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Research Article

Microwave-assisted Solvent Free One-pot Three-component Synthesis of Novel Pyrano pyrimidine trione Derivatives.

Vijay N. Bhosale*[,1] Navanand B. Wadwale[1], Ashok R.Karad[2], Gopinath S. Khansole[3], Jaman A. Angulwar[4], Sunil S.Choudhare[5]

[1]P.G.Research Centre, Department of Chemistry, Y. M. Nanded, Maharashtra, India.

[2] Department of Chemistry, M. G. M. Ahmedpur, Latur, Maharashtra, India.

[3] Department of Chemistry, D. A. B. N. College, Chikhali, Sangli, Maharashtra, India.

[4]Department of Chemistry, D. S. C., Latur, Maharashtra, India.

[5] Department of Chemistry, S. D. College, Soegaon, Dist. - Aurangabad, Maharashtra, India.

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***Corresponding author E-mail address:** *vijaynbhosale77@gmail.com*

ABSTRACT
Multicomponent reactions (MCRs) have been developed in recent years in form of commanding and constructive tools in synthetic organic chemistry and have paid attention because complex molecules and drugs can be prepared from cheap and easily available starting materials. A green, mild, most efficient, eco-friendly, time saving, solvent-free, simple procedure has been developed for the synthesis of pyrano[2,3-*d*]pyrimidine-2,4,7-triones derivatives using substituted aromatic aldehydes, barbituric acid and Meldrum acid in the single vessel under microwave condition using Cesium carbonate (Cs_2CO_3) as an efficient and mild base catalyst. Synthesized compounds were screened for their antimicrobial activity. These newly synthesized compounds were evaluated by their spectral analysis.

KEYWORD
Barbituric acid, Aromatic Aldehydes, Meldrum acid, Solvent-free, MCRs.

1. INTRODUCTION

Multicomponent reactions (MCRs) have been developed in recent years in form of commanding and constructive tools in synthetic organic chemistry and have paid attention because complex molecules and drugs can be prepared from cheap and easily available starting materials [1-6]. Besides, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and "Green chemistry" with the increasing public concern over environmental degradation, the use of environmentally benign solvents like water or solvent-free become most essential. Multicomponent reactions have become very popular in the discovery of biologically active novel compounds because of simple experimentation, atom economy and high yield of the products. Multicomponent reactions (MCRs) being highly flexible, selective, and convergent in nature constitute a significant group of methods in organic synthesis [7-8]. These types of reactions have led to attention-grabbing heterocyclic scaffolds, and are very valuable in the construction of diverse chemical libraries of 'drug-like' molecules [9-10].

In the last decade, the microwave irradiation technique has been utilized as a high-ranking tool for the various organic transformations [11].The main benefits of the use of microwave irradiation include significant enhancement of the rate of the reactions, solvent-free, improvement in the yields, and selectivity [12].

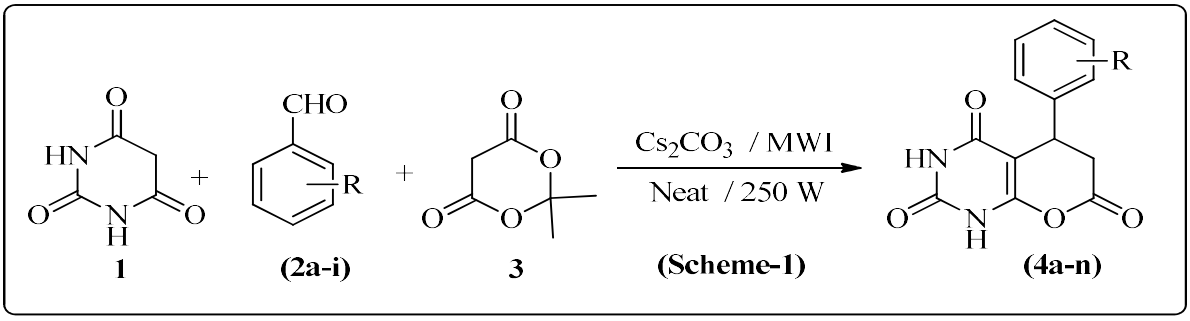
Pyrimidine derivatives are very attractive due to their wide range of biological activities [13]. The synthesis of naturally occurring molecules containing a uracil ring shows considerable synthetic challenges [14].The development of clinically useful anticancer (5-fluorouracil) [15]and antiviral drugs (AZT, DDI, BVDU) [16-18] has renewed the interest in the synthetic manipulation of uracils [19].All the compounds which have a uracil moiety in the skeleton of an organic molecule show antitumor, antibacterial, bronchodilator, vasodilator, antihypertensive, cardiotonic, hepatoprotective, and antiallergic activities; some of them also exhibit antimalarial, analgesic, antifungal and herbicidal properties [20].As a part of our ongoing research program on the development of new protocols in the heterocyclic synthesis of biological interest using readily available, inexpensive, and environmentally friendly catalysts.

