JKAU: Sci., **Vol. 20** No. 2, pp: 93-100 (2008 A.D. / 1428 A.H.)

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

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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 ^{o}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 ^{1}H NMR spectro scopic techniques and elemental analysis.

Introduction

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

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

The approach reported here deals with the synthesis of some new intensely colored 4-arylidenepyrazolones 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 (ν in 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 δ values in ppm). The UV-*vis* Spectra were recorded in ethanol using Shimadzu, Carry 50 (λ in nm). Elemental analyses were preformed 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
1a	$C_9H_9N_3O$ (175.19)	109 (White)	EtOH (85)	61.70 61.56	5.18 5.14	23.99 23.81
1b	$C_{10}H_9N_2OCl$ (208.65)	167 (white)	EtOH (90)	57.57 57.44	4.35 4.33	13.43 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-arylidenepyrazolones (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
2a	$C_{16}H_{13}N_3O$ (263.30)	153 (Pink)	P.E. (63)	72.99 72.83	4.98 4.95	15.96 15.79
2b	$C_{17}H_{15}N_3O$ (277.33)	70 (Yellow)	P.E. (61)	73.63 73.55	5.45 5.41	15.15 15.02
2c	$C_{17}H_{15}N_3O_2$ (293.33)	Oily (Orange)	P.E. (43)	69.61 69.47	5.15 5.13	14.33 14.19
2d	$C_{16}H_{12}N_3OCl$ (297.74)	86 (Yellow)	P.E. (65)	64.54 64.40	4.06 4.02	14.11 14.02
2e	$C_{16}H_{12}N_3OBr$ (342.19)	88 (Yellow)	P.E. (64)	56.16 56.05	3.53 3.50	12.28 12.11
2f	$C_{17}H_{13}N_3O_3$ (307.31)	222 (Orange)	EtOH (67)	66.44 66.32	4.26 4.21	13.67 13.54
3a	$C_{17}H_{13}N_2OCl$ (296.76)	141 (Orange)	EtOH (62)	68.81 68.64	4.42 4.38	9.44 9.29
3b	$C_{18}H_{15}N_2OCl$ (310.78)	186 (Orange)	EtOH (69)	69.57 69.43	4.86 4.83	9.01 8.88
3c	$C_{18}H_{15}N_2O_2Cl$ (326.78)	140 (Brown)	EtOH (68)	66.16 66.03	4.63 4.60	8.57 8.43
3d	$C_{17}H_{12}N_2OCl_2$ (331.20)	203 (Red)	EtOH (76)	61.65 61.50	3.65 3.61	8.46 8.33
3e	$C_{16}H_{12}N_2OClBr$ (363.64)	196 (Red)	EtOH (72)	52.85 52.69	3.33 3.31	7.70 7.56
3f	$C_{18}H_{13}N_2O_3Cl$ (340.77)	198 (Orange)	EtOH (80)	63.44 63.26	3.85 3.81	8.22 8.09

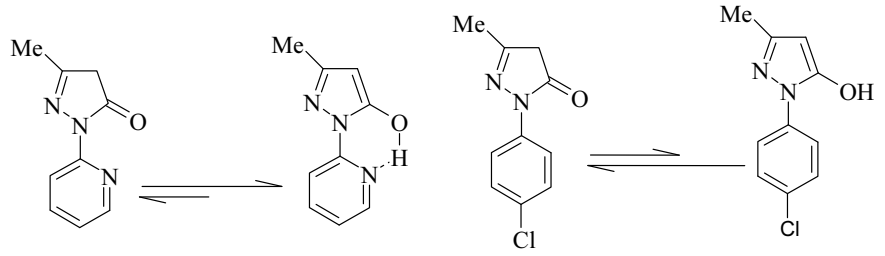
Results and Discussion

Heating of ethyl acetoacetate and hydrazine derivatives, namely, pyrid-2-ylhydrazine or 4-chlorophenylhydrazine hydrochloride at 150 – 160 ^{o}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 tautoumerism, The spectral data proved that pyrazolone **(1a)** exists mainly in enol form due to interamolecular chelation by H-bond while **(1b)** exists in keto form [17,18] (Scheme 1).

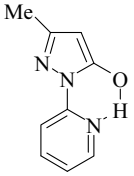
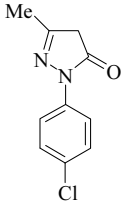
This phenomenon is confirmed by ^{1}H NMR IR absorption spectra as shown in Table 3.



(1a) **(1b)**

Scheme 1

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

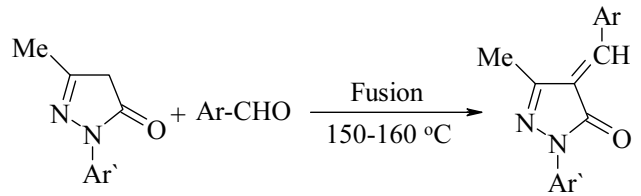
Comp. No	Structure	IR (ν in cm^{-1})	^{1}H-NMR in CDCl3 (δ in ppm)
1a		1614(C=O cyclic lactam) 3050 (CH aromatics). 3420 (enolic OH).	2.26 (s,3H,C3-C<u>H</u>$_3$),5.43 (s,1H,C4-<u>H</u>),7.11-8.53(m, 4H,Ar<u>H</u>),12.80 (b,1H, O<u>H</u>).
1b		1669(C=O cyclic lactam) 3059 (CH aromatics).	2.20 (s,3H,C3-C<u>H</u>$_3$),3.44 (s,2H,C4-<u>H</u>),7.26-7.95(m, 4H ,Ar<u>H</u>),

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.

