Synthesis of Newly Substituted Pyrazoles and Substituted Pyrazolo[3,4-*b*]pyridines Based on 5-Amino-3-methyl-1-phenylpyrazole

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The reaction of the aminopyrazole **1** with benzenesulfonyl chloride, arenediazonium salt, chloroacetyl chloride, ethoxy methyleneamlononitrile and with ethyl 2-cyano-3-ethoxyacrylate gave the substituted 3-methyl-1-phenylpyrazole **2-5a,b**. Compound **5b** was cyclized to **6** and to **7** by treating it with $AlCl_3$ and with $POCl_3$, respectively. Compound **6** converted to **7** by boiling it in $POCl_3/PCl_5$. Compound **10b** was produced through reaction of **9** with acetophenone. Reaction of **1** with benzylidinemalononitrile afforded **11**. New methods for preparation of **15** and **16** are described. The reaction of **8** with malononitrile, thiosemicarbazide, phenyl hydrazine and acetophenone afforded compounds **18-21**. The reaction of **21** with malononitrile gave **22**. Compounds **23-26** were produced upon reaction of **10a** with malononitrile, phenyl hydrazine, thiosemicarbazide, semicarbazide and with benzaldehyde, respectively.

Keywords: Pyrazole; Pyrazolo[3,4-*b*]pyridine.

INTRODUCTION

The synthesis and the chemistry of the pyrazole nucleus has received much attention[1-5a,b] during recent decades due to its outstanding biological activities. It has been used as an antipyretic, as an analgesic and as an anti-inflammatory drug.[6a,b] It also has antimalarial,[6c] antitumor,[6d] antibacterial, antifungal,[7a-e] antiparasitic[7d,e] and antiviral uses.[8a] As well, it can be used as a protein kinase inhibitor,[8b] and as a potent cannabinoid CB1 receptor antagonist.[9a,b] It is found to be useful as a potential glucocorticoid receptor ligand for positron emission tomography (PET).[9c]

Taking all the above into consideration and in continuation of our previous work directed to synthesis of new heterocycles engaged with pyrazole nuclei,[3a-d,7b-e,11a] we describe herein the utilization of the 5-amino-3-methyl-1-phenylpyrazole (**1**) as the key intermediate in the synthesis of newly substituted pyrazoles and pyrazolo[3,4-*b*]pyridines.

RESULTS AND DISCUSSION

The reaction of 5-amino-3-methyl-1-phenylpyrazole (**1**)[10] with benzene sulfonyl chloride, benzene diazonium chloride, *p*-toluidine diazonium chloride, *p*-anisidine diazonium chloride, chloroacetyl chloride, ethoxy methyleneamlononitrile and with ethyl 2-cyano-3-ethoxyacrylate gave the substituted pyrazoles **2-5a,b** (Scheme I).

The ethylaminocyanoacrylate function at the 5-position in ethyl-2-cyano-3-(3-methyl-1-phenyl-1*H*-pyrazol-5-ylamino)methylene)acrylate (**5b**) was used in preparing a fused pyrazole. Thus, boiling of **5b** in nitrobenzene in the presence of anhydrous $AlCl_3$ at reflux temperature led to cyclization and the formation of 3-methyl-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**6**) (Scheme I).

Boiling **5b** in $POCl_3$[11a-c] at reflux temperature furnished 4-chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (**7**) (Scheme I).

Compound **6** was converted to **7** by heating it at reflux temperature in a mixture[11a] of $POCl_3$ and PCl_5 (Scheme I).

The reaction of 5-amino-3-methyl-1-phenylpyrazole-4-carbaldehyde (**9**)[12] with acetophenone furnished 3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**10b**) (Scheme I).

In an ethanolic solution containing piperidine as a basic catalyst, the reaction of 5-amino-3-methyl-1-phenylpyrazole (**1**) with benzylidinemalononitrile yielded 6-amino-3-methyl-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-

