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Microwave-assisted synthesis of dihydropyridones from curcumin

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Abstract

Dihydropyridones were prepared by microwave-assisted reaction between curcumin and primary amines or their acetates in the presence of Montmorillonite (K-10) as a catalyst. The reaction was complete within a few minutes and the yield depends on the amine used.

Keywords: Curcumin; Dihydropyridones; Montmorillonite K-10; Microwave

1. Introduction

Dihydropyridones are important intermediates for the synthesis of natural products, particularly alkaloids, and many approaches to their synthesis have been developed.[1–5] In general, two main approaches are used for their preparation (a) from acyclic precursors[6–11] and (b) from pyridines.[11,12]

Curcumin is a yellow pigment and an active component of turmeric powder extracted from *Curcuma longa* L. As well as being anti-inflammatory, extensive research has revealed that this polyphenol can both prevent and treat cancer.[13–20]

In this work, we report on the synthesis of dihydropyridones from the reaction of curcumin and amines or amine acetates under microwave irradiation, an approach, that to our knowledge, has not been previously undertaken.

The dihydropyridones were prepared by microwave-assisted reaction of curcumin with either primary amines (in the case of aliphatic amines) or the amine acetate (in the case of aromatic amines) in the presence Montmorillonite K-10 as a catalyst. The experimental procedure involved absorbing the reactants on Montmorillonite K-10, then irradiating the mixture with microwaves. The products were extracted with a suitable solvent. The reaction times ranged from 50 to 120 s and the yields ranged from 7% to 41%. The structures of the dihydropyridones (Scheme 1) were confirmed by an elemental analysis and by ^{1}H NMR, ^{13}C NMR and MS analyses. The products were also characterized by comparison with 2,3-dihydro-1,2-diphenyl-6-(2-phenylethenyl)-4-pyridone that was prepared by Sugiyama et al.[21] from the reaction of 6-methyl-1,2-diphenyl-2,3-dihydro-4-pyridone with benzaldehyde.

The ^{1}H NMR spectra of the products were characterized by two singlets for both the OMe and OH groups, while the spectrum of curcumin[22] contained only one singlet for each of these groups. This indicates that the products are non-symmetrical in comparison with the symmetric curcumin. In addition, characteristic signals due to the nitrogen-containing heterocyclic ring were present.

For compound **1** (as an example), the ^{1}H NMR spectrum showed two doublets of doublets at 2.42 ppm ($J = 16$ Hz and 4 Hz) and 2.84 ppm ($J = 16$ Hz and 7 Hz) due to the two (geminal) methylene protons (3-H) that coupled with each other as confirmed by the HOMO-COSY spectrum. Further, the HETCOR spectrum indicated that these protons were attached to the same carbon atom

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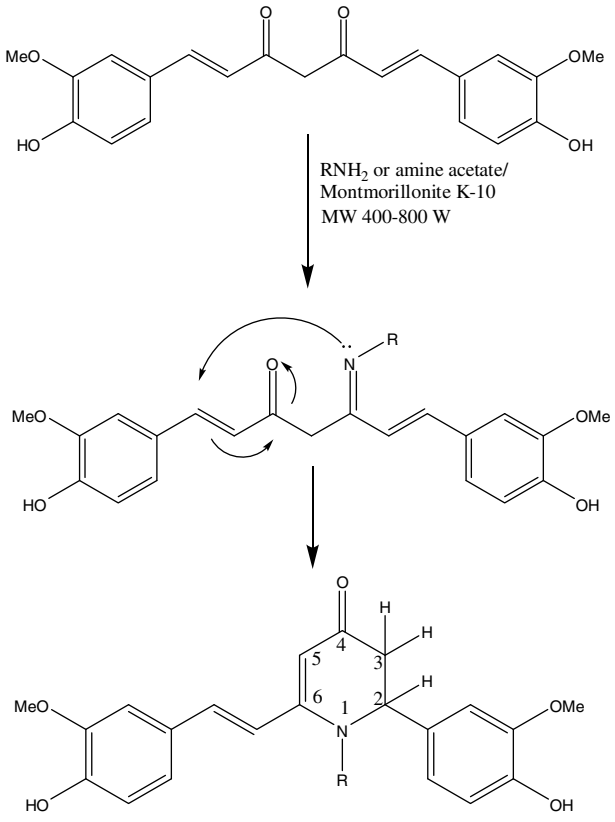

1 R= Me
2 R= Et
3 R= *n*-Pr
4 R= *n*-Bu
5 R= *n*-hexyl
6 R= benzyl
7 R= phenyl
8 R= *p*-tolyl

Scheme 1.

