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Efficient CAN catalyzed synthesis of 1*H*-indazolo[1,2-*b*] phthalazine-1,6,11-triones: An eco-friendly protocol

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A convenient, economical and green approach to the synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione derivatives has been achieved via a one-pot protocol using phthalhydrazide, a cyclic-β-diketone and an aldehyde in the presence of a ceric ammonium nitrate catalyst in polyethylene glycol. The simple work up, mild conditions, excellent yields, inexpensive and non-toxic catalyst and simple solvent recyclability render this protocol both attractive and economically viable.

ceric ammonium nitrate, polyethylene glycol, 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones, recyclability, green chemistry

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Multi-component reactions (MCRs) offer a number of fascinating and challenging transformations in organic synthesis [1–7]. Atom-economy, convergent character, operational simplicity, structural diversity, and complexity are the major advantages associated with multi-component reactions. Furthermore, multi-component reactions are emerging as a powerful tool for the synthesis of biologically important compounds [8,9]. In drug discovery, as well as "Green Chemistry", MCRs are the techniques of choice for the high-throughput synthesis of compounds from a cost- and time point of view [10,11].

Over the past few decades, a tremendous upsurge of interest has been observed in the synthesis of nitrogen-containing heterocyclic compounds, owing to their abundance in nature and essentiality to life. Their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are also becoming increasingly important [12–16]. Phthalazine derivatives, that comprise two bridgehead nitrogen atoms in a fused ring system, have attracted considerable attention because of their pharmacological, and biological properties, and potential clinical application [17–34]. These compounds have also proved to be promising luminescence materials and fluorescence probes [35]. Several methods have been reported for the synthesis of phthalazine derivatives [36–41]. Unfortunately, many of these methods are plagued with a number of limitations, such as harsh reaction conditions, unsatisfactory yields, tedious work-up procedures, relatively long reaction times, poor solvent scope and the use of stoichiometric and relatively expensive reagents. Therefore, improved methods, in terms of operational simplicity, reusability and economic viability are highly desirable.

Recently, ceric ammonium nitrate (CAN) has been utilized for various organic transformations [42–45]. The most characteristic feature of CAN is that it can act as a water-compatible Lewis acid in aqueous solvents. Additionally, advantages such as low-cost, eco-friendly nature, ease of handling, non-toxic nature make CAN an attractive catalyst for a variety of synthetic transformations. Regulatory pressures are increasingly focusing on the use, manufacture and disposal of organic solvents, and thus, the development of non-hazardous alternatives (one of the several goals for green chemistry and engineering) is vitally important for the continued and sustainable development of the chemical processes. Recently, polyethylene glycol (PEG) and solutions thereof have been introduced as potential green

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solvent systems [46–48]. They have replaced a number of other "neoteric solvents", such as ionic liquids, super critical carbon dioxide, and micellar systems, whose toxicological properties, short and long-term hazardous nature, and biodegradability are not completely understood. Their low cost, reduced flammability, reduced toxicity, recyclability, non-halogenated composition, easy degradability, and miscibility with wide variety of organic solvents are just some of the key features that render PEG an attractive alternative solvent in organic synthesis [49–53]. Keeping within our theme of green chemistry and in a continuation of our studies for the development of cheap and environmentally benign methodologies for organic synthesis [54–56], we decided to examine the versatility of CAN as a catalyst and PEG 400 as solvent for the synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones.

1 Experimental

1.1 Materials and methods

All chemicals were used as received from Sigma-Aldrich without any further purification. All reactions were monitored by thin-layer chromatography (TLC), using aluminium plates coated with silica gel F_{254}; (Merck) using ethyl acetate, and hexane (40/60) as eluent. Spots were visualized using either UV light or an iodine chamber. Melting points were determined in using a Thomas Hoover melting point apparatus (uncorrected). IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer, using KBr pellets/-nujol film. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECX 400P FT NMR spectrometer with TMS as the internal standard. Chemical shifts are on a δ scale and coupling constant values (J) are in Hertz (Hz). Elemental analyses were performed on a Hereaus CHN rapid analyzer. The temperature of the reaction mixture was measured using a non-contact infrared mini gun thermometer (AZ minigun type, model 8868).