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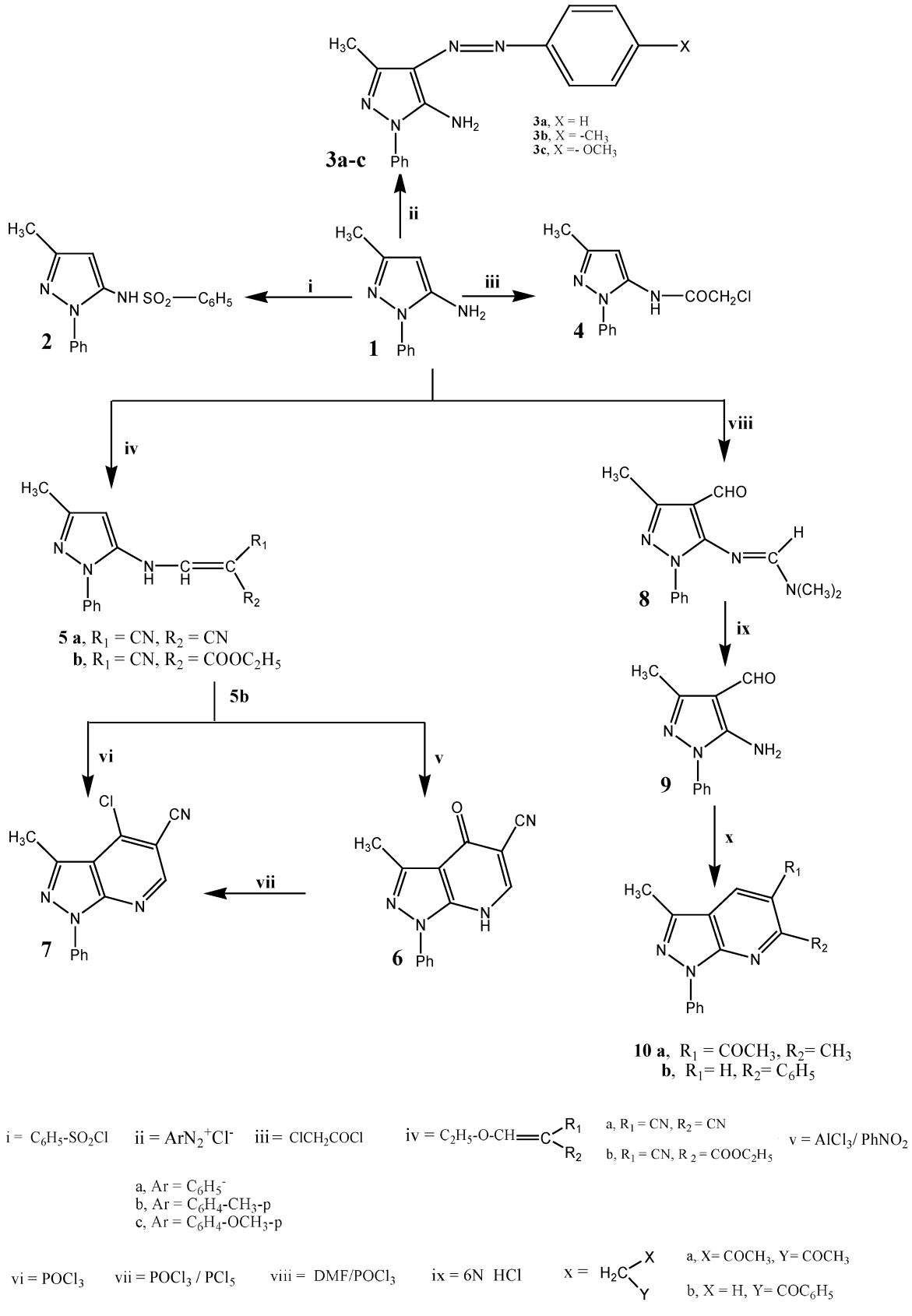
Scheme I

