# 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

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Synthesis of 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitriles by a one-pot green and an eco-friendly reaction of phthalic acid, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of $Et_3N$ as catalyst and Glycerol mediated at 100-105 °C for 45-60 min. This one-pot reaction proceeded in a short time with good yields and the desired products obtained without using column purifications.

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## INTRODUCTION

Multi-component reactions (MCRs) are one-pot processes in which three or more compounds react in a single reaction vessel to form a product containing substantial components of all the reactants.[1] Thus, design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of steps in the synthesis of compounds with interesting properties is essential for drug discovery and synthesis of natural products.[2] MCRs have attracted much attention in combinatorial and medicinal chemistry and have been designed to produce biologically active compounds.[3,4]

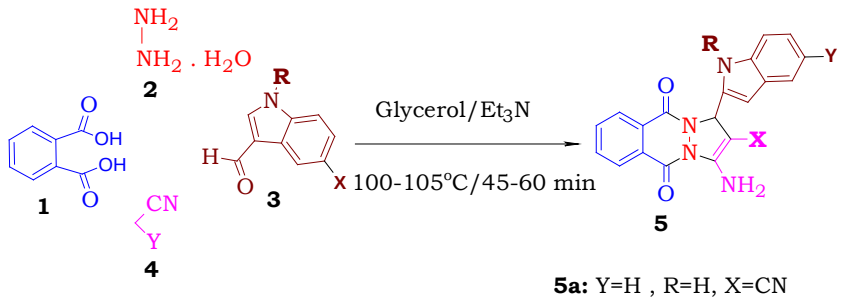
Phthalazines are important heterocycles that are known to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer and anti-inflammatory.[5] Carling et al. reported[6] the synthesis of 3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazines and analogs which were found to be a critical structural element of specific CNS - active drugs. Jain et al. reported[7] the synthesis of keto-glutamine tetrapeptide analogs containing a 2-oxopyrrolidine ring as a glutamine side chain mimic which showed improved inhibition against hepatitis A virus 3C proteinase. Grasso et al. reported[8] the synthesis of 6,7-methylenedioxyphthalazin-1(2H)-ones which were found to be potent anticonvulsant agents. Nomoto et al. reported[9] the synthesis of 6,7-dimethoxyphthalazine derivatives which showed relatively potent cardiotonic activity comparable to that of amrinone. Watanabe et al. reported[10] the synthesis of 4-benzylamino-1-chloro-6-substituted phthalazines which were found to be vasorelaxant and some methods have been reported for the synthesis of phthalazine derivatives.[11] Therefore, it was considered worthwhile to synthesize phthalazine moiety containing 4H-pyrans.

Keeping above discussion in our mind, we now wish to report 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivatives by reaction of phthalic acid, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of $Et_3N$ as catalyst and glycerol as a medium at 100-105 °C for 30-60 min.

## RESULTS AND DISCUSSION:

Firstly, we have initiated the optimization of the one-pot four-component reaction by using phthalic acid (**1**) and hydrazine hydrate (**2**) to in-situ formation of phthalic hydrazide as intermediate in the presence of $Et_3N$ and glycerol medium. To this reaction mixture, 5-nitroindole-3-carboxaldehyde (**3a**) and malononitrile (**4a**) were added for preparation of 3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5a**) in the presence of different solvents (glycerol, ethylene glycol and DMF) and different bases ($Et_3N$ and pyridine) at different temperature (RT, 50 °C, 100 °C and 120 °C) as a simple model reaction (Table 1 entries 1–3). However, it was found that the one-pot reaction of **1** (10 mM), **2** (10 mM), **3a** (10 mM) and **4a** (10 mM) in the presence of $Et_3N$ (2 mM) as catalyst and glycerol (50 ml) as medium for 45 min at 100 °C gave the highest yield (88 %) and clean product (**5a**) (Table 1, entry 1). 1H-NMR, IR and mass spectroscop**5a**y have confirmed the structure of the compound **5a**.

