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# Efficient One-Pot Solvent-Free Synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-diones Catalyzed by Sulfonic Acid Functionalized Nanoporous Silica (SBA-Pr-$SO_3H$)

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A green protocol has been developed for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by one-pot cyclocondensation reaction of phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate using sulfonic acid functionalized SBA-15 (SBA-Pr-$SO_3H$) as a heterogeneous solid acid catalyst under solvent-free conditions.

**Keywords:** Multicomponent reaction; Phthalhydrazide; Functionalized SBA-15; One-pot synthesis; Heterogeneous catalysis.

## INTRODUCTION

Heterogeneous catalysts have attracted considerable attention in organic synthesis due to their unique catalytic properties. These catalysts have advantages such as an ease for removal, recyclability and reusability. In this regard, organic–inorganic hybrid mesoporous silica materials have become a promising candidate for heterogeneous catalysts. Ordered mesoporous silica such as SBA-15 with large pore size and high surface area, hexagonal arrangement of uniform pores, thick walls, and high hydrothermal stability, has been used in many fields including heterogeneous catalysis,[1] separation,[2] electrochemistry,[3] optics,[4] biology and medical practice.[5-6] SBA-15 functionalized with organic and inorganic moieties exhibits efficient catalytic activity in a variety of organic transformations.[7-9]

Heterocyclic compounds containing phthalazine moiety are important targets in synthetic and medicinal chemistry due to their pharmacological and biological activities.[10-11] Pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives were reported as antibacterial,[12] anti-inflammatory, analgesic, antipyretic, and antihypoxant compounds.[13] Therefore, the development of simple methods for the synthesis of titled compounds is very important.

To our knowledge, there are only several literatures about the multicomponent synthesis of this class of compounds which were synthesized by one-pot three-component reactions of phthalhydrazide, malononitrile or ethyl cyanoacetate, and aromatic aldehydes in the presence of various catalysts.[14-17] In another study, 2-chloro-3-formyl quinolines have been used as an alternative for aromatic aldehydes.[12] Four-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives was also investigated.[18-19]

In continuation of our research on nanoporous heterogeneous solid catalysts and their applications in organic synthesis,[20-23] herein we wish to report the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives using SBA-Pr-$SO_3H$ as an efficient nano catalyst.

## RESULTS AND DISCUSSION

In this paper, we want to report a simple, mild and effective method for the one-pot synthesis of 1*H*-pyrazolo-[1,2-*b*]phthalazine-5,10-dione derivatives via a multicomponent reaction of phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate in the presence of SBA-Pr-$SO_3H$ (Scheme 1).

**Scheme 1** Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones using SBA-Pr-$SO_3H$ as an efficient nano acid catalyst


In order to optimize the reaction condition, initially, evaluation of various solvent systems was carried out. The

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results revealed when the reaction proceeded under solvent-free conditions, the desired product was obtained in high yield (Table 1). In the absence of any catalyst under solvent-free conditions, this reaction afforded compound 4a after 4 h in low yield (50%). Different substituted aldehydes were subjected to this reaction to investigate the generality of this method and corresponding products were successfully synthesized (Table 2). It was reported that this reaction almost could not be observed when the aliphatic aldehyde was used as a starting material.[14] The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was dissolved in ethanol, filtered for removing the unsolvable catalyst and then the filtrate was cooled to afford the pure product as a solid. The catalyst was washed subsequently with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without loss of significant activity.

A reasonable mechanism was proposed for this reaction (Scheme 2). Initially, the solid acid catalyst protonates the carbonyl group of aldehyde **3** which then condenses with CH-acidic group of malononitrile or ethyl cyanoacetate **2** through a fast Knoevenagel condensation to afford benzylidenemalononitrile **8**. Michael-type addition of phthalhydrazide **1** to the C=C bond of this compound followed by cyclization and tautomerism produces the desired products **4a-i** in high yields.

