



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 2*H*-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 benign.

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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 Me₃SiCl⁴, silica sulfuric acid⁵, H₂SO₄⁶, Mg(HSO₄)₂,⁷ and [bimm]Br under ultra-sonication⁸ as catalysts. One-pot, four-component synthesis of phthalic anhydride, hydrazine, dimedone and aromatic aldehydes using various catalytic systems such as starch sulfate,⁹ CeSO₄·4H₂O¹⁰ and PEG-SO₃H¹¹ have also been performed.

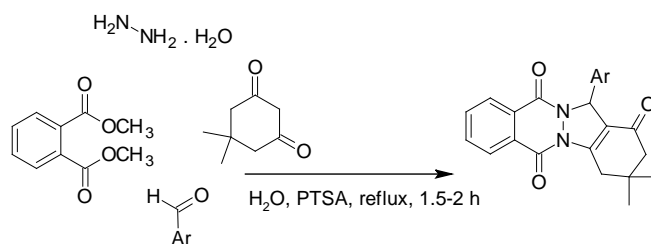
However, many of these methodologies are associated with one or more disadvantages such as the use of expensive catalyst or toxic organic solvents,¹² strong acidic conditions,⁶ and harsh reaction conditions,^{6,7} the formation of by-products and tedious work-up procedures. According to the principle 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 2*H*-indazolo[2,1-b

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-ClC₆H₄, 4-BrC₆H₄, 2-O₂NC₆H₄, 3-O₂NC₆H₄, 4-ClC₆H₄, 4-CH₃C₆H₄, 2-CH₃C₆H₄

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 °C 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 °C

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*]phthalazine-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 ₂ O	50	8	80
5	H ₂ O	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.

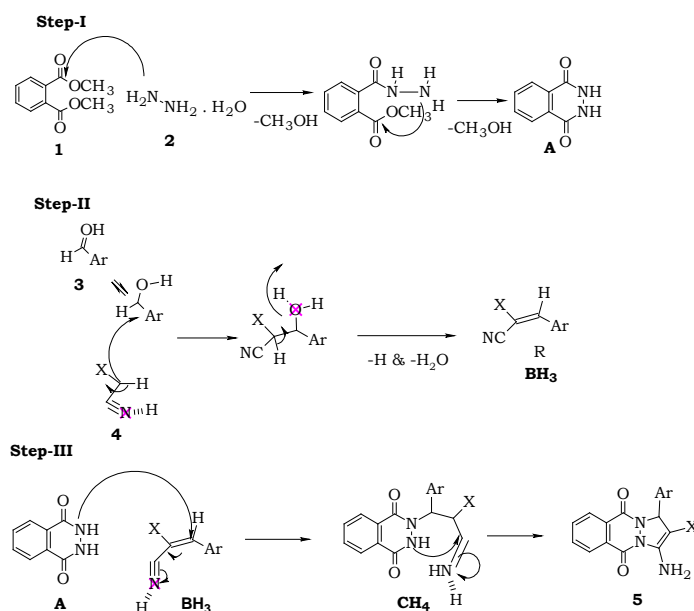
Table 3. Characterization data, reaction time and yields of compounds **5a-5h** obtained from **1**, **2**, **3** and **4a-4h** via one-pot, four component synthesis

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 (¹H NMR & ¹³C 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. ¹H 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 °C 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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.89 (s, 3H, -CH₃), 1.03 (s, 3H, -CH₃), 2.05 (AB system, 2H, -CH₂), 2.54 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₃H₂₀N₂O₃ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.99 (s, 3H, -CH₃), 1.04 (s, 3H, -CH₃), 2.15 (AB system, 2H, -CH₂), 2.54 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₃H₁₉ClN₂O₃ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.91 (s, 3H, -CH₃), 1.34 (s, 3H, -CH₃), 2.12 (AB system, 2H, -CH₂), 2.53 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₃H₁₉BrN₂O₃ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.92 (s, 3H, -CH₃), 1.24 (s, 3H, -CH₃), 2.13 (AB system, 2H, -CH₂), 2.52 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₃H₁₉N₃O₄ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.92 (s, 3H, -CH₃), 1.23 (s, 3H, -CH₃), 2.13 (AB system, 2H, -CH₂), 2.54 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₃H₁₉N₃O₄ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.99 (s, 3H, -CH₃), 1.24 (s, 3H, -CH₃), 2.03 (AB system, 2H, -CH₂), 2.53 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₃H₁₉ClN₂O₃ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 1.2 (s, 3H, -CH₃), 1.26 (s, 3H, -CH₃), 2.7 (s, 3H, -CH₃), 2.13 (AB system, 2H, -CH₂), 2.58 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₄H₂₂N₂O₃ [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); $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 0.98 (s, 3H, -CH₃), 1.22 (s, 3H, -CH₃), 2.70 (s, 3H, -CH₃), 2.13 (AB system, 2H, -CH₂), 2.48 (AB system, 2H, -CH₂), 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); $^{13}\text{C-NMR}$ (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 C₂₄H₂₂N₂O₃ [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 benign.

