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Article

Microwave-assisted Synthesis of Naphthyl Pyrimidinones and their Antioxidant Activity

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ABSTRACT

Microwave-assisted synthesis of naphthyl pyrimidinones (**4-6**) was successfully completed after reacting naphthyl thiosemicarbazones (**1-3**) with ethyl cyanoacetate in the presence of neutral alumina (Al_2O_3) and few drops of piperidine under solvent-free conditions. The characterization of compounds (**4-6**) was done by spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and MS) and analytical data. The new compounds were screened for antioxidant activity by DPPH radical scavenging assay, during which compounds depicted moderate to good DPPH radical scavenging activity.

Key words: Antioxidant activity, Microwave synthesis, Naphthyl pyrimidinones.

1. INTRODUCTION

Pyrimidinones have been paid increasing attention, due to their various therapeutic and pharmacological properties, such as antiviral, antibacterial, antihypertensive, and antitumor effects [1]. More recently, they emerged as integral backbones of several calcium blockers, antihypertensive agents, α-1a-antagonists, and neuropeptide Y antagonists [2]. Pyrimidinone derivatives are found as core units in many marine alkaloids (batzelladine and carambine), which have been found to be potent to HIV-gp-120 CD4 inhibitors [3]. Due to the remarkable biological utilization, the pyrimidinones attract many researchers as well as academicians.

Recently, several methods improved the procedure using phosphorus pentoxide-methanesulfonic acid [4], potassium *tert*-butoxide (*t*-BuOK) [5], ammonium dihydrogen phosphate [6], silica gel [7], mesoporous molecular sieve MCM-41 [8], cyanuric chloride [9], nano-BF3·SiO_2 [10], silica gel supported polyphosphoric acid [11], zirconium (IV) chloride [12], and indium (III) bromide [13] as catalysts. However, some of these one-pot procedures generally require strong protic or Lewis acids, prolonged reaction times, and high temperature. Consequently, there is a scope for further modification toward mild reaction condition, increased variation of the substituents, and improved yields.

Microwave promoted solvent-free reactions [14] are well known as environmentally benign methods that also usually provide improved selectivity, enhanced reaction rates, cleaner products, and manipulative simplicity [15] but these procedures are practically limited as the solvents in microwave oven at elevated temperatures create high pressures, which may cause explosion. To circumvent these problems, there is a need for the development of newer methods which proceed under mild and solvent-free condition. Nowadays, solvent-free reactions gained much importance in organic synthesis because of the high yields and shorter reaction times. Hence, herein, we represent the microwave-assisted, solvent-free synthesis of naphthyl pyrimidinones and will depict their antioxidant behavior.

2. EXPERIMENTAL

2.1. General

The Kofler apparatus was used to determine the melting points in degrees Celsius and is uncorrected. The PerkinElmer RXI Spectrophotometer was used to record the IR spectra on with and values are given in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were run in $CDCl_3$ on a JEOL Eclipse (400 MHz) instrument with TMS as internal standard and values are given in ppm (δ). Mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer. The elemental analyses were performed using thermo EA 2110 series. For microwave irradiation, a microwave oven equipped with a turntable was used (LG smart chef MS-255R operating at 2450 MHz having maximum output of 900 W) for reaction. Thin-layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapors to check the homogeneity as well as the progress of reaction. Petroleum ether refers to a fraction of boiling point 60–80°C. Sodium sulfate (anhydrous) was used as a drying agent. All the chemicals were purchased from Merck India and were used after distillation.

2.2. Microwave-assisted synthesis of naphthyl pyrimidinones (4-6).

A mixture of compound (**4-6**) [16], (1 mmol), ethyl cyanoacetate (1 mmol), 1 g of neutral alumina (Al_2O_3), and 2–3 drops of piperidine was irradiated in a microwave oven operating medium power (600 watts) for 45 s. The progress of a reaction was monitored by TLC using ethyl acetate: hexane (2:8) solvent system. After completion of a reaction, reaction mixture was cooled to room temperature and poured on crushed ice. Recrystallization was done in acetic acid and neutral alumina was recovered by simple filtration.

