Microwave-assisted synthesis of azetidines derived from curcumin.

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Abstract

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

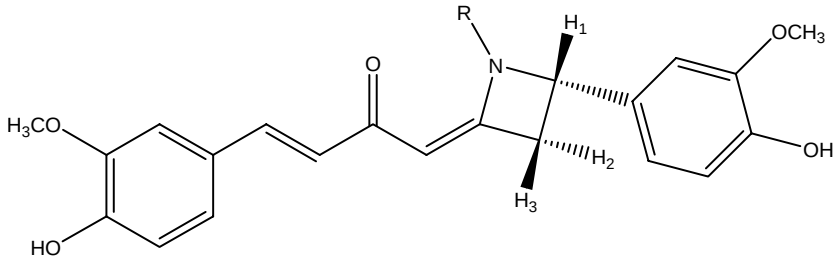
Introduction

Curcumin a major yellow pigment and active component of turmeric powder extracted from Curcuma longa L. As well as to its anti-inflammatory activity, extensive research has indicated that this poly phenol can both prevent and treat cancer (10; 8).

Azetidines which are of chemotherapeutic importance (7; 4) have received attention in recent years and several synthetic routs have been developed for their synthesis, the most important Being (10), the ester enolate-imine condensation (9), cyclization of beta-amino carboxylic acids and esters (3), cyclocondensation of ketens, and ketenimines with imines (11), cycloaddition of chromium-carbene complexes with imines (2), cyclization of imides, imidates, and hydroxamates (5; 1). In this work the synthesis of azetidines that derived from curcumin is discussed.

Experimental

The preparation of the azetidines (Typical procedure):



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

Scheme 1

Curcumin 2g, 5.4 mmol and montmorillonite K-10 3g mixed thoroughly in a mortar then placed in a 10mL beaker.

The appropriate amount of the amine or the amino acetate 5.4 mmol was added to the mixture and stirred for 24h by a magnetic stirrer.

The reaction mixture was then irradiated in a commercial microwave oven for 50-120 second at 400W in the case of the aliphatic amines and at 800W in the case of the amine acetate.

The progress of the reaction was monitored by TLC using ethanol-chloroform (4:96) as the eluent.

The mixture was then extracted with ethanol (three times using 20 ml each time) and the Montmorillonite was filtered off and the solvent was removed by the aid of rotary evaporation.

The products were separated by column chromatography (silica gel) using a mixture of THF-chloroform 20:100 as the eluent.

The collected fractions were separated by TLC (silica gel) using ethanol-chloroform 4:96 as the eluent.

The azetidines were collected as yellow sparingly soluble powders in most solvents.

Data for (1): yellow powder (yield 41%) mp 244-246 ºC. EI-MS: m/z 381 (M^+), CIMS: m/z 382 $(M+1)^+$.
^{1}H NMR (600 MHz, DMSO) δ =2.42 (dd, J= 16 and 4 Hz, 1H, H2), 2.84 (dd, J = 16 and 7 Hz,1H, H3), 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, N-CH-Ar), 5.09(s, 1H, vinylic-H), 6.65-7.29(olefinic+Ar-H), 8.97(s, 1H, OH), 9.37(s,1H, OH). Anal. Calcd. for (381) $C_{23}H_{22}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.88; H, 6.39; N, 3.36; IR (KBr discs, cm-1): 3200 (OH str.); 3080 (C=C-H str.); 1630 (C=O str.).

Data for (2): yellow powder (yield 23%). Mp 218-220 ºC. CIMS: m/z = 396$(M+1)^+$. ^{1}H NMR (600 MHz, DMSO) δ = 1.10 (t, J=6 Hz, 3H, N-CH_2-CH_3), 2.42(dd, J= 16 and 4 Hz, 1H, H2), 2.80(dd, J= 16 and 7 Hz, 1H, H3), 3.07(m, 1H, N-CH_2), 3.74(m, 1H, OH), 3.80(m, 1H, N-CH_2), 3.82(s, 3H, CH3), 4.73(m, 1H, N-CH-Ar), 5.06(s, 1H, vinylic-H), 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. IR (KBr discs, cm-1): 3200 (OH str.); 3080 (C=C-H str.); 1630 (C=O str.).