1.2 General procedure for the synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione derivatives

To a 50 mL round-bottom flask, phthalhydrazide **1**, aldehyde (RCHO) **2a**–**2q**, cyclic β-diketone **3a** ($C_6H_8O_2$), **3b** ($C_8H_{12}O_2$) and PEG 400 (2 mL) were added. CAN (5 mol%) was then added and reaction mixture was stirred at 50°C for the appropriate time, as summarized in Table 1. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled in a dry ice-acetone bath, to precipitate the PEG 400, and extracted with ether (PEG is insoluble in ether). The ether layer was decanted, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired product. The crude product was purified by column chromatography on silica gel (100–200 mesh size), using hexane/ethyl acetate as eluent. This provided the pure respective 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione derivative, (**4a**–**4s**). The recovered PEG 400 phase was reused for consecutive reactions. All products were characterized on the basis of their spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and elemental analysis) and melting point determination [37,57–60].

Table 1 CAN catalyzed synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones[a)]

Entry	R	R'	Product	Time (h)	Yield (%)[b)]
1	Ph (**2a**)	H (**3a**)	**4a**	2	94
2	4-Br-C_6H_4 (**2b**)	H	**4b**	2.5	92
3	3-NO_2-C_6H_4 (**2c**)	H	**4c**	3.5	94
4	4-Me-C_6H_4 (**2d**)	H	**4d**	2	94
5	3-HO-C_6H_4 (**2e**)	H	**4e**	2	92
6	4-HO-3-MeO-C_6H_3 (**2f**)	H	**4f**	3	94
7	4-Me_2N-C_6H_4 (**2g**)	H	**4g**	2.5	90
8	Ph	Me (**3b**)	**4h**	2	94
9	4-Cl-C_6H_4 (**2h**)	Me	**4i**	2	90
10	4-MeO-C_6H_4 (**2i**)	Me	**4j**	2	92
11	4-NO_2-C_6H_4 (**2j**)	Me	**4k**	3.5	90
12	4-Me-C_6H_4	Me	**4l**	2.5	94
13	2-HO-C_6H_4 (**2k**)	Me	**4m**	2	90
14	Piperonyl (**2l**)	Me	**4n**	3	88
15	2-HO-1-Naphthyl (**2m**)	Me	**4o**	3.5	89
16	Ethyl (**2n**)	H	**4p**	4	62
17	Propyl (**2o**)	H	**4q**	4	64
18	Isobutyl (**2p**)	Me	**4r**	4	62
19	Hexyl (**2q**)	Me	**4s**	4	63

a) Reaction conditions: phthalhydrazide **1** (1 mmol), aldehyde **2a**–**2q** (1 mmol), cyclic β-diketone **3a**, **3b** (1 mmol); catalyst: CAN (5 mol%); *T*: 50°C; solvent: PEG 400 (2 mL). b) Isolated yields.

1.3 Spectral data for the synthesized compounds

(1) 2,3,4,13-Tetrahydro-13-phenyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4a**). Yellow solid, mp. 222–225°C [58]. IR (KBr, ν_{max} cm^{-1}): 2920, 1655, 1630, 1360, 1310, 1284, 754. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.24–8.35 (m, 2H), 7.80–7.88 (m, 2H), 7.17–7.38 (m, 5H, Ar-H), 6.42 (s, 1H, Ar-CH), 3.26–3.63 (m, 2H), 2.41–2.64 (m, 2H), 2.21–2.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.1, 164.2, 157.3, 150.8, 145.5, 133.9, 129.4, 128.7, 127.8, 127.3, 126.5, 119.4, 65.4, 36.3, 26.8, 21.4. Anal. Calcd. for $C_{21}H_{16}N_2O_3$ (%): C, 73.24; H, 4.68; N, 8.13; Found (%): C, 73.11; H, 4.60; N, 8.05.