2. MATERIALS AND METHODS

Melting points of synthesized compounds were determined by open capillary tubes and uncorrected. The purity of all the products was routinely checked by thin-layer chromatography (TLC) on pre-coated sheets of silica gel-C (Merck 60 F_{254}) plates of 0.25 mm thickness using UV Chamber for detection. Perkin-Elmer FT-IR spectra were recorded in KBr pellets on the infrared spectrophotometer. Bruckner advance spectrophotometer 300 or 400 MHz was used to record ^{1}H and ^{13}C-NMR spectra in DMSO-d_6 using TMS as the internal standard. Mass spectra were recorded on the FT-VC-7070H Mass spectrometer using the EI technique at 70 eV.

We report a new, facile, and rapid one-pot three-component route to the synthesis of some novel 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones by the reaction of aromatic aldehydes, Meldrums acid, and barbituric acid in the presence of readily available,

inexpensive, mild, green, solvent, mild, basic catalyst under neat microwave condition as shown in Scheme 1.



Scheme 1. Synthesis of pyrano [2, 3-*d*] pyrimidine-2, 4, 7-trione derivatives.

3. RESULTS AND DISCUSSION

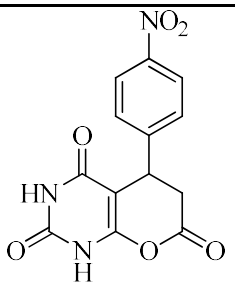
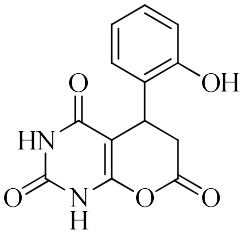
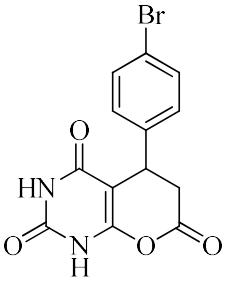
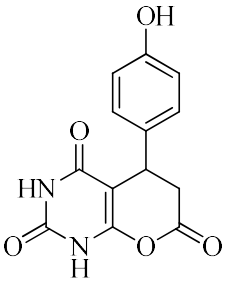
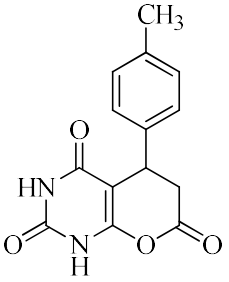
Initially, we choose the model reaction of barbituric acid (1), p-nitrobenzaldehyde (2a), and Meldrum acid (3) in the presence of 15 mol % Cs_2CO_3 under microwave condition without solvent for certain period of time to give 5-(4-Nitrophenyl)-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7(3*H*)-trione. The progress of the reaction was monitored by TLC. The product obtained was washed by n-hexane to remove unreacted aldehyde and recrystallized using ethanol. Also, we have tried to check the effect of different solvent on the rate of reaction as well as the yield of a product but it is observed that there was no effective role of solvent in reaction. So, we have not used the solvent under-reported reaction condition. Also, we tried to optimize the catalyst quantity. It is observed that 15 mol % is the optimized quantity for the reaction. (Table 2 entry-4) Moreover, there is no remarkable effect on yield due to electron-withdrawing and releasing substituents. A series of substituted aromatic aldehydes were successfully employed to prepare the corresponding product in excellent yield (4a-n) summarized in (Table 2).

