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Synthesis of new curcumin analogues from Claisen-Schmidt condensation

Nouara Ziani [a,*], Assia Sid [b], Albert Demonceau [c], Quentin Willem [c], Benjamin Dassonneville [c] and Kaddour Lamara [b]

[a] *Département de Chimie, Faculté des Sciences, Université Ferhat Abbas, Sétif, 19000, Algérie*
[b] *Laboratory of Applied Chemistry and Materials Technology, Chemistry Institute, University Larbi Ben M'hidi of Oum El Bouaghi, Rue de Constantine, 04000, Algeria*
[c] *Laboratoire de Chimie Macromoléculaire et de Catalyse Organique, Département de Chimie, Université de Liège, Sart-Tilman (B.6a), B-4000 Liège, Belgique*

**Corresponding author at: Département de Chimie, Faculté des Sciences, Université Ferhat Abbas, Sétif, 19000, Algérie.*
Tel.: +213.36620139; fax: +213.36620139. E-mail address: nouarachem2013@hotmail.com (N. Ziani).

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ABSTRACT

A series of new curcumin analogues were obtained by Claisen-Schmidt condensation of substituted benzaldehydes with cyclohexanone derivatives using the ratio of 1:2 of ketone to aldehyde in dilute ethanolic solution under base catalyzed (NaOH) conditions at room temperature in good yields. The structures of the synthesized compounds were confirmed by data of IR, ^{1}H NMR, and ^{13}C NMR spectra.

1. Introduction

Curcumin, 1,7-*bis*-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, (Figure 1), is a yellow compound isolated from the rhizome of the herb *curcuma longa* L., which has been used for centuries as a dietary pigment, spice, and traditional medicine in India and China [1,2]. This naturally occurring and synthetic compound is regarded as a promising drug and has received considerable attention due to its antioxidant, anticancer, anti-inflammatory, anti-HIV and antimalarial properties [3-7]. Curcumin has a surprisingly wide range of chemo-therapeutic activities and is under investigation for the treatment of various human cancers. However, the clinical application of curcumin has been significantly limited by its instability and poor metabolic property [8-10]. Various curcumin analogues have been synthesized to overcome the poor metabolic property. These compounds have been attracting much more attention, not only due to their intriguing biological activities such as cyto-toxicity [11], antimycotic [12], antitumor [13,14], antibacterial [15,16], anti-inflammatory [17], and antileishmaniatic activities [18], but also as important precursors for the synthesis of heterocyclic compounds such as pyrazolines. Generally, these compounds are prepared by Claisen-Schmidt condensation from aromatic aldehydes and ketons [19].

In the present work, we synthesized a series of new curcumin analogues **3a** and **6a-c** (Scheme 1) by Claisen-Schmidt condensation from the reaction of benzaldehydes **2** and **5** with cyclohexanone derivatives **1** and **4** using NaOH as catalyst. Structures of the synthesized compounds were determined by IR and their spectroscopic analyses. These compounds are using as precursors to prepare a series of pyrazoline derivatives. This study and bioactivities of all synthesis compounds [20,21] will be the subject of future publication.

2. Experimental

2.1. Instrumentation

Melting points were determined with a (Bransted/-Electrothermal) apparatus and are uncorrected. IR spectra were recorded in KBr pellets on (a Perkin-Elmer FT-IR-01 and a Shimadzu FT- IR- 8400S) spectrophotometers. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker Advance DRX 400 spectrometer (400.13 MHz for ^{1}H NMR and 100.62 MHz for ^{13}C NMR) and Bruker Advance 250 spectrometer (250.13 MHz for ^{1}H NMR and 62.89 MHz for ^{13}C NMR). Chemical shift values are reported in ppm relative to TMS as internal reference in $CDCl_3$.

2.2. Synthesis

A mixture of the aromatic aldehyde (20 mmol, 2 eq.) and the appropriate cyclohexanone derivative (10 mmol, 1 eq.) were dissolved in 15 mL of ethanol in a simple necked round bottomed flask and stirred for several minutes at 0 °C (ice bath). Into this solution, 10 mL of a 40 % NaOH solution in water was then added drop wise over several minutes. The mixture is then allowed to stir at room temperature for approximately 4 h. The solid was separated and washed with cold water and dried. The product, so-obtained, was crystallized from ethanol to obtain pure **3a** and **6a-c** (Scheme 1).

