Supplementary Information

EcoScale MCR sustainability to impart rapid access to pyrrolo[1,2-*b*]pyrazoles scaffolds assisted by recyclable $HClO_4 \bullet SiO_2$ heterogeneous catalytic system

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Received 9 May 2023; accepted (revised) 17 October 2023

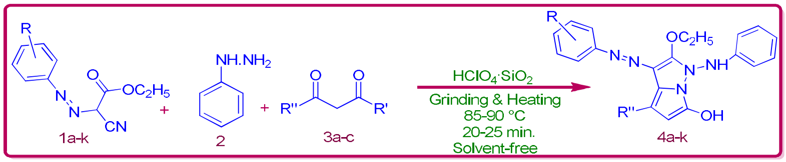
Present work elicits an account of synthesizing a new series of pyrrolo[1,2-*b*]pyrazole scaffolds involving multi component reaction (MCR) strategy, assisted by silica-supported perchloric acid $HClO_4 \cdot SiO_2$ as the heterogeneous catalyst. It embraces methyl 2-cyano-2-(phenyldiazenyl)acetate as the key precursor. The reusability of the catalyst up to five- synthetic cycles is the value-added advantage of the protocol. Moreover, feasibility of the strategy has been endorsed on the basis of EcoScale values in the sustainable limits. Structural corroboration of all the newly synthesized compounds and catalyst was ascertained by different spectroanalytical data *viz*., IR, ^1H NMR, mass, XRD, TG/DTA, FE-SEM.

Keywords: Pyrrolo[1,2-*b*]pyrazole, Solvent-free, $HClO_4 \cdot SiO_2$

Multi component reactions (MCRs) are a distinct class of synthetically viable organic reactions, affording the product(s) in more efficient and atomic economic way.[1,2] Also, convergence, efficiency, facile execution, and high product yields associated with MCRs, have attracted much attention from the vantage point of preparing a library of the compounds.[3] Moreover, organic reactions under solvent-free environment have gained prominent attention owing to the number of associated advantages over to the stereotyped methods *viz*., improved selectivity, cleaner reaction profile, ease of manipulation and moderately benign conditions.[4] Furthermore, heteroaromatic molecules containing *N*-fused bicyclic fragments are important scaffolds in a large number of domains ca., pharmaceuticals, agrochemicals, and natural products.[5-7] In particular context , antibacterial and antifungal activities have been attributed to many of these *N*-fused heterocycles. Also, some of them have been identified as potential anxiolytic,[8] antineoplastic,[9] antiplasmodial,[10] and anticancer agents.[11] More specifically, five membered skeleton of pyrazole nuclie manifests a significant role owing to their omnipresence in natural products, pharmaceuticals and in biologically active compounds.[12] Literature encompasses a number of synthetic strategies leading to tailor the heterocyclic skeleton of pyrazole nuclei.

Accordingly, accomplishment of new methodologies to synthesize a number of structurally diverse *N*-fused pyrazoles, *viz.,* pyrrolo[1,2-*b*]pyrazole scaffolds, is very much needed to cope the substantial demand of this amalgamated heterocyclic system. Likewise, in an effort to design an eco-friendly, benign approach to develop this heterocycle, it was endeavored to consider a heterogeneous catalyst mediated synthetic strategy. Consequently, an unprecedented synthesis of fused 2-ethoxy-4-methyl-1-(phenylamino)-3--(phenyldiazenyl)-1H-pyrrolo[1,2-*b*] pyrazol-6-ol derivatives in which one of the nitrogen is flaunted between two rings has been carried out and reported herein. Thus, in continuation of our work,[13-21] a novel method for the synthesis of fused pyrrolo[1,2-*b*]pyrazole compounds considering MCR among methyl 2-cyano-2-(phenyldiazenyl)acetate, phenylhydrazine, and β-diketones on silica-supported perchloric acid as a heterogeneous catalyst,[22,23] has been devised (scheme 1) and reported thereof. Furthermore, in view of several advantages associated with mechanochemistry *viz.* short reaction time, possibility of solvent-free condition, minimum loading of catalyst and high yields efforts have been endeavoured to explore this protocol for achieving targeted synthesis. Also, accessibility of the protocol has been supported by evaluating the requisite EcoScale values.

