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Solvent-free, one-pot, four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones using sulfuric acid-modified PEG-6000 as a green recyclable and biodegradable polymeric catalyst

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ABSTRACT

A green practical method for the efficient synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones using sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO_3H) as an eco-friendly polymeric catalyst from the four-component condensation reaction of phthalic anhydride, hydrazinium hydroxide, 1,3-cyclohexanedione or 5,5-dimethyl 1,3-cyclohexanedione (dimedone) and aromatic aldehydes under solvent-free conditions at 80 °C is described. This approach allowed the environmental impact factor (E-factor) to be minimized.

1. Introduction

Multi-component synthesis is an important way for the efficient and rapid synthesis of a wide variety of complex organic compounds. These reactions have been investigated extensively in diversely oriented synthesis; primarily due to their ability to produce complex molecular functionality from simple starting materials *via* one-pot reaction [1–4].

The best solvent from the green chemistry point of view is no solvent due to minimization of environmental impact factor. Because of the higher concentration of the reactants, these reactions proceed with higher yield and often lead to short reaction times and easier workup [5–8]. The combination of solvent-free conditions with multi-component reaction has been shown to be a powerful strategy to yield complex molecular structures in few synthetic steps [9,10].

Recent developments for sustainable chemistry are being driven by a shift from conventional liquid acid catalysts to chemically stable and biodegradable solid catalysts [11–13]. There is considerable interest in exploiting biodegradable polymers such as polyethylene glycol-based polymers [14–19], to create environmentally friendly catalysts with high-performance [20]. Sulfuric acid-modified PEG-6000 (PEG-OSO_3H) is an example of polyethylene glycol supported catalyst that is functionalized by acidic groups and is a mild, non-volatile and non-corrosive solid organic acid. Recently we have used this catalyst for the solvent-free synthesis of poly-substituted quinolones, synthesis of acylals and synthesis of bis(indolyl)methanes and 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s [21–24].

Sheldon introduced the concept of the E-factor to estimate the value of environmental impact of manufacturing processes [25]. The E-factor is designated as the weight of waste generated per weight of product and waste is defined as everything produced in the process except the desired product.

Aza heterocycles are an important class of compounds and have many applications in pharmaceutical, agrochemical, and functional materials [26,27]. Among them, phthalazine derivatives possess a wide range of biological activities [28–31]. 2*H*-Indazolo[2,1-*b*]phthalazinetriones are a group of phthalazine derivatives that the development of an efficient method for the synthesis of these derivatives is an active ongoing research area. There are some reports on the solution or solid phase synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones [32–40]. Most of the mentioned methods suffer from at least one of the limitations such as; low yield, long reaction times, effluent pollution, harsh reaction conditions, formation of by-products, the use of toxic organic solvents, the use

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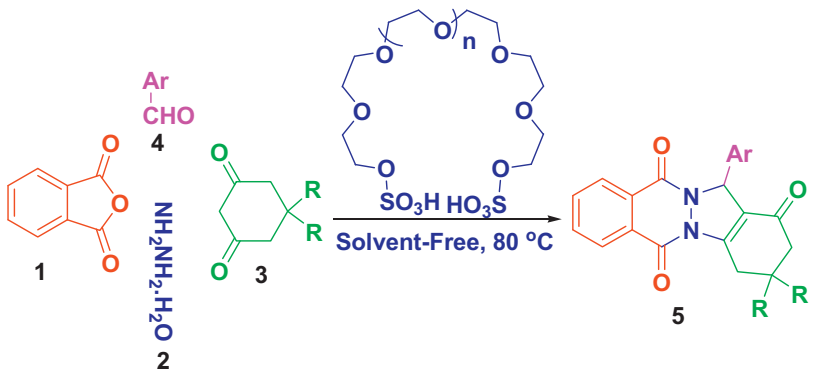


Scheme 1. The synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-triones from phthalic anhydride (**1**), hydrazinium hydroxide (**2**), dimedone or 1,3-cyclohexanedione (**3**), and arylaldehydes (**4**) using PEG-OSO_3H.

of additional instruments such as ultra sound and tedious workup procedures. Moreover PEG-based catalysts are very cheaper in comparison with ionic liquids. In the present study, we report an efficient, E-factor minimized, one-pot, four-component method for the preparation of 2*H*-indazolo[1,2-*b*]phthalazine-trione derivatives (**5**) by condensation of phthalic anhydride (**1**), hydrazinium hydroxide (**2**), dimedone or 1,3-cyclohexanedione (**3**) and aromatic aldehydes (**4**) under solvent-free conditions at 80 °C (Scheme 1).

2. Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a BrukerAvance DPX-250, FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.1. Preparation of PEG-OSO_3H

At 0 °C, chlorosulfonic acid (1.16 g, 10 mmol) was added to a solution of $PEG_{(6000)}$ (6.0 g, 1 mmol) in CH_2Cl_2 (10 ml). Then the resulting solution was stirred at room temperature overnight, and the solution was concentrated under vacuum. Appropriate ether (50 ml) was added, and the precipitate filtered and washed with ether (30 ml) three times to afford the PEG-OSO_3H [20]. Different molecular weights of PEG-OSO_3H were prepared according to above procedure.

2.2. Typical procedure for the synthesis of 2H-indazolo[2,1-b]phthalazine-trione derivatives

Hydrazinium hydroxide (1.2 mmol), phthalic anhydride (1 mmol), cyclic 1,3-dicarbonyl compounds (1 mmol), aldehyde (1 mmol) and PEG-OSO_3H (8 mol%) was heated at 80 °C. The completion of reaction is monitored on TLC. The 2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives were synthesized. After satisfactory completion of the reaction, the mixture was cooled to room temperature and H_2O (5 ml) was added to this mixture and was shaken for a few minutes to dissolve PEG-OSO_3H. The crude product (insoluble in water) was filtered and recrystallized from hot ethanol for more purification. The desired pure products were characterized by comparison of their physical data with those of known compounds. In order to recover the catalyst, H_2O was evaporated under reduced pressure, and the resulting solid was washed with *t*-butylmethyl ether, and dried. The recovered catalyst was reused another time.

2.2.1. Selected spectral data for 2H-indazolo[2,1-b]phthalazine-trione derivatives:

3,4-Dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3a**): M.P. = 207–209 °C (lit. [28] 204–206 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (s, 6H), 2.36 (s, 2H), 3.27 (1H, dd, J = 19.03 Hz and 2.07 Hz), 3.44 (d, 1H, J = 19.03 Hz), 6.4 (s, 1H), 7.29–7.37 (m, 5H), 7.44 (d, 2H, J = 7.2 Hz), 7.86–7.87 (m, 2H), 8.28–8.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.9, 29.1, 35.0, 38.4, 51.3, 95.4, 119.0, 127.5, 128.2, 128.4, 129.1, 129.4, 129.5, 133.9, 134.9, 136.8, 151.2, 154.7, 156.4, and 192.5.

3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3b**): M.P. = 225–227 °C (lit. [28] 227–229 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.17 (s, 6H), 2.25 (s, 3H), 2.28 (s, 2H), 3.18 and 3.37 (AB system, s, 2H, J = 18.85 Hz), 6.36 (s, 1H), 7.08–7.2 (m, 4H), 7.8 (m, 2H), 8.2–8.3 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.6, 28.8, 29.1,35.0, 38.4, 51.3, 65.1, 118.9, 127.4, 128.0, 128.3, 129.3, 129.5, 129.7, 133.8, 134.8, 138.8, 151.1, 154.6, 156.3, and 192.5.

3,4-Dihydro-13-(4-isopropylphenyl)-3,3-dimethyl-2-*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (**3c**): M.P. = 226–228 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.22–1.25 (m, 12H), 2.37 (s, 2H), 2.9 (m, 1H), 3.26 (AB system, d, 1H, J = 19.0 Hz), 3.42 (AB system, d, 1H, J = 19.0 Hz), 6.47 (s, 1H), 7.19–7.36 (m, 4H), 7.86–7.88 (m, 2H), 8.3–8.4 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 24.2, 28.5, 29.0, 34.1, 35.3, 35.9, 51.9, 64.8, 111.3, 112.0, 114.6, 118.3, 119.2, 121.4, 123.0, 123.9, 127.2, 127.5, 128.3, 128.4, 132.2, 132.3, 135.5, 136.8, 156.4, 158.8, 191.3. m/z (%) = 414 (M^+, 63), 349 (23), 295 (100), 239 (15), 104 (23), and 76 (15).

3,4-Dihydro-3,3-dimethyl-13-(2-nitrophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3d**): M.P. = 238–240 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.21 (s, 3H), 1.24 (s, 3H), 2.25 (s, 3H), 2.31–2.39 (m, 2H), 3.28 (AB system, dd, J = 2.04 Hz and J = 19.1 Hz, 1H), 3.41 (AB system, d, J = 19.1 Hz, 1H), 7.2 (s, 1H), 7.45–7.59 (m, 3H), 7.87–7.96 (m, 3H), 8.27–8.4 (m, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.9, 29.2, 34.9, 38.4, 51.2, 68.1, 115.3, 128, 128.5, 128.8, 129.5, 129.8, 130.1, 130.2, 133.4, 134.0, 134.9, 137.9, 153.3, 154.5, 156.7, 192.4. m/z (%) = 417 (M^+,10), 400 (100), 370 (23), 314 (30), 295 (68), 239 (15), 130 (15), 104 (39), and 76 (31).

