

## Synthesis of 4-Pyrazolymethylidene-2-Oxazoline and -2-Imidazoline Derivatives

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ABSTRACT. 4-Formyl-2-pyrazolin-5-ones (**1a,b**) is condensed with hippuric acid derivatives (**2a,b**) to give the corresponding pyrazolymethylidene azalactones (**3a-d**). Aminolysis of oxazolones (**3**) with aromatic amines in boiling acetic acid afforded imidazolones (**4a-l**). Treatment of oxazolones (**3**) with benzene in the presence of  $AlCl_3$  afforded  $\alpha$ -benzamidoacetophenone (**5**). Structural assignments of the new products were based on elemental analysis and IR,  $^1H$  NMR spectral data.

### Introduction

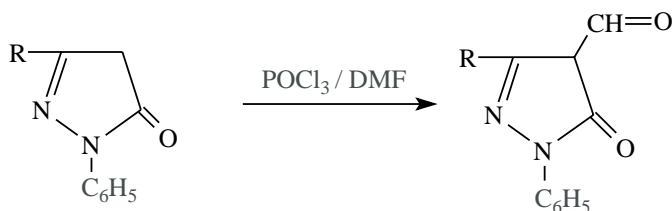
It was reported that pyrazolone derivatives are used as biologically active compounds such as drugs, agrochemicals, antibacterial<sup>[1]</sup>, antifungal<sup>[2]</sup> microbicides and herbicides<sup>[3]</sup> in addition to the well-known antipyretic and anti-inflammatory effects.

The synthesis and reactions of some new pyrazolymethylidene oxazolones (**3**) is reported here with the hope that they may add some new biological activity to the reported ones<sup>[1-3]</sup>.

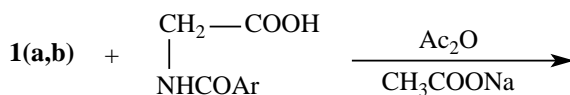
### Results and Discussion

Vilsmeier formylation of 3-substituted-1-phenyl-2-pyrazolin-5-ones with  $POCl_3/DMF$  mixture yielded the corresponding 4-formyl-2-pyrazolin-5-one derivatives (**1a,b**)<sup>[4-6]</sup>, which are condensed with N-(4-substituted) benzoylglycines (**2a,b**) in hot acetic anhydride- sodium acetate mixture<sup>[7]</sup> to give the corresponding 2-aryl-4-(5-hydroxy-1-phenyl-3-substituted-pyrazol-4-yl) methylidene-2-oxazolin-5-ones (**3a-d**).

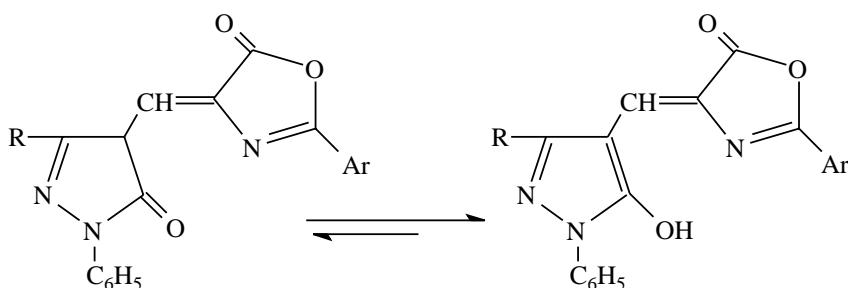
The IR spectra of azalactones (**3**) displayed an absorption bands in the regions  $3430 - 3410 \text{ cm}^{-1}$  ( $\nu_{\text{OH}}$  broad enolic OH of pyrazolones),  $1815 - 1775 \text{ cm}^{-1}$  ( $\nu_{\text{C=O}}$  of 5-oxazolones),  $1665 - 1645 \text{ cm}^{-1}$  ( $\nu_{\text{C=O}}$  of 5-pyrazolones) and  $1605 - 1595 \text{ cm}^{-1}$  ( $\nu_{\text{C=C}}$  or  $\nu_{\text{C=N}}$ ), which confirmed their existence in keto-enol tautomeric mixture.