In our initial investigation reaction was performed under catalyst-free and solvent-free conditions at ambient temperature. However, the reaction did not turn into any productive yield even after 24 h of the reaction time (Table 1 Entry 1). We also carried out the experiment using a minimal amount of acetic acid as the catalyst in ethanol at 80°C for 12-14 h however, no product formation was resulted (Table 1 Entry 3). Later on, the study was carried out using perchloric acid under neat reaction condition, which resulted in the 48% yield of the product (Table 1 Entry 4). Furthermore, upon using bare silica as the catalyst has resulted in a very feeble outcome of the yield. Hence, upon critic evaluation of these two conditions and to overcome the bottlenecks, it was decided to use the perchloric acid supported on silica ($HClO_4 \cdot SiO_2$) as the heterogeneous catalytic system (Table 1 Entry 5). Hence, silica-supported perchloric acid $HClO_4 \cdot SiO_2$ (Table 1 Entry 6) was added as the catalyst, which was resulted in improved yield to certain extent.



Scheme 1. Multicomponent Solvent-free Synthesis of pyrrolo[1,2-*b*]pyrazole derivatives 4(a-k) using $HClO_4 \cdot SiO_2$ as a supported catalyst

However, in order to further enhance the yield percentage, the experiment was performed under solvent-free condition in the presence of $HClO_4 \cdot SiO_2$ as the catalyst at 85-90°C. To our delight, this reaction system was resulted in an excellent yield of 92% (**Table 1 Entry 7**). The reaction optimization has revealed the catalytic activity of $HClO_4 \cdot SiO_2$ with an impressive increment in the product yield and reduced of reaction time when compared with the reaction in precursor of homogeneous $HClO_4$ and unsupported silica as a heterogeneous catalytic system (Table 1).

Table 1. Optimization of catalyst, solvent, and temperature for the synthesis of compound 4d

Entry	Catalyst	Solvent	Time	Temperature	Yield^b (%)
1	Catalyst-free	Solvent-free	24 h	RT	-
2	Catalyst-free	Solvent-free	10 h	Reflux	-
3	AcOH	Ethanol	12-14 h	Reflux	-
4	$HClO_4$	Solvent-free	10 h	85-90 °C	48
5	SiO_2	Solvent-free	10 h	85-90 °C	30
6	$HClO_4 \cdot SiO_2$	Ethanol	7-8 h	Reflux	63
7	$HClO_4 \cdot SiO_2$	Solvent-free	20-25	85-90 °C	92

			min.		
8	$HClO_4·SiO_2$	Solvent-free	20-25 min.	100-120 °C	49
9	$HClO_4·SiO_2$	Solvent-free	20-25 min.	RT	-

Reaction conditions: [a] ethyl 2-cyano-2-(4-nitrophenyldiazenyl)acetate **1d** (5 mmol), phenylhydrazine **2** (5 mmol) and ethyl acetoacetate **3b** (5 mmol), $HClO_4·SiO_2$(1eq.) 85-90 °C. [b] yields are those of pure isolated product.

After ascertaining the finalization of optimal reaction condition and in order to test further increment in product yield, the effect of increase in temperature was studied. For this purpose, the reaction was performed at 100-120 °C, however, it was resulted in exponential decrease to approximately half of the initial yield (Table 1 Entry 8). Hence, it was inferred that 85-90 °C was the best operating reaction temperature for the desired transformation to occur. No product was formed when the reaction was performed at room temperature using $HClO_4·SiO_2$ catalytic system (Table 1 Entry 9).

The acidity of silica supported perchloric acid was investigated by measuring Hammett acidity parameter (H_0) determined by titration with NaOH.[24-25] The amount of H^+ obtained by titration was found to be 9.8 mmol H^+ g^{-1}. Hammett acidity function used to express the acidic strength of an acid in aprotic organic solvent was calculated by the equation:

$$H_0 = {}_{p}K(ln)_{aq} + \log([ln]_s/[Hln]_s)$$

Where, $[ln]_s$ and $[Hln]_s$ are concentrations of indicator and protonated indicator, respectively that can be determined by UV-Vis spectrophotometer. Dichloromethane was chosen as aprotic solvent and 4-nitroaniline as the basic indicator.[22] The acidity of catalyst (H_0) was found to be 0.78.