3,4-Dihydro-3,3-dimethyl-13-(3-nitrophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3e**): M.P. = 269–271 °C (lit. [28] 270–272 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.2 (s, 6H), 2.38 (s, 2H), 3.30 (AB system, dd, 1H, J = 19.0 Hz and J = 2.1 Hz), 3.46 (AB system, d, 1H, J = 19.2 Hz), 6.5 (s, 1H), 7.59 (t, 1H, J = 7.85 Hz), 7.89–7.93 (m, 3H), 8.19 (d, J = 8.7 Hz, 2H), 8.26–8.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.8, 29.1, 35.1, 38.4, 51.2, 64.6, 117.6, 121.9, 124.1, 128.1, 128.7, 129.1, 129.4, 130.1, 134.3, 134.6, 135.2, 139.05, 152.2, and 192.5.

3,4-Dihydro-3,3-dimethyl-13-(4-nitrophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3f**): M.P. = 225–227 °C (lit. [28] 223–225 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.21 (s, 3H), 1.24 (s, 3H), 2.1 (s, 2H), 3.2 (AB system, dd, 1H, J = 19.1 Hz and J = 2.2 Hz), 3.43 (AB system, d, 1H, J = 19.2 Hz), 6.53 (s, 1H), 7.61–7.64 (m, 2H), 7.90–7.91 (m, 2H), 8.20–8.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.8, 29.1, 31.3, 35.1, 38.4, 51.2, 64.5, 117.7, 128.2, 128.4, 128.6, 129.1, 129.3, 134.3, 135.2, 143.8, 148.3, 152.1, 154.9, 156.3, and 192.4.

3,4-Dihydro-3,3-dimethyl-13-(2-chlorophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3g**): M.P. = 265–267 °C (lit. [28] 264–266 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (s, 6H), 2.34 (s, 2H), 3.26 (AB system, d, 1H, J = 18.9 Hz), 3.42 (AB system, d, 1H, J = 19.0 Hz), 6.7 (s, 1H), 7.24–7.50 (m, 4H), 7.87–8.39 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.8, 29.2, 35.0, 38.4, 51.3, 64.4, 116.7, 127.6, 128.1, 128.4, 129.1, 129.4, 130.2, 130.9, 132.0, 133.0, 133.9, 134.9, 152.2, 154.6, 156.6, and 192.4.

3,4-Dihydro-3,3-dimethyl-13-(3-chlorophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3h**): M.P. = 209–211 °C (lit. [30] 204–206 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.24 (s, 6H), 2.37 (s, 2H), 3.27 (AB system, d, 1H, J = 19.07 Hz), 3.43 (AB system, d, 1H, J = 19.09 Hz), 6.43 (s, 1H), 7.27–7.40 (m, 4H), 7.88–7.90 (m, 2H), and 8.29–8.40 (m, 2H).

3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3i**): M.P. = 260–262 °C (lit. [28] 262–264 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (s, 6H), 2.36 (s, 2H), 3.26 (AB system, d, 1H, J = 18.98 Hz), 3.43 (AB system, d, 1H, J = 18.82 Hz), 6.44 (s, 1H), 7.29–7.38 (m, 4H), 7.88–7.90 (m, 2H), and 8.29–8.38 (m, 2H).

3,4-Dihydro-3,3-dimethyl-13-(2,6-chlorophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13H)-trione (**3j**): M.P. = 260–262 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.24 (s, 6H), 2.35 (s, 2H), 3.26 (AB system, d, 1H, J = 19.03 Hz), 3.39 (AB system, d, 1H, J = 19.13 Hz), 7.47 (s, 1H), 7.19–7.32 (m, 3H), 7.88–7.90 (m, 2H), 8.27–8.36 (m, 2H). MS: m/z (%) = 440 (52), 405 (34), 295 (100), 239 (13), 162 (36), 104 (57), and 76 (34).

3,4-Dihydro-3,3-dimethyl-13-(4-CN-phenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3k**): M.P. = 224–226 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.22 (s, 3H), 1.24 (s, 3H), 2.36 (s, 2H), 3.29 (AB system, d, 1H, J = 19.1 Hz), 3.42 (AB system, d, 1H, J = 19.1 Hz), 6.48 (s, 1H), 7.61–7.64 (m, 2H), 7.56 (d, 2H, J = 8.05 Hz), 7.6 (d, 2H, 8.04 Hz), 7.90–7.92 (m, 2H), 8.2–8.4 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.4, 29.1, 35.1, 38.4, 51.2, 64.8, 112.9, 117.8, 118.8, 128.2, 128.3, 128.6, 129.1, 129.3, 133.0, 134.3, 135.2, 141.9, 151.9, 154.9, 156.3, 192.4. m/z (%) = 397 (M^+, 63), 295 (100), 239 (15), 130 (10), 104 (44), and 76 (31).

