

## **Thermal Condensation of 1-Aryl/ hetaryl-3-methyl-2-pyrazolin-5-ones with Aromatic Aldehydes. Synthesis of 4-arylidene-pyrazolones**

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*Abstract.* Heating of 3-methyl-1-(pyrid-2-yl / 4-chlorophenyl)-2-pyrazolin-5-ones (**1**) and some aromatic aldehydes at 150 – 160 °C affords the corresponding 4-arylidene-2-pyrazolin-5-ones (**2**) as colored products with high yields. These new products were characterized by UV-*vis*, FT-IR and <sup>1</sup>H NMR spectroscopic techniques and elemental analysis.

### **Introduction**

5-Pyrazolones are very important class of heterocycles due to their biological and pharmacological activities <sup>[1,2]</sup> which exhibit an anti-inflammatory <sup>[3]</sup>, herbicidal<sup>[4]</sup>, fungicidal <sup>[5]</sup>, bactericidal <sup>[5]</sup>, plant growth regulating properties <sup>[4]</sup>, antipyretic <sup>[6]</sup> and protein kinase inhibitors <sup>[7]</sup>, Also, they are used as key starting material for the synthesis of commercial aryl/hetarylazopyrazolone dyes <sup>[8,9]</sup>.

On the other hand, it is well known that the most important commercial application of 4-arylidene-pyrazolones that some of them have anti-fungal properties <sup>[10-13]</sup>, while, others were used as photographic dyes or intermediates in pharmaceuticals <sup>[14-16]</sup>.

The approach reported here deals with the synthesis of some new intensely colored 4-arylidene-pyrazolones which might have new pharmacological and commercial applications.

## Experimental

All melting points reported are uncorrected. IR spectra were recorded using Perkin Elmer's Spectrum RXIFT-IR spectrophotometer ( $\nu$  in  $\text{cm}^{-1}$ ) The NMR spectra were recorded on Bruker Avance DPX400 spectrometer, using pyridine- $d_5$  as a solvent and TMS as an internal standard (chemical shifts in  $\delta$  values in ppm). The UV-*vis* Spectra were recorded in ethanol using Shimadzu, Carry 50 ( $\lambda$  in nm). Elemental analyses were performed on Perkin Elmer 2400, series II micro-analyzer. Pyrid-2-ylhydrazine and 4-chlorophenylhydrazine hydrochloride are an Aldrich products and they are used without any further purification.

### *Condensation of Ethyl Acetoacetate with Arylhydrazines. Formation of 1-aryl-3-methyl-2-pyrazolin-5-ones (1a,b)*

A mixture of ethyl acetoacetate (0.024 mol) and Pyrid-2-ylhydrazine and 4-chlorophenylhydrazine hydrochloride (0.025 mol) was heated under water condenser in an oil bath at 150-160°C for 3h then cooled and triturated with diethyl ether (20 ml). The ether was removed by filtration and the solid residue was crystallized from ethanol to give 3-methyl-1-(pyrid-2-yl)-2-pyrazolin-5-one (**1a**) and 1-(4-chlorophenyl)-3-methyl-2-pyrazolin-5-one (**1b**), respectively. The physical data of 1-aryl-3-phenyl-2-pyrazolin-5-ones (**1**) are listed in Table 1.

**Table 1. Physical data of 1-aryl-3-phenyl-2-pyrazolin-5-ones (1a,b).**

Comp. No.	Mol. Formula (M.wt)	m.p.(°C) (Color)	Yield %	Elemental analysis Calculated / Found		
				C	H	N
<b>1a</b>	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> O (175.19)	109 (White)	EtOH (85)	61.70	5.18	23.99
				61.56	5.14	23.81
<b>1b</b>	C <sub>10</sub> H <sub>9</sub> N <sub>2</sub> OCl (208.65)	167 (white)	EtOH (90)	57.57	4.35	13.43
				57.44	4.33	13.30

### *Knoevenagel Condensation of Aromatic Aldehydes with Pyrazolones (1a,b). Formation of 1-aryl-4-arylidene-3-methyl-4,5-dihydro-1H-pyrazol-5-ones (2, 3)*

