ONE POT, FOUR-COMPONENT SYNTHESIS 2-AMINO-6-(1,4-DIOXO-3,4-DIHYDROPHTHALAZIN-2(1H)-YL)-4-ARYL-4H-PYRAN-3,5-DICARBONITRILES IN AN IONIC LIQUID

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[DBUH][OAc] (1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate) mediated, green synthesis of 2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-aryl-4H-pyran-3,5-dicarbonitriles have been synthesized by condensing diethyl phthalate, ethyl cyanohydrazide, benzaldehydes and malononitrile in [DBUH][OAc] medium, at 60-65 ºC for 2 h. Particularly valuable features of this method include high yield, broad substrate scope, shorter reaction times and straightforward procedure

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INTRODUCTION

Non-volatile, room-temperature ionic liquids (RTILs) have been extensively used as solvents and catalysts in ‘‘green chemistry’’,[1] a major driving force motivating organic chemists to develop environmentally benign methods of preparation of organic compounds.[2] Ionic liquids are widely used in many fields of chemistry and industry.[3] Their use as catalysts has attracted much attention in organic synthesis because product isolation and catalyst recycling are straightforward; occasionally, improvements in reaction rate and/or selectivity are also observed.[4]

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.[5] 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 important for drug discovery and synthesis of natural products.[6] MCRs have attracted much attention in combinatorial and medicinal chemistry and have been designed to produce biologically active compounds.[7] One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules.[8]

Phthalazines are important heterocycles that are known to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer and anti-inflammatory.[9] Carling *et* al. reported[10] 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 key structural element of certain CNS - active drugs. Jain *et* al. reported.[11] the synthesis of keto-glutamine tetrapeptide analogs 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[12] the synthesis of 6,7-methylenedioxyphthalazin-1(2*H*)-ones which were found to be potent anticonvulsant agents. Nomoto *et* al. reported[13] the synthesis of 6,7-dimethoxyphthalazine derivatives which showed relatively potent cardiotonic activity comparable to that of amrinone. Watanabe *et* al. reported[14] the synthesis of 4-benzylamino-1-chloro-6-substituted phthalazine which was found to be vasorelaxant activities and a number of methods have been reported for the synthesis of phthalazine derivatives.[15] Therefore, it was considered worthwhile to synthesize phthalazine moiety containing 4*H*-pyrans.

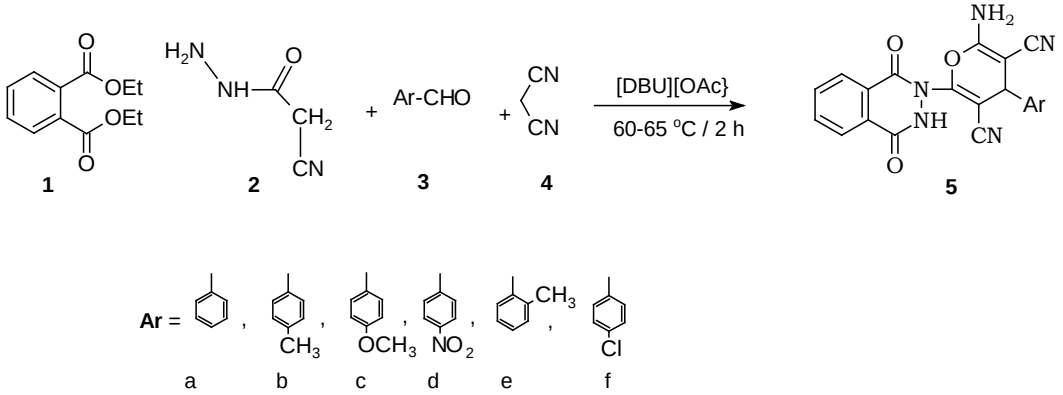
Keeping these results in our mind, we now wish to report one-pot, three-component synthesis of title compounds in weakly basic [DBUH][OAc] medium.

