Tetrahedron Letters 51 (2010) 5798–5800

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of novel 2,3-dihydro-4-pyridinones from bisdemethoxycurcumin under microwave irradiation

Bahjat A. Saeed [a,*], Wisam A. Radhi [a], Rita S. Elias [b]

[a] Department of Chemistry, College of Education, University of Basrah, Iraq
[b] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah, Iraq

ARTICLE INFO

Article history:
Received 2 July 2010
Revised 30 July 2010
Accepted 31 August 2010
Available online 9 September 2010

Keywords:
Bisdemethoxycurcumin
Microwaves
Montmorillonite K-10
Dihydropyridones

ABSTRACT

A novel synthesis of 2,3-dihydro-4-pyridinones via the reaction of bisdemethoxycurcumin and primary amines or amine acetates is demonstrated. The structures of the products were established by elemental analysis and from mass, ^{1}H and ^{13}C NMR spectra.

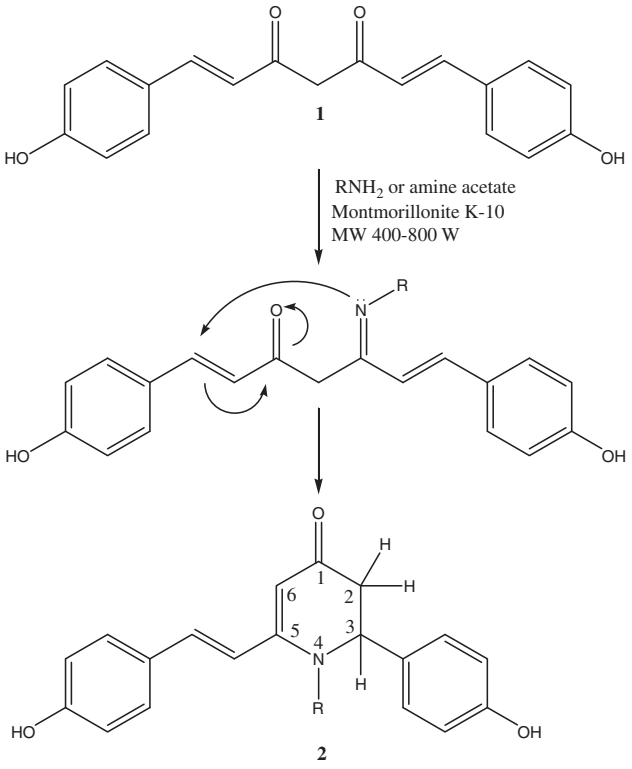
Dihydropyridones are important intermediates for the synthesis of natural products, particularly alkaloids, and have been investigated extensively as valuable building blocks for the construction of piperidines, perhydroquinolines, indolizidines, quinolizidines, and other alkaloid ring systems possessing a wide range of biological and pharmacological properties.[1–5] For their synthesis, the addition of Grignard reagents to 1-acyl-4-methoxypyridinium salts has been exploited by Commins.[6–10] Hetero Diels–Alder reactions or stepwise, formal [4+2] transformations involving imines have also been employed.[11–13] Recently, they have been synthesised via cyclization of α,β-unsaturated 1,3-diketones in acidic medium[14] and through catalytic metathesis of *o*-alkynylanilines and aldehydes. [15] A facile route to functionalized dihydropyridones has been developed involving formal [5C+1N] annulations of α-alkynoyl ketene-(*S*,*S*)-acetals with aliphatic amines.[16] In addition, partial reduction of pyridinium salts has been exploited for their synthesis.[17] In this connection, we previously reported the microwave-assisted formation of 2,3-dihydro-4-pyridinones from curcumin and simple primary amines in the presence of Montmorillonite K-10 via a transient imine.[18] Bisdemethoxycurcumin is an α,β-unsaturated 1,3-diketone that constitutes one of the three major components of the Indian herb *Curcuma longa*.[19,20] In continuation of our interest in the reactions of unsaturated 1,3-diketones and amines for the synthesis of dihydropyridones under microwave irradiation, we report herein the microwave-assisted synthesis of novel dihydropyridones from the reaction of bisdemethoxycurcumin and primary amines or amine acetates.

