5-Sulphosalicylic acid: An expeditious organocatalyst for one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

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Abstract

Green and atom economic protocol has been developed for one-pot, multi-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in presence of 5-sulphosalicylic acid as an organocatalyst under solvent-free conditions. Non-toxic, cost-effective catalyst, high yields, shorter reaction times, simple experimental and work-up procedure are salient features of our synthetic route.

Graphic abstract

Keywords 5-Sulphosalicylic acid · One-pot · 2*H*-indazolo[2,1-*b*]phthalazine-triones · Solvent-free

1 Introduction

Nowadays, the challenges for maintaining ecological balance of our planet are among the most complicated and daunting ever faced by society. In order to protect

the environment, researchers are highly engage in facing these challenges fiercely through their systematic improvements and breakthrough innovations. Further, they are trying to create advanced product by generating the series of drug-like organic molecules involving

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complex molecular functionality that significantly accelerate the innovations in chemical sector [1–3]. In this regards, multi-component reactions (MCRs) has received great attention in drug architecture and diversely oriented synthesis and proven to be a valuable asset in medicinal and pharmaceutical chemistry [4–6]. Further, multi-component reactions such as three components (3-CRs) or four components (4-CRs) shows remarkable performance in exceptional synthetic efficiency, high atom economy, decrease in waste generation and energy consumption as well as selection of eco-friendly solvent which are the essential drivers of green chemistry [7–9]. Hence, MCRs are one of the most powerful and worldwide acceptable techniques which motivate organic chemists for the creation of libraries of structurally diverse and medicinally relevant heterocyclic scaffolds.

Recently, the great deal of attention has been given to the use of organocatalyst in organic reaction [10–12]. Organo-catalyzed reactions are handy technique for the synthesis of structurally resembled drug like molecules having potential applications in the diverse fields [13]. Organocatalyst are cost-effective, stable and non-toxic, easy to handle, metal-free, accelerates the reaction rate and often used in stoichiometric amounts [14]. Most exciting features of organocatalyst are the minimization of waste and environmentally safe disposal in various synthetic processes for building cleaner synthetic routes [15]. Further, organic reactions under solvent-free conditions have attracted much attention from chemists, particularly from the viewpoint of green chemistry [16–19].

5-sulphosalicylic acid (5-SSA) is an efficient organocatalyst having potential application in the diverse fields such as in the determination of total proteins in spinal fluids [20], used as spray reagent for detection of sugars on thin-layer chromatogram [21], as a redox indicator [22], in the study of pulse radiolysis [23] and as chelating agent [24]. However, despite of its remarkable catalytic potential and hydrophilic nature, only few reports are available in literature [25–27]. Here, our working hypothesis is based on the molecular synergism of 5-sulphosalicylic acid (Fig. 1). Due to the presence of strong electron withdrawing sulphonate group ($-\text{SO}_3\text{H}$), hydrogen atom abstraction by aldehyde molecule become easier which forms more resonance stabilized aromatic anion thereby enhances the bronsted acidic character of 5-sulphosalicylic acid [28].

Indazole [2,1-*b*]phthalazine-triones are prominent *N*-heterocyclic phthalazine derivatives having bridgehead hydrazine heterocycle and are bioisosteres of indoles. Further, they are privileged core in natural product which exhibits illustrious biological and pharmacological activities such as antimicrobial [29], anticonvulsant [30], antifungal [31], anti-tumor activity [32], high binding affinity for the estrogen receptor [33], 5-HT₂ receptor antagonism [34], inhibition of

Fig. 1 Molecular Synergism of 5-sulphosalicylic acid

protein kinase C- β [35], etc. Owing to such unique biological profile of phthalazine derivatives, a considerable amount of research has been paid for the synthesis of their structurally resembled drug like heterocyclic scaffolds. Therefore, number of protocols including varieties of catalysts has been developed for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones [36–50]. A thorough scrutiny of the literature reveals that although various catalyst have been employed for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones, the use of 5-sulphosalicylic acid remains ignored. With these observations in mind, we focus our attempt towards the development of green and easily adaptable protocol by using 5-SSA as highly efficient organocatalyst. Our earlier experience with 5-sulphosalicylic acid [51], encouraged us to explore its catalytic efficiency to develop general method for synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones via one-pot, three-component reaction of phthalhydrazide, dimedone with various aromatic aldehydes by using 5-SSA as an efficient organocatalyst under the solvent-free conditions.