In order to examine the quantity of $Et_3N$, the one-pot reaction has been carried out at different quantity (1 mM, 2 mM and 5 mM) of $Et_3N$ with respect of phthalic acid 1. However, it was found that the one-pot reaction of **1** (10 mM), **2** (10 mM), **3a** (10 mM) and **4a** (10 mM) in the presence of $Et_3N$ (2 mM) as catalyst and glycerol medium (50 ml) for 45 min at 100-105 °C gave the highest yield (88 %) (Table 2, entry 2).




**3a:** X=H , R=H
**3b:** X=$NO_2$, R=H
**3c:** X=H , R=$CH_3$
**3d:** X=H , R=$C_2H_5$

Y= CN, COOEt

**5a:** Y=H , R=H, X=CN
**5b:** Y=$NO_2$, R=H, X= CN
**5c:** Y=H , R=$CH_3$, X=CN
**5d:** Y=H , R=$C_2H_5$, X=CN
**5e:** Y=$NO_2$, R=H, X=COOEt
**5f:** Y=H, R=H, X=COOEt
**5g:** Y=H, R=$CH_3$, X=COOEt
**5h:** Y=H, R=$C_2H_5$, X=COOEt

**Scheme 1.** The general reaction route to prepare the pyrazolo[1,2-b]phthalazine derivatives

In the next step, the scope of the reaction process was explored, using the best-optimized conditions by changing the phthalic acid, the aldehyde & the nitrile (Table 3). The results are displayed in Table 3. The structures of the products were assigned on the basis of their spectral properties - IR, NMR and mass spectra (for details, please see the experimental section).

**Table 1.** Effect of solvent/catalyst and temperature on the one-pot reaction of 1, 2, 3a and 4a at RT yielding 5a.

| No. | Solvent/Catalyst | T, ºC | Time, min | Yield 5a, % |
|---|---|---|---|---|
| 1 | Glycerol/$Et_3N$ | 100 | 45 | 88 |
| 2 | Ethylene glycol /$Et_3N$ | 100 | 55 | 80 |
| 3 | DMF/$Et_3N$ | 100 | 100 | 80 |
| 4 | Glycerol/pyridine | 100 | 40 | 80 |
| 5 | Ethylene glycol/pyridine | 100 | 50 | 78 |
| 6 | DMF/pyridine | 100 | 90 | 72 |
| 7 | Glycerol/$Et_3N$ | RT | 300 | 85 |
| 8 | Ethylene glycol/$Et_3N$ | RT | 320 | 82 |
| 9 | DMF/$Et_3N$ | RT | 450 | 78 |
| 10 | Glycerol/$Et_3N$ | 50 | 80 | 82 |
| 11 | Ethylene glycol/$Et_3N$ | 50 | 85 | 81 |
| 12 | DMF/$Et_3N$ | 50 | 100 | 79 |
| 13 | Glycerol/$Et_3N$ | 120 | 40 | 75 |
| 14 | Ethylene glycol/$Et_3N$ | 120 | 45 | 70 |
| 15 | DMF/$Et_3N$ | 120 | 60 | 73 |

A schematic mechanism for the catalytic activity of $Et_3N$ in the synthesis of titled compounds **5** can be postulated as shown in Scheme 2. This mechanism contains three steps. In the first step, the formation of phthalic hydrazide (**X1**) by nucleophilic addition of hydrazine hydrate (**2**) to phthalic acid (**1**) takes place followed by dehydration. The second step involves forming heterodiene (**Y1**) by standard Knoevenagel condensation of indole-3-carboxaldehyde (**3**) and malononitrile/ethyl cyanoacetate (**4**). Then, in the third step, Michael-type addition of the phthalic hydrazide **X1** to heterodiene **Y1** takes place forming the intermediary iminomethylene derivative **Z** which undergoes cyclisation affording 5.

