

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

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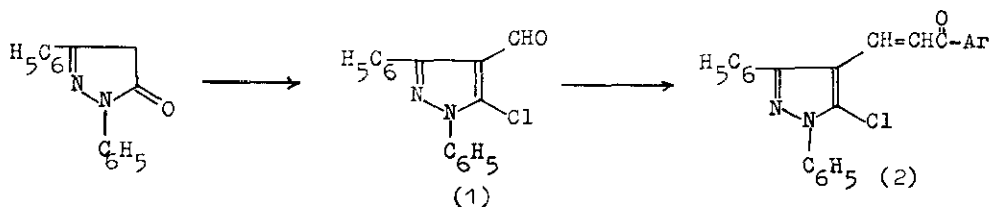
Sana'a, Yemen

**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,  $^1\text{H}$ -nmr, and  $^{13}\text{C}$ -nmr.

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

As an extension of our previous work<sup>8</sup>, 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<sup>9,10</sup> 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.



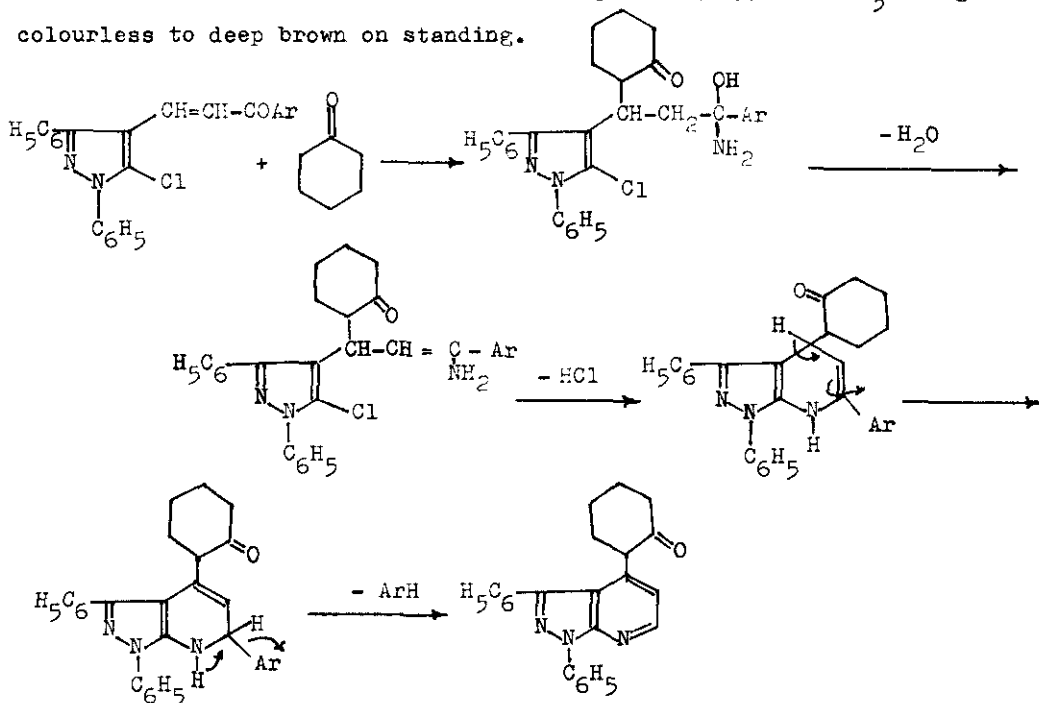
a) Ar = C<sub>6</sub>H<sub>5</sub>, b) Ar = C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-*p*

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<sup>11</sup> is confirmed by <sup>1</sup>H-nmr, <sup>13</sup>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] pyridine-5-carboxylate derivatives (5 a,b), while diethyl malonate reacted with (2) under the same conditions<sup>12</sup> 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).