The dihydropyridones were synthesized by microwave-assisted reaction of bisdemethoxy-curcumin with either primary amines (R = Me, Et or *n*-Pr) or amine acetates (R = *n*-Bu, *n*-pentyl, *n*-hexyl or aromatic) in the presence of Montmorillonite K-10 as the catalyst. The experimental procedure involved absorbing the reactants on Montmorillonite K-10, then irradiating with microwaves. The product was extracted from the clay with ethanol and the products were separated by column chromatography and then by preparative TLC chromatography. The reaction time was 60 s and the yields ranged from 18% to 38%. Attempts to enhance the yield using longer reaction times were unsuccessful. The structures of the dihydropyridones (Scheme 1) were confirmed by elemental analysis and by mass, ^{1}H and ^{13}C NMR spectroscopy.

The ^{1}H NMR spectra of the products showed two characteristic singlets within the range 8.29–9.82 ppm assigned to the two OH groups occupying different chemical environments, which proved the asymmetrical structure of the products. In contrast the ^{1}H NMR spectrum of symmetrical bisdemethoxycurcumin contained only one singlet within the same region. In addition, two doublets of doublets were also apparent at about 2.40 ppm ($J \approx 16$ and 4 Hz) and 2.80 ppm ($J \approx 16$ and 7 Hz), which were assigned to two geminal protons (C-2) coupled to each other as was confirmed by the HOMO-COSY spectra. Further, the HETCOR spectra indicated that these protons were attached to the same carbon atom (C-2) and each was coupled to the methine proton (3-H), which occurred as a multiplet within the range 4.65–5.10 ppm. The protons of the methylene groups in the *N*-alkyl-substituted compounds were

* Corresponding author
E-mail address: bahjat.saeed@yahoo.com (B.A. Saeed).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.115



Scheme 1. The mechanism, reaction conditions and prepared compounds.

diastereotopic, especially those directly attached to the nitrogen atoms. The N–CH_2-protons occurred as two distinct signals within the ranges 2.90–4.14 and 3.73–4.18 ppm. This was confirmed by HOMO-COSY and HETCOR spectroscopy. The ^{13}C NMR spectra revealed the C=O signals within the range 181.71–189.80 ppm. The UV–vis spectra (ethanol) of the products were characterized by a band within the range 334–342 nm, which was strongly blue-shifted (ca. 70 nm) compared to the starting material which appeared at 418 nm. This blue shift reflects the reduction of conjugation in the products due to participation of one of the olefinic groups of bisdemethoxycurcumin in the ring-closure to give the corresponding dihydropyridone.

For the synthesis of the dihydropyridones the method described by Elias et al.[18] was employed with minor modifications. Typically, bisdemethoxycurcumin (2 g, 6.5 mmol) and Montmorillonite K-10 (3 g) were mixed in a mortar and placed in a 10 mL beaker. The appropriate amount of amine or amine acetate (6.5 mmol) was added to the mixture, which was then thoroughly mixed. The mixture was irradiated in a commercial microwave oven (Samsung 800 MW) for 60 s at 400 W (for amines) and 800 W (for amine acetates). The extent of reaction was monitored by TLC using THF/chloroform (30:70) as the eluent. On completion, the mixture was extracted with EtOH (5 × 3 mL). The Montnorillonite was removed by filtration and the solvent was evaporated. The products were separated by column chromatography (silica gel) using THF/chloroform (1:5) as the eluent. The product fractions were further separated by preparative TLC (silica gel) using the same eluent. The dihydropyridones were obtained as yellow powders.