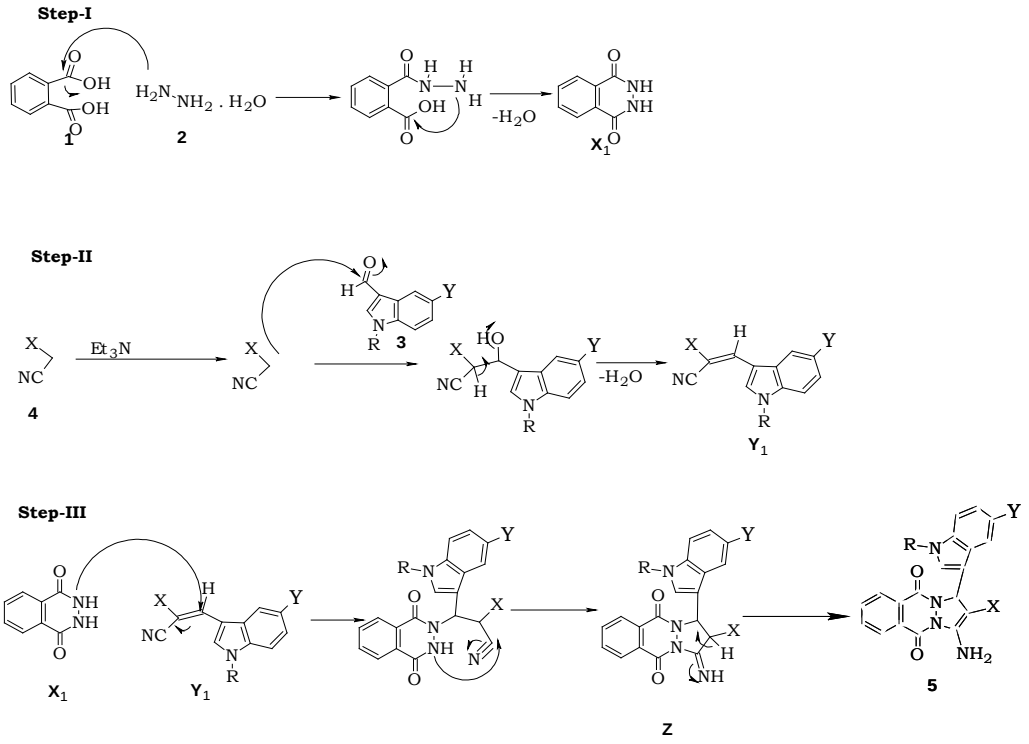
**Table 2.** Effect of $Et_3N$ catalyst quantity on the one-pot reaction of 1, 2, 3a and 4a at 100-105 ºC yielding 5a in glycerol.

| No. | Catalyst concentration | T, ºC | Time, min | Yield, 5a, % |
|---|---|---|---|---|
| 1 | 1 mM | 100 | 120 | 75 |
| 2 | 2 mM | 100 | 45 | 88 |
| 3 | 5 mM | 100 | 40 | 78 |

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

| Starting materials (1, 2, 3 and 4) | | Product | Time, min | Yield, % |
|---|---|---|---|---|
| **3a** (R=H, Y=$NO_2$) | **4a** (X= CN) | **5a** | 45 | 88 |
| **3b** (R=H, Y=H) | **4a** (X= CN) | **5b** | 48 | 86 |
| **3c** (R=$CH_3$,Y=H) | **4a** (X= CN) | **5c** | 50 | 85 |
| **3d** (R=$C_2H_5$,Y=H) | **4a** (X= CN) | **5d** | 55 | 84 |
| **3a** (R=H, Y=$NO_2$) | **4b** (X=COOEt) | **5e** | 50 | 87 |
| **3b** (R=H, Y=H) | **4b** (X=COOEt) | **5f** | 60 | 86 |
| **3c** (R=$CH_3$,Y=H) | **4b** (X=COOEt) | **5g** | 60 | 84 |
| **3d** (R=$C_2H_5$,Y=H) | **4b** (X=COOEt) | **5h** | 60 | 86 |

≠ Refers to yields of crude products only.




**Scheme 2.** A plausible mechanism for **5** from **1**, **2**, **3** and **4**.

## EXPERIMENTAL SECTION

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 vapor 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 at 400 MHz operating frequency. Mass spectra were recorded on an Agilent-LC-MS instrument.

