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Research Article

BORON SULFONIC ACID AS A RECYCLABLE SOLID ACID ATALYST FOR THE SYNTHESIS OF 2H-INDAXOLO [1, 2-B] PHTHALAZINE-TRIONES IN SOLVENT-FREE CONDITIONS

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Abstract

Boron sulfonic acid was applied as an efficient heterogeneous and reusable catalyst for the synthesis of 2*H*-indazolo[1,2-*b*] phthalazine-trione derivatives. A broad range of aromatic aldehydes were condensed *via* a one-pot three component reaction with phthalhydrazide and dimedone. The process was done under solvent-free conditions. High yields, short reaction times, easy work-up, eco-friendly, easy handling, availability and reusability of the catalyst are the main aspects of the present method.

Keywords: Boron sulfonic acid, Indazolo[1,2-*b*]phthalazine-trione, Multi-component reaction, Solvent-free synthesis

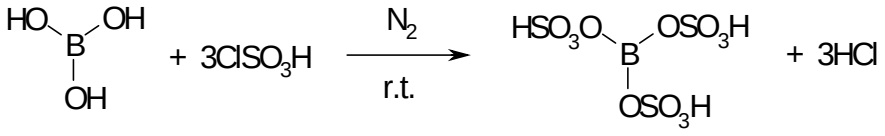
Introduction

Multi-component reactions (MCRs) play an important role in combinatorial chemistry. These reactions are able to synthesize target compounds with greater efficiency and atom economy. They generate structural complexity in a single operation without the isolation of intermediates[1] from three or more reactants. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions[2]. Heterocyclic compounds containing the phthalazine ring are important targets in synthetic and medicinal chemistry, because this fragment is a key moiety in different pharmacological active compounds[3,4]. Phthalazine derivatives were found to possess cytotoxic[5], antimicrobial[6], anticonvulsant[7], antifungal[8], anticancer[9], and anti-inflammatory[10] activities. Phthalazine-containing compounds are also highly potent inhibitors of vascular endothelial growth factor receptor II (VEGFR-2)[11-13]. Moreover, these compounds exhibited good promise as new luminescence materials or fluorescence probes[14]. Therefore, it is not surprising that many synthetic methods have been developed for this compounds[15-27]. However, most of these reported procedures describe synthesis of only a narrow range of phthalazines. Furthermore, some of these methods suffered with one or more drawbacks such as hazardous organic solvents, use of strong acids, long reaction time, high costs and harsh reaction conditions with non-recyclable catalyst. Thus, the development of a new, efficient, and general protocol for the synthesis of heterocycles containing phthalazine ring fragment is an active ongoing research area, and there is further potential improvement toward green chemistry and improved yields.The principlesen Chemistry"of"Gre emphasize the catalysts and chemicals in order to have minimal adverse effects on the environment[28].One of the most suitable strategies to design environmentally benign catalytic systems is the preparation of solid acid catalysts with strong acidic sites. It is obviously deducible from the literature that the applications of solid acid catalysts have become more prominent in organic transformations, since they have unique properties and several advantages[29-31] over traditional liquid acids[32], such as facile handling, easy separation of products, easy recovery and reusability of the catalyst. In

combination with the application of heterogeneous solid acids, solvent-free reactions promise to be an essential facet of 'Green Chemistry'-freereactionshave. attracted much interest because of their ease of experimental procedures and workup, low cost and environmentally benign nature[33].

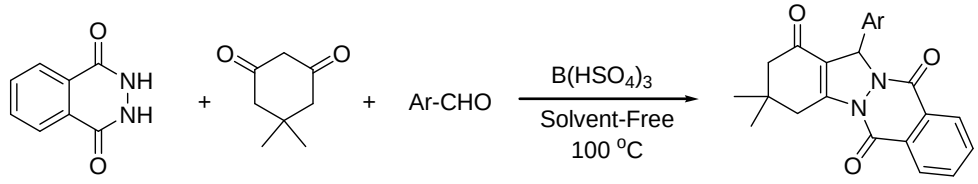
The application of boron reagents in organic synthesis led to Herbert C. Brown (1912-2004) being awarded the Nobel Prize in Chemistry in 1979[34] and since that time this relatively rare element has remained on the cutting-edge of modern synthetic chemistry. Recently, Kiasat[35] has reported regioselective conversion of epoxides to thiocyanohydrins using Boron sulfonic acid as a new solid acid catalyst, under solvent-free conditions.

Boron sulfonic acid was easily prepared by addition of chlorosulfonic acid to boric acid under N2 atmosphere at room temperature[35]. This reaction was easy and clean, because HCl gas was evolved from the reaction vessel immediately (Scheme 1).



Scheme 1 Preparation of $B(HSO_4)_3$

Now, as we continued our studies for developing efficient and environmentally benign synthetic protocols[36, 37] we found out a highly efficient methodology for the synthesis of 2*H*-indazolo[1,2-*b*]-phthalazine-trione derivatives (**4a-n)***via* a one-pot three-component condensation reaction of dimedone (**1**), phthalhydrazide (**2**) and aromatic aldehydes (**3a-n**) in the presence of catalytic amount of boron sulfonic acid under solvent-free conditions (Scheme 2).