Data for (2a): Yellow powder (yield 38%), mp 254–255 °C. EI-MS: *m/z* 321 (M+). ^1H NMR (400 MHz, DMSO-*d*6) δ 2.34 (dd, J = 16.1 and 3.4 Hz, 1H, 2-H), 2.87 (dd, J = 16.1 and 7.2 Hz, 1H, 2-H), 3.05 (s, 3H, N–CH_3), 4.65 (m, 1H, 3-H), 5.10 (s, 1H, 6-H), 6.19–7.70 (m, 10H, olefinic + Ar), 9.41 (s, 1H, OH), 9.82 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.20, 157.67, 156.80, 142.19, 141.50, 136.81, 129.98, 128.82, 128.46, 127.90, 127.47, 124.87, 118.73, 115.88, 115.36, 99.52, 64.05, 42.88, 27.86. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.57; H, 5.96; N, 4.36. Found: C, 74.83; H, 5.58; N, 4.40.

Data for (**2b**): Yellow powder (yield 32%), mp 227–228 °C. EI-MS: *m/z* 335 (M^+). ^1H NMR (400 MHz, DMSO-d_6) δ 1.09 (t, J = 6 Hz, 3H, N–CH_2–CH_3), 2.35 (dd, J = 16 and 3.6 Hz, 1H, 2-H), 2.81 (dd, J = 16 and 6.8 Hz, 1H, 2-H), 3.08 (m, 1H, N–CH_2), 3.75 (m, 1H, N–CH_2), 4.71 (m, 1H, 3-H), 5.06 (s, 1H, 6-H), 6.70–7.77 (m, 10H, olefinic + Ar), 8.29 (s, 1H, OH), 9.48 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.21, 157.64, 156.67, 142.18, 141.19, 136.19, 129.38, 129.03, 128.32, 127.97, 127.49, 127.20, 124.92, 118.75, 115.88, 115.24, 99.47, 64.03, 42.88, 27.51, 15.33. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.38; H, 6.36; N, 4.02.

Data for (**2c**): Yellow powder (yield 26%), mp 221–222 °C. EI-MS: *m/z* 349 (M^+). ^1H NMR (400 MHz, DMSO-d_6) δ 0.80 (t, J = 6 Hz, 3H, N–CH_2–CH_2–CH_3), 1.52 (m, 2H, N–CH_2–CH_2), 2.26 (dd, J = 16 and 3.6 Hz, 1H, 2-H), 2.83 (dd, J = 16 and 6.8 Hz, 1H, 2-H), 3.09 (m, 1H, N–CH_2), 3.73 (m, 1H, N–CH_2), 4.70 (m, 1H, 3-H), 5.02 (s, 1H, 6-H), 6.67–7.48 (m, 10H, olefinic + Ar), 8.29 (s, 1H, OH), 9.48 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 186.68, 157.60, 157.01, 143.00, 141.51, 136.20, 129.14, 129.01, 128.25, 127.86, 127.52, 127.26, 124.81, 116.81, 115.72, 115.36, 99.12, 64.13, 42.67, 30.50, 26.68, 16.74. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.88; H, 6.56; N, 4.12.

Data for (**2d**): Yellow powder (yield 26%), mp 207–208 °C. EI-MS: *m/z* 363 (M^+). ^1H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, J = 6 Hz, 3H, N–$(CH_2)_3$–CH_3), 1.25 (m, 2H, N–$(CH_2)_2$–CH_2), 1.50 (m, 2H, N–CH_2–CH_2), 2.32 (dd, J = 16 and 3.5 Hz, 1H, 2-H), 2.83 (dd, J = 16 and 6.8 Hz, 1H, 2-H), 2.96 (m, 1H, N–CH_2), 3.77 (m, 1H, N–CH_2), 4.70 (m, 1H, 3-H), 5.04 (s, 1H, 6-H), 6.70–7.76 (m, 10H, olefinic + Ar), 8.30 (s, 1H, OH), 9.51 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.71, 160.39, 159.59, 156.75, 151.80, 137.08, 129.39, 129.27, 127.46, 118.08, 115.79, 115.19, 95.58, 60.25, 49.70, 42.81, 31.34, 19.24, 13.62. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.81; H, 6.59; N, 4.02.