A mixture of 1-aryl-3-methyl-2-pyrazolin-5-one (**1a,b**) (0.01 mol) and aromatic aldehydes (0.012 mol) namely, benzaldehyde, 4-methylbenzaldehyde (*p*-tolualdehyde), 4-methoxybenzaldehyde (*p*-anisaldehyde), 4-chlorobenzaldehyde, 4-bromobenzaldehyde and 3,4-

methylene-dioxybenzaldehyde (piperonal) was heated in an oil bath at 150-160°C for 4h, cooled, triturated with ether (20 ml) and filtered off. The coloured residues were crystallized from the proper solvent to give the corresponding, 1-aryl-4-arylidene-3-methyl-4,5-dihydro-1*H*-pyrazol-5-ones (2a-f, 3a-f) respectively, as coloured products. The physical data of 4-arylidene-3-methyl-4,5-dihydro-1*H*-pyrazol-5-ones (2, 3) are listed in Table 2 respectively.

**Table 2. Physical data of 4-arylidene-1-(4-chlorophenyl)-3-methyl-4,5-dihydro-1*H*-pyrazol-5-ones (2,3).**

Compd. No.	Mol. Formula (M.wt)	m.p.(°C) (Color)	Solvent of crystallization (Yield %)	Elemental analysis Calculated/Found		
				C	H	N
<b>2a</b>	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> O (263.30)	153 (Pink)	P.E. (63)	72.99 72.83	4.98 4.95	15.96 15.79
<b>2b</b>	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O (277.33)	70 (Yellow)	P.E. (61)	73.63 73.55	5.45 5.41	15.15 15.02
<b>2c</b>	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> (293.33)	Oily (Orange)	P.E. (43)	69.61 69.47	5.15 5.13	14.33 14.19
<b>2d</b>	C <sub>16</sub> H <sub>12</sub> N <sub>3</sub> OCl (297.74)	86 (Yellow)	P.E. (65)	64.54 64.40	4.06 4.02	14.11 14.02
<b>2e</b>	C <sub>16</sub> H <sub>12</sub> N <sub>3</sub> OBr (342.19)	88 (Yellow)	P.E. (64)	56.16 56.05	3.53 3.50	12.28 12.11
<b>2f</b>	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> (307.31)	222 (Orange)	EtOH (67)	66.44 66.32	4.26 4.21	13.67 13.54
<b>3a</b>	C <sub>17</sub> H <sub>13</sub> N <sub>2</sub> OCl (296.76)	141 (Orange)	EtOH (62)	68.81 68.64	4.42 4.38	9.44 9.29
<b>3b</b>	C <sub>18</sub> H <sub>15</sub> N <sub>2</sub> OCl (310.78)	186 (Orange)	EtOH (69)	69.57 69.43	4.86 4.83	9.01 8.88
<b>3c</b>	C <sub>18</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> Cl (326.78)	140 (Brown)	EtOH (68)	66.16 66.03	4.63 4.60	8.57 8.43
<b>3d</b>	C <sub>17</sub> H <sub>12</sub> N <sub>2</sub> OCl <sub>2</sub> (331.20)	203 (Red)	EtOH (76)	61.65 61.50	3.65 3.61	8.46 8.33
<b>3e</b>	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> OClBr (363.64)	196 (Red)	EtOH (72)	52.85 52.69	3.33 3.31	7.70 7.56
<b>3f</b>	C <sub>18</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> Cl (340.77)	198 (Orange)	EtOH (80)	63.44 63.26	3.85 3.81	8.22 8.09

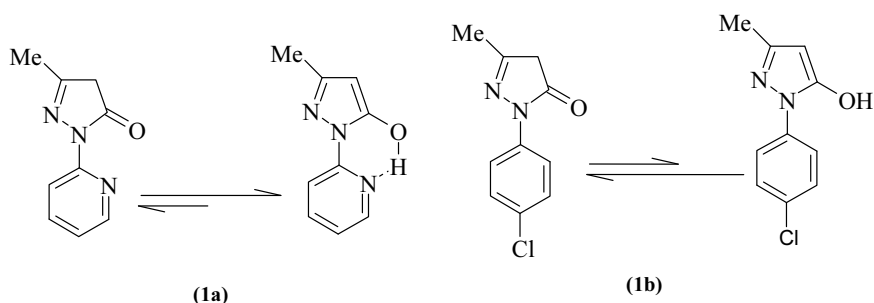
## Results and Discussion

Heating of ethyl acetoacetate and hydrazine derivatives, namely, pyrid-2-ylhydrazine or 4-chlorophenylhydrazine hydrochloride at 150 – 160 °C underwent cyclocondensation to give the corresponding 3-

methyl-1-(pyrid-2-yl)-2-pyrazolin-5-one (**1a**) and 1-(4-chlorophenyl)-3-methyl-2-pyrazolin-5-one (**1b**), respectively, which are used as key starting of the synthesis of the new 4-arylidene-5-pyrazolones.