3,4-Dihydro-3,3-dimethyl-13-(4-fluorophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3l**): M.P. = 216–218 °C (lit. [29] 218–220 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.24 (s, 6H), 2.36 (s, 2H), 3.26 (AB system, dd, 1H, J = 19.06 Hz and J = 2.2 Hz), 3.43 (AB system, dd, 1H, J = 19.4 Hz and J = 1.15 Hz), 6.46 (s, 1H), 7.02–7.06 (m, 2H), 7.40–7.44 (m, 2H), 7.86–7.89 (m, 2H), 8.27–8.39 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.8, 29.1, 35.1, 38.4, 51.3, 64.7, 116.0, 116.2 (d, $^1J_{C-F}$ = 275 Hz), 118.6, 128.1, 128.4, 129.3, 129.4, 132.6, 134.0, 135.0, 151.4, 154.8, 156.4, 162.1, 164.1, and 192.5.

3,4-Dihydro-3,3-dimethyl-13-(4-bromophenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3 m**): M.P. = 262–264 °C (lit. [29] 266–268 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (s, 6H), 2.36 (s, 2H), 3.26 (AB system, d, 1H, J = 19.02 Hz), 3.42 (AB system, d, 1H, J = 18.9 Hz), 6.42 (s, 1H), 7.29–7.4 (m, 4H), 7.8–8.3 (m, 4H).

3,4-Dihydro-3,3-dimethyl-13-(3-methoxyphenyl)-2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (**3n**): M.P. = 210–212 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (s, 6H), 2.36 (s, 2H), 3.26 (AB system, d, 1H, J = 19.07 Hz), 3.42 (AB system, d, 1H, J = 19.03 Hz), 3.8 (s, 1H), 6.44 (s, 1H), 6.4 (d, 1H, J = 7.9 Hz), 6.9 (s, 1H), 7.03, (d, 1H, J = 7.5 Hz), 7.25–7.22 (m, 1H), 7.87 (t, 2H, J = 4.2 Hz), 8.2–8.3 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.9, 29.1, 35.0, 38.4, 51.4, 55.6, 65.2, 110.3, 113.5, 114.2, 118.9, 119.8, 128.1, 128.4, 129.4, 129.5, 130.1, 133.9, 134.9, 138.4, 151.2, 154.7, 156.4, 160.1, 192.5. m/z (%) = 402 (M^+, 19), 295 (100), 239 (8), 104 (11), and 76 (8).

13-Benzoyl-3,3-dimethyl-3,4-dihydro-1-*H*-indazolo[1,2-*b*]phthalazine-1,6,11(2*H*, 13*H*)-trione (**3o**): M.P. = 228–230 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.21 (s, 3H), 1.24 (s, 3H), 2.36 (s, 2H), 3.27 (AB system, d, 1H, J = 19.1 Hz), 3.42 (AB system, d, 1H, J = 19.04 Hz), 6.88 (s, 1H), 7.57 (t, 2H, J = 7.5 Hz), 7.68 (t, 1H, J = 7.5 Hz), 7.8–7.9 (m, 2H), 8.2–8.4 (m, 4H), (d, 1H, J = 7.5 Hz), 7.25–7.22 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.6, 29.1, 35.3, 38.5, 51.0, 63.2, 116.5, 128.1, 128.6, 128.8, 129.0, 129.6, 129.7, 134.2, 134.5, 134.9, 136.1, 154.2, 154.7, 156.2, 192.5, 194.6. m/z (%) = 400 (M^+, 5), 295 (100), 239 (65), 130 (35), 104 (50), 77 (70), and 51 (20).

3,3-Dimethyl-13-(naphthalen-2-yl)-3,4-dihydro-2-*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (**3p**): M.P. = 251–253 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.16 (s, 6H), 2.27 (s, 2H), 3.22 (d, 1H, J = 19.09 Hz), 3.41 (d, 1H, J = 19.1 Hz), 6.54 (s, 1H), 7.37–7.42 (m, 3H), 7.71–7.89 (m, 6H), 8.16–8.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.7, 29.0, 35.0, 38.4, 51.3, 65.4, 118.8, 124.6, 126.6, 126.7, 127.2, 128.0, 128.0, 128.3, 128.6, 129.0, 129.4, 133.5, 133.7, 133.9, 134.1, 134.9, 151.3, 154.7, 156.4, 192.4. m/z (%) = 422 (M^+, 68), 295 (100), 239 (21), 104 (22), and 76 (17).

