Microwave Assisted Synthesis of Pyrimidine Carboxamide Catalyzed by Ruthenium Chloride and their Antioxidant Studies

K. Venkatesan
Asst. Professor, CVR College of Engineering/H&S Department (Chemistry), Hyderabad, India
Email: venkippk@gmail.com

Abstract: **A systematic and simple method for the preparation of pyrimidinone compound utilizing RuCl3.2H2O catalyst under traditional and microwave method. The preparation of dihydro pyrimidinone utilizing ruthenium chloride dihydrate had generated lots of interest which includes easy work up, less reaction period and better yields under the usage of CH_3CN as a solvent. The structures of the new substances have been affirmed throgh FT-IR, ^{13}C NMR, ^{1}H NMR and mass spectra. All the new substances were screened for antioxidant nature.**

Index Terms: **Ruthenium chloride, Antioxidant, Microwave, Dihydropyrimidine**

I. Introduction

The multicomponent single step reactions (MCRs) are the most used procedure in medicinal chemistry and organic synthesis. Nitrogen based compounds provides huge range of bio applications. Due to the presence of nitrogen atom it contains a lone pair electron which acts as donor group for building supramolecular blocks. MCRs are important in the field of organic synthesis, that is extensively used to prepare dissimilar target molecules in single step reaction, and in the usage of three or greater number of initial substances. In 1893 Biginelli has describe the new route for the preparation of DHPMs via a simple single step condensation reaction of ethyl acetoacetate, urea and benzaldehyde [1]. The availability is restricted for the natural products which provide interesting goals for total synthesis [2]. The DHPM is the main structure in synthesis of various pharmacological and medicinally used agents like antiviral [3], antibacterial [4], antihypertensive agents [5], antitumor [6], neuropeptic agents [7], antagonists [8], α-1a-antagonists [9] anti-inflammatory and Ca channel blockers [10]. Further, DHPM ring present in alkaloid batzelladine hinder the binding of HIV protein gp-120 to human CD4 cells and the possibility of new substances prepared for AIDS treatment [11-12]. Hence, synthesis of DHPMs shows continuous interest and attraction to organic chemists.

Recent report reveals that mortal kinesin Eg5, plays a crucial part in cellular division by organizing the bipolar group, it has been checked the consideration of drug for the advancement of cancer therapy. Monastrol, the first Biginelli compound, exhibit excellent anticancer activity. The dihyropyrimidinones derived from natural aquatic sources such as Batzelladine A, B [13] is the first low M.Wt products occurs naturally it shows good anti-HIV property and hence DPHM were examined as powerful molecules in AIDS treatment.

Biginelli reaction was carried out by mixing active 1,3-dicarbonyl, different substituted aldehydes, and thiourea or urea is combined with different catalysts like $ZrCl_4$ [14], $Cu(OTf)_2$ [15], AcOH [16], $CdCl_2$[17], Ionic liquids [18], SiO_2/H_2SO_4[19], ion-exchange resin[20], $La(OTf)_3$ [21], LiBr[22],p-TSA[23], $(NH_4)_2Ce(NO_3)_6$ [24], $MgBr_2$[25], $InBr_3$ [26], ultrasound irradiation[27] microwave[28] and solvent-free conditions [29], $ZnCl_2$/TBAB [30]. $Co(NO_3)_2.6H_2O$ [31], $Mn(OAc)_3$ [32]. Microwave reactions have good interest in the last two decades in synthetic organic chemistry because of their low response times and excessive yield and more selectivity.

TABLE I.
Experimental Results And Physical Data Of Arylpyrimidine-5-Carboxamide Derivatives

Compound	R	R_1	X	Reaction time (min.)		Yield (%)[a]		m.p. (°C)
				MW	Con.	MW	Con.	
4a	H	Phenyl	O	16	430	90	78	225-228
4b	H	Phenyl	S	17	440	88	81	214-217
4c	H	3-OEt-4-OH-Ph	O	18	460	87	78	254-256
4d	H	3-OEt-4-OH-Ph	S	21	440	82	76	243-245
4e	H	2,4-Cl-Ph	O	21	460	83	77	207-209
4f	H	2,4-Cl-Ph	S	20	470	83	74	189-191
4g	H	2-C_4H_3S	O	17	400	84	78	191-193
4h	H	2-C_4H_3S	S	17	400	81	73	202-204
4i	H	Ph-4-OH-3-OMe	O	18	410	87	82	231-233
4j	4-Cl	2,4-Cl-Ph	O	16	450	86	80	206-208

