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Microwave assisted synthesis of new curcumin analogues conjugated dihydro-4-pyridones

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ABSTRACT

New curcumin analogues, conjugated dihydro-4-pyridones were synthesized via reaction of curcumin with primary amines or amine acetates under microwave irradiation. Montmorillonite K-10 was used as a catalyst and reaction times within the period 60-90 s. The synthesized compounds were characterized on the basis of their IR, UV-Vis, ^{1}H, ^{13}C NMR and mass spectra.

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1. Introduction

Due to their importance as intermediates for the synthesis of natural products, dihydropyridones have been studied extensively as precursors for the synthesis of piperidines, hydroquinolines, indolizidines, quinolizidines, dienoic amides and other alkaloids that have a wide range of biological and pharmacological properties [1-5]. For their synthesis, the addition of Grignard reagents to 1-acyl-4-methoxy pyridinium salts have been used by Comins [6-9]. Hetero-Diels-Alder reactions or stepwise, formal [4+2] transformations involving imines have also been employed [10-14]. They have also been synthesized via cyclization of α,β-unsaturated 1,3-diketones in acidic medium [15] and through catalytic metathesis of *o*-alkynylanilines and aldehydes [16]. A facile route to functionalized dihydropyridones has been developed via formal [5C+1N] of α-alkanoyl ketene-(S,S)-acetals with aliphatic amines [17]. In addition, partial reduction of pyridinium salts had also been used for their synthesis [18]. Enantiopure dihydropyridones were synthesized from intramolecular hydride addition to pyridinium salts [19]. Recently, dihydropyridones were synthesized via the asymmetric annulations of α,β-unsaturated acyl ammonium intermediates with either 1,3-dicarbonyls, β-ketoesters or aza-aryl ketones [20]. Within this field we used microwave radiation (MWI) to induce the reaction between curcuminoids and simple amines or amine acetates in the presence Montmorillonite K-10 to synthesize dihydropyridones [21-23].

In continuation with our interest in using green chemistry to prepare such important compounds we report her the microwave assisted synthesis of novel dihydropyridones from the reaction of the 1,3-diketone (**1**) with amines or amine acetates. The reported compounds had not been previously obtained by conventional methods.

2. Experimental

2.1. General

Melting points were determined in a Buchi-510 apparatus. NMR spectra were recorded on a Bruker 400 MHz spectrometer in DMSO-d_6 with tetramethylsilane as an internal standard. Mass spectra were determined on Shimadzu GCMS-QP 1000 EX instrument. Infrared spectra were recorded as KBr discs on Agilent Cary 660 FT-IR spectrometer. UV-Visible spectra were recorded on CECIL 7600 spectrophotometer in ethanol using quartz cells with 1cm bath length.

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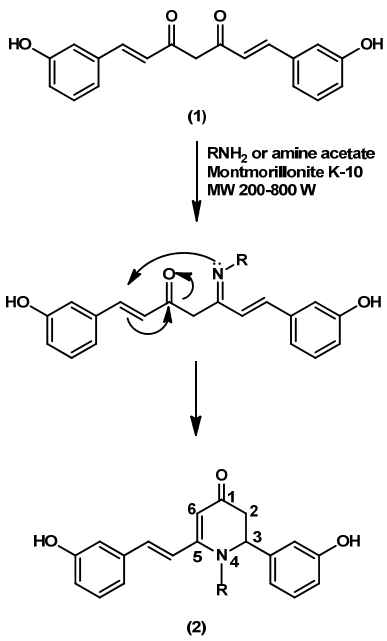

R: **2a** = *n*-Methyl
2b = *n*-Ethyl
2c = *n*-Propyl
2d = *n*-Butyl
2e = *n*-Pentyl
2f = 4-Aminophenyl
2g = 4-Amino-2-hydroxyphenyl

Scheme 1

2.2. General method for the synthesis of dihydropyridones

The curcuminoid (**1**) was prepared according to previously described method [24]. The new dihydropyridones were synthesized following the method described by Elias *et al*. [21]. The curcuminoid (**1**) (2.0 g, 6.16 mmol) and Montmorillonite clay K-10 (3 g) were thoroughly mixed and placed in a 10 mL beaker. The adequate amount of the amine (in case of aliphatic amines) or the amine acetate (in case of aromatic amines) was added to the mixture and mixed. The mixture then subjected to microwave radiations in a commercial microwave oven (Samsung 800 MW) for 60 s at 200 W (in the case of aliphatic amines) and at 800 W for 90 s (in the case of amine acetate). The reaction was monitored by TLC using ethanol:chloroform (15:85, *v:v*) as an eluent. On reaction completion, the mixture was extracted with ethanol (5 × 3 mL) and filtered to remove the Montmorillonite and the solvent was evaporated under vacuum and the products were recrystallized from ethanol (Scheme 1).

