Syntheses and Characterizations of some New Pyrazolines Derived from Chalcone Compounds

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Abstract

An efficient and practical synthesis of six compounds of pyrazoline derivatives structures was achieved through cyclization of hydrazine hydrate with α,β--unsaturated ketones (chalcons) using glacial acetic acid as catalyst under thermal conditions. These compounds have been characterized by FT-IR, elemental analysis (C.H.N.) and $^1$H NMR spectroscopy.

Keywords: Pyrazoline, Chalcone.
Introduction

Chalcones constitute an important class of naturally occurring flavonoid compounds that exhibit a wide spectrum of biological activities and are well-known intermediates for the synthesis of various heterocycles. Chalcones are useful synthons in the synthesis of a large number of bioactive molecules, such as pyrazolines and isoxazoles that are well-known nitrogen-containing heterocyclic compounds (Wattenberg et al., 1968; Shah and Desi, 2007; Mostahar et al., 2007; Patange et al., 2008 and Yar et al., 2007).

The discovery of this class of compounds provides an outstaynding case history of modern drug development and also emphasizes the unpredictability of biological activity from structural modification of a prototype drug molecule. Considerable interest has been focused on the pyrazoline structure, which is known to possess a broad spectrum of biological activities, such as antitumor (Taylor et al., 1992), immunosuppressive (Karthikeyan et al., 2007), antibacterial (Holla et al., 2000), anti-inflammatory (Bansal et al., 2001), anticancer (Manna et al., 2005), antidiabetic (Ahn et al., 2004) and antidepressant activities (Prasad et al., 2005). Thus, the synthesis of the 1,3,5-trisubstituted 2-pyrazolines moiety is always a great challenge.

Among various pyrazolines derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type of compounds. Various procedures have been developed for the synthesis of pyrazolines (Elguero et al., 1984; Elguero et al., 1996 and Dabholkar and Gavande, 2003). After the pioneering work of Fischer and Knoevenagel in the
19th century, the reaction of \( \alpha,\beta \)-unsaturated aldehydes and ketones with phenylhydrazine in acetic acid under reflux became one of the most popular methods for the preparation of 2-pyrazolines (Levai 2005; Li et al., 2007 and Kamble et al., 2008).

**Experimental**

**General.** Melting points were uncorrected. FT-IR-8400 SHIMADZU. NMR spectra were acquired with a Bruker Ultra Shield (\(^1\)H: 300 MHz) (University of AL-al-Bayt, Jordan). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. The elemental analysis were performed by using Euro Vector EA3000A (University of AL-al-Bayt, Jordan).

**Synthesis of pyrazoline derivatives (2a-f)**

**General procedure.** To a stirred solution of chalcone (1a–f) which was prepared as mentioned in the literature) (Karamana et al., 2010) (1.0 mmol) in 10 ml EtOH (96 \%) was added hydrazine hydrate (2.0 mmol) and glacial acetic acid (2.5 ml) at room temperature. The reaction mixture was heated to reflux overnight. The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 8:2). The EtOH was removed under reduced pressure and the residue was recrystallized from EtOH to afford the pure products (2a–f).

5-(furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole (2a)

It was prepared from the reaction of 3-(furan-2-yl)-1-phenylprop-2-en-1-one (1a) with hydrazine hydrate and gave a 73\% yield with a m.p. (202-204)\(^\circ\)C. The
CHN analysis for C$_{13}$H$_{12}$N$_2$O : C 73.56; H 5.70; N 13.20 Found C 73.52; H 5.68; N 13.13, FT-IR spectra (KBr pellet) $\nu$(cm$^{-1}$) 3330 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1219 (C–N stretching of pyrazoline ring), $\delta$H(CDCl$_3$) (7.912-7.921 ppm (1H,d,1); (7.518-7.581 ppm (5H,m,8,9,10,11,12); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7$^\gamma$) 5-(furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (2b)