The 1-aryl-3-methyl-2-pyrazolin-5-ones (**1 a,b**) exist in two tautomeric forms (**I and II**) due to their keto-enol tautomerism, The spectral data proved that pyrazolone (**1a**) exists mainly in enol form due to intermolecular chelation by H-bond while (**1b**) exists in keto form [17,18] (Scheme 1).

This phenomenon is confirmed by  $^1\text{H}$  NMR IR absorption spectra as shown in Table 3.



**Scheme 1**

**Table 3. The spectral data of 1-aryl-3-methyl-2-pyrazolin-5-ones (1a,b).**

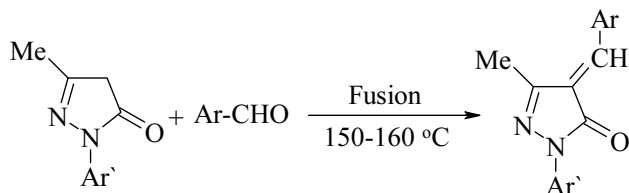
Comp. No	Structure	IR (v in $\text{cm}^{-1}$ )	$^1\text{H}$ -NMR in $\text{CDCl}_3$ ( $\delta$ in ppm)
<b>1a</b>		1614(C=O cyclic lactam) 3050 (CH aromatics). 3420 (enolic OH).	2.26 (s,3H,C3-CH <sub>3</sub> ),5.43 (s,1H,C4-H),7.11-8.53(m, 4H,ArH),12.80 (b,1H, OH).
<b>1b</b>		1669(C=O cyclic lactam) 3059 (CH aromatics).	2.20 (s,3H,C3-CH <sub>3</sub> ),3.44 (s,2H,C4-H),7.26-7.95(m, 4H ,ArH),

Fusion of an equimolar amounts of Ethyl acetoacetate with pyrid-2-ylhydrazine or 4-chlorophenylhydrazine hydrochloride at 150-160 °C

afforded 3-methyl-1-(pyrid-2-yl)-2-pyrazolin-5-one (**1a**) and 1-(4-chlorophenyl)-3-methyl-2-pyrazolin-5-one (**1b**), respectively in high yields.

The most characteristic behavior of 2-pyrazolin-5-ones is the outstanding reactivity of the methylene group at C-4. Therefore, this position undergoes the characteristic condensation and substitution reactions of the active methylene group<sup>[19-21]</sup>.

Fusion of an equimolar amounts of 1-aryl-3-methyl-2-pyrazolin-5-ones (**1a,b**) with aromatic aldehydes, namely: benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde and 3,4-methylenedioxybenzaldehyde (piperonal) at 150-160°C afforded 1-aryl-4-arylidene-3-methyl-4,5-dihydro-1H-pyrazol-5-ones (**2a-f**, **3a-f**) respectively, as intense coloured products in high yields (Scheme 2).

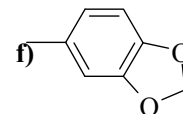
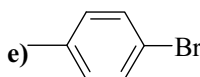
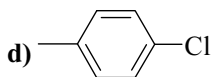
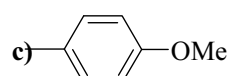
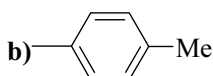
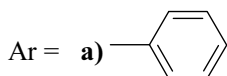


**1a)** Ar' = Pyrid-2-yl,

**2 a-f)** Ar' = pyrid-2-yl.

**1b)** Ar' = 4-chlorophenyl,

**3 a-f)** Ar' = 4-chlorophenyl.



**Scheme 2**

The structure of 4-arylidene-pyrazolones (**2,3**) have been established by IR, HNMR and UV-vis spectral data which are listed in Tables 4 and 5, respectively, and elemental analysis of Table 2.