(2) 2,3,4,13-Tetrahydro-13-(4-bromo-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4b**). Yellow solid, mp. 279–282°C [60]. IR (nujol, ν_{max} cm^{-1}): 2926, 1656, 1621, 1368, 1309, 1284, 755, 668. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.23–8.37 (m, 2H), 7.82–7.88 (m, 2H), 7.15–7.46 (m, 4H, Ar-H), 6.43 (s, 1H, Ar-CH), 3.43–3.66 (m, 2H), 2.44–2.67 (m, 2H), 2.23–2.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.4, 155.6, 154.2, 153.2, 135.3, 134.5, 132.8, 132.6, 129.4, 128.3, 127.9, 123.7, 120.3, 51.7, 40.0, 36.5, 29.2. Anal. Calcd. for $C_{21}H_{15}BrN_2O_3$ (%): C, 59.59; H, 3.57; N, 6.62; Found (%): C, 59.50; H, 3.52; N, 6.51.

(3) 2,3,4,13-Tetrahydro-13-(3-nitro-phenyl)-1*H*-indazolo-[1,2-*b*]phthalazine-1,6,11-trione (**4c**). Light yellow solid, mp. 228–232°C [59]. IR (KBr, ν_{max} cm^{-1}): 2923, 1667, 1624, 1371, 1307, 1284, 958, 703. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.24–8.34 (m, 2H), 7.81–7.87 (m, 2H), 7.29–7.45 (m, 4H, Ar-H), 6.38 (s, 1H, Ar-CH), 3.46–3.64 (m, 2H), 2.52–2.67 (m, 2H), 2.20–2.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 165.5, 156.0, 154.8, 153.4, 145.6, 135.2, 134.8, 129.4, 128.6, 127.3, 124.5, 120.4, 116.4, 64.2, 36.8, 26.9, 21.3. Anal. Calcd. for $C_{21}H_{15}N_3O_5$ (%): C, 64.78; H, 3.88; N, 10.79; Found (%): C, 64.65; H, 3.76; N, 10.65.

(4) 2,3,4,13-Tetrahydro-13-(4-methyl-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4d**). Yellow solid, mp. 244–246°C [59]. IR (KBr, ν_{max} cm^{-1}): 2954, 1657, 1621, 1365, 1308, 1265, 957, 704. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.24–8.36 (m, 2H), 7.81–7.86 (m, 2H), 7.11–7.34 (m, 4H, Ar-H), 6.39 (s, 1H, Ar-CH), 3.52–3.61 (m, 2H), 2.43–2.62 (m, 2H), 2.29 (s, 3H, CH_3), 2.00–2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.0, 193.2, 164.2, 156.4, 142.4, 136.4, 133.9, 133.4, 129.7, 129.3, 127.7, 127.5, 120.4, 116.9, 65.5, 37.6, 29.4, 21.6, 21.0. Anal. Calcd. for $C_{22}H_{18}N_2O_3$ (%): C, 73.73; H, 5.06; N, 7.82; Found (%): C, 73.65; H, 4.89; N, 7.65.

(5) 2,3,4,13-Tetrahydro-13-(3-hydroxy-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (4e). White solid, mp. 266–268°C [60]; IR (nujol, ν_{max} cm^{-1}): 3404, 2853, 1640, 1618, 1378, 1311, 1214, 771, 674. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.24–8.38 (m, 2H), 7.83–7.89 (m, 2H), 6.73–7.06 (m, 4H, Ar-H), 6.43 (s, 1H, Ar-CH), 4.76 (br s, 1H, OH), 3.52–3.62 (m, 2H), 2.53–2.68 (m, 2H), 2.22–2.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 165.2, 163.0, 158.8, 156.2, 139.3, 138.4, 133.7, 132.7, 131.8, 131.5, 130.3, 129.3, 124.2, 119.3, 68.4, 37.5, 29.8, 25.7. Anal. Calcd. for $C_{21}H_{16}N_2O_4$ (%): C, 69.99; H, 4.48; N, 7.77; Found (%): C, 69.75; H, 4.38; N, 7.62.

