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ORIGINAL PAPER

Synthesis of a diversified combinatorial library of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives applying sustainable carbon-based solid acid catalyst involving a domino four-component reaction

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Abstract A SO_3H-bearing carbonaceous solid catalyst has been synthesized through sulfonation followed by the hydrothermal carbonization method from renewable resource polyethylene glycol. The biodegradable catalyst was characterized by XRD, TEM, FT-IR, and energy dispersive X-ray. The surface area and pore diameter of the catalyst were determined by a nitrogen adsorption–desorption isotherm experiment. A highly efficient multicomponent heteroannulation protocol for the synthesis of a library of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives has been developed by applying the solid acid catalyst. This synthesis was established to follow the group-assistant-purification chemistry process avoiding traditional chromatography. The aqueous reaction medium, easy recovery of the catalyst, and high yield of the products make the protocol attractive, sustainable, and economic. This work may not only lead to environmentally benign systems, but also will provide a new aspect of organic chemistry in water.

Keywords PEG-SAC · Heteroannulation · Group-assistant purification · Pyrazolo[1,2-*b*]phthalazine

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Introduction

New developments in the chemical industries are driven by environmental regulations, safety, energy efficiencies, and the need for improved performance. The increasing environmental regulations require the use of green technology in various areas [1, 2]. Particularly, catalysts are attractive in green technology because of their importance in petrochemicals and fine chemical synthesis. Usually chemical syntheses involve homogeneous catalysts that are highly selective, economical, and efficient. However, many homogeneous catalytic systems cannot be commercialized because of difficulties associated with product isolation, equipment corrosion, solvent recycling, and reusability of the catalyst. The utilization of heterogeneous catalysts such as zeolites, transition-metal ions, and strong acid cation exchange resins has the potential to overcome some of the above limitations because of the ease of separation of catalysts [3–8], but these catalysts require a longer reaction time to carry out the reactions because of their very low reactivity [9, 10].

However, using heterogeneous catalysts such as mesoporous materials could be more reactive owing to their high surface-to-volume ratio leading to a larger number of active sites. In recent years, mesoporous carbon material consisting of small polycyclic aromatic carbon sheets with a high density of sulfonic acid sites has gained prominence [11, 12] because of their significant advantages over the homogeneous catalytic systems such as increased activity, selectivity, longer catalyst life, negligible equipment corrosion, ease of product separation, reusability, and overall environmentally safe disposal [13–16]. These carbon-based catalysts, obtained by partial carbonization of organic compounds (glucose, starch, and cellulose), followed by sulfonation in fuming H_2SO_4 [17–19], have proven to be highly active in various organic reactions [20, 21].

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Herein, we have demonstrated a two-step synthesis of SO_3H-bearing carbonaceous solids by hydrothermal carbonization using polyethylene glycol as the carbon precursor in a reversed mode from previously reported methods. In this protocol, the SO_3H group was first introduced into the carbon precursor polyethylene glycol by using chlorosulfonic acid (step A, Fig. 1). Mesoporous carbonaceous solid acid was then obtained through incomplete carbonization of SO_3H group functionalized polyethylene glycol (step B, Fig. 1) at higher temperature.

Nitrogen-containing heterocyclic compounds are employed as important skeletons in organic synthesis owing to their tremendous application in biologically active pharmaceuticals, agrochemicals, and functional materials [22–25]. Pyrazole core-containing compounds, including drugs such as celecoxib, viagra, pyrazofurine, and many others, possess a variety of biological activities [26–28]. Celecoxib (Fig. 2) occupies a unique position as a potent and GI-safe anti-inflammatory and analgesic agent. It is considered as a typical model of the diaryl heterocycles template that is known to inhibit the COX-2 enzyme selectively [29]. On the other hand, much attention has been focused toward pyrazoles as antimicrobial [30], antiviral [31], and anticancer [32, 33] agents after the discovery of the natural pyrazole C-glycoside pyrazofurin (Fig. 2). This antibiotic was reported to possess a broad spectrum of antimicrobial and antiviral activities in addition to being active against several tumor cell lines [34]. Phthalazine derivatives (Fig. 2) exhibit properties such as anticonvulsant [35], cardiotonic [36], vasorelaxant [37], cytotoxic [38, 39], antihypoxic, antipyretic [40], antifungal [41], anticancer [42], and anti-inflammatory [43]. It was thought that molecules containing two active pharmacophores, pyrazole and phthalazine, would produce novel molecular templates that are likely to exhibit interesting biological properties.

Quite a good number of methods have already been reported in the literature for the synthesis of pyrazolo[1,2-*b*]phthalazine derivatives [44–49]. However, these methods suffer from one or more disadvantages, such as the use of hazardous organic solvents, pollution discharge, high reaction temperature, expensive moisture-sensitive catalysts, tedious workup conditions, longer reaction times, or large volume of catalyst loadings. Based on their extensive application and lack of proper efficiency, and being inexpensive and environmentally benign methods for the synthesis of this heterocyclic scaffold, it is necessary to further develop more convenient methods to construct such significant compounds.

SO_3H-bearing amorphous carbon materials can function as stable and highly active solid acid catalysts for various acid-catalyzed reactions such as esterification, transesterification, and hydrolysis reactions [11, 12, 17–19]. In continuation of our research program dedicated to the design and synthesis of novel heterocyclic systems [50–53], herein, we wish to disclose PEG-derived SO_3H-bearing amorphous carbon materials that catalyzed a general, rapid, high yielding, green synthetic protocol for a variety of pyrazolo[1,2-*b*]phthalazine derivatives.

