solvent at 100°C[7].

One-pot four component reactions involving phthalimide, hydrazine hydrate, malononitrile/ethyl cyanoacetate and benzaldehyde were also reported using basic ionic liquids such as 1,8-diazabicyclo[5,4,0]-undec-7-en-8-ium acetate[19], pyrrolidinium acetate[13] and triethyl amine as a catalyst[6]. However, conventional techniques have a number of limitations including prolonged reaction times, high temperatures, adverse reaction conditions, the use of toxic and costly catalysts and catalyst recyclability. As a result, there is scope to create environmentally friendly ways for producing 1H-pyrazolo [1,2-b]phthalazine- 5,10-diones.

In this study, we discuss the synthesis of functionalized 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives as a development of our study on multicomponent reactions[1-3]. Under reflux conditions, 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives were produced through a four-component condensation process of hydrazine monohydrate, phthalic anhydride, malononitrile and aromatic aldehydes with SiO_2 composite $PbCrO_4$ as catalyst (Scheme 1).

Material and Methods

Lead oxide (PbO, Sigma-Aldrich, 99.99 %), chromium oxide (CrO_3, Sigma-Aldrich, 99.90 %), silicon dioxide (SiO_2, Merck, 99.00%) and sodium hydroxide (NaOH, Merck, 99 %) were purchased and used without purification. Similarly, organic chemicals were purchased and used without purification

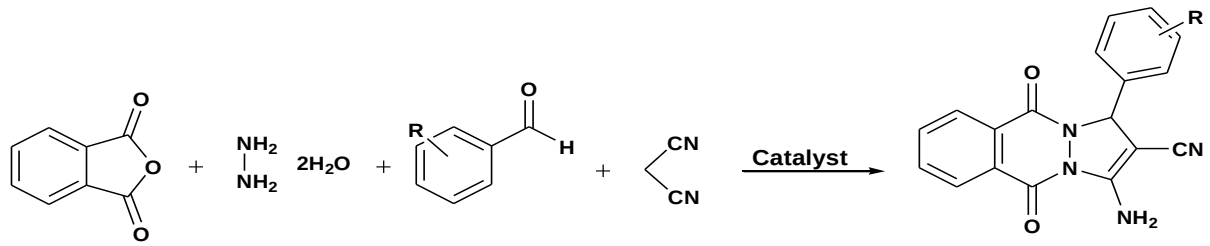
General procedure for synthesis of $PbCrO_4$ as catalyst: In this procedure, an equimolar mixture of PbO (1mol) and CrO_3 (1mol) was ground to a fine powder using a mortar and pestle for 20 minutes before being calcined at 300°C for 3 hours. After milling, the resulting powder was calcined at 400 ^{0}C for a second time after every two-hour interval.

For 12 hours, the temperature of the Muffle furnace was designed to increase at a rate of 10^{0}C/min from one temperature to the next. The material was cooled and ground using a mortar and pestle after being heated at 400°C for 1 hour. The ground material was then heated for another 12 hours at 600°C. Finally, $PbCrO_4$ polycrystalline powder was produced. The generated catalyst was utilized to characterize and synthesize SiO_2 composite $PbCrO_4$ catalysts.

Synthesis of SiO_2:$PbCrO_4$ catalyst: In a buffer solution, the required amount of SiO_2 (1 mol percent) and synthesized $PbCrO_4$ powder (1 mol percent) were mixed to make the SiO_2:$PbCrO_4$ catalyst. This reaction mixture was stirred for 1 hour and then placed in a steel-lined Teflon autoclave and heated at 120°C for 24 hours. The precipitate was filtered, rinsed with distilled water and dried for 12 hours at 100^{0}C. The polycrystalline product was placed immediately in the furnace for 4 hours of calcination at 300^{0}C. The obtained catalyst was used for characterization and synthesis of phthalazine-5,10-dione derivatives.

