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Thermal condensation of 3-trifluoromethyl- / and 3-amino-1-phenyl-2-pyrazolin-5-ones with aromatic aldehydes. Synthesis of 4-arylidene-pyrazolones and pyrazolopyranopyrazoles

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1-Phenyl-3-trifluoromethyl-2-pyrazolin-5-one **1** on heating with aromatic aldehydes at 160–70 °C affords the corresponding 4-arylidene-2-pyrazolin-5-ones **3**, while 3-amino-1-phenyl-2-pyrazolin-5-one **2** on heating with aldehydes gives pyrazolo-pyranopyrazole derivatives **4** with high yields. These new products have been characterized by spectroscopic techniques and elemental analysis.

Keywords: Thermal condensation, aromatic aldehydes, arylidene-pyrazolones, pyrazolopyranopyrazoles, pyrazolinones

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5-Pyrazolones are very important class of heterocycles due to their biological and pharmacological activities[1,2] which exhibit anti-inflammatory[3], herbicidal[4], fungicidal[5], bactericidal[5] and plant growth regulating properties[4]. They are also antipyretic[6] and protein kinase inhibitors[7]. They are used as key starting materials for the synthesis of commercial aryl/hetarylazopyrazolone dyes[8,9]. It is well known that 4-arylidenepyrazolones have anti-fungal properties[10-13], and are used as photographic dyes or intermediates in pharmaceuticals[14-16].

We report herein the synthesis of some new intensely coloured 4-arylidene-pyrazolones which may have pharmacological properties.

Results and Discussion

Heating of an equimolar amounts of ethyl 4,4,4-trifluoroacetoacetate and phenylhydrazine at 150-60 °C for 3 hr resulted in the formation of 1-phenyl-3-trifluoromethyl-2-pyrazolin-5-one[17] **1** in 89% yield. The product **1** and the commercial 3-amino-1-phenyl-2-pyrazolin-5-one **2** are used as key starting for the synthesis of 4-arylidene-5-pyrazolones.

When equimolar amounts of 1-phenyl-3-trifluoromethyl-2-pyrazolin-5-one **1** and aromatic aldehydes are heated at 160-70°C, they result in the formation of 4-arylidene-1-phenyl–3-trifluoromethyl-2-pyrazolin-5-ones **3a-i** (**Scheme I**).

The structures of compounds **3a-i** have been confirmed by UV-Vis, IR and ^{1}H NMR spectra and elemental analysis (**Table I**).

Substitution of amino group in position-3 causes the reaction to take a different pathway. Treatment of 3-amino-1-phenyl-2-pyrazolin-5-one **2** with aromatic aldehydes (1:3 molar ratio) at 160-70°C in the absence of solvent resulted in the condensation of 3 molecules of aromatic aldehydes with two molecules of pyrazolone **2**. The reaction resulted in the formation of 4-aryl-*N*,*N*'-diarylidene-1,7-diphenyl-1*H*,4*H*,7*H*-pyrazolo[4',3':5,6] pyrano[2,3-*c*] pyrazole-3,5-diamines **4a-g** (**Scheme II**).

The IR spectra of pyrazolopyranopyrazoles **4** showed the absence of the stretching frequencies of C=O of cyclic lactam, enolic OH and amino group.

The structures of compounds **4a-g** have been established by IR and ^{1}H NMR spectral data and elemental analysis (**Table II**).

Experimental Section

All the melting points reported are uncorrected. IR spectra were recorded on a Perkin Elmer's Spectrum RXIFT-IR spectrophotometer (ν in cm^{-1}); ^{1}H NMR spectra on a Bruker Avance DPX400 spectrometer using pyridine-d_5 as a solvent and TMS as an internal standard (chemical shifts in δ, ppm); and UV-Vis spectra in ethanol using Shimadzu, Carry 50 (λ in nm). Elemental analyses were preformed on Perkin-Elmer 2400, series II micro-analyzer. Ethyl 4,4,4-trifluoroacetoacetate and 3-amino-1-phenyl-2-pyrazolin-5-one were Aldrich products and were used without any further purification.

Synthesis of 1-phenyl-3-trifluoromethyl-2-pyrazolin-5-one[17] 1. A mixture of ethyl 4,4,4-trifluoroacetoacetate (9.2 g, 0.05 mole) and phenylhydrazine (4.5 g, 0.055 mole) was heated under air condenser in an oil-bath at 150-60°C for 3 hr, then cooled and triturated with diethyl ether (20 mL). The ether was removed by filteration and the solid residue was crystallized from ethanol to give 1-phenyl-3-

trifluoromethyl-2-pyrazolin-5-one **1** (10.13 g, 89 %) as white crystals, m.p. 200°C; FTIR: 1676 (C=O cyclic lactam), 3065 (CH aromatics) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 1H, C_4-H), 5.89 (s, 1H, C_4-H), 7.37-7.82 (m, 5H, Ar-H); Anal. Calcd for $C_{10}H_7N_2OF_3$: C, 52.62 ; H, 3.09; N, 12.28. Found: C, 52.53 ; H, 3.04; N, 12.17 %.

Synthesis of 4-arylidene-1-phenyl-3-trifluoromethyl-2-pyrazolin-5-ones 3a-i. A mixture of **1** (2.28 g, 0.01 mole) and aromatic aldehydes (0.012 mole) was heated in an oil-bath at 160-70 °C for 4 hr, cooled, triturated with ether (20 mL) and filtered off. The coloured residues were crystallized from the proper solvents to get the corresponding, 4-arylidene-1-phenyl-3-trifluoromethyl-2-pyrazolin-5-ones **3a-i** as coloured crystals. The characterization data of arylidenepyrazolones **3** are listed in **Table I**.

Synthesis of 4-aryl-N,N'-diarylidene-1,7-diphenyl-1*H*,4*H*,7*H*-pyrazolo[4',3':5,6]- pyrano[2,3-c] pyrazole-3,5-diamine 4a-g. A mixture of **2** (1.75 g, 0.01 mole) and aromatic aldehydes (0.032 mole) was heated in an oil-bath at 160-70°C for 4 hr, cooled, triturated with ether (20 mL) and filtered off. The solid products were crystallized from suitable solvents to give the corresponding **4a-g**. The characterization data of pyrazolopyranopyrazoles **4a-g** are listed in **Table II**.