RESULTS AND DISCUSSION

Initially, one pot, four-component reaction of diethyl phthalate **1** (1 mmol), ethyl cyanohydrazide[16] **2** (1 mmol), benzaldehyde **3a** (1 mmol), and malononitrile **4** (1 mmol) in different ionic liquid medium (([DBUH][OAc], [bmim][Br] and [bmim][OH]) at 60-65 ºC to form 2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-phenyl-4H-pyran-3,5-dicarbonitrile **5a** have been taken as a model reaction. However, it was found that the one-pot reaction of in the presence of [DBUH][OAc] as a medium for 2 h at 60-65 ºC gave the highest yield (92 %) and the clean product **5a** (Table 1, entry 1). Here, initially compound **1** was reacted with **2** in [DBUH][OAc] at 60-65 ºC for 20 min to form 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxo-propanenitrile as intermediate **6** (confirmed by TLC that means the absence of starting materials). Then to this reaction mixture added **3a** and **4** and again heated at 60-65 ºC for 1.5 h to form 2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-phenyl-4H-pyran-3,5-

dicarbonitrile **5a**. The product i.e 2-amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-phenyl-4H-pyran-3,5-dicarbonitrile **5a** were obtained in excellent yield (92%) on simple work-up of reaction mixture. The structure of the compound **5a** has been confirmed by ^{1}H-NMR, IR and mass spectroscopy.

Encouraged by above optimization results conditions, the one-pot reaction has been carried out at different temperature (RT, 40, 60 and 80 ^{o}C) in the presence of [DBUH][OAc] mediated to get desired compound **5a**. However, it was found that the one-pot reaction of **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and **4a** (1 mmol)] in the presence of [DBUH][OAc] as medium (1 mmol) for 120 min at 60-65 ^{o}C gave the highest yield (92 %) and the clean product **5a** (Table 1, entry 1). In order to examine the quantity of [DBUH][OAc], the one-pot reaction has been carried out at different quantity (0.5, 1 and 2 mmol) of [DBUH][OAc] with respect of diethyl phthalate **1**. However, it was found that the one-pot reaction of [1 (1 mmol), 2 (1 mmol), 3a (1 mmol) & 4a (1 mmol)] in the presence of [DBUH][OAc] as medium (1 mmol) for 2 h at 60-65 ^{o}C gave the highest yield (92%) (Table 2, entry 2).

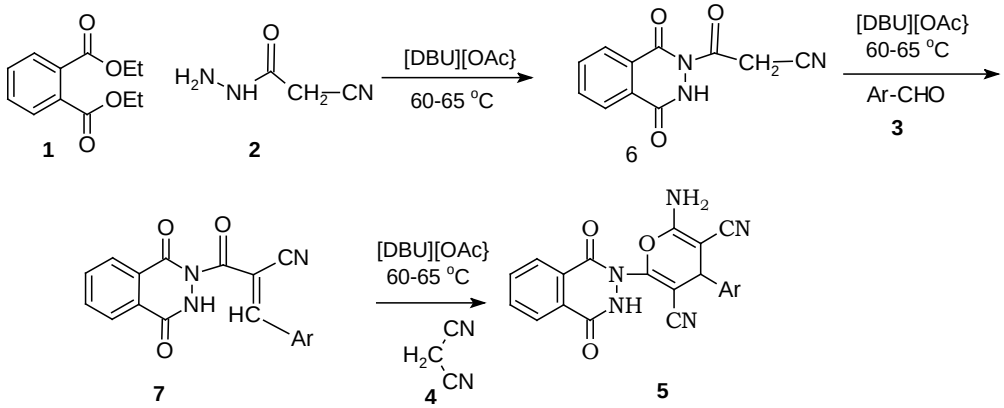


Scheme 1. Preparation of compound **5** by one-pot synthesis

After having optimized the reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of several others **3b-3f** respectively in [DBUH][OAc] medium at 60-65 ^{o}C for 2 h giving **5b-5f** 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 worthy of mentioning that the reaction of compounds **1**, **2**, **3a-3f** and **4** could get higher yield and require shorter reaction time for the formation of **5a-5f**.

The synthesis of **5** could also be achieved in step-wise syntheses. Thus, a mixture of 1 and 2 was heated at 60-65 ^{o}C for 0.5 h in [DBUH][OAc] medium to form intermediate **6**.[17] Then, 6 was reacted with **3** at 60-65 ^{o}C for 0.5 h in [DBUH][OAc] medium to form intermediate **7**[18] followed by **7** was reacted with **4** at 60-65 ^{o}C for 0.5 h in [DBUH][OAc] medium to form **5**. The reaction was monitored by TLC. The structures of these products have been established earlier based on their spectral data (Scheme 2).