(1)

1 R = CH<sub>3</sub> or C<sub>6</sub>H<sub>5</sub>a) R = CH<sub>3</sub>; b) R = C<sub>6</sub>H<sub>5</sub>

(2)

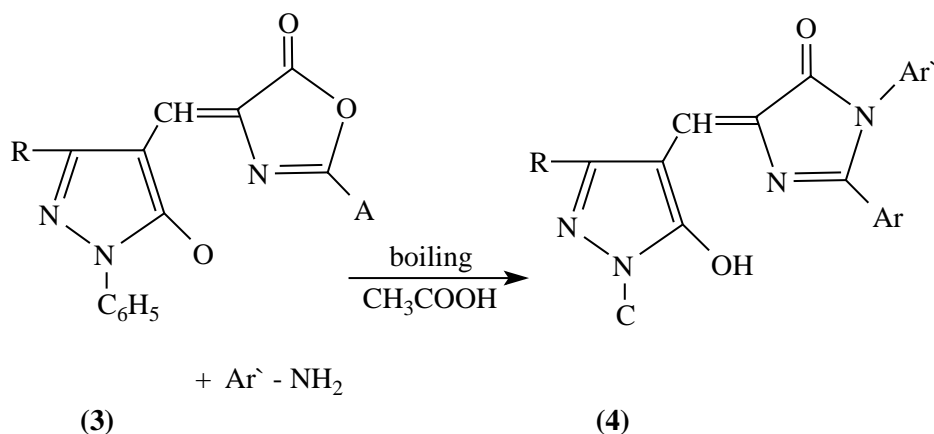
a) Ar = C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-4b) Ar = C<sub>2</sub>H<sub>4</sub>Cl-4

(3)

R Ar

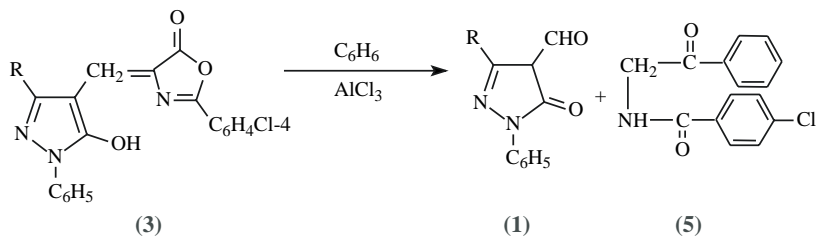
a) CH<sub>3</sub> C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-4b) C<sub>6</sub>H<sub>5</sub> C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-4c) CH<sub>3</sub> C<sub>6</sub>H<sub>4</sub>Cl-4d) C<sub>6</sub>H<sub>5</sub> C<sub>6</sub>H<sub>4</sub>Cl-4

Aminolysis of **(3)** with primary aromatic amines, namely, aniline, p-anisidine, and p-chloroaniline in boiling acetic acid yielded 1,2-diaryl-4-(5-hydroxy-1-phenyl-3-substituted-pyrazol-4-yl) methylidene-2-imidazoline-5-ones **(4a-l)** respectively. The infrared spectra of imidazolones **(4)** showed absorption bands in the regions  $3430\text{--}3425\text{ cm}^{-1}$  ( $\nu_{\text{OH}}$  broad enolic OH),  $1730\text{--}1710\text{ cm}^{-1}$  ( $\nu_{\text{C=O}}$  of imidazolones),  $1670\text{--}1645\text{ cm}^{-1}$  ( $\nu_{\text{C=O}}$  of 5-pyrazolones) and  $1610\text{--}1590\text{ cm}^{-1}$  ( $\nu_{\text{C=C}}$  or  $\nu_{\text{C=N}}$ ).



	R	Ar	Ar'
a)	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4	C <sub>6</sub> H <sub>5</sub>
b)	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4
c)	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4	C <sub>6</sub> H <sub>4</sub> Cl-4
d)	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> Cl-4	C <sub>6</sub> H <sub>5</sub>
e)	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> Cl-4	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4
f)	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> Cl-4	C <sub>6</sub> H <sub>4</sub> Cl-4
g)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4	C <sub>6</sub> H <sub>5</sub>
h)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4
i)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4	C <sub>6</sub> H <sub>4</sub> Cl-4
j)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> Cl-4	C <sub>6</sub> H <sub>5</sub>
k)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> Cl-4	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> -4
l)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> Cl-4	C <sub>6</sub> H <sub>4</sub> Cl-4

Friedel-Crafts reaction of oxazolones **(3c,d)** with benzene in the presence of anhydrous AlCl<sub>3</sub> proceeds via depyrazolization and ring opening of oxazolone ring to give a mixture of 4-formyl-2-pyrazolin-5-ones **(1a,b)** and  $\alpha$ -(4-chloro)benzamidoacetophenone **(5)**. The infrared spectrum of acetophenone derivatives **(5)** displayed bands at  $3360\text{ cm}^{-1}$  ( $\nu_{\text{NH}}$ ),  $3060\text{--}2970\text{ cm}^{-1}$  ( $\nu_{\text{CH}}$  aliphatic)  $1705\text{ cm}^{-1}$  ( $\nu_{\text{C=O}}$  ketone) and  $1660\text{ cm}^{-1}$  ( $\nu_{\text{C=O}}$  amide).