Results and discussion

The carbon-based solid acid was prepared by hydrothermal treatment of PEG-OSO_3H. The mesoporous carbonaceous

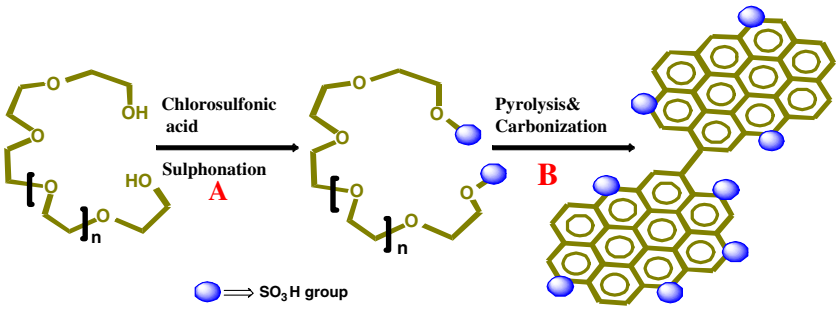
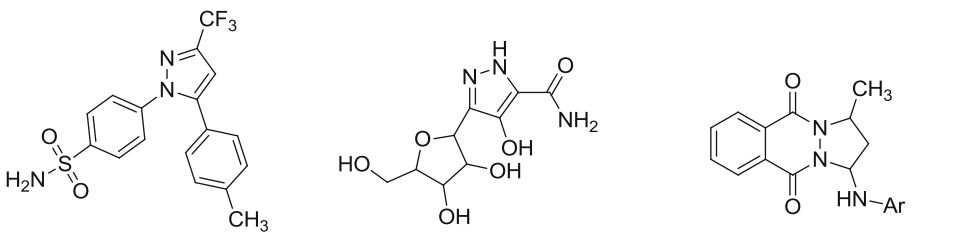


Fig. 1 Synthesis of solid acid catalyst PEG-SAC



Celecoxib C-glycoside pyrazofurin Antihypoxic and antipyretic agent

Fig. 2 Biologically active molecules containing pyrazole and phthalazine nucleus

PEG-derived solid acid catalyst was denoted PEG-SAC. Figure 3 shows the XRD patterns of the PEG-SAC catalyst. The XRD pattern exhibits a broad C (002) diffraction peak ($2\theta = 10°–30°$) attributable to amorphous carbon, and it also consists of a weak diffraction peak C (101) at $2\theta = 35°–50°$ because of the axis of the graphite structure of the carbonaceous material. Hence, the XRD pattern indicates that the amorphous carbon is composed of aromatic carbon sheets oriented in a random manner (Fig. 1). The FT-IR spectra of PEG-SAC catalyst is shown in Fig. 4. The strong peak at around 1,710 cm^{-1} and weak peak at around 1,117 cm^{-1} could be typically assigned to the stretching modes of the SO_3H groups, which are regarded as "active sites" of this catalyst [54].

HR-TEM was used to study the morphology of the surface of the solid acid catalyst PEG-SAC synthesized from PEG-6000 by the hydrothermal method (Fig. 5). Amorphous carbons were found on the HR-TEM images of the catalyst. From the HR-TEM images, it is evident that the carbonaceous material PEG-SAC has a sponge-like morphology.

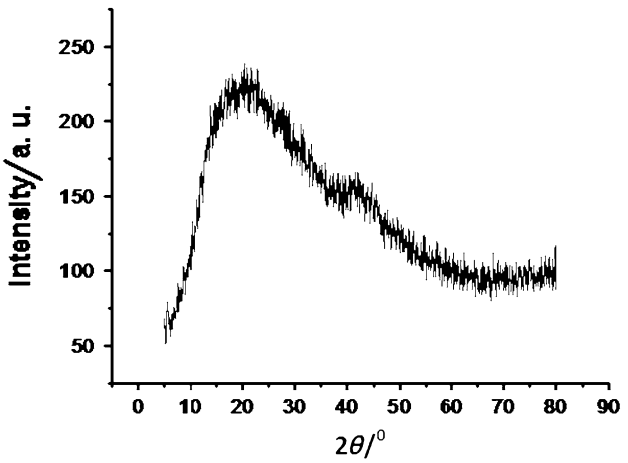


Fig. 3 XRD patterns of the catalyst

Two independent methods, acid–base back titration and elemental analysis, have been applied to more or less come up with the same result aiming at quantifying the acid content of the catalyst. Elemental analyses of the as-synthesized PEG-SAC catalyst were performed by energy dispersive X-ray analysis (EDX) equipped onto TEM. Quantitative EDX analysis in Fig. 6 clearly showed that C, O, and S were the main elemental components of the catalyst. The acid–base titration of the prepared catalyst was performed using 0.03 M NaOH solution with a 50 cm^3 dispersed solution (50 cm^3 water was stirred with 1 g of the catalyst for 30 min at rt) of the catalyst in water. From the acid–base back titration, it was observed that the acid density ($–SO_3H$) is 1.52 mmol g^{-1}, and elemental analysis (EDX) revealed that the S content of the catalyst is 1.48 mmol g^{-1}.

