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An efficient one-pot four-component synthesis of 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-dione derivatives catalyzed by proline

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The present report articulates a potential and green method for the synthesis of pyrazolo[1,2-*b*]phthalazine-5,10-dione by one-pot four component reaction involving phthalimide (**1**), hydrazine hydrate (**2**), aldehyde (**3**) and malononitrile (**4**). Proline has been utilized as organo-catalyst in a mixed solvent of ethanol and water in the ratio of 2:1 at 80°C. The reaction reveals excellent reactivity, functional group tolerance, and quite high yields without using any extreme reaction condition like strong acid or metal catalyst. Eighteen compounds have been synthesised by this method including five new compounds.

Keywords: Multi-component reactions, phthalimide, hydrazine hydrate, malononitrile, aldehyde, proline

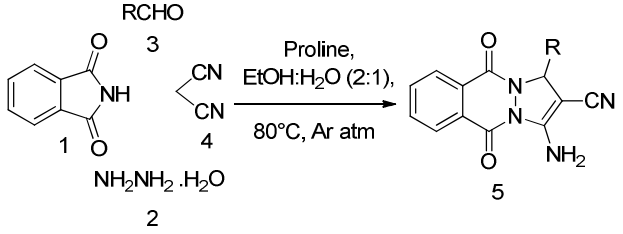
Multi-component reactions (MCRs) are one of those special types of synthetic organic reactions that three or more simple starting materials are allowed to react in one pot to produce rather complex useful products. These reactions have been widely used in synthetic chemistry for generating carbon-carbon and carbon-heteroatom bonds[1] to produce highly functionalized organic molecules from readily available starting molecules in a single step with inherent flexibility for creating molecular complexity and diversity[2]. In general, MCR satisfies principles of green chemistry including economy of steps as well as many criteria of an ideal organic synthesis. Therefore, others development of MCR protocols for the synthesis of heterocyclic compounds have attracted significant attention of the pharmaceutical industry due to the fact that the polyfunctionalized heterocycles substantially take part in the drug discovery process[3].

Nitrogen-containing heterocyclic compounds have attracted prime interest because of their wide-spread applications in bioactive pharmaceuticals, agrochemicals, and functional materials[4-6]. The development of efficient methods to synthesize N-heterocycles with structural diversity is one of the active areas of research for modern synthetic organic chemists[7–9]. Among the large variety of nitrogen-containing heterocyclic compounds, pyrazoles are important class of compounds for new drug development, as they resembles the core structure of numerous biologically active compounds, including blockbuster drugs such as celecoxib, viagra, pyrazofurine, and many others[10-14]. Furthermore, heterocycles containing a phthalazine moiety are of current interest due to their biological and pharmacological activities[15,16] such as anticonvulsant[17], cardiotonic[18], and vasorelaxant[19] activities. Likewise, the titled compounds, 1*H*-pyrazolo[1,2-*b*]phthalazine-dione is reported as an anti-inflammatory, analgesic, antihypoxic, and anti-pyretic agent[20]. Therefore, the development of simple methods for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione demands serious attention.

Literature consists of several multicomponent synthetic routes for 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives including one-pot three components reaction of phthalhydrazide, aromatic aldehyde, and malononitrile or ethyl cyanoacetate using $NaHCO_3$[21], Et_3N[22], mesoporous solid acid catalysts (Al-KIT-6)[23], [bmim]Br/PTSA[24], [Bmim]OH[25], $InCl_3$[26], CAN[27], TBBDA and PBBS[28], SBA@$BiPy^{2+}2Cl^-$ [29], hydroxyapatite-coated $Ni_{0.5}Zn_{0.5}Fe_2O_4$ magnetic nanoparticles (NZF@HAP-Cs)[30], (SBA-Pr-SO_3H)[31], crown ether complex cation ionic liquids (CECILs)[32], silica gel-supported tungstic acid (STA)[33], protic ionic liquids (PILs)[34]. Electrocatalytic multicomponent transformation of phthalhydrazide, aromatic aldehydes and malononitrile in *n*-propanol in an undivided cell in the presence of sodium bromide as an electrolyte resulting in generation of 1*H*-