General Procedure for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives: Phthalic anhydride (1 mmol), hydrazine (1 mmol), an aromatic aldehyde (1 mmol) and malononitrile were heated for 15-50 minutes in an oil bath at 120^{0}C. TLC was used to observe the response. After the reaction was completed, the reaction mixture was cooled to room temperature before being poured into ice water. The resulting product was filtered and rinsed with warm water with several times, then the catalyst was separated from the chemicals using ethanol. Various analytical methods were used to characterize the resulting products which were recrystallized.

Characterization: Various analytical methods were used to characterize the pure compounds. The XRD pattern was recorded at a scan rate of 0.17° 2θ S^{-1} using a multifunctional X-ray diffractometer (Philips-1710 diffractometer with CuKα, = 1.5406). The scanning electron microscope (SEM) was used to scan the material with a high-energy electron beam. Electron micrographs were taken using a Schottky electron gun on a Hitachi SU 70 FESEM. TEM with SAED on a Phillips CM-200 microscope was used to investigate the structure and particle size of the produced materials. The N_2 adsorption–desorption isotherm was used to determine the BET surface area on Quantachrome Autosorb Automated Gas Sorption System Autosorb-1, NOVA-1200 and Mercury Porosimeter Autosorb-1c.



Scheme 1: Synthesis of phthalazine-5,10-dione derivatives.

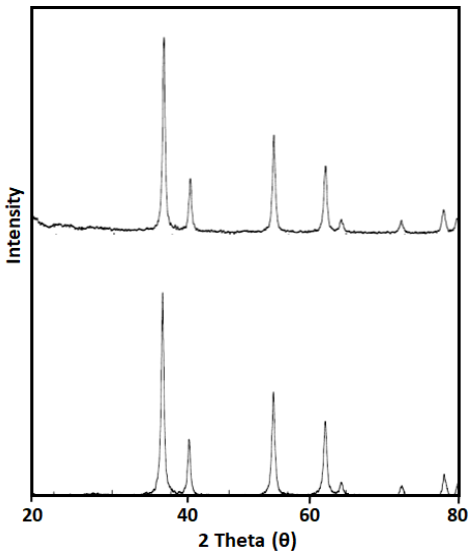


Figure 1: XRD analysis of a) $PbCrO_4$ b) SiO_2:$PbCrO_4$ catalyst.

Spectral Data

3-amino-5,10-dihydro-5,10-dioxo-1-phenyl-1H-pyrazolo [1,2-b]phthalazine-2-carbonitrile (5a): M.P.: 276-278 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.58 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.79-7.63 (10 H, m, H-Ar and NH_2), 6.65 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 167.56, 158.19, 143.43, 141.65, 139.23, 135.73, 131.21, 128.43, 126.21, 125.64, 123.12, 122.87, 121.09, 62.97, 60.52; EIMS: 316 (M+1) m/z.

3-amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-1H -pyrazolo[1,2-b]phthalazine-2-carbonitrile (5b): M.P.: 270-272 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.39 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.98-7.65 (10 H, m, H-Ar and NH_2), 6.08 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 170.23, 166.34, 153.32, 142.56, 138.54, 136.87, 134.43, 133.43, 132.78, 130.67, 129.54, 127.21, 124.65, 59.45, 54.87; EIMS: 351 (M+1) m/z.

3-amino-1-(2-chlorophenyl)-5,10-dihydro-5,10-dioxo-1H -pyrazolo[1,2-b]phthalazine-2-carbonitrile (5c): M.P.: 250-252 ^{0}C; ; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.44 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.85-7.63 (10 H, m, H-Ar and NH2), 6.08 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 168.45, 162.42, 152.45, 142.87, 139.97, 136.37, 134.87, 134.90, 132.28, 130.52, 129.78, 126.95, 124.32, 61.53, 58.47; EIMS: 351 (M+1) m/z.

3-amino-1-(4-flurophenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5d): M.P.: 262-264 ^{0}C; ; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.48 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.87-7.78 (10H, m, H-Ar and NH2), 6.07 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 170.35, 163.65, 152.56, 141.87, 138.35, 136.72, 132.43, 129.23, 127.89, 126.65, 124.38, 123.87, 122.20, 61.73, 59.38; EIMS: 336 (M^+) m/z.

3-amino-1-(4-bromophenyl)-5,10-dihydro-5,10-dioxo-1 H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5e): M.P.: 266-268 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.37 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.03-7.94 (10H, m, H-Ar and NH2), 5.98 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 169.54, 154.52, 143.17, 139.97, 135.78, 133.45, 131.32, 129.47, 128.13, 126.64, 124.59, 123.54, 122.27, 61.73, 60.38; EIMS: 396 (M+2) m/z.

3-amino-1-(4-N,Ndimethylphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5f): M.P.: 222-224 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.32 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.09-7.89 (10H, m, H-Ar and NH_2), 6.10 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 176.76, 165.80, 154.35, 147.70, 143.80, 139.76, 136.72, 133.87, 131.23, 130.12, 129.34, 127.54, 124.27, 65.23, 62.12; EIMS: 360 (M+1) m/z.

3-amino-1-(4-ethylaminephenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b] phthalazine-2-carbonitrile (5g): M.P.: 244-248 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.41 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.86-7.69 (10H, m, H-Ar and NH2), 6.22 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 169.67, 165.43, 154.12, 147.21, 143.76, 137.54, 133.62, 129.66, 129.13, 127.64, 126.59, 125.54, 123.27, 65.43, 62.54; EIMS: 359 (M+1) m/z.

3-amino-1-(3-Nitrophenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5h): M.P.: 266-268 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.43 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.05-7.65 (10H, m, H-Ar and NH_2), 6.23 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 175.54, 162.76, 156.54, 146.85, 139.97, 135.57, 132.69, 132.36, 129.73, 128.64, 128.59, 128.14, 122.27, 63.23, 60.31; EIMS: 362 (M+1) m/z.

3-amino-1-(3-thiophene)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5i): M.P.: 244-246 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.28 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.03-7.65 (10H, m, H-Ar and NH2), 6.21 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 168.43, 163.58, 149.24, 143.32, 141.23, 139.32, 136.62, 134.78, 132.89, 130.43, 128.32, 127.54, 124.43, 64.87, 62.43 EIMS: 351 (M+1) m/z.

3-amino-1-(4-pyridine)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5j): M.P.: 230-232 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.31 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.83-7.59 (10H, m, H-Ar and NH2), 5.87 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 178.34, 169.43, 154.65, 147.83, 141.90, 139.43, 135.22, 133.45, 132.34, 130.64, 127.59, 127.43, 124.28, 64.73, 60.65 EIMS: 318 (M+1) m/z.

3-amino-1-(4-methyl phenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine- 2-carbonitrile (5k): M.P.: 253-255 ^{0}C; Solvent system: Hexane : Ethyl acetate (9:1), Rf value: 0.45 cm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.20-7.850 (10H, m, H-Ar and NH_2), 5.98 (1H, S, CH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 162.32, 158.23, 147.23, 136.34, 135.16, 133.54, 132.62, 130.66, 129.83, 129.14, 127.59, 127.54, 124.27, 63.23, 60.28; EIMS: 330 (M+1) m/z.

Results and Discussion

Hydrothermally synthesized products were calcined for 3 hrs at 600 ^{0}C before being examined using the X-ray diffraction technique. Both products have XRD pattern indicating that they are polycrystalline in nature. The XRD pattern for pure $PbCrO_4$ (Fig. 1a) reveals 2θ as well as (hkl) planes at 25.6 (100), 28.4 (110), 33.5 (200), 34.5 (200) and 50.1 (200). These peaks in the XRD profile match well to JCPDS data (Card No. 270997) indicating that the crystals are cubic.

Figure 1b shows the XRD pattern for SiO_2:$PbCrO_4$, the 2θ with (hkl) plane of 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 XRD pattern demonstrates that there is no amorphous phase present, indicating that the product is strongly polycrystalline and cubic in nature.

TEM images and SAED patterns for nanocrystalline $PbCrO_4$ and SiO_2:$PbCrO_4$ products are presented in fig. 2a-b. The majority of $PbCrO_4$ crystals are cubic in form as seen in fig. 2a. $PbCrO_4$ has a particle size of 187 nm which is determined by TEM. The particle size of SiO_2:$PbCrO_4$ measured by TEM is 32.27 nm as shown in fig. 3b which also includes a TEM image and an SAED pattern for SiO_2:$PbCrO_4$. The TEM study clearly shows that the crystals are cubic in form which is compatible with the XRD analysis. Some of the crystals are large and hexagonal, while the majority are cubic in form as seen in the diagram. In catalysis, the material's surface area is important.

The usual N_2 adsorption/desorption isotherm and BJH pore distribution of manufactured $PbCrO_4$, SiO_2:$PbCrO_4$ are almost same in curve in the current study as shown in fig. 3a-b. A close examination of $PbCrO_4$ has the greatest surface area of 163.7 m^2/g, with average pore volume (Vp) and pore diameter (dp) of 0.0106 cc/g and 18.88 A^0 respectively. The average pore volume (Vp) and pore diameter (dp) for SiO_2:$PbCrO_4$ with surface area 187.9 m^2/g were 0.0202 cc/g and 16.73 A^0 respectively.

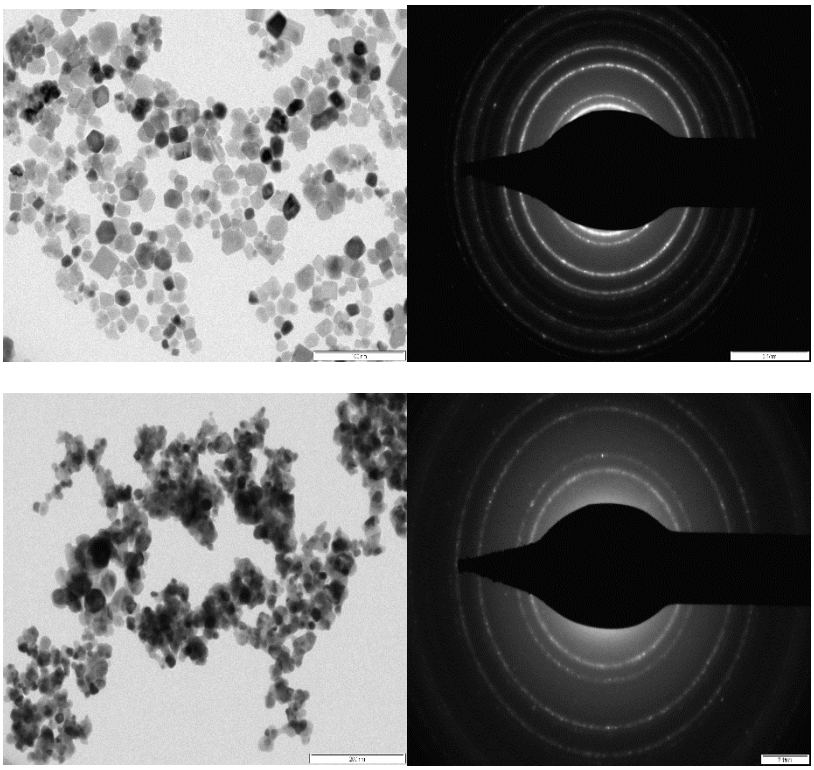


Figure 2: TEM and SAED analysis of a) $PbCrO_4$ b) SiO_2:$PbCrO_4$ catalyst.