(1) **(2)** **(3a-n)** **(4a-n)**

Entry	3	Ar-CHO	Product (**4a-n**) / Ar-
1	**a**	Ph-CHO	Ph-
2	**b**	4-Cl-Ph-CHO	4-Cl-Ph-
3	**c**	3-Cl-Ph-CHO	3-Cl-Ph-
4	**d**	2,4-Cl_2-Ph-CHO	2,4-Cl_2-Ph-
5	**e**	3-Br-Ph-CHO	3-Br-Ph-
6	**f**	4-Br-Ph-CHO	4-Br-Ph-
7	**g**	4-F-Ph-CHO	4-F-Ph-
8	**h**	3-NO_2-Ph-CHO	3-NO_2-Ph-
9	**i**	4-NO_2-Ph-CHO	4-NO_2-Ph-
10	**j**	4-CH_3-Ph-CHO	4-CH_3-Ph-
11	**k**	3-CH_3-Ph-CHO	3-CH_3-Ph-
12	**l**	2-CH_3-Ph-CHO	2-CH_3-Ph-
13	**m**	3-OCH_3,4-OH-Ph-CHO	3-OCH_3,4-OH-Ph-
14	**n**	3,4,5-$(OCH_3)_3$-Ph-CHO	3,4,5-$(OCH_3)_3$-Ph-

Scheme 2 One-pot three component synthesis of *2H*-indazolo[1,2-*b*]phthalazine-triones in the presence of $B(HSO_4)_3$ under solvent-free conditions at 100 °C.

Results and Discussion

At first $B(HSO_4)_3$ was prepared *via* the reaction of chlorosulfonic acid and boric acid[35]. One of the informative techniques for the investigation of the catalyst formation is FT-IR spectroscopy. So, the structure of catalyst was characterized by FT-IR spectroscopy (Fig. 1). As seen in Fig. 1 the spectrum of $B(HSO_4)_3$ is different from that of boric acid. The FT-IR spectrum of $B(HSO_4)_3$ shows absorption bands at 1400 (υ S=O asymmetric stretching), 1200 cm^{-1} corresponding-O.Moreovertoa broadυ bandS from 3400-2700 cm^{-1} corresponding to acidic O-H stretching.

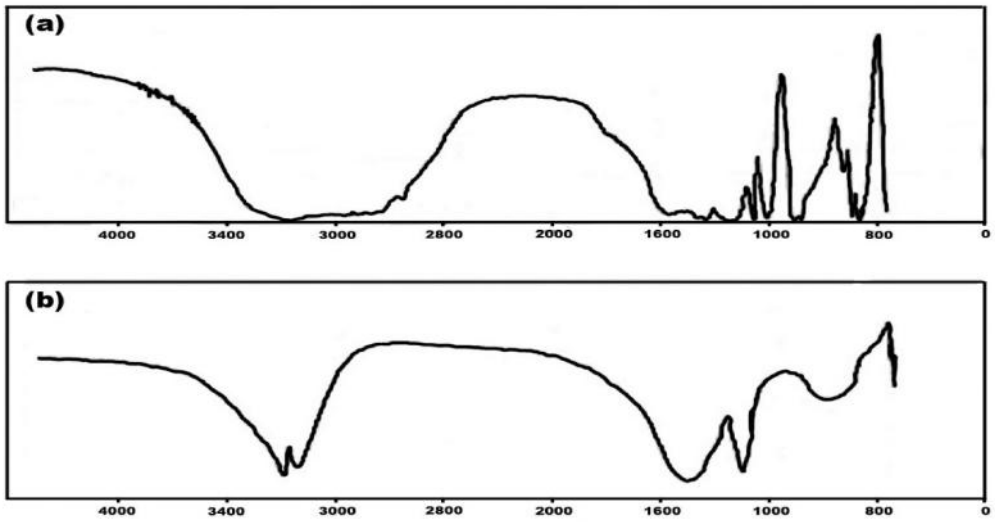
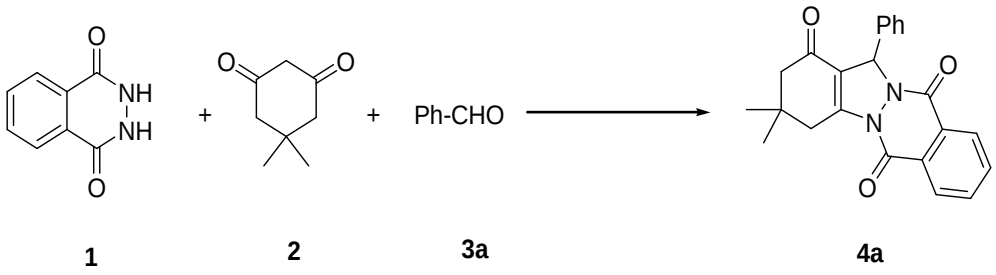


Fig.1IR spectra of $B(HSO_4)_3$ (a) and $B(OH)_3$ (b)

As we continued in order to optimize the reaction conditions, the one-pot three component condensation reaction between benzaldehyde (1.2 mmol), dimedone (1 mmol) and phthalhydrazide (1 mmol) was chosen as a model reaction. (Scheme 3)



1 **2** **3a** **4a**

Scheme 3 Condensation reaction of benzaldehyde ,dimedone and phthalhydrazide

At first, the influence of various amounts of catalyst on the reaction time and obtained yields were studied (Table I). We found that 75% yield of **4a** was obtained when 0.7 mole % catalyst was used. This yield increased to 92 % as $B(HSO_4)_3$ loading went up to 5.3 mole % (entries, 1 and 4). 5.3 mole % of catalyst was sufficient and excess $B(HSO_4)_3$ did not increase the yield substantially(entries, 5 and 6).

