FACILE SYNTHESIS OF PYRAZOLO[3,4-b]PYRIDINES

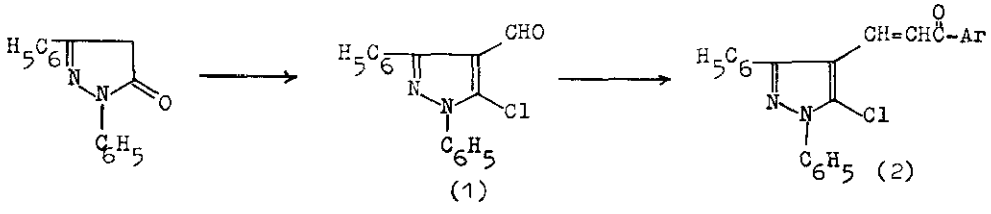
Abdulla Babaqi, Ali El-Shekeil*, Mohammed Hassan, and
Sayed Shiba
Chemistry Department, Faculty of Science, Sana'a University
Sana'a, Yemen

Abstract — The base-catalyzed Michael addition of cyclohexanone, 1,3-diphenyl-2-pyrazolin-5-one, ethyl acetoacetate, and diethyl malonate on 1-aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)-prop-2-en-1-ones (2) in the presence of ammonium acetate at 130°C gave the corresponding pyrazolo[3,4-b]pyridine derivatives (3-6). Structures were confirmed by microanalysis, ir, ^{1}H-nmr, and ^{13}C-nmr.

Pharmacological studies of pyrazolones as respiratory and cardio-vascular agents[1] fungicides, herbicides, insecticides[2,3] and antibacterial compounds[4] have been recently reported. Also, the antianxiety activities have been investigated[5,6] and the carcinogenicity of some pyrazolones has been established.[7]

As an extension of our previous work[8], we report here the facile synthesis of some new pyrazolo[3,4-b]pyridines from available chemicals by simple experimental procedures in high yields.

The Vilsmeier-Haack formylation of 1,3-diphenyl-2-pyrazolin-5-one was reported earlier[9,10] to give 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (1). The key-starting 1-aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)prop-2-en-1-ones (2 a,b) were prepared as a major product of Knoevenagel condensation of aldehyde (1) with acetophenone or p-methylacetophenone in alcoholic KOH.



(1) (2)

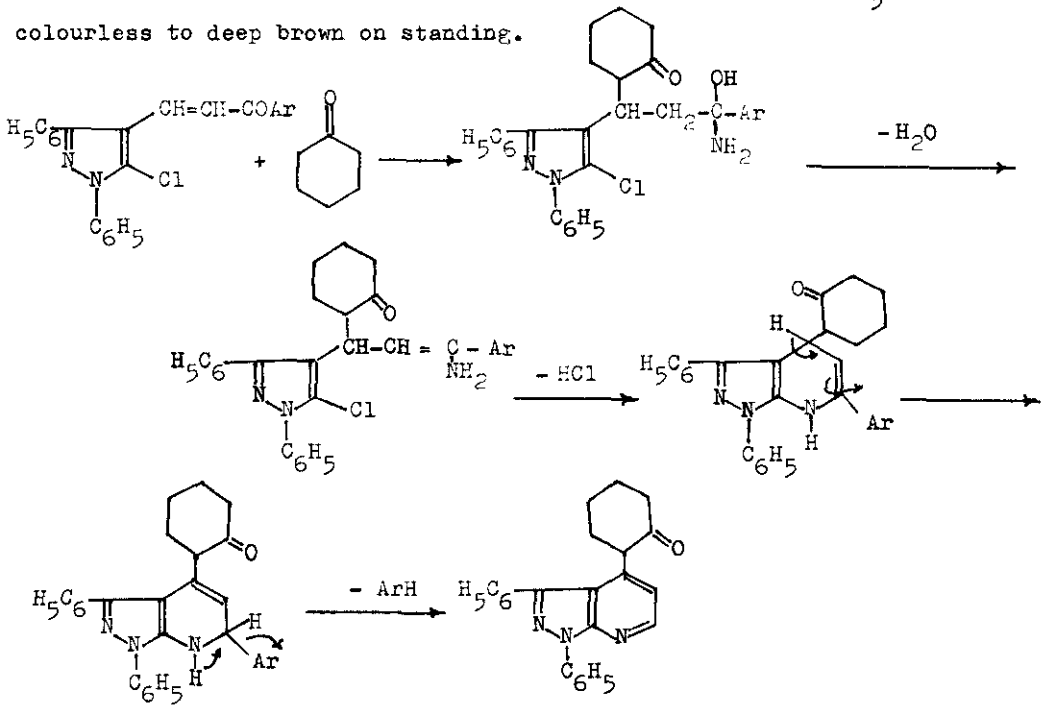
a) Ar = C_6H_5, b) Ar = C_6H_4-CH_3-p

Treatment of (2 a,b) with cyclohexanone or 1,3-diphenyl-2-pyrazolin-5-one in the presence of ammonium acetate at 130°C underwent Michael addition, cyclization, and dearylation to give 1,3-diphenyl-4-(6-oxocyclohexyl)-1H-pyrazolo[3,4-b]-pyridine (3) or 4,7-dihydro-1,3-diphenyl-4-(4,5-dihydro-1,3-diphenyl-5-oxo-1H-4-pyrazolyl)-1H-pyrazolo[3,4-b]pyridine (4), respectively. The dearylation[11] is confirmed by ^{1}H-nmr, ^{13}C-nmr and elemental analysis, and mechanism is proposed.