Data for (**2e**): Yellow powder (yield 23%), mp 107–108 °C. EI-MS: *m/z* 377 (M^+). ^1H NMR (400 MHz, DMSO-d_6) 0.59 (t, J = 6 Hz, 3H, N–$(CH_2)_4$–CH_3), 1.18 (m, 4H, N–CH_2–$(CH_2)_2$), 1.49 (m, 2H, N–CH_2–CH_2), 2.26 (dd, J = 16.1 and 3.4 Hz, 1H, 2-H), 2.80 (dd, J = 16.1 and 7 Hz, 1H, 2-H), 2.90 (m, 1H, N–CH_2), 3.74 (m, 1H, N–CH_2), 4.66 (m, 1H, 3-H), 5.01 (s, 1H, 6-H), 6.55–7.47 (m, 10H, olefinic + Ar), 8.30 (s, 1H, OH), 9.51 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 184.16, 160.27, 159.32, 157.02, 152.41, 137.07, 129.31, 129.20, 127.88, 118.08, 116.02, 115.21, 95.62, 60.24, 49.70, 42.83, 31.16, 19.25, 17.63, 12.67. Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 75.98; H, 7.47; N, 3.68.

Data for (**2f**): Yellow powder (yield 18%), mp 100–101 °C. EI-MS: *m/z* 391 (M^+). ^1H NMR (400 MHz, DMSO-d_6) δ 0.77 (t, J = 6 Hz, 3H, N–$(CH_2)_5$–CH_3), 1.20 (m, 6H, N–CH_2–$(CH_2)_3$), 1.51 (m, 2H, N–CH_2–CH_2), 2.34 (dd, J = 16.2 and 3.8 Hz, 1H, 2-H), 2.83 (dd, J = 16.2 and 7.2 Hz, 1H, 2-H), 2.96 (m, 1H, N–CH_2), 3.76 (m, 1H, N–CH_2), 4.70 (m, 1H, 3-H), 5.04 (s, 1H, 6-H), 6.70–7.48 (m, 10H, olefinic + Ar), 8.35 (s, 1H, OH), 9.57 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.76, 160.39, 159.06, 156.62, 136.96, 129.50, 129.27, 127.50, 126.41, 118.44, 115.66, 115.16, 95.65, 60.22, 49.88, 42.32, 30.77, 29.03, 25.56, 21.91, 16.23. Anal. Calcd for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47; N, 3.58. Found: C, 77.08; H, 7.28; N, 3.44.

Data for (**2g**): Yellow powder (yield 18%), mp 139–140 °C. EI-MS: *m/z* 397 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (dd, J = 16 and 3.6 Hz, 1H, 2-H), 2.82 (dd, J = 16 and 7.1 Hz, 1H, 2-H), 4.14 (s, 1H, N–CH_2), 4.18 (s, 1H, N–CH_2), 4.68 (m, 1H, 3-H), 5.16 (s, 1H, 6-H), 6.19–7.25 (m, 15H, olefinic + Ar), 8.46 (s, 1H, OH), 9.39 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 188.08, 160.45, 158.69, 156.68, 138.50, 137.25, 129.32, 129.09, 128.69, 128.22, 127.59, 127.22, 126.60, 118.58, 115.55, 115.24, 96.19, 60.40, 53.05, 42.66. Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.78; H, 5.68; N, 3.31.

Data for (**2h**): Yellow powder (yield 21%), mp 129–130 °C. EI-MS: *m/z* 383 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.66 (dd, J = 16.1 and 3.6 Hz, 1H, 2-H), 3.08 (dd, J = 16.1 and 6.4 Hz, 1H, 2-H), 5.10 (m, 1H, 3-H), 5.38 (m, 1H, 6-H), 6.70–7.48 (m, 15H, olefinic + Ar), 8.35 (s, 1H, OH), 9.57 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.19, 158.62, 157.13, 142.61, 138.78, 129.18, 128.38, 127.92, 125.08, 120.13, 119.51, 116.24, 99.86, 64.09, 42.78. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.76; H, 5.58; N, 3.57.

