



Efficient one-pot syntheses of 2*H*-indazolo[2,1-*b*] phthalazine-triones by catalytic H₂SO₄ in water–ethanol or ionic liquid

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ABSTRACT

Sulfuric acid-catalyzed, three-component, one-pot condensation of phthalhydrazide, aromatic aldehydes and 1,3-dicarbonyl compounds has been reported for the synthesis of a series of 2*H*-indazolo[2,1-*b*] phthalazine-triones in water–ethanol or in ionic liquid. The protocol proves to be efficient and environmentally benign in terms of high yields, low reaction times, ease of recovery, and reusability of reaction medium (ionic liquid).

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1. Introduction

Phthalazine derivatives, constituting a bridgehead hydrazine are reported to possess a multiplicity of pharmacological properties including anticonvulsant,¹ vasorelaxant,² and cardiotoxic³ activities. Albeit there are methods available for the synthesis of different phthalazine derivatives,^{4–8} their broad utility range has accentuated the need to develop newer synthetic routes for scaffold manipulation of N-heterocycles containing phthalazine moiety. The recent protocols directed toward designing structural motifs containing phthalazine ring fragment, usually employ multi-component condensation of aldehydes and active methylene compounds (malononitrile, ethyl cyanoacetate, and dimedone) with 2,3-dihydro-1,4-phthalazinedione also known as phthalhydrazide.^{9–11} These protocols have their own limitations. Furthermore, the use of water as a promising solvent for organic reactions has received considerable attention in the arena of organic synthesis owing to its green credentials.¹² Ionic liquids have also proved to be efficient alternatives to the traditional volatile organic solvents¹³ owing to their negligible vapor pressure, recyclability, solvophobic properties, and to promote association of reactants in solvent cavity during the activation process. Thus ionic liquids are well suited as reaction media for MCRs in which the entropy of the reaction is decreased in transition state.

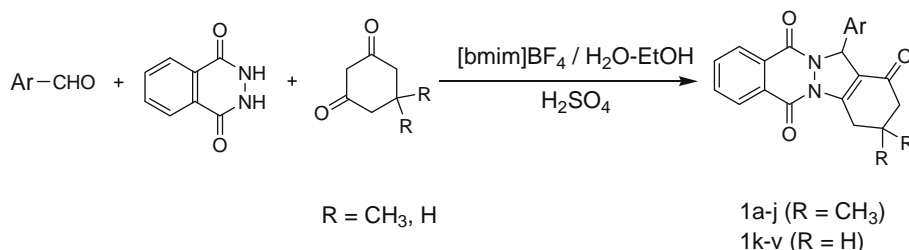
In continuation of our efforts to explore newer reactions for the synthesis of heterocyclic compounds,¹⁴ we decided to explore the possibility of synthesizing 2*H*-indazolo[2,1-*b*] phthalazine-trione derivatives by one-pot, three-component condensation of phthalhydrazide, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds in aqueous media and/ or in ionic liquids.

2. Results and discussion

We herein present efficient and environmentally benign protocols for the synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-1,6,11(13*H*)-trione derivatives by three-component condensation of 2,3-dihydro-1,4-phthalazinedione (phthalhydrazide), aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds catalyzed by sulfuric acid in water–ethanol solvent system and also in [bmim]BF₄ ionic liquid.

In order to achieve optimum conditions, we initially investigated the reaction of phthalhydrazide (1.0 mmol), 4-bromobenzaldehyde (1.2 mmol), and 5,5-dimethylcyclohexane-1,3-dione (1.0 mmol) in the presence of acid catalysts such as HCl, HNO₃, CH₃COOH, and H₂SO₄ in different media. Best result was obtained when water–ethanol (1:1, v/v) was chosen as the solvent in the presence of catalytic amount of sulfuric acid under reflux conditions. The reaction afforded 93% of 3,4-dihydro-3,3-dimethyl-13-(4-bromophenyl)-2*H*-indazolo[2,1-*b*] phthalazine-1,6,11(13*H*)-trione (**1a**) by a simple work-up after 30 min. The reaction when repeated under similar conditions in the presence of HCl, HNO₃, and CH₃COOH was found