A. Experimental procedure

General: All the chemical substances had been bought from SD Fine, Aldrich and Qualigens and utilized without cleaning. The proton NMR spectra was acquired from spectrometer BRUKER AV-400 MHz with DMSO-d6 as the solvent utilizing TMS as the inner standard. The MW experiment was conducted using household MW oven with a turntable was used and the operating frequency was 2200 MHz. Infrared (IR) spectra was recorded at room temperature with potassium bromide (KBr) pellets utilizing

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Avatar (330) instrument with DTGS indicator. Mass spectra was obtained from JEOL 1400 HRMS spectrometer. Melting point was obtained using an open capillary tube and the results were uncorrected.

Procedure for the synthesis of pyrimidine-5-carboxamide (**4a-j**):

B. Conventional Method

In a 100 ml RB flask blend of acetoaetanilide (1 milli mol), aldehyde (1 milli mol), thiourea or urea (1.5 milli mol), $RuCl_3.2H_2O$ (5 mole %) and 30 mL CH_3CN have been refluxed according to time interim said in Table 3. The reaction fulfillment was appeared by TLC. After completion, the reaction blend was putting into a pulverized ice, mixed for 25-30 min. The solid product obtained was filtered by using funnel, washed with large amount water and then recrystallization was done using hot ethanol to get pure products 4a-j.

C. Microwave Irradiation

In a small beaker acetoaetanilide (1 milli mol), aldehyde (1 milli mol), thiourea or urea (1.4 milli mol), $RuCl_3.2H_2O$ (5 mol%) and acetonitrile (4 mL) have been taken and the reaction blend were subjected to MW condition at an interim of 5 min at 145 W for around 16-22 min; various time intervals are displayed in Table 3. The reaction completion was observed by using TLC. After completion, the mixture was poured into ice, stirred thoroughly and the separated solid was filtered, air dried and recrystallization was done using hot ethanol to get pure products 4a-j. The physical properties of the prepared compounds are displayed in Table I.

Compound (**4c**): mp. 254-257 ºC; IR (KBr) νmax (cm^{-1}): 3540, 3257, 2975, 2928, 1704, 1663, 1606, 1593, 1584, 1493, 1434, 1412, 1372, 1334, 1284, 1225, 1153, 1120, 1094, 1062, 1040; ^{1}H NMR (400 MHz, ppm, DMSO- d_6,) δ_H 1.18–1.32 (m, CH_3, 3H) , 2.48 (s, CH_3, 3H), 3.77–3.84 (m, OCH_2, 2H), 5.23 (s, CH, 1H), 6.35–7.29 (m, Ph-H, 8H), 7.53 (s, NH, 1H), 8.85 (s, NH & OH, 2H), 9.13 (s, CONH, 1H); ^{13}C NMR (125.757 MHz, ppm, DMSO-d_6,) δ_C = 164.5, 162.3, 151.7, 152.5, 147.8, 146.7, 146.5, 146.4, 143.1, 142.0, 135.9, 131.2, 128.7, 127.3, 126.0, 125.5, 119.3, 118.0, 115.7, 115.5, 112.6, 102.5, 64.2, 64.1, 63.8, 53.1, 37.8, 15.2, 14.9; HRMS: m/z [M^+] calc. 367.1530; obtained: 367.1533.

Compound (**4d**): mp. 243-246 ºC; IR (KBr) νmax (cm^{-1}): 3347, 3190, 2976, 2931, 1670, 1624, 1596, 1571, 1511, 1466, 1434, 1400, 1282, 1234, 1216, 1189, 1148, 1120, 1107, 1084, 1037, 1011; ^{1}H NMR (400 MHz, ppm, DMSO-d_6), δH 1.17–1.34 (m, CH_3, 3H), 2.46 (s, CH_3, 3H), 3.54–3.94 (m, OCH_2, 2H), 5.24 (s, CH, 1H), 6.38–7.26 (m, Ph-H, 8H), 8.88–8.94 (split peak, NH & OH, 2H), 9.51 (s, NH, 1H),10.28 (s, CONH, 1H); HRMS: m/z [M^+] calc. 383.1306; obtained: 383.1304.

