WATER MEDIATED ONE-POT, FOUR COMPONENT SYNTHESIS OF 3,3-DIMETHYL-13-ARYL-3,4-DIHYDRO-1*H*-INDAZOLO[1,2-*b*]PHTHALAZINE-1,6,11(2*H*,13*H*)-TRIONES

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Water mediated one-pot, four-component synthesis of substituted 2H-indazolo[2,1-*b*]phthalazine-triones from dimethyl phthalate, hydrazine, dimedone and aromatic aldehydes have been reported in the presence of p-toluenesulfonic acid (PTSA) as catalyst at 100 °C for 1.5-2.0 h. This methodology offers several advantages such as good yields, short reaction time, simple procedure, mild condition and environmentally begins.

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INTRODUCTION

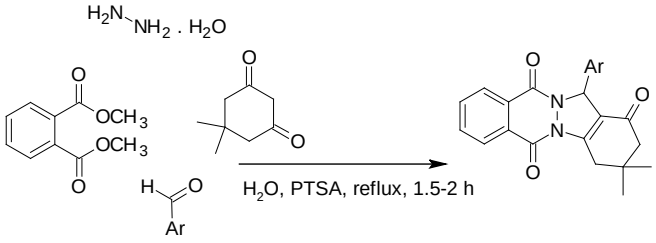
Phthalazines are important heterocycles that are known to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer and anti-inflammatory activities.[1-3] Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives. Nevertheless, the development of new synthetic methods for the efficient preparation of heterocycles containing a phthalazine ring fragment is an interesting challenge. Recent protocols have been employed for the synthesis of title compounds either by one-pot, three-component condensation of phthalhydrazide, dimedone and aromatic aldehydes using Me_3SiCl[4], silica sulfuric acid[5], H_2SO_4[6]. $Mg(HSO_4)_2$,[7] and [bimm]Br under ultra-sonication[8] as catalysts. One-pot, four-component synthesis of phthalic anhydride, hydrazine, dimedone and aromatic aldehydes using various catalytic systems such as starch sulfate,[9] $CeSO_4$-$4H_2O$[10] and PEG-SO_3H[11] have also been performed.

However, many of these methodologies are associated with one or more disadvantages such as the use of expensive catalyst or toxic organic solvents,[12] strong acidic conditions,[6] and harsh reaction conditions,[6,7] the formation of by-products and tedious work-up procedures. According to the principle of safe chemistry, synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and the environment.[13] Nonetheless the development of new synthetic methods for the proficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge.

Keeping these results in mind, we now aim to report the one-pot, four-component synthesis of 2H-indazolo[2,1-*b*]phthalazine-triones from dimethyl phthalate, hydrazine, dimedone and aromatic aldehydes in water as a solvent in the presence of p-toluenesulfonic acid (PTSA) as a catalyst at 100 ˚C for 1.5-2.0 h.

RESULTS AND DISCUSSION

To find out an appropriate reaction conditions for synthesis of the title compounds by one-pot, four-component reaction among dimethyl phthalate **1** (1 mmol), hydrazine hydrate **2** (1 mmol), dimedone **3** (1 mmol) and benzaldehyde **4** (1 mmol) was selected as a model **(**Scheme 1) and examined with different catalysts in several solvents at different temperatures. The obtained results are summarized in Table 1 and 2.



Ar=Ph, 2-ClC_6H_4, 4-BrC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$

Scheme 1. Synthesis of 3,3-dimethyl-13-aryl-3,4-dihydro-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11(2*H*,13*H*)-triones

The best results were obtained using water as solvent at 100 ºC for 1.5 hr in the presence of PTSA (1 mmol/10 mmol substrate) as catalyst compares to other solvents like DMF, glycerol, ethylene glycol and PEG-400 at different temperature. It is clear that, water and PTSA are playing very important role in the synthesis of title compound by this method.