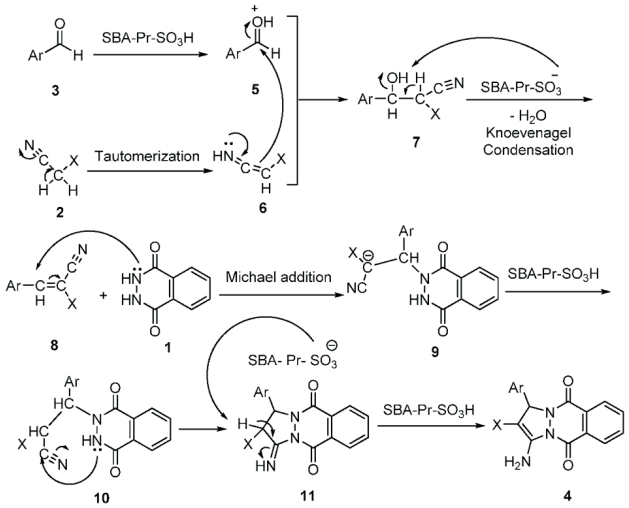
Literature surveys revealed that various conditions have been employed in this reaction as demonstrated in Table 3. The results illustrated that the present methodology, using SBA-Pr-$SO_3H$ as the catalyst offers several advantages such as simple procedure, short reaction times, simple work-up and greener conditions in contrast with other existing methods.

Table 1. Solvent effect on the synthesis of compound **4a**

| Entry | Solvent | Time (h) | Yield (%)[a] |
|---|---|---|---|
| 1 | EtOH | 4 | 70 |
| 2 | EtOH:$H_2O$ (1:1) | 4 | 60 |
| 3 | MeCN | 3 | 65 |
| 4 | Neat (80 °C) | 20 min | 90 |

[a] Isolated yield.

**Scheme 2** Proposed mechanism




The SBA-15 as a new nanoporous silica can be prepared by using commercially available triblock copolymer Pluronic P126 as a structure directing agent.[24] Integration of acidic functional groups (e.g., -$SO_3H$) into ordered mesoporous SBA-15 has been explored to produce promising solid acids. The sulfonic acid functionalized SBA-15 was usually synthesized through direct synthesis or post-grafting.[1,25] The surface of the catalyst was analyzed by dif-

Table 2. The SBA-Pr-$SO_3H$ catalyzed the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4a-i** under solvent-free condition

| Entry | Ar | X | Product | Time (min) | Yield (%)[a] | M.p (°C) | M.p (Lit.) |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | CN | **4a** | 20 | 90 | 272-274 | 276-278 [14] |
| 2 | 4-$ClC_6H_4$ | CN | **4b** | 15 | 75 | 266-268 | 270-272 [14] |
| 3 | 2,3-$(Cl)_2C_6H_3$ | CN | **4c** | 15 | 88 | 282-284 | New |
| 4 | 2,4-$(Cl)_2C_6H_3$ | CN | **4d** | 20 | 90 | 242-244 | New |
| 5 | 4-$OMeC_6H_4$ | CN | **4e** | 20 | 78 | 270 (dec.) | - |
| 6 | 3-$OMeC_6H_4$ | CN | **4f** | 15 | 70 | 264-266 | New |
| 7 | 4-Me-$C_6H_4$ | $CO_2Et$ | **4g** | 30 | 75 | 201-203 | 204-206 [14] |
| 8 | 4-$NO_2C_6H_4$ | $CO_2Et$ | **4h** | 25 | 80 | 239-241 | 241-243 [14] |
| 9 | 3-$NO_2C_6H_4$ | $CO_2Et$ | **4i** | 30 | 70 | 236-238 | 239-240 [14] |

[a] Isolated yield.

Table 3. Comparison of different conditions in the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

| Entry | Catalyst | Solvent | Condition | Temp. (°C) | Time (h) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | *p*-TSA[a] | [bmim]Br[b] | Reflux | 100 | 3 | 94 | 2008 [14] |
| 2 | $Et_3N$ | EtOH | Sonication | 50 | 1 | 92 | 2010 [15] |
| 3 | [bmim]OH | - | MW | 45 | 4 min | 94 | 2011 [16] |
| 4 | Al-KIT-6[c] | EtOH | Reflux | 60 | 4 | 93 | 2012 [17] |
| 5 | SBA-Pr-$SO_3H$ | - | Heating | 80 | 20 min | 90 | This work |

[a] *p*-Toluenesulfonic acid
[b] Ionic liquid 1-butyl-3-methylimidazolium bromide
[c] Cubic mesoporous aluminosilicate

ferent methods such as TGA, BET and other methods which were demonstrated that the organic groups (propyl sulfonic acid) were immobilized into the pores.[26]

Figure 1 illustrates the SEM and TEM images of SBA-Pr-$SO_3H$. SEM image (Figure 1, a) shows uniform particles about 1 μm. The same morphology was observed for SBA-15. It can be concluded that morphology of solid was saved without change during the surface modifications. On the other hand, the TEM image (Figure 1, b) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-$SO_3H$ was not collapsed during two-steps reactions.

In conclusion, a facile multi-component approach for the synthesis of a series of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones under solvent-free conditions utilizing SBA-Pr-$SO_3H$ as an efficient nano catalyst has been described. The process is simple, mild and efficient, generates a diverse range of the titled compounds in good yields.

## EXPERIMENTAL

All chemicals were obtained commercially and used without further purification. IR spectra were recorded from KBr disks using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The $^1$H NMR (250 or 300 MHz) and $^{13}$C NMR (300 or 75 MHz) were run on a Bruker DPX, using TMS as an internal standard ($CDCl_3$ or DMSO-$d_6$ solution). GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV while TEM was carried out on a Tecnai $G^2$ F30 at 300 kV.

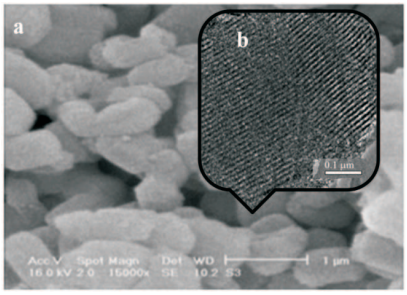



Fig. 1. SEM image (a) and TEM image (b) of SBA-Pr-$SO_3H$.

**Synthesis and functionalization of SBA-15:** The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report[26] and the modified SBA-15-Pr-$SO_3H$ was used as nanoporous solid acid catalyst in the following reaction.

**General procedure for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones:** SBA-Pr-$SO_3H$ was activated in vacuum at 100 °C, then, after cooling to room temperature, phthalhydrazide (1 mmol), aromatic aldehydes (1 mmol), and malononitrile or ethyl cyanoacetate (1 mmol) were added to it. The mixture was heated in 80 °C for appropriate time as shown in Table 2. After completion of the reaction, as monitored by TLC, the crude product was dissolved in hot ethanol and then filtered to remove the solid catalyst. Filtrate was cooled to give the pure product. The solid acid catalyst was subsequently washed with dilute acid solution, distilled water, and acetone, and dried under vacuum. It can be used for several times without significant loss of activity. Spectroscopic data for selected examples are shown below.

**3-Amino-1-phenyl-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile 4a:** M.p = 272-274 °C; IR (KBr): 3359, 3190, 2197, 1690, 1658 $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 6.13 (s, 1H), 7.29-7.47 (m, 5H), 7.93-8.26 (m, 4H), 8.09 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 62.4, 63.6, 116.1, 127.2, 127.3, 127.7, 128.7, 128.9, 129.2, 134.1, 135.1, 138.7, 151.2, 154.2, 157.1; MS: *m/z*: 316 ($M^+$). **3-Amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo-**