(C-3). Each of these protons was coupled to the methine proton (2-H), which occurred as a multiplet at 4.66 ppm as confirmed by the COSY spectrum. The proton spectrum of **1** also contained a vinylic singlet at 5.09 ppm, which appeared at 6 ppm in the spectrum of curcumin. The olefinic protons of the disubstituted alkene and aromatic protons occurred as a multiplet at 6.65–7.29 ppm, while in curcumin the alkene protons appeared as two doublets (4H). The ^{13}C NMR spectrum confirmed the presence of two OMe groups at 55.3 and 55.5 ppm, and two C–OH groups at 145.8 and 147.6 ppm. Compounds **2**–**8** provided similar spectral data.

In this work, it was demonstrated that the synthesis of dihydropyridones can be achieved by the direct reaction of curcumin with amines or amine acetates under microwave irradiation in the presence of Montmorillonite K-10 as a catalyst.

2. Typical procedure for the preparation of dihydropyridones

Curcumin (2 g, 5.4 mmol) and Montmorillonite K-10 (3 g) were mixed thoroughly in a mortar and placed in a 10 mL beaker. The appropriate amount of amine or amine acetate (5.4 mmol) was added to the mixture, which was then stirred for 24 h. The reaction mixture was then irradiated in a commercial microwave oven (Samsung 800 MW) for 50–120 s at 400 W in the case of the aliphatic amines and at 800 W in the case of amine acetates. The extent of the reaction was monitored by TLC using ethanol–chloroform 4:96 as an eluent. On completion, the mixture was extracted with ethanol, Montmorillonite K-10 was filtered off and the solvent was removed by rotary evaporation. The products were separated by column chromatography (silica gel) using a mixture of THF chloroform 1:5 as an eluent. The product fractions were further purified by a preparative TLC (silica gel) using ethanol–chloroform 4:96 as an eluent. The dihydropyridones were collected as yellow, sparingly soluble (in most solvents), powders.

2.1. Data for (**1**)

Yellow powder (yield 41%) mp 244–246 °C. EI-MS: m/z 381 (M^+), CIMS: m/z 382 $(M+1)^+$. ^1H NMR (600 MHz, DMSO-d_6) δ 2.42 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 2.84 (dd, $J = 16$ and 7 Hz, 1H, 3-H), 3.05 (s, 3H, N–CH_3), 3.74 (s, 3H O–CH_3), 3.82 (s, 3H, O–CH_3), 4.66 (m, 1H, 2-H), 5.09 (s, 1H, 5-H), 6.65–7.29 (m, 8H, olefinic + Ar-H), 8.97 (s, 1H, OH), 9.37 (s, 1H, OH). Anal. Calcd for (381) $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.88; H, 6.39; N, 3.36.

2.2. Data for (**2**)

Yellow powder (yield 23%). Mp 218–220 °C. CIMS: $m/z = 396$ $(M+1)^+$. ^1H NMR (600 MHz, DMSO-d_6) δ 1.10 (t, $J = 6$ Hz, 3H, N–CH_2–CH_3), 2.42 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 2.80 (dd, $J = 16$ and 7 Hz, 1H, 3-H), 3.07 (m, 1H, N–CH_2), 3.74 (s, 3H, OCH_3), 3.80 (m, 1H, N–CH_2), 3.82 (s, 3H, OCH_3), 4.73 (m, 1H, 2-H), 5.06 (s, 1H, 5-H), 6.65–7.27 (m, 8H, olefinic + Ar), 8.93 (s, 1H, OH), 9.36 (s, 1H, OH). Anal. Calcd for (395) $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.54; H, 6.73; N, 3.21.