Compound (**4e**): mp. 207-210 ºC; IR (KBr) νmax (cm^{-1}): 3398, 3264, 3167, 3084, 3005, 1669, 1628,1593, 1563, 1524, 1498, 1476, 1435, 1380, 1334, 1236, 1176, 1140, 1101, 1073, 1043 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm), δH 2.02 (s, CH_3, 3H), 5.72 (d, J = 2.3 Hz, CH, 1H), 7.02 (t, J = 7.27 Hz, Ph-H, 1H), 7.26 (t, J = 8.2 Hz, Ph-H, 2H), 7.37 (d, J = 8.5 Hz, Ph-H, 1H), 7.51 (d, J = 7.4 Hz, Ph-H, 3H), 7.56 (d, J = 2.6 Hz, m-Ph-H, 1H), 9.36 (s, 1H, NH), 9.86 (s, NH, 1H), 10.11 (s, CONH, 1H); ^{13}C NMR (100.612 MHz, ppm, DMSO-d_6,), δC 173.1, 165.3, 137.3, 136.7, 134.0, 132.0, 131.1, 130.8, 128.7, 127.0, 122.3, 118.4, 105.3, 51.4, 15.2; HRMS: m/z [M^+] calc. 375.0541; obtained: 375.0531.

Compound (**4f**): mp. 189-192 ºC; IR (KBr) νmax (cm^{-1}): 3396, 3275, 3086, 2361, 2340, 1671, 1653, 1628, 1597, 1561, 1541, 1521, 1496, 1471, 1438, 1329, 1233,1202, 1181, 1143, 1103, 1076, 1044; ^{1}H NMR (400 MHz, DMSO-d_6, ppm), δ_H 2.05 (s, CH_3, 3H), 5.75 (d, J = 2.5 Hz, CH, 1H), 7.02 (t, J = 7.26 Hz, p-Ph-H, 1H), 7.24 (t, J = 8.1 Hz, m, m'-Ph-H, 2H), 7.39 (d, J = 8.7 Hz, o'- Ph-H, 1H), 7.51 (d, J = 8.8 Hz, o, o' & m'-Ph-H, 3H), 7.54 (d, J = 2.0 Hz, m-Ph-H, 1H), 9.35 (s, NH, 1H), 9.87 (s, NH, 1H), 10.12 (s, CONH, 1H); HRMS (EI): m/z [M+] calc. 391.0313; obtained: 391.0315.

Compound (**4g**): mp. 193-196 ºC; IR (KBr) νmax (cm^{-1}): 3248, 2360, 1698, 1641, 1590, 1508, 1491, 1451, 1398, 1305, 1287, 1252, 1209, 1146, 1088, 1038, 1010; ^{1}H NMR (400 MHz, DMSO-d_6, ppm), δ_H 2.06 (s, CH_3, 3H), 5.58 (d, J = 3.0 Hz, CH, 1H), 6.91–7.37 (m, Ph-H, 6H),7.57 (d, J = 8.0 Hz, o, o'-Ph-H, 2H), 7.81 (s, NH, 1H), 8.84 (s, NH, 1H), 9.56 (s, CONH, 1H); HRMS (EI): m/z [M^+] calc. 313.0884; obtained: 313.0882.

Compound (**4h**): mp. 202-205 ºC; IR (KBr) νmax cm^{-1}): 3367, 3283, 1677, 1632, 1565, 1547, 1523, 1498, 1476, 1439, 1361, 1326, 1232, 1188, 1116, 1074, 1034; ^{1}H NMR (400 MHz, DMSO-d_6, ppm), δ_H 2.13 (s, CH_3, 3H), 5.64 (d, J = 3.2 Hz, CH, 1H), 6.96–7.68 (m, Ph-H, 8H), 9.63 (s, NH, 1H), 9.72 (s, NH, 1H), 10.11 (s, CONH, 1H),; ^{13}C NMR (100.614 MHz, DMSO-d_6, ppm), δ_C 173.1, 163.5, 147.9, 137.9, 138.6, 127.5, 125.7, 125.6, 123.2, 122.3, 118.7, 106.0, 50.3, 16.5; HRMS: m/z [M^+] calc. 329.0658; obtained: 329.0656.