pyrazolo[1,2-*b*] phthalazine-5,10-diones[35]. Recently, catalyst-free reaction condition has been generated by Deshmukh *et al.* using glycerol as solvent[36]. Additionally two other methods have also been developed for one-pot four component synthesis of these heterocyclic compounds catalyzed by $NiCl_2.6H_2O$[37], PEG-OSO_3H[38]. Preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by the four-component condensation reaction of phthalic anhydride, hydrazine monohydrate, aromatic aldehydes and malononitrile/ethyl cyanoacetate was established under solvent-free conditions in presence of CuI nanoparticles[39], weak basic ionic liquids containing 1,8-diazabicyclo [5.4.0]-undec-7-en-8-ium acetate (DBU[CH_3COO]), pyrrolidinium formate ([Pyrr][HCOO]) and pyrrolidinium acetate ([Pyrr][CH_3COO])[40], magnetic Fe_3O_4 nanoparticles coated by (3-aminopropyl)-triethoxysilane[41]. Many of these above mentioned methods compromise one or more disadvantages such as the use of expensive moisture sensitive metallic reagents, ionic liquids and catalysts, longer reaction times, use of toxic solvent and large amount of catalyst loading which in turn results in the generation of huge amount of metal wastes into the environment. Hence the development of a green, easy efficient method for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione is still a challenging task. Recently proline has been effectively used as a versatile organo-catalyst in view of its remarkable ability to catalyze organic transformations such as Mannich, Knoevenagel and Michael type reactions by carbonyl activation through enamine-iminium ion intermediate formation[42].

In continuation of our efforts towards the development of novel MCRs methodologies under green chemical approaches, herein we wish to report a mild, efficient, and facile one-pot synthesis of 3-amino-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile derivatives (Scheme I) through the four component condensation of phthalimide (**1**), hydrazine hydrate (**2**), benzaldehyde (**3**) and malononitrile (**4**), catalyzed by proline, an organo-catalyst. Following this protocol, five new compounds have been synthesized using aliphatic or aromatic aldehydes.



Scheme I

Results and Discussion

In order to optimize the reaction, we have tried different reaction conditions. It was observed that in absence of any catalyst, reaction proceeds smoothly with moderate yield for aldehyde containing electron withdrawing group in ethanol medium. When the same reaction was carried out with aldehyde containing electron donating group, the expected product was obtained in very low yield (Table I). Therefore, at first the four-component reaction of phthalimide, hydrazine hydrate, methylbenzaldehyde and malonitrile was investigated as a model reaction in ethanol and in presence of 5 mol % of proline catalyst.

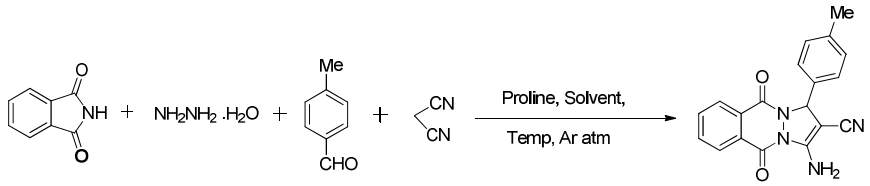
The catalyst loading on the model reaction was examined. When 5 mol % of catalyst was used, the desired compound was obtained with moderate yield, 69% (Table II, entry 1). On increasing the catalyst loading up to 10 mol % led to a very good yield of 78% (Table II, entry 2), however no further enhancement of product was observed by further increasing the catalyst loading to 15-20 mol %, which gave a yield of 73-72% (Table II, entry 3, 4). Therefore, 10 mol % of proline was used as an optimized catalyst loading for further study. The use of proline (10 mol %) in different solvents promoted the reaction to a reasonable extent (16-78%) in 40-100°C; whereas the mixed solvent system of ethanol and H_2O in a ratio of 2:1 brought about an excellent conversion (87%) at 80°C (Table II, entry 14). Encouraged by this observation, the reaction was explored in detail by varying the temperature and solvent systems. After examining the reaction at different temperature and also in mixed solvent system, it was found that the best result was

Table I — Synthesis of 3-amino-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivatives using catalyst-free condition [a]

Entry	R	Time (h)	Yield[b] (%)
1	4-Nitrophenyl	4	62
2	4-Chlorophenyl	4	48
3	4-Fluorophenyl	4	45
4	4-Tolyl	12	16
5	4-Methoxyphenyl	12	18

[a] Reaction condition: Phthalimide (1.0 mmol), Hydrazine hydrate (1.0 mmol), Ethanol (3.0 mL), 2 h; Then aldehydes (1.0 mmol) and malononitrile (1.0 mmol) added. [b] Isolated yields.

Table II — The effect of different conditions on the model reaction [a]



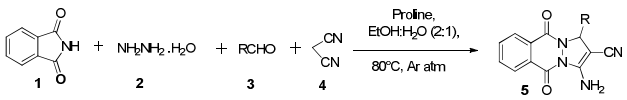
Entry	Proline (mol %)	Solvent	Temp (°C)	Time (min)	Yield [b] (%)
1	5	EtOH	80	30	69
2	10	EtOH	80	30	78
3	15	EtOH	80	30	73
4	20	EtOH	80	30	72
5	10	MeOH	65	60	65
6	10	^{i}PrOH	80	60	66
7	10	Acetone	60	240	–
8	10	DCM	40	60	47
9	10	AcCN	80	60	40
10	10	THF	70	60	53
11	10	H_2O	80	30	55
12	10	EtOH:H_2O (1:1)	80	30	80
13	10	EtOH:H_2O (1:2)	80	30	76
14	10	EtOH:H_2O (2:1)	80	30	87
15	10	EtOH:H_2O (2:1)	100	30	80
16	10	EtOH:H_2O (2:1)	70	30	68
17	10	EtOH:H_2O (2:1)	60	30	56

[a] Reaction conditions: Phthalimide (1.0 mmol), hydrazine hydrate (1.0 mmol), solvents (3.0 mL), 1 h; Then aldehydes (1.0 mmol) and malononitrile (1.0 mmol) added. [b] Isolated yields.

obtained at 80°C in the above mentioned mixture of water and ethanol.

In order to extend the scope of the above reaction (Scheme I) to generate a library of the title compounds, various kind of aldehydes (**3a-r)**, were subjected to react with phthalimide (**1**), hydrazine hydrate (**2**), malononitrile (**4**) to give the corresponding 3-amino-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivatives (**5a-r**) (Table III). All the aromatic aldehydes **3a-r** gave the expected products in high yields. From the Table III it was found that the electron withdrawing groups in the aromatic aldehydes gave better yield than with the electron donating groups under similar conditions. Aliphatic aldehyde (Table III, entry 18) showed significant reactivity and gave 83% yield, even though they have the enolisable hydrogen atom. Various functional groups were found to be compatible under the reaction condition. In general, this protocol offers flexibility in tuning the molecular complexity and diversity. The reaction proceeds smoothly and pure products were obtained, without using any chromatographic separation techniques, simply by recrystallization from ethanol. Structures of all the compounds were characterized by ^{1}H and ^{13}C NMR and HRMS.

Table III — Proline catalyzed synthesis of 3-amino-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivatives [a]



Entry	Product (**5**)	R	Time (min)	Yield [b] (%)
1	**5a**	Phenyl	35	90
2	**5b**	4-Cyanophenyl	25	96
3	**5c**	4-Nitrophenyl	24	95
4	**5d**	3-Nitrophenyl	23	93
5	**5e**	4-Chlorophenyl	28	88
6	**5f**	3-Chlorophenyl	24	82
7	**5g**	2,5-Dichlorophenyl	38	83
8	**5h**	5-chloro-2-nitrophenyl	36	86
9	**5i**	4-Bromophenyl	27	90
10	**5j**	3-Bromophenyl	33	93
11	**5k**	4-Fluorophenyl	28	94
12	**5l**	4-Methylphenyl	30	87
13	**5m**	4-Methoxylphenyl	34	91
14	**5n**	3,4-Dimethoxyphenyl	40	77
15	**5o**	3,4,5-Trimethoxyphenyl	45	89
16	**5p**	2,6-Dichlorophenyl	60	66
17	**5q**	1-Naphthyl	85	62
18	**5r**	Cyclohexyl	77	83

[a] Reaction conditions: Phthalimide (1.0 mmol), Hydrazine hydrate (1.0 mmol), Solvent (3.0 mL), 1 h; Then aldehydes (1.0 mmol) and malononitrile (1.0 mmol) added. [b] Isolated yields