2.3. Data for (**3**)

Yellow powder (yield 16%), mp 205–207 °C. CIMS: $m/z = 410$ $(M+1)^+$. ^1H NMR (600 MHz, DMSO-d_6) δ 0.83 (t, $J = 6$ Hz, 3H, N–$(CH_2)_2$–CH_3), 1.55 (m, 2H, N–CH_2–CH_2), 2.47 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 2.83 (dd, $J = 16$ and 7 Hz, 1H, 3-H), 2.92 (m, 1H, N–CH_2), 3.74 (s, 3H, OCH_3), 3.77 (m, 1H, N–CH_2), 3.82 (s, 3H, OCH_3), 4.74 (m, 1H, 2-H), 5.05 (s, 1H, 5-H), 6.64–7.29 (m, 8H, olefinic + Ar-H), 8.96 (s, 1H, OH), 9.41 (s, 1H, OH). Calcd for (409) $C_{24}H_{27}NO_5$: C, 70.39; H, 6.64; N, 3.42. Found: C, 69.92; H, 6.90; N, 3.25.

2.4. Data for (**4**)

Yellow powder (yield 16%), mp 122 °C. CIMS: $m/z = 424$ $(M+1)^+$. ^1H NMR (600 MHz, DMSO-d_6) δ

0.83 (t, $J = 6$ Hz, 3H, CH_2–CH_3), 1.26 (m, 2H, CH_2–CH_3), 1.52 (m, 2H, N–CH_2–CH_2), 2.44 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 2.82 (dd, $J = 16$ and 7 Hz, 1H, 3-H), 2.98 (m, 2H, N–CH_2), 3.73 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.72 (m, 1H, 2-H), 5.05 (s, 1H, 5-H), 6.67–7.27 (m, 8H, olefinic + Ar-H), 8.93 (s, 1H, OH), 9.37 (s, 1H, OH). Anal. Calcd for (423) $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.77; H, 7.22; N, 2.92.

2.5. Data for (**5**)

Yellow powder (yield 7%) mp 130 °C. CIMS: $m/z = 452$ $(M+1)^+$. ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.78 (t, $J = 6$ Hz, 3H, CH_2–CH_3), 1.21 (m, 6H, $(CH_2)_3$–CH_3), 1.56 (m, 2H, N–CH_2–CH_2), 2.40 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 2.82 (dd, $J = 16$ and 7 Hz, 1H, 3-H), 2.99 (m, 2H, N–CH_2), 3.74 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.71 (m, 1H, 2-H), 5.05 (s, 1H, 5-H), 6.65–7.24 (m, 8H, olefinic + Ar-H). The OH protons could not be seen in the spectrum of this compound. Anal. Calcd for (452) $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.92; H, 7.69; N, 2.85.

2.6. Data for (**6**)

Yellow powder (yield 13%) mp 128 °C. CIMS: $m/z = 458$ $(M+1)^+$. ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.40 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 2.82 (dd, $J = 16$ and 7 Hz, 1H, 3-H), 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.20 (s, 2H, N–CH_2), 4.72 (m, 1H, 2-H), 5.18 (s, 1H, 5-H), 6.71–7.37 (m, 13H, olefinic + Ar-H), 9.00 (s, 1H, OH), 9.43 (s, 1H, OH). Anal. Calcd for (457) $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.08.; H, 6.22; N, 2.87.

2.7. Data for (**7**)

Yellow powder (yield 13%) mp 111 °C. EI-MS: $m/z = 443$ $(M)^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 3.00 (dd, $J = 16$ and 6 Hz, 1H, 3-H), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 5.08 (m, 1H, 2-H), 5.42 (s, 1H, 5-H), 6.70–7.36 (m, 13H, olefinic + Ar-H). The OH protons could not be seen in the spectrum of this compound. Anal. Calcd for (443) $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.98; H, 5.93; N, 2.92.

2.8. Data for (**8**)

Yellow powder (yield 14%) mp 190 °C. EI-MS: $m/z = 457$ (M^+). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H, Ar-CH_3), 2.65 (dd, $J = 16$ and 4 Hz, 1H, 3-H), 3.08 (dd, $J = 16$ and 6 Hz, 1H, 3-H), 3.71 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.08 (s, 1H, 2-H), 5.42 (s, 1H, 5-H), 6.29 (d, $J = 16$ Hz, 1H, olefinic-H), 6.60–7.22 (m, 11H, olefinic + Ar-H), 8.96 (s, 1H, OH), 9.41 (s, 1H, OH). Anal. Calcd for (457) $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.36; H, 6.21; N, 2.86.

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