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Scheme 1.

to be sluggish and incomplete. Also, when only water was employed as the solvent medium under the same reaction protocol, the reaction did not proceed to completion even after 5 h of reflux and only 57% of **1a** was isolated. Thus, water–ethanol (1:1, v/v) and catalytic amount of H₂SO₄ were chosen as the optimum system to extend the protocol. Subsequent reactions of variously substituted aromatic aldehydes with phthalhydrazide and dimedone were attempted under similar conditions. The reactions proceeded smoothly and equally well for electron-withdrawing as well as electron-donating substituents on aldehydes to afford the corresponding phthalazine-triones in excellent yields (Scheme 1). The results are summarized in Table 1 (entries 1–10, Method A).

To further explore the scope of this protocol, we decided to investigate the condensation reaction of phthalhydrazide and aromatic aldehydes with another cyclic 1,3-dicarbonyl compound, that is, cyclohexane-1,3-dione. The reaction of 4-bromobenzaldehyde (1.2 mmol), phthalhydrazide (1.0 mmol), and cyclohexane-1,3-dione (1.0 mmol) in H₂O–EtOH (1:1, v/v) using H₂SO₄ as a catalyst under reflux yielded 89% of 3,4-dihydro-13-(4-bromophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**1k**) after 30 min. Other substituted benzaldehydes also underwent successful condensation with cyclohexane-1,3-dione and phthalhydrazide yielding novel phthalazine-triones in good yields. (Table 1, entries 11–22, Method A).

We decided to investigate the scope of the scheme further by employing ionic liquids as the reaction media. A reaction of 4-bromobenzaldehyde with phthalhydrazide and dimedone in 1.2:1:1

molar ratio was attempted in [bmim]BF₄ at room temperature without the aid of a catalyst. TLC analysis showed the reaction to be incomplete after 6 h and even on heating the reaction mixture to 80 °C, only 32% of 3,4-dihydro-3,3-dimethyl-13-(4-bromophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**1a**) could be isolated after 8 h. However, the yield of **1a** improved remarkably to 92% when the three components were heated at 80 °C in [bmim]BF₄ in the presence of catalytic amount of sulfuric acid for 30 min. The reaction was also attempted under similar conditions in [bmim]Br but only to result in lower yield (80%) of **1a** after longer reaction time (2.5 h). Other substituted aromatic aldehydes also underwent condensation successfully under these conditions in [bmim]BF₄ and the corresponding phthalazine derivatives were obtained in high yields (Table 1, Method B, entries 1–10). Also when cyclohexane-1,3-dione was used in the place of dimedone, promising results were obtained (Table 1, Method B, entries 11–22). Comparative results were obtained by both the methods A and B. The ionic liquid utilized in method B could be recycled for subsequent usage. A plausible mechanism for the formation of 2H-indazolo[2,1-b]phthalazine-triones (**1a–1v**) in the presence of H₂SO₄ is proposed in Scheme 2.

3. Conclusion

We have described an efficient one-pot, three-component condensation strategy for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones. This MCR is proficiently catalyzed by sulfuric acid