The surface area and pore diameter of the catalyst were determined by nitrogen adsorption. Figure 7 shows the N_2 adsorption-desorption isotherm by plotting the adsorbed volume as a function of the gas pressure (P) normalized by the adsorptive saturation pressure at 77 K (P_o). The measured BET surface area and NLDFT pore diameter of the PEG-SAC catalyst were 480 m^2 g^{-1} and 6.1 nm, respectively. According to the International Union of Pure and Applied Chemistry (IUPAC), the hysteresis loop in Fig. 7 indicates the existence of mesoporous structures in the PEG-SAC catalyst. The carbonaceous material PEG-SAC is insoluble in most of the organic solvents (ethanol, DMF,

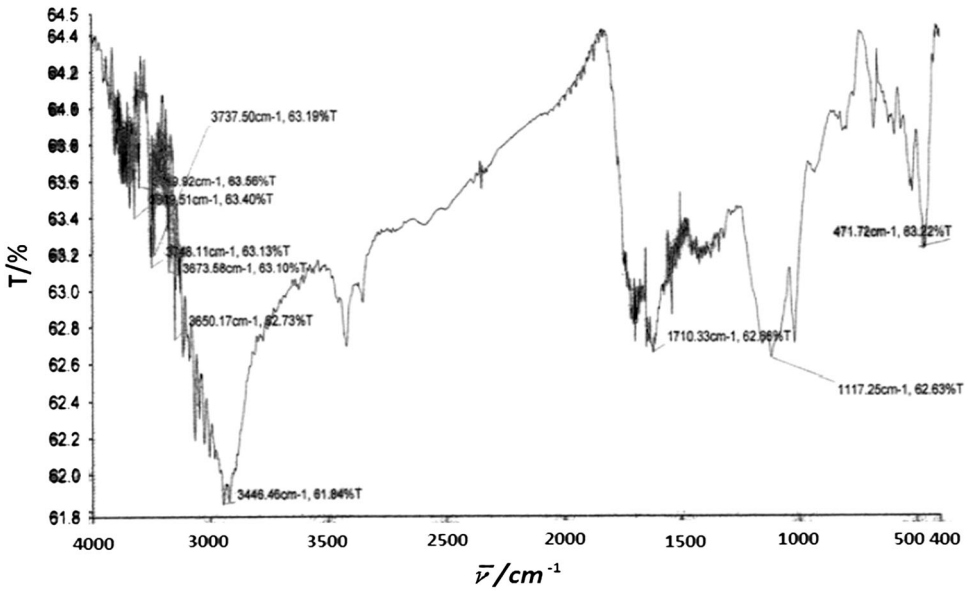


Fig. 4 FTIR analysis of the catalyst

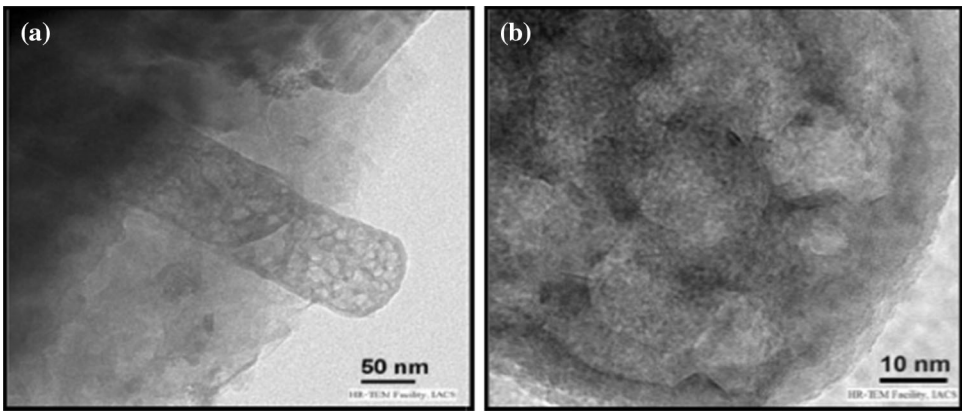


Fig. 5 HR-TEM images of the catalyst

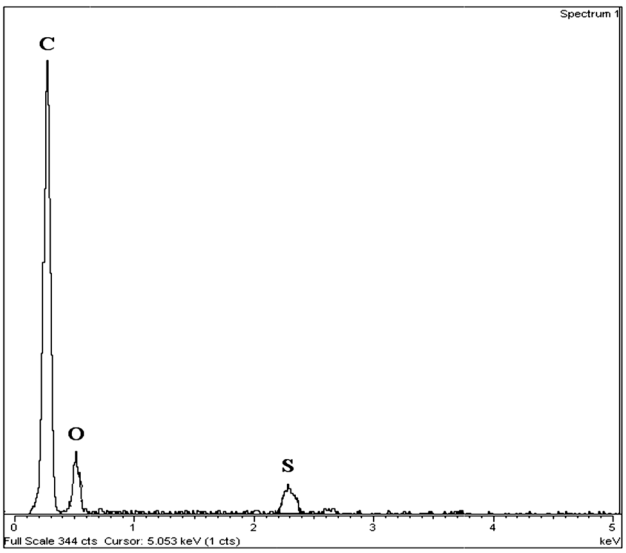


Fig. 6 Energy dispersive X-ray analysis (EDX) of the catalyst

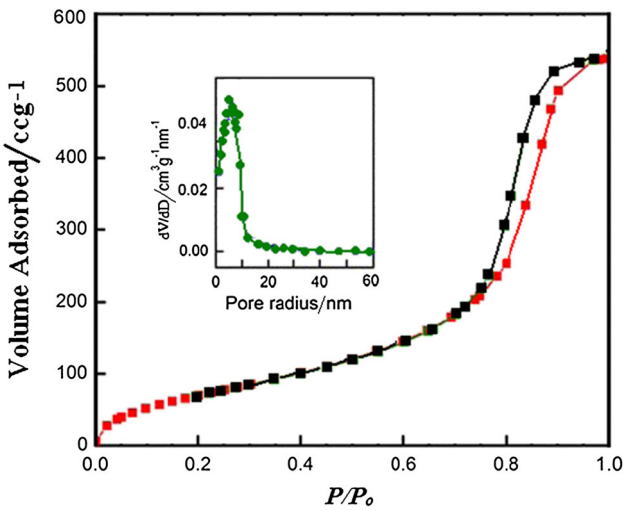


Fig. 7 Nitrogen adsorption-desorption isotherms and pore size distributions of the as-prepared PEG-SAC catalyst

methanol, toluene, DCM, DMSO), including water. Hence, the synthesized carbonaceous material can be used as a heterogeneous catalyst in a wide range of solvents.

We then focused on synthesizing 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives by using the carbon-based solid acid catalyst. During initial exploratory reactions, to find an optimized condition we studied the condensation among equimolar amounts of phthalimide, hydrazine hydrate, malononitrile, and 3-nitrobenzaldehyde (Scheme 1). Initially, that particular reaction was carried out in the presence of various solvents such as toluene, acetonitrile, DMF, DMSO, ethanol, and water at 60 °C with 70 mg of PEG-SAC; results are summarized in Table 1. The results clearly indicate that water showed superiority over the other solvents. This phenomenon can be attributed to the high ionization of the sulfonic acid group functionalized catalyst to provide the H^+ ion in aqueous medium. To find the optimized amount of solid acid catalyst as shown in Table 