### Experimental

All melting points are not corrected. The IR absorption spectra were measured on a Nicolet Magna 520 FT IR spectrophotometer using KBr Water technique. <sup>1</sup>H-NMR were recorded in δ (ppm) on a Bruker DPX 400 MHz spectrometer using TMS as internal standard. The micro-elemental analyses were carried out using a Perkin Elmer 240 B analyzer.

#### 2-Aryl-4-(5-Hydroxy-1-Phenyl-3-Substituted Pyrazol-4-yl)Methylidene-2-Oxazolin-5-Ones (3a-d)

An equimolar mixture of 4-formyl-1-phenyl-3-substituted-2-pyrazolone (1a,b; 0.01 mol), finely powdered N-(4-substituted)benzoylglycine (2a,b; 0.01 mol) and anhydrous sodium acetate (0.05 mol) in acetic anhydride (20 ml) was heated on steam-bath for 3 h, cooled and ethanol (20 ml) was added. The mixture was kept 12 h at room temperature.

The solid product which separated was filtered, washed successively with water (3 × 50 ml), dried and recrystallized from acetic acid to give the corresponding azalactones (3) as yellow crystals. The results are listed in Table 1.

TABLE 1. The physical data of oxazolones (3a-d).

Compound	m.p °C	Yield %	Mol. formula (m. wt)	Analysis % calculated/found		
				C	H	N
<b>3a*</b>	241	83	C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> (375)	67.20	4.53	11.20
				67.06	4.47	11.03
<b>3b</b>	249	80	C <sub>26</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub> (437)	73.39	4.35	9.61
				71.21	4.29	9.48
<b>3c</b>	232	79	C <sub>20</sub> H <sub>14</sub> N <sub>3</sub> O <sub>3</sub> Cl (379.5)	63.24	3.69	11.07
				63.07	3.73	10.91
<b>3d**</b>	254	81	C <sub>25</sub> H <sub>16</sub> N <sub>3</sub> O <sub>3</sub> Cl (441.5)	67.95	3.62	9.51
				67.74	3.55	9.28

\*PMR (CDCl<sub>3</sub>); δ (ppm): 1.48 (s, 1H, enolic OH), 2.67 (s, 3H, CH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 7.03 (s, 1H, C<sub>4</sub>-CH=), 7.13-7.38 (m, 9H, Ar-H).

\*\*PMR (CDCl<sub>3</sub>); δ (ppm): 1.53 (s, 1H, enolic OH), 6.87(s, 1H, C<sub>4</sub>-CH=), 7.18-7.43 (m, 14H, Ar-H).

**1,2-Diaryl-4-(5-Hydroxy-1-Phenyl-3-Substituted Pyrazol-4-yl)Methylidene-2-Imidazolin-5-Ones (4a-l).**

A solution of oxazolones (**3**, 0.01 mol) and primary aromatic amines, namely, aniline, p-anisidine or p-chloroaniline (0.01 mol) in glacial acetic acid (50 ml) was refluxed for 5 h. The solid which separated after concentration and cooling was filtered and recrystallized from acetic acid to give the corresponding pyrazolymethylideneimidazolones (**4a-l**) as yellow crystals. The results are listed in Table 2.

TABLE 2. The physical data of benzamidoacrylamides (4a-l)