13-(2,6-Dichlorophenyl)-3,4-dihydro-3,3-dimethyl-2-*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (**3 s**): M.P. > 280 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.09–2.12 (m, 2H), 2.3 (m, 2H), 3.26–3.30 (m, 2H), 7.04–7.11 (m 3H), 7.29 (s, 1H), 7.73–7.75 (m, 2H), 8.07–8.2 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 10.9, 21.4, 33.2, 56.9, 105.9, 122.4, 125.6, 127.5, 127.9, 130.1, 130.5, 131.8, 135.1, 138.4, 142.1, 144.7, 158.8, 159. 1, 193.5. m/z (%) = 412 (M^+, 5), 267 (100), 239 (65), 104 (52), 77 (65), and 51 (20).

4-(2,3,4,6,11,13-Hexahydro-3,3-dimethyl-1,6,11-trioxo-1-*H*-indazolo[1,2-*b*]phthalazin-13-yl)benzonitrile (**3t**): M.P. > 280 °C ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.2 (m, 2H), 2.4 (m, 2H), 3.28 (d, 1H, J = 18.4 Hz), 3.49 (d, 1H, J = 18.5 Hz), 6.39 (s, 1H), 7.51–7.82 (m, 6H), 8.18–8.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.7, 24.9, 32.9, 55.91, 106.0, 114.7, 118.8, 124.3, 127.5, 128.8, 129.2, 133.3, 138.5, 144.4, 152.5, 158.8, 159.4, 193.8. m/z (%) = 369 (M^+, 68), 267 (100), 217 (18), 130 (18), 104 (52), and 76 (47).

3-Benzoyl-3,4-dihydro-1-*H*-indazolo[1,2-*b*]phthalazine-1,6,11(2*H*,13*H*)-trione (**3v**): M.P. = 254–256 °C ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.26 (m, 2H), 2.48 (m, 2H), 3.35–3.57 (m, 2H), 6.8 (s, 1H), 7.56–7.9 (m, 5H), and 8.3–8.4 (m, 3H).

3,4-Dihydro-13-(naphthalen-2-yl)-2-*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (**3w**): M.P. = 248–250 °C ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.29 (m, 2H), 2.49 (m, 2H), 3.41–3.68 (m, 2H), 6.65 (s, 1H), 7.47–7.53 (m, 3H), 7.82–7.94 (m, 6H), 8.27–8.40 (m, 2H). m/z (%) = 394 (M^+, 34), 267 (100), 217 (7), 104 (12), 76 (10), and 51 (20).

3. Results and discussion

In order to establish the optimum conditions for this reaction, initially the influence of the reaction temperature, the amounts of catalyst and the reaction time were tested and optimized. For this purpose, a reaction between phthalic anhydride (1 mmol), hydrazinium hydroxide (1.2 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) and benzaldehyde (1 mmol) were examined as the model reaction in the presence of PEG-OSO_3H. To evaluate the effect of reaction temperature, system was carried out at different temperatures. At room temperature, the reaction rate was found to be very slow, and it was increased in higher

Table 1
The reaction of phthalic anhydride (1 mmol), hydrazinium hydroxide (1.2 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) and benzaldehyde (1 mmol) in the presence of different catalysts (8 mol%) at 80 °C.

Entry	Catalyst	Time (min)	Yield (%)[a]
1	$HO_3SO-PEG_{10000}-OSO_3H$	10	92
2	$HO_3SO-PEG_{6000}-OSO_3H$	10	92
3	$HO_3SO-PEG_{4000}-OSO_3H$	10	85
4	$HO_3SO-PEG_{400}-OSO_3H$	10	70
5	$HO-PEG_{10000}-OH$	180	–
6	$HO-PEG_{6000}-OH$	180	–
7	$HO-PEG_{4000}-OH$	180	–
8	$HO-PEG_{400}-OH$	180	–

[a] Isolated yield.

temperatures. At 80 °C, the reaction rate was found to be a maximum, and further increases in temperature did not show any enhancement. It should be noted that the optimal catalyst loading in the synthesis of 2,2-dimethyl-13-phenyl-2,3-dihydro-1*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione product peaked at a concentration of 8 mol%. When the amount of catalyst was lower, the yield of the product decreased, whereas raising the catalyst concentration did not lead to a pronounced increase to the product yield. During our optimization studies, various solvents were examined and solvent-free conditions was found to be the most optimum in terms of reaction rate, and isolated yield, therefore optimized conditions is shown in Scheme 1.