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2.2.1. 1-[(4-chloro-1,2-dihydronaphthalen-3-yl)-1-methylene]-6'-amino-2'-thioxo-4'-oxo-3',4'-dihydro pyrimidine (4)

Red crystals; yield 82%; mp 163°C; IR (KBr, cm^{-1}): 3335 (NH), 1665 (*CO*NH), 1640 (C=N), 1630 (C=C arom), 1622 (C=C), 1230 (C=S), 1140 (N-N), 1020 (C-N), 740 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 7.61–7.36 (m, 4H, arom.), 6.8 (s, 1H, N*H*, exchangeable with D_2O), 5.1 (s, 1H, C_5'-H), 5.3 (s, 1H, C*H*=N), 2.6 (q, 2H, CH_2), 2.3 (t, 2H, CH_2), 2.0 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$), δ: 181 (C=S), 169 (C=O), 160.8 (C=N), 131 (C_5'), 111 (C_6'), 122-128 (6C, Arom.), 64.0, 62 (2×CH_2), 42 (C-Cl). Anal. calcd for $C_{15}H_{15}N_4OSCl$: C, 53.81, H, 4.52, N, 16.73 found: C, 53.44, H, 4.07, N, 16.31; ESI MS: *m/z* 334/336 [M^+].

2.2.2. 1-[(4-hydroxy-1,2-dihydronaphthalen-3-yl)-1-methylene]-6'-amino-2'-thioxo-4'-oxo-3',4'-dihydro pyrimidine (5)

Red crystals; yield 77%; mp 171 C; IR (KBr, cm^{-1}): 3673 (OH), 3332 (NH), 1667 (*CO*NH), 1644 (C=N), 1624 (C=C arom), 1620 (C=C), 1233 (C=S), 1136 (N-N), 1080 (C-O), 1020 (C-N). ^{1}H-NMR ($CDCl_3$) δ: 7.61–7.35 (m, 4H, arom.), 7.1 (s, 1H, OH, exchangeable with D_2O), 6.7 (s, 1H, N*H*, exchangeable with D_2O), 5.3 (s, 1H, C_5'-H), 5.5 (s, 1H, C*H*=N), 2.3 (q, 2H, CH_2), 2.1 (t, 2H, CH_2), 2.4 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$), δ: 183 (C=S), 167 (C=O), 161 (C=N), 133 (C_5'), 114 (C_6'), 124-129 (6C, Arom.), 66.0, 63.2 (2×CH_2), 72 (C-O). Anal. calcd for $C_{15}H_{16}N_4O_2S$: C, 56.94, H, 5.10, N, 17.71 found: C, 56.71, H, 4.93, N, 16.98; ESI MS: *m/z* 316 [M^+].

2.2.3. 1-[(1,2-dihydronaphthalen-3-yl)-1-methylene]-6'-amino-2'-thioxo-4'-oxo-3',4'-dihydro pyrimidine (6)

Dark red crystals; yield 79%; mp 167°C; IR (KBr, cm^{-1}): 3331 (NH), 1665 (*CO*NH), 1641 (C=N), 1621 (C=C arom), 1626 (C=C), 1233 (C=S), 1136 (N-N), 1020 (C-N). ^{1}H-NMR ($CDCl_3$) δ: 7.60–7.33 (m, 4H, arom.), 6.4 (s, 1H, N*H*, exchangeable with D_2O), 5.2 (s, 1H, C_5'-H), 5.4 (s, 1H, C*H*=N), 5.0 (s, 1H, C_4-*H*), 2.3 (q, 2H, CH_2), 2.1 (t, 2H, CH_2), 2.4 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$), δ: 180 (C=S), 166 (C=O), 160 (C=N), 133 (C_5'), 114 (C_6'), 124–130 (6C, Arom.), 66.0, 63.2 (2×CH_2). Anal. calcd for $C_{15}H_{16}N_4OS$: C, 59.98, H, 5.37, N, 18.65 found: C, 59.77, H, 5.01, N, 18.10; ESI MS: *m/z* 300 [M^+].