It was prepared from the reaction of 3-(furan-2-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (1b) with hydrazine hydrate and gave a 75% yield with a m.p. (200-202) °C. The CHN analysis for C$_{14}$H$_{14}$N$_2$O$_2$ : C 69.41; H 5.82; N 11.56 Found C 69.31; H 5.80; N 11.55, FT-IR spectra (KBr pellet) $\nu$(cm$^{-1}$) 3332 (NH stretching of pyrazoline ring), 3022 (C–H stretching of aromatic ring), 2883 (C–H stretching of aliphatic), 1619 (C=N stretching of pyrazoline ring), 1594 (C=C stretching of aromatic ring), 1216 (C–N stretching of pyrazoline ring), $\delta$H(CDCl$_3$) (7.912-7.921 ppm (1H,d,1); (7.455-7.465) ppm (2H,d,8,12); (7.259-7.269) ppm (2H,d,9,11); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); 4.111 ppm (3H,s,10); (3.350-3.360) ppm (2H,d,7,7$^\gamma$)

5-(furan-2-yl)-3-(4-bromoxyphenyl)-4,5-dihydro-1H-pyrazole (2c)

This was prepared from the reaction of 3-(furan-2-yl)-1-(4-bromophenyl) prop-2-en-1-one (1c) with hydrazine hydrate and gave a 79% yield with m.p. (206-208) °C. The CHN analysis for
C_{13}H_{11}N_{2}OBr; C 53.63; H 3.81; N 9.62 Found C 53.60; H 3.80; N 9.61, FT-IR spectra (KBr pellet) \( \nu(\text{cm}^{-1}) \) 3334 (NH stretching of pyrazoline ring), 3023 (C–H stretching of aromatic ring), 2884 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1596 (C=C stretching of aromatic ring), 1217 (C–N stretching of pyrazoline ring), \( \delta_H(\text{CDCl}_3) \) (7.912-7.921 ppm (1H,d,1); (7.709-7.719) ppm (2H,d,8,12); (7.402-7.412) ppm (2H,d,9,11); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7')

5-(furan-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (2d)

It was prepared from the reaction of 3-(furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (1d) with hydrazine hydrate and gave a 85% yield with a m.p. (205-207)\(^\circ\)C. The CHN analysis for C_{13}H_{11}N_{3}O_{3}; C 60.70; H 4.31; N 16.33 Found C 60.60; H 4.30; N 16.27, FT-IR spectra (KBr pellet) \( \nu(\text{cm}^{-1}) \) 3338 (NH stretching of pyrazoline ring), 3021 (C–H stretching of aromatic ring), 2881 (C–H stretching of aliphatic), 1625 (C=N stretching of pyrazoline ring), 1597 (C=C stretching of aromatic ring), 1212 (C–N stretching of pyrazoline ring), \( \delta_H(\text{CDCl}_3) \) (8.321-8.331) ppm (2H,d,9,11); (8.111-8.121) ppm (2H,d,8,12); (7.912-7.921) ppm (1H,d,1); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7')

5-(furan-2-yl)-3-(3-aminophenyl)-4,5-dihydro-1H-pyrazole (2e)

It was prepared from the reaction of 3-(furan-2-yl)-1-(3-aminophenyl)prop-2-en-1-one (1e) with hydrazine hydrate and
gave a 71% yield with a m.p. (198-200) °C. The CHN analysis for C_{13}H_{13}N_{3}O; C 68.70; H 5.77; N 18.49 Found C 68.65; H 5.71; N 18.45, FT-IR spectra (KBr pellet) \( \nu (\text{cm}^{-1}) \) 3336 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1620 (C=N stretching of pyrazoline ring), 1590 (C=C stretching of aromatic ring), 1210 (C–N stretching of pyrazoline ring), \( \delta_{H} (\text{CDCl}_3) \) (7.912-7.921) ppm (1H,d,1); (7.218-7.281) ppm (6H,m,2,3,8,10,11,12); 7.065 ppm (1H,s,5); 5.500 ppm (2H,s,9); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7')

5-(furan-2-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole (2f)