(6) 2,3,4,13-Tetrahydro-13-(4-hydroxy-3-methoxy-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4f**). Yellow solid, mp. 202–206°C. IR (nujol, ν_{max} cm^{-1}): 3536, 2920, 1668, 1596, 1468, 1364, 1272, 1215, 1128, 960, 630. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.25–8.36 (m, 2H), 7.82–7.88 (m, 2H), 6.52–6.56 (m, 3H, Ar-H), 6.38 (s, 1H, Ar-CH), 4.73 (br s, 1H, OH), 3.97 (s, 3H, OCH_3), 2.51–2.64 (m, 2H), 2.25–2.42 (m, 2H), 1.96–2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 164.3, 152.6, 146.4, 143.2, 137.6, 130.5, 129.5, 127.3, 120.7, 115.2, 112.1, 110.4, 64.9, 55.7, 37.8, 27.0, 22.8. Anal. Calcd. for $C_{22}H_{18}N_2O_5$ (%): C, 67.69; H, 4.65; N, 7.18; Found (%): C, 67.56; H, 4.58; N, 7.02.

(7) 2,3,4,13-Tetrahydro-13-(4-dimethylamino-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4g**). Red solid, mp. 255–256°C [59]. IR (nujol, ν_{max} cm^{-1}): 2924, 1672, 1624, 1365, 1313, 1226, 671. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.22–8.32 (m, 2H), 7.79–7.83 (m, 2H), 7.16 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 6.40 (s, 1H, Ar-CH), 3.07 (s, 6H, $N(CH_3)_2$), 2.50–2.64 (m, 2H), 2.25–2.37 (m, 2H), 1.93–2.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 164.5, 154.6, 153.1, 137.2, 133.4, 129.0, 128.4, 128.0, 126.3, 118.3, 112.6, 65.3, 41.3, 40.7, 30.1, 21.8. Anal. Calcd. for $C_{23}H_{21}N_3O_3$ (%): C, 71.30; H, 5.46; N, 10.85; Found (%): C, 71.16; H, 5.33; N, 10.74.

(8) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-phenyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4h**). Light yellow solid, mp. 202–204°C [37]. IR (KBr, ν_{max} cm^{-1}): 2959, 1662, 1623, 1361, 1308, 1262, 791. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.25–8.35 (m, 2H), 7.83–7.85 (m, 2H), 7.20–7.41 (m, 5H, Ar-H), 6.44 (s, 1H, Ar-CH), 3.20 and 3.42 (AB-q system, J = 19.04 Hz, 2H), 2.45 (s, 2H), 1.08 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 162.2, 155.9, 150.7, 144.0, 128.9, 128.7, 128.3, 127.7, 127.1, 126.3, 115.6, 64.9, 50.9, 40.8, 28.4, 27.3. Anal. Calcd. for $C_{23}H_{20}N_2O_3$ (%): C, 74.18; H, 5.41; N, 7.52; Found (%): C, 74.03; H, 5.29 ; N, 7.40.

(9) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-(4-chloro-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4i**). Light yellow solid, mp. 262–266°C [37]. IR (KBr, ν_{max} cm^{-1}): 2962, 1660, 1624, 1362, 1310, 1263, 791. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.25–8.36 (m, 2H), 7.85–7.87 (m, 2H), 7.29–7.36 (m, 4H, Ar-H), 6.41 (s, 1H, Ar-CH), 3.20 and 3.42 (AB-q system, J = 19.04 Hz, 2H), 2.35 (s, 2H), 1.20 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 162.4, 155.7, 151.0, 142.6, 134.6, 132.0, 129.7, 128.5, 128.2, 127.7, 115.2, 64.3, 50.8, 40.8, 29.3, 27.3. Anal. Calcd. for $C_{23}H_{19}ClN_2O_3$ (%): C, 67.90; H, 4.71; N, 6.89; Found (%): C, 67.76; H, 4.62; N, 6.75.

(10) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-(4-methoxy-

phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4j**). White solid, mp. 202–206°C [58]. IR (KBr, ν_{max} cm^{-1}): 3015, 2898, 1664, 1495, 1377, 1304, 1262, 791. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.25–8.33 (m, 2H), 7.80–7.86 (m, 2H), 6.71–7.18 (m, 4H, Ar-H), 6.39 (s, 1H, Ar-CH), 3.71 (s, 3H, OCH_3), 3.19 and 3.42 (AB-q system, J = 19.1 Hz, 2H), 2.42 (s, 2H), 1.07 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 162.0, 159.4, 157.7, 143.1, 136.2, 132.5, 129.3, 128.7, 127.6. 115.8, 113.4, 55.1, 50.7, 40.8, 32.2, 29.3, 27.3. Anal. Calcd. for $C_{24}H_{22}N_2O_4$ (%): C, 71.63; H, 5.51; N, 6.96; Found (%): C, 71.51; H, 5.38; N, 6.85.