2 Experimental

Phthalhydrazide (Sigma Aldrich), Dimedone (Thomas Baker), 5-sulphosalicylic acid (Spectrochem) and aromatic aldehydes (Spectrochem and Thomas Baker) were used as received. NMR spectra were recorded on Bruker AC (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) spectrometer using TMS as an internal standard in CDCl_3 . The δ -values are expressed in parts per million (ppm) and coupling constants (*J*) are expressed in hertz (Hz). The FT-IR spectra were measured with Perkin-Elmer Spectrum one FT-IR spectrometer. Mass spectra were recorded on Shimadzu QP2010 gas chromatograph mass spectrometer.

2.1 Representative procedure for synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones

2.1.1 Synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones by using three-component reaction of phthalhydrazide, dimedone and aryl aldehydes (Method A)

5-sulphosalicylic acid (0.042 g, 20 mol%) was added to the mixture of phthalhydrazide (0.162 g, 1 mmol), dimedone (0.140 g, 1 mmol) and aryl aldehyde (1.2 mmol). Materials were heated for appropriate time under solvent-free condition at 100 °C. After the completion of reaction as indicated by TLC, reaction mixture was allowed to cool at room temperature and water (10 mL) was added and stirred until a free-flowing solid obtained in reaction flask. The resultant solid was filtered, washed with water and then dried. The solid was further washed successively with the mixture of hexane: chloroform (70:30, v/v) and then dried. All the resulting products were pure and characterized by spectroscopic techniques.

2.1.2 Synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones by using four-component reaction of hydrazinium hydroxide, phthalic anhydride, dimedone and aryl aldehydes (Method B)

In 25 mL RB flask, mixture of hydrazinium hydroxide (0.06 g, 1.2 mmol) and phthalic anhydride (0.148 g, 1 mmol) were heated for 10 min at 100 °C. Phthalhydrazide, as white solid mixture were separated and which was used as a precursor for synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones. Thereafter, aromatic aldehyde (1 mmol), dimedone (0.140 g, 1 mmol) and 5-sulphosalicylic acid (0.042 g, 20 mol%) were added to precursor. Materials were heated for appropriate time under solvent-free condition at 100 °C. Upon the completion of reaction as indicated by TLC, reaction mixture was allowed to cool at room temperature and water (10 mL) was added afterward, the procedure is similar to method A.

2.1.3 Selected spectral data

3,3-dimethyl-13-(phenyl)-3,4-dihydro-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (4a) Yellow Solid, Mp. 201–202 °C, ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.14–8.22 (m, 2H, phthalhydrazide H₇, H₁₀), 7.75–7.82 (m, 2H phthalhydrazide H₈, H₉), 7.33–7.41 (m, 5H Ar–H), 6.45 (s, 1H, CH), 3.34 and 3.43 (AB system, *J* = 19.2 Hz, 2H, CH₃H₆CO), 2.36 (s, 2H, CH₂), 1.21 (s, 6H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 27.3, 31.7, 38.0, 50.8, 54.1, 114.1, 127.3, 127.4,

128.7, 128.8, 133.9, 134.8, 135.2, 156.5, 158.9, 192.0; IR (KBr) (cm^{−1}): 3022, 2971, 1673, 1654, 1617, 1362, 1045, 953, 855, 778, 696, 578; MS(EI): *m/z* 372 [M⁺].

3,3-dimethyl-13-(4-methoxyphenyl)-3,4-dihydro-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (4b) Yellow Solid, Mp. 217–219 °C, ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.12–8.23 (m, 2H, phthalhydrazide H₇, H₁₀), 7.81–7.88 (m, 2H, phthalhydrazide H₈, H₉), 7.45 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.31 (d, *J* = 8.4 Hz, 2H, Ar–H), 6.56 (s, 1H, CH), 3.23 and 3.28 (AB system, *J* = 18.2 Hz, 2H, CH₃H₆CO), 2.25 (s, 2H), 1.18 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 27.3, 28.6, 31.7, 37.4, 38.0, 50.8, 54.1, 114.1, 127.3, 127.4, 128.7, 128.8, 133.9, 134.8, 135.2, 150.8, 156.5, 158.9, 192.3; IR (KBr) (cm^{−1}): 3027, 2968, 1664, 1655, 1645, 1360, 1268, 954, 844, 733, 676, 584; MS(EI): *m/z* 402 [M⁺].