It was as prepared from the reaction of 3-(furan-2-yl)-1-(3-nitrophenyl)prop-2-en-1-one (1f) with hydrazine hydrate and gave a 87% yield with a m.p. (201-203)°C. The CHN analysis for C_{13}H_{11}N_{3}O_3; C 60.70; H 4.31; N 16.33 Found C 60.65; H 4.28; N 16.30, FT-IR spectra (KBr pellet) \( \nu (\text{cm}^{-1}) \) 3333 (NH stretching of pyrazoline ring), 3024 (C–H stretching of aromatic ring), 2885 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1214(C–N stretching of pyrazoline ring), \( \delta_{H} (\text{CDCl}_3) \) 8.711 ppm (1H,s,8), (8.318-8.381) ppm (3H,m,10,11,12); (7.900-7.910) ppm (1H,d,1); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7')
Results and discussion

Treatment of chalcones derivatives (1a-f) with hydrazine hydrate in boiling ethanol gave pyrazoline derivatives compounds, after purification by recrystallization from ethanol, pure pyrazoline derivatives compounds as shown in (scheme 1) in (71-87)% yield were obtained. The structures of these products were established from their elemental analysis, FT-IR, C.H.N and $^1$H NMR spectra. The FT-IR spectra of pyrazoline compounds were characterized by the disappearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1672-1710) cm$^{-1}$. These fact confirmed the correct expected chemical structure of these compounds. The representative absorption bands are shown in table (1). All the IR spectra of pyrazoline derivatives showed a peak at (1614-1625) cm$^{-1}$ which related to (C=N) stretching of pyrazoline ring, a peak at (1210-1219) cm$^{-1}$ which appeared due to (C-N) stretching of pyrazoline ring and a peak at (1590-1597) cm$^{-1}$ which appeared due to (C=C stretching of aromatic ring). While, the C-H stretching aromatic rings showed a peak within the range (3020-3024) cm$^{-1}$ and the C-H stretching aliphatic showed a peak within the range (2880-2885) cm$^{-1}$. The N-H stretching showed a peak within the range (3330-3338) cm$^{-1}$.
Table (1): Data of the FT-IR spectra of pyrazoline compounds

<table>
<thead>
<tr>
<th>Sym.</th>
<th>C=N Str. (w)</th>
<th>C-N Str. (m)</th>
<th>C=C Ar.Str. (w)</th>
<th>C-H Ar.Str. (m)</th>
<th>C-H, alip. Str. (w)</th>
<th>NH.Str.(m)</th>
</tr>
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<tbody>
<tr>
<td>2a</td>
<td>1614</td>
<td>1219</td>
<td>1595</td>
<td>3020</td>
<td>2880</td>
<td>3330</td>
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<tr>
<td>2b</td>
<td>1619</td>
<td>1216</td>
<td>1594</td>
<td>3022</td>
<td>2883</td>
<td>3332</td>
</tr>
<tr>
<td>2c</td>
<td>1622</td>
<td>1217</td>
<td>1596</td>
<td>3023</td>
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<td>1212</td>
<td>1597</td>
<td>3021</td>
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<tr>
<td>2e</td>
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<td>1210</td>
<td>1590</td>
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<td>1614</td>
<td>1219</td>
<td>1595</td>
<td>3020</td>
<td>2880</td>
<td>3333</td>
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</table>

Str. = stretching, w= weak, m = medium, Ar.=aromatic, alip.= aliphatic

The $^1$H NMR spectra of pyrazoline compounds are shown in figures (1-6). $^1$H NMR data of these compounds are summarized in table (2). All the $^1$H NMR spectra of pyrazoline ring were characterized (Silverstien et al., 2005; Cooper, 1980 and Shriner and Hermann, 2004) by the presence protons (5) of pyrazoline ring showed singlet signals within the range 7.065 ppm and showed triplet signals within the range (4.625-4.725) ppm which appeared to proton in (4) position because interaction with two protons in (7 and 7') position , while the two protons in (7 and 7') position showed doublet signals within the range (3.350-3.937) ppm because interaction with protons in (4) position. These peaks confirmed the correct expected chemical structure of pyrazoline compounds. The proton in
position (1) of furan ring showed doublet signals at (7.900-7.921) ppm, while the other two protons in positions (2 and 3) of furan ring showed multiplet signals within the range (6.211-7.281) ppm. The protons of aromatic rings in compound (2a) showed multiplet signals within the range (7.518-7.581) ppm which appeared to five protons in (8,9,10,11 and 12). While the compounds (2b,2c and 2d) including AB system in $^1$H NMR spectra therefore showed doublet signals within the range (7.455-8.121) ppm which appeared to the two protons in (8 and 12) positions. The other two protons in positions (9 and 11) showed doublet signals within the range (7.259-8.331) ppm. The four protons in compound (2e) appeared multiplet signals for aromatic ring in (7.218-7.281) ppm, while compound (2f) showed singlet signal at the range 8.711 ppm which related to proton in position (8) and showed multiplet signals within the range(8.318-8.381) ppm which appeared to the three protons in positions (10,11 and 12). The OCH$_3$ protons showed singlet signal for three protons at 4.111 ppm. The NH$_2$ protons showed singlet signal for two protons in the region $\delta$=5.500 ppm.
Table (2): Chemical shift (ppm) of the synthesized pyrazoline compounds