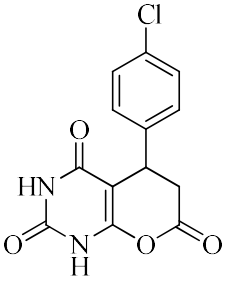
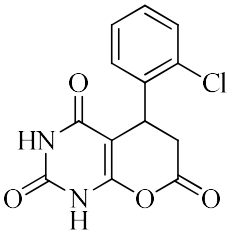
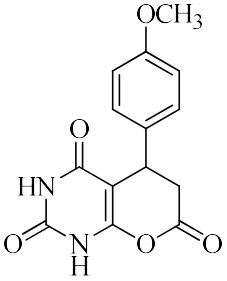
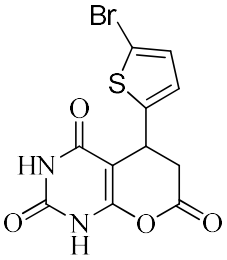
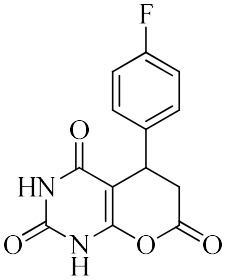
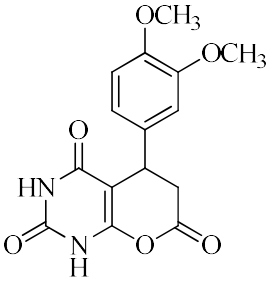
Table 1. Optimization Study for the amount of catalyst (Cs_2CO_3) [a].

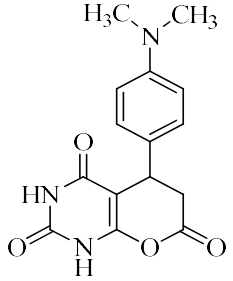
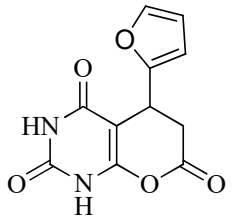
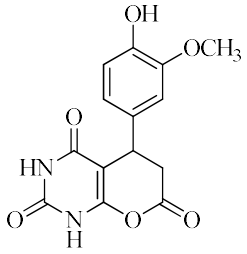
Entry No	Catalyst (mole %)	Reaction Time (second)	Yield (%)[a]
1	05	120	40
2	08	100	55
3	10	80	80
4	15	60	92
5	20	60	92

[a]***Reaction conditions:*** Barbituric acid (**1**) (1.0 mmol), substituted aromatic aldehydes (**2**) (1.0 mmol), and Meldrum acid (**3**) (1.0 mmol) under microwave condition [a] Isolated yields.