Data for (**2i**): Yellow powder (yield 19%), mp 141–142 °C. EI-MS: *m/z* 401 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (dd, J = 16.4 and 3.6 Hz, 1H, 2-H), 2.83 (dd, J = 16.4 and 6 Hz, 1H, 2-H), 4.70 (m, 1H, 3-H), 5.04 (s, 1H, 6-H), 6.70–7.48 (m, 14H, olefinic + Ar), 8.40 (s, 1H, OH), 9.59 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.80, 159.08, 156.99, 156.62, 146.24, 146.13, 136.43, 130.50, 129.12, 129.05, 127.56, 126.30, 121.03, 119.96, 115.75, 115.28, 112.21, 111.87, 111.65, 101.38, 63.92, 42.86. Anal. Calcd for $C_{25}H_{20}FNO_3$: C, 74.80; H, 5.02; N, 3.49. Found: C, 74.56; H, 5.10; N, 3.25.

Data for (**2j**): Yellow powder (yield 20%), mp 131–132 °C. EI-MS: *m/z* 411 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, 3H, N–CH_2–CH_3), 1.62 (m, 2H, N–CH_2), 2.51 (dd, J = 16 and 3.7 Hz, 1H, 2-H), 3.09 (dd, J = 16 and 7.2 Hz, 1H, 2-H), 5.06 (m, 1H, 3-H), 5.39 (s, 1H, 6-H), 6.19–7.21 (m, 14H, olefinic + Ar), 8.38 (s, 1H, OH), 9.55 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.21, 157.64, 156.67, 142.18, 141.19, 136.19, 129.38, 129.03, 128.32, 127.97, 127.49, 127.20, 124.92, 119.75, 115.88, 99.47, 64.03, 42.88, 27.51, 15.33. Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.81; H, 6.12; N, 3.40. Found: C, 79.04; H, 6.02; N, 3.68.

In conclusion, we have synthesized new dihydropyridones through the direct reaction of an α,β-unsaturated 1,3-diketone(bis-demethoxycurcumin) with amines or amine acetates under microwave irradiation in the presence of Montmorillonite K-10 as the catalyst.

References and notes

1. Kuethe, J. T.; Commins, D. L. *J. Org. Chem.* **2004**, *69*, 5219.
2. Huang, S.; Commins, D. L. *Chem. Commun.* **2000**, 569.
3. Kuethe, J. T.; Commins, D. L. *Org. Lett.* **2000**, *2*, 588.
4. Avenoza, A.; Busto, J. H.; Cativiela, C.; Corazana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **2002**, *67*, 598.
5. Commins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574.
6. Commins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035.
7. Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851.
8. Commins, D. L.; Fulp, A. B. *Org. Lett.* **1999**, *1*, 1031.
9. Young, D. W.; Commins, D. L. *Org. Lett.* **2005**, *7*, 5661.
10. McCall, W. S.; Grillo, T. A.; Commins, D. L. *J. Org. Chem.* **2008**, *73*, 9744.
11. Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444.
12. Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321.
13. Alaimo, P. J.; O'Brien, R., III; Johanson, A. W.; Slauson, S. R.; O'Brien, J. M.; Tyson, E. L.; Marshall, A. L.; Ottinger, C. E.; Chacon, G. J.; Wallace, L.; Paulino, C.; Connel, S. *Org. Lett.* **2008**, *10*, 5111.
14. McDonald, F. K.; Burnell, D. J. *J. Org. Chem.* **2009**, *74*, 6973.
15. Saito, A.; Kasai, J.; Odaira, Y.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 5644.
16. Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580.
17. Donohoe, T. J.; Johanson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435.
18. Elias, R. S.; Saeed, B. A.; Saour, K. Y.; Al-Masoudi, N. A. *Tetrahedron Lett.* **2008**, *49*, 3049.
19. Portes, E.; Gardart, C.; Castellan, A. *Tetrahedron* **2007**, *63*, 9092.
20. Scotter, M. J. *Food Sci. Tech.* **2009**, *42*, 1345.