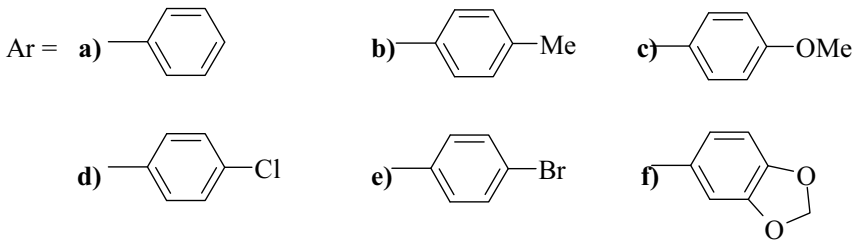
The most characteristic behavior of 2-pyrazolin-5-ones is the outstanding reactivity of the methylene group at C-4. Therefore, this position undergoes the characteristic condensation and substitution reactions of the active methylene group[19-21] .

Fusion of an equimolar amounts of 1-aryl-3-methyl-2-pyrazolin-5-ones **(1a,b)** with aromatic aldehydes, namely:, benzaldehyde, 4-methylbenzaldehyde, 4-methoxy- benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde and 3,4-methylenedioxy- benzaldehyde (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-arylidenepyrazolones (**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-1*H*-pyrazol-5-ones (2a-e).

Compd. No.	UV-vis (λ in nm)	IR (ν in cm^{-1})			^{1}H-NMR in $CDCl_3$0 (δ in ppm)
		C=N C=C	C=O	CH	
2a	334	1566	1636	2933 3022	2.18(s,3H,C3-C<u>H</u>$_3$), 7.14-8.25(m,9H, Ar<u>H</u>+1H,C4=C<u>H</u>).
2b		1565	1644	2925 3052	2.12(s,3H,C3-C<u>H</u>$_3$), 2.35(s,3H,ArC<u>H</u>$_3$) 6.9-8.5 (m,8H,Ar<u>H</u>+1H, C4=C<u>H</u>).
2c	336	1578	1669	2934 3064	2.11(s,3H,C3-C<u>H</u>$_3$),3.82(s,3H,OC<u>H</u>$_3$), 6.79-8.60(m,8H, Ar<u>H</u>+1H,C4=C<u>H</u>).
2d	360	1569	1676	2935 3062	2.12(s,3H,C3-C<u>H</u>$_3$), 7.0 8.6(m,8H, Ar<u>H</u>+1H,C4=C<u>H</u>).
2e	335	1559	1666	2931 3060	2.12(s,3H,C3-C<u>H</u>$_3$),7.09-8.2(m,8H, Ar<u>H</u>+1H,C4=C<u>H</u>).
2f	377	1578	1685	2924 3072	2.40(s,3H,C3-C<u>H</u>$_3$),6.11(s,2H, O_2C<u>H</u>$_2$), 6.92-8.7(m,7H,Ar<u>H</u>+1H, C4=C<u>H</u>).

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 (λ in nm)	IR (ν in cm^{-1})			^{1}H-NMR in $CDCl_3$ (δ in ppm)
		C=N C=C	C=O	CH	
3a	335	1591	1680	3074	2.36(s,3H,C3-C<u>H</u>$_3$),7.17-8.48(m,9H, Ar<u>H</u> +1H,C4=C<u>H</u>).
3b	340	1595	1690	2928 3058	2.34(s,3H,C3-C<u>H</u>$_3$), 2.45(s,3H,Ar C<u>H</u>$_3$), 7.26-8.42 (m,8H,Ar<u>H</u>+1H, C4=C<u>H</u>).
3c	371	1583	1677	2945 3079	2.34(s,3H,C3-C<u>H</u>$_3$), 3.91(s,3H,OC<u>H</u>$_3$) 6.99-8.59(m,8H, Ar<u>H</u> +1H,C4=C<u>H</u>).
3d	330	1582	1676	2924 3084	2.34(s,3H,C3-C<u>H</u>$_3$), 7.25-8.46(m,8H, Ar<u>H</u> +1H,C4=C<u>H</u>).
3e	334	1585	1673	2928 3086	2.36(s, 3H,C3-C<u>H</u>$_3$), 7.26-8.27(m,8H, Ar<u>H</u> +1H,C4=C<u>H</u>).
3f	383-325	1489 1582	1680	2923 3072	2.32(s, 3H,C3-C<u>H</u>$_3$), 6.09 (s, 2H, O_2C<u>H</u>$_2$), 6.91-8.63(m,8H, Ar<u>H</u>+1H, C4=C<u>H</u>).

It was observed from UV-*vis* absorption spectra in ethanol (*Table 2,3*) of 4-arylidenepyrazolones that λ_{max} ranges from 334 to 383 nm proved that 4-arylidene substituents with electron donating groups 4-OMe and 3,4 –O-CH_2-O results in bathochromic shifts.

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

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المستخلص. تسخين مشتقات ٣ – مثيل –١– (٢– بيريـــديل/ ٤– كلوروفنيل) – ٢ – بيرازولين – ٥– ون مع بعـــض الألدهيـــدات الأروماتية عند درجة حرارة ١٥٠ – ١٦٠ درجة مئوية، أعطـــت نواتج ملونة من ٤– أريليدين – ٢– بيرازولين– ٥– ون بمـــردود مرتفع. تم إثبات تراكيب النواتج باستخدام أطياف الأشـــعة تحـــت الحمراء، الأشعة فوق البنفـــسجية وطيـــف الـــرنين المغنطيـــسي للبروتون، وكذلك التحاليل الدقيقة للعناصر.