Data for (3): yellow powder (yield 16%) mp205-207 ºC. CIMS: m/z= 410(M+1) ^{1}H NMR (600 MHz, DMSO) δ = 0.8 (t, J= 6 Hz, N-$(CH_2)_2$-CH_3), 1.55(m, 2H, N-CH_2-CH_2), 2.47(dd, 1H, H2), 2.83(dd, J= 16 and 7 Hz, 1H, H3), 2092(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, N-CH-Ar), 5.05(s, 1H, vinylic-H), 6.64-7.29(m, 10H, olefinic+Ar-H), 8.96(s, 1H, OH), 9.41(s, 1H, OH). Anal. 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. IR (KBr discs, cm-1): 3200 (OH str.); 3080 (C=C-H str.); 1632 (C=Ostr.).
Data for (4): yellow powder (yield 16%) mp 122 ºC. CIMS: m/z= 422$(M+1)^+$.
^{1}HNMR (600 MHz, DMSO) 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), 4.44(dd, 1H, H2), 2.83(dd, J= 16 and 7, 1H, H3), 2.98(m, 1H, N-CH_2), 3.73(s, 3H, OCH_3), 3.81(m, 1H, N-CH_2), 3.93(s, 1H, OCH_3), 6.67-7.27(m, 10H, olefinic+Ar-H), 8.93(s, 1H, OH), 9.37(s, 1H, OH). Anal. Calc. 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. IR (KBr discs, cm-1): 3236 (OH str.); 3082 (C=C-H str.); 1631 (C=O str.).

Data for (5): yellow powder (yield 7%) mp 130 ºC. CIMS: m/z= 452$(M+1)^+$.
^{1}H NMR (250 MHz, DMSO) δ = 0.78(t, J= 6 Hz, 3H, CH2-CH3), 1.21(m, 6H, $(CH_2)_3$-CH_3), 1.56(m, 2H, N-CH_2-CH_2), 2.40 (dd, 1H, H2), 2.82(dd, J= 16 and 7 Hz, 1H, H3), 2.99(m, 1H, N-CH_2), 3.74(s, 1H, OCH_3), 3.80(s, 1H, OCH_3),

4.71(m, 1H, N-CH-Ar), 5.05(s, 1H, vinylic-H), 6.65-7.24(m, 10H, olefinic+Ar-H). Anal. Calc. for (452) $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.29; H, 7.69; N, 2.85. IR (KBr discs, cm-1): 3206 (OH str.); 3080 (C=C-H str.); 1632 (C=O str.)

Data for (6): yellow powder (yield 13%) mp 128 ºC. CIMS: m/z= 458$(M+1)^+$. ^{1}H NMR (250 MHz, DMSO) δ = 2.40(dd, 1H, H2), 2.82(dd, J= 16 and 7 Hz, 1H, H3), 4.20(d, 2H, N-CH_2), 4.72(m, 1H, N-CH-Ar), 5.18(t, 1H, vinylic-H), 6.71-7.37(m, 15H, olefinic+Ar-H), 9.00(s, 1H, OH), 9.43(s, 1H, OH). Anal. Calcd. for (457) C28H27NO5, C, 73.51; H, 5095; N, 3.06. Found: C, 73.08.; H, 6.22; N, 2.87. IR KBr discs, cm-1): 3224 (OH str.); 3080 (C=C-H str.); 1632 (C=O str.).

Data for (7): yellow powder (yield 13%) mp 190 ºC. ^{1}H NMR (300 MHz, DMSO) δ = 2.60(dd, J= 16 and 4 Hz, 1H, H2), 3.00(dd, J= 16 and 6 Hz, 1H, H3), 5.08(m, 1H, CH-Ar), 5.42(s, 1H, vinylic-H), 6.36(d, 1H, olefinic), 6.72-7.15(m, 14H, olefinic+Ar-H). Anal. Calcd. For (442) $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; 3.16. Found: C, 72.98; H, 5.93; N, 2.92. IR (KBr discs, cm-1): 3227 (OH str.); 3040 (C=C-H str.); 163 (C=O str.).

Data for (8): yellow powder (yield 14%) mp 190 ºC. EI-MS: m/z= 457(M^+). ^{1}HNMR (300 MHz, DMSO) δ = 2.26 (s, 3H, Ar-CH3), 2.65(dd, J= 16 and 4 Hz, 1H, H2), 3.06(dd, J= 16 and 6 Hz, 1H, H3), 3.71(s, 3H, OCH_3), 3.72(s, 3H, OCH_3), 5.08(m, 1H, N-CH-Ar), 5.42(s, 1H, vinylic-H), 6.29(d, 1H, olefinic-H), 6.60-7.22(m, 13H, 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. . IR (KBr discs, cm-1): 3224 (OH str.); 3040 (C=C-H str.); 1630 (C=O str.).

Results and discussion

The compounds were prepared by microwave assisted reaction of curcumin with either the primary amines (in the case of aliphatic amines) or the amine acetate (in the case of aromatic amines).