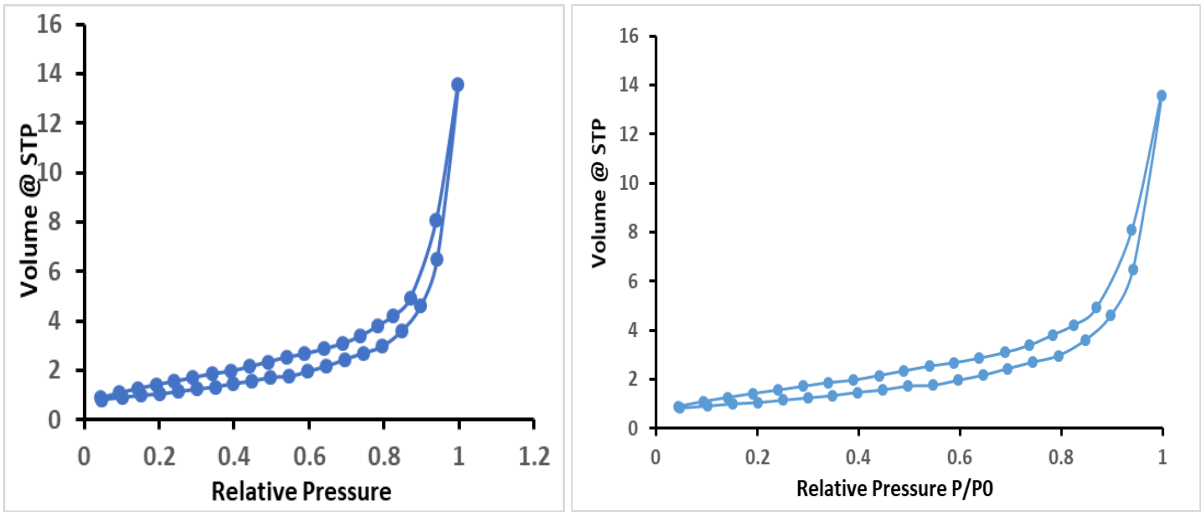


Figure 3: BET surface area of a) $PbCrO_4$ b) SiO_2:$PbCrO_4$ catalyst.

Catalytic results: The reaction conditions were modified in order to get successful results. For the synthesis of phthalazine-5,10-dione derivatives, phthalic anhydride (1.0 mol), hydrazine hydrate (1.0 mol), malononitrile (1.0 mol), substituted benzaldehyde (1.0 mol) and SiO_2:$PbCrO_4$ (0.5 mol) were used (Scheme 1). The following reaction variables were used to optimize the reaction conditions.

For the synthesis of phthalazine-5,10-dione derivatives in methanol at reflux temperature, a blank reaction was carried out using phthalic anhydride (1.0 mol), hydrazine hydrate (1.0 mol), malononitrile (1.0 mol), substituted benzaldehyde (1.0 mol) and SiO_2:$PbCrO_4$ (0.5 mol), which generated no phthalazine-5,10- dione product even after 5 hrs. The required phthalazine-5,10-dione was obtained in 25 minutes using the same process with a catalytic amount of SiO_2:$PbCrO_4$.

We used synthesized SiO_2, $PbCrO_4$ and SiO_2:$PbCrO_4$ for the cyclization reaction of phthalic anhydride, hydrazine hydrate, malononitrile and p-chloro benzaldehyde (1.0 mol). SiO_2 decomposes the product whereas $PbCrO_4$ offered high yield but took longer time than SiO_2:$PbCrO_4$. Table 1 summarizes the findings.

We examined various mol equivalents of the catalyst relative to the quantity of phthalic anhydride to optimize the amount of catalyst necessary for the cyclization (Table 2). The cyclization rate was determined to be 90% when the reaction was carried out using 0.5 mol equivalents. The cyclization procedure was carried out in a variety of solvents including DMF, MeOH, EtOH, CH_3CN and CH_2Cl_2, with these results clearly indicating that methanol was the best option as shown in table 3.

