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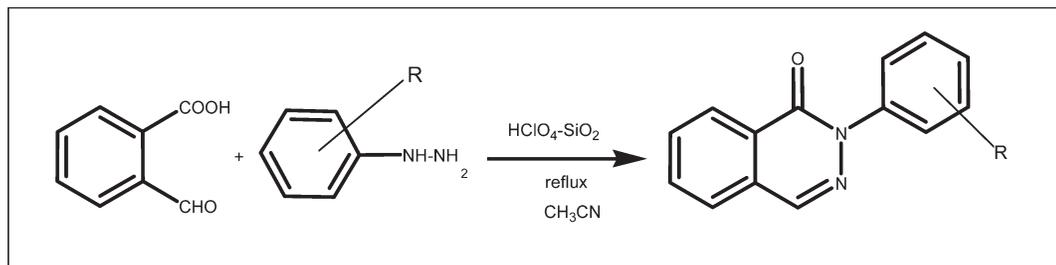
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A simple and efficient synthesis of 1(2*H*)-phthalazinone derivatives was achieved *via* reaction of phthalaldehydic acid and various phenyl hydrazines in acetonitrile using $\text{HClO}_4\text{-SiO}_2$ as a catalyst in very good yields.

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INTRODUCTION

Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life [1]. Phthalazine scaffold have shown its potential as a privileged structure for the generation of drug-like libraries in drug-discovery process [2]. 2*H*-Phthalazin-1-ones are of considerable interest due to their antidiabetic [3] and antiallergic activities [4], and its bioactivity has been researched extensively [5–8]. They are also useful intermediates for the synthesis of inhibitors of the VEGF (vascular endothelial growth factor) receptor tyrosine kinases for the treatment of cancer [9]. However, phthalazinone derivatives have attracted considerable attention in the development of novel antiasthmatic agents with dual activities of thromboxane A_2 (TXA_2) synthetase inhibition and bronchodilation [10]. Consequently, there is a need to develop new methods to synthesis of these compounds.

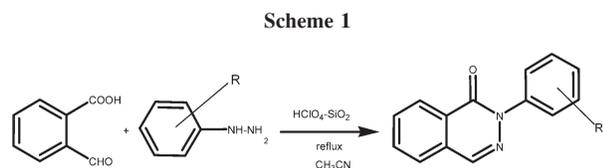
Solid-supported reagents are unique catalysts that have become popular over the last 2 decades [11]. The high catalytic activity, low toxicity, moisture, and air tolerance, their recyclability and particularly low price make the use of solid supported reagents attractive alternatives to conventional Lewis acids and triflates [12]. Although the catalytic applications of solid supported reagents for organic synthesis have been well established, relatively few examples are reported on the use

of $\text{HClO}_4\text{-SiO}_2$ [13]. We have recently used $\text{HClO}_4\text{-SiO}_2$ for the synthesis of 14-aryl or alkyl-14-*H*-dibenzoxanthenes [14]. As part of our program aimed at developing new selective and environmental friendly methodologies for the preparation of fine chemicals [15–18], herein we report an efficient and convenient procedure for the synthesis of 1(2*H*)-phthalazinones using $\text{HClO}_4\text{-SiO}_2$ as a reusable and heterogeneous catalyst in good yields (Scheme 1).

RESULTS AND DISCUSSION

1(2*H*)-Phthalazinone were obtained by phthalaldehydic acid and various phenyl hydrazines in CH_3CN using $\text{HClO}_4\text{-SiO}_2$ as a reusable catalyst (Scheme 1) in good yields (Table 1). It has been proven recently that $\text{HClO}_4\text{-SiO}_2$ is a mild, worthwhile heterogeneous catalyst, which efficiently and selectively catalyzes various organic transformations and synthesis. The effect of temperature was studied by carrying out the reactions at different temperature (25°C), 50°C and under refluxing temperature (82°C). As it shown in Table 1, the yields of reactions increased as the reaction temperature was raised. These results showed that refluxing temperature would be the temperature of choice for all reactions. The reaction proceeded very cleanly under reflux condition and were free of side products.

Influences of solvents are the important parameter for the determination of yield of the products. The reaction was conducted in various solvents on the synthesis of 3a using $\text{HClO}_4\text{-SiO}_2$ as a reusable catalyst.



As shown in Table 2, the performance of various solvents are in the following order: acetonitrile > ethyl acetate > THF > toluene > dichloromethane.

Acetonitrile shows better yields, when compared with other solvents. In addition, the time required for

Table 1
Synthesis of 2,4,5-triaryl-imidazoles using various heteropolyacids under refluxing condition.

Entry	Substrate	Product	Time (h)	Mp (°C)		Yield (%) ^a		
				Observed	Reported	25°C	50°C	82°C
1			1	104	104–105 [19]	50	85	95
2			1.5	206	204–206 [20]	43	76	92
3			2	176	175–177 [21]	40	63	80
4			2	170	168–169 [22]	45	70	81
5			1.5	121	120.5–121.5 [19]	50	79	90
6			1.5	136	135 [23]	50	75	90
7			2	127	126–127 [24]	43	70	80

^a Yields were analyzed by GC.