Table 1influence of different amount of catalyst ($B(HSO_4)_3$; mole %) on the one-pot three component reaction between benzaldehyde (1.2 mmol), dimedone (1 mmol) and phthalhydrazide (1 mmol) under solvent-free condition at 100^oC.

Entry	amount of catalyst, mole %	*T* /^oC	*t* / min	Yield, %[a]
1	0.7	100	31	75
2	2.6	100	17	77
3	4	100	12	86
4	5.3	100	12	92
5	6.5	100	11	88
6	8	100	11	87

[a] Yields refer to the isolated pure products.

It is indisputable that temperature is a crucial factor for organic reactions, so we examined the reaction in the various temperatures (Table II).The best result was obtained at 100 ^oC (entry 2).

Table 2 Effect of temperature on the yield of reaction between benzaldehyde (1.2 mmol), dimedone (1 mmol), phthalhydrazide (1 mmol) and catalyst ($B(HSO_4)_3$; 5.3 mole %) under solvent-free condition.

Entry	*T* /^oC	*t* / min	Yield, %[a]
1	120	12	92
2	100	12	92
3	80	12	83

[a] isolated Yields refer to the pure products.

Therefore, we kept the reaction temperature as 100 ^oC and amount of catalyst; 5.3 mole%. (giving proper reaction time and high yield). In order to establish the crucial role of $B(HSO_4)_3$ as a catalyst for the synthesis of titled compounds, the model reaction was examined without catalyst under optimized temperature and it was found that negligible conversion to desired product occurred even after 1 h of heating.

In order to establish the generality and efficiency of our presented methodology for the synthesis of *2H*-indazolo[1,2-*b*] phthalazine-triones, a broad range of aromatic aldehydes (**3a-n**) were condensed with phthalhydrazide (**1**) and dimedone (**2**) under optimized conditions. The results of reaction are summarized in Table III.Inall cases, the reactions gave the corresponding products in good yield. This protocol tolerates a variety of aromatic aldehydes containing both electron-withdrawing and electron-donating substituents. As it is clear from Table III, substituents on the aromatic ring had no obvious effect on yields or reaction times under the above optimal conditions. The reactions are clean, efficient and swift and is accomplished with a simple procedure.

Table 3 Solvent-free one-pot three component synthesis of 2*H*- indazolo[1,2-*b*]phthalazine-trione derivatives in the presence of $B(HSO_4)_3$ as a catalyst at 100 ^oC.

Entry	Aldehyde	Product	*T* / min	Yield, %[a]	*m.p.* / ^oC(Lit.)
1	**3a**	**4a**	12	92	206-207(204-206)[15]
2	**3b**	**4b**	11	93	261-262(262-264)[15]
3	**3c**	**4c**	17	84	204-205(204-206)[33d]
4	**3d**	**4d**	9	92	218-220(219-221)[33d]
5	**3e**	**4e**	14	81	224-225(224-226)[31]
6	**3f**	**4f**	12	89	260-262(258-267)[15,33d]
7	**3g**	**4g**	13	82	222-221(217-226)[15,33d]
8	**3h**	**4h**	13	87	271-272(270-272)[15]
9	**3i**	**4i**	10	94	220-222(223-225)[15]
10	**3j**	**4j**	18	81	226-227(226-228)[33d]
11	**3k**	**4k**	17	82	231-232(232-233)[31]
12	**3l**	**4l**	21	79	240-241(241-243)[33d]
13	**3m**	**4m**	14	94	250-251(250-252)[33d]
14	**3n**	**4n**	11	93	231-233(232-234)[33d]

[a]Yields refer to pure isolated products.

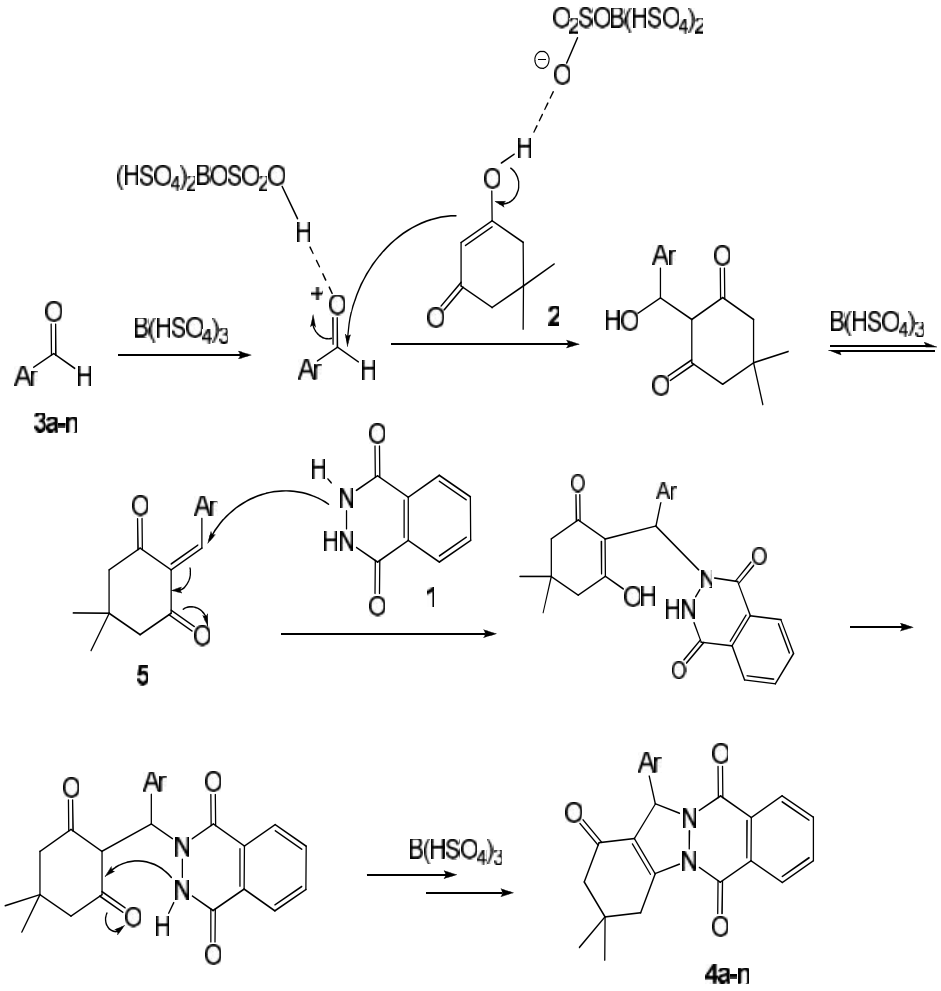
The catalyst recovery and reuse was evaluated taking the one-pot three component condensation reaction of benzaldehyde as a model reaction (scheme 3). After the reaction was completed, the crude products were dissolved in hot ethanol and insoluble catalyst was isolated by simple filtration. Then it was reused after washing with hot ethanol. Recovered catalyst showed the same activity as fresh catalyst (Table IV).In continuation of work up, the filtrate was concentrated under reduced pressure. Then obtained crude products were recrystalized from $EtOH/H_2O$ 3:1.

Table 4 Evaluation of The catalyst reusability in one-pot three component reaction between benzaldehyde (1.2 mmol), dimedone (1 mmol), phthalhydrazide (1 mmol) and catalyst ($B(HSO_4)_3$; 5.3 mole %) under solvent-free condition at 100^oC.

No. of cycles	*t* / min	Yield, %[a]
Fresh catalyst	12	92
1	12	92
2	12	91
3	12	89
4	12	88
5	12	86

[a] Yields refer to the isolated pure products.

A possible mechanism for the formation of (**4a-n**) is proposed in Scheme 4. It is reasonable to assume that (**4a-n**) results from initial formation of a heterodiene (**5**) by standard Knoevenagel condensation of the dimedone (**2**) and aldehyde (**3**). Then, the subsequent Michael-type addition of the phthalhydrazide (**1**) to the heterodyne (**5**) followed by cyclization affords the corresponding products (**4**) (Scheme 4).



Scheme 4 Proposed mechanism for the synthesis of *2H*-indazolo[1,2-*b*]phthalazine-triones via a one-pot three component condensation reaction between phthalhydrazide, dimedone and aldehydes.

The results were good in terms of yields and product purity. The nature of these compounds are 1:1:1 adducts. This was apparent by mass spectroscopy. In each case, mass spectrum was shown the molecular ion peak at appropriate *m/z* values. All compounds (**4a-n**) are known and stable solids. Their physical and spectroscopic data were matched with those of authentic samples. The products were characterized by IR, ^{1}H, and ^{13}C NMR spectral data, mass spectrometry, and elemental analysis.

In order to show the merits and accessibility of the present work in comparison with reported results in the literature, we compared some of the results of our present methodology with the reported methods for the one-pot three component synthesis of *2H*-indazolo[1,2-*b*] phthalazine-trione derivatives (Table V). As shown in Table 5, boron sulfonic acid (BSA) can act as an effective catalyst with respect to reaction kinetic, inexpensive protocol and broad applicability in terms of yield.

Table 5 Comparison of $B(HSO_4)_3$ with reported catalysts for the reaction of benzaldehyde, dimedone and phthalhydrazide.

Reaction conditions	Catalyst load, mol%	*t* / min	Yield, %[a]	Ref.
p-Toluenesulfonic acid/solvent-free/80 ^oC	30	10	86	15
H_2SO_4/[bmim][BF_4]/80 ^oC	15	30	86	16
Poly phosphoric acid-SiO_2/solvent-free/100 ^oC	5	8	92	33d
SiWA/solvent-free/100 ^oC	1	16	92	31
N,N,N´,N´-tetrabromobenzene-1,3-disulfonamide [TBBDA]/solvent-free/100 ^oC	1	10	89	21
prolinetriflate/solvent-free/80^oC	10	180	92	23
(S)-camphorsulfonic acid/solvent-free/80^oC	20	15	90	24
Phosphomolybdic acid (PMA) – SiO_2/solvent-free/80^oC	5	30	85	25
$B(HSO_4)_3$/solvent-free/100 ^oC	5.3	12	92	This work

[a] isolated pure Yields.

Experimental section

All reagents were used as received without further purification. All yields refer to isolated products after purification. $B(HSO4)_3$ was prepared according to the reported procedure[35]. Products were characterized by comparison of spectroscopic data (IR, ^1H NMR, ^{13}C NMR spectra) and melting points with authentic samples. Elemental analyses for C, H, and N were performed using a CHN-O-Rapid analyzer. The NMR spectra were recorded on a DPX 300- MHz instrument. The spectra were measured in $CDCl_3$ relative to TMS (0.00 ppm). IR spectra were recorded on a RXi FT-IR spectrophotometer. All of the compounds were solid and solid state IR spectra were recorded using the KBr disk technique. Mass spectra were recorded on an technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with melting point apparatus.

Preparation of boron sulfonic acid

A 50 mL kitasato flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25 mmol) was charged in the flask and chlorosulfonic acid (8.74 g, *ca.* 5 mL, 75 mmol) was added drop wise over a period of 1 h at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 1 h, while the residual HCl was eliminated by suction. Then the mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid. Finally, a grayish solid material was obtained in 89% yield (6.7 g).

Typical procedure for the preparation of 3,4-dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[1,2-b] phthalazine-1,6,11(13H)-trione (4a)

To a mixture of benzaldehyde (1.2 mmol), phthalhydrazide (1 mmol) and dimedone (1 mmol), $B(HSO4)_3$ (5.3 mmol %) was added and the mixture was stirred at 100^oC for appropriate time (Table 4). Completion of the reaction was followed by TLC. After the completion of the reaction, ethanol was added and the reaction mixture was heated until solid crude product was dissolved. Then, the heterogeneous catalyst was isolated by simple filtration and after washing with ethanol reused for other reactions. In continuation of work up, the filtrate was concentrated under reduced pressure. The crude products were recrystalized from EtOH/H_2O 3:1 to afford the pure product (**4a**) (0.34g, 92%) as a yellow powder.

M.p.: 206-207 °C(204-206 °C)[15]; IR (KBr) (*v*, cm^{-1}): 2959, 1661, 1618, 1469, 1421, 1358, 1302, 1273, 1141, 1074, 749, 691; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 6H), 2.33 (s, 2H), 3.21-3.45 (AB system, *J* = 19.0 Hz, 2H), 6.45 (s, 1H), 7.27-7.40 (m, 5H), 7.85 (m, 2H), 8.27-8.35 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 28.6, 34.5, 38.0, 50.9, 64.9, 118.5, 127.0, 127.6, 127.9, 128.61, 12864, 128.9, 129.0, 133.4, 134.4, 136.3, 150.7, 154.2, 155.9, 192.0 ppm; MS, *m/z* (%) = 372 (M^+, 21), 295 (100), 104 (67), 76 (53). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%. Found: C, 74.23; H, 5.39; N, 7.48%.

3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4b)

White powder (93%); M.p.: 261-262 °C (262-264 °C)[15]; IR (KBr) (*v*, cm^{-1}): 2957, 1662, 1624, 1469, 1393, 1352, 1312, 1268, 1149, 827, 745; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 6H), 2.33 (s, 2H), 3.20-3.43 (AB system, *J* = 19.1 Hz, 2H), 6.40 (s, 1H), 7.28-7.37 (m, 4H), 7.85 (m, 2H), 8.25-8.34 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 28.6, 34.5, 37.9, 50.8, 64.2, 115.5, 115.8, 118.1, 127.6, 127.9, 128.8, 128.91, 128.95, 128.99, 132.1, 132.2, 133.5, 134.5, 150.9, 154.3, 155.9, 192.0 ppm; MS, *m/z* (%) = 406 (M^+, 8), 295 (100), 104 (39), 76 (22); Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%. Found: C, 67.84; H, 4.63; N, 6.81%.

3,4-Dihydro-3,3-dimethyl-13-(3-chlorophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4c).

Yellow powder (84%); M.p.: 204-205 °C (204-206 °C)[33d]; IR (KBr) (*v*, cm^{-1}) ; 2957, 2872, 1649, 1626, 1578, 1467, 1360, 1315, 1268, 1147, 791, 701; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 6H), 1.22 (s, 3H), 2.35(s, 2H), 3.22-3.41 (AB system, *J* = 19.1 Hz, 2H), 6.39 (s, 1H), 7.22-8.40 (m, 8H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5, 28.6, 34.6, 37.9, 50.9, 64.4, 118.0, 125.8, 126.9, 127.7, 128.1, 128.9, 129.0, 130.0, 133.7, 134.6, 138.5, 151.2, 154.5, 155.9, 192.1 ppm; MS: *m/z* (%) = 406 (M^+, 21), 295 (100), 104 (31), 76 (27).), Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%.Found: C, 67.88; H, 4.72; N, 6.87 %.

3,4-Dihydro-3,3-dimethyl-13-(2,4-Dichlorophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4d).

Yellow powder (92%); M.p.: 218-220 °C (219-221°C)[15]; IR (KBr) (*v*, cm^{-1}): 2964, 1660, 1628, 1468, 1391,1351, 1312, 1267, 1146, 1101, 832, 701 ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.23(s, 3H), 2.34 (s, 2H), 3.25-3.40 (AB system, *J* = 19.1 Hz, 2H), 6.59 (s, 1H), 7.26-8.37(m, 8H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5, 28.8, 34.6, 38.1, 50.8, 63.6, 127.7, 127.8, 128.1, 128.6, 129.1, 130.8, 131.8, 133.4,133.8, 134.6, 134.9, 152.1, 154.3, 156.1, 192.2 ppm; MS, *m/z* (%) = 441 (M^+, 4),295(100), 104 (37), 76 (23), Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.59; H, 4.12; N, 6.35%.Found: C, 62.56; H, 4.10; N, 6.26 %.

3,4-Dihydro-3,3-dimethyl-13-(3-bromophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4e)

Yellow powder (81%), M.p.: 224-225 °C(224-226 °C)[31]; IR (KBr) (*v*, cm^{-1}): 2981, 1622, 1448, 1419, 1361, 1312, 1267, 1123, 1056, 948, 861; ^{1}HNMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3H), 1.21 (s, 3H), 2.34 (s, 2H), 3.23-3.41 (AB system, *J* = 19.1 Hz, 2H), 6.38 (s, 1H), 7.28-8.38 (m, 8H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$): δ = 28.4, 28.7, 34.5, 38.1, 50.9, 64.1, 116.7, 122.7, 126.4, 127.6, 127.9, 129.1, 129.7, 130.4, 131.9, 133.5, 134.6, 138.6, 151.2, 154.3, 155.9, 191.8 ppm; MS, *m/z* (%) = 451 (M^+, 7), 295(100), 104(28), 76(34). Anal. Calcd for $C_{23}H_{19}BrN_2O_3$: C, 61.21; H, 4.17; N, 6.21%. Found: C, 61.14; H, 4.17; N, 6.30 %.

3,4-Dihydro-3,3-dimethyl-13-(4-bromophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4f)

White powder (89%); M.p.: 260-262 °C (258-267 °C)[15, 33d]; IR (KBr) (*v*, cm^{-1}): 2959, 1655, 1623, 1469, 1388, 1360, 1309, 1267, 1141, 843, 769; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 6H), 2.33 (s, 2H), 3.20-3.44 (AB system, *J* = 19.1 Hz, 2H), 6.40 (s, 1H), 7.28-7.37 (m, 4H), 7.85 (m, 2H), 8.25-8.34 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 28.6, 34.5, 37.9, 50.8, 64.2, 115.5, 115.8, 118.1, 127.6, 127.9, 128.8, 128.91, 128.95, 128.99, 132.1, 132.2, 133.5, 134.5, 150.9, 154.3, 155.9, 192.0 ppm; MS, *m/z* (%) = 451 (M^+, 11), 295 (100), 104 (32), 76 (43); Anal. Calcd for $C_{23}H_{19}BrN_2O_3$: C, 61.21; H, 4.17; N, 6.21%. Found: C, 61.19; H, 4.27; N, 6.18%.

3,4-Dihydro-3,3-dimethyl-13-(4-fluorophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4g)

Yellow powder (82%); M.p.: 221-223 °C (217-226 °C)[15, 33d]; IR (KBr) (*v*, cm^{-1}): 2958, 2880, 1664, 1626, 1517, 1468, 1369, 1312, 1263, 1219, 1024, 843, 791; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 6H), 2.34 (s, 2H), 3.27-3.38 (AB system, *J* = 19.0 Hz, 2H), 6.43 (s, 1H), 7.02 (m, 2H), 7.40 (m, 2H), 7.85 (m, 2H), 8.27-8.34 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 28.6, 34.6, 37.9, 50.8, 64.2, 115.5, 115.8, 118.1, 127.6, 127.9, 128.8, 128.93, 128.99, 132.1, 132.2, 133.5, 134.5, 150.9, 154.3, 155.9, 192.1 ppm; MS, *m/z* (%) = 390 (M^+, 12), 295 (100), 104 (58), 76 (8). Anal. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18%. Found: C, 70.62; H, 4.99; N, 7.11%.

3,4-Dihydro-3,3-dimethyl-13-(3-nitrophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4h)

Yellow powder (87%); M.p.: 271-272 ^{o}C (270-272 ^{o}C)[15]; IR (KBr) (*v*, cm^{-1}): 2945, 1683, 1672, 1615, 1358, 1273, 1152, 1104, 749; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 6H), 2.35 (s, 2H), 3.47-3.24 (AB system, *J* =19.2 Hz, 2H), 6.52 (s, 1H), 7.53-8.39 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 28.9, 34.6, 38.3, 51.6, 64.2, 116.8, 127.3, 127.3, 128.4, 128.8, 129.2, 129.8, 131.5, 132.8, 133.1, 133.6, 134.5, 135.4, 151.8, 154.4, 156.3, 192.2; MS, m/z (%) = 417 (M^+, 12), 295 (100), 104 (49), 76 (79). Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; N, 10.07; H, 4.59%. Found: C, 66.15; N, 10.23; H, 4.61%.

3,4-Dihydro-3,3-dimethyl-13-(4-nitrophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4i)

Yellow powder (94%); M.p.: 220-222 ^{o}C (223-225 ^{o}C)[15]; IR (KBr) (*v*, cm^{-1}): 2943, 1695, 1659, 1616, 1519, 1359, 1276, 1170, 1109,861,793; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3H), 1.22 (s, 3H), 2.34 (s, 2H), 3.22-3.44 (2H, AB system, *J* = 18.99 Hz, 2H), 6.51 (s, 1H), 7.59-7.89 (m, 4H), 8.19-8.37 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 28.6, 34.6, 37.9, 50.7, 64.0, 117.2, 123.8, 123.9, 127.6, 128.0, 128.1, 128.5, 128.6, 128.8, 133.8, 134.7, 143.4, 147.8, 151.6, 154.5, 155.8, 191.9; MS, *m/z* (%) = 417 (M^+, 6), 295 (100), 104 (46), 76 (69). Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07%. Found: C, 66.21; H, 4.68; N, 9.99%.

3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4j)

Yellow powder (81%); M.p.: 226-227 ^{o}C (226-228 ^{o}C)[33d]; IR (KBr) (*v*, cm^{-1}): 2956, 1663, 1627, 1463, 1360, 1312, 1269, 1080, 1024,829, 789; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 6H), 2.29 (s, 3H), 2.33 (s, 2H), 3.20-3.45(AB system, *J* = 19.0 Hz, 2H), 6.42 (s, 1H), 7.12-7.15 (m, 2H), 7.29-7.31 (m, 2H), 7.84 (m, 2H), 8.27-8.35 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 28.4, 28.6, 34.5, 38.0, 50.9, 64.7, 118.6, 127.0, 127.6, 127.8, 128.9, 129.1, 129.3, 133.3, 134.3, 138.4, 150.6, 154.1, 155.9, 192.0 ppm; MS, *m/z* (%) = 386 (M^+, 9), 295 (100), 104 (43), 76 (42). Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25% Found: C, 74.51; H, 5.75; N, 7.29 %.

3,4-Dihydro-3,3-dimethyl-13-(3-methylphenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione(4k)

Yellow powder(82%), M.p.: 231-232 ^{o}C (232-233 ^{o}C)[31]; IR (KBr) (*v*, cm^{-1}): 2958, 1639, 1660,1610, 1428, 1356, 1315, 1271, 1120, 1076, 941, 853; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3H), 1.21 (s, 3H), 2.31 (s, 3H), 2.32 (s, 2H), 3.24-3.44 (AB system, *J* = 18.9 Hz, 2H), 6.41 (s, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.18-7.23 (m, 3H), 7.83-7.87 (m, 2H), 8.26–8.30 (m, 1H), 7.05-8.38 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 28.5, 28.8, 34.9, 38.1, 51.0, 64.8, 119.0, 124.4, 127.2, 127.9, 128.1, 128.6, 129.1, 129.3, 129.6, 133.1, 134.4, 136.3, 138.4, 150.7, 154.0, 156.1, 192.2 ppm; MS*: m/z* (%) = 386 (M^+, 14), 295 (100),104 (23), 76 (36). Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25%. Found: C, 74.57; H, 6.76; N, 7.21 %.

3,4-Dihydro-3,3-dimethyl-13-(2-methylphenyl)-2H-indazolo[1,2-b]phthalazine 1,6,11(13H)-trione (4l).

Yellow powder (79%); M.p.: 240-241 ^{o}C (241-243 ^{o}C)[33d]; IR (KBr) (*v*, cm^{-1}): 2949, 1662, 1603, 1439,1359, 1315, 1275, 1149, 1080, 864, 799; ^{1}H NMR (300 MHz, CDCl3): δ = 1.20 (s, 3H), 1.22 (s, 3H), 2.31(s, 3H), 2.33 (s, 2H), 3.24-3.42 (AB system, *J* = 19.0 Hz, 2H), 6.39 (s, 1H), 7.09- 8.32 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 28.3, 28.8, 34.7, 38.1, 50.9, 64.3, 119.1, 124.1, 127.4, 127.6, 128.0, 128.4, 129.0, 129.2, 129.8, 133.5, 134.5, 136.3, 138.1, 150.6, 154.2, 156.0, 192.1 ppm; MS: *m/z* (%) = 386 (M^+, 12), 295 (100), Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25% Found: C, 74.55; H, 5.76; N, 7.26 %.