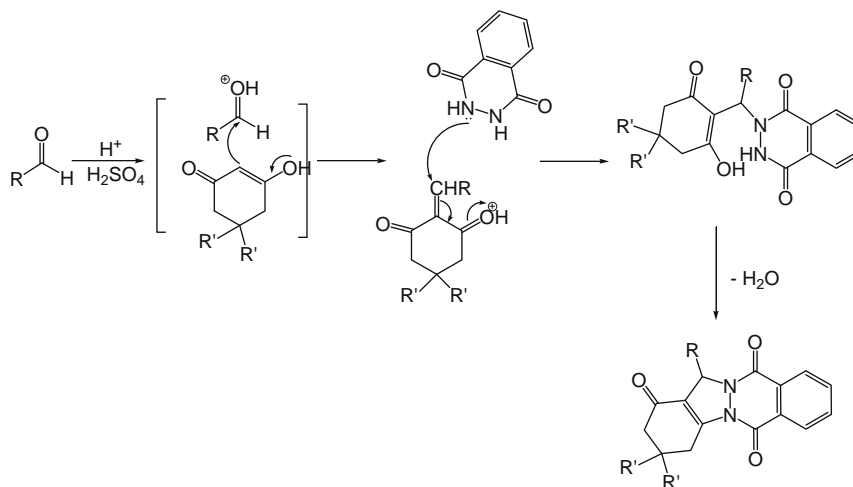
Table 1

Synthesis of 2H-indazolo[2,1-b]phthalazine-trione derivatives by the condensation of aldehydes, phthalhydrazide, and 5,5-dimethylcyclohexane-1,3-dione/ cyclohexane-1,3-dione using H₂SO₄ as a catalyst

Entry	Ar	Product	Method A		Method B	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	4-BrC ₆ H ₄	1a	30	93	30	92
2	4-ClC ₆ H ₄	1b	25	88	30	88
3	C ₆ H ₅	1c	30	86	30	89
4	4-CH ₃ C ₆ H ₄	1d	30	85	30	88
5	2,4-Cl ₂ C ₆ H ₃	1e	25	91	30	92
6	4-O ₂ NC ₆ H ₄	1f	30	92	30	90
7	4-CH ₃ OC ₆ H ₄	1g	30	87	35	88
8	2-Naphthyl	1h	25	90	30	90
9	4-FC ₆ H ₄	1i	30	88	30	90
10	3,4-(CH ₃ O) ₂ C ₆ H ₃	1j	35	82	40	83
11	4-BrC ₆ H ₄	1k	30	89	35	92
12	4-ClC ₆ H ₄	1l	30	92	30	94
13	C ₆ H ₅	1m	30	88	35	91
14	2,4-Cl ₂ C ₆ H ₃	1n	25	90	30	93
15	3,4-(CH ₃ O) ₂ C ₆ H ₃	1o	30	80	35	83
16	3-O ₂ NC ₆ H ₄	1p	25	90	30	90
17	4-CH ₃ OC ₆ H ₄	1q	30	82	35	85
18	4-CH ₃ C ₆ H ₄	1r	30	84	35	86
19	2-Naphthyl	1s	30	88	30	90
20	4-HO C ₆ H ₄	1t	30	82	30	84
21	4-FC ₆ H ₄	1u	30	88	30	90
22	4-(CH ₃) ₂ N C ₆ H ₄	1v	30	85	35	86

Method A: Reaction in EtOH–H₂O (1:1) under reflux.

Method B: Reaction in [bmim]BF₄ at 80 °C.



Scheme 2.

in water–ethanol (1:1, v/v) under reflux conditions and in ionic liquid at 80 °C. Mild reaction conditions, operational simplicity, enhanced rates, and high isolated yields of pure products are significant advantages of the protocol described here.

4. Experimental

4.1. General

The products were characterized by IR spectra, ^1H NMR, ^{13}C NMR, and mass spectra. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance Spectrospin 300 MHz using TMS as the internal standard. Mass spectra were recorded on KC-455-TOF mass spectrometer (Micromass, Manchester, and UK). Melting points were recorded on a Tropical Labequip apparatus and are uncorrected.