Furthermore, compound **5** was assigned E-configuration on the presumption that bulky groups in a trans position would confer thermal stability on the molecule. This is the 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 was a minimum number of steric interactions in the E-configuration.



Scheme 2. Stepwise synthesis of compound **5**.

Table 1. Effect of ionic liquid, the temperature on the reaction of compounds **1**, **2**, **3a** and **4** to yielding **5a**.

Entry	Ionic liquid	T, °C	Time, h	5a, %
1	[DBUH][OAc]	60-65	2	92
2	[bmim][Br]	60-65	5	75
3	[bmim][OH]	60-65	3	78
4	[DBUH][OAc]	RT	12	81
5	[DBUH][OAc]	40-45	3.5	71
6	[DBUH][OAc]	80-85	1.5	62

Table 2. The effect of the amount of [DBUH][OAc] in the preparation of compounds **5a** from **1, 2**, **3a** and **4**.

Entry	[DBUH][OAc], mmol/mmol of 1	Time, h	5a, %
1	0.5	4	85
2	1	2	90
3	2	2	80

EXPERIMENTAL SECTION

Melting points are uncorrected and were 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. All reagents were purchased from Merck or Aldrich and used without further purification. [DBUH][Ac] was prepared as reported elsewhere.[17]

Preparation of compounds 5a-5f from compounds 1, 2, 3a-3f and 4 by one-pot synthesis:

A mixture of **1** (1 mmol) and **2** (1 mmol) were heated at 60-65 °C for 0.5 h in [DBUH][OAc] (1 mmol) for 0.5 h. (until no starting materials could be detected on thin-layer chromatography (TLC)). To this reaction mass added compounds **3** and **4** and heated again at at 60-65 °C for 1.5 h. (until no starting materials could be detected on thin-layer chromatography). After the reaction was complete, cold water was added to the reaction mixture and solid part was separated by filtration. The product was recrystallised from ethanol solvent to obtain compounds **5.**

5a: Mp: 139–141 °C; 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 6.1 (s, 1H, -CH), 7.5-8.0 (m, 9H, Ar-H), 9.6 (s, 2H, –NH_2), 11.6 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 48.5, 75.5, 86.3, 114.6, 115.1, 124.5, 127.9, 128.6, 129.7, 130.7, 134.1, 136.0, 155.8, 157.4, 163.0, 163.6; HRMS calcd for $C_{21}H_{13}N_5O_3$ $[M+H]^+$: 384.0427. Found: 384.0424.

5b: Mp: 181–182 °C; IR (KBr): 3309-3405 cm^{-1} (broad, medium, -NH-), 2210 cm^{-1} (sharp, strong, -CN-), 1716 cm^{-1} (sharp, strong, -CO- of amide group), 1656 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.1 (s, 1H, -CH), 7.5-8.0 (m, 9H, Ar-H), 8.1 (s, 2H, –NH2), 11.6 (s, 1H, -NH, D2O exchangeable); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 2.2 (s, 1H, -CH_3), 6.2 (s, 1H, -CH), 7.5-8.1 (m, 8H, Ar-H), 9.7 (s, 2H, –NH_2), 11.4 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 33.4, 47.3, 74.3, 82.9, 110.2, 111.3, 123.5, 124.3, 125.7, 128.3, 131.5, 135.3, 137.1, 153.4, 155.2, 163.3, 164.5; M^++1 =398.

5c: Mp: 141–143 °C; 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 6.1 (s, 1H, -CH), 7.5-8.0 (m, 9H, Ar-H), 9.4 (s, 2H, –NH_2), 11.6 (s, 1H, -NH, D_2O exchangeable); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 3.2 (s, 1H, -OCH_3), 6.3 (s, 1H, -CH), 7.5-8.2 (m, 8H, Ar-H), 9.3 (s, 2H, –NH_2), 11.4 (s, 1H, -NH, D_2O exchangeable); 13C-NMR (DMSO-d_6, 400 MHz): δ 38.5, 43.4, 73.4, 84.2, 111.4, 112.4, 123.4, 125.3, 127.3, 128.3, 131.6, 133.4, 134.3, 156.3, 157.3, 163.1, 164.1; M^++1 =414.