2-(2-Fluorobenzylidene)-5-methylcyclohexanone (**3a**): Color: Yellow crystals. Yield: 86%. M.p.: 77-78 °C. IR (KBr, ν, cm^{-1}): 2935 (C-H), 1678 (C=O), 1610 (C=C).

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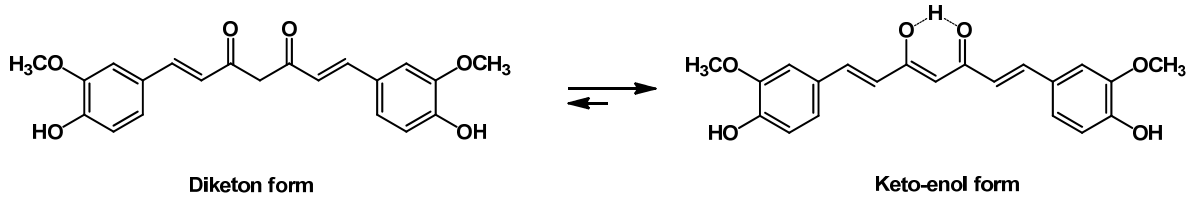
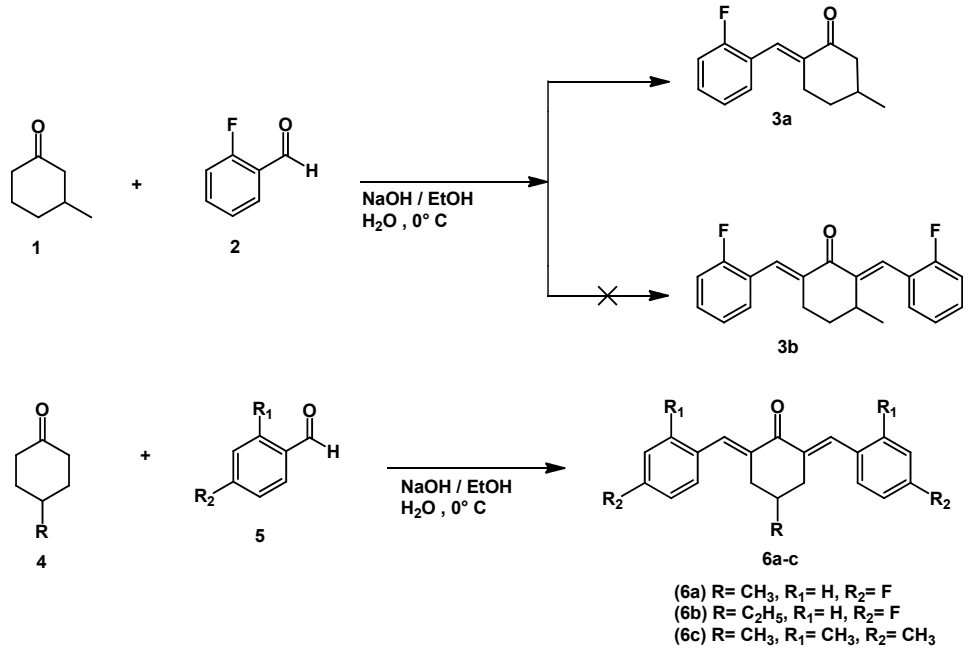


Figure 1. The keto-enol tautomerization of curcumin.



Scheme 1

^{1}H NMR (250.13 MHz, $CDCl_3$, δ, ppm): 1.05 (d, 3H, *J* = 5.7 Hz, CH_3), 1.33-1.37 (m, 1H, C-H), 1.86-1.93 (m, 1H, C-H), 2.07-2.17 (m, 2H, C-H), 2.55-2.70 (m, 2H, C-H), 2.86-2.92 (m, 1H, C-H), 7.05-7.30 (m, 4H, Ar-H), 7.46 (s, 1H, CH=C).

2,6-Bis(4-fluorobenzylidene)-4-methylcyclohexanone (**6a**): Color: Yellow powder. Yield: 96%. M.p.: 124-125 °C. IR (KBr, ν, cm^{-1}): 2947 (C-H), 1663 (C=O), 1595 (C=C). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 1.09 (d, 3H, *J* = 8.0 Hz, CH_3), 1.87-1.89 (m, 1H, C-H), 2.45-2.51 (m, 2H, CH_2), 2.99-3.04 (m, 2H, CH_2), 7.08-7.12 (m, 4H, Ar-H), 7.43-7.46 (m, 4H, Ar-H), 7.75 (s, 2H, 2 CH=C). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 21.6 (CH_3), 29.3 (CH), 36.4 (2 CH_2), 115.5 (d, *J* = 21.1 Hz, 4 CH of Ar-H), 132.0 (d, *J* = 3.0 Hz, 2 Ar-C), 132.3 (d, *J* = 8.0 Hz, 4 CH of Ar-H), 134.9 (d, *J* = 2.0 Hz, 2 CH), 136.1 (2 C=C), 162.6 (d, *J* = 249.5 Hz, 2 Ar-C), 189.8 (C=O).