4.2. General procedure for the synthesis of 2H-indazolo[2,1-b]phthalazine-trione derivatives (1a–1v)

4.2.1. Method A

A mixture of phthalhydrazide (1.0 mmol), aldehyde (1.2 mmol), 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione (1.0 mmol), H_2SO_4 (0.15 mmol), and 10 mL H_2O –EtOH (1:1, v/v) was stirred magnetically under reflux for an appropriate time as mentioned in Table 1. After completion of the reaction as monitored by TLC using ethyl acetate–petroleum ether (60:40, v/v), the reaction mixture was allowed to cool to room temperature. The precipitate formed was collected by filtration at pump, washed with water, and dried. The crude product was washed well with hot ethanol to yield pure 2H-indazolo[2,1-b]phthalazine-trione derivatives.

4.2.2. Method B

Phthalhydrazide (1.0 mmol), aldehyde (1.2 mmol), 5,5-dimethyl-1,3-cyclohexanedione/1,3-cyclohexanedione (1.0 mmol), and H_2SO_4 (0.15 mmol) were placed in a 10 mL round-bottomed flask containing 0.5 mL of [bmim]BF₄. The mixture was stirred at 80 °C for an appropriate time as mentioned in Table 1. After completion of the reaction as monitored by TLC using ethyl acetate–petroleum ether (60:40, v/v), the reaction mixture was allowed to cool to room temperature and the reaction was quenched with water (~5 mL). The precipitate formed was collected by filtration at pump, washed with water, and dried. The filtrate was concentrated under

reduced pressure and dried at 100 °C to recover the ionic liquid for subsequent use. The crude product was washed well with hot ethanol to yield pure 2H-indazolo[2,1-b]phthalazine-trione derivatives.

4.3. Spectral data of all unknown products are given below

4.3.1. Compound 1g

^1H NMR (300 MHz, CDCl_3): δ = 8.25–8.35 (m, 2H), 7.82–7.85 (m, 2H), 6.84–7.35 (m, 4H), 6.42 (s, 1H), 3.76 (s, 3H), 3.23 and 3.42 (2H, AB system, J = 19.2 Hz), 2.34 (s, 2H), 1.21 (s, 6H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.23, 159.74, 156.07, 154.28, 150.75, 134.47, 133.47, 129.18, 128.98, 128.51, 128.36, 127.93, 127.71, 118.58, 114.14, 64.59, 55.21, 50.99, 38.07, 34.65, 28.71, 28.51. IR (ν_{max} , cm^{-1}) (KBr): 2959, 1655, 1626, 1363, 1314, 1267, 700. MS (ESI): m/z = 402. mp: 218–220 °C.

4.3.2. Compound 1h

^1H NMR (300 MHz, CDCl_3): δ = 8.22–8.39 (m, 2H), 7.75–7.92 (m, 6H), 7.42–7.48 (m, 3H), 6.61 (s, 1H), 3.27 and 3.46 (2H, AB system, J = 19.2 Hz), 2.33 (s, 2H), 1.236 (s, 6H). ^{13}C NMR (300 MHz, CDCl_3): δ = 196.85, 160.64, 159.03, 155.93, 139.34, 138.86, 138.45, 137.99, 137.79, 133.81, 133.67, 133.28, 132.88, 132.77, 132.39, 132.15, 131.65, 131.17, 131.12, 129.14, 122.86, 69.81, 55.63, 42.72, 39.39, 33.49, 33.10. IR (ν_{max} , cm^{-1}) (KBr): 2952, 1665, 1618, 1362, 1306, 1257, 697. MS (ESI): m/z = 422. mp: 251–252 °C.

4.3.3. Compound 1j

^1H NMR (300 MHz, CDCl_3): δ = 8.26–8.36 (m, 2H), 7.83–7.88 (m, 2H), 6.79–7.00 (m, 3H), 6.41 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.22 and 3.44 (2H, AB system, J = 19.2 Hz), 2.35 (s, 2H), 1.22 (s, 6H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.24, 156.12, 154.41, 150.76, 149.30, 134.53, 133.52, 129.16, 128.97, 128.79, 127.96, 127.74, 119.31, 118.52, 111.17, 111.05, 64.77, 55.98, 55.82, 50.99, 38.09, 34.64, 28.83, 28.33. IR (ν_{max} , cm^{-1}) (KBr): 2959, 1662, 1630, 1361, 1313, 1267, 699. MS (ESI): m/z = 432. mp: 185–186 °C.