The rate of reaction was examined using electron-donating and electron-withdrawing substituents on the aromatic ring. As shown in table 4, electron-donating groups and electron-withdrawing substituents have an impact on the reaction, with electron-donating groups providing the corresponding phthalic anhydride in high yield with less time (Table 4, entries 5f, 5g, 5k and 5l), while electron-withdrawing substituents required a longer reaction time with low yield (Table 4, entries 5b, 5c, 5d,5e and 5h).

Table 1
Effect of catalyst on reaction time and yield.

S.N.	Catalyst	Time (Min)	% Yield
1	SiO_2	50	46
2	$PbCrO_4$	50	50
3	SiO_2:$PbCrO_4$	35	89
4	SiO_2:$PbCrO_4$ (30%)	50	65
5	SiO_2:$PbCrO_4$ (60%)	50	75

Table 2
Effect of Solvent and Temperature on reaction.

Entry	solvent	Temperature	Time	Yield of product %
1	Solvent Free	R.T.	50	35
2	Solvent Free	Reflux	50	89
3	MeOH	R.T.	35	45
4	MeOH	70	35	78
5	MeOH	Reflux	35	75
6	EtOH	Reflux	35	85
7	CH_3CN	Reflux	35	56
8	DMF	Reflux	35	59
9	CH_2Cl_2	Reflux	35	48

Table 3
Effect of mole percentage of catalyst.

Entry	Catalyst quantity (g)	Yield of product %
1	0.2	56
2	0.4	67
3	0.6	74
4	0.8	89
5	1.0	86
6	1.2	78
7	1.4	65

Table 4
Synthesis of 1H-pyrazolo [1,2-b] phthalazine-5, 10-dione derivatives using SiO_2:$PbCrO_4$ catalyst.

S.N.	Substituted benzaldehyde	Time (min)	Yield (%)
5a	H	50	78
5b	P-Cl	35	89
5c	O-Cl	45	85
5d	P-F	40	81
5e	P-Br	45	76
5f	P-N,N dimethyl	50	83
5g	P-Ethyl amino	40	85
5h	M-NO_2	35	79
5i	Thiophene 3-Carboxaldehyde	40	81
5j	3-pyridine Carboxaldehyde	40	83
5k	P-OH	60	71

Table 5
Reusability of SiO_2:$PbCrO_4$ catalyst.

Run	Yield of product %
1	89
2	89
3	88
4	87
5	86

Furthermore, it has been shown that the electrical characteristics of benzaldehyde's aromatic ring have an impact on yield and reaction timings.

The catalyst was filtered, washed with methanol and then calcined in an oven at 200°C for 2 hours to see if it could be reused. The catalysts reusability was examined on multiple times under identical reaction conditions. Table 5 shows that the catalyst was determined to be stable and reusable after five cycles with no significant decrease in activity.

A conventional leaching experiment was carried out to demonstrate that the reaction is heterogeneous. At the reaction temperature, the catalyst was filtered out and the reaction was allowed to proceed without it. Even after 12 hours of reflux, there was no change in yield, showing that no homogeneous catalyst was involved.

Conclusion

Finally, utilizing environmentally friendly nanocrystalline silica composite $PbCrO_4$, we established a straight forward and efficient four component procedure for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile in one pot. According to the findings of the catalytic activity studies, the SiO_2: $PbCrO_4$ catalyst has outstanding catalytic activity. Most notably, this catalyst speeds up reaction rates and increases product yields when used with solid supports.

Acknowledgement

Authors are thankful to BCUD, Savitribai Phule Pune University, for providing literature support. Authors are also thankful to IIT SAIF, Bombay for providing the analysis.

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(Received 01st May 2022, accepted 03rd July 2022)