For further study on different catalyst of the some nature, the model reaction was examined in the presence of different molecular weight of PEG and PEG-OSO_3H (Table 1). As it can be seen from Table 1, the reaction did not proceed at all in the presence of PEG alone with different molecular weights. To recognize the role of poly(ethylene glycol) skeleton in PEG-OSO_3H, the reaction was examined in the presence of different molecular weight of PEG-OSO_3H. As it is clear from Table 1, entry 2 $PEG_{(6000)}$-OSO_3H is the best catalyst and the yield of product in the presence of this catalyst is high.

The generality and functional group tolerance of this procedure in the direct synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione derivatives was examined using a number of substituted aromatic aldehydes in the presence of $PEG_{(6000)}$-OSO_3H as catalyst under the optimized conditions (Scheme 1 and Table 2). In all cases, the reactions gave the corresponding products in good to excellent yields (Table 2) and in very short reaction times. This method offers significant improvements with regard to the scope of the transformation, simplicity, and green aspects by avoiding expensive or corrosive catalysts.

As shown in Table 2, aromatic aldehydes bearing electron-donating or -withdrawing substituents gave the desired 2*H*-indazolo[1,2-*b*]phthalazine-trione in high yields. The method tolerates key functional groups such as halides, alkyl, nitro, methoxy, thiomethoxy and nitrile and besides the *para* and *meta* positions on the aromatic ring of aldehyde, different functional groups were also introduced to *ortho* position indicating the method is not sensitive to steric or electronic *ortho* variation of substituents. In the same way, the reaction of 1,3-cyclohexanedione for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-triones under the optimum conditions were examined and the desired products were obtained in high yields (Table 1, entries **3s–3w**).

To assess the feasibility application of this method on a preparative scale, the model reaction for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione was performed on a 20-mmol scale. As expected, the reaction preceded similarly to the smaller scale, providing the desired product in high yield.

We also determined the E-factor of our method to evaluate that this method minimizes environmental impacts. For the case studied, data involved for the E-factor calculation, such as the amount of reactants and the volume of solvents used in the synthesis step and in the workup. The E-factor was calculated from the equation described by Sheldon [25]. For example; the E-factor calculation for the condensation of hydrazinium hydroxide (1.2 mmol), phthalic anhydride (1 mmol), dimedone (1 mmol) and benzaldehyde (1 mmol) in the presence of PEG-OSO_3H as catalyst has given as bellow:

E-factor = {{0.14 g (phthalic anhydride) + 0.06 g (hydrazinium hydroxide) + 0.14 g (dimedone) + 0.106 g (benzaldehyde) + 5 g (water) + 7.8 g (ethylaetate) – 0.32 g product}/0.32 g product} = 40.4.

To assess the capability and efficiency of our catalyst, from the green chemistry point of view, with respect to the reported catalysts for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-triones, E-factor values for application of these catalysts are tabulated in Table 3. As is clear from Table 3, better E-factor value was obtained for products **3a** in the presence of PEG-OSO_3H.

To explore the mechanism of the reaction, in model compound for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione, the phthalhydrazide is formed within the first 2 min of the beginning of reaction. So, it is not necessary to prepare the phthalhydrazide in advance. The rate-determining step was found to be the dehydrative cyclization step. We can directly use phthalic anhydride, hydrazinium hydroxide, 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexandione and benzaldehyde as starting materials in the presence of PEG-OSO_3H, which should be synthetically useful and practical. A plausible pathway for the formation of 2*H*-indazolo[1,2-*b*]phthalazine-trione involves initial nucleophilic addition of hydrazinium hydroxide (**2**) to phthalic anhydride (**1**), followed by dehydration to form phthalhydrazide **A**. In the next step, *via* a PEG-OSO_3H catalyzed Knoevenagel condensation of 1,3-dione (**3**) with aromatic aldehyde (**4**) intermediate **B** was formed. Subsequent Michael addition of **A** to intermediate **B** was occurred in the catalytic media, followed cyclization affords the corresponding product (**5**) in the catalytic cycle (Scheme 2).