The base-catalyzed Michael addition of ethyl acetoacetate on (2) followed by cyclization, under the same conditions, yielded ethyl 1,3-diphenyl-6-methyl-4-phenacyl-1H-pyrazolo[3,4-b]pridine-5-carboxylate derivatives (5 a,b), while diethyl malonate reacted with (2) under the same conditions[12] to give ethyl 1,3-diphenyl-6-oxo-4-phenacyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridine -5-carboxylates (6 a,b).

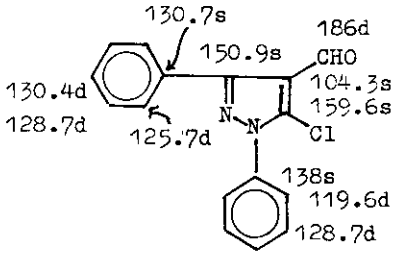
The structures of compounds (1-6) have been established by elemental analysis, ir and ^{1}H-nmr spectral data[13,14], which are listed in Table 1 together with yields, melting points, colour of crystals, and solvents of recrystallization.

The ^{13}C-nmr chemical shifts (δ ppm) and off-resonance data[15-18] are written on the structures below. The solution of compounds (3-5) in $CDCl_3$ changed from colourless to deep brown on standing.

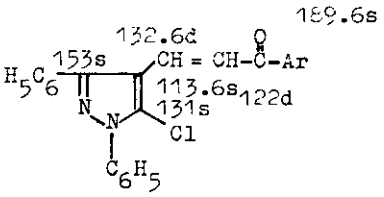


EXPERIMENTAL

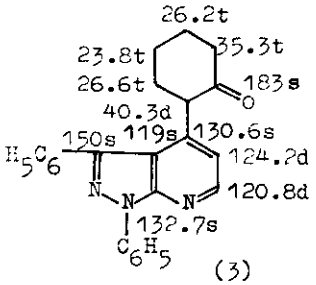
Melting points reported are uncorrected. Ir spectra were determined in KBr on Pye Unicam SP 200 G spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian T-60 spectrometer. The ^{13}C-nmr spectra were measured on a Jeol FX 90 Q Fourier Transform instrument operating at 22.50 MHz, 8192 data points were collected and a sweep width of 5000 Hz, i.e. digital resolution of 0.6 Hz (0.03 ppm). Pulse intervals of 5 seconds or more were used to achieve reasonable signal-to-noise ratios especially for the signal of carbons of long relaxation times e.g. C=O, C=N. The broad band proton noise decoupled and off-resonance spectra were recorded. In all nmr experiments the internal standard was TMS and the solvent was $CDCl_3$. All chemical shifts are in ppm downfield from TMS.



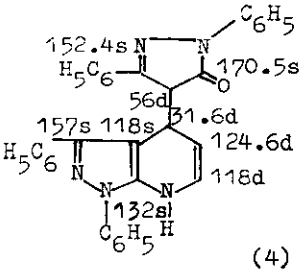
(1)



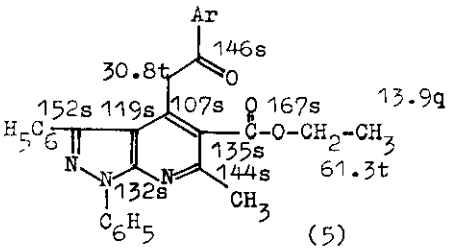
(2)



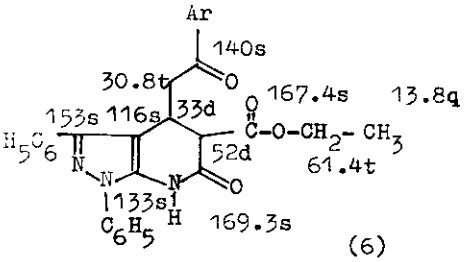
(3)



(4)



(5)



(6)

5-Chloro-1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (1) - A solution of 1,3-diphenyl-5-pyrazolone (47.5 gm, 0.2 mol) in DMF (100 ml) was cooled to 0°C in an ice - acetone bath. Then phosphoryl chloride (55 ml, 0.6 mol) was added dropwise at such as a rate as to maintain the temperature between 10-20°C. The reaction mixture was heated on steam-bath after complete addition for 90 min. The mixture was poured onto ice-water (2l). The resulting mixture was allowed to stand overnight at 25°C. The solid product thus obtained was filtered, washed with water, dried and crystallized from pet. ether (80-100°C) to give (1) as colourless crystals in 60% yield.