3,3-dimethyl-13-(4-methylphenyl)-3,4-dihydro-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (4c) Yellow Solid, Mp. 224–226 °C, ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.12–8.23 (m, 2H, phthalhydrazide H₇, H₁₀), 7.79–7.86 (m, 2H, phthalhydrazide H₈, H₉), 7.22–7.33 (m, 2H, Ar–H), 6.48 (s, 1H, CH), 3.28 and 3.42 (AB system, *J* = 19.2 Hz, 2H, CH₃H₆CO), 2.38 (s, 2H, CH₂), 2.33 (s, 3H, Ar–CH₃), 1.22 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 23.4, 27.4, 27.5, 31.5, 38.1, 50.1, 56.3, 118.6, 127.4, 127.9, 128.3, 128.8, 129.5, 133.4, 136.4, 138.3, 140.3, 155.6, 156.9, 192.5; IR (KBr) (cm^{−1}): 3042, 2969, 2886, 1687, 1649, 1370, 1224, 924, 872, 765, 677, 581; MS(EI): *m/z* 386 [M⁺].

3,3-dimethyl-13-(4-hydroxyphenyl)-3,4-dihydro-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (4d) Off white, Mp. 259–262 °C, ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.89 (s, 1H, OH), 8.21–8.29 (m, 2H, phthalhydrazide H₇, H₁₀), 7.51–7.66 (m, 2H, phthalhydrazide H₈, H₉), 6.73–7.12 (m, 4H, Ar–H), 6.41 (s, 1H, CH), 3.31 and 3.56 (AB system, *J* = 18.4 Hz, 2H, CH₃H₆CO), 2.44 (s, 2H, CH₂), 1.24 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.2, 28.4, 32.7, 38.7, 52.1, 54.6, 116.2, 117.3, 117.5, 128.1, 128.4, 128.8, 129.0, 132.6, 133.8, 137.7, 138.2, 160.5, 162.2, 196.2; IR (KBr) (cm^{−1}): 3382, 3067, 2939, 2841, 1688, 1677, 1373, 1243, 925, 847, 735, 657, 555; MS(EI): *m/z* 388 [M⁺].

3,3-dimethyl-13-(4-nitrophenyl)-3,4-dihydro-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (4e) Yellow Solid, Mp: 223–226 °C, ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.38–8.41 (m, 2H, phthalhydrazide H₇, H₁₀), 8.20–8.28 (m, 2H, Ar–H), 7.88–7.92 (m, 2H, phthalhydrazide H₈, H₉), 7.60–7.63 (d, *J* = 8.7 Hz, 2H, Ar–H), 6.52 (s, 1H, CH), 3.23 and 3.45 (AB System, *J* = 19.2 Hz, 2H, CH₃H₆CO), 2.34–2.35 (d, *J* = 1.8 Hz, 2H, CH₂), 1.23 (s, 6H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.3, 28.7, 34.7, 38.0, 50.8, 64.1, 117.3, 124.0, 127.7, 128.0, 128.2, 128.6, 128.9, 133.9, 134.8,

143.4, 147.9, 151.6, 154.5, 155.9, 192.0; IR (KBr) (cm^{-1}): 3076, 2971, 1693, 1654, 1617, 1394, 1362, 1290, 1272, 1078, 1017, 974, 954, 856, 791, 694, 623, 578, 535; MS(EI): m/z 417 [M^+].

3,3-dimethyl-13-(4-cyanophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4f) Yellow solid, Mp: 212–214 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.25–8.40 (m, 2H, phthalhydrazide H_7 , H_{10}), 7.88–7.91 (t, J =Hz, 2H, phthalhydrazide H_8 , H_9), 7.54–7.66 (m, 4H, Ar–H), 6.47 (s, 1H, CH), 3.23 and 3.44 (AB system, J =18.3 Hz, 2H, CH_2), 2.35 (s, 2H, CH_2), 1.21 (s, 6H, CH_3); ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 28.4, 28.6, 34.7, 38.0, 50.8, 64.4, 112.5, 117.3, 118.4, 127.7, 127.8, 128.2, 128.6, 128.9, 132.6, 133.9, 134.8, 141.5, 151.5, 154.5, 155.9, 192.0; IR (KBr) (cm^{-1}): 3041, 2959, 2231, 1690, 1650, 1619, 1359, 1263, 1148, 1124, 1024, 973, 854, 790, 699, 556; MS(EI): m/z 398 $[\text{M} + \text{H}]$.