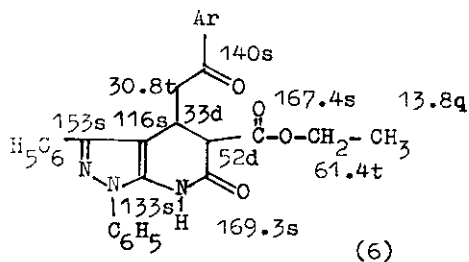
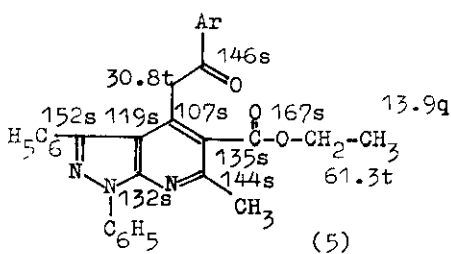
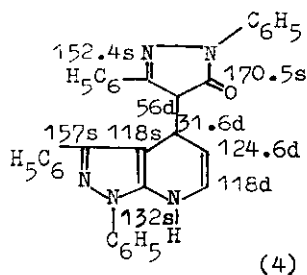
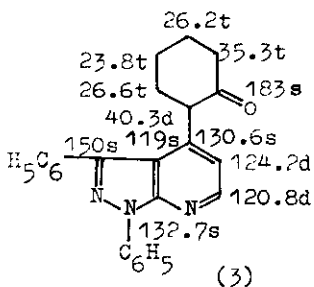
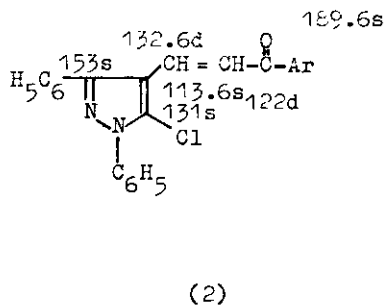
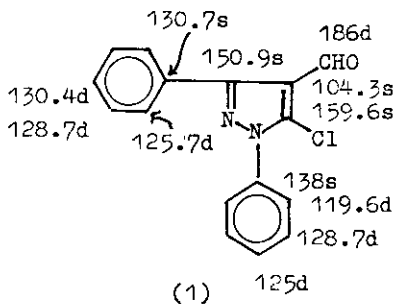
The structures of compounds (1-6) have been established by elemental analysis, ir and <sup>1</sup>H-nmr spectral data<sup>13,14</sup>, which are listed in Table 1 together with yields, melting points, colour of crystals, and solvents of recrystallization.

The <sup>13</sup>C-nmr chemical shifts (δ ppm) and off-resonance data<sup>15-18</sup> are written on the structures below. The solution of compounds (3-5) in CDCl<sub>3</sub> 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  $^1\text{H}$ -nmr spectra were recorded on a Varian T-60 spectrometer. The  $^{13}\text{C}$ -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  $\text{CDCl}_3$ . All chemical shifts are in ppm downfield from TMS.



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 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 (21). 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 %			Ir spectra (cm <sup>-1</sup> )
				Calc./	(found)		
1*	110 (colourless)	B+ P (60)	C <sub>16</sub> H <sub>11</sub> N <sub>2</sub> OCl	C 68.0 (67.7)	H 3.9 4.0	N 9.9 9.9)	1590(C=N,C=C),1670 (C=O).
2a**	150 (colourless)	B+ P (80)	C <sub>24</sub> H <sub>17</sub> N <sub>2</sub> OCl	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 <sub>25</sub> H <sub>19</sub> N <sub>2</sub> OCl	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 <sub>24</sub> H <sub>21</sub> N <sub>3</sub> O	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 <sub>33</sub> H <sub>25</sub> N <sub>5</sub> O	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 <sub>30</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub>	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 <sub>31</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>	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 <sub>29</sub> H <sub>25</sub> N <sub>3</sub> O <sub>4</sub>	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 <sub>30</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub>	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, <sup>1</sup>H-nmr : 7.2-7.9 ppm (m, 10H, Ar-H), and 10.0 (s, 1H, COH).
- \*\* 2a, <sup>1</sup>H-nmr : 7.2-8.3 ppm (m, Ar-H and CH = CH), while 2b gives additional 2.4 (s, 3H, Ar-CH<sub>3</sub>).
- + 3, <sup>1</sup>H-nmr : 0.8-2.4 (m, 9H, cyclohexyl-H), and 6.8-8.0 (m, 12H, Ar-H, and olefinic C<sub>5</sub>-H & C<sub>6</sub>-H).
- ++ 4, <sup>1</sup>H-nmr : 4.0 (d, J=5Hz, 1H, C<sub>4</sub>-H), 5.7 (d, J=5Hz, 1H, C<sub>4</sub>-CH), 6.9-7.7 (m, 22H, Ar-H and olefinic C<sub>5</sub>-H and C<sub>6</sub>-H) and 8.2 (broad s, 1H, NH).
- † 5a, <sup>1</sup>H-nmr : 1.0 (t, J=7Hz, 3H, ester CH<sub>2</sub>-CH<sub>3</sub>), 2.15 (s, 3H, C<sub>6</sub>-CH<sub>3</sub>), 2.7 (s, 2H, C<sub>4</sub>-CH<sub>2</sub>), 4.15 (q, J=7Hz, ester CH<sub>2</sub>-CH<sub>3</sub>), and 7.2-8.0 (m, 15H, Ar-H), 5b gives also 2.4 (s, 3H, Ar-CH<sub>3</sub>).
- \*\*\* 6a, <sup>1</sup>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<sub>3</sub>).

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