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ONE POT, THREE-COMPONENT, ENVIRONMENTALLY FRIENDLY SYNTHESIS OF NOVEL 1, 4-DIOXO-3, 4 – DIHYDROPHTHALAZIN - 2(1H) - YL) - 4- HETEROYL - 4H – PYRANS

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ABSTRACT

One pot, three-component environment-friendly synthesis of novel 2 -amino - 6 - (1, 4 - dioxo - 3, 4 - dihydrophthalazin - 2(1H) - yl - 4- heteroyl - 4H -pyran - 3, 5 - dicarbonitriles **4** have been prepared by condensing 3-(1,4-dioxo-3, 4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile **1**, heteroaromatic aldehydes **2** and active methylene compounds **3** using L-proline as catalyst in EtOH at RT.

KEYWORDS: Green Chemistry, Phthalic anhydride, Hetero aromatic aldehydes Active methylene compounds

INTRODUCTION:

Multi-component reactions have been proved as a important tool for the syntheses of many multi-substituted heterocyclic ring-containing compounds.[I] Synthesis of different substituted 4*H*-pyrans has been studied in the literature.[II-V] Probably, phthalazine moieties containing different substituted 4*H*-pyrans have not been studied so far.

Phthalazines are important heterocycles that are known to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer and anti-inflammatory.[VI] Carling *et. al* reported[VII] the synthesis of 3-phenyl-6-(2-pyridyl)methyloxy-1, 2, 4-triazolo[3, 4 - *a*]phthalazines and analogues which were found to be a key structural element of certain CNS -

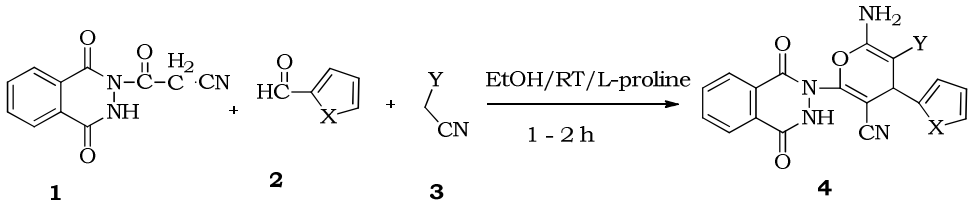
active drugs. Jain *et. al* reported[VIII] the synthesis of keto-glutamine tetra peptide analogues containing a 2-oxo-pyrrolidine ring as a glutamine side chain mimic which showed improved inhibition against hepatitis A virus 3C proteinase. Grasso *et. al* reported[IX] the synthesis of 6,7-methylenedioxyphthalazin - 1(2*H*) - ones which were found to be potent anticonvulsant agents. Nomoto *et. al* reported[X] the synthesis of 6,7-dimethoxyphthalazine derivatives which showed relatively potent cardiotonic activity comparable to that of amrinone. Watanabe *et. al* reported[XI] the synthesis of 4-benzylamino-1-chloro-6-substitutedphthalazines which were found to be vasorelaxant activatives and a number of methods have been reported for the synthesis of phthalazine derivatives.[XII] Therefore, it was considered worthwhile to synthesize phthalazine moiety containing 4*H*-pyrans.

Keeping these results in our mind, we now wish to report one-pot, three component synthesis of novel 2 -amino – 6 - (1, 4 – dioxo - 3, 4 - dihydrophthalazin - 2(1H) - yl - 4- heteroyl - 4H – pyran - 3, 5-dicarbonitriles.

RESULTS AND DISCUSSION:

As illustrated in **scheme-1**, in one pot, three-component reaction of **1**, thiophene aldehyde **2a** and malononitrile **3a** were stirred together for 1 hr at RT in the green solvent ethanol in the presence of the green catalyst L-proline. The product i.e novel 2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(thiophen-2-yl)-4H-pyran-3,5-dicarbonitrile **4a** were obtained in excellent yield on simple work-up of reaction mixture.

Both the catalyst and the solvent play a vital role in determining the success of the reaction in terms of rate and yields. In the absence of catalyst in any solvent, there was hardly any progress in the reaction even after stirring the reactants for 5 hrs. Various catalysts were also screened for this reaction in the present work, which include L-proline, piperidine, triethylamine and pyridine (Table 1). The solvents used were EtOH, MeOH and DMSO. Among all the catalysts and solvents used, L-proline in ethanol proved to be the best combination **(TABLE 1, entry 1)**.



1 2 3 4

X = S , O , NH Y = CN, $COOC_2H_5$

SCHEME1: Synthesis of **4** by one-pot synthesis

To find out the optimum concentration of the catalyst, the one-pot reaction was carried out by varying the amount of L-proline **(Table 2).** It was found in this study that 30 mol% L-proline as a catalyst at RT for 1 hr in EtOH gave good yield (88%) **(TABLE 2, entry 4).** Further increase in amount of L-proline in mentioned reaction did not have any significant effect on the product yield.

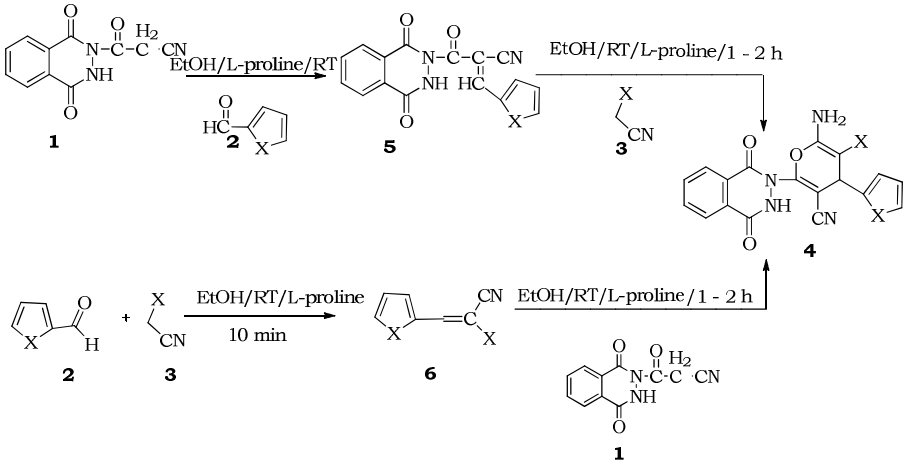
After having optimized the reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of several others **2a-2c** with **3a-3b** respectively

using L-proline as a catalyst at RT for 1-2 hr in EtOH giving **4a-4f** very good yields and no side product formation was detected. It was found that this method works with a wide variety of substrates. It is worth to mention that the reaction of **1, 2** & **3a** (malononitrile) could get higher yield and require shorter reaction time than the reaction of **1, 2** and **3b** (ethyl cyanoacetate). This can be ascribed to the C–H acidity of the active methylene compounds. Cyano functional group has a stronger electron- withdrawing ability than the ester group, so it is easier for malononitrile bearing two cyano groups to generate an anion than with ethyl cyanoacetate in the presence of base and hence react much faster in one-pot synthesis. The structures of these products have been established on the basis of their spectral data.

The synthesis of **4** could also be achieved in two variables but identical end-product giving step-wise syntheses. Thus, a mixture of **1** and **2** was stirred at RT for 20 min in the presence of 30 mol% L-proline in EtOH to form **5**. The reaction was monitored by TLC. The structures of these products have been established earlier on the basis of their spectral data (**SCHEME 2**).

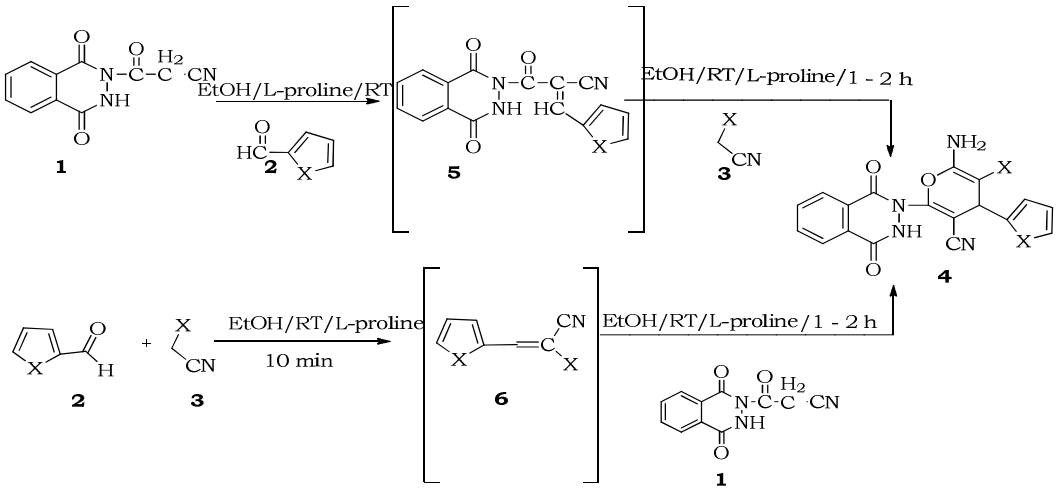
Furthermore, the compound **5** was assigned E - configuration on the presumption that bulky groups in a trans position would confer thermal stability on the molecule. This has been found to be case by a careful examination of the Frame-work molecular models of both E and Z-configurations of **5** wherein it was observed that there were minimum number of steric interactions in the E – configuration.

Then, **5** was reacted with **3** in the presence of 30 mol% L-proline in EtOH to form the final product **4.** Similarly, a mixture of **2** and **3** was stirred at RT for 20-30 min in the presence of 30 mol% L-proline in EtOH to form **6**. The reaction was monitored on TLC. Then, **6** was reacted with **1** in the presence of 30 mol% L-proline in EtOH to form the final product **4** (**SCHEME** 2).



SCHEME 2: Step-Wise Synthesis of **4.**

Encouraged by the above results, synthesis of **4** has been achieved successfully through tandem method by using step-wise sequences **(1+2 → 5 $\xrightarrow{3}$ 4) & (2+3 → 6 $\xrightarrow{1}$ 4)**. **(SCHEME 3).**



SCHEME 3: Tandem Synthesis of **4.**

TABLE 1.

Effect of **Solvent, catalyst & temperature** on reaction of **1, 2a & 3a** at RT yielding **4a.**

Entry	Solvent	Catalyst	Time /h	4a (%)
1	**Ethanol**	**L-proline**	**1**	**88**
2	Ethanol	Pyridine	2.5	67
3	Ethanol	Triethyl amine	2.5	60
4	Ethanol	Piperdine	1.5	75
5	Methanol	Piperdine	2	75
6	Methanol	Pyridine	2.5	60
7	Methanol	Triethyl amine	3	65
8	Methanol	L-proline	1.5	70
9	DMSO	Piperdine	3.5	60
10	DMSO	Pyridine	4	55
11	DMSO	Triethyl amine	4.5	50
12	DMSO	L-proline	3	50

TABLE 2.

The effect of amount of L-proline in the preparation of **4a** by **1, 2a & 3a** in EtOH.

Entry	Solvent	Mol % of L-Proline	Time /h	4a (%)
1	Ethanol	-	5	-
2	Ethanol	10	4	70
3	Ethanol	20	3	75
4	**Ethanol**	**30**	**1**	**88**
6	Ethanol	50	1	88
7	Ethanol	100	1	88

EXPERIMENTAL SECTION

Melting points are uncorrected and determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine vapour or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard at 400 MHz operating frequency. Mass spectra were recorded on Agilent-LCMS instrument. Starting materials **1, 2a-2c** and **3a-3b** were obtained from commercial sources and used as such.

Preparation of 3-(1,4-dioxo-3, 4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile 1:

A mixture of phthalic anhydride and ethylcyanohydrazide were heated at 100 ^{o}C in DMF in the presence of PTSA as catalyst for 2 hr. After the completion of the reaction as monitored by TLC, the reaction mixture was poured into ice-cold water. The product was precipitated out, filtered, washed with water, dried and recrystallised from ethanol. Yield 65%. M.P. 151-153˚C [Lit M.P. 150-152 ^{o}C][19].

Preparation of 4a-4f from 1, 2a-2c & 3a-3b by one-pot synthesis:

A mixture of **1** (10 mM), **2a-2c** (10 mM), **3a-3b** (10 mM), 30 mol % L-proline and EtOH (20 ml) was stirred at RT for 1-2 hr. At the end of this period, a colourless solid was separated out from reaction mixture which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from ethanol to obtain pure **4a-4f**.

2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(thiophen-2-yl)-4H-pyran-3,5-dicarbonitrile 4a: Mp: 188–190 ^{o}C; Yield: 88% ; IR (KBr) : 3306-3401 cm^{-1} (broad, medium, -NH-), 2218 cm^{-1} (sharp, strong, -CN-), 1706 cm^{-1} (sharp, strong, -CO- of amide group), 1659 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.5 (s, 1H, -CH), 7.4-8.1 (m, 7H, Ar-H), 9.8 (s, 2H, –NH_2), 12.1 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 49.5, 74.5, 87.3, 113.9, 115.1, 124.2, 127.8, 128.6, 129.1, 130.7, 134.3, 137.0, 155.8, 157.3, 163.0, 163.5; $M^{+\cdot}$+1 =390.

2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(furan-2-yl)-4H-pyran-3,5-dicarbonitrile 4b: Mp: 206–208 ^{o}C; Yield: 86%; IR (KBr) : 3302-3406 cm^{-1} (broad, medium, -NH-), 2211 cm^{-1} (sharp, strong, -CN-), 1715 cm^{-1} (sharp, strong, -CO- of amide group), 1655 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.2 (s, 1H, -CH), 7.0-8.2 (m, 7H, Ar-H), 9.6 (s, 2H, –NH_2), 11.4 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 44.7, 74.6, 85.4, 113.7, 114.3, 123.6, 126.7, 127.8, 129.6, 131.8, 133.2, 137.1, 155.4, 157.5, 163.1, 163.8; $M^{+\cdot}$+1 =374

2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(1H-pyrrol-2-yl)-4H-pyran-3,5-dicarbonitrile 4c: Mp: 190–192 ^{o}C; Yield: 84%; IR (KBr) : 3303-3405 cm^{-1} (broad, medium, -NH-), 2217 cm^{-1} (sharp, strong, -CN-), 1704 cm^{-1} (sharp, strong, -CO- of amide group), 1658 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.0 (s, 1H, -CH), 7.2-8.4 (m, 7H, Ar-H), 9.3 (s, 2H, –NH_2), 11.4 (s, 1H, -NH, D_2O exchangeable); 11.9 (s, 1H, -NH, D_2O exchangeable);^{13}C-NMR (DMSO-d_6, 100 MHz): δ 47.5, 74.6, 86.3, 115.7, 116.2, 123.4, 126.7, 127.4, 128.8, 132.4, 133.2, 134.1, 154.5, 156.3, 163.1, 163.4; $M^{+\cdot}$+1 =373.

Ethyl 2-amino-5-cyano-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(thiophen-2-yl)-4H-pyran-3-carboxylate 4d: Mp: 220–222 ^{o}C; Yield: 83%; IR (KBr) : 3310-3416 cm^{-1} (broad, medium, -NH-), 2216 cm^{-1} (sharp, strong, -CN-), 1713 cm^{-1} (sharp, strong, -CO- of amide group), 1654 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.2 (t, 3H, -

CH_3), 3.9 (m, 2H, -CH_2), 5.4 (s, 1H, -CH), 7.5-7.9 (m, 7H, Ar-H), 9.1 (s, 2H, –NH_2), 11.3 (s, 1H, -NH, D_2O exchangeable);^{13}C-NMR (DMSO-d_6, 100 MHz): δ 19.4, 46.6, 48.3, 58.6, 79.6,110.8, 114.1, 116.3, 117.3, 120.3, 123.3, 125.2, 126.8, 127.7, 130.3, 135.2, 138.4, 141.6, 149.1, 163.1, 163.4; $M^{+\cdot}$+1 =437.

Ethyl 2-amino-5-cyano-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(furan-2-yl)-4H-pyran-3-carboxylate 4e: Mp: 205–207 ^{o}C; Yield: 82; IR (KBr) : 3315-3418 cm^{-1} (broad, medium, -NH-group), 2214 cm^{-1} (sharp, strong, -CN-), 1716 cm^{-1} (sharp, strong, -CO- of amide group), 1655 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): 1.3 (t, 3H, -CH_3), 3.8 (m, 2H, -OCH_2), 5.4 (s, 1H, -CH), 7.5-7.8 (m, 7H, Ar-H), 9.1 (s, 2H, –NH_2), 11.2 (s, 1H, -NH, D_2O exchangeable); 12.0 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 18.9, 45.6, 48.2, 58.7, 79.7,111.9, 114.2, 116.4, 117.4, 120.4, 123.4, 125.3, 126.6, 127.7, 131.4, 135.2, 138.3, 140.6, 149.2, 163.2, 163.9; $M^{+\cdot}$+1 =421.

Ethyl 2-amino-5-cyano-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(1H-pyrrol-2-yl)-4H-pyran-3-carboxylate 4f: Mp: 225–227 ^{o}C; Yield: 86; IR (KBr) : 3312-3435 cm^{-1} (broad, medium, -NH-), 2219 cm^{-1} (sharp, strong, -CN-), 1718 cm^{-1} (sharp, strong, -CO- of amide group), 1653 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.6 (t, 3H, -CH_3), 3.4 (m, 2H, -OCH_2), 5.9 (s, 1H, -CH), 7.4-8.1 (m, 7H, Ar-H), 9.0 (s, 2H, –NH_2), 11.2 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 19.4, 46.5, 49.3, 57.6, 78.7,112.1, 115.3, 116.6, 117.6, 121.8, 124.7, 125.6, 126.6, 127.3, 131.4, 135.5, 138.3, 141.6, 150.7, 164.1, 164.5; $M^{+\cdot}$+1 =420.

Preparation of 5a-5c from 1 & 2a-2c:

A mixture of **1** (10 mM), **2a-2c** (10 mM), 30 mol% L-proline and EtOH (20 ml) was stirred at RT for 20 min. At the end of this period, a colourless solid was separated out from the mixture which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from ethanol to obtain pure **5a-5c**.

(E)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(thiophen-2-yl)acrylonitrile 5a: Mp: 160–162 ^{o}C; IR (KBr) : 3294-3519 cm^{-1} (broad, medium, -NH-), 2258 cm^{-1} (sharp, strong, -CN-), 1794 cm^{-1} (sharp, strong, -CO- group), 1748 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 7.3 (s, 1H, -CH), 7.9-8.6 (m, 7H, –ArH), 11.3 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 81.3, 81.3, 117.2, 122.8, 124.0, 127.2, 128.2, 128.5, 129.0, 129.1, 129.5, 133.1, 136.0,164.4, 164.4, 164.7; $M^{+\cdot}$+1= 324.

(E)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(furan-2-yl)acrylonitrile 5b: Mp: 168–170 ^{o}C; IR (KBr) : 3140-3438 cm^{-1} (broad, medium, -NH-), 2258 cm^{-1} (sharp, strong, -CN-), 1743 Cm^{-1} (sharp, strong, -CO- group), 1730 Cm^{-1} (sharp, strong, -CO- group), 1683 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.8 (s, 1H, -CH), 7.5-8.2 (m, 7H, –ArH), 11.3 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 81.2, 81.2, 117.2, 122.4, 124.2, 127.4, 128.2, 128.6, 129.1, 129.1, 129.3, 133.1, 136.2, 164.3, 164.4, 164.8; $M^{+\cdot}$+1= 308.

(E)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(1H-pyrrol-2-yl)acrylonitrile 5c: Mp: 169–171 ^{o}C; IR (KBr) : 3046-3444 cm^{-1} (broad, medium, -NH-), 2258 cm^{-1} (sharp, strong, -CN-), 1773 Cm^{-1} (sharp, strong, -CO- group), 1730 Cm^{-1} (sharp, strong, -CO- group), 1673 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.5 (s, 1H, -CH), 7.4-8.1 (m, 7H, –ArH), 11.1 (s, 1H, -NH, D_2O exchangeable), 12.1 (s, 1H, -NH, D_2O

exchangeable); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 81.0, 81.2, 117.1, 122.6, 124.5, 127.2, 128.2, 128.7, 129.1, 129.2, 129.3, 133.1, 136.2, 164.3, 164.6, 164.8; $M^{+\cdot}$+1= 307.

Preparation of 4a-4f from 5a-5c & 3a-3b via step-wise reaction:

A mixture of **5a-5c** (10 mM), **3a-3b** (10 mM), 30 mol % L-proline and EtOH (20 ml was stirred at RT for 1-2 hr. At the end of this period, a colourless solid was separated out from reaction mixture which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from ethanol to obtain pure **4a-4f**.

Preparation of 6a-6f from 2a-2c & 3a-3b:

A mixture of **2a-2c** (10 mM), **3a-3b** (10 mM), L-proline and EtOH (20 ml) was stirred at RT for 20 min. At the end of this period, a colourless solid separated out from the mixture which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from ethanol to obtain pure **6a-6f**.

Preparation of 4a-4f from 1 & 6a-6f via step-wise reaction:

A mixture of **1** (10 mM), **6a-6f** (10 mM), L-proline and EtOH (20 ml) was stirred at RT for 1-2 hr. At the end of this period, a colourless solid was separated out from reaction mixture which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from ethanol to obtain pure **4a-4f**.

CONCLUSION

In summary, we have successfully adapted a simple one pot as well as step-wise and tandem process for synthesis of novel 2 -amino – 6 - (1, 4 – dioxo - 3, 4 – dihydrophthalazin - 2(1H) - yl - 4- heteroyl - 4H –pyran - 3, 5-dicarbonitriles or ethyl 2-amino-4-argio-5-cyano-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4H-pyran-3-carboxylates with simple work up procedures in green methods.

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