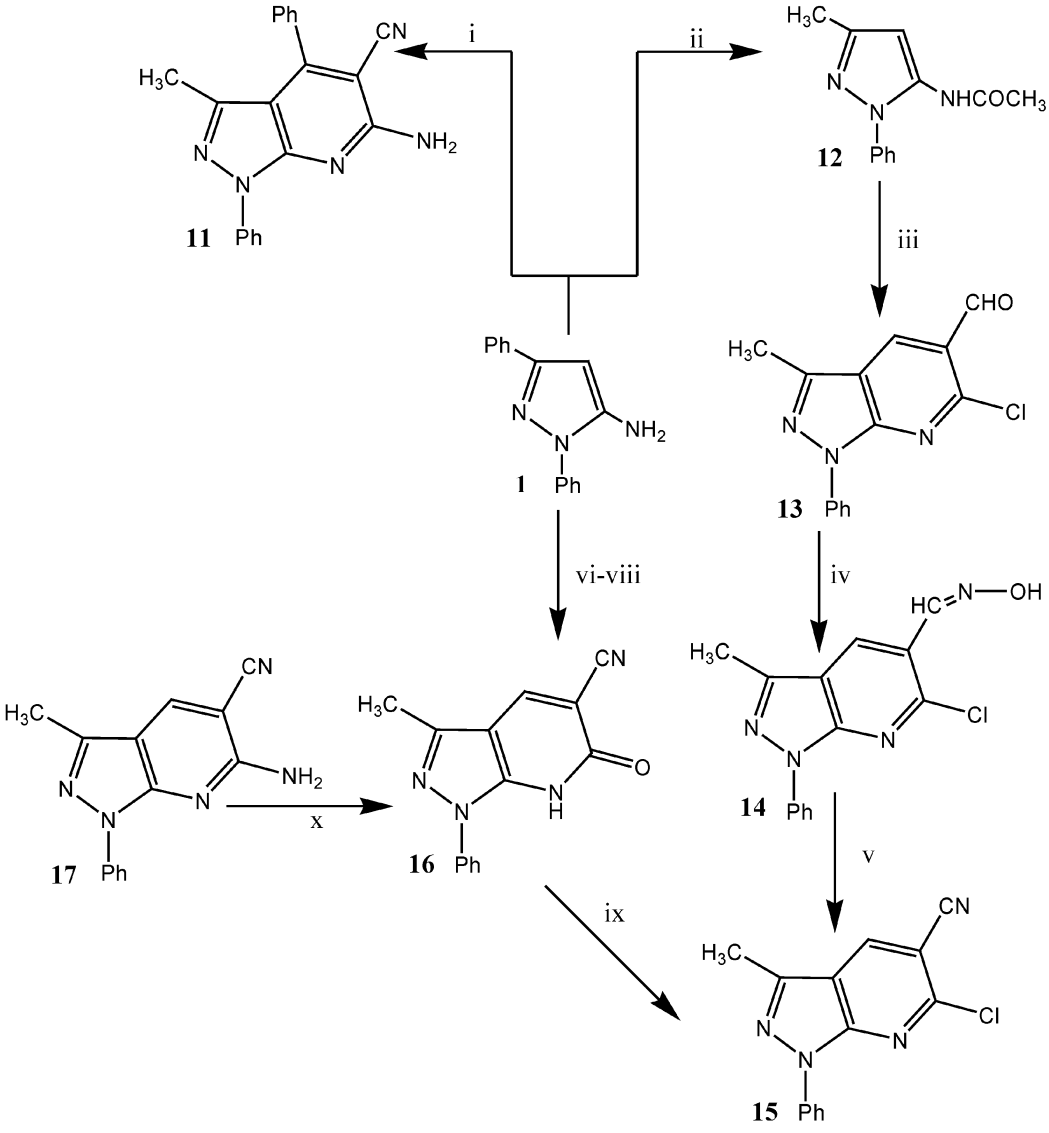

3a-c
3a, X = H
3b, X = -CH3
3c, X =- OCH3
ii
i
iii
2
1
4
iv
viii
5 a, R1 = CN, R2 = CN
b, R1 = CN, R2 = COOC2H5
8
ix
9
5b
vi
v
vii
7
6
x
10 a, R1 = COCH3, R2= CH3
b, R1= H, R2= C6H5
i = C6H5-SO2Cl
ii = ArN2+Cl-
a, Ar = C6H5-
b, Ar = C6H4-CH3-p
c, Ar = C6H4-OCH3-p
iii = ClCH2COCl
iv = C2H5-O-CH=C(R1)(R2)
a, R1 = CN, R2 = CN
b, R1 = CN, R 2 = COOC2H5
v = AlCl3/ PhNO2
vi = POCl3
vii = POCl3 / PCl5
viii = DMF/POCl3
ix = 6N HCl
x = H2C(X)(Y)
a, X= COCH3, Y= COCH3
b, X = H, Y= COC6H5

carbonitrile (**11**) (Scheme II).

A new method for preparing 6-chloro-5-cyano-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**15**)[11a] is reported herein. Thus, when 5-amino-3-methyl-1-phenyl pyrazole (**1**) was treated with an AcOH/Ac_2O mixture, it gave 5-acetylamino-3-methyl-1-phenylpyrazole (**12**). The later on treatment with Vilsmeier-Haack reagent ($POCl_3$/DMF) gave 6-chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**13**). Reacting **13** with hydroxyl amine[13a] afforded 6-chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehydeoxime (**14**). Boiling **14** in Ac_2O yielded **15** (Scheme II).