2.3. DPPH Radical Scavenging Assay

Compounds (**4-6**) were tested for *in vitro* antioxidant activities by DPPH free radical scavenging assay method [17]. Total volume of assay mixtures was 1 mL and contained methanolic DPPH solution (0.1 mM) and different concentrations of new compounds (**4-6**). After incubation in the dark at R.T for 45 min, absorbance of the samples (A_{sample}) was measured at 517 nm. Assay mixture without compound (**4-6**) was used as a control (control absorbance, Acontrol). All experiments were in triplicates and results were expressed as the mean ± standard deviation. Citric acid was used as a positive control. Free radical scavenging effect was calculated using the formula given below

$$\text{Scavenging effects (\%)} = \frac{\text{A(control)-A(sample)}}{\text{A(control)}}$$

3. RESULTS AND DISCUSSION

3.1. Chemistry

In the view of the above-mentioned limitations of the already reported methods [4-13], pharmacological importance of dihydropyrimidinones [1-3], and our ongoing endeavors to conduct organic synthesis under solvent-free conditions [18], we describe an expeditious solvent less microwave accelerated approach for the rapid synthesis of naphthyl dihydropyrimidinones. The naphthyl thiosemicarbazone derivatives (**1-3** 1 mmol) on reaction with ethyl cyanoacetate (1 mmol) and 1 g of neutral alumina (Al_2O_3) using dry conditions yielded corresponding naphthyl dihydropyrimidinones (**Scheme 1**). The procedure was carried out by varying microwave power from 150 watts to 700 watts. It was observed that by increase in power up to 600 watts, there was increase in yield and shortened reaction time. Beyond the 600 watts, there was no significant change in reaction time and yield.

The mechanism (**Scheme 2**) for the formation of compounds **4-6** involves the nucleophilic attack of the nitrogen of thiosemicarbazone on the carbonyl carbon of ethyl cyanoacetate, making the ethoxy group to leave, with a simultaneous attack of another nitrogen of thiosemicarbazone on the cyano group of ethyl cyanoacetate, converting it to =C–NH_2, which leads to the formation of a pyrimidinone heterocyclic moiety.

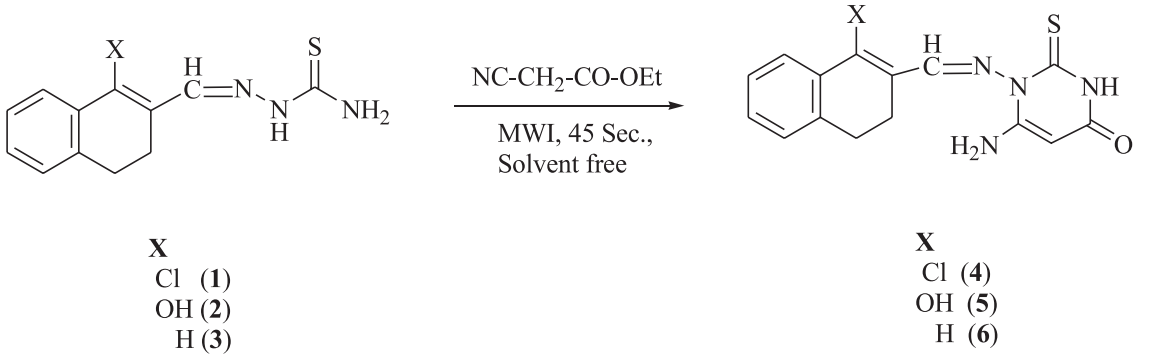
The characterization studies are in good agreement with the proposed structures for naphthyl pyrimidinones **4-6** shown in **Scheme 1**. In the IR spectra, the absorption bands in the ranges 3331–3335 cm^{-1} were attributed to the NH, group, respectively, while a strong absorption bands at 1665–1667, 1640–1644, and 1621–1630 cm^{-1} confirmed the presence of the *CO*NH, C=N, and C=$C_{(arom.)}$ groups, respectively, in compounds **4-6**. In our ^{1}H-NMR study, the two singlets in the range δ 6.4–6.8 and 2.0–2.4 confirmed the presence of N*H* and NH_2, respectively, while the singlet at δ 5.1–5.3 and δ 5.4 depicted the presence of an olefinic protons, that is, C_5'-*H* and C*H*=N groups, respectively, in compounds **4-6**. In our ^{13}C-NMR study, the signals at δ 181–183, 166–169, 160–161, and 122–130 confirmed the presence of the C=S, C=O, C=N, and aromatic C=C groups, respectively, in compounds **4-6**. Finally, the presence of distinct molecular ion peaks [M^+] at m/z 334/336, 316, and 300 in the MS spectra also proved the formation of the compounds **4-6**. This strategy can also be applied to diverse thiosemicarbazones; in that way, pyrimidinones may also allow further modifications on the substituted heterocyclic systems.