Compound (**4i**): mp. 231-234 ºC; IR (KBr) νmax (cm^{-1}): 3410, 3284, 2363, 2340, 1683, 1652, 1626, 1597, 1538, 1521, 1486, 1442, 1384, 1330, 1260, 1241, 1163, 1123, 1073, 1032; ^{1}H NMR (300 MHz, DMSO-d_6, ppm), δ_H 2.07 (s, CH_3, 3H), 3.65 (s, OCH_3, 3H), 5.33 (s, CH, 1H), 6.70–7.55 (m, NH & Ph-H, 9H), 8.66 (s, NH, 1H), 8.92 (s, OH, 1H), 9.51 (s, CONH, 1H); ^{13}C NMR (100.614 MHz, DMSO-d_6, ppm), δ_C 164.4, 149.5, 145.3, 144.8, 137.1, 136.8, 135.1, 125.4, 121.0, 118.5, 117.4, 112.2, 110.7, 103.5, 57.4, 54.7, 19.9; HRMS: m/z [M^+] calc. 353.1366; obtained: 353.1363.

Compound (**4j**): mp. 206-209 ºC; IR (KBr) νmax (cm^{-1}): 3396, 3192, 1672, 1633,1598, 1563, 1532, 1467, 1438, 1382, 1233, 1201, 1101, 1043; ^{1}H NMR (400 MHz, DMSO-d_6, ppm), δ_H 2.02 (s, CH_3, 3H) 5.73 (d, J = 2.2 Hz, CH, 1H), 7.26–7.31 (split peak, o' & m'-Ph-H, 2H), 7.43 (d, *J* = 2.1 Hz, m, m'-Ph-H,2H),7.51–7.53 (m, o, o' & m-Ph-H, 3H) 7.57 (s, NH, 1H),8.88 (s, NH, 1H), 9.81 (s, CONH, 1H); HRMS: m/z [M^+] calc. 409.0151; obtained: 409.0141.

D. Screening of Antioxidant Activity

The free radical-scavenging property of prepared derivatives was predicted utilizing the standard ascorbic acid by DPPH radical scavenging method. This

investigation is generally in view of the measurement of the consolidating ability of products towards the radical DPPH.

The extinction of absorbance of buyable radical is estimated using spectrophotometer at 517 nm in a dimethyl sulfoxide (DMSO) solution use of UV/Vis-spectrophotometer underneath thermostatic conditions at 25 ºC. DPPH has a single electron and it has a descent absorption band observed at 517 nm. At the point when the odd electron ends up matched, the absorption band diminishes respectively and the number of atoms becomes paired.

The change in absorbance has been widely used to test the potential of synthesized compounds to act as a radical scavenger. Therefore, faster is the lowering of absorbance; greater is the antioxidant property of the substance.

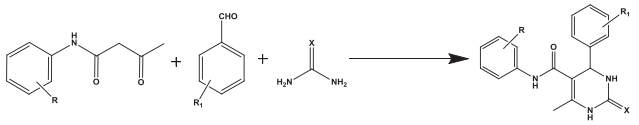
In a test tube 3.0 mL solution of a newly prepared DPPH of 6.02 x 10^{-5} Molar solution in dimethyl sulfoxide and 100 micro litre of a DMSO solution of each synthesized product was added. After this the test sample was kept at room temperature for 30 min in dull condition and the absorbance of the solution was measured at 517 nm. The control has all reagents except prepared compound. The analysis was done thrice and the average absorbance values are considered. The DPPH scavenging property was expressed in hinderance rate (I %) as depicted by Sokmen *et al.,* 2006[33].

Inhibition percentage (%) = [(control Optical Density– sample Optical Density)/control Optical Density] X 100.

II. Results and Discussion

The one pot three component reaction for the synthesis of 4-aryl pyrimidine-5-carboxamide via reaction between substituted benzaldehyde, actoacetanilide, urea or thiourea using ruthenium(III) chloride dihydrate $RuCl_3.2H_2O$ under traditional heating and microwave irradiation methods were reported (Scheme 1). $RuCl_3.2H_2O$ is a powerful catalyst for the preparation of DHPM, when compared with other catalysts like Lewis acid which are represented in the old report.

SCHEME I
SYNTHETIC PROTOCOL OF COMPOUND 4A-J



To enhance the reaction condition, the condensation reaction was chosen using acetoacetanilides, benzaldehyde and urea using $RuCl_3.2H_2O$ under traditional and microwave method. The different solvent systems like dichloromethane, chloroform, methanol, ethanol, acetonitrile and different synergist mole percent of catalyst was additionally analyzed and the outcomes were exhibited in Table II & III.