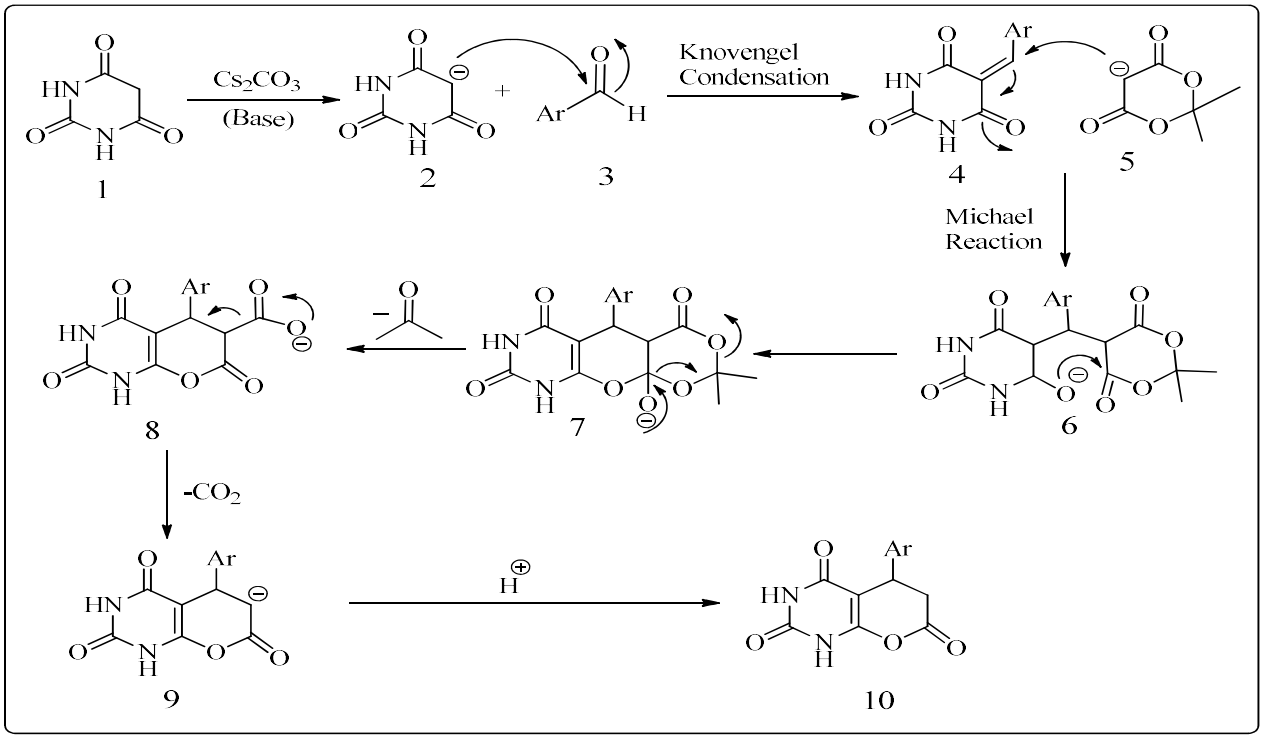
Table 2. Barbituric acid (1) (1.0 mmol), substituted aromatic aldehydes (2) (1.0 mmol), and Meldrum acid (3) (1.0 mmol) under microwave condition for the synthesis of (4a-n).

Sr. No	Compound Code	Structure of compound	Time (Second)	Yield (%)	M.P. (^{0}C)
1	4a		120	92	248-250
2	4b		130	90	292-294
3	4c		120	86	284-286
4	4d		120	84	298-300
5	4e		120	90	252-256

6	4f		120	88	282-284
7	4g		120	82	240-242
8	4h		120	88	237-238
9	4i		120	72	220-222
10	4j		120	84	166-267
11	4k		120	90	277-278

12	4l		120	92	182-184
13	4m		130	70	230-231
14	4n		130	84	256-258

POSSIBLE MECHANISM



Scheme 2. A Possible mechanism for synthesis of 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones.

3.1 Spectral Characterizations

5-(4-Nitrophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7(3H)-trione (4a)

IR (KBr/cm^{-1}) :3380, 3290, 2965, 1740, 1675, 1580, 1170; ^{1}H NMR (300 MHz, DMSO-d_6/ *ppm*): δ 11.00 (s, 1H, NH), 11.20 (s, 1H, NH), 8.12 (d, *J* = 8.4 Hz, 2H, Ph), 7.62 (d, *J* = 8.4 Hz, 2H, Ph), 4.39 (t, *J* = 7.2 Hz, 1H, CH), 3.40 (d, *J* = 6.9 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6/ *ppm*): δ 160.2, 163.6, 152.8, 150.9, 144.6, 130.2, 126.7, 124.5, 120.1, 120.7, 92.0, 32.1, 23.4.EI-MS (m/z: RA %):303 (100.0%)**.** Elemental Analysis (Calculated): $C_{13}H_9N_3O_6$: C, 51.49; H, 2.99; N, 13.86%. Elemental Analysis (Found): C, 51.40; H, 2.90; N, 13.80%;

5-(2-Hydroxyphenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7(3H)-trione (4b)

IR(KBr/cm^{-1}): 3600, 3380, 3290, 2970, 1740, 1680, 1580, 1165 cm-^{1}; ^{1}H NMR (300 MHz, DMSO-d_6/ *ppm*): δ 11.32 (s, 1H, NH), 10.01 (s, 1H, NH), 7.94-8.02 (m, 2H, Ph), 7.62-7.70 (m, 2H, Ph), 4.30 (t, *J* = 7.2 Hz, 1H, CH), 4.10 (s, 1H, OH), 3.33 (d, *J* = 6.9 Hz, 2H, CH2); ^{13}C NMR (75 MHz, DMSO-d_6 / *ppm*): δ 172.3, 160.6, 153.8, 150.7, 130.1, 125.7, 127.1, 122.4, 122.4, 118.1, 91.8, 33.2, 24.2.EI-MS (m/z: RA %):274 (100.0%)**.**Elemental Analysis (Calculated): $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22%. Elemental Analysis (Found):C, 56.12; H, 3.60; N, 10.20%;

5-(2-Chlorophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine- 2,4,7(3H)-trione (4g)

IR(KBr/cm^{-1}): 3412, 3260, 2980, 1725, 1690, 1584, 1170 cm-^{1}; ^{1}H NMR (300 MHz, DMSO-d_6 / *ppm*): δ 11.30 (s, 1H, NH), 11.10 (s, 1H, NH), 7.720-7.70 (m, 2H, Ph), 7.30- 7.35 (m, 2H, Ph), 4.30 (t, *J* = 7.2 Hz, 1H, CH), 3.30 (d, *J* = 6.9 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6/ *ppm*): δ 160.5, 16.1, 152.1, 150.5, 140.9, 132.1, 122.5, 120.2, 118.7, 117.8, 92.3, 31.8, 23.9.; EI-MS (m/z: RA %):292 (100.0%);Elemental Analysis (Calculated): $C_{13}H_9ClN_2O_4$: C, 53.35; H, 3.10; N, 9.57%. Elemental Analysis (Found): C, 53.30; H, 3.10; N, 9.50%;

5-(4-Fluorophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine- 2,4,7(3H)-trione (4j)

IR(KBr/cm^{-1}): 3440, 3280, 2966, 1735, 1682, 1589, 1162 ; ^{1}H NMR (300 MHz, DMSO-d_6 / *ppm*): δ 11. (s, 1H, NH), 11.21 (s, 1H, NH), 8.04 (d, *J* = 8.4 Hz, 2H, Ph), 7.28 (d, *J* = 8.4 Hz, 2H, Ph), 4.36 (t, *J* = 7.2 Hz, 1H, CH), 3.38 (d, *J* = 7.2 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6 / *ppm*): δ 168.7, 163.4, 158.2, 155.4, 146.5, 133.8, 128.5, 127.8, 119.2, 92.3, 31.4, 24.6. Elemental Analysis (Calculated): $C_{13}H_9FN_2O_4$: C, 56.53; H, 3.28; N, 10.14%; Elemental Analysis (Found): C, 56.38; H, 3.17; N, 10.10%;

4. CONCLUSION

We have developed a novel efficient and eco-friendly synthesis for the preparation of pyrano pyrimidines derivatives by a one-pot three-component cyclo condensation reaction of Barbituric acid, Substituted aromatic aldehydes, and Meldrum acid was treated under microwave condition for a very short time gives excellent yield using an easily available base catalyst. The product formed is recrystallized by ethanol, solvent-free, short reaction time, excellent isolated yields and easy work up to make this methodology more facile for the synthesis of pyrano pyrimidine derivatives.

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