1, the reaction was carried out by varying the amount of the catalyst (35–90 mg) on the model reaction. The conversion of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivative increased linearly with the catalyst weight up to 70 mg and became almost steady when the amount of catalyst was further increased beyond this.

In order to show the accessibility of this catalyst-solvent system for the specific synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine from phthalimide, hydrazine hydrate, 3-nitrobenzaldehyde and malononitrile, a comparative study has been done with other reported methods (Table 2). The study revealed that PEG-SAC in aqueous medium is the most acceptable condition in every aspect, such as lower temperature, less reaction time, ecofriendly solvent, higher yield, as well as biodegradable and reusable catalyst.

Having identified these optimal conditions, we set out to explore the scope for this new reaction; the results are summarized in Table 3. All reactions were performed under

Scheme 1

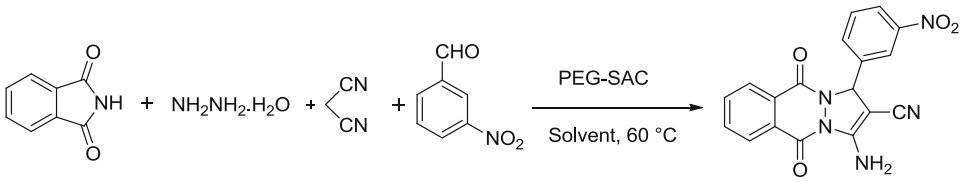


Table 1 Standardization of reaction condition

Entry	Catalyst loading/mg	Solvent	*t*/h	Yield[a]/%
1	70	Toluene	3.0	49
2	70	Acetonitrile	3.0	52
3	70	DMF	3.0	67
4	70	DMSO	3.0	69
5	70	Ethanol	2.0	70
6	70	H_2O	0.5	97
7	35	H_2O	0.5	48
8	45	H_2O	0.5	69
9	55	H_2O	0.5	80
10	80	H_2O	0.5	97
11	90	H_2O	0.5	97

Phthalimide (1 mmol) and hydrazine hydrate (1 mmol) were stirred in 5 cm^3 solvent in the presence of PEG-SAC catalyst at 60 °C for first 10 min, and then 3-nitrobenzaldehyde (1 mmol) and malononitrile (1 mmol) were added and stirred for the rest of the time

[a] Isolated yield of the pure product

Table 2 Comparison of different catalysts for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivative **1b**

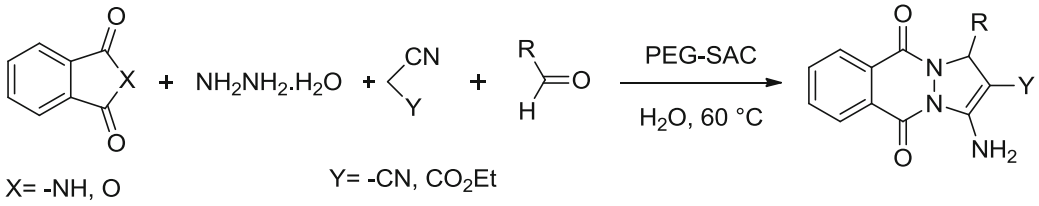
Entry	Catalyst	Solvent	*T*/°C	*t*/h	Yield/%	References
1	Al-KIT-6 (33)	Ethanol	60	4.0	84	[44]
2	Al-KIT-6 (33)	Water	100	4.0	29	[44]
3	PTSA	[bmim]Br	100	3.8	92	[45]
4	$NiCl_2{\cdot}6H_2O$	Ethanol	80	4.0	90	[46]
5	$NiCl_2{\cdot}6H_2O$	Water	100	4.0	75	[46]
6	PEG-SAC	Water	60	0.5	97	Present work