**General procedure for preparation of 5**

Phthalic acid (**1**) (10 mM) and hydrazine hydrate (**2**) (10 mM) were charged in glycerol (50 ml) in the presence of $Et_3N$ (3 mM) and heated for 10 min at 100-105 °C to form phthalic acid hydrazide. Then, 5-nitroindole-3-carboxaldehydes (**3a**) (10 mM) and malononitrile/ethylcyano acetate (**4**) (10 mM) were added to this reaction mixture and again heated for 20-35 min (until no starting materials could be detected on thin-layer chromatography). After the reaction was completed, cold water was added to the reaction mixture and solid part was separated by filtration. The product was recrystallised from ethanol solvent to obtain **5**.

**3-Amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5a)**

M.p.:>220 °C; IR (KBr): 3116-3440 cm$^{-1}$ (broad, medium, -NH group), 2218 (sharp, strong, -CN group), 1669 cm$^{-1}$ (sharp, strong, -CO of amide group ), 1686 cm$^{-1}$ (sharp, strong, -CO of amide group);

$^1$H-NMR (DMSO-$d_6$, 400 MHz): δ 5.67 (s, 1H, -CH), 7.26-8.68 (m, 10H, Ar-H and $NH_2$), δ 11.87 (s, 1H, -NH,); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 61.5, 69.1, 110.6, 111.5, 115.8, 115.9, 119.2, 122.9, 123.6, 127.6, 134.6, 135.6, 138.4, 144.6, 145.8, 161.6, 164.5; $[M+H]^+$: 400

**3-Amino-1-(1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5b)**

M.p.: >220 °C; IR (KBr): 3116-3440 cm$^{-1}$ (broad, medium, -NH group), 2218 (sharp, strong, -CN group), 1669 cm$^{-1}$ (sharp, strong, -CO of amide group ), 1686 cm$^{-1}$ (sharp, strong, -CO of amide group); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ 5.67 (s, 1H, -CH), 7.26-8.68 (m, 11H, Ar-H and $NH_2$), δ 11.87 (s, 1H, -NH); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 61.0, 69.0, 110.1, 111.5, 115.9, 119.2, 122.9, 123.9, 127.3, 134.6, 135.8, 138.4, 144.6, 145.8, 161.0, 164.5; $[M+H]^+$: 356

**3-Amino-1-(1-methyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5c)**

M.p.:>220 °C; IR (KBr) 2213 (sharp, strong, -CN group), 1668 cm$^{-1}$ (sharp, strong, -CO- of amide group ), 1682 cm$^{-1}$ (sharp, strong, -CO of amide group); $^1$H- NMR (DMSO-$d_6$, 400 MHz): δ 2.20 (s, 3H, -$CH_3$), 5.30 (s, 1H, -CH), 7.21-8.68 (m, 11H, Ar-H and $NH_2$); $^{13}$C-NMR (DMSO-$d_6$, 400 MHz): δ 23.4, 60.1, 68.1, 111.3, 111.4, 114.8, 118.1, 122.9,

123.6, 127.4, 133.5, 134.7, 138.3, 144.2, 145.9, 161.4, 164.4; $[M+H]^+$: 370

**3-Amino-1-(1-ethyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5d)**

M.p.:>220 °C; IR (KBr) 2216 (sharp, strong, -CN group), 1663 $cm^{-1}$ (sharp, strong, -CO of amide group ), 1678 $cm^{-1}$ (sharp, strong, -CO of amide group); $^1$H- NMR (DMSO-$d_6$, 400 MHz): δ 1.81 (t, 3H, $CH_3$) 2.22 (q, 2H, -$CH_2$), 5.26 (s, 1H, -CH), 7.21-8.94 (m, 11H, Ar-H and $NH_2$); $^{13}$C-NMR (DMSO-$d_6$, 400 MHz): δ 19.2, 23.2, 60.4, 68.5, 111.2, 111.5, 114.2, 118.2, 122.4, 123.2, 127.1, 133.0, 134.3, 138.2, 144.0, 145.2, 161.5, 164.9; $[M+H]^+$: 384