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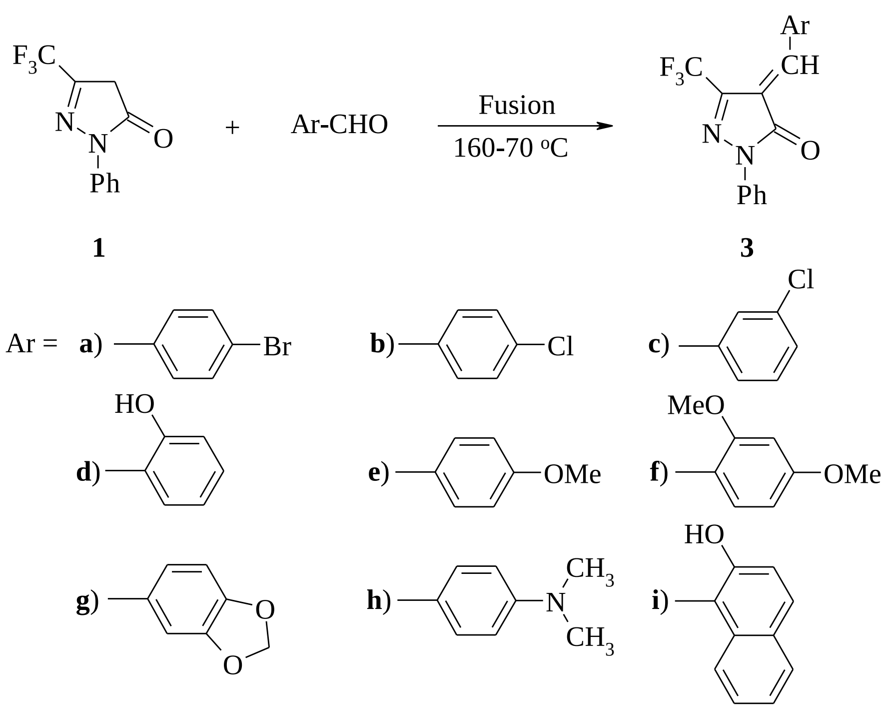
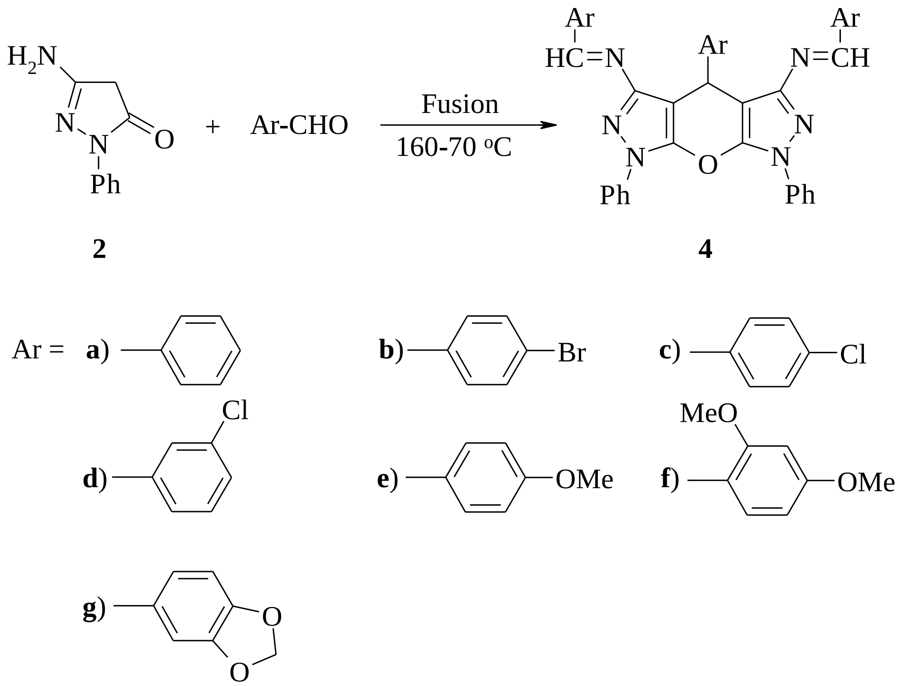


Scheme I


H2N
N
N
O
Ph
+ Ar-CHO
Fusion
160-70 °C
Ar
HC=N
Ar
Ar
N=CH
N
N
O
N
N
Ph
Ph
2
4
Ar = a)
b)
Br
c)
Cl
Cl
d)
e)
OMe
MeO
f)
OMe
g)
O
O

Scheme II

Table I—The characterization data of compounds **3a-i**

Compd	Mol. Formula (Mol. wt)	m.p., °C (Colour)	Solvent of crystallization (yield %)	Calcd (Found) %			UV-Vis in ethanol (**λ** in nm)	^{1}H NMR in $CDCl_3$ (δ, ppm)
				C	H	N		
3a	$C_{17}H_{10}BrF_3N_2O$ (395.17)	157-59 (yellow)	B + P.E (94)	51.67 (51.58	2.55 2.50	7.09 6.96)	--	7.12-8.04 (m, 10H, 9×Ar-H, C_4-CH)
3b	$C_{17}H_{10}ClF_3N_2O$ (350.72)	166-67 (orange)	P.E. 60-80 (89)	58.22 (58.11	2.87 2.83	7.99 7.85)	--	7.19-8.51 (m, 10H, 9× Ar-H, C_4-CH)
3c	$C_{17}H_{10}ClF_3N_2O$ (350.72)	245-46 (yellow)	Acetic acid (77)	58.22 (58.14	2.87 2.85	7.99 7.82)	--	7.16-7.98 (m, 10H, 9×Ar-H, C_4-CH)
3d	$C_{17}H_{11}F_3N_2O_2$ (332.28)	222 (orange)	Ethanol (85)	61.45 (61.27	3.34 3.26	8.43 8.33)	395	7.37-8.02 (m, 10H, 9×Ar-H, C_4-CH), 17.56 (s, 1H, OH)
3e	$C_{18}H_{13}F_3N_2O_2$ (346.30)	128-30 (orange)	Ethanol (91)	62.43 (62.25	3.78 3.67	8.09 7.88)	375	3.94 (s, 3H, OCH_3), 7.03-8.69 (m, 10H, 9×Ar-H, C_4-CH)
3f	$C_{19}H_{15}F_3N_2O_3$ (376.33)	192 (orange)	Ethanol (93)	60.64 (60.49	4.02 3.98	7.44 7.27)	405	3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.43-9.54 (m, 9H, 8×Ar-H, C_4-CH)
3g	$C_{18}H_{11}F_3N_2O_3$ (360.29)	204-05 (orange)	THF (93)	60.01 (59.77	3.08 3.01	7.78 7.69)	405	6.12 (s, 2H, O_2CH_2), 6.94-7.91 (m, 8H, Ar-H), 8.70 (s, 1H, C_4-CH)
3h	$C_{19}H_{16}F_3N_3O$ (359.35)	185-87 (red)	Ethanol (93)	63.51 (63.42	4.49 4.38	11.69 11.56)	380	3.15 (s, 6H, $2CH_3$), 6.85-7.93 (m, 9H, Ar-H), 8.56 (s, 1H, C_4-CH)
3i	$C_{21}H_{13}F_3N_2O_2$ (382.34)	223 (yellow)	Ethanol (65)	65.97 (65.81	3.43 3.40	7.33 7.23)	395	7.03-8.02 (m, 12H, 11×Ar-H, C_4-CH), 17.56 (s, 1H, OH)