Acidic PEG-based catalysts have been shown a dual role in organic reactions: as a catalyst to activate the substrate molecules and as a solvent to soluble organic reactants due to their low melting points [15–17]. As a matter of fact, in the presented reaction, we propose that not only the substrate molecules are activated by the catalyst, but also PEG-OSO_3H as a solvent increases the collapse of organic reactants and they are also accompanied by inherent Bronsted acidity of SO_3H groups, which are capable of bonding with carbonyl oxygen of the substrates assisting in generation of ionic intermediates through activation of reactants. In other words, these intermediates are generated inside the crown-shape moiety by sufficient energy released during the collapse and strong polarity of the SO_3H groups. By using PEG-OSO_3H, the reaction rates and yields under the reaction condition are enhanced, whereas in the absence of mentioned Bronsted acid no product is obtained. Regarding the solvent effect in the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione it should be noted that since by cyclization of intermediate **B**, the nucleophilic nitrogen is already incorporated to the skeleton of this intermediate, because of the proper spatial orientation caused by simple rotation of the carbon-carbon and carbon–oxygen bonds

Table 2
PEG-OSO_3H-catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives *via* a one-pot, four-component reaction.

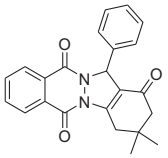
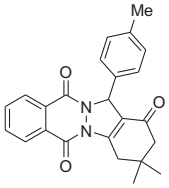
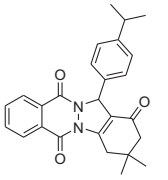
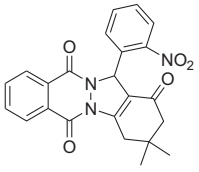
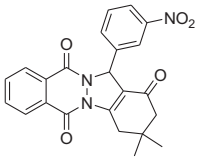
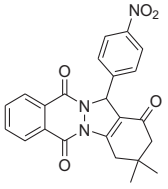
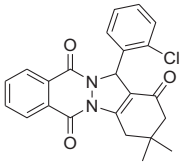
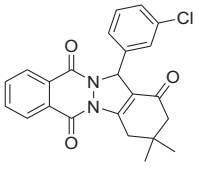
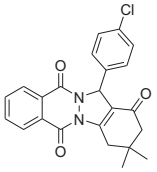
Entry	R	Ar	Product	Time (min)	Yield (%)[a]
3a	Me	C_6H_5		13	87
3b	Me	4-Me—C_6H_4		15	90
3c	Me	4-isopropyl-C_6H_4		17	83
3d	Me	2-NO_2—C_6H_4		15	90
3e	Me	3-NO_2—C_6H_4		10	92
3f	Me	4-NO_2—C_6H_4		15	90
3g	Me	2-Cl—C_6H_4		10	87
3h	Me	3-Cl—C_6H_4		15	91
3i	Me	4-Cl—C_6H_4		10	92

Table 2 (*Continued*)

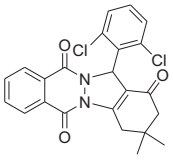
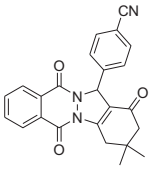
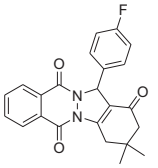
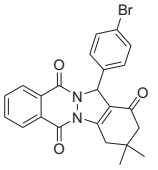
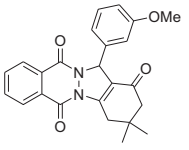
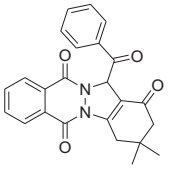
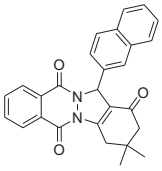
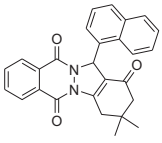
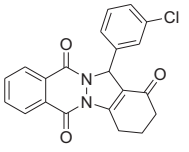
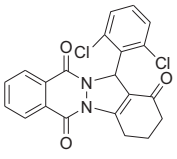
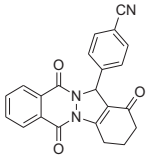
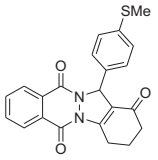
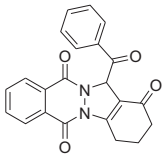
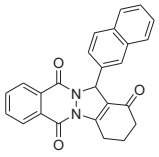
Entry	R	Ar	Product	Time (min)	Yield (%)[a]
3j	Me	2,6 di-Cl—C_6H_3		20	80
3k	Me	4-CN—C_6H_4		15	93
3l	Me	4-F—C_6H_4		10	85
3m	Me	4-Br—C_6H_4		15	87
3n	Me	3-MeO—C_6H_4		18	86
3o	Me	C_6H_5—CO		10	92
3p	Me	2-Naphthyl		10	91
3q	Me	1-Naphthyl		15	89
3r	H	3-Cl—C_6H_4		10	90
3s	H	2,6-di Cl—C_6H_3		20	80

Table 2 (*Continued*)

Entry	R	Ar	Product	Time (min)	Yield (%)[a]
3t	H	4-CN—C_6H_4		15	92
3u	H	4-MeS—C_6H_4		10	85
3v	H	C_6H_5—CO		10	90
3w	H	2-Naphthyl		10	90

[a] Isolated yield.