standard conditions without individual optimization. A variety of aromatic aldehydes was surveyed to prepare different 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carbonitriles and carboxylates. At the R position, various aryl rings containing electron-donating and electron-withdrawing groups are compatible with the reaction conditions. Substrates possessing electron-donating groups at the benzene ring reacted smoothly and afforded the desired products in good yield (Table 3, entries 6, 7, 16, 17). Unsubstituted aromatic aldehydes and aldehydes possessing electron-withdrawing groups at the benzene ring, such as fluoro, nitro and bromo, also reacted smoothly, providing highly substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (Table 3). Aliphatic and acid-/base-sensitive heterocycles such as 2-thienyl and 2-furyl groups are also compatible with this Brønsted acid-catalyzed four-component reaction (products **1h**, **1i**, **1j**, **2h**). Not only that, the one-pot, four-component reaction was also well established with phthalic anhydride, but in that case the desired products were obtained with a slight decrease in the product yield.

So far, a number of methods have been reported for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives using malononitrile and ethyl cyanoacetate as the active methylene component. However, there is a maiden report for the synthesis of carboxamide derivatives installing cyanoacetamide as the active methylene counterpart of the four-component reaction. To expand the generality of this novel catalytic method, we have applied cyanoacetamide as the active methylene part for the first time under the optimized conditions; the results are presented in Table 4. At the R position, a large number of aryl groups were well tolerated to provide multifunctionalized 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carboxamides. Besides, phthalic anhydride was also studied and underwent smooth transformation, affording the desired products in good yields. Under the optimized condition, the carboxamide derivative synthesis is completely regio-controlled. The Brønsted acid PEG-SAC catalyst entirely ruled out the probability of N-nucleophilic attack at the amide carbonyl center of the intermediate **IV** (Scheme 2), and no trace of the 1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivative (**4**) was detected (Table 4).

With these outstanding results in hand, we are now in a position to propose the mechanism of the reaction (Scheme 2). In the presence of PEG-SAC, at first phthalimide/phthalic anhydride (**I**) and hydrazine hydrate react to form phthalhydrazide (**II**). After that, aldehyde and the active methylene compound undergo acid-catalyzed Knoevenagel condensation to obtain the intermediate (**III**), which is consumed by phthalhydrazide via Michael type addition followed by cyclization to

Table 3 Substrate scope for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives



Entry	R	Y	Prod.	*t*/min	Yield[a]/%	Yield[b]/%	M.p./°C	Lit m.p./°C	References
1	C_6H_5	CN	**1a**	35	91	87	276–278	275–276	[48]
2	3-NO_2-C_6H_4		**1b**	30	97	94	270–272	269–271	[48]
3	4-F-C_6H_4		**1c**	30	96	93	264–266	265–266	[48]
4	2-Cl-C_6H_4		**1d**	35	93	90	258–260	257–259	[48]
5	4-Cl-C_6H_4		**1e**	30	95	92	270–272	272–274	[48]
6	4-OCH_3-C_6H_4		**1f**	40	89	86	240–242	–	[46]
7	4-CH_3-C_6H_4		**1g**	45	90	88	236–238	–	[46]
8	2-Furyl		**1h**	45	88	84	290–292	–	–
9	2-Thienyl		**1i**	45	88	85	244–246	244–246	[49]
10	Isobutyl		**1j**	50	86	83	230–232	228–230	[49]
11	C_6H_5	COOEt	**2a**	40	90	87	246–248	–	[46]
12	3-NO_2-C_6H_4		**2b**	35	95	93	238–240	239–240	[45]
13	4-F-C_6H_4		**2c**	35	95	92	230–232	–	[46]
14	4-Cl-C_6H_4		**2d**	35	93	90	276–278	–	[44]
15	2,3-Cl_2-C_6H_3		**2e**	40	90	87	262–264	260–263	[48]
16	4-OCH_3-C_6H_4		**2f**	45	89	86	260–262	–	[44]
17	3-CH_3-C_6H_4		**2g**	45	88	85	200–202	–	–
18	Isobutyl		**2h**	50	83	80	158–160	160–162	[49]

Phthalimide/phthalic anhydride (1 mmol) and hydrazine hydrate (1 mmol) were stirred in 5 cm^3 water in the presence of 70 mg PEG-SAC at 60 °C for 10 min, and then aldehyde (1 mmol) and malononitrile/ethyl cyanoacetate (1 mmol) were added and stirred for rest of the time

[a] Isolated yield of the pure product when X = –NH

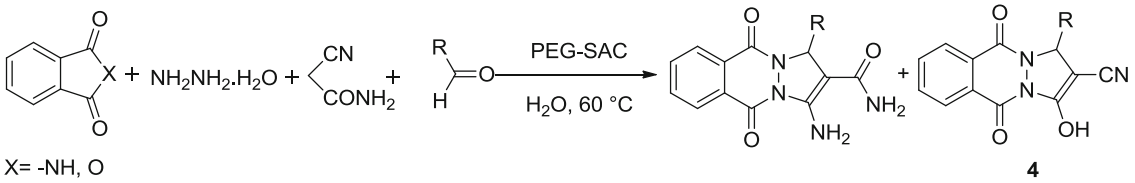
[b] Isolated yield of the pure product when X = –O

afford 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives (**P**). The high surface area of the catalyst not only reduces the reaction time, but also enhances the yield of the chromene derivatives because of its very large number of reaction sites.