<table>
<thead>
<tr>
<th>Symbol</th>
<th>δ (ppm) of Proton (1)</th>
<th>δ (ppm) of Protons (2 and 3)</th>
<th>δ (ppm) of Proton (4)</th>
<th>δ (ppm) of Protons (5)</th>
<th>δ (ppm) of Protons (7 and 7')</th>
<th>δ (ppm) of Protons NH₂</th>
<th>δ (ppm) of OCH₃</th>
<th>δ (ppm) of Aromatic Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>(7.912-7.921) d</td>
<td>(6.211-6.481) m</td>
<td>(4.625-4.725) t</td>
<td>7.06 s</td>
<td>(3.927-3.937) d</td>
<td>---</td>
<td>---</td>
<td>(7.518-7.581) m (8,9,10,11 and 12)</td>
</tr>
<tr>
<td>2b</td>
<td>(7.912-7.921) d</td>
<td>(6.211-6.481) m</td>
<td>(4.625-4.725) t</td>
<td>7.00 s</td>
<td>(3.350-3.360) d</td>
<td>---</td>
<td>4.11 1 s</td>
<td>(7.455-7.465) d (8 and 12)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>2c</th>
<th>(7.912-7.921) d</th>
<th>(6.211-6.481) m</th>
<th>(4.625-4.725) t</th>
<th>7.065s</th>
<th>(3.927-3.937) d</th>
<th>---</th>
<th>(7.709-7.719) d (8 and 12) (7.402-7.412) d (9 and 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2e</td>
<td>(7.912-7.921) d</td>
<td>(7.218-7.281) m Me.wi. arom.</td>
<td>(4.625-4.725) t</td>
<td>7.065s</td>
<td>(3.927-3.937) d</td>
<td>5.500s</td>
<td>(7.218-7.281) m (8,10,11 and 12) Me.wi. (2 and 3)</td>
</tr>
<tr>
<td>2f</td>
<td>(7.900-7.910) d</td>
<td>(6.211-6.481) m</td>
<td>(4.625-4.725) t</td>
<td>7.065s</td>
<td>(3.927-3.937) d</td>
<td>---</td>
<td>8.711 s (8) (8.318-8.381) m (10,11 and 12)</td>
</tr>
</tbody>
</table>

Symb. = symbol, s = singlet, d = doublet, t = triplet, m=multiplet, Me.wi.= merge with
Figure (1): H NMR spectrum of compound (2a)

Figure (2): H NMR spectrum of compound (2b)
Figure (3): H NMR spectrum of compound (2c)

Figure (4): H NMR spectrum of compound (2d)
Figure (5): H NMR spectrum of compound (2e)

Figure (6): H NMR spectrum of compound (2f)
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تحضیر وتشخيص بعض مركبات البايرازولين الجديدة المشتقة من الجالكونات

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حضر في هذا البحث ستة مركبات من مشتقات البايروزولين من خلال تأحلق الهيدرازين المائي مع مشتقا (α-كيتون غير مشبع) باستخدام حامض الخليك الثلجي كعامل مساعد تحت ظروف حرارية. وشخصت المركبات الجديدة باستخدام مطية الأشعة تحت الحمراء وتحليل العناصر الدقيق ومطية الرنين النووي المغناطيسي للبروتون.