**Table 4. The spectral data of 4-arylidene-1-(pyrid-2-yl)-3-methyl-4,5-dihydro-1H-pyrazol-5-ones (2a-e).**

Compd. No.	UV-vis ( $\lambda$ in nm)	IR ( $\nu$ in $\text{cm}^{-1}$ )			$^1\text{H-NMR}$ in $\text{CDCl}_3$ ( $\delta$ in ppm)
		C=N C=C	C=O	CH	
<b>2a</b>	334	1566	1636	2933 3022	2.18(s,3H,C3- $\text{CH}_3$ ), 7.14-8.25(m,9H, ArH+1H,C4= $\text{CH}$ ).
<b>2b</b>		1565	1644	2925 3052	2.12(s,3H,C3- $\text{CH}_3$ ), 2.35(s,3H,Ar $\text{CH}_3$ ) 6.9-8.5 (m,8H,ArH+1H, C4= $\text{CH}$ ).
<b>2c</b>	336	1578	1669	2934 3064	2.11(s,3H,C3- $\text{CH}_3$ ),3.82(s,3H,O $\text{CH}_3$ ), 6.79-8.60(m,8H, ArH+1H,C4= $\text{CH}$ ).
<b>2d</b>	360	1569	1676	2935 3062	2.12(s,3H,C3- $\text{CH}_3$ ), 7.0 8.6(m,8H, ArH+1H,C4= $\text{CH}$ ).
<b>2e</b>	335	1559	1666	2931 3060	2.12(s,3H,C3- $\text{CH}_3$ ),7.09-8.2(m,8H, ArH+1H,C4= $\text{CH}$ ).
<b>2f</b>	377	1578	1685	2924 3072	2.40(s,3H,C3- $\text{CH}_3$ ),6.11(s,2H, O $_2\text{CH}_2$ ), 6.92-8.7(m,7H,ArH+1H, C4= $\text{CH}$ ).

**Table 5. The spectral data of 4-arylidene-1-(4-chlorophenyl)-3-methyl-4,5-dihydro-1H-pyrazol-5-ones (3a-e).**

Compd. No.	UV-vis ( $\lambda$ in nm)	IR ( $\nu$ in $\text{cm}^{-1}$ )			$^1\text{H-NMR}$ in $\text{CDCl}_3$ ( $\delta$ in ppm)
		C=N C=C	C=O	CH	
<b>3a</b>	335	1591	1680	3074	2.36(s,3H,C3- $\text{CH}_3$ ),7.17-8.48(m,9H, ArH +1H,C4= $\text{CH}$ ).
<b>3b</b>	340	1595	1690	2928 3058	2.34(s,3H,C3- $\text{CH}_3$ ), 2.45(s,3H,Ar $\text{CH}_3$ ), 7.26-8.42 (m,8H,ArH+1H, C4= $\text{CH}$ ).
<b>3c</b>	371	1583	1677	2945 3079	2.34(s,3H,C3- $\text{CH}_3$ ), 3.91(s,3H,O $\text{CH}_3$ ) 6.99-8.59(m,8H, ArH +1H,C4= $\text{CH}$ ).
<b>3d</b>	330	1582	1676	2924 3084	2.34(s,3H,C3- $\text{CH}_3$ ), 7.25-8.46(m,8H, ArH +1H,C4= $\text{CH}$ ).
<b>3e</b>	334	1585	1673	2928 3086	2.36(s, 3H,C3- $\text{CH}_3$ ), 7.26-8.27(m,8H, ArH +1H,C4= $\text{CH}$ ).
<b>3f</b>	383-325	1489 1582	1680	2923 3072	2.32(s, 3H,C3- $\text{CH}_3$ ), 6.09 (s, 2H, O $_2\text{CH}_2$ ), 6.91-8.63(m,8H, ArH+1H, C4= $\text{CH}$ ).

It was observed from UV-vis absorption spectra in ethanol (Table 2,3) of 4-arylidene-pyrazolones that  $\lambda_{\max}$  ranges from 334 to 383 nm proved that 4-arylidene substituents with electron donating groups 4-OMe and 3,4 -O-CH<sub>2</sub>-O results in bathochromic shifts.