As well, a new route for preparing compound 6,7-dihydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyri-

Scheme II



dine-5-carbonitrile (**16**)[12] is reported herein. Thus, the treatment of 6-amino-5-cyano-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**17**)[3a] with nitrous acid at (0-5 °C) followed by heating the resulting mixture at 60-70 °C for 1 h resulted in the formation of **16** (Scheme II).

Compound **16** was transformed to **15**[11a] by heating it in a mixture of $POCl_3/PCl_5$ (Scheme II). Elemental and spectral data combined with mp and mp of compounds **15** and **16** prepared by this method and that reported in the literature[11a,12] are in consistent.

Newly substituted 3-methyl-1-phenyl pyrazoles carrying varieties of heteromoieties at the 4-position have been prepared using 5-[(N,N-dimethylamino)methyleneamino]-3-methyl-1-phenylpyrazole-4-carbaldehyde (**8**).[12] Thus, reacting **8** with malononitrile, thiosemicarbazide, phenyl hydrazine[13b,c] and with acetophenone[13d] yielded **18**-**21**, respectively (Scheme III).

The reaction of N,N-dimethyl-N′-(3-methyl-4-(3-oxo-3-phenylprop-1-enyl)-1-phenyl-1*H*-pyrazol-5-yl)formimidamide (**21**) with malononitrile[13e] in ethanol containing morpholine as a basic catalyst at reflux afforded 4-(2-amino-6-phenyl-4*H*-pyran-3-carbonitrile)-5-[(N,N-dimethylamino)methyleneamino)]-3-methyl-1-phenylpyrazol (**22**) (Scheme III).

Finally, the reaction of 5-acetyl-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**10a**)[12] with malononitrile,[13e] phenyl hydrazine,[13f] thiosemicarbazide,[13c] semicarbazide,[13c] and benzaldehyde[13f,g] yielded the substituted pyrazolo[3,4-*b*]pyridines **23-26**, respectively (Scheme IV).

EXPERIMENTAL SECTION

Melting points are uncorrected and determined using a Gallenkamp melting point apparatus. IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer and on GNM-LA (400 MHz) in $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts δ are expressed in ppm. Elemental analyses were carried out at the Microanalytical Center of Cairo University (Egypt) and at the Microanalytical Unit at Assiut University (Egypt). The IR and ^{1}H NMR characterization data of all newly synthesized compounds are given in Tables 1 & 2.

Compounds **1** and **12** were prepared according to the literature.[10] Compounds **8**, **9**, **10a** and an authentic sample of **16** were prepared according to the literature.[12] Compound **17** and an authentic sample of **15** were prepared according to our recorded method.[11a]

N-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzenesulfonamide (2)

A mixture of **1** (0.52 g, 3 mmol) and benzenesulfonyl chloride (0.53 g, 3 mmol) in pyridine (25 mL) was heated at 80 °C for 3 h and then allowed to cool. The reaction mixture was then poured into 50 g crushed ice acidified with concd HCl (5 mL). The solid product was filtered off, washed with water, dried and crystallized from the proper solvent to give **2** as buff coloured crystals (cf. Tables 1 and 2).

Coupling of 1 with Arenediazonium Salts: formation of 3-methy-1-phenyl-4-(arenyldiazenyl)-1*H*-pyrazol-5-amine 3a-d: General Procedure

To a stirred cold solution of **1** (0.52 g, 3 mmol) in ethanol (25 mL) containing sodium acetate (0.33 g, 4 mmol) was added a cold solution of appropriate diazonium chloride prepared by addition of sodium nitrite (0.24 g, 3.5 mmol) to appropriate aromatic amine (aniline, *p*-toluidine and or *p*-anisidine) (3 mmol) in HCl (5 mL) at 0-5 °C over a period of 30 min. The reaction mixture was left at room temperature for 1 h. The solid product was collected by filtration, washed with water, dried and crystallized from ethanol to afford **3a-c** as red crystals (cf. Tables 1 and 2).