The catalyst follows the 3R concept, i.e. recoverability, recyclability and reusability as the important aspect of the cost-effective and eco-friendly motif. Consequently, keeping these issues under consideration, it was our endeavour to recover and check the reusability of the catalyst. Therefore, after the initial first run, the catalyst was recovered, washed with dry ether, dried under low pressure, and subjected again to the reaction (up to five runs) under identical conditions. The comparable yields of the product showed no significant diminution in catalytic activity. The results of the reusability of the catalyst are summarized in figure 1. Such recyclability allows the repetitious use of a small amount of catalyst in several runs. FE-SEM imgae of recovered catayst is in supplemetary data(Figure 1).

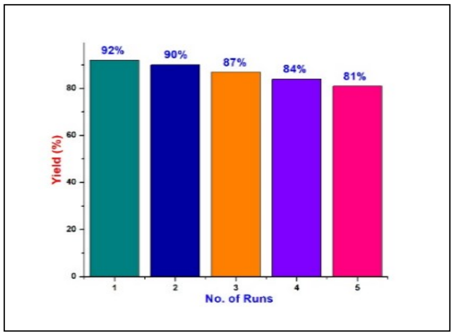


Figure 1. Representation of reusability of the catalyst

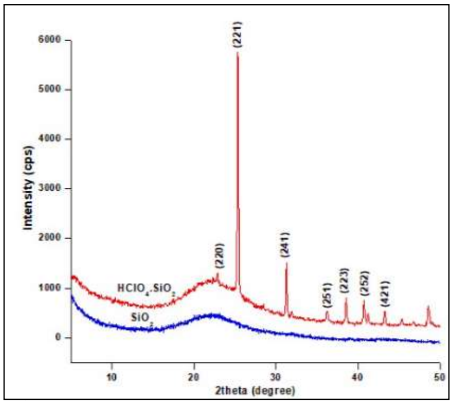


Figure 2. XRD pattern of $HClO_4{\cdot}SiO_2$

The structural property of the catalyst was examined by XRD studies. Figure 2, depicts the XRD pattern of pure silica particles, eliciting a broad scattering maximum centred at 22.38° corresponding to the amorphous silica.[26] Further the XRD pattern of $HClO_4{\cdot}SiO_2$ embracing the peaks centred at 22.93°, 25.41°, 31.44°, 36.29°, 38.66°, 40.74°, 43.32° attributable to the presence of (220), (221), (241), (251), (223), (252), (421) indices, respectively. This was in accord with the standard JCPDS card no. 78-2454.

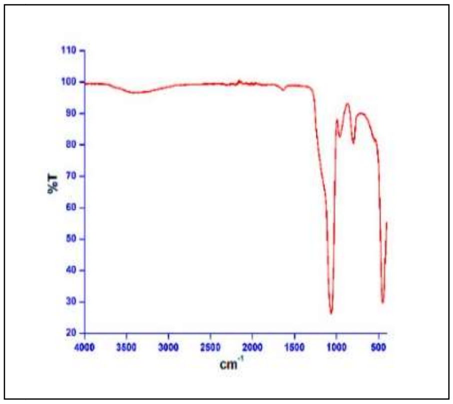


Figure 3. The FT-IR spectra of $HClO_4{\cdot}SiO_2$

Figure 3 depicts the FT-IR spectrum of the synthesized catalyst. Presence of a peak at 3418 cm^{-1} can be attributed to the surface hydroxyl groups,[27] whereas peaks at 1063.28 cm^{-1} and 451.52 cm^{-1} are assignable to Si-O-Si asymmetric vibration and Si-O-Si bending vibration, respectively. Also, the symmetric stretching of Si-O-Si bond was observed at 962 cm^{-1} and 795 cm^{-1}.[28-30]