3.2. DPPH Radical Scavenging Assay

The radicals are inactivated by the antioxidants by their free radical scavenging or hydrogen donation abilities [19]. DPPH is a stable nitrogen-centered free radical and is well known scavenger used in antioxidant assay because of fast and simple method [20]. The radical scavenging activities of compounds (**4-6**) in comparison with citric acid were determined by DPPH assay and the results are shown in **Table 1**. The stock solution of the compounds was prepared in water at 1 mM and their DPPH radical scavenging activity tested at 20, 40, 60, and 80 µM concentrations. As shown in **Table** 1, of DPPH free radical scavenging values of Compound 4 ranged from 15.22 ± 0.21% (20 µM) to 33.22 ± 0.32 % (80 µM). Compound **5** showed better potential DPPH free radical scavenging activity at all of the concentrations (17.71 ± 0.24%, 23.26 ± 0.61%, 28.61 ± 0.2%, and 31.33 ± 0.41%), respectively. The compound **6** also exhibited the potential DPPH free radical scavenging activity from 14.12 ± 0.22% to 35.17 ± 0.14% inhibition from 20 µM to 80 µM of compounds. Citric acid (positive control) showed more DPPH free radical scavenging activity than all of tested compounds (**4-6**).

Table 1: Radical scavenging activity on DPPH radicals (%) of the compound (4-6).

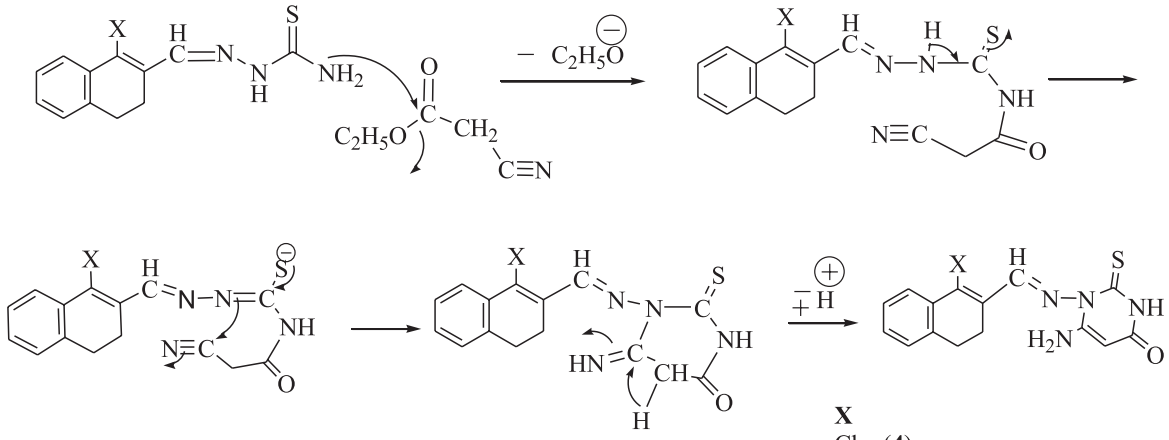
Conc. (µM)	4	5	6	Citric acid
20	15.22±0.21	17.71±0.24	14.12±0.22	70.31±0.42
40	24.51±0.30	23.26±0.61	21.61±0.31	75.22±0.35
60	26.21±0.63	28.61±0.27	27.26±0.51	79.45±0.14
80	33.22±0.32	31.33±0.41	35.17±0.14	82.51±0.23



X
Cl (**1**)
OH (**2**)
H (**3**)

X
Cl (**4**)
OH (**5**)
H (**6**)

Scheme 1: Pathway for the formation of naphthyl pyrimidinones **4-6.**



X
Cl (**4**)
OH (**5**)
H (**6**)

Scheme 2: Mechanism for the formation of naphthyl pyrimidinones (**4-6**).

4. CONCLUSION

We have successfully prepared the strategy for the microwave-assisted synthesis of naphthyl pyrimidinone derivatives under solvent-free reaction condition. Another advantage of this method is better yields in shorter reaction time with high purity of the products. The antioxidant activity investigation of these compounds showed that they have moderate DPPH radical scavenging activity.

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***Bibliographical Sketch**

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