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ONE POT, STEP-WISE AND TANDEM SYNTHESIS OF NOVEL DIHYDROPHTHALAZINE-1, 4-DIONES

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Abstract
One pot, three-component synthesis of novel 2-(7-amino-2,2-dimethyl-4-oxo-5-phenyl-4,5-dihydropyrano[2,3-*d*][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-diones prepared condensing 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile , benzaldehydes and meldrum's acid using L-Tyrosine as catalyst in EtOH at RT for 20-30 min. The products have been isolated in good yields as clean compounds without using column chromatography.

Keywords: Green Chemistry, Phthalic anhydride, Benzaldehydes and meldrum's acid.

Introduction:

Multi-component reactions (MCR's) have become a powerful tool for the syntheses of several multi-substituted heterocyclic ring containing compounds [I]. Notable in this class of reactions are the Biginelli[II], Passerini[III], Ugi[IV] and Hantzsch[V] syntheses.
Nitrogen-containing heterocyclic compounds spread out over a large area in nature, and their act of applying to biologically active pharmaceuticals, agrochemicals, and functional materials are
becoming important to a larger and larger degree [VI]. Among a large variety of nitrogen-containing compounds, heterocycles containing hydrazine moiety have received considerable attention because of their pharmacological properties and clinical applications [VII]. Phthalazine derivatives were reported to possess anticonvulsant [VIII], cardiotonic [IX], and vasorelaxant [X] activities.Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives [VIII, XI–XII]. Nevertheless the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge.

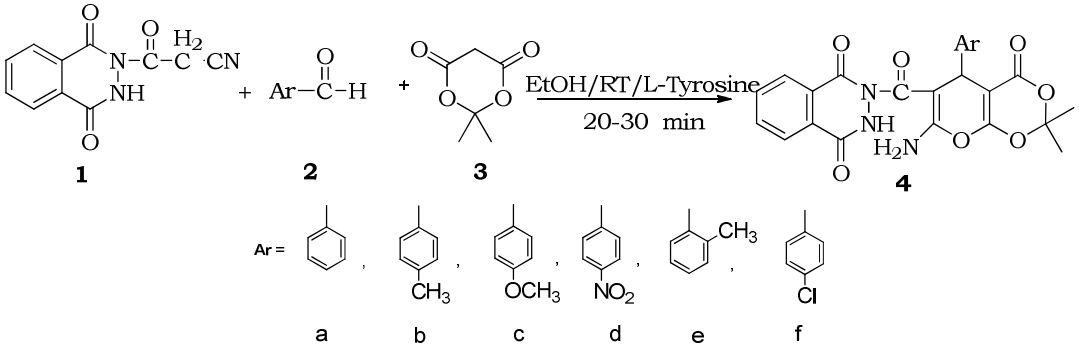
Keeping these observations in mind, we now wish to report efficient & one-pot, three component synthesis of novel 2-(7-amino-2, 2 – dimethyl – 4 – oxo - 5-phenyl- 4, 5-dihydropyrano [2, 3 - *d*] [1, 3]dioxine-6-carbonyl) - 2, 3 -dihydrophthalazine-1,4-dione.

Results and Discussion:

A mixture of 3-(1, 4-dioxo-3, 4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile **1**, benzaldehyde **2a** and meldrum's acid **3** in the green solvent ethanol in the presence of L-Tyrosine as green catalyst was stirred together, for 20-30 min at RT as illustrated in **Scheme-1**. Simple processing of the reaction mixture led to the isolation of the product 2-(7-amino-2,2-dimethyl-4-oxo-5-phenyl-4,5-dihydropyrano[2,3-*d*] [1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione **4a** whose structure was established based on its spectral data.

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 h. Various catalysts were also screened for this

reaction in the present work, which include L-Tyrosine, piperidine, triethylamine, and pyridine whereas the solvents used in the present work were EtOH, MeOH, DMSO and DMF. Among all the catalysts and solvents used in the present work, L-Tyrosine with ethanol combination proved to be the best **(Table-1)**.



Scheme-2: Synthesis of 4a-4f by one-pot synthesis from 1, 2a-2f & 3.