3,3-dimethyl-13-(4-bromophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4g) White solid, Mp: 184–186 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.26–8.35 (m, 2H, phthalhydrazide H_7 , H_{10}), 7.77–7.84 (m, 2H, phthalhydrazide H_8 , H_9), 7.14–7.32 (m, 2H, Ar–H), 6.45 (s, 1H, CH), 3.25 and 3.40 (AB system, J =17.2 Hz, 2H, CH_2), 2.35–2.36 (d, J =1.8 Hz, 2H, CH_2), 1.22 (s, 6H); IR (KBr) (cm^{-1}): 3026, 2953, 1682, 1651, 1352, 976, 691; MS(EI): m/z 451 [M^+].

3,3-dimethyl-13-(4-chlorophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4h) Yellow solid, Mp: 170–173 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.24–8.36 (m, 2H, phthalhydrazide H_7 , H_{10}), 7.87–7.89 (m, 2H, phthalhydrazide H_8 , H_9), 7.32 (d, J =8.8 Hz, 2H, Ar–H), 7.23 (d, J =8.8 Hz, 2H, Ar–H), 6.44 (s, 1H, CH), 3.22 and 3.37 (AB system, J =17.2 Hz, 2H, CH_2), 2.20 (s, 2H, CH_2), 1.22 (s, 6H); IR (KBr) (cm^{-1}): 3028, 2957, 1663, 1652, 1362, 855, 712, 696, 555; MS(EI): m/z 406 [M^+].

3,3-dimethyl-13-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4i) Yellow solid, Mp: 233–235 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.78–8.23 (m, 4H, phthalhydrazide H_7 , H_8 , H_9 , H_{10}), 6.79 (s, 2H, Ar–H), 6.39 (s, 1H, CH), 3.8 (s, 9H, OCH_3), 3.20 and 3.41 (AB system, J =19.2 Hz, 2H, CH_2), 2.33 (s, 2H, CH_2), 1.21 (s, 6H, CH_3); IR (KBr) (cm^{-1}): 3018, 2958, 1664, 1651, 1323, 844, 787, 691, 517; MS(EI): m/z 462 [M^+].

3,3-dimethyl-13-(thiophen-3-yl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4j) Yellow solid, Mp: 217–220 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.26–8.47 (m, 2H, phthalhydrazide H_7 , H_{10}),

7.79–7.87 (m, 2H, phthalhydrazide H_8 , H_9), 7.31–7.55 (m, 3H), 6.41 (s, 1H, CH), 3.27 and 3.52 (AB system, J =18.6 Hz, 2H, CH_2), 2.27 (d, J =1.8 Hz, 2H, CH_2), 1.20 (s, 6H, CH_3); ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 28.1, 28.8, 34.1, 37.9, 50.3, 60.4, 117.2, 125.7, 127.3, 127.8, 128.3, 128.9, 129.1, 133.6, 134.4, 138.7, 150.6, 154.6, 192.4; MS(EI): m/z 378 [M^+].

3,3-dimethyl-13-(naphthalen-2-yl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4k) Yellow solid, Mp: 251–253 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.82–8.25 (m, 4H, phthalhydrazide H_7 , H_8 , H_9 , H_{10}), 7.25–7.72 (m, 7H, Ar–H), 6.64 (s, 1H, CH), 3.24 and 3.49 (AB system, J =18.6 Hz, 2H, CH_2), 2.22 (s, 2H, CH_2), 1.25 (s, 6H, CH_3); IR (KBr) (cm^{-1}): 2956, 1664, 1640, 1635; MS(EI): m/z 422 [M^+].

3,3-dimethyl-13-(anthracen-10-yl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4l) Orange solid, Mp: 234–236 °C, ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.89–8.35 (m, 4H, phthalhydrazide H_7 , H_8 , H_9 , H_{10}), 7.43–7.69 (m, 9H, Ar–H), 6.22 (s, 1H, CH), 3.29 and 3.52 (AB system, J =16.4 Hz, 2H, CH_2), 2.15 (d, J =1.8 Hz, 2H, CH_2), 1.23 (s, 6H, CH_3); IR (KBr) (cm^{-1}): 3048, 2956, 1722, 1669, 1644, 1364, 711, 676, 578; MS(EI): m/z 472 [M^+].

3 Result and discussion

In order to acquire the most appropriate reaction condition and examine the catalytic evaluation of 5-SSA, initially model reaction of phthalhydrazide (1 mmol), dimedone (1 mmol) and 4-nitrobenzaldehyde (1.2 mmol) in presence of 5-SSA (20 mol%) was carried out in common organic solvents and under solvent-free condition at 100 °C. It was observed that, various organic solvents such as DMF, THF, EDC, water and ethanol at reflux condition provides the desired products in lower yield (Table 1, entries 1–5). The model reaction efficiently marches under solvent-free condition furnishing the anticipated product in excellent yield (Table 1, entry 9). This result reveals that, the solvent-free condition is the most suitable for mentioned reaction in terms of yield and reaction time.