### References

- [1] Scheibye, S., El-Barbary, A.A., Lawesson, S.O., Fritz, H. and Rihs, G., *Tetrahedron* **38**: 3753 (1982).
- [2] Weissberger, A., Wiley, R.H. and Wiley, P., editor: "The Chemistry of Heterocyclic Compounds: Pyrazolinones, Pyrazolidones and Derivatives", Jhon Wiley, New York (1964).
- [3] Hiremith, S.P., Rudresh, K. and Saundan, A.R., *Indian J. Chem.*, **41B (2)**: 394 (2002).
- [4] Joerg, S., Reinhold, G., Otto, S., Joachim, S.H., Robert, S. and Klaus, L., *Ger. Offen.*, 04 Feb. 1988; DE 3, 625, 686 (Cl C07D 231/22) [*C. A.* **108**: 167465 (1988)].
- [5] Dhol, P.N., Achary, T.E. and Nayak, A., *J. Indian Chem. Soc.*, **52**: 1196 (1975).
- [6] Souza, F.R., Souza, V.T., Ratzlaff, V., Borges, L.P., Olivera, M.R., Bonacorso, H.G., Zanatta, N., Martina, M.A. and Mello, C.F., *Eur. J. Pharma.*, **451(2)**: 141 (2002).
- [7] Singh, J. and Tripathy, R., *PCT Int. Appl.*, **138** (2001).
- [8] Karci, F. and Ertan, N., *Dyes Pigments*, **55**: 99 (2002).
- [9] Ho, Y.W., *Dyes Pigments*, **64**: 223 (2005).
- [10] Ishihara, *Japan Kokai Tokkyo Koho*, **81**: 127, 360 (Cl C07D 231/20), 06 Oct. 1981, Appl. 80/29, 11 May, 829 (1980).
- [11] Pathak, R.B. and Bahel, S.C., *J. Indian Chem. Soc.*, **57**: 1108 (1980).
- [12] Sammour, A., Zimaity, A. and El-Borai, T., *J. Prakt. Chim.*, **314**: 612 (1972).
- [13] Wrzeciono, U. and Jobke, E., *Acta Pol. Pharm.*, **36**: 264, 629 (1978).
- [14] Wariishi, K., *Japan Kokai Tokkyo Koho*, JP 08 20, 582 96 20, 582, C. A., **124**: 317154k (1996).
- [15] Ubeda, T. and Akama, Y., *Chem. Phys. Lett.*, **222**: 559 (1994).
- [16] Li-Jiau, H., Sheng-Chu, K., and Hantch, L., *Taiwan Yao Hsueh Hsueh Chih*, **31**: 47 (1979). [*C. A.*, **93**: 71631 (1980)].
- [17] Khalil, A.Kh., Hassan, M.A., Mohamed, M.M. and El-Sayed, A.M., *Dyes Pigments*, **66**: 241 (2005).
- [18] Ertan, N., *Dyes and Pigments*, **44**: 41 (2000).
- [19] El-Shekeil, A., Babaqi, A., Hassan and M.A., Shiba, S., *Heterocycles*, **27**: 2577 (1988).
- [20] Hassan, M.A. and Döpp, D., *Heterocycles*, **45**: 451 (1997).
- [21] Hassan, M.A., El-Kasaby, M. and Abou El-Regal, M.K., *Phosphorus Sulfer and Silicon*, **104**: 15 (1995).

التكاثف الحراري لمشتقات ١ - أرييل هيتاريل - ٣ - ميثيل  
 ٢- بيرازولين - ٥ - ون: اصطناع مشتقات ٤- أرييل  
 يدين - ٥ - بيرازولون

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جدة - المملكة العربية السعودية

المستخلص. تسخين مشتقات ٣ - ميثيل - ١ - (٢- بيريديل) / ٤-  
 كلوروفنيل) - ٢ - بيرازولين - ٥ - ون مع بعض الأدهيدات  
 الأروماتية عند درجة حرارة ١٥٠ - ١٦٠ درجة مئوية، أعطت  
 نواتج ملونة من ٤- أريليدين - ٢- بيرازولين - ٥ - ون بمردود  
 مرتفع. تم إثبات تراكيب النواتج باستخدام أطيف الأشعة تحت  
 الحمراء، الأشعة فوق البنفسجية وطيف الرنين المغنطيسي  
 للبروتون، وكذلك التحليل الدقيقة للعناصر.