(11) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-(4-nitro-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4k**). Creamy white solid, mp. 224–226°C [58]. IR (KBr, ν_{max} cm^{-1}): 3013, 2959, 1661, 1593, 1375, 1345, 1262, 851. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.22–8.38 (m, 2H), 7.86–7.89 (m, 2H), 7.23–7.62 (m, 4H, Ar-H), 6.51 (s, 1H, Ar-CH), 3.23 and 3.43 (AB-q system, J = 21.2 Hz, 2H), 2.47 (s, 2H), 1.23 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 162.9, 151.2, 148.7, 146.5, 146.1, 133.7, 132.3, 129.2, 127.6, 123.5, 114.9, 63.8, 50.4, 46.9, 46.3, 29.5, 27.4; Anal. Calcd. for $C_{23}H_{19}N_3O_5$ (%): C, 66.18; H, 4.59; N, 10.07; Found (%): C, 66.08; H, 4.44; N, 10.02.

(12) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-(4-methyl-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4l**). Yellow solid, mp. 226–228°C [37]. IR (KBr, ν_{max} cm^{-1}): 3017, 2960, 2898, 1664, 1492, 1350, 1263, 791. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.23–8.33 (m, 2H), 7.80–7.86 (m, 2H), 6.98–7.16 (m, 4H, Ar-H), 6.39 (s, 1H, Ar-CH), 3.19 and 3.41 (AB-q system, J = 20.5 Hz, 2H), 2.40 (s, 2H), 2.22 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 162.1, 158.3, 142.7, 141.1, 136.3, 135.7, 132.3, 128.8, 128.2, 126.7, 115.5, 64.5, 50.7, 40.8, 29.2, 27.3, 20.5. Anal. Calcd. for $C_{24}H_{22}N_2O_3$ (%): C, 74.59; H, 5.74; N, 7.25; Found (%): C, 74.50; H, 5.65; N, 7.12.

(13) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-(2-hydroxy-phenyl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4m**). Yellow solid, mp. 184–188°C. IR (KBr, ν_{max} cm^{-1}) 2896, 1662, 1492, 1377, 1329, 1262, 1081, 791. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 10.99 (br s, 1H, OH), 8.25–8.33 (m, 2H), 7.84–7.86 (m, 2H), 6.96–7.55 (m, 4H, Ar-H), 6.34 (s, 1H, Ar-CH), 2.43 and 2.60 (AB-q system, J = 17.3 Hz, 2H), 2.32 (s, 2H), 1.02 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.0, 196.1, 169.4, 161.5, 150.7, 137.0, 133.4, 131.8, 128.7, 128.0, 127.5, 124.6, 120.6, 115.7, 111.0, 52.2, 43.2, 41.5, 27.2, 26.4. Anal. Calcd. for $C_{23}H_{20}N_2O_4$ (%): C, 71.12; H, 5.12; N, 7.21; Found (%): C, 70.98; H, 5.03; N, 7.08.

(14) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-benzo-[1,3]-dioxol-5-yl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4n**). Yellow solid, mp. 194–198°C; IR (KBr, ν_{max} cm^{-1}): 2958, 1662, 1624, 1489, 1361, 1261, 825. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.26–8.36 (m, 2H), 7.84–7.86 (m, 2H), 6.64–6.77 (m, 3H, Ar-H), 6.34 (s, 1H, Ar-CH), 5.92 (s, CH_2-piperonyl), 3.20 and 3.42 (AB-q system, J = 19.8 Hz, 2H), 2.43 (s, 2H), 1.10 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 162.1, 155.7, 147.7, 145.9, 138.3, 134.6, 133.2, 129.8, 127.8, 121.5, 118.8, 115.6, 109.07, 100.7, 64.7, 50.7, 40.8, 29.2, 27.4. Anal. Calcd. for $C_{24}H_{20}N_2O_5$ (%): C, 69.22; H, 4.84; N, 6.73; Found (%): C, 69.16; H, 4.73; N, 6.70.