Table 1. Effect of acid catalysts on one-pot reaction for yielding 3,3-dimethyl-13-phenyl-3,4-dihydro-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11(2*H*,13*H*)-trione (**5a**) in water at 100 ºC

Entry	Catalyst	mmol/10 mmol substrate	Time, h	5a, %
1	PTSA	0.5	3.0	84
2	PTSA	1.0	1.5	88
3	PTSA	1.5	1.5	80
4	Boric acid	0.5	3.5	82
5	Boric acid	1.0	4.5	80
6	Boric acid	1.5	4.0	81
7	$AlCl_3$	0.5	3.5	80
8	$AlCl_3$	1.0	2.5	78
9	$AlCl_3$	1.5	2.5	74

Table 2. Effect of solvent on the one-pot reaction for yielding 3,3-dimethyl-13-phenyl-3,4-dihydro-1*H*-indazolo[1,2-*b*]phthala-zine-1,6,11(2*H*,13*H*)-trione (**5a**) in the presence of 1 mmol/10 mmol substrate PTSA as catalyst.

Entry	Solvent	Temp., °C	Time, h	5a, %
1	Glycerol	50	10	80
2	Glycerol	100	4	82
3	Glycerol	120	2.5	80
4	H_2O	50	8	80
5	H_2O	100	1.5	88
6	PEG-600	50	12	76
7	PEG-600	100	4.5	78
8	Ethylene glycol	50	4.0	75
9	Ethylene glycol	100	3.0	78
10	DMF	50	8.0	68
11	DMF	100	2.5	65

In the next step, the scope and efficiency of the process were explored under the optimized conditions for the synthesis of title compounds. For this purpose, a broad range of structurally diverse dimethyl phthalate (**1**) were condensed with hydrazinium hydroxide (**2**), aromatic aldehydes (**4a-4h**) and dimedone (**3**) in the presence of water at 100 ˚C temperature, and the results are shown in Table 3.

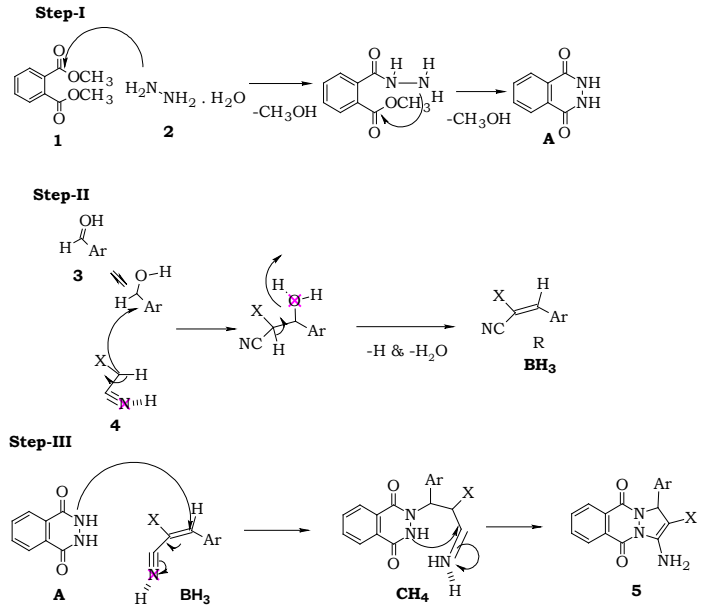
Table 3. Characterization data, reaction time and yields of compounds **5a-5h** obtained from **1**, **2**, **3** and **4a-4h** via one-pot, four component synthesis

Starting materials				Product	Yield, %≠	Melting point, °C
1	**2**	**3a**	**4a**	**5a**	88	203-205
1	**2**	**3b**	**4b**	**5b**	83	268-270
1	**2**	**3c**	**4c**	**5c**	82	262-264
1	**2**	**3d**	**4d**	**5d**	86	239-240
1	**2**	**3e**	**4e**	**5e**	85	267-269
1	**2**	**3f**	**4f**	**5f**	83	258-259
1	**2**	**3g**	**4g**	**5g**	84	226-268
1	**2**	**3h**	**4h**	**5h**	85	243-245

≠ Refers to yields of crude products only.

The yields obtained were good to excellent without the formation of any side-products and all reactions proceed rapidly in short times. The structures of the products were established from their spectral properties (^{1}H NMR & ^{13}C NMR).

Our proposed mechanism contains two steps. The initial formation of phthalhydrazide by nucleophilic addition of hydrazinium hydroxide **2** to dimethyl phthalate **1**. The second step involves the initial formation of heterodiene **(X)** by standard knoevenagel condensation of dimedone **3** and aromatic aldehydes **4**. Then, subsequent Michael-type addition of the phthalhydrazide followed by cyclization affords the corresponding product **5** (Scheme 2).



Scheme 2. Proposed mechanism

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes in a sulphuric acid bath. TLC was run on silica gel–G and visualization were done using iodine or UV light. IR spectra were recorded using a Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO–d_6 using TMS as an internal standard using a 400 MHz spectrometer. Mass spectra were recorded on an Agilent-LCMS instrument under CI conditions and given by Q+1 values only. Starting materials **1, 2, 3** and **4** were obtained from commercial sources and used as such.

General procedure for preparation of 5a-5h

Dimethyl phthalate **(1)** (10 mmol) and hydrazine hydrate **(2)** (10 mmol) was refluxed at 100 ºC in water for 10-15 min to form phthalhydrazide as intermediate in the presence of PTSA (1 mmol). Then, dimedone **(3)** (10 mmol) and substituted benzaldehydes **(4a-4h)** (10 mmol) were added and the mixture refluxed again for 1.5-2.0 h. After completion of the reaction, ice-cold water (50 mL) was added to the reaction mixture and neutralized (pH: 6.5 to 7.0) with 20 % sodium bicarbonate solution; the solid that separated out was filtered, washed with water (20 mL) two times and dried. The product was recrystallized from ethanol to obtain final compounds.

3,3-Dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-*b*]phthalazine-1,6,11(2H,13H)-trione (5a)

IR (KBr) in cm^{-1}: 1661, 1625 , 1601(-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.89 (s, 3H, -CH_3), 1.03 (s, 3H, -CH_3), 2.05 (AB system, 2H, -CH_2), 2.54 (AB system, 2H, -CH_2), 4.54 (s, 1H, -CH), 7.09 (m, 1H, Ar-H), 7.11 (m, 4H, Ar-H), 7.87 (d, 2H, Ar-H), 8.07 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 26.3, 28.7, 31.2, 31.8, 50.0, 114.4, 125.1, 126.1, 127.8, 128.0, 132.5, 144.2, 154.6, 162.8, 196.0; HRMS calcd for $C_{23}H_{20}N_2O_3$ $[M+H]^+$: 373.1268. Found: 373. 1238.

13-(2-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-*b*]phthalazine-1,6,11(2H,13H)-trione (5b)

IR (KBr) in cm^{-1}: 1670, 1655, 1631(-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.99 (s, 3H, -CH_3), 1.04 (s, 3H, -CH_3), 2.15 (AB system, 2H, -CH_2), 2.54 (AB system, 2H, -CH_2), 4.53 (s, 1H, -CH), 7.03 (m, 1H, Ar-H), 7.21 (m, 3H, Ar-H), 7.86 (d, 2H, Ar-H), 8.12 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 24.4, 28.6, 30.1, 32.5, 50.3, 114.3, 124.2, 126.5, 127.4, 128.1, 131.4, 143.1, 153.3, 162.5, 196.1; HRMS calcd for $C_{23}H_{19}ClN_2O_3$ $[M+H]^+$: 408.1453. Found: 408.1483.

13-(4-Bromophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-*b*]phthalazine-1,6,11(2H,13H)-trione (5c)

IR (KBr) in cm^{-1}: 1672, 1642 , 1622 (-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (s, 3H, -CH_3), 1.34 (s, 3H, -CH_3), 2.12 (AB system, 2H, -CH_2), 2.53 (AB system, 2H, -CH_2), δ 4.50 (s, 1H, -CH), 7.08 (m, 1H, Ar-H), 7.23 (m, 3H, Ar-H), 7.86 (d, 2H, Ar-H), 8.12 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 24.2, 28.1, 30.2, 32.2, 50.2, 114.2, 123.2, 126.2, 127.3, 128.2, 131.0, 143.2, 153.2, 162.4, 196.1; HRMS calcd for $C_{23}H_{19}BrN_2O_3$ $[M+H]^+$: 451.2372. Found: 451.2343.

13-(2-Nitrophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-*b*]phthalazine-1,6,11(2H,13H)-trione (5d)

IR (KBr) in cm^{-1}: 1674, 1652, 1632 (-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.92 (s, 3H, -CH_3), 1.24 (s, 3H, -CH_3), 2.13 (AB system, 2H, -CH_2), 2.52 (AB system, 2H, -CH_2), 4.52 (s, 1H, -CH), 7.12 (m, 1H, Ar-H), 7.23 (m, 3H, Ar-H), 7.86 (d, 2H, Ar-H), 8.24 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 24.3, 28.2, 30.2, 32.3, 50.2, 114.1, 123.2, 126.3, 127.3, 128.3, 131.1, 143.2, 153.2, 162.5, 196.2; HRMS calcd for $C_{23}H_{19}N_3O_4$ $[M+H]^+$: 418.1330. Found: 418.1360.

13-(3-Nitrophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-*b*]phthalazine-1,6,11(2H,13H)-trione (5e)

IR (KBr) in cm^{-1}: 1672, 1662, 1651 (-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.92 (s, 3H, -CH_3), 1.23 (s, 3H, -CH_3), 2.13 (AB system, 2H, -CH_2), 2.54 (AB system, 2H, -CH_2), 4.49 (s, 1H, -CH), 7.23 (m, 1H, Ar-H), 7.45 (m, 3H, Ar-H), 7.67 (d, 2H, Ar-H), 8.17 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 24.2, 28.0, 30.1, 32.3, 50.1, 114.1, 123.3, 126.4, 127.3, 128.2, 131.0, 143.1, 153.1, 162.4, 195.9; HRMS calcd for $C_{23}H_{19}N_3O_4$ $[M+H]^+$: 418.1330. Found: 418.1372.

13-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-*b*]phthalazine-1,6,11(2H,13H)-trione (5f)

IR (KBr) in cm^{-1}: 1670, 1660, 1653 (-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.99 (s, 3H, -CH_3), 1.24 (s, 3H, -CH_3), 2.03 (AB system, 2H, -CH_2), 2.53 (AB system, 2H, -CH_2), 4.44 (s, 1H, -CH), 7.34 (m, 1H, Ar-H), 7.41 (m, 3H, Ar-H), 7.85 (d, 2H, Ar-H), 8.03 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 24.3, 28.5, 30.1, 32.3, 50.2, 114.3, 123.3, 126.2, 127.3, 128.2, 131.0, 143.3, 153.1, 162.4, 195.8; HRMS calcd for $C_{23}H_{19}ClN_2O_3$ $[M+H]^+$: 408.1453. Found: 408.1492.

13-(4-Methylphenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (5g)

IR (KBr) in cm^{-1}: 1673, 1665, 1651 (-C=O); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.2 (s, 3H, -CH_3), 1.26 (s, 3H, -CH_3), 2.7 (s, 3H, -CH_3), 2.13 (AB system, 2H, -CH_2), 2.58 (AB system, 2H, -CH_2), 4.46 (s, 1H, -CH), 7.44 (m, 1H, Ar-H), 7.51 (m, 3H, Ar-H), 7.89 (d, 2H, Ar-H), 8.13 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 24.1, 28.3, 29.1, 30.3, 32.7, 50.2, 114.1, 123.0, 126.4, 127.2, 128.1, 131.1, 143.3, 153.5, 162.3, 195.1; HRMS calcd for $C_{24}H_{22}N_2O_3$ $[M+H]^+$: 386.1251. Found: 386.1223.

13-(2-Methylphenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (5h)

IR (KBr) in cm^{-1}: 1671, 1658, 1656 (-C=O); ^{1}H-NMR (DMSO-d $_6$, 400 MHz): δ 0.98 (s, 3H, -CH_3), 1.22 (s, 3H, -CH_3), 2.70 (s, 3H, -CH_3), 2.13 (AB system, 2H, -CH_2), 2.48 (AB system, 2H, -CH_2), 4.42 (s, 1H, -CH), 7.31 (m, 1H, Ar-H), 7.44 (m, 3H, Ar-H), 7.84 (d, 2H, Ar-H), 8.13 (d, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 20.2, 28.2, 30.2, 31.2, 32.4, 51.3, 113.2, 123.1, 125.1, 127.2, 128.1, 131.3, 143.2, 153.0, 162.1, 195.2; HRMS calcd for $C_{24}H_{22}N_2O_3$ $[M+H]^+$: 386.1251. Found: 386.1223.

CONCLUSION

In summary, water-mediated one-pot, four-component synthesis of substituted 2H-indazolo[2,1-*b*]phthalazine-triones have been reported with several advantages such as good yields, short reaction time, simple procedure, mild condition and environmentally begins.

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