To find out the optimum concentration of the catalyst, the reaction was carried out by varying the amount of L-Tyrosine **(Table-2)**. However, reaction with 30 mol% L-Tyrosine as a catalyst at RT for 20-30 min in EtOH gave good yield (85%) (**Table-2, entry 1)**. Further increase in amount of piperidine did not have any significant effect on the product yield.

Table-1

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

Entry	**Solvent**	**catalyst**	**Time /min**	**4a (%)**
1	**Ethanol**	**L-Tyrosine**	**18**	**85**
2	Ethanol	pyridine	20	75[XV]
3	Ethanol	Triethyl amine	15	75 [XV]
4	Ethanol	piperidine	20	75 [XV]
5	Methanol	L-Tyrosine	15	80 [XV]
6	Methanol	pyridine	20	65 [XV]
7	Methanol	Triethyl amine	15	70 [XV]
8	Methanol	piperdine	20	75 [XV]
9	DMSO	L-Tyrosine	20	75 [XV]
10	DMSO	pyridine	25	75 [XV]
11	DMSO	Triethyl amine	25	65 [XV]

12	DMSO	piperdine	25	60 [XV]
13	DMF	L-Tyrosine	20	70 [XV]
14	DMF	pyridine	25	65 [XV]
15	DMF	Triethyl amine	25	60 [XV]
16	DMF	piperdine	25	60 [XV]

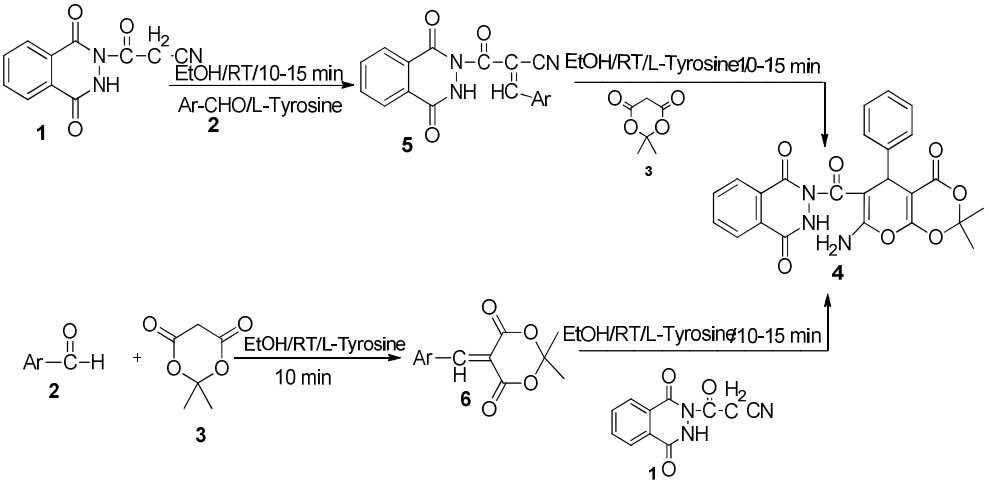
Table-2

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

Entry	**Solvent**	Mol % of L-Tyrosine	**Time /min**	**6a (%)**
1	Ethanol	-	240	-
2	Ethanol	10	30	70
3	Ethanol	20	25	75
4	**Ethanol**	**30**	**15**	**85**
5	Ethanol	50	15	80

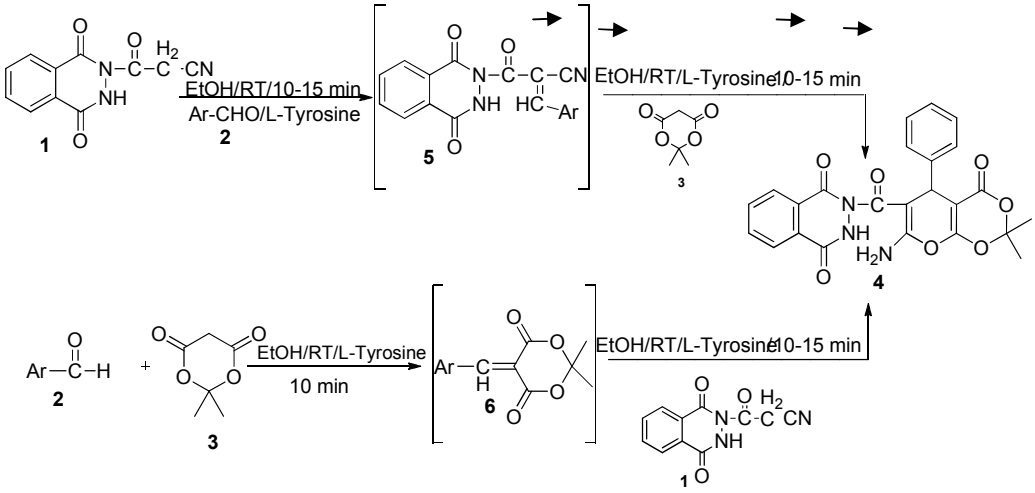
After having optimized the reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of several others **2a-2f** using 30 mol% L-Tyrosine as a catalyst at RT for 20-30 min in EtOH giving **4a-4f** in good yields and no side product formation was detected. As shown in **Table-3**, it was found that this method works with a wide variety of substrates.