5d: Mp: 162–163 °C; IR (KBr): 3304-3402 cm^{-1} (broad, medium, -NH-), 2211 cm-1 (sharp, strong, -CN-), 1704 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 6.1 (s, 1H, -CH), 7.5-8.0 (m, 9H, Ar-H), 8.1 (s, 2H, –NH_2), 11.6 (s, 1H, -NH, D_2O exchangeable); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 6.2 (s, 1H, -CH), 7.4-8.0 (m, 8H, Ar-H), 9.1 (s, 2H, –NH_2) 11.6 (s, 1H, -NH, D2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 49.3, 74.3, 85.3, 113.1, 114.6, 123.4, 124.5, 127.3, 128.4, 131.1, 133.2, 135.3, 145.4, 150.2, 163.1, 163.3; M^++1 =429.

5e: Mp: 181–183 °C; IR (KBr): 3306-3404 cm^{-1} (broad, medium, -NH-), 2214 cm^{-1} (sharp, strong, -CN-), 1702 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 6.1 (s, 1H, -CH), 7.5-8.0 (m, 9H, Ar-H), 8.1 (s, 2H, –NH2), 11.6 (s, 1H, -NH, D_2O exchangeable); 1H- NMR (DMSO-d_6, 400 MHz): δ 2.3 (s, 1H, -CH3), 6.1 (s, 1H, -CH), 7.4-8.1 (m, 8H, Ar-H), 9.2 (s, 2H, –NH_2), 11.3 (s, 1H, -NH, D2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 28.3, 43.2, 74.1, 80.0, 109.5, 110.4, 118.4, 120.8, 125.4, 127.6, 131.6, 134.3, 135.2, 150.1, 153.2, 164.1, 164.7; M^++1 =398.

5f: Mp: 178–180 °C; IR (KBr): 3302-3401 cm^{-1} (broad, medium, -NH-), 2217 cm^{-1} (sharp, strong, -CN-), 1707 cm^{-1} (sharp, strong, -CO- of amide group), 1653 cm^{-1} (sharp, strong, -CO- of amide group); 1H- NMR (DMSO-d_6, 400 MHz): δ 6.1 (s, 1H, -CH), 7.5-8.0 (m, 9H, Ar-H), 8.1 (s, 2H, –NH_2), 11.6 (s, 1H, -NH, D2O exchangeable); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.1 (s, 1H, -CH), 7.5-8.0 (m, 8H, Ar-H), 9.3 (s, 2H, –NH_2), 11.3 (s, 1H, -NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 42.3, 74.4, 85.2, 110.5, 114.3, 122.4, 126.5, 128.6, 129.1, 131.4, 134.4, 136.3, 155.6, 157.4, 163.3, 163.9; M^+.+1 =418.

Preparation of compound 6 from compounds 1 and 2 via step-wise reaction

A mixture of diethyl phthalate **1** and ethylcyanohydrazide **2** were heated at 60-65 °C in [DBUH][OAc] (1 mmol) for 0.5 h. 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=72 %. M.P. 152-154˚C [Lit M.P. 150-152 °C].[17]

Preparation of compounds 7 from compound 6 and compounds 3

A mixture of **6** (1 mmol), **3a-3f** (1 mmol) and [DBUH][OAc] (1 mmol) were heated at 60-65 °C for 0.5 h. 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 =88 %.

7a: Mp: 200–202 °C; IR (KBr): 3267-3518 cm^{-1} (broad, medium, -NH-), 2258 cm^{-1} (sharp, strong, -CN-), 1749 cm-1 (sharp, strong, -CO- group), 1683 cm^{-1} (sharp, strong, -CO- of amide group),1613 cm-1 (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 7.6-8.4 (m, 10H, Ar-H and NC-C=CH), 11.4 (s, 1H, -OH, D_2O exchangeable); 13C-NMR (DMSO-d_6, 400 MHz): δ 35.5, 81.3, 81.4, 117.2, 122.9, 124.0, 127.2, 128.4, 128.5, 129.0, 129.1, 129.6, 133.0, 136.1, 143.4, 164.4, 164.5, 164.8; HRMS calcd for C18H11N3O3 $[M+H]^+$: 318.0423. Found: 318.0426.