Table 2
Synthesis of 3a with HClO₄-SiO₂ in the
presence of different solvents.

Entry	Solvent	Temperature	Time (min)	Yield (%) ^a
1	Acetonitrile	reflux	1	95
2	Ethyl acetate	reflux	1	92
3	THF	reflux	1.20	90
4	Toluene	reflux	2	90
5	Dichloromethane	reflux	2	89

^a Yields were analyzed by GC.

completion of the reaction was found to be less in acetonitrile. This is due to higher solvent polarity of acetonitrile when compared with that of other solvents. We expect that the solvent removes products from the active surface of the catalyst. Therefore, more polar solvents may remove the product better and thus regenerate the catalyst active sites allowing continuation of the catalytic reaction.

The reactions proceeded efficiently at mild conditions and are completed within 1–2 h, in contrast to conventional methods that require long reaction times. This method not only affords the products in good yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. This catalyst is eco-friendly for a variety of organic transformations. It is nonvolatile, nonexplosive, easy to handle, and thermally robust. The time required for completion of the reaction was found to be less for phenyl hydrazine when compared with substrates bearing electron withdrawing groups (Table 1, entries 2–7). Moreover, the steric hindrance seems to have significant effects on reaction times and yields (Table 2, entries 3, 4, 7).

In conclusion, we are reporting an efficient process for the synthesis of biologically interesting functionalized 1(2*H*)-phthalazinone derivatives starting from readily available and inexpensive reagents. It can be concluded that HClO₄-SiO₂ is an efficient and excellent catalyst for the synthesis of these compounds in high yields and mild conditions in short reaction times. This method offers some advantages in terms of simplicity of performance. The low cost of the catalyst, low toxicity of the catalyst, fast reaction times, recyclability of the catalyst, and high yields of the products are the other advantages for this synthesis. We believe our procedure will find important applications in the synthesis of 1(2*H*)-phthalazinones. The method is also relatively environmentally benign.

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ¹H NMR, and GC/MS. Melting points were meas-

ured by using the capillary tube method with an electro thermal 9200 apparatus. ¹H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard (CDCl₃ solution). IR spectra were recorded from KBr disk on the FTIR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Preparation of 2-phenyl-2*H*-phthalazin-1-one (3a): A typical procedure. To a mixture of phthalaldehydic acid (1 mmol, 15 g) and phenylhydrazine (1 mmole, 1 mL) in acetonitrile (5 mL), a catalytic amount of HClO₄-SiO₂ (0.01 mmol) was added and refluxing was continued for 1 h. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was then filtrated (in order to separation of catalyst from the mixture). The filtrate was then diluted with 5% NaHCO₃ (5 mL) and the product was extracted with diethyl ether (2 × 5 mL) and dried over MgSO₄. The solvent was evaporated under reduced pressure and the crude product was obtained. The resulting solid product was recrystallized from ethanol to give the pure product.

3a: mp. 104°C; IR: 1620 (C=N), 1670 (C=O) cm⁻¹; ¹H NMR: δ 7.59–8.27 (m, 9H, Ar-H), 8.8 (s, 1H); ms: *m/z* 222 (M⁺).

3c: mp. 176°C; IR: 1633 (C=N), 1674 (C=O) cm⁻¹; ¹H NMR: δ 7.61–8.43 (m, 7H, Ar-H); ms: *m/z* 301 (M⁺).

Preparation of the HClO₄-SiO₂ catalyst [13]. HClO₄ (1.8 g, 12.5 mmol, as a 70% aq. solution) was added to a suspension of SiO₂ (230–400 mesh, 23.7 g) in Et₂O (70.0 mL). The mixture was concentrated and the residue was heated at 100°C for 72 h under vacuum to furnish HClO₄-SiO₂ (0.5 mmol/g) as a free flowing powder (50 mg = 0.025 mmol of HClO₄).

Caution. Although no explosions were reported under these conditions, extreme care has to be taken for large scale reactions. The preparation of the catalyst should be performed with special care and in a safe environment.

Reusability of catalyst. Next, we investigated the reusability of HClO₄-SiO₂. When the reaction was completed, the catalyst was separated by simple filtration and recovered with CHCl₃ (2 × 5 mL) and subsequently dried at 80°C in order to be. HClO₄-SiO₂ can be reused in subsequent reactions without significant decrease in activity even after five runs (Table 3).

Table 3

Reuse of the HClO₄-SiO₂ for synthesis
of 2-phenyl-2*H*-phthalazin-1-one (3a).

Entry	Time (h)	Yield (%) ^a
1	1	95
2	1	93
3	1.20	92
4	2	90
5	2.20	90

^a Yields were analyzed by GC.

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