The synthesis of **4** could also be achieved in two variable 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-Tyrosine to form **5** in EtOH. The structures of these products have been established earlier on the basis of their spectral data [XIII] **(Scheme-2) (Table-2)**. Then, **5** was reacted with **3** in the presence of 30 mol% L-Tyrosine in EtOH to form the final product **4 (Scheme-2) (Table-3)**. Similarly, a mixture of **2** and **3** was stirred at RT for 20 min in the presence of 30 mol% L-Tyrosine in EtOH to form **6**. The product was characterized by comparison of its physical data with that of the same product reported[XIV] earlier. Then, **6** was reacted with **1** in the presence of 30 mol% L-Tyrosine in EtOH to form the final product **4. (Scheme-2) (Table-3)**.



Scheme-2: Step-Wise Synthesis of 4.

Encouraged by above results, synthesis of **4** has been achieved successfully through tandem synthesis by using step-wise sequences **(1+2 5 [3] 4) & (2+3 6 [1] 4)**.



Scheme-3: Tandem Synthesis of 4.

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 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 using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument. Starting materials **2a-2f & 3** were obtained from commercial sources and used as such and compound **1** prepared by reported method[18].

Conclusion

In summary, we have successfully adapted a simple one pot as well as step-wise and tandem process for synthesis of novel 2-(7-amino-2,2-dimethyl-4-oxo-5-phenyl-4,5-dihydropyrano[2,3-*d*][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione with simple work up procedures in green methods.

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

A mixture of **1** (10 mM), **2a-2f** (10 mM), **3** (10 mM), L-Tyrosin and EtOH (20 ml) was stirred at RT for 15-20 min. At the end of this period, a colourless solid separated out from reaction mixture after neutralization with 5% HCl solution which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain pure **4a-4f**.

4a[XV]**:** Mp: 158–160 ^{o}C; IR (KBr) : 3146-3434 cm^{-1} (broad, medium, -NH-), 1793 Cm^{-1} (sharp, strong, -CO- group), 1740 Cm^{-1} (sharp, strong, -CO- group), 1693 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -CH_3), 1.5 (s, 3H, -CH_3), 5.3 (s, 1H, -CH), 7.0-7.9 (m, 9H, Ar-H), 8.2 (s, 2H, –NH_2), 11.3 (s, 1H, -NH,); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 21.5, 22.1, 43.7, 72.9, 74.9,78.2, 99.7, 118.5, 123.6, 125.4, 127.3, 127.6, 128.1, 129.2, 135.2, 142.9, 155.2, 158.9, 165.0; HRMS calcd for $C_{24}H_{19}N_3O_7$ $[M+H]^+$: 462.0467. Found: 462.0426.

4b[XV]**:** Mp: 168–170 ^{o}C; IR (KBr) : 3140-3438 cm^{-1} (broad, medium, -NH-), 1790 Cm^{-1} (sharp, strong, -CO- group), 1750 Cm^{-1} (sharp, strong, -CO- group), 1696 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -CH_3), 1.6 (s,

3H, -CH_3), 2.2 (s, 1H, -CH_3), 5.4 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.1 (s, 2H, –NH_2), 11.4 (s, 1H, -NH,); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 20.4, 21.2, 42.6, 72.8, 73.9,77.1, 99.6, 117.4, 123.5, 124.3, 127.3, 127.6, 128.2, 128.5, 135.2, 142.9, 155.1, 157.8, 165.1; HRMS calcd for $C_{25}H_{21}N_3O_7$ $[M+H]^+$: 476.1433. Found: 476.1482.