B = Benzene, P.E. = Petroleum ether (60–80), THF = Tetrahydrofuran.

Table II—The characterization data of compounds **4a-g**

Compd	Mol. Formula (Mol. wt)	m.p., °C (Colour)	Solvent of crystallization (yield %)	Calcd (Found) %			^{1}H NMR in $CDCl_3$ (δ, ppm)
				C	H	N	
4a	$C_{39}H_{28}N_6O$ (596.70)	204-06 (white)	Methanol (61)	78.50 (78.35	4.73 4.69	14.08 13.94)	5.37 (s, 1H, C_4-H), 6.99-7.75 (m, 27H, 25×Ar-H, 2×N=CH)
4b	$C_{39}H_{25}Br_3N_6O$ (833.39)	239-41 (white)	Methanol (59)	56.21 (56.09	3.02 2.98	10.08 9.95)	5.29 (s, 1H, C_4-H), 7.08-7.79 (m, 24H, 22×Ar-H, 2×N=CH)
4c	$C_{39}H_{25}Cl_3N_6O$ (700.03)	233-35 (white)	Methanol (57)	66.92 (66.75	3.60 3.52	12.01 11.86)	5.34 (s, 1H, C_4-H), 7.09-7.50 (m, 24H, 22×Ar-H, 2×N=CH)
4d	$C_{39}H_{25}Cl_3N_6O$ (700.03)	214-16 (white)	Ethanol (58)	66.92 (66.81	3.60 3.53	12.01 11.95)	5.47 (s, 1H, C_4-H), 7.10-7.63 (m, 24H, 22×Ar-H, 2×N=CH)
4e	$C_{42}H_{34}N_6O_4$ (686.78)	244-46 (white)	Benzene (56)	73.45 (73.28	4.99 4.97	12.24 12.10)	3.66 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.24 (s, 1H, C_4-H), 6.74-7.54 (m, 24H, 22×Ar-H, 2× N=CH)
4f	$C_{45}H_{40}N_6O_7$ (776.86)	231-33 (white)	Methanol (53)	69.58 (69.46	5.19 5.14	10.82 10.68)	3.50 (s, 6H, 2×OCH_3), 3.59 (s, 3H, OCH_3), 3.69 (s, 6H, 2×OCH_3), 3.78 (s, 3H, OCH_3), 5.21 (s, 1H, C_4-H), 7.03-7.88 (m, 21H, 19×Ar-H, 2× N=CH)
4g	$C_{42}H_{28}N_6O_7$ (728.73)	222-25 (white)	Ethanol (53)	69.23 (69.15	3.87 3.80	11.53 11.36)	5.26 (s, 1H, C_4-H), 5.79 (s, 2H, O_2CH_2), 5.88 (s, 2H, O_2CH_2), 5.95 (s, 2H, O_2CH_2), 6.64-7.44 (m, 21H, 19×Ar-H, 2× N=CH)