4.3.4. Compound 1m

^1H NMR (300 MHz, CDCl_3): δ = 8.24–8.36 (m, 2H), 7.82–7.85 (m, 2H), 7.31–7.43 (m, 5H), 6.44 (s, 1H), 3.29–3.60 (m, 2H), 2.44–2.62 (m, 2H), 2.23–2.27 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.50, 156.01, 154.21, 152.29, 144.35, 136.33, 134.51, 133.52, 129.04, 128.65, 128.07, 127.95, 127.69, 119.64, 64.94, 36.89, 24.47, 22.26. IR (ν_{max} , cm^{-1}) (KBr): 2954, 1659, 1623, 1366, 1304, 1267, 702. MS (ESI): m/z = 344. mp: 222–224 °C.

4.3.5. Compound 1o

^1H NMR (300 MHz, CDCl_3): δ = 8.26–8.36 (m, 2H), 7.83–7.86 (m, 2H), 6.78–7.05 (m, 3H), 6.42 (s, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.34–3.61 (m, 2H), 2.45–2.51 (m, 2H), 2.24–2.30 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.59, 156.11, 154.35, 152.14, 149.29, 148.98, 134.53, 133.51, 129.15, 128.94, 128.77, 127.97, 127.74, 119.62, 119.00, 111.34, 111.15, 64.75, 56.04, 55.83, 36.97, 24.52, 22.34. IR (ν_{max} , cm^{-1}) (KBr): 2928, 1662, 1627, 1368, 1304, 1267, 699. MS (ESI): m/z = 404. mp: 205–206 °C.

4.3.6. Compound 1p

^1H NMR (300 MHz, CDCl_3): δ = 8.22–8.40 (m, 2H), 8.14–8.17 (m, 2H), 7.52–7.92 (m, 4H), 6.52 (s, 1H), 3.31–3.65 (m, 2H), 2.46–2.50 (m, 2H), 2.23–2.38 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.46, 164.62, 155.99, 154.65, 153.21, 148.53, 138.60, 134.78, 129.62, 128.27, 127.76, 123.69, 121.70, 118.26, 64.25, 36.79, 24.54, 22.23. IR (ν_{max} , cm^{-1}) (KBr): 2926, 1662, 1624, 1369, 1305, 1285, 697. MS (ESI): m/z = 389. mp: 228–230 °C.

4.3.7. Compound 1q

^1H NMR (300 MHz, CDCl_3): δ = 8.25–8.35 (m, 2H), 7.82–7.86 (m, 2H), 7.32–7.37 (m, 2H), 6.83–6.87 (m, 2H), 6.42 (s, 1H), 3.75 (s, 3H), 3.28–3.60 (m, 2H), 2.44–2.49 (m, 2H), 2.23–2.30 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.60, 159.73, 156.05, 154.22, 152.19, 134.48, 133.47, 129.16, 128.94, 128.55, 128.30, 127.93, 127.69, 119.65, 114.09, 64.58, 55.23, 36.96, 24.51, 22.34. IR (ν_{max} , cm^{-1}) (KBr): 2950, 1657, 1624, 1365, 1306, 1246, 703. MS (ESI): m/z = 374. mp: 254–255 °C.

4.3.8. Compound 1r

^1H NMR (300 MHz, CDCl_3): δ = 8.25–8.36 (m, 2H), 7.81–7.87 (m, 2H), 7.12–7.32 (m, 4H), 6.42 (s, 1H), 3.29–3.60 (m, 2H), 2.44–2.48 (m, 2H), 2.29 (s, 3H), 2.23–2.27 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.49, 156.06, 154.19, 152.12, 138.48, 134.45, 133.44, 133.34, 129.40, 129.17, 128.95, 127.93, 127.73, 127.06, 119.80, 64.84, 36.93, 24.49, 22.30, 21.20. IR (ν_{max} , cm^{-1}) (KBr): 2924, 1660, 1627, 1369, 1305, 1269, 701. MS (ESI): m/z = 358. mp: 244–246 °C.