(15) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-(2-hydroxy-naphthalen-1-yl)-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4o**). Brown solid, mp. 156–160°C; IR (KBr, ν_{max} cm^{-1}): 3155, 2958, 2927, 2855, 2253, 1718, 1628, 1466, 1376, 1293, 908, 734. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 10.72 (br s, 1H, OH), 8.23–8.30 (m, 2H), 7.90–7.93 (m, 2H), 7.54–7.74 (m, 6H, Ar-H), 6.32 (s, 1H, Ar-CH), 3.48 and 3.61 (AB-q system, J = 17.6 Hz, 2H), 2.34 (s, 2H), 1.12 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.2, 164.8, 160.2, 153.4, 139.1, 132.8, 132.4, 131.3, 129.4, 129.1, 128.5, 127.7, 125.2, 124.4, 122.9, 119.1, 118.5, 111.2, 49.6, 46.1, 43.1, 25.2, 22.7. Anal. Calcd. for $C_{27}H_{22}N_2O_4$ (%): C, 73.96; H, 5.06; N, 6.39; Found (%): C, 73.85; H, 4.93; N, 6.32.

(16) 2,3,4,13-Tetrahydro-13-ethyl-1*H*-indazolo[1,2-*b*]-phthalazine-1,6,11-trione (**4p**). Yellow solid, mp. 164–166°C. IR (KBr, ν_{max} cm^{-1}): 3461, 2877, 1731, 1652, 1456, 1372, 1291, 1176, 956, 892, 795, 701. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.28–8.32 (m, 2H), 7.81–7.85 (m, 2H), 5.67 (m, 1H, CHN), 2.45–2.54 (m, 2H, CH_2), 2.27–2.33 (m, 2H, CH_2), 2.17–2.23 (m, 2H, CH_2), 1.96–2.06 (m, 2H, CH_2CH_3), 0.70 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 165.5, 162.2, 141.5, 134.4, 133.4, 128.9, 128.7, 127.8, 127.4, 117.6, 61.5, 37.0, 29.6, 22.3, 20.4, 9.9. Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (%): C, 68.91; H, 5.44; N, 9.45; Found (%): C, 68.74; H, 5.27; N, 9.34.

(17) 2,3,4,13-Tetrahydro-13-propyl-1*H*-indazolo[1,2-*b*]-phthalazine-1,6,11-trione (**4q**). White solid, mp. 172–174°C [58]. IR (KBr, ν_{max} cm^{-1}): 3165, 2963, 1662, 1492, 1377, 1262, 1081, 825, 791, 683. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.07–8.22 (m, 2H), 7.67–7.70 (m, 2H), 4.91 (m, 1H, CHN), 2.41–2.46 (m, 2H, CH_2), 2.10–2.17 (m, 2H, CH_2), 1.47–1.54 (q, 2H, CH_2CH_2), 1.31–1.43 (m, 2H, CH_2CH_3), 1.17–1.26 (m, 2H, CH_2), 0.76–0.83 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 161.2, 158.9, 143.3, 132.5, 132.3, 128.4, 121.3, 52.2, 41.3, 32.2, 29.7, 18.4, 18.2, 13.9. Anal. Calcd. for $C_{18}H_{18}N_2O_3$ (%): C, 69.66; H, 5.85; N, 9.03; Found (%): C, 69.53; H, 5.76; N, 8.94.

(18) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-isobutyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4r**). Yellow solid, mp. 135–137°C [57]. IR (KBr, ν_{max} cm^{-1}): 3166, 2896, 1663, 1492, 1377, 1262, 1082, 825, 791, 683. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 7.90–7.95 (m, 2H), 7.51–7.56 (m, 2H), 4.98 (m, 1H, CHN), 3.26 and 3.43 (AB-q system J = 20.52 Hz, 2H), 2.33 (s, 2H, CH_2), 2.10–2.15 (m, 2H, CH-CH_2), 1.87–1.92 (m, 1H, $CH(CH_3)_2$), 1.10 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.83–0.85 (d, 3H, CH_3), 0.66–0.69 (d, 3H, CH_3);

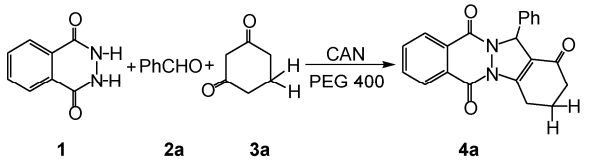
^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.7, 160.3, 158.8, 137.7, 130.4, 129.2, 126.8, 119.3, 51.2, 38.3, 36.4, 31.4, 26.3, 24.2, 22.3, 20.1. Anal. Calcd. for $C_{21}H_{24}N_2O_3$ (%): C, 71.57; H, 6.86; N, 7.95; Found (%): C, 71.44; H, 6.74; N, 7.80.

(19) 2,3,4,13-Tetrahydro-3,3-dimethyl-13-hexyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (**4s**). Yellow solid, mp. 84–86°C [57]. IR (KBr, ν_{max} cm^{-1}): 2958, 2926, 1660, 1632, 1462, 1375, 1288, 1180, 960, 892, 793, 699. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.24–8.34 (m, 2H), 7.86–7.94 (m, 2H), 5.67 (m, 1H, CHN), 3.18 and 3.34 (AB-q system J = 19.6 Hz, 2H), 2.47–2.51 (m, 1H, CHN), 2.40–2.44 (dd, 2H, CH_2C), 2.12–2.14 (m, 1H, CH), 1.15–1.33 (m, 12H, 2 CH_3 and 3 CH_2), 1.10–1.14 (m, 2H, CH_2), 0.85–0.87 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.7, 160.2, 158.6, 142.2, 132.5, 131.8, 128.2, 121.7, 55.8, 52.4, 33.1, 31.4, 28.6, 27.0, 25.1, 23.5, 17.4, 14.5. Anal. Calcd. for $C_{23}H_{28}N_2O_3$ (%): C, 72.60; H, 7.42; N, 7.36; Found (%): C, 72.53; H, 7.31; N, 7.25.

2 Results and discussion

Initially, equimolar amounts of phthalhydrazide **1**, benzaldehyde **2a** and cyclohexane-1,3-dione **3a** were stirred at ambient temperature in ethanol. After 22 h, yields of only 36% were obtained. To both improve the yield and optimize the reaction conditions, various Lewis acids were screened in a model reaction and the best yield was obtained using CAN as a catalyst (Scheme 1). The results are tabulated in Table 2.

A study was then done to determine the optimal loading of CAN. The reaction was carried out with varying amounts of catalyst, in the synthesis of **4a**. With 2 mol% CAN, under similar conditions, a significant improvement was observed



Scheme 1 Model reaction for the synthesis of 1*H*-indazolo[1,2-*b*]-phthalazine-1,6,11-triones.

Table 2 Screening of various Lewis acids for the model reaction[a)]

Entry	Catalyst	Time (h)	Yield (%)[b)]
1	$InCl_3$	12	62
2	$FeCl_3$	8	46
3	I_2	5.5	66
4	$CuSO_4$	7	71
5	CAN	2	94
6	$ZnCl_2$	10	53
7	$AlCl_3$	8.5	57

a) Reaction conditions: phthalhydrazide **1** (1 mmol), benzaldehyde **2a** (1 mmol), cyclohexane-1,3-dione **3a** (1 mmol); catalyst: 5 mol%; solvent: PEG 400 (2 mL); *T*: 50°C. b) Isolated yields.

and the yield of **4a** was dramatically enhanced to 68% after stirring the mixture for 8 h (Table 3, Entry 2). Upon increasing the loading to 5 mol%, a decreased reaction time of only 2 h was required, and the product yield increased remarkably from 68% to 94% (Table 3, Entry 3). Although required reaction time remained the same upon using 10 mol% CAN, the yield actually decreased from 94% to 76% (Table 3, Entry 4). A possible explanation for this lower product yield, is that the substrate (aldehyde) or product may be destroyed in the presence of excess amounts of CAN (10 mol%). This shows that the catalyst concentration plays a major role in the optimization of the product yield.