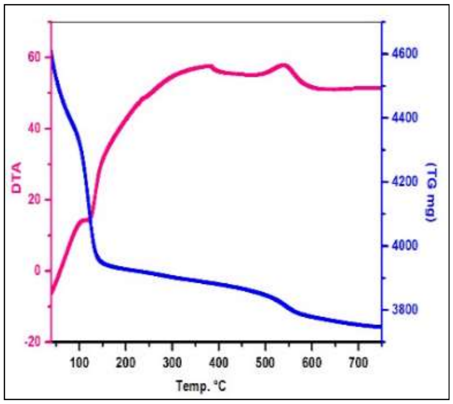


Figure 4. The FE-SEM images of HClO4·SiO2 with various magnifications

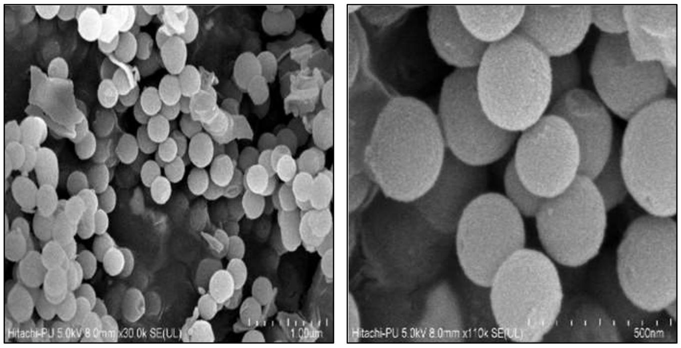
The morphology of the catalyst was further determined by FE-SEM analysis (Figure 4). The images clearly indicated the spherical morphology of the synthesized catalyst with an average size of approximately 187 nm.

To evaluate the thermal stability of the catalyst $HClO_4 \cdot SiO_2$, TG/DTA studies were performed (Figure 5). The sample was heated up to 700 °C at a constant rate of 20 °C/min in the N_2-atmosphere.

Figure 5. The TG/DTA curve of $HClO_4 \cdot SiO_2$

It is revealed from the thermogram that the observed weight losses are in accordance with the expected decomposition of silica supported perchloric acid. TGA curve depicted in Figure 5 indicate two-stage decomposition: first weight loss of 11.9% between 100 - 150 °C can be attributed to the evaporation of surface-physiosorbed water, whereas Second weight loss of 2.45% between 500 - 600 °C can be ascribed to the decomposition of the loaded perchloric acid. Further evidence for the loss of physiosorbed water on the catalyst was provided by DTA analysis. The results denoted the thermal stability of the catalyst up to 700 °C temperature.[31,32]

In order to assist the feasibility of reaction in context to green chemistry approach, EcoScale points were determined.[33,34] Hence, EcoScale evaluation of all the substrates involved along with catalyst, accessories and required conditions was performed (Scheme 1). It was inferred from the penalty points (total = 39) that protocol is quite feasible with 61% value of overall EcoScale factor



(Table 2 supplementary file). This indicates the easy accessibility of synthetic strategy to provide the synthesized compounds in substantial yields.

In conclusion, a practical, simple and clean process has been designed for the synthesis of *N*-fused pyrrolo[1,2-*b*]pyrazole derivatives. Exploration of $HClO_4{\cdot}SiO_2$ as the heterogeneous catalytic system for this transformation under solvent-free condition makes this protocol economically viable and environmentally benign as per the green chemistry tenets. Also, feasibility of the reaction has been validated by screening various factors like price, technical setup, temperature, time and workup procedure. To our glee, this protocol embraces 61% EcoScale results with precise concerned to environmental safety and excellent yield. Furthermore, the reusability of the catalyst up to five-synthetic cycles with simple workup procedure leads to acceptability of methodology as very fascinating among the heterocyclic/synthetic chemists.

This work is supported by the financial assistance received from UGC-SAP-DRS-I [No. F.540/13/DRS-I/2016(SAP-I)] and T.S. is thankful to UGC-NET [(F.16-6(DEC.2016)/2017(NET)] for Junior Research Fellowship. The authors are thankful to Sophisticated Analytical Instrumentation Facility Punjab University, Chandigarh, for providing ^1H NMR, mass and FESEM results and UGC-DAE Consortium for Scientific Research, DAVV, Indore (for powder XRD).

Characterization data including melting point, FTIR, ^1H NMR, and mass of all the synthesized compounds are available in the supporting information.

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