Experimental Section

All reactions were carried out under argon atmosphere using oven-dried reaction vessels. Unless otherwise noted, all commercially available compounds were used as purchased without further purification. All aldehydes were purified either by distillation or washing with $NaHCO_3$ after dissolving in ether before use. ^{1}H NMR spectra were recorded as solutions in DMSO-d_6. Chemical shifts are expressed in parts per million (δ, ppm) with reference to the residual chloroform in DMSO-d_6 (δ 3.35) as an internal standard. All coupling constants are absolute values and are expressed in Hz. The description of the signals in ^{1}H NMR include: s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet and dd = doublet of doublets. ^{13}C NMR spectra were recorded in a solution of DMSO-d_6 with complete proton decoupling. High-Resolution Mass Spectra (HRMS) were performed with a Qtof Micro YA263 spectrometer. IR (infrared spectroscopy) was recorded in an FT-IR spectrometer; the IR spectra of solid compounds were recorded in KBr pellet. The reactions were monitored routinely with pre-coated silica gel on aluminum plates (Merck), which were analyzed with $KMnO_4$ solution. Solvents, reagents and chemicals were purchased from Aldrich, Merck, SRL, Spectrochem and Process Chemicals.

General procedure for the synthesis of compounds, 5a-r

A mixture of phthalimide (1.0 mmol) and hydrazine hydrate (1.0 mmol) in ethanol (1.0 mL) was stirred under reflux for 1 h. Then aldehyde (1.0 mmol), malononitrile (1.0 mmol) and proline (0.10 mmol) in mixed solvent of ethanol and water (2.0 mL, ratio 1:1) were added, and the mixture was refluxed for a specified time. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to RT. The residue precipitated during the process was filtered, and the filter cake was washed with ethanol and residue was recrystallized from ethanol to afford the pure product **5**.

Spectral data

The structures of all the products were confirmed from physical and spectroscopic data such as melting points, IR, ^{1}H and ^{13}C NMR spectra and mass spectra. Spectroscopic data for a selected compound (**5a**) is given below.

3-Amino-5,10-dioxo-1-phenyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 1): Yellow powder solid, Yield 90%. m.p.275-277°C (lit. 276–278°C)[24]. IR (KBr): 3360, 2198, 1651, 1567, 1439, 1384, 1248, 1167, 1028, 955, 784, 703, 691 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.11 (s, 1H), 7.28-7.37 (m, 3H), 7.43-7.45 (m, 2H), 7.94-7.97 (m, 2H), 8.05-8.09 (m, 3H), 8.23-8.26 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 61.9, 63.5, 116.5, 127.2, 127.3, 127.8, 128.8, 129.0, 129.1, 129.3, 134.2, 135.1, 138.9, 151.1, 154.1, 157.1; HRMS (ES$^+$): Calcd for $[C_{18}H_{12}N_4O_2]Na^+$: 339.0853. Found: 339.0856.

3-Amino-1-(4-cyanophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 2): Yellow powder solid, Yield 96%. m.p.275-277°C. IR (KBr): 3363, 2202, 1650, 1573, 1438, 1376, 1250, 1176, 1031, 945, 776, 701, 695 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.21 (s, 1H), 7.70 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 2H), 7.96-7.98 (m, 2H), 8.05-8.09 (m, 1H), 8.14 (bs, 2H), 8.24-8.26 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.9, 62.8, 111.5, 116.3, 119.1, 127.2, 127.8, 128.2, 128.9, 129.5, 133.1, 133.4, 134.3, 135.1, 144.4, 151.4, 154.3, 157.2; HRMS (ES$^+$): Calcd for $[C_{19}H_{11}N_5O_2]$ Na$^+$: 364.0805. Found: 364.0803.

3-Amino-1-(2,5-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 7): Yellow powder solid, Yield 83%. m.p.238-240°C. IR (KBr): 3357, 3176, 2204, 85, 1652, 1563, 1471, 1384, 1281, 1141, 1053, 852, 787, 694 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.43 (s, 1H), 7.40-7.42 (m, 1H), 7.65-7.69 (m, 2H), 7.96-7.99 (m, 2H), 8.06-8.09 (m, 1H), 8.17 (bs, 2H), 8.25-8.28 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 59.8, 60.6, 116.0, 127.2, 127.8, 128.5, 128.8, 129.3, 129,6, 132.8, 134.1, 134.4, 135.0, 135.2, 151.7, 154.1, 157.2; HRMS (ES$^+$): Calcd for $[C_{18}H_{10}Cl_2N_4O_2]Na^+$: 407.0074. Found: 407.0077.