In all the cases, the progress of the reaction was monitored by TLC. The structures of desired products were characterized by ^{1}H and ^{13}C NMR, IR, and elemental analysis. The X-ray crystal structure of **2d** shown in Fig. 8 further confirmed the product identity.

After the completion of the reaction (monitored by TLC), water was removed under reduced pressure from the reaction mixture, and acetone was added to it for dissolution of the crude product. The catalyst was filtered, washed with acetone, and dried under vacuum at 100 °C for 12 h. As revealed in Table 5, the catalyst was recovered in excellent yield after each new set of reaction. This recycled catalyst was used for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives applying the developed protocol. For this purpose, the reusability of the catalyst was tested for the reaction of phthalimide, hydrazine hydrate, malononitrile, and 3-nitrobenzaldehyde (Scheme 1). The catalyst was found to be reusable for at least six cycles without considerable loss of activity (Table 5). The morphology of the recovered catalyst was confirmed by the HR-TEM image of the six-times reused catalyst, which clearly demonstrated the high stability of the carbon-based solid acid catalyst (Fig. 9).

Table 4 Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione carboxamides



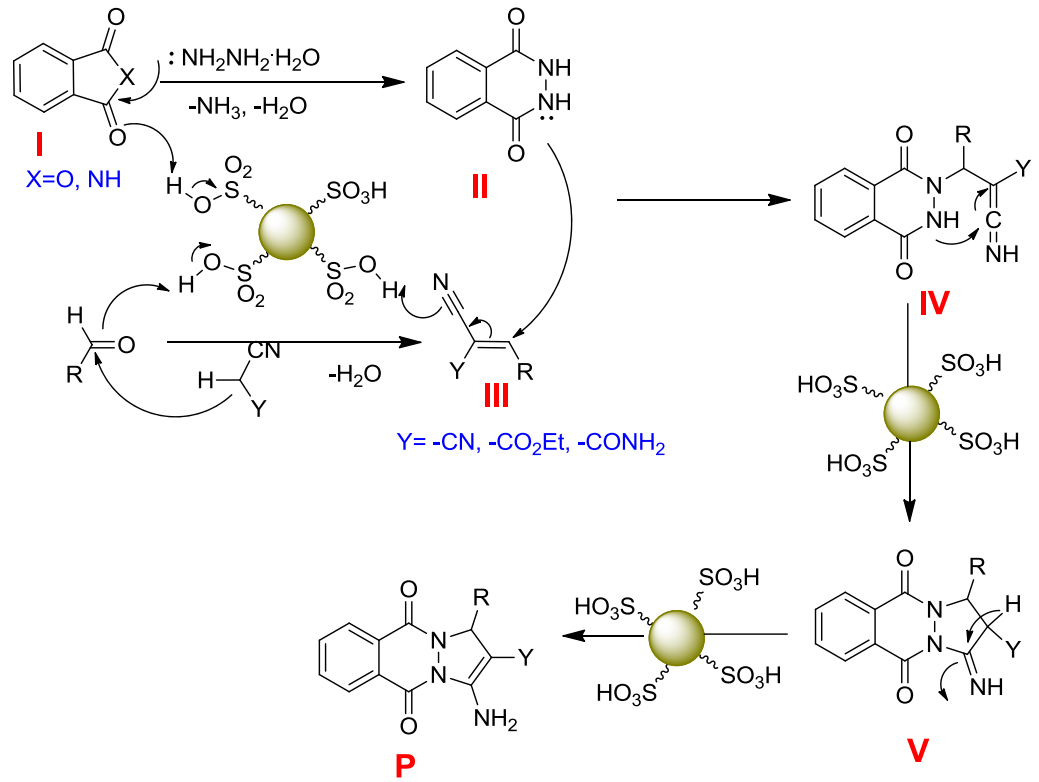
Entry	R	Product	*t*/min	Yield[a]/%	Yield[b]/%	M.p./°C
1	C_6H_5	**3a**	40	88	85	230–232
2	3-NO_2-C_6H_4	**3b**	35	95	92	240–242
3	4-F-C_6H_4	**3c**	35	95	93	210–212
4	4-Cl-C_6H_4	**3d**	35	93	90	226–228
5	2,3-Cl_2-C_6H_3	**3e**	40	90	87	240–242
6	4-Br-C_6H_4	**3f**	40	91	88	220–222
7	3-CH_3-C_6H_4	**3g**	45	86	83	230–232

Phthalimide/phthalic anhydride (1 mmol) and hydrazine hydrate (1 mmol) were stirred in 5 cm^3 water in the presence of 70 mg PEG-SAC at 60 °C for 10 min, and then aldehyde (1 mmol) and cyanoacetamide (1 mmol) were added and stirred for the rest of the time

[a] Isolated yield of the pure product when X = –NH

[b] Isolated yield of the pure product when X = –O

Scheme 2



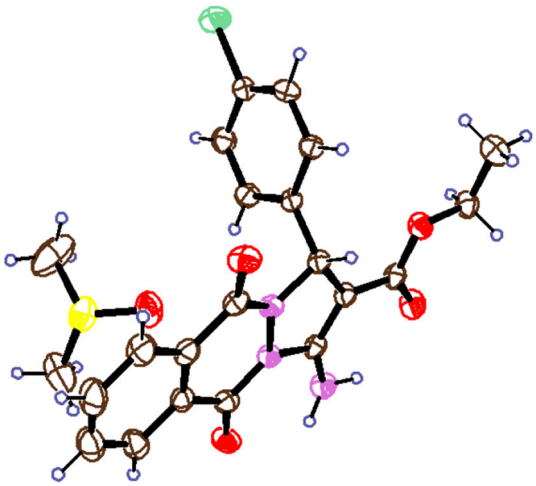


Fig. 8 ORTEP diagram of compound **2d**

Table 5 Reusability of PEG-SAC

Runs	Weight percentage of the recovered catalyst/%	Yield[a]/%
1	100	97
2	98	95
3	97	94
4	97	94
5	96	92
6	96	92