The effect of temperature was also evaluated for the model reaction. The reaction proceeded poorly at room temperature. Elevating the reaction temperature proved helpful and the yield of the desired product **4a** increased considerably. We were pleased to find that the reaction proceeded smoothly, and to almost complete conversion at 50°C, affording **4a** in 94% yield within 2 h. Increasing the temperature beyond 50°C, reduces the product yield due to the oxidation of the reactant (aldehyde) by CAN at high temperature. To assess the reaction efficiencies in different solvents, a variety of solvent systems were screened using the model reaction. The results are summarized in Figure 1. PEG 400 is the optimal solvent for this reaction giving excellent yields.

The optimum conditions for the model case were then applied to various aromatic and aliphatic aldehydes as

Table 3 Catalytic activity evaluation for the synthesis of 1*H*-indazolo [1,2-*b*]phthalazine-1,6,11-triones[a)]

Entry	CAN (mol%)	Time (h)	Yield (%)[b)]
1	0	18	35
2	2	8	68
3	5	2	94
4	10	2	76

a) Reaction conditions: phthalhydrazide **1** (1 mmol), benzaldehyde **2a** (1 mmol), cyclohexane-1,3-dione **3a** (1 mmol); solvent: PEG 400 (2 mL); *T*: 50°C. b) Isolated yields.

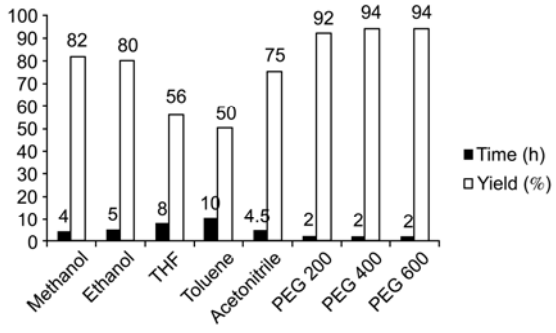
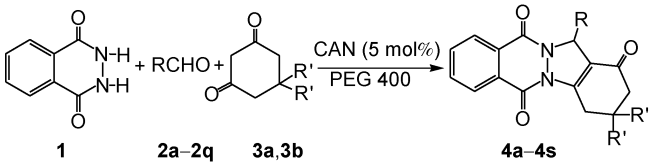


Figure 1 Effect of various solvents on the synthesis of 1*H*-indazolo [1,2-*b*]phthalazine-1,6,11-triones. Reaction conditions: phthalhydrazide **1** (1 mmol), benzaldehyde **2a** (1 mmol), cyclohexane-1,3-dione **3a** (1 mmol); catalyst: CAN (5 mol%); solvent: x (2 mL); *T*: 50°C. Isolated yields.

shown in Table 3. Aromatic aldehydes with both electron-donating and electron-withdrawing substituents proceeded smoothly to give excellent product yields. They also required reduced reaction times compared to aliphatic aldehydes, which reacted slowly to give only moderate yields (Scheme 2, Table 1, Entries 1–15). It is noteworthy that until now there has only been one report on the synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones using aliphatic aldehydes [57].

To establish the recyclability of the PEG 400, the reaction mixture was kept in a dry ice-acetone bath to precipitate the PEG 400. The desired product was extracted with solvent ether, in which the PEG 400 is immiscible. The remaining PEG 400 phase was reused in subsequent reactions. The reaction proceeded cleanly, exhibiting consistent results for up to four runs. A weight loss of approximately 5% was observed from cycle to cycle because of mechanical losses.



Scheme 2 CAN promoted synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones.

3 Conclusion

A novel and efficient catalytic method has been developed for the preparation of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione derivatives, using a ceric ammonium nitrate catalyst. The notable features of this clean one-pot procedure are the mild reaction conditions, improved yields, enhanced reaction rates, solvent recyclability and operational simplicity. This protocol represents a useful and attractive process for the synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione derivatives.

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