**[1,2-*b*]phthalazine-2-carbonitrile 4b:** M.p = 266-268 °C; IR (KBr): 3375, 3264, 2200, 1662, 1655 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 6.15 (s, 1H), 7.41-7.53 (m, 4H), 7.93-8.26 (m, 4H), 8.13 (s, 2H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 61.3, 62.7, 116.4, 127.1, 127.7, 128.9, 129.3, 133.3, 134.2, 135.1, 137.9, 151.2, 154.1, 157.1; MS: *m/z*: 350 ($M^+$). **3-Amino-1-(2,3-dichlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile 4c:** M.p = 282-284 °C; IR (KBr): 3162, 3017, 2895, 2581, 2226, 1660, 1580, 1492, 822 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): δ 6.52 (s, 1H), 6.75 (s, 2H), 7.30-7.61 (m, 3H), 8.16-8.28 (m, 4H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$): δ 59.2, 60.9, 115.5, 125.1, 126.7, 127.3, 128.2, 128.8, 129.3, 130.3, 132.0, 132.5, 133.9, 134.7, 138.0, 151.2, 153.6, 156.6; MS: *m/z*: 384 ($M^+$). **3-Amino-1-(2,4-dichlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile 4d:** M.p = 242-244 °C; IR (KBr): 3370, 3232, 3172, 2896, 2209, 1660, 1562, 1493, 824 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): δ 6.53 (s, 1H), 6.74 (s, 2H), 7.29-7.61 (m, 3H), 8.16-8.28 (m, 4H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$): δ 56.0, 59.2, 115.5, 126.7, 127.3, 128.0, 128.2, 128.8, 129.1, 130.4, 132.3, 133.6, 133.9, 134.4, 134.7, 151.1, 153.5, 156.6; MS: *m/z*: 384 ($M^+$). **3-Amino-1-(4-methoxyphenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile 4e:** M.p = 270 °C (dec.); IR (KBr): 3016, 2895, 2220, 1660, 1555, 825 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): δ 3.94 (s, 3H), 6.23 (s, 1H), 7.03-7.29 (m, 4H), 7.68-7.95 (m, 5H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$): δ 55.8, 61.8, 76.8, 113.8, 114.8, 115.1, 124.0, 125.1, 125.4, 127.1, 132.5, 133.3, 154.6, 160.3, 164.3; MS: *m/z*: 346 ($M^+$). **3-Amino-1-(3-methoxyphenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile 4f:** M.p = 264-266 °C; IR (KBr): 3011, 2897, 2227, 1661, 1598, 1571, 1493, 952 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.10 (s, 1H), 6.22-7.06 (m, 4H), 7.29-7.55 (m, 4H), 8.30 (s, 2H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$): δ 56.2, 58.8, 59.0, 111.5, 121.4, 121.6, 122.0, 122.2, 123.8, 124.3, 124.6, 127.2, 132.6, 154.6, 158.2, 160.9; MS: *m/z*: 346 ($M^+$). **Ethyl 3-amino-1-(p-tolyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate 4g:** M.p = 201-203 °C; IR (KBr): 3447, 3333, 1706, 1658, 1624 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 1.04 (t, *J* = 8.9 Hz, 3H), 2.25 (s, 3H), 3.96 (q, *J* = 9.0 Hz, 2H), 6.04 (s, 1H), 7.07-7.38 (m, 4H), 7.69 (br s, 2H), 7.92-8.27 (m, 4H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 14.6, 21.1, 59.1, 63.4, 82.1, 127.1, 127.7, 128.9, 129.1, 129.3, 134.0, 135.1, 137.2, 137.2, 150.1, 153.4, 157.2, 164.5; MS: *m/z*: 377 ($M^+$). **Ethyl 3-amino-1-(4-nitrophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]-phthalazine-2-carboxylate 4h:** M.p = 239-241 °C; IR (KBr): 3386, 3210, 1694, 1655, 1630 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 1.03 (t, *J* = 6.8 Hz, 3H), 3.95 (q, *J* = 6.7 Hz, 2H), 6.18 (s, 1H), 7.73-8.29 (m, 10H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 14.6, 59.2, 63.0, 81.1, 123.5, 125.5, 127.1, 127.7, 129.0, 129.2, 133.0, 134.2, 135.1, 147.3, 147.7, 153.8, 157.3, 164.2; MS: *m/z*: 408 ($M^+$). **Ethyl 3-amino-1-(3-nitrophenyl)-5,10-dihydro-5,10- dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate 4i:** M.p = 236-238 °C; IR (KBr): 3360, 3249, 1693, 1651, 1613 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 0.99 (t, *J* = 9.2 Hz, 3H), 3.94 (q, *J* = 7.8 Hz, 2H), 6.22 (s, 1H), 7.56-8.30 (m, 10H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ14.5, 59.1, 63.1, 81.1, 122.5, 123.1, 127.1, 127.6, 129.0, 129.4, 129.9, 134.1, 134.5, 135.0, 142.6, 147.9, 150.5, 153.9, 157.3, 164.3; MS: *m/z*: 408 ($M^+$).

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