[a] Isolated yield of the pure product **1b**

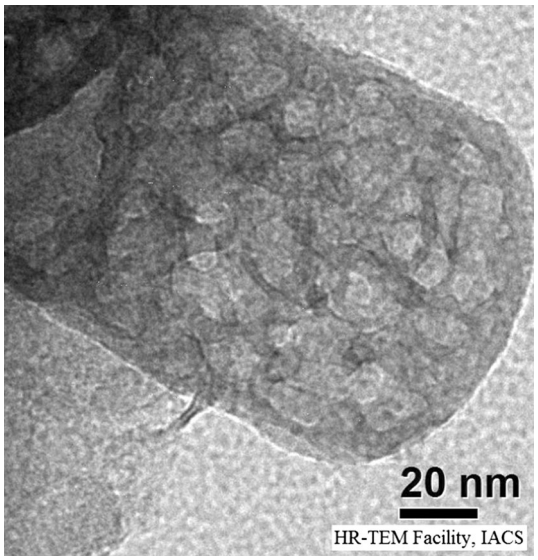


Fig. 9 HR-TEM image of the recovered catalyst after the sixth run

Conclusion

In summary, we have developed a green, sustainable, and economic protocol for the one-pot, four-component synthesis of a combinatorial library of diversified 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione fused heterocyclic molecules with the aid of an SO_3H-bearing carbonaceous solid catalyst (PEG-SAC). The sulfonated carbon material was prepared by low-temperature carbonization of PEG-SO_3H, resulting in a highly active, stable solid acid catalyst. All the products were isolated by filtration, avoiding the use of silica gel column chromatography. The reactions showed a broad substrate scope and readily available, inexpensive commercial starting materials. The catalysts are composed of polycyclic aromatic carbon with an SO_3H group. The very high surface area and high acid density of the catalyst would surely grab the attention of the biological as well as pharmaceutical industries for the very good replacement of homogeneous acid catalysts in achieving the synthesis of organic molecules in the future.

Experimental

PEG-6000 and chlorosulfonic acid were purchased from Aldrich (98 % pure). Phthalimide/phthalic anhydride was purchased from Aldrich (99 % pure), and malononitrile, ethylcyanoacetate, cyanoacetamide, and various aldehydes (98 % pure) were purchased from SRL Biochem/Spectrochem (India), Ltd., and were used without further purification.

Catalyst preparation

At 0 °C, chlorosulfonic acid (10 mmol) was added to a solution of PEG-6000 (1 mmol) in 10 cm^3 CH_2Cl_2, and the resulting solution was stirred at room temperature overnight. Then, the solution was concentrated under vacuum, and ether was added to it. The resulting precipitate was filtered and washed with ether three times to afford PEG-OSO_3H as a gummy solid.

Carbon-based solid acid was prepared by hydrothermal treatment of PEG-OSO_3H. Carbon and SO_3H precursor PEG-OSO_3H (6 g) were heated at 200 °C in a 100-cm^3 Teflon hydrothermal reactor. Conditions were maintained for 6 h at autogenous pressure and then on cooling to room temperature formed a black amorphous solid. The mesoporous carbonaceous PEG-derived solid acid catalyst was denoted as PEG-SAC.

General procedure for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives

A mixture of phthalimide/phthalic anhydride (1 mmol) and hydrazine hydrate (1 mmol) was stirred in 5 cm^3 water in the presence of 70 mg PEG-SAC at 60 °C for 10 min, and then aldehyde (1 mmol) and active methylene component (1 mmol) were added and stirred for the required period of time (TLC). After completion of the reaction, water was removed under reduced pressure from the reaction mixture, and acetone was added to it for the dissolution of crude product. The acetone solution was filtered to remove the catalyst. The solid was obtained upon concentrating the acetone solution of the crude product extract. The product thus appearing was collected by filtration, washed with chilled aqueous ethanol, and finally recrystallized from ethanol to obtain pure product.

3-Amino-1-(furan-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile
(**1h**, $C_{16}H_{10}N_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.44$ (dd, $J_1 = 3$ Hz, $J_2 = 1.8$ Hz, 1H), 6.59 (d, $J = 3.3$ Hz, 1H), 7.61 (s, 1H), 7.95 (t, $J = 4.5$ Hz, 2H), 8.10 (t, $J = 4.2$ Hz, 3H), 8.20–8.23 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 56.7$, 58.4, 110.1, 111.1, 116.2, 127.1, 127.8, 128.9, 134.3, 135.3, 143.7, 143.8, 149.5, 151.5, 154.2, 157.0 ppm; IR (KBr): $\bar{\nu} = 2{,}203$, 1,659, 1,385 cm^{-1}.