1-Aryl-3-(5-chloro-1,3-diphenyl-1H-4-pyrazolyl)prop-2-en-1-ones (2 a,b) - A mixture of aldehyde (1) (7.8 g., 0.01 mol) and acetophenone/or p-methylacetophenone (0.02 mol) in ethanolic KOH (2 g. in 100 ml) was stirred at 0°C for 2 h. The solid product which separated during stirring was filtered off, washed with water , dried and crystallized from benzene-pet. ether (80-100°C) mixture to give (2) as colourless crystals in 80-86% yield.

General procedure of base-catalyzed cycloaddition of active methylene compounds on (2) : Formation of pyrazolo[3,4-b]pyridines (3-6): A mixture of propenones (2)(0.01 mol), active methylene compounds (0.02 mol), namely, cyclohexanone, 1,3-diphenyl-2-pyrazolin-5-one, ethyl acetoacetate, or diethyl malonate, and dry ammonium acetate (0.04 mol) was heated in an oil-bath at 130°C for 3 h. The reaction mixture was cooled, triturated with hot water (50 ml), filtered, washed with water, dried and crystallized from a suitable solvent to give (3-6) respectively.

Table 1- Physical data of compounds 1-6 :

Compd.	Mp(°C) (colour)	Solvent of crystn. (yield %)	Mol. formula	Analysis % Calc./(found) C	H	N	Ir spectra (cm^{-1})
1*	110 (colourless)	B+P (60)	$C_{16}H_{11}N_2OCl$	68.0 (67.7	3.9 4.0	9.9 9.9)	1590(C=N,C=C),1670 (C=O).
2a**	150 (colourless)	B+P (80)	$C_{24}H_{17}N_2OCl$	74.9 (74.7	4.4 4.4	7.3 7.3)	1590(C=N,C=C),1660 (C=O).
2b**	142 (colourless)	B+P (86)	$C_{25}H_{19}N_2OCl$	75.3 (75.4	4.8 4.7	7.0 6.7)	1595(C=N,C=C),1680 (C=O).
3+	170 (pale yellow)	B+P (60)	$C_{24}H_{21}N_3O$	78.5 (78.8	5.7 5.9	11.4 11.2)	1595(C=N,C=C),1660 (C=O).
4++	220 (colourless)	B (66)	$C_{33}H_{25}N_5O$	78.1 (78.2	5.0 4.7	13.8 13.6)	1590(C=N,C=C),1705 (C=O),3300-3600(NH).
5a++	165 (pale yellow)	B+P (72)	$C_{30}H_{25}N_3O_3$	75.8 (75.9	5.3 5.5	8.8 9.1)	1595(C=N,C=C),1660 (C=O),1720(C=O ester).
5b‡	172 (pale yellow)	B+P (75)	$C_{31}H_{27}N_3O_3$	76.1 (75.9	5.5 5.7	8.6 8.9)	1595(C=N,C=C),1655 (C=O),1720(C=O ester).
6a***	185 (colourless)	B+P (85)	$C_{29}H_{25}N_3O_4$	72.6 (72.7	5.3 5.1	8.8 8.6)	1595(C=N,C=C),1680 (C=O),1740(C=O ester), 3230(NH).
6b***	220 (colourless)	B+P (87)	$C_{30}H_{27}N_3O_4$	73.0 (73.2	5.5 5.3	8.5 8.8)	1590(C=N,C=C),1670 (C=O),1740(C=O ester), 3210(NH).

B = benzene; P = pet. ether 80-100°C

* 1, ^{1}H-nmr : 7.2-7.9 ppm (m, 10H, Ar-H), and 10.0 (s, 1H, COH).

** 2a, ^{1}H-nmr : 7.2-8.3 ppm (m, Ar-H and CH = CH), while 2b gives additional 2.4(s, 3H, Ar-CH_3).

+ 3, ^{1}H-nmr : 0.8-2.4 (m, 9H, cyclohexyl-H), and 6.8-8.0(m, 12H, Ar-H, and olefinic C_5-H & C_6-H).

++ 4, ^{1}H-nmr : 4.0(d, J=5Hz, 1H, C_4-H), 5.7(d, J=5Hz, 1H, C_4-CH), 6.9-7.7 (m, 22H, Ar-H and olefinic C_5-H and C_6-H) and 8.2 (broad s, 1H, NH).

‡ 5a, ^{1}H-nmr : 1.0(t, J=7Hz, 3H, ester CH_2-CH_3), 2.15(s, 3H, C_6-CH_3), 2.7(s, 2H, C_4-CH_2), 4.15(q, J=7Hz, ester CH_2-CH_3), and 7.2-8.0 (m, 15H, Ar-H), 5b gives also 2.4(s, 3H, Ar-CH_3).

*** 6a, ^{1}H-nmr : Similar to 5a but with no peak at 2.15 but with s, 1H, NH at 8.3 ppm, but 6b gives additional signal at 2.4 (s, 3H, Ar-CH_3).

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