1-Methyl-2-(3-hydroxyphenyl)-6-(3-hydroxystyryl)-2, 3-di hydropyridin-4(1H)-one (**2a**): Color: Yellow. Yield: 18%. M.p.: 206-208 °C. FT-IR (KBr, ν, cm^{-1}): 3234 (OH) (br, phenol), 1630 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.85 (dd, *J* = 15.6 and 2.6 Hz, 1H, 2-H), 2.97 (dd, *J* = 15.6 and 7.2 Hz, 1H, 2-H), 3.09 (s, 3H, N -CH_3), 4.70 (m, 1H, 3-H), 5.09 (s, 1H, 6-H), 6.53-7.16 (m, 10H, Olefinic + Ar-H), 9.44 (br, 2H, OH). MS (ESI, *m/z* (%)): 321.1363 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 345 (6650).

1-Ethyl-2-(3-hydroxyphenyl)-6-(3-hydroxystyryl)-2, 3-di hydropyridin-4(1H)-one (**2b**): Color: Yellow. Yield: 20%. M.p.: 215-217 °C. FT-IR (KBr, ν, cm^{-1}): 3375 (OH) (br, phenol), 1630 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (t, *J* = 7.2 Hz, 3H, N-CH_2-CH_3), 2.35 (dd, *J* = 15.6 and 2.6 Hz, 1H, 2-H), 2.89 (dd, *J* = 15.6.4 and 7.2 Hz, 1H, 2-H), 3.08 (m, 1H, NCH_2), 3.77 (m, 1H, NCH_2), 4.78 (m, 1H, 3-H), 5.0 (s, 1H, 6-H), 6.63-7.20 (m, 10H, Olefinic + Ar-H), 9.44 (s, 1H, OH), 9.54 (s, 1H, OH). MS (ESI, *m/z* (%)): 335.1513 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 345 (5640).

1-Propyl-2-(3-hydroxyphenyl)-6-(3-hydroxystyryl)-2, 3-di hydropyridin-4(1H)-one (**2c**): Color: Yellow. Yield: 20%. M.p.: 242-243 °C. FT-IR (KBr, ν, cm^{-1}): 3304 (OH) (br, phenol), 1630 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.84 (t, *J* = 7.2 Hz, 3H, N-$(CH_2)_2$-CH_3), 1.56 (m, 2H, N-CH_2–CH_2), 2.35 (dd, *J* = 15.6 and 2.6 Hz, 1H, 2-H), 2.92 (dd, *J* = 15.6 and 7.2 Hz, 1H, 2-H), 2.96 (m, 1H, NCH_2), 3.43 (m, 1H, NCH_2), 4.78 (m, 1H, 3-H), 5.06 (s, 1H, 6-H), 6.63-7.20 (m, 10H, Olefinic + Ar-H), 9.44 (broad, 2H, OH). MS (ESI, *m/z* (%)): 349.1668 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 346 (7150).