The synthesis was conducted by the catalytic action of montmorillonite clay K-10 as a catalyst. The experimental procedure consists of absorbing the reactants on montmorillonite , the mixture was stirred for 24 hours then microwave irradiated and the products extracted with a suitable solvent.

The reaction times ranged from 50 to 120 seconds and the yields ranged from 7 to 41%.

The structures of the resulting derivatives (scheme 1) were confirmed by their elemental analyses and by their spectral properties (^{1}H NMR and ^{13}C NMR, and MS).

NMR spectra of the products are characterized by two singlets for both the OMe and the OH groups while the spectrum of curcumin (6) contains only one singlet for each group.

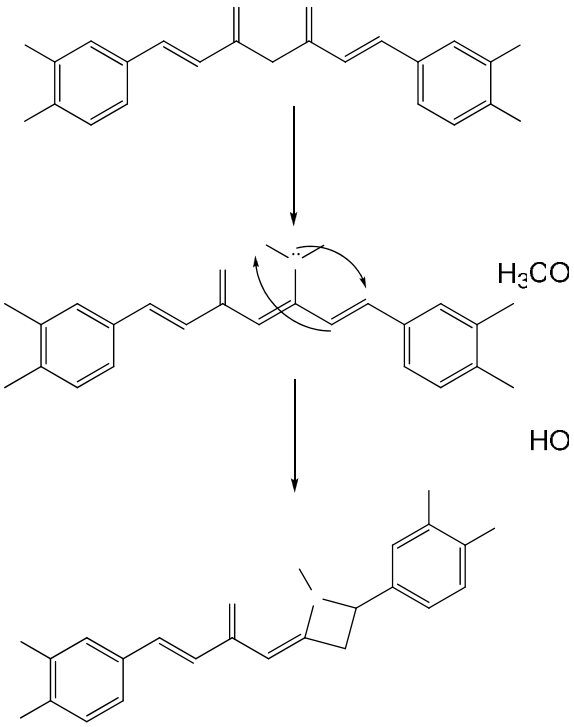
This means that these molecules have non-symmetrical ends due to structural changes in comparison with the symmetric curcumin. In addition there are another characteristic signals belong to the nitrogen containing heterocyclic ring include two doublets of doublets with J=16Hz and their positins depend on the substituent on the nitrogen atom. The first appears at 2.4-2.6 ppm which further splits by J=4Hz while the second appears at 2.8-3.0 ppm with further splitting of J=7 Hz.

These signals are due to two geminal protons that coupled with each other as the homo- COSY spectra indicated, further the HETCOR spectra indicate that these protons attached to the same carbon atom that has a ^{13}C NMR signal at 42.6 ppm.

Each of these protons were coupled to the same vicinal proton of the multiplet at 4.7 ppm with J=4 and 7 Hz this is also confirmed by COSY spectra. All the spectra of the studied compounds also charecterised by the vinylic singlet at about 5 ppm which appeared at 6 ppm in the spectrum of curcumin. In addition two doublets of 2H are present in the spectra belong to the olefinic protons at the carbonyl site of the molecules while in curcumin there are two doublets of 4H are present for the two olefinic moieties.

^{13}C NMR spectra indicated the presence of two OMe signals at 55.3 and 55.5 ppm and two C-OH signals at 145.8 and 147.6 ppm. Both NMR and dynamic NMR spectra indicated that the molecules appear in the form of one isomer in the solution despite the fact that they could be in both syn and anti forms as based on the directions of the N- substituent and the methyne proton.

The suggested mechanism for the reaction is as follows: The enol-imine is produced from the reaction of the curcumin and the amine then this species is undergo rearrangement under the microwave conditions to give the azetidines as the final product (Scheme 1).



Scheme 1 the suggested mechanism for the azetidine preparation.

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تحضير بعض الأزيتيدينات المشتقة من الكركمين تحت تأثير أشعة المايكروويف.

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الخلاصة

أهتمت هذه الدراسة بتحضير مجموعة من الأزيتيدينات المشتقة من الكركمين وذلك بمفاعلته مع الأمينات الأولية أو خلات الامينات الأولية. وقد جرى التفاعل تحت التشعيع بالمايكروويف وبوجود مادة المونتموريلونايت بوصفه عاملاً مساعداً. وكانت فترة التفاعل لا تتجاوز الدقيقتين في كل حالة. وقد شخصت المركبات المحضرة بوساطة التحليل العناصري الدقيق وأطياف الكتلة وأطياف الرنين النووي المغناطيسي للبروتون والكاربون -13 اضافة لاطياف تحت الحمراء.