7b: Mp: 195–197 °C; IR (KBr): 3266-3513 cm^{-1} (broad, medium, -NH-), 2253 cm^{-1} (sharp, strong, -CN-), 1742 cm^{-1} (sharp, strong, -CO- group), 1684 cm^{-1} (sharp, strong, -CO- of amide group),1617 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.8 (s, 3H, CH_3), 7.6-8.4 (m, 9H, Ar-H and NC-C=CH), 11.5 (s, 1H, -OH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 34.4,101.5, 106.3, 107.3, 114.4, 116.6, 122.2, 125.3, 131.4, 132.1, 133.1, 134.3, 138.3, 139.2, 140.4, 143.9, 154.8, 161.8, 164.9; M^+.+1 =332.

7c: Mp: 228–230 °C; IR (KBr): 3263-3515 cm^{-1} (broad, medium, -NH-), 2252 cm^{-1} (sharp, strong, -CN-), 1743 cm^{-1} (sharp, strong, -CO- group), 1682 cm^{-1} (sharp, strong, -CO- of amide group), 1616 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 4.0 (s, 3H, OCH_3), 7.1-8.3 (m, 9H, Ar-H and NC-C=CH), 11.3 (s, 1H, -OH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 44.5, 100.2, 104.2, 105.5, 110.6, 113.7, 121.3, 123.6, 128.4, 131.2, 132.8, 134.2, 135.6, 138.3, 141.3, 144.2, 158.1, 161.4, 163.5; M^+.+1 =348.

7d: Mp: 220–222 °C; IR (KBr): 3263-3512 cm^{-1} (broad, medium, -NH-), 2251 cm^{-1} (sharp, strong, -CN-), 1740 cm^{-1} (sharp, strong, -CO- group), 1681 cm-1 (sharp, strong, -CO- of amide group),1616 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 7.4-8.3 (m, 9H, Ar-H and NC-C=CH), 11.0 (s, 1H, -OH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 101.4, 103.2, 104.2, 109.1, 111.6, 118.3, 120.4, 124.6, 129.1, 132.4, 134.6, 135.7, 138.4, 140.2, 144.3, 158.1, 162.3, 165.3; M^+.+1 =363.

7e: Mp: 230–232 °C; IR (KBr): 3263-3512 cm^{-1} (broad, medium, -NH-), 2250 cm^{-1} (sharp, strong, -CN-), 1741 cm^{-1} (sharp, strong, -CO- group), 1681 cm^{-1} (sharp, strong, -CO- of amide group), 1618 cm-1 (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 2.9 (s, 3H, CH3), 7.6-8.4 (m, 9H, Ar-H and NC-C=CH), 11.6 (s, 1H, -OH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 34.6,100.3, 104.2, 105.3, 113.4, 114.6, 121.2, 126.3, 130.3, 133.4, 134.5, 135.6, 138.5, 139.2, 140.4, 143.6, 156.4, 161.6, 164.4; M^+.+1 =332.

7f: Mp: 170–172 °C; IR (KBr): 3267-3518 cm^{-1} (broad, medium, -NH-), 2258 cm^{-1} (sharp, strong, -CN-), 1749 cm-1 (sharp, strong, -CO- group), 1683 cm^{-1} (sharp, strong, -CO- of amide group), 1613 cm^{-1} (sharp, strong, -CO- of amide group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 7.4-8.3 (m, 9H, Ar-H and NC-C=CH), 11.1 (s, 1H, -OH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 101.3, 103.4, 105.5, 108.3, 110.5, 119.2, 121.3, 123.5, 129.1, 131.4, 132.6, 134.7, 135.6, 141.2, 144.2, 158.4, 161.4, 166.2; M^+.+1 =352.

Preparation of compound 5 from compounds 7 and 4

A mixture of **7** (1 mmol), **4** (1 mmol) and [DBUH][OAc] (1 mmol) were heated at 60-65 °C for 1.0 h . 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 recrystallized from ethanol to form **5**. Yield =85%.

CONCLUSION

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

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