1-Butyl-2-(3-hydroxyphenyl)-6-(3-hydroxystyryl)-2, 3-di hydropyridin-4(1H)-one (**2d**): Color: Yellow. Yield: 18%. M.p.: 205-206 °C. FT-IR (KBr, ν, cm^{-1}): 3292 (OH) (br, phenol), 1631 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.85 (t, *J* = 7.2 Hz, 3H, N-$(CH_2)_3$-CH_3), 1.28 (m, 2H, N-$(CH_2)_2$-CH_2), 1.59 (m, 2H, N-CH_2-CH_2), 2.35 (dd, *J* = 15.6 and 2.6 Hz, 1H, 2-H), 2.92(dd, *J* = 15.6 and 7.2 Hz, 1H, 2-H), 2.96(m, 1H, NCH_2), 3.82 (m, 1H, NCH_2), 4.82 (m, 1H, 3-H), 5.09 (s, 1H, 6-H), 6.66-7.23 (m, 10H, Olefinic + Ar-H), 9.45 (br, 2H, OH). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 13.7 (1C, CH_3), 19.3 (1C, CH_2-CH_3), 31.4 (1C, CH_2-CH_2-CH_3), 40.1 (1C, CH_2-CH_2-CH_2-CH_3), 50.1 (1C, C-C=O), 60.5 (1C, C-N), 96.3 (1C, CH-C=O), 113.1 (1C, CH=CH-N), 114.1 (1C, O=C-CH=CH-N), 116.3 (1C, Ar-C), 116.9 (1C, Ar-C), 118.5 (1C, Ar-C), 122.1(1C, Ar-C) ,129.5 (1C, Ar-C), 129.7 (1C, Ar-C), 136.9 (1C, Ar-C), 137.0 (1C, Ar-C), 141.0 (1C, Ar-C), 157.4 (1C, Ar-C), 157.6 (1C, C-OH), 160.0 (1C, C-OH), 187.8 (1C, C=O). MS (ESI, *m/z* (%)): 363.1826 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 346 (8300).

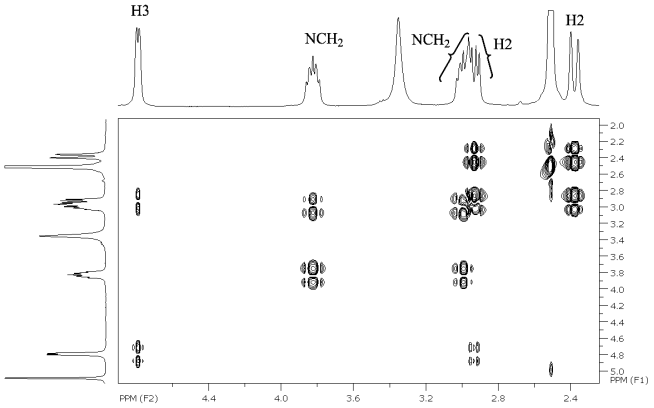

Figure 1. HOMO-COSY spectrum of the compound **2d** (the aromatic region is not included).

1-Pentyl-2-(3-hydroxyphenyl)-6-(3-hydroxystyryl)-2, 3-di hydropyridin-4(1H)-one (**2e**): Color: Yellow. Yield: 23%. M.p.: 192-194 °C. FT-IR (KBr, ν, cm^{-1}): 3365 (OH) (br, phenol), 1630 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.79 (t, *J* = 7.2 Hz, 3H, N-$(CH_2)_4$-CH_3), 0.82 (m, 2H, N-$(CH_2)_3$-CH_2), 1.22 (m, 2H, N-$(CH_2)_2$-CH_2), 1.50 (m, 2H, N-CH_2-CH_2), 2.35 (dd, *J* = 15.6 and 2.6 Hz, 1H, 2-H), 2.89 (dd, *J* = 15.6 and 7.2 Hz, 1H, 2-H), 2.96 (m, 1H, NCH_2), 3.79 (m, 1H, NCH_2), 4.76 (m, 1H, 3-H), 5.06 (s, 1H, 6-H), 6.62-7.20 (m, 10H, Olefinic + Ar-H), 9.50 (s, br, 2H, OH). MS (ESI, *m/z* (%)): 377.1985 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 346 (6724).

1-*(4-Aminophenyl)-2-(3-hydroxyphenyl)-6-(3-hydroxy styryl)-2,3-dihydropyridin-4(1H)-one* (**2f**): Color: Yellow. Yield: 16%. M.p.: 198-200 °C. FT-IR (KBr, ν, cm^{-1}): 3188 (OH) (br, phenol), 1631 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.57 (dd, *J* = 16. 6 and 1.7 Hz, 1H, 2-H), 3.19 (dd, *J* = 16.6 and 5.6 Hz, 1H, 2-H), 4.5 (s, br, 2H, NH_2), 5.17 (m, 1H, 3-H), 5.48 (s, 1H, 6-H), 6.41-7.56 (m, 14H, Olefinic + Ar- H), 9.59 (s, br, 2H, OH). MS (ESI, *m/z* (%)): 398.4903 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 357 (5770).