For study of catalyst loading, the model reaction was carried out by using varying amount of catalyst (Table 1). It is worthy to mention that catalyst amount had a marked influence on the reaction progress. When the quantity of 5-SSA was increased from 5 to 20 mol%, the yield of resultant product elevated significantly (42 to 92%; Table 1, entries 6–9). Further increase in catalyst quantity did not have a profound influence on the yield of product (Table 1, entry 10). Further, model reaction was examined

Table 1 Optimization of reaction condition for synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones

Entries	Catalyst loading	Condition	Time (min)	Yield (%) ^a
1	5-SSA (20 mol%)	DMF/Reflux	90	27
2	5-SSA (20 mol%)	THF/Reflux	90	30
3	5-SSA (20 mol%)	EDC/Reflux	90	32
4	5-SSA (20 mol%)	Water/Reflux	90	60
5	5-SSA (20 mol%)	Ethanol/Reflux	90	75
6	5-SSA (5 mol%)	Solvent-free/100 °C	10	42
7	5-SSA (10 mol%)	Solvent-free/100 °C	10	58
8	5-SSA (15 mol%)	Solvent-free/100 °C	10	72
9	5-SSA (20 mol%)	Solvent-free/100 °C	10	92
10	5-SSA (30 mol%)	Solvent-free/100 °C	10	92
11	5-SSA (20 mol%)	Solvent-free/80 °C	10	86
12	5-SSA (20 mol%)	Solvent-free/120 °C	10	92
13	–	Solvent-free/100 °C	60	–

Reaction conditions: Phthalhydrazide (1 mmol), Dimedone (1 mmol), 4-nitrobenzaldehyde (1.2 mmol) and 5-SSA at given condition

^aIsolated yields

at different temperatures under solvent-free temperature conditions. Decreasing the temperature to 80 °C (Table 1, entry 11) led to a lower yield whereas at 120 °C did not increase the yield of the product significantly (Table 1, entry 12). Finally, the model reaction carried out in absence of catalyst at 100 °C under solvent-free condition, no yield was obtained even after prolonged reaction time (Table 1, entry 13).

With optimized condition in hand, we focused our attempts on the synthesis of various 2*H*-indazolo[2,1-*b*]phthalazinetriones using phthalhydrazide, dimedone with structurally diverse aryl aldehydes in presence of 5-SSA (20 mol%) under solvent-free condition at 100 °C and the results are summarized in Table 2. The aldehydes carrying electron-donating as well as electron-withdrawing groups on aromatic ring, the corresponding 2*H*-indazolo[2,1-*b*]phthalazinetriones were obtained in good to excellent yield (85–93%) highlighting the general applicability of the given protocol (Table 2, entries 2–4 and 5–8). Fascinatingly, sterically crowded 3,4,5-trimethoxybenzaldehyde (Table 2, entry 9) found to be equally effective providing anticipated product in moderate yield (82%). Hetero-aromatic thiophene-2-carbaldehyde (Table 2, entry 10) was examined which provides good yield (84%). To our delight,

polycyclic aromatic aldehydes such as 2-naphthaldehyde and 9-anthraldehyde (Table 2, entries 11–12) also tolerated efficiently furnishing the desired product in good to moderate yield (85–76%). Unfortunately, aliphatic aldehydes such as *n*-heptanal and *n*-octanal were found to be intact in the mentioned reaction (Table 2, entries 13, 14).

Further, to broaden the scope of the present protocol, 5-SSA was scrutinized for analogous synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones using reaction of hydrazinium hydroxide, phthalic anhydride and dimedone with diverse aryl aldehydes under the optimized reaction conditions. It was observed that 5-SSA efficiently catalyzes the above reactions providing the corresponding 2*H*-indazolo[2,1-*b*]phthalazinetriones in good to excellent yield (Table 3).

The tentative mechanism for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetrione is depicted in Scheme 1. Initially, 5-SSA causes electrophilic activation of the aromatic aldehydes 1, which undergo Knoevenagel condensation with dimedone followed by the removal of water to obtain Knoevenagel product 2. Further, rapid azamichael addition of phthalhydrazide takes place on intermediate 2 followed by cyclodehydration which affords the target molecule 3.