4-Ethyl-2,6-bis(4-fluorobenzylidene)cyclohexanone (**6b**): Color: Yellow crystals. Yield: 95%. M.p.: 118-119 °C. IR (KBr, ν, cm^{-1}): 2952 (C-H), 1600 (C=O), 1508 (C=C). ^{1}H NMR (250 MHz, CD_2Cl_2, δ, ppm): 0.88 (t, 3H, *J* = 7.5 Hz, CH_3), 1.42 (q, 2H, *J* = 7.5 Hz, CH_2), 1.65 (m, 1H, C-H), 2.45-2.56 (m, 2H, CH), 3.03-3.10 (m, 2H, CH), 7.09-7.16 (m, 4H, Ar-H), 7.45-7.51 (m, 4H, Ar-H), 7.71 (s, 2H, 2 CH=C). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 11.3 (CH_3), 28.6 (CH_2), 34.0 (2 CH_2), 35.7 (CH), 115.5 (d, *J* = 21.1 Hz, 4 CH of Ar-H), 132.3 (d, *J* = 9.0 Hz, 4 CH of Ar-H), 132.4 (2 CH), 135.3 (d, *J* = 1.0 Hz, 2 Ar-C), 135.6 (2 C=C), 162.7 (d, *J* = 249.5 Hz, 2 Ar-C), 189.6 (C=O).

2,6-Bis(2,4-dimethylbenzylidene)-4-methylcyclohexanone (**6c**). Color: Yellow crystals. Yield: 91%. M.p.: 178-179 °C. IR (KBr, ν, cm^{-1}): 2949 (C-H), 1662 (C=O), 1599 (C=C). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ, ppm): 0.98 (d, 3H, *J* = 4.0 Hz, CH_3), 1.80-1.82 (m, 1H, CH), 2.33 (s, 6H, 2 CH_3), 2.37 (s, 6H, 2 CH_3) 2.37-2.41 (m, 2H, CH), 2.87-2.92 (m, 2H, CH), 7.02–7.07 (m, 4H, Ar-H), 7.16–7.18 (m, 2H, Ar-H), 7.89 (s, 2H, 2 CH=C). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 20.0 (2 CH_3), 21.3 (2 CH_3), 21.4 (CH_3), 29.9 (CH), 36.6 (2 CH_2), 126.1 (2 CH of Ar-H), 129.1 (2 CH of Ar-H), 131.0 (2 CH of Ar-H), 132.2 (2 Ar-C), 135.4 (2 Ar-C), 136.1 (2 Ar-C), 138.1 (2 C=C), 138.4 (2 CH), 190.2 (C=O).

3. Results and discussion

With a view to synthesize compound **3b**, 3-methylcyclohexanone, **1**, was allowed to react with 2-fluoro benzaldehyde, **2**, in ethanol, compound **3a** were obtained rather than the compound **3b**. Curcumin analogues, **6a-c**, were obtained by condensation of cyclohexanone derivatives, **4**, with substituted benzaldehydes **5** in good yields.

Compounds **3a** and **6a-c** were four new Curcumin analogues characterized by melting points, IR and ^{1}H NMR, ^{13}C NMR spectra. Their spectra IR showed a strong band for the conjugated carbonyl at (1678-1600 cm^{-1}) (1609-1585 cm^{-1} [22]) and a band at (1610-1508 cm^{-1}) for C=C group (1515-1446 cm^{-1} [22]). In the ^{1}H NMR spectra of new α,β-unsaturated ketones, the olefinic proton gave a singlet signal at (7.89-7.46 ppm) (7.82-7.16 ppm, [22]). ^{13}C NMR chemical shifts of the C=O group have been assigned at (190.2-189.6 ppm) (191.3-188.5 ppm [22]).