4c[XV]**:** Mp: 156–159 ^oC; IR (KBr) : 3142-3444 cm^{-1} (broad, medium, -NH-), 1780 Cm^{-1} (sharp, strong, -CO- group), 1754 Cm^{-1} (sharp, strong, -CO- group), 1690 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -CH_3), 1.6 (s, 3H, -CH_3), 3.9 (s, 1H, -CH_3), 5.3 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.2 (s, 2H, –NH_2), 11.2 (s, 1H, -NH,); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 21.4, 22.3, 42.4, 72.8, 74.6,76.2, 98.5, 118.3, 122.4, 125.4, 127.4, 127.5, 128.2, 129.1, 134.2, 142.8, 154.2, 158.5, 164.5; HRMS calcd for $C_{25}H_{21}N_3O_8$ $[M+H]^+$: 492.1365. Found: 492.1313.

4d[XV]**:** Mp: 172–174 ^oC; IR (KBr) : 3130-3446 cm^{-1} (broad, medium, -NH-), 1785 Cm^{-1} (sharp, strong, -CO- group), 1759 Cm^{-1} (sharp, strong, -CO- group), 1696 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.4 (s, 3H, -CH_3), 1.7 (s, 3H, -CH_3), 5.4 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.4 (s, 2H, –NH_2), 11.3 (s, 1H, -NH); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 21.1, 22.1, 43.3, 72.5, 74.7,78.3, 99.4, 118.2, 123.3, 125.5, 127.3, 127.6, 128.6, 129.2, 135.3, 142.5, 155.1, 158.6, 165.7; HRMS calcd for $C_{24}H_{18}N_4O_9$ $[M+H]^+$: 507.2431. Found: 507.2484.

4e[XV]**:** Mp: 165–167 ^oC; IR (KBr) : 3143-3435 cm^{-1} (broad, medium, -NH-), 1793 Cm^{-1} (sharp, strong, -CO- group), 1754 Cm^{-1} (sharp, strong, -CO- group), 1690 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -CH_3), 1.6 (s, 3H, -CH_3), 2.3 (s, 1H, -CH_3), 5.3 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.1 (s, 2H, –NH_2), 11.3 (s, 1H, -NH); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 21.3, 22.3, 43.5, 72.7, 74.8,78.2, 99.7, 118.3, 123.5, 125.3, 127.3, 127.4, 128.2, 129.3, 135.3, 142.8, 155.4, 158.6, 165.2; HRMS calcd for $C_{25}H_{21}N_3O_7$ $[M+H]^+$: 476.1433. Found: 476.1479.

4f[XV]**:** Mp: 152–154 ^oC; IR (KBr) : 3120-3396 cm^{-1} (broad, medium, -NH-), 1770 Cm^{-1} (sharp, strong, -CO- group), 1769 Cm^{-1} (sharp, strong, -CO- group), 1670 cm^{-1} (sharp, strong, -CO- of amide group), ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -CH_3), 1.8 (s, 3H, -CH_3), 5.1 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.1 (s, 2H, –NH_2), 11.3 (s, 1H,); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 20.4, 21.5, 43.2, 71.4, 73.6,77.4, 96.3, 116.1, 122.1, 125.4, 127.1, 127.4, 128.5, 129.1, 135.3, 142.5, 154.2, 158.4, 164.4; HRMS calcd for $C_{24}H_{18}ClN_3O_7$ $[M+H]^+$: 496.5234. Found: 496.5291.

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

A mixture of **5a-5f** (10 mM), **3** (10 mM), L-Tyrosine and EtOH (20 ml) was stirred at RT for 10-15 min. At the end of this period, a colourless solid separated out from reaction mixture neutralization with 5% HCl solution which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from suitable solvent to obtain pure **4a-4f**.

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

A mixture of **6a-6f** (10 mM), **1** (10 mM), L-tyrosin and EtOH (20 ml) was stirred at RT for 15-20 min. At the end of this period, a colourless solid separated out from reaction mixture neutralization with 5% HCl solution which was collected by filtration of the mixture, washed with hexane (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain pure **4a-4f**.

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