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

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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 CH3CN as a solvent. The structures of the new substances have been affirmed through FT-IR, 13C NMR, 1H 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], neuroepetic 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 dihydropyrimidinones 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 ZrCl4 [14], Cu(OTf)2 [15], AcOH [16], CdCl2[17], Ionic liquids [18], SiO2/H2SO4[19], ion-exchange resin[20], La(OTf)3 [21], LiBr[22],p-TSA[23], (NH4)2Ce(NO3)6 [24], MgBr2[25], InBr3 [26], ultrasound irradiation[27] microwave[28] and solvent-free conditions [29], ZnCl2/TOAB [30], Co(NOs)2.6H2O [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.

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.

| Table I. Experimental Results and Physical Data of Arylpymidine-5-carboxamide Derivatives |
| --- |
| Co | mp ond | R | R | X | Reaction time (min.) | Yield (%) | m.p. (°C) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 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-Cl-Ph | O | 18 | 460 | 87 | 78 | 254-256 |
| 4d | H | 3-OEt-4-OMe-Ph | S | 21 | 440 | 82 | 76 | 243-245 |
| 4e | H | 2,4-Ci-Ph | O | 21 | 460 | 83 | 77 | 207-209 |
| 4f | H | 2,4-Ci-Ph | S | 20 | 470 | 83 | 74 | 189-191 |
| 4g | H | 2-CiH5 | O | 17 | 400 | 84 | 78 | 191-193 |
| 4h | H | 2-CiH5 | 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-Ci-Ph | O | 16 | 450 | 86 | 80 | 206-208 |

Microwave, Dihydropyrimidine

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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 acetoacetanilide (1 milli mol), aldehyde (1 milli mol), thiourea or urea (1.5 milli mol), RuCl3·2H2O (5 mole %) and 30 mL CH3CN have been refluxed according to time interval 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 acetoacetanilide (1 milli mol), aldehyde (1 milli mol), thiourea or urea (1.4 milli mol), RuCl3·2H2O (5 mol%), aldehyde (1 milli mol), thiourea or urea (1.4 milli mol), RuCl3·2H2O (5 mol%) and acetonitrile (4 mL) have been taken and the reaction blend were subjected to MW condition at an interim (5 mol%) and acetonitrile (4 mL) have been taken and the reaction blend were subjected to MW condition at an interim 1H), 7.02 (t, J = 7.26 Hz, p-Ph-H, 1H), 7.24 (t, J = 8 Hz, m'-Ph-H, 2H), 7.39 (d, J = 8.7 Hz, o'- Ph-H, 1H), 7.51 (d, J = 8.8 Hz, 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+H]+ calc. 391.0313; obtained: 391.0315.

Compound (4f): mp: 198-205 °C; IR (KBr) vmax (cm⁻¹): 3248, 2360, 1698, 1641, 1590, 1504, 1451, 1398, 1305, 1287, 1252, 1209, 1146, 1088, 1038, 1010; 1H NMR (400 MHz, DMSO-d6, ppm), δH 2.06 (s, CH3, 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); 13C NMR (100.614 MHz, DMSO-d6, ppm), δC 173.1, 163.5, 147.9, 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. 367.1550; obtained: 367.1533.

**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

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The 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 underneathtermostatic conditions at 25 °C. 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].

\[
\text{Inhibition percentage (\%) = } \left[ \frac{(\text{control Optical Density} - \text{sample Optical Density})}{\text{control Optical Density}} \right] \times 100.
\]

### II. RESULTS AND DISCUSSION

The one pot three component reaction for the synthesis of 4-aryl pyrimidine-5-carboxamide via reaction between substituted benzaldehyde, acetoacetanilide, urea or thiourea using ruthenium(III) chloride dihydrate RuCl₃.2H₂O under traditional heating and microwave irradiation methods were reported (Scheme 1). RuCl₃.2H₂O 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 RuCl₃.2H₂O under traditional heating and microwave method. The different solvent systems like dichloromethane, chloroform, methanol, ethanol, acetonitrile and different synregist 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, CHCl₃ Results obtained indicate that CH₃CN is a suitable solvent for this conversion.

### TABLE II.

**EFFECT OF SOLVENT SYSTEM**

| S. No | Solvents  | mol % | Time (min.) | Yield (%) |
|-------|-----------|-------|-------------|-----------|
| 1     | CHCl₃     | 5     | 25          | 33        |
| 2     | DCM       | 5     | 25          | 29        |
| 3     | C₃H₆OH    | 5     | 16          | 75        |
| 4     | CH₃OH     | 5     | 16          | 73        |
| 5     | CH₃CN     | 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 dihydroxypyrindine utilizing various aldehydes, thiourea or urea and different acetoacetanilide under customary warming and microwave method to produce dihydroxypyrindinone substances by RuCl₃.2H₂O as a catalyst. (Table I).

### TABLE III.

**EFFECT OF CATALYSTS LOADING**

| S. No | Catalyst | mol % | Reaction Period (min.) | Yield (%) |
|-------|----------|-------|------------------------|-----------|
| 1     | RuCl₃.2H₂O | 5     | 15                     | 91        |
| 2     | RuCl₃.2H₂O | 10    | 15                     | 91        |
| 3     | RuCl₃.2H₂O | 15    | 15                     | 91        |

The catalyst RuCl₃.2H₂O 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, 4e, 4f and 4i 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 4a-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.

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 acetoacetamidines, thiourea or urea and different aldehydes under traditional heating and MW method by utilizing RuCl$_3$.2H$_2$O 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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### TABLE IV.

| Compound | % Antioxidant activity | % Antioxidant activity |
|----------|------------------------|------------------------|
| 4c | 1.93 | 73.47 |
| 4d | 1.75 | 76.13 |
| 4e | 2.26 | 68.81 |
| 4f | 1.43 | 80.77 |

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