**Ethyl-3-amino-1-(5-nitro-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5e)**

M.p.:>220 °C; IR (KBr): 3076-3360 $cm^{-1}$ (broad, medium, -NH group), 2297 (sharp, strong, -CN group), 1660 $cm^{-1}$ (sharp, strong, -CO of amide group ), 1666 $cm^{-1}$ (sharp, strong, -CO of amide group); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.32 (t, 3H, -$CH_3$ ), 4.46 (q, 2H, -$CH_2$), 6.02 (s, 1H, -CH), 7.20-8.69 (m, 10H, Ar-H and $NH_2$), δ 11.79 (s, 1H, -NH,); $^{13}$C-NMR (DMSO-$d_6$, 400 MHz): δ 14.0, 61.9, 69.1, 74.0, 110.6, 111.1, 115.8, 115.9, 119.1, 122.9, 123.6, 127.1, 134.6, 135.7, 140.6, 143.7, 151.6, 155.6; $[M+H]^+$: 402

**Ethyl-3-amino-1-(1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5f)**

M.p.:>220 °C; IR (KBr): 3112-3453 $cm^{-1}$ (broad, medium, -NH group), 2204 (sharp, strong, -CN group), 1668 $cm^{-1}$ (sharp, strong, -CO of amide group ), 1672 $cm^{-1}$ (sharp, strong, -CO of amide group) ; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.24 (t, 3H, -$CH_3$ ), 4.18 (q, 2H, -$CH_2$), 5.42 (s, 1H, -CH), 7.22-8.68 (m, 11H, Ar-H and $NH_2$), δ 11.78 (s, 1H, -NH,); $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 15.3, 55.2, 60.5, 68.1, 110.3, 111.4, 115.0, 117.2, 122.0, 123.5, 127.2, 133.0, 134.9, 137.3, 142.5, 144.5, 150.1, 156.4; $[M+H]^+$: 403

**Ethyl-3-amino-1-(1-methyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate (5g)**

M.p.:>220 °C; IR (KBr) 2213 (sharp, strong, -CN group), 1664 $cm^{-1}$ (sharp, strong, -CO of amide group ), 1683 $cm^{-1}$ (sharp, strong, -CO of amide group) ; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.12 (t, 3H, -$CH_3$), 2.24 (s, 3H, -$CH_3$), 4.00 (q, 2H, -$CH_2$), 5.42 (s, 1H, -CH), 7.22-8.64 (m, 11H, Ar-H and $NH_2$); $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 15.3, 22.5, 56.3, 61.4, 67.0, 111.4, 113.5, 114.7, 118.0, 122.0, 122.7, 125.0, 132.4, 134.6, 138.0, 144.1, 143.5, 152.2, 153.5; $[M+H]^+$: 417

**Ethyl-3-amino-1-(1-ethyl-1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate (5h)**

M.p.:>220 °C; IR (KBr): 2215 $cm^{-1}$ (sharp, strong, -CN group), 1666 $cm^{-1}$ (sharp, strong, -CO of amide group ), 1673 $cm^{-1}$ (sharp, strong, -CO of amide group); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.18 (t, 3H, -$CH_3$ ), 1.69 (t, 3H, $CH_3$) 2.39 (q, 2H, -$CH_2$), 4.15 (q, 2H, -$CH_2$), 5.26 (s, 1H, -CH), 7.22-8.93 (m, 11H, Ar-H and $NH_2$); $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 15.2, 19.4, 23.6, 54.3, 60.2, 68.4, 111.5, 111.7, 114.0, 118.1, 122.3, 124.1, 126.8, 133.4, 134.9, 138.1, 144.2, 145.5, 151.6, 154.6; $[M+H]^+$: 431

## CONCLUSION

In summary, a novel method to prepare 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 derivatives have been developed by the reaction of phthalic acid, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of $Et_3N$ and glycerol mediated at 100-105 °C for 30-60 min. This one-pot reaction proceeds in a short time with good yields and the desired products obtained without using column chromatographic purifications.

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