3-Amino-1-(5-chloro-2-nitrophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 8): Dark yellowish powder solid, Yield 86%. m.p.265-267°C; IR (KBr): 3376, 3179, 2212, 1683, 1657, 1528, 1412, 1380, 1275, 1141, 1031, 844, 722, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.56 (s, 1H), 7.67 (dd, J = 8.8 Hz, 2.2Hz, 1H), 7.95-7.98 (m, 2H), 8.04-8.10 (m, 3H), 8.21 (bs, 2H), 8.26-8.28 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 58.5, 59.5, 116.1, 126.9, 127.1, 127.7, 128.7, 129.1, 129.8, 130.3, 134.4, 135.1, 136.0, 139.7, 147.4, 152.3, 154.5, 157.3; HRMS (ES$^+$): Calcd for $[C_{18}H_{10}ClN_5O_4]Na^+$: 418.0314. Found: 418.0313.

3-Amino-1-(2,6-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 16): Light yellowish powder solid, Yield 66%. m.p.267-269°C (lit. 268-270°C)[2b]. IR (KBr): 3399, 3271, 2200, 1683, 1652, 1560, 1414, 1374, 1279, 1144, 1030, 787, 706, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 6.91 (s, 1H), 7.39-7.44 (m, 2H), 7.60-7.62 (m, 1H), 8.00-8.03 (m, 2H), 8.10-8.11 (m, 1H), 8.26 (bs, 2H), 8.29-8.32 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.9, 59.8, 115.7, 127.3, 128.0, 128.3, 128.8, 129.5, 129.6, 130.7, 131.0, 131.3, 133.1, 134.6, 135.6, 135.6, 152.5, 153.8, 157.1; HRMS (ES^+): Calcd for $[C_{18}H_{10}Cl_2N_4O_2]Na^+$: 407.0074. Found: 407.0076.

3-Amino-1-(naphthalen-1-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 17): Dark yellowish powder solid, Yield 62%. m.p.181-183°C (lit. 182-184°C)[7]. IR (KBr): 3363, 3232, 2199, 1656, 1544, 1478, 1372, 1265, 1147, 1037, 956, 788, 700, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): 6.98 (s, 1H), 7.44-7.49 (m, 1H), 7.54-7.64 (m, 3H), 7.89-8.06 (m, 5H), 8.11 (bs, 2H), 8.29-8.32 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 62.3, 116.4, 123.3, 126.2, 126.4, 126.9, 127.2, 127.9, 129.0, 129.3, 130.5, 133.9, 134.3, 135.3, 151.2, 157.3; HRMS (ES^+): Calcd for $[C_{22}H_{15}N_4O_2]^+$: 367.1190. Found: 367.1190.

3-Amino-1-cyclohexyl-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (Table III, entry 18): Yellow powder solid, Yield 83%, m.p.274-275°C. IR (KBr): 3364, 2929, 2188, 1652, 1381, 1276, 1163, 1029, 954, 894, 786, 691 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.07-1.74 (m, 10H), 2.25-2.29 (m, 1H), 5.17 (s, 1H), 7.95-7.99 (m, 4H), 8.19-8.21 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.2, 26.4, 26.5, 28.6, 56.2, 64.6, 117.6, 127.3, 127.7, 128.8, 129.2, 134.1, 135.2, 152.6, 154.4, 157.0; HRMS (ES^+): Calcd for $[C_{18}H_{19}N_4O_2]^+$: 323.1503. Found: 323.1502.

Conclusion

In summary, we have developed a one-pot four component high yielding synthetic protocol to achieve 3-amino-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile derivatives using proline as an organocatalyst in a green reaction medium. This methodology offers several advantages including quite simple, time saving, high yielding, and most importantly an eco-friendly reaction procedure. Use of easily available, cheap starting materials and environmentally benign catalyst, high yields, simple experimental and work-up procedures, less waste production and absence of any strong acids or metal promoters make the process green.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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