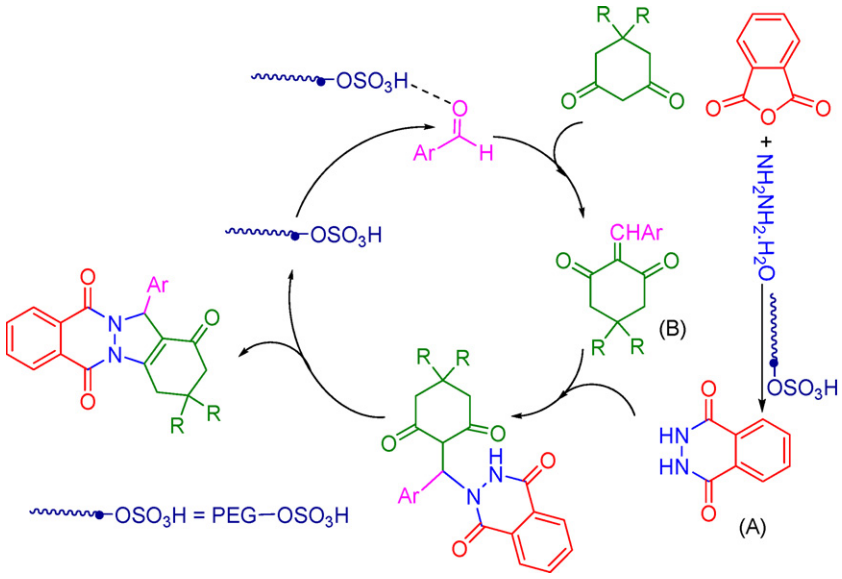
("symphoria") between this aza group and the carbonyl group, an intramolecular cyclization occurs without the assist of solvent.

The reusability of the catalyst in the reaction of 4-chlorobenzaldehyde, dimedone, phthalic anhydride, and hydrazinium hydroxide under solvent-free conditions at 80 °C was studied. In this procedure, after completion of each reaction, H_2O was added to the reaction mixture and was shaken for a few minutes to dissolve PEG-OSO_3H. The crude product (insoluble in water) was filtered and recrystallized from hot ethanol for more purification. In order to recover the catalyst, H_2O was evaporated under reduced pressure, and the resulting solid was washed with *t*-butylmethyl ether, and dried. The recovered catalyst was reused

Table 3
Comparison of the E-factor for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione **3a** using the reported catalysts *versus* PEG-OSO_3H.

Entry	E-factor	Ref.
1	>73[a]	[32]
2	>85.2[a]	[40]
3	>98.4[a]	[33]
4	40.4	This work
5	>72[a]	[39]

[a] E-factor for the preparation of phthalhydrazide has not added.



Scheme 2. Proposed mechanism for the PEG-OSO_3H-catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione.

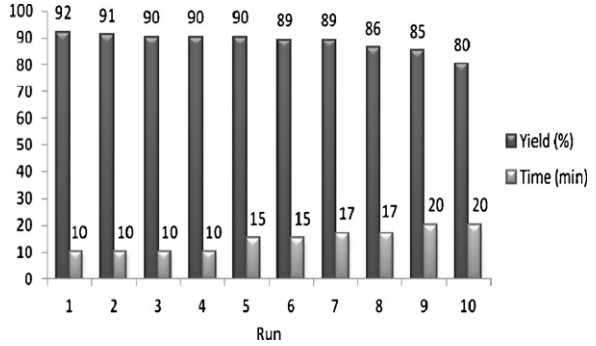


Fig. 1. The catalytic activity of PEG-OSO3H in ten cycles for the reaction of 4-chlorobenzaldehyde, dimedone, phthalic anhydride, and hydrazinium hydroxide.

ten times and smooth loss of catalytic activity was observed from the 7th time of reuse (Fig. 1).

4. Conclusion

In summary, an efficient protocol for the one-pot synthesis of 2-*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives by a four-component condensation reaction of phthalic anhydride, hydrazinium hydroxide, 1,3-cyclohexanedione or 5,5-dimethyl 1,3-cyclohexanedione (dimedone) and aromatic aldehydes has been described under thermal solvent-free conditions using PEG-OSO_3H as a recoverable and biodegradable polymeric catalyst. Mild reaction conditions, operational simplicity, enhanced rates and high isolated yields of pure products are significant advantages of the protocol described here. This easy removal and reusability of the catalyst makes this method a better choice for chemical industries. This approach allowed the E-factor, a measure of the waste of a reaction, to be minimized.

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