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REFERENCES

- ¹El-Sakka, S. S., Soliman, A. H., Imam, A. M., Synthesis, antimicrobial activity and Electron Impact of Mass Spectra of Phthalazine-1,4-dione Derivatives, *Afinidad*, **2009**, *66*, 167. <https://core.ac.uk/download/pdf/39152404.pdf>
- ²Rao, R. K., and Kankala, S., One-pot green synthesis of 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile and related compounds. *Eur. Chem. Bull.* **2018**, *7*, 324-328. DOI: [10.17628/ecb.2018.7.324-328](https://doi.org/10.17628/ecb.2018.7.324-328)
- ³Grasso, S., DeSarro, G., Micale, N., Zappala, M., Puia, G., Baraldi, M., Demicheli, C., Synthesis and Anticonvulsant Activity of Novel and Potent 6,7-Methylenedioxyphthalazin-1(2H)-ones, *J. Med. Chem.*, **2000**, *43*, 2851. DOI: [10.1021/jm001002x](https://doi.org/10.1021/jm001002x)
- ⁴Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A, One-pot, three-component route to 2H-indazolo [2,1-*b*]phthalazine-triones, *Tetrahedron* **2008**, *64*, 2375. DOI: [10.1016/j.tet.2008.01.006](https://doi.org/10.1016/j.tet.2008.01.006)
- ⁵Shaterian, H. R., Hosseinian, A., Ghashang, M., Reusable silica-supported polyphosphoric acid-catalyzed three-component synthesis of 2H-indazolo[2,1-*b*]phthalazine-trione derivatives *Arkivoc* **2009**, *ii*, 59. <https://www.arkat-usa.org/get-file/27703/>
- ⁶Khurana, J. M., Magoo, D., Efficient one-pot syntheses of 2H-indazolo[2,1-*b*] phthalazine-triones by catalytic H₂SO₄ in water-ethanol or ionic liquid, *Tetrahedron Lett.* **2009**, *50*, 7300. <https://doi.org/10.1016/j.tetlet.2009.10.032>
- ⁷Shaterian, H. R., Khorami, F., Amirzadeh, A., Doostmohammadi, R., Ghashang, M., Preparation of heterocyclic containing phthalazine skeletons: 2H-indazolo [2,1-*b*] phthalazine-1,6,11(13H)-triones, *J. Iran. Chem. Res.* **2009**, *2*, 57. <https://www.sid.ir/en/journal/viewpaper.aspx?Id=201649>
- ⁸Shekouhy, M., Hasaninejad, A., Ultrasound and microwave-assisted synthesis of isoindolo-1,2-diazine: a comparative study. *Ultrasonics Sonochemistry*, **2012**, *19*, 307-313. DOI: [10.1016/j.ultsonch.2012.02.012](https://doi.org/10.1016/j.ultsonch.2012.02.012)
- ⁹Shaterian, H., Rigi, F., Starch sulfate as an efficient and biodegradable polymer catalyst for one-pot, the four-component reaction of 2H-indazolo[2,1-*b*]phthalazine-triones, *Starch*, **2011**, 1-7. <https://onlinelibrary.wiley.com/doi/abs/10.1002/star.201000144>
- ¹⁰Mosaddegh, E., Hassankhani, A., A rapid, one-pot, four-component route to 2H-indazolo[2,1-*b*]phthalazine-triones, *Tetrahedron Lett.* **2011**, *52*, 488-490. DOI: [10.1016/j.tetlet.2010.08.099](https://doi.org/10.1016/j.tetlet.2010.08.099)
- ¹¹Hasaninejad, A., Kazerooni, M. R., Zare A. K., catalysis today, **2012**, *196*, 148-155.
- ¹²Nagarapu, L.; Bantu, R.; Mereyala, H. B, Synthesis of 2,3-dichloroquinoxalines via Vilsmeier reagent chlorination, *J. Heterocyclic Chem.* **2009**, *46*, 728. <https://onlinelibrary.wiley.com/doi/abs/10.1002/jhet.56>
- ¹³Anastas, P. T. and Warner, J. C., In *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, UK, **1998**; (b) Anastas, P.T. Williamson, T., In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Process*, Oxford University Press, Oxford, UK, **1998**. <https://pdfs.semanticscholar.org/172e/58dab55656bc8ffc4362ad7940368e49cac.pdf>

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