Compound	m.p °C	Yield % %	Mol. formula (m. wt)	Analysis % calculated/found		
				C	H	N
<b>4a*</b>	212	63	C <sub>27</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub> (450)	72.00	4.88	12.44
				71.85	4.79	12.37
<b>4b</b>	209	65	C <sub>28</sub> H <sub>24</sub> N <sub>4</sub> O <sub>4</sub> (480)	70.00	5.00	11.66
				69.86	4.94	11.57
<b>4c</b>	215	61	C <sub>27</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> (484.5)	66.87	4.33	11.55
				66.75	4.27	11.40
<b>4d***</b>	218	68	C <sub>26</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>2</sub> (484.5)	68.64	4.18	12.32
				68.53	4.08	12.19
<b>4e</b>	222	64	C <sub>27</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> (484.5)	66.87	4.33	11.55
				66.81	4.28	11.47
<b>4f</b>	226	68	C <sub>26</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> (489)	63.93	3.68	11.47
				63.82	3.61	11.33
<b>4g</b>	235	58	C <sub>32</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub> (512)	75.00	4.68	10.93
				74.87	4.62	10.78
<b>4h***</b>	231	61	C <sub>33</sub> H <sub>26</sub> N <sub>4</sub> O <sub>4</sub> (542)	73.06	4.79	10.33
				73.38	4.71	10.26
<b>4i</b>	241	57	C <sub>32</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>3</sub> (546.5)	70.26	4.20	10.24
				70.11	4.17	10.13
<b>4j</b>	232	63	C <sub>31</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>2</sub> (516.5)	72.02	4.06	10.86
				71.88	4.00	10.73
<b>4k+*</b>	219	66	C <sub>32</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>3</sub> (546.5)	70.26	4.20	10.24
				70.11	4.13	10.05
<b>4l</b>	225	68	C <sub>31</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> (551)	67.51	3.63	10.18
				67.38	3.55	10.03

\*PMR (CDCl<sub>3</sub>); δ (ppm): 1.46 (s, 1H, enolic OH), 2.50 (s, 3H, CH<sub>3</sub>), 3.65 (s, 3H, OCH<sub>3</sub>), 6.58 (s, 1H, CH=), 7.18-7.57 (m, 14H, Ar-H).

\*\*PMR (DMSO); δ (ppm): 1.53 (s, 1H, enolic OH), 2.67 (s, 3H, CH<sub>3</sub>), 6.43 (s, 1H, CH=), 7.21-7.53 (m, 14H, Ar-H).

\*\*\*PMR (DMSO); δ (ppm): 1.47 (s, 1H, enolic OH), 3.68 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 6.42 (s, 1H, CH=), 7.13-7.48 (m, 18H, Ar-H).

+\*PMR (DMSO); δ (ppm): 1.58 (s, 1H, enolic OH), 3.72 (s, 3H, OCH<sub>3</sub>), 6.37 (s, 1H, CH=), 7.18-7.47 (m, 18H, Ar-H).

**$\alpha$ -(4-Chloro)Benzamidoacetophenone (5)**

A solution of azlactones (**3c,d**, 1.0 g), anhydrous  $\text{AlCl}_3$  (3 g) in dry benzene (50 ml) was stirred at room temperature for 1 h. Then under reflux for 3 h and left overnight at room temperature. The solution was poured onto ice (100 g) containing Conc. HCl (2.0 ml). The organic layer was separated, washed with water ( $3 \times 50$  ml), and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The oil residue which separated after evaporation of benzene was triturated with hot petroleum ether (60-80°C) to give benzamidoacetophenone (**5**) as colourless crystals, while the left residue was recrystallized from ethanol to give 4-formyl pyrazolone (**1a,b**)<sup>[4-6]</sup>.  $\alpha$ -(4-Chloro)benzamidoacetophenone (**5**), m.p 156°C,  $\text{C}_{15}\text{H}_{12}\text{ClNO}_2$  (273.5); calculated, C, 65.81; H, 4.39; N, 5.12; found; C, 65.70; H, 4.30; N, 5.01.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ );  $\delta$  (ppm): 2.72 (s, 1H,  $\text{NH}$ ), 4.72 (s, 2H,  $\text{CH}_2$ ) and 7.14-7.42 (m, 9H, Ar-H).

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## تحضير مشتقات ٤-بيرازولاييل ميثيليدين -٢-أوكسازولين و-٢-إيميدازولين

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المستخلص. تم في هذا البحث تكاثف مركبات ٤-فورمايل-٢-بيرازولين-٥-أون (1a,b) مع مشتقات حمض الهيبيوريك (2a,b) لتعطي مركبات بيرازولاييل ميثيليدين أزا لاكتون (3a-d). التحلل الأميني لمركبات الأزا لاكتون (٣) مع أمينات عطرية في حمض الخل عند الغليان أدى إلى تكوين مركبات إيميدازولون (4a-l)، كما أدت معالجة مركبات الأزا لاكتون (٣) بالبنزين في وجود كلوريد الألمنيوم الجاف إلى تكون مركبات ألفا بنزاميدو أسيتوفينون (٥). تم التعرف على تركيب النواتج الجديدة من خلال تحليل العناصر، وأطياف الأشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون.