IMPROVED SYNTHESIS OF SUBSTITUTED PYRIMIDIN-2-ONE DERIVATIVES USING MICROWAVE AND ULTRASOUND IRRADIATION

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ABSTRACT

Various substituted 4-oxo-2-thioxo tetrahydropyrimidine, 2-oxo dihydropyrimidine, 3,6-disubstituted and 4,5-disubstituted tetrahydropyrimidin-2-one derivatives containing different functional groups have been synthesized under microwave and ultrasound irradiation. The 3,6-disubstituted derivatives were prepared by reacting substituted pyrimidine derivatives synthesized under ultrasound irridation, with ethybromoacetate and product formed was converted to respective hydrazide derivatives, which were further condensed with various aromatic aldehydes. The 4,5-disubstituted tetrahydropyrimidines derivatives were synthesized simply by reacting substituted pyrimidine derivatives synthesized using modified biginelli reaction with various aromatic amines. The IR, ^{1}H NMR and mass spectral data confirmed the structure of the newly synthesized compounds.

Keywords:

Biginelli reaction, pyrimidine, Microwave, Ultrasound.

INTRODUCTION

Pyrimidine is a parent group of various heterocyclic compounds, which have attracted attention for long time. Pyrimidine derivatives play a vital role in many biological processes, the ring system being present in nucleic acids, several vitamins and coenzymes, uric acid and other purines. Uracil, thymine, and cytosine are three of the six bases found in the nucleotides, which contain pyrimidine ring. It is evident from the literature that pyrimidine derivatives have been found to have various pharmacological activities. Pyrimidine ring is the backbone of several calcium channel blocker[1], antibacterial[2], antifungal[3], antiviral[4-5], anticancer[6-7],analgesic and anti-inflammatory drugs[8]. Considering the scope of pyrimidine derivatives we have synthesized some new 5-carbonitrile-3,6-disubstituted-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (scheme-I) and 4,5-disubstituted-2-oxo-6-methyl-1,2,3,4- tetrahydropyrimidine (scheme-II) derivatives[9]. A survey of literature shows that many organic reactions have been accelerated applying microwave and ultrasonic irradiation. Herein, we report a facile sonochemical and microwave synthesis of pyrimidin-2-one derivatives, and the comparison of the conventional synthesis with the microwave and the sonochemical synthesis.

EXPERIMENTAL

Melting points of synthesized compounds were determined by an open capillary method and are uncorrected. Analytical TLC was performed on Silica gel-G. Spot was detected by using iodine vapours or under UV light (254 nm). The IR (KBr) spectra were recorded on a Jasco- FTIR 4100 instrument. The 1H NMR spectra of the compounds were carried on 400 MHz Varian NMR. The solvent used was DMSO. The mass spectra of the compounds were carried on Q- Tof micro (YA-105) and MDS Sciex (API 3000) LC-MSMS spectrometer. The reactions are carried out in spectralab ultrasonicator and catalyst microwave synthesizer

General procedure

Scheme-I

Step-I:Synthesis of 5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine:[10]

A mixture of ethyl cyanoacetate (0.01 mol), an aldehyde (0.01 mol) and thiourea (0.01 mol) in ethanol (20 ml) containing potassium carbonate (0.01 mol) was refluxed for 5 h. The potassium salt of product, which is precipitated during reaction, was collected and washed with ethanol and tetrahydrofuran. The crude salt was stirred in water at approximately 80° C; stirring was continued until the clear solution is obtained. After cooling the solution was acidify by acetic acid, and stirring was continued for 30 min. The deposited crystals thus formed were collected and washed well with water and dried in air. Recrystallization from acetic acid gave pure product.

Microwave synthesis: A mixture of ethyl cyanoacetate (0.01 mol), an aldehyde (0.01 mol) and thiourea (0.01 mol) in ethanol (20 ml) containing potassium carbonate (0.01 mol) was added in a pyrex flask (100 ml) and the mixture was stirred under microwave irridation for 7-8 min. The product obtained was washed with ethanol and tetrahydrofuran. The crude product was recrystallized from acetic acid. The yield was enhanced to 65-70%

Ultrasound synthesis: A mixture of ethyl cyanoacetate (0.01 mol), an aldehyde (0.01 mol) and thiourea (0.01 mol) in ethanol (20 ml) containing potassium carbonate (0.01 mol) was added in a pyrex flask (100 ml) and the mixture was stirred under ultrasound irridation for 40-50 min. The product obtained was washed with ethanol and tetrahydrofuran. The crude product was recrystallized from acetic acid. The yield was increased up to 70%.

IR (KBr), 3220.54, 3266.2 (N-H); 2229.31 (C≡N); 1662.2 (C=O) amide, NMR (DMSO-d_6), 3.79 (s, 3H, OCH_3); 7.15 (d, 2H, arom); 7.37 (d, 2H, arom); 9.9 (s, 2H, NH).

Step-II: Synthesis of [5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-3-yl] ethyl ethanoate

A mixture of step-I product (0.01 mol) and ethyl bromoacetate (0.01 mol) in acetone (100 ml) containing potassium carbonate (0.01 mol) was heated under reflux on water bath for 6 h. During reflux temperature was maintained around 60 - 65° C. The white colored potassium salt of product obtained was dissolved in hot water. After cooling the solution was acidify by dilute hydrochloric acid to precipitate the product. The product was filtered and washed with water. The crude product was dried and recrystallised from ethanol to obtain pure product.

IR (KBr), 3220.54, 3266.2 (N-H); 2225.45 (C≡N); 1739.48 (C=O) ester; 1654 (C=O) amide

Step-III: Synthesis of [5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin- 3-yl] ethanoic acid hydrazide

A solution of step-II product (0.01 mol) and hydrazine hydrate (0.01 mol) or phenylhydrazine (0.01 mol) in ethanol (100 ml) was refluxed on water bath for 4h. After cooling the reaction mixture the product obtained was filtered and dried in air. The solids product was recrystallised from ethanol to obtain the pure product.

IR (KBr), 3313.11, 3235.97 (NH_2, N-H); 2217.74 (C≡N); 1673.91 (C=O) amide. ^{1}H NMR (DMSO-d_6), 2.50 (s, 2H, CH_2); 3.84 (s, 3H, OCH_3); 7.19 (d, 2H, arom); 7.48 (d, 2H, arom); 7.70 (s, 2H, NH_2); 9.9 (s, 2H, NH). MS (m/z): M^+ 331.3 (22.85%); 301.33 (54.5%); 272.2 (100%); 258.4 (19.5%); 57 (47.51%).

Step IV: Synthesis of [5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-3-yl] ethanoic acid arylidinehydrazide

A mixture of step-III product (AH1 or BH1) (1 mmol) and aryl aldehyde (1 mmol) in ethanol (20 ml) the mixture was irradiated in the water bath of an ultrasonic cleaner at 50 ^{0}C. Sonication was continued until crystals were appeared.

IR (KBr), 3266.82, 3221.12 (N-H); 2206.17 (C≡N); 1604.48 (C=N); 1033.16 (Ar-Cl). ^{1}H NMR (DMSO-d_6), 2.50 (s, 2H, CH_2); 3.84 (s, 3H, OCH_3); 7.1 (d, 2H, arom); 7.51 (d, 2H, arom); 7.91 (d, 2H, arom); 8.09 (d, 2H, arom); 8.15 (s, 1H, CH=N); 12.75 (br, 2H, NH). MS (m/z): M^+ 453.90 (30.65%); M+1 455.73 (9.48%); 315.32 (100%); 273.21 (10.94%); 258.42 (21.16%); 185 (3.7%); 151.28 (15.32%); 139.61 (1.45%); 57 (60.58%).

Scheme-II

Step-I: Synthesis of 3,4-dihydropyrimidin-2(1H)-one:

Solution of β-ketoester (10 mmol), appropriate aldehyde (10 mmol), urea (15 mmol), ferric chloride hexahydrate (2.5 mmol) and conc. hydrochloric acid (1-2 drops) in ethanol (20ml) was heated under reflux for 4 hours. After cooling, the reaction mixture was poured into crushed ice (100 gm). Stirring was continued for several minutes. The solid product was filtered, washed with cold water (2x50 ml) and a mixture of ethanol:water (1:1). The solid product was recrystallised from ethanol.

Microwave synthesis: A mixture of β-ketoester (10 mmol), appropriate aldehyde (10 mmol), urea (15 mmol), ferric chloride hexahydrate (2.5 mmol) and conc. hydrochloric acid (1-2 drops) in ethanol (20ml) was taken in pyrex flask (100 ml) and treated with microwave radiation for 7-8 min. The product obtained was recrystallized in ethanol.

Ultrasound synthesis: A mixture of β-ketoester (10 mmol), appropriate aldehyde (10 mmol), urea (15 mmol), ferric chloride hexahydrate (2.5 mmol) and conc. hydrochloric acid (1-2 drops) in ethanol (20ml) was taken in pyrex flask (100 ml) and treated with ultrasound radiation for 50 min. The product obtained was recrystallized in ethanol.

IR (KBr), 3245.72, 3119.81 (N-H); 2939.7 (C-H); 1649.22 (C=O) amide. ^{1}H NMR (DMSO-d_6), 2.12 (s, 3H, CH_3); (t, 3H, CH_3), 3.68 (s, 1H, CH); (q, 2H, CH_2), 7.06-7.17 (m, 5H, arom); 7.59 (s, 1H, NH); 9.19 (s, 1H, NH).

Step-II: Synthesis of 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid arylamide: [11]

Aromatic amine (10 mmol) was added in flask containing step-I product (10 mmol) in ethanol (20ml). Then catalytic amount of conc. sulphuric acid (5 drops) was added The mixture was irradiated in the water bath of an ultrasonic cleaner at 50 ^{0}C .Sonication was continued until crystals were appeared.

IR (KBr), 3239.82, 3162.18 (N-H); 2946.7 (C-H); 1654.62 (C=O) amide. ^{1}H NMR (DMSO-d_6), 2.23 (s, 3H, CH_3); 3.70 (s, 1H, CH); 5.08 (s, 1H, NH); 7.16-7.27 (m, 10H, arom); 7.65 (s, 1H, NH); 9.25 (s, 1H, NH). MS (m/z): M^+ 307 (12.8%); 187.2 (100%); 120.1(35%); 111.2(5.05%); 44.1(44%).

Results and discussion

Most products described herein were prepared by the conventional, microwave assisted and also under ultrasound sonication. In the scheme-I the 5-carbonitrile-6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines (I) were prepared by procedure given by Kambe. In this the ethyl cyanoacetate, aromatic aldehyde and thiourea were reacted in presence of base potassium carbonate to form corresponding product. The reaction proceeds by knoevenagel condensation and the condensed product reacts with thiourea to form an intermediate, which is subsequently cyclized by nucleophilic attack of nitrogen on carbonyl carbon. The IR spectrum showed peaks in the region 3070-3220 cm^{-1} (N-H stretching), 2229-2235 cm^{-1} (C≡N), 1662-1690 cm^{-1} (C=O) amide as diagnostic absorptions. The yield of the reaction was very low around 30-40%. The low yields of products tempted to carry out same reactions under microwave and ultrasound irridation, which lead to increase in yield in very short time. The compounds synthesized by microwave and ultrasound irradiation were authenticated by the TLC and spectral studies. In second step the product of the first step was reacted with ethyl bromoacetate. In IR spectrum the peak for carbonyl group of ester (1735 cm^{-1}) is seen which is absent in IR of the first step product. Also the intensity of the N-H stretching appears decreased but the peak is present indicating a mono substituted product. In third step the nucleophilic attack by hydrazine hydrate on the electron deficient carbonyl carbon of the ester group is brought about to form the corresponding hydrazide. In IR spectrum of the hydrazide the peak for carbonyl group shifts to a lower wavenumber and a strong stretching for amino (NH_2NH-) group is seen in the region 3100-3360 cm^{-1}. In the last step the hydrazide was reacted with various aromatic aldehydes to form corresponding imines. Table 1 shows the various substitutions. This step though yielded the product in sufficient amount required longer time, so the synthesis were performed under microwave and ultrasound irradiation. Peak for imine in region of 1590-1620 cm^{-1} is seen for all synthesized compounds in IR spectral analysis. All the synthesized final derivatives were confirmed by NMR and Mass spectral analysis.

Similarly in the second scheme all the 4,5-disubstituted-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine derivatives were. The first step is synthesis of 4-substituted-3,4-dihydropyrimidin-2-one. These 3,4-dihydropyrimidin-2-ones were synthesized and the products confirmed by IR and physicochemical data analysis. Modified Biginelli reaction was used so as to obtain good yield (80-95%). The microwave and ultrasound though did not increase the yield, decrease in reaction time from 4h to 40 min. In the second step, ester group of the 3,4-dihydropyrimidin-2-one was reacted with various aromatic amines in presence of sulphuric acid to form 4,5-disubstituted-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine. Table 2 shows the various substitutions. Results of IR and NMR analysis confirmed formation of the desired product. The results of the all the convectional as well as under ulrasonication and microwave are compared and from the finding it is clear that the ultasonication synthesis gives a better results with respect to product yield and purity. Microwave accelerated the pyrimidin-2-one synthesis, whereas under ultrasonication the purity of the product obtained was around 90-95%. Table 3,4 show a significant difference in the yield and purity for different substrates.

Conclusion

Synthesis of Pyrimidine-2-one derivatives was carried out in good yields for the under microwave and ultrasound radiation. The present procedure is carried out in a shorter reaction time good yield and easier work-up. Though the time taken by the microwave synthesis may be lesser than the ultrasound synthesis, the purity of the compounds obtained by the ultrasound is highest of the three methods utilized for the synthesis of the pyrimidine-2-one derivatives. Thus the use of ultrasound of chemical synthesis is leading to time and cost effective manner.

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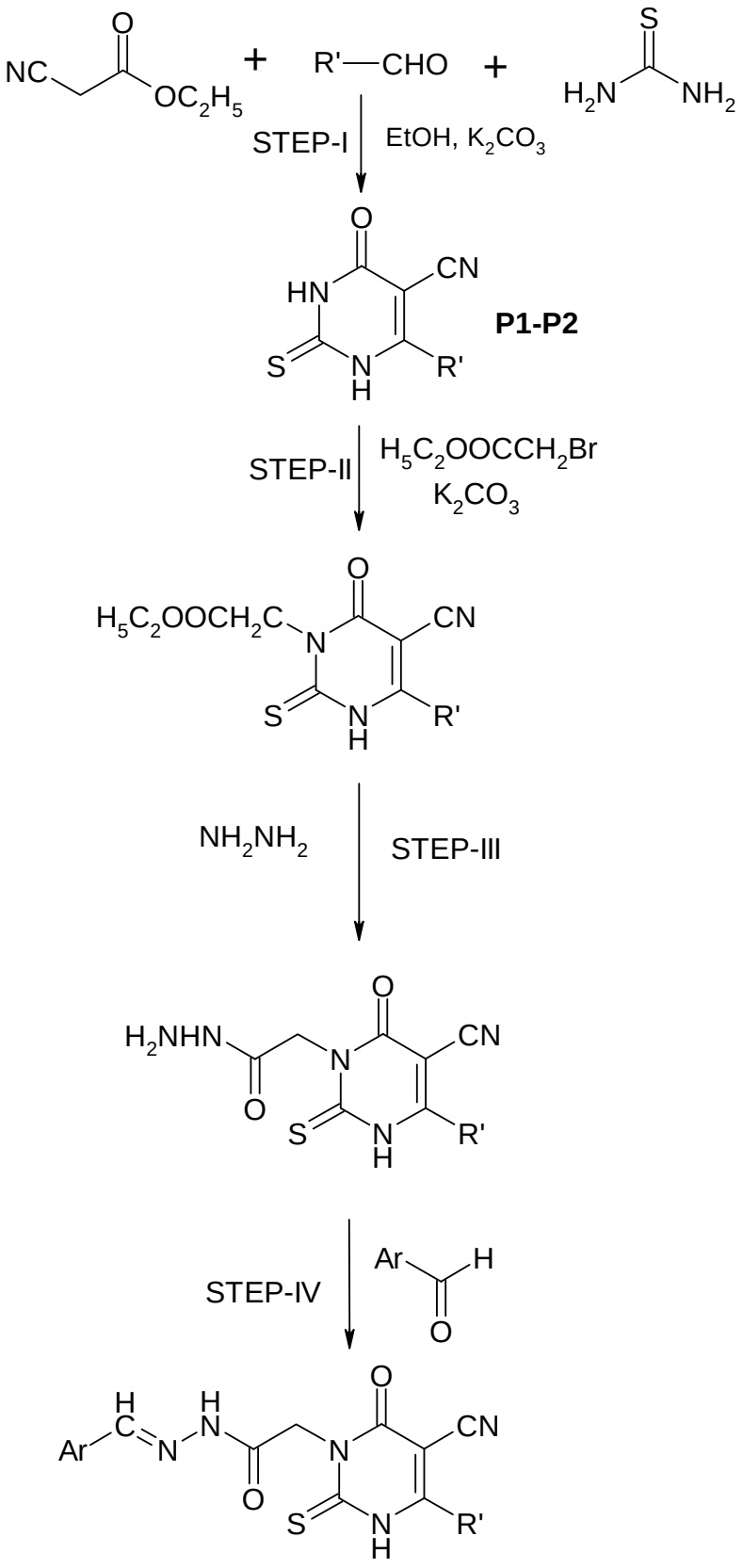
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+
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+
S
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N
H
R'
P1-P2
STEP-II
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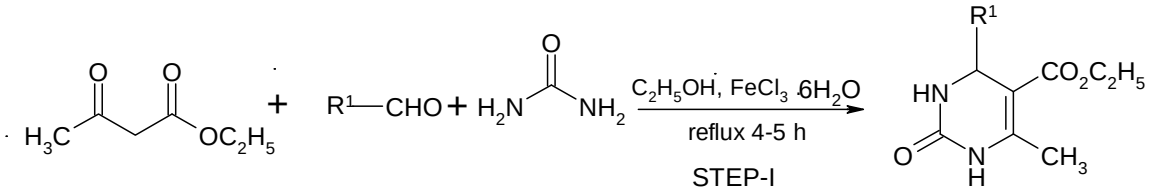
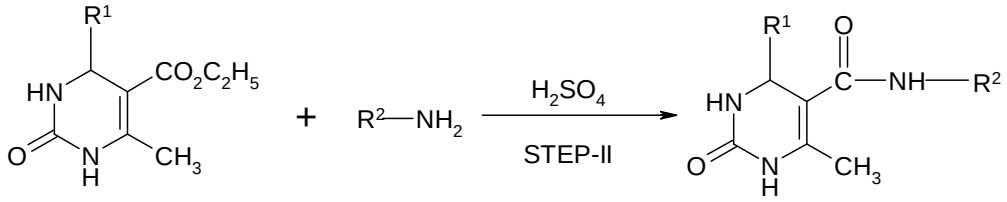
STEP-IV
1-10

Scheme: I



P-3,P-4



11-20

Scheme: II

Table 1: Physical data of the 5-carbonitrile-3,6–disubstituted-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives (scheme-I).

Comp code	R'	Ar	M. P. °C	Rf value
1	4-methoxy phenyl	4-chloro phenyl	318	0.4
2	4-methoxy phenyl	4-fluro phenyl	322	0.439
3	4-methoxy phenyl	3,5-dimethoxy phenyl	286	0.528
4	4-methoxy phenyl	furfural	266	0.6
5	4-methoxy phenyl	4-dimethylamino phenyl	309-310	0.56
6	4-methoxy phenyl	3,4,5-trimethoxy phenyl	298-299	0.4
7	phenyl	4-chloro phenyl	320	0.83
8	phenyl	4-methoxy phenyl	328	0.62
9	phenyl	phenyl	306-308	0.45
10	phenyl	4-methyl phenyl	311-312	0.49

Solvent for TLC: Tetrahydrofuran : hexane (1:1)

Table2: Physical data of the 4,5-disubstituted-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine derivatives (scheme-II).

Comp code	R^1	R^2	M. P. °C	Rf value
11	phenyl	phenyl	181	0.62
12	phenyl	2-nitrophenyl	204	0.55
13	phenyl	3-nitrophenyl	210	0.60
14	phenyl	4-nitrophenyl	216	0.47
15	phenyl	4-fluro phenyl	208	0.44
16	4-methoxy phenyl	phenyl	190	0.55
17	4-methoxy phenyl	2-nitrophenyl	175	0.72
18	4-methoxy phenyl	3-nitrophenyl	195	0.59
19	4-methoxy phenyl	4-nitrophenyl	198	0.63
20	4-methoxy phenyl	4-fluro phenyl	187	0.68

Solvent for TLC: carbon tetrachloride: methanol: Tetrahydrofuran (9:1:0.2)

Table 3: Table showing the percentage yield of the products

Compound code	Convectional method	Microwave synthesis	Ultrasonic synthesis
P-1	60	62	70
P-2	40	40	54
P-3	85	85	90
P-4	61	85	87
1	60	82	92
2	55	80	72
3	65	82	90
4	60	88	83
5	65	88	48
6	58	78	35
7	59	75	82
8	45	68	88
9	65	85	95
10	70	85	78
11	65	85	80
12	60	90	91
13	65	95	80
14	58	80	80
15	59	82	77
16	55	83	88
17	65	86	88
18	60	89	82
19	55	90	92
20	63	70	77

Table 4: Showing the percentage purity of the products

Compound code	Convectional method	Microwave synthesis	Ultrasonic synthesis
P-1	80	62	82
P-2	70	61	80
P-3	82	60	82
P-4	77	55	88
1	90	65	88
2	95	60	78
3	85	65	75
4	80	58	68
5	75	59	85
6	88	45	85
7	79	65	85
8	85	70	90
9	85	65	95
10	80	60	82
11	95	65	82
12	80	58	83
13	85	59	86
14	78	55	89
15	79	65	90
16	85	60	70
17	72	55	86
18	69	63	82
19	75	65	83
20	73	61	86