4. Conclusion

Due to the importance of curcumin analogues, their wide range of biological activities, and applications in synthesis of pyrazolines, we have synthesized a series of new curcumin analogues **3a**, **6a-c** by Claisen-Schmidt condensation. These compounds can be as precursors to prepare a series of pyrazoline derivatives. The bioactivities of all synthesized compounds will be the subject of future publication. The synthesized curcumin analogues are very stable compounds, a property which may render them as important synthetic precursors in organic chemistry and useful substances in drug research to overcome the poor metabolic property of curcumin.

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References

[1]. Kuttan, R.; Sudheeran, P. C.; Josph, C. D. *Cancer Lett.* **1985**, *29*, 197-202.
[2]. Kuttan, R.; Sudheeran, P. C.; Josph, C. D. *Tumori.* **1987**, *73*, 29-31.
[3]. Cole, G. M. T.; Morihara, G. P.; Yang, F. A.; Begum, S. A.; Frautschy, A. N. Y. *Acad. Sci.* **2004**, *1035*, 68-84.
[4]. Cheng, A. L.; Hsu, C. H.; Lin. J. K.; Hsu, M. M.; Ho, Y. F.; Shen, T. S.; Ko, J. Y.; Lin, J. T.; Lin, B. R.; Ming-Shiang, W.; Yu, H. S.; Jee, S. H.; Chen, G. S.; Chen, T. M.; Chen, C. A.; Lai, M. K.; Pu, Y. S.; Pan, M. H.; Wang, Y. J.; Tsai, C. C.; Hsieh, C. Y. *Anticancer Res*. **2001**, *21*, 2895-2900.
[5]. Gescher, A. *J. Chemother*. **2004**, *4*, 3-6.
[6]. Vajragupta, O.; Boonchoong, P.; Morris, G. M.; Olson, A. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3364-3368.
[7]. Reddy, R. C.; Vatsaala, P. G.; Keshamouni, V. G.; Padmanaban, G.; Rangarajan, P. N. *Biochem. Biophy. Res. Commun.* **2005**, *326*, 472-474.
[8]. Hsu, C. H.; Cheng, A. L. *Adv. Exp. Med. Biol.* **2007**, *595*, 471-480.
[9]. Pan, M. H.; Huang, T. M.; Lin, J. K. *Drug Metab. Dispos*. **2000**, *27*, 486-494.
[10]. Sharma, R. A.; Steward, W. P.; Gescher, A. J. *Adv. Exp. Med. Biol.* **2007**, *595*, 453-470.
[11]. Dimmock, J. R.; Arora, V. K.; Wonko, S. L.; Hamon, N. W.; Quail, J. W.; Jia, Z.; Warrington, R. C.; Fang, W. D.; Lee, J. S. *Drug Des. Deliv*. **1990**, *6*, 183-194.
[12]. Dimmock, J. R.; Nyathi, C. B.; Smith, P. J. *J. Pharm. Sci.* **1978**, *67*, 1543-1546.
[13]. Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem*. **1976**, *41*, 1095-1099.
[14]. Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327-329.
[15]. Matsumoto, J.; Minami, S. *J. Med. Chem.* **1975**, *18*, 74-79.
[16]. Suzuki, N. *Chem. Pharm. Bull.* **1980**, *28*, 761-763.
[17]. Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropytov, B. Y.; Kolla, V. E.; Konshin, M. E. *Khim. Farm. Zh*. **1991**, *25*, 26-28.
[18]. Agarwal, A.; Ashutosh, R.; Goyal, N.; Chauhan, P. M. S.; Gupta, S. *Bioorg. Med. Chem.* **2005**, *13*, 6226-6232.
[19]. Behr, L. C.; Fusco, F.; Jarboe, C. H. In Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings; Wiley, R.H., Ed. The Chemistry of Heterocyclic compounds; Wiley- Interscience: New York, NY. 1967.
[20]. Sid, A.; Lamara, K.; Moktari, M.; Ziani, N.; Mosset, P. *Eur. J. Chem.* **2011**, *2(3)*, 311-313.
[21]. Ziani, N.; Lamara, K.; Sid, A.; Willem, Q.; Dassonneville, B.; Demonceau, A. *Eur. J. Chem.* **2013**, *4(2)*, 176-179.
[22]. Kok, W. L.; Chau, L. T.; Choi, Y. L.; Ahmad, S. M; Basyaruddin, A, R.; Daud, A. I.; Nordin, H. L. *Med. Chem. Res.* **2012**, *21*, 333-344.