4.3.9. Compound 1s

^1H NMR (300 MHz, CDCl_3): δ = 8.20–8.38 (m, 2H), 7.75–7.91 (m, 6H), 7.41–7.50 (m, 3H), 6.60 (s, 1H), 3.28–3.65 (m, 2H), 2.43–2.47 (m, 2H), 2.21–2.29 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.47, 156.12, 154.32, 152.30, 134.54, 133.68, 133.55, 133.45, 133.19, 129.10, 129.00, 128.65, 128.27, 128.00, 127.75, 127.67, 126.78, 126.32, 126.23, 124.36, 119.72, 65.17, 36.92, 24.55, 22.31. IR (ν_{max} , cm^{-1}) (KBr): 2924, 1661, 1626, 1367, 1304, 1264, 701. MS (ESI): m/z = 394. mp: 262–264 °C.

4.3.10. Compound 1t

^1H NMR (300 MHz, CDCl_3): δ = 8.83 (s, 1H), 8.23–8.35 (m, 2H), 7.83–7.86 (m, 2H), 7.23 (d, 2H, J = 8.7 Hz), 6.78 (d, 2H, J = 8.4 Hz), 6.37 (s, 1H), 3.35–3.60 (m, 2H), 2.46–2.47 (m, 2H), 2.24–2.28 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 197.29, 162.42, 160.57, 158.79, 157.08, 139.25, 138.28, 137.07, 133.73, 133.38, 132.66,

132.09, 131.80, 130.27, 124.18, 120.28, 69.25, 41.68, 29.16, 27.02. IR (ν_{max} , cm^{-1}) (KBr): 3424, 2899, 1642, 1612, 1371, 1310, 1279, 703. MS (ESI): m/z = 360. mp: 265–266 °C.

4.3.11. Compound 1u

^1H NMR (300 MHz, CDCl_3): δ = 8.25–8.36 (m, 2H), 7.84–7.87 (m, 2H), 7.39–7.43 (m, 2H), 6.99–7.04 (m, 2H), 6.43 (s, 1H), 3.27–3.62 (m, 2H), 2.45–2.53 (m, 2H), 2.24–2.33 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.37, 160.77, 155.74, 154.16, 152.49, 134.45, 133.53, 132.32, 132.27, 129.77, 129.06, 127.87, 127.38, 118.89, 115.49, 115.20, 64.06, 36.72, 24.29, 22.10. IR (ν_{max} , cm^{-1}) (KBr): 2925, 1660, 1621, 1370, 1305, 1284, 702. MS (ESI): m/z = 362. mp: 258–260 °C.

4.3.12. Compound 1v

^1H NMR (300 MHz, CDCl_3): δ = 8.25–8.34 (m, 2H), 7.80–7.83 (m, 2H), 7.26–7.29 (m, 2H), 6.63–6.66 (m, 2H), 6.40 (s, 1H), 3.35–3.61 (m, 2H), 2.89 (s, 6H), 2.46–2.48 (m, 2H), 2.24–2.28 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3): δ = 192.59, 156.12, 154.12, 151.89, 150.64, 134.34, 133.28, 129.39, 128.98, 128.92, 128.21, 127.84, 127.70, 123.41, 119.95, 112.40, 112.26, 64.83, 40.64, 40.36, 37.02, 24.53, 22.39. IR (ν_{max} , cm^{-1}) (KBr): 2923, 1661, 1616, 1364, 1305, 1280, 699. MS (ESI): m/z = 387. mp: 256–258 °C.

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