Table 2 5-SSA catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones

Entries	Aryl aldehyde (3)	Product (4)	Time (min)	Yield (%) ^a	Mp (°C) [lit.]	References
1	Benzaldehyde	4a	10	90	201–202 [201–203]	[52]
2	4-Methoxybenzaldehyde	4b	10	88	217–219 [216–218]	[52]
3	4-Methylbenzaldehyde	4c	12	86	224–226 [223–225]	[52]
4	4-Hydroxybenzaldehyde	4d	15	85	259–262 [258–260]	[40]
5	4-Nitrobenzaldehyde	4e	10	92	223–226 [224–225]	[52]
6	4-Cyanobenzaldehyde	4f	08	90	212–214 [213–215]	[40]
7	4-Bromobenzaldehyde	4g	10	88	184–186 [185–187]	[36]
8	4-Chlorobenzaldehyde	4h	12	87	170–173 [170–172]	[36]
9	3,4,5-Trimethoxy benzaldehyde	4i	15	82	233–235 [234–236]	[48]
10	Thiophen-2-Carbaldehyde	4j	15	84	217–220 [217–219]	[53]
11	2-Napthaldehyde	4 k	13	85	251–253 [252]	[54]
12	9-Anthraldehyde	4l	15	76	234–236 [235]	[54]
13	n-Heptanal	4m	720	–	–	–
14	n-Octanal	4n	720	–	–	–

Reaction conditions: Phthalhydrazide (1 mmol), Dimeone (1 mmol), aryl aldehyde (1.2 mmol), and 5-SSA (20 mol%) at 100 °C under solvent-free condition

^aIsolated yields

Table 3 5-SSA catalyzed reaction between hydrazinium hydroxide, phthalic anhydride, and dimeone with aryl aldehydes.^a

Entries	Aryl aldehyde (2)	Product	Time (min)	Isolated yield (%)
1	Benzaldehyde	7a	10	88
2	4-Nitrobenzaldehyde	7b	10	90
3	3-Nitrobenzaldehyde	7c	12	87
4	4-Cyanobenzaldehyde	6d	10	88
5	4-Bromobenzaldehyde	7e	10	85

Reaction conditions: Phthalhydrazide (1 mmol), Dimeone (1 mmol), aryl aldehyde (1.2 mmol), and 5-SSA (20 mol%) at 100 °C under solvent-free condition

^a Isolated yields

Scheme 1 Plausible mechanistic pathway for the formation of 2H-indazolo[2,1-b]phthalazinetriones

Fig. 2 Reusability study of 5-SSA in the synthesis of 2H-indazolo[2,1-b]phthalazinetriones

The reusability of 5-sulphosalicylic acid was investigated for template reaction under optimized reaction condition (Fig. 2). The catalyst being water soluble, recovered

by removal of solvent from the filtrate under vacuum, dried, and then used for the next cycle. It was found that the catalyst can be reused for three times without a significant decrease in the yield of desired product.

A comparison of the results reveals that 5-sulphosalicylic acid is a highly effective catalyst under solvent-free condition in terms of reaction time and product yield for the synthesis of 2H-indazolo-[2,1-b]phthalazinetriones than other reported catalysts (Table 4).

4 Conclusion

We have described the simple and efficient protocol for one-pot, three-component synthesis of 2H-indazolo[2,1-b]phthalazinetriones by the reaction of phthalhydrazide, dimedone with various aryl aldehydes in presence of environmentally benign and cost-effective 5-sulphosalicylic

Table 4 The comparison of 5-SSA with reported catalysts for the reaction of phthalhydrazide, dimedone with 4-Nitrobenzaldehyde

S. no.	Catalyst used	Reaction conditions	Time (min)	Yield (%)	References
01	5-SSA (20 mol%)	Solvent-free/100 °C	10	92	This work
02	[Simp]H ₂ SO ₄ (10 mol%)	Solvent-free/100 °C	20	83	[37]
03	Polymer supported sulfonic acid (30 mol%)	Glycerol/80 °C	55	80	[39]
04	Cellulose-SO ₃ H	Solvent-free/80 °C	10	89	[47]
05	Melamine trisulfonic acid (15 mol%)	Solvent-free/100 °C	10	83	[55]
06	Nano-alumina sulfuric acid (0.04 gm)	Neat/110 °C	15	72	[56]

acid as an organocatalyst under solvent-free condition. This eco-friendly promising strategy offered several advantages such as high yield, short reaction time, greener reaction profile, ease of separation of product, simple experimental and work-up procedure.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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