3,4-Dihydro-3,3-dimethyl-13-(4-Hydroxy-3-methoxyphenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4m)*.*

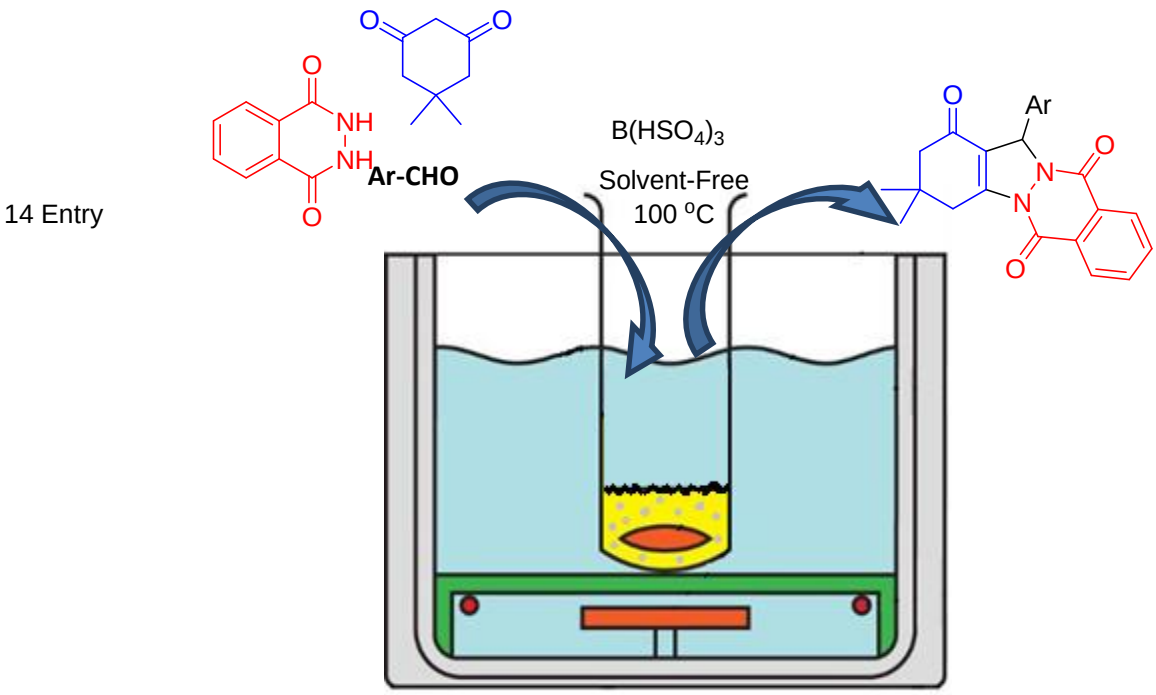
Yellow powder (94%); M.p.: 250-251 ^{o}C (250-252 ^{o}C)[33d]; IR (KBr) (*v*, cm^{-1}): 2958, 1661, 1600, 1489, 1362, 1270, 1229, 1135, 1031, 790, 647: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (s, 6H), 1.23(s, 3H), 2.35 (s, 2H), 3.23-3.46 (AB system, *J* = 19.0 Hz, 2H), 3.91 (s, 3H),5.32-5.34 (br, 1H), 6.40 (s, 1H), 6.77-7.10 (m, 3H), 7.87-8.41 (m,4H) ppm; ^{13}C NMR (75MHz, $CDCl_3$): δ = 28.4, 28.8, 34.7, 38.1, 51.1, 56.3, 64.8, 110.9, 114.6, 118.6, 119.3, 127.8, 128.0,128.2, 129.0, 129.3, 133.4, 134.5, 145.9, 146.4, 150.7, 156.0, 192.2 ppm; MS: *m/z* (%) = 418 (M^+, 11), 295(100), 104(92), 76(46); 295 (100),104 (92), 76 (46). Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69%. Found: C, 68.86; H, 5.31; N, 6.73%.

3,3-Dimethyl-13-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4n).

Yellow powder (93%); M.p.: 231-233 ^{o}C (232-234 ^{o}C)[33d]; IR (KBr) (*v*, cm^{-1}): 2960, 1656, 1632, 1601,1466, 1432, 1361, 1313, 1268, 1125, 989, 704; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.24 (s, 3H), 2.36 (s, 2H), 3.21 (d, *J* = 19.1 Hz, 1H), 3.47 (AB system, *J* = 19.2 Hz, 2H), 3.79 (s, 3H), 3.82 (s, 6H),

6.41 (s, 1H), 6.62 (s, 1H), 7.81-8.37 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 29.0, 34.5, 38.1, 51.1, 56.2, 60.8, 65.1, 104.6, 118.4, 127.7, 128.1, 130.0, 129.0, 131.8, 133.7, 134.6, 138.3, 150.9, 153.5, 154.6, 156.1, 192.2 ppm; MS: *m/z* (%) = 462 (M^+, 34), 295 (100),104 (9), 76 (8). Anal. Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06% Found: C, 67.43; H, 5.67; N, 6.11. %.

Graphical Abstract



Solvent-free Condensation reactionof benzaldehyde derivatives, dimedone and phthalhydrazide in one-pot three component synthesis of 2*H*- indazolo[1,2-*b*]phthalazine-trione derivatives in the presence of $B(HSO_4)_3$ as a catalyst at 100 °C.

Conclusion

In summary, an efficient protocol for the preparation of 2*H*-indazolo[1,2-*b*] phthalazine-trione derivatives *via* one-pot three-component condensation reaction between phthalhydrazide, dimedone and aldehydes using $B(HSO_4)_3$ as an efficient and reusable catalyst was described. The reactions were completed under thermal solvent- free conditions in short times and produced the corresponding products in good yields. The one-pot nature and the use of a heterogeneous solid acid as an eco-friendly catalyst make it an interesting alternative method in terms of 2*H*-indazolo[1,2-*b*] phthalazine-triones synthesis.

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