1-(4-Amino-2-hydroxyphenyl)-2-(3-hydroxyphenyl)-6-(3-hydroxystyryl)-2,3-dihydropyridin-4(1H)-one (**2g**): Color: Yellow. Yield: 16%. M.p.: 251-253 °C. FT-IR (KBr, ν, cm^{-1}): 3275 (OH) (br, phenol), 1630 (C=O) (ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.54 (dd, *J* = 16.6 and 1.7 Hz, 1H, 2-H), 3.19 (dd, *J* = 16.6 and 5.6 Hz, 1H, 2-H), 4.5 (s, br, 2H, NH_2), 5.12 (m, 1H, 3-H), 5.46 (s, 1H, 6-H), 6.43-7.25 (m, 13H, Olefinic + Ar-H), 9.60 (s, br, 3H, OH). MS (ESI, *m/z* (%)): 414.1165 [M^+]. UV/Vis (EtOH, λ_{max}, nm, (ε)): 356 (5740).

3. Results and discussion

The dihydropyridones were synthesized by the microwave irradiation of a mixture of curcumin and either primary amines or amine acetates (aromatic amines) in the presence of Montmorillonite K-10 as catalyst. The experimental procedure involved absorbing the reactants on the Montmorillonite K-10, then irradiating the mixture under microwave irradiation. The reaction was proceeded under argon atmosphere. The product was extracted from the clay with ethanol, and then separated by column chromatography and then by preparative TLC chromatography. The reaction time was 60 s in the case of aliphatic amines with mild microwave irradiation power (200 W) while it was 90 s in the case of amine acetates with a higher microwave power (800 W). The yields ranged from 16 to 23%. Despite the low yields of the prepared dihydropyridones this method is the only way to synthesize such compounds. The dihydropyridones were synthesized via transient imine mechanism (Scheme 1) and were confirmed by precision mass spectra, ^{1}H and ^{13}C NMR spectroscopy.

The ^{1}H NMR spectra of the synthesized compounds were characterized by presence of a singlet at the regions 9.44-9.59 ppm assigned for the phenolic hydroxyl groups and the other singlet at the range 5.00-5.17 nm assigned for the vinyl proton. The most characteristic signals are two doublets of doublets at the regions δ 2.35-2.57 ppm (*J* = 15.6 and 2.6 Hz) and 2.60-3.19 ppm (*J* = 15.6 and 7.2 Hz) which were attributed to the geminal protons (C-2) which coupled to each another with *J* = 15.6 Hz and both to the methine protons at (C-3) (*J* = 2.6 and 7.2 Hz). The C-3 proton itself appeared as a multiplet at the regions 4.70-5.17 ppm. This is confirmed by the HOMO-COSY spectra (Figure 1). Figure 1 shows the extended region of the HOMO-COSY spectrum of compound **2d**. This region includes the resonances of the protons H2, H3 and -NCH_2. It is clear from the figure that both H2 protons correlate each other meanwhile they correlated with proton H3. It is worthy to note that the methylene group attached to the nitrogen (NCH_2) in the alkyl substituted derivatives were diaseteriotopic and appeared as multiplets as could be seen from Figure 1. In ^{13}C NMR spectrum of compound **2d**, the most important resonance appeared at 187.9 ppm due to the carbonyl group and at 96.3 ppm which assigned for the vinyl carbon atom (C-6).

The infrared spectra were characterized by a broad and strong band within the range 3365-3188 cm^{-1} due to the stretching vibration of the phenolic OH. In the case of compounds **7** and **8** this band was overlapped with the stretching vibration of the OH and the NH_2 groups of the aromatic substituents. There was also a strong band within the range 1631-1627 cm^{-1} which assigned to the stretching vibration of the C=O group. The clear red shift of this band is due to the conjugation of this group with conjugated system that includes the steryl residue. The UV-Vis spectra (ethanol) were characterized by the 345-357 nm absorption band, which was blue shifted (*ca.* 50 nm) in comparison for those of the parent curcumin. This shift is the result of the reduction of conjugation in the products due to the participation of one of the olefinic groups of the parent curcumin in the ring-closure to give the corresponding dihydropyridone. The precession ESI-MS of the products showed the peak at M+1 supporting their suggested structures.

4. Conclusion

The work demonstrated the superiority of the microwave irradiations to induce reactions that are impossible or at least

difficult to accomplish via conventional methods within relatively short times.

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