Ethyl 3-amino-5,10-dioxo-1-(m-tolyl)-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate
(**2g**, $C_{21}H_{19}N_3O_4$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.02$ (t, $J = 7.2$ Hz, 3H), 2.24 (s, 3H), 3.93–3.96 (m, 2H), 6.01 (s, 1H), 7.02 (d, $J = 5.7$ Hz, 1H), 7.11–7.18 (m, 4H), 7.93–8.27 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 14.2$, 21.0, 58.7, 63.3, 81.9, 124.5, 126.7, 127.3, 127.7, 127.8, 128.3, 128.8, 128.9, 133.6, 134.7, 137.0, 139.8, 149.7, 153.2, 156.8, 164.1 ppm; IR (KBr): $\bar{\nu} = 1{,}694$, 1,663, 1,289 cm^{-1}.

3-Amino-5,10-dioxo-1-phenyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxamide (**3a**, $C_{18}H_{14}N_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.34$–6.40 (m, 3H), 7.21–7.29 (m, 3H), 7.48 (d, $J = 6.9$ Hz, 2H), 7.60 (s, 2H), 7.88–7.91 (m, 2H), 8.02–8.05 (m, 1H), 8.20 (t, $J = 1.8$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 62.3$, 84.2, 126.7, 127.2, 127.7, 128.0, 128.2, 128.8, 129.0, 133.6, 134.4, 139.4, 148.2, 153.0, 156.2, 166.6 ppm; IR (KBr): $\bar{\nu} = 1{,}686$, 1,500, 1,337 cm^{-1}.

3-Amino-1-(3-nitrophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxamide
(**3b**, $C_{18}H_{13}N_5O_5$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.49$ (s, 3H), 7.57 (t, $J = 8.1$ Hz, 1H), 7.68 (s, 2H), 7.88–7.94 (m, 3H), 8.02–8.22 (m, 3H), 8.45 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 61.9$, 83.5, 123.5, 123.7, 127.1, 127.6, 129.0, 129.6, 130.2, 134.0, 134.8, 141.8, 147.9, 149.1, 153.7, 156.7, 166.8 ppm; IR (KBr): $\bar{\nu} = 1{,}683$, 1,526, 1,349 cm^{-1}.

3-Amino-1-(4-fluorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxamide
(**3c**, $C_{18}H_{13}FN_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.36$ (s, 2H), 6.40 (s, 1H), 7.09 (t, $J = 8.7$ Hz, 2H), 7.51–7.61 (m, 4H), 7.88–8.22 (m, 4H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 61.8$, 84.0, 115.2, 125.3, 126.9, 127.4, 128.9, 129.1, 130.1, 130.2, 133.7, 134.6, 135.5, 148.5, 153.2, 154.9, 166.7 ppm; IR (KBr): $\bar{\nu} = 1{,}684$, 1,526, 1,343 cm^{-1}.

3-Amino-1-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxamide
(**3d**, $C_{18}H_{13}ClN_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.35$ (s, 1H), 6.42 (s, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 4.2$ Hz, 2H), 7.63 (s, 2H), 7.88–8.22 (m, 4H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 61.6$, 83.7, 126.7, 127.2, 128.1, 128.7, 129.0, 129.8, 132.6, 133.6, 134.4, 138.3, 148.4, 153.1, 156.2, 166.5 ppm; IR (KBr): $\bar{\nu} = 1{,}680$, 1,522, 1,349 cm^{-1}.

3-Amino-1-(2,3-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxamide
(**3e**, $C_{18}H_{12}Cl_2N_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.19$ (s, 2H), 6.59 (s, 1H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.59 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H), 7.73–7.79 (m, 3H), 7.96 (d, $J = 4.5$ Hz, 2H), 8.05–8.29 (m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 62.4$, 127.1, 127.6, 128.5, 128.7, 129.2, 130.7, 132.8, 134.2, 135.0, 138.4, 149.5, 153.4, 156.5, 166.7 ppm; IR (KBr): $\bar{\nu} = 1{,}684$, 1,526, 1,349 cm^{-1}.

3-Amino-1-(4-bromophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxamide
(**3f**, $C_{18}H_{13}BrN_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.33$ (s, 1H), 6.42 (s, 2H), 7.46 (s, 4H), 7.62 (s, 2H), 7.88–8.22 (m, 4H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 61.7$, 83.7, 121.2, 126.7, 127.2, 128.7, 129.0, 130.1, 131.1, 133.6, 134.4, 138.7, 148.4, 153.1, 156.2, 166.5 ppm; IR (KBr): $\bar{\nu} = 1{,}683$, 1,524, 1,349 cm^{-1}.

3-Amino-5,10-dioxo-1-(m-tolyl)-5,10-dihydro-1H-pyrazolo-[1,2-b]phthalazine-2-carboxamide (**3g**, $C_{19}H_{16}N_4O_3$)
^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H), 6.29 (s, 1H), 6.35 (s, 2H), 7.15 (t, $J = 8.1$ Hz, 1H), 7.29 (d, $J = 6.3$ Hz, 2H), 7.60 (s, 2H), 7.83–8.06 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.4$, 62.7, 84.5, 125.5, 127.0, 127.5, 128.4, 129.0, 129.1, 129.3, 132.9, 133.9, 134.7, 137.7, 139.6, 148.5, 153.3, 156.5, 166.9 ppm; IR (KBr): $\bar{\nu} = 1{,}687$, 1,503, 1,335 cm^{-1}.

X-ray crystal structure

Crystallographic data for the structure **2d** (crystallized from DMSO) have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-925979. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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