Table one reveals that polar protic solvents like ethanol, methanol and acetonitrile gave high yields. In comparison the nonpolar solvent such as DCM, $CHCl_3$. Results obtained indicate that CH_3CN is a suitable solvent for this conversion.

TABLE II.
EFFECT OF SOLVENT SYSTEM

S. No	Solvents	mol %	Time (min.)	Yield (%)
1	$CHCl_3$	5	25	33
2	DCM	5	25	29
3	C_2H_5OH	5	16	75
4	CH_3OH	5	16	73
5	CH_3CN	5	15	91

The results indicate these reactions proceeded more effectively under microwave condition when compared with that of traditional heating. Further, impact of loading of catalyst was examined. The viable catalyst mole percent is seen to be 5 mol %, while expanding the mole level of catalyst did not display any improvement in the yield rate. After enhancement, the best reaction condition was utilized for preparation of 5-carboxamide dihydropyrimidine utilizing various aldehydes, thiourea or urea and different acetoacetanilide under customary warming and microwave method to produce dihydropyrimidinone substances by $RuCl_3.2H_2O$ as a catalyst. (Table I).

TABLE III.
EFFECT OF CATALYSTS LOADING

S. No	Catalyst	mol %	Reaction Period (min.)	Yield (%)
1	$RuCl_3.2H_2O$	5	15	91
2	$RuCl_3.2H_2O$	10	15	91
3	$RuCl_3.2H_2O$	15	15	91

The catalyst $RuCl_3.2H_2O$ has exceptional solvency in water and is effectively evacuated by washing with water. All the prepared substances were described through spectroscopic techniques.

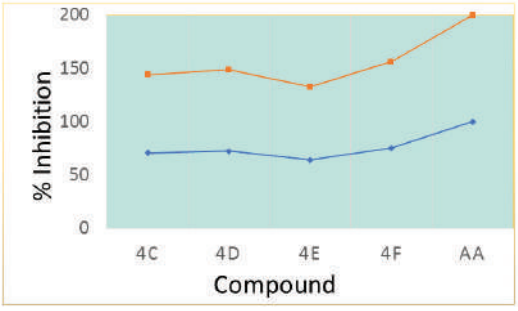


Figure 1. Comparison of antioxidant property of compound 4a-j.

Antioxidant Activity

Antioxidant studies of all the prepared compounds 4(a-j) were accomplished using radical scavenging technique. The antioxidant reports exhibited that compound 4d, 4c, 4e and 4f show acceptable radical scavenging property when compared to that of standard ascorbic acid (100%), while that of compounds 4a, 4b, 4g, 4h, and 4i did not indicate

antioxidant property even at 100 µg/mL and one hour of incubator time.

Radical scavenging properties of the new substances 4(**a-j**) and ascorbic acid at 100 µg/mL after 30 minutes and one hour of incubatory interval in dark at 25 °C are appeared in Figure. 1.

TABLE IV.

ANTIOXIDANT PROPERTY OF SUBSTANCES **4A-J** UTILIZING FREE RADICAL SCAVENGING TECHNIQUE

Incubation for 30 min			Incubation for one hour		
Compound	Absorbance	% Antioxidant activity	Compound.	Absorbance	% Antioxidant activity
4c	2.02	70.68	4c	1.93	73.47
4d	1.98	72.45	4d	1.75	76.13
4e	2.59	64.02	4e	2.26	68.81
4f	1.67	75.34	4f	1.43	80.77
Control	7.00				

The radical scavenging property for dimethyl sulfoxide solutions of new substances **4a-j** are represented in (Table 4) compared with standard ascorbic acid.

III. CONCLUSIONS

Easy and greener technique for the preparation of pyrimidine-5-carboxamide compounds via single step three substance cyclisation reaction of various substituted acetoacetanilides, thiourea or urea and different aldehydes under traditional heating and MW method by utilizing $RuCl_3.2H_2O$ catalyst. The main benefits of this procedure are moderate reaction conditions, shorter response times, easy work-up and excessive yields. The prepared substances **4a-j** have been monitored for antioxidant studies using radical scavenging technique. The products 4c, 4d, 4e and 4f showed acceptable antioxidant property when compared to that of other synthesized compounds.

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