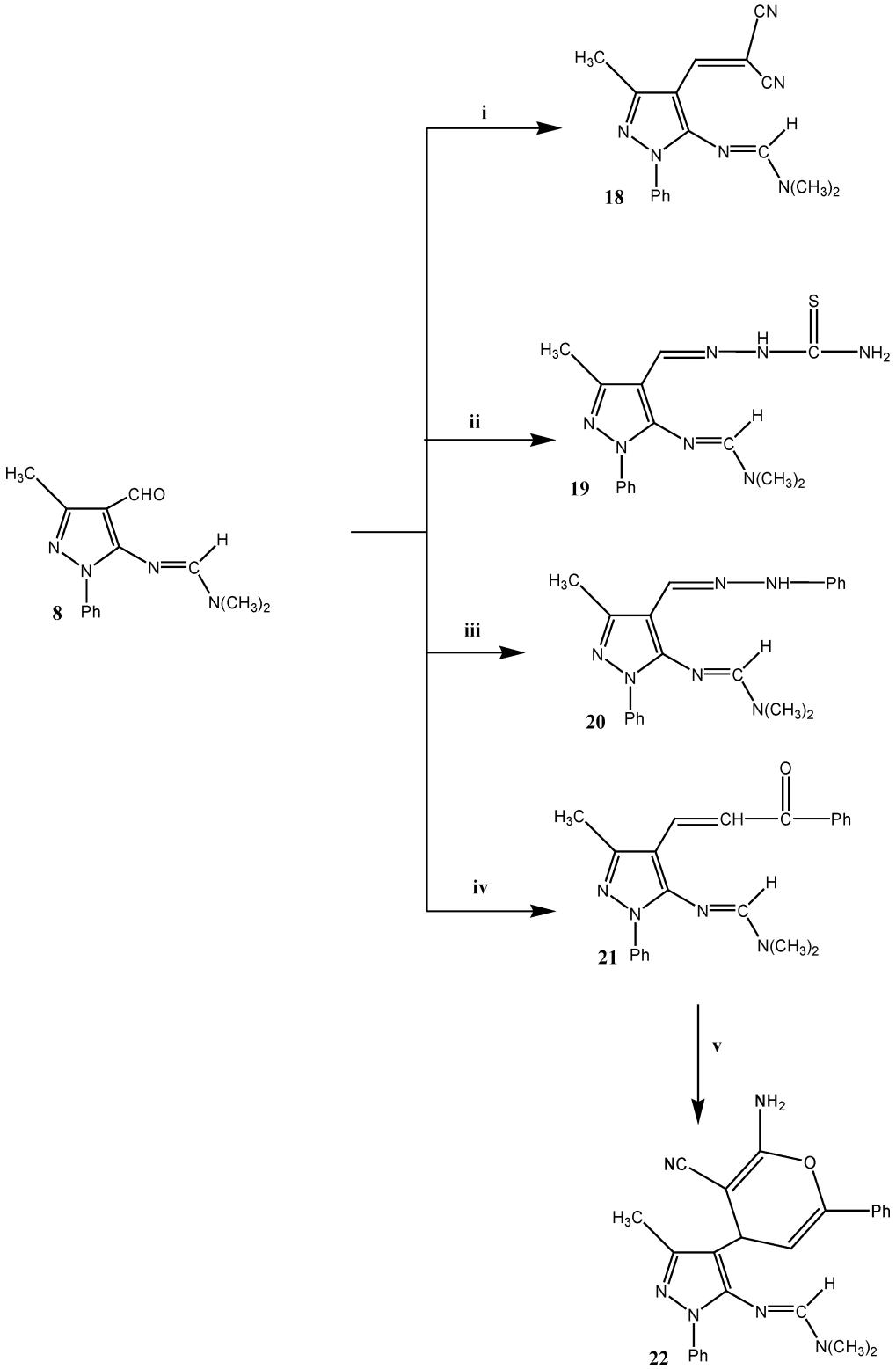
2-Chloro-N-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)acetamide (4)

To a cold solution of **1** (0.52 g, 3 mmol), anhyd. K_2CO_3 (1.24 g, 9 mmol) in dioxane (25 mL), chloroacetyl chloride (0.34 g, 3 mmol) in dioxane (10 mL) was added dropwise over a period of 1 h and then allowed to stir at room temperature for a further 8 h. The reaction mixture was then poured into crushed ice (100 g) and left overnight. The solid product was filtered off and crystallized from the proper solvent to give **4** as colourless needles (cf. Tables 1 and 2).

2-((3-Methyl-1-phenyl-1*H*-pyrazol-5-ylamino)methylene)malononitrile (5a)

A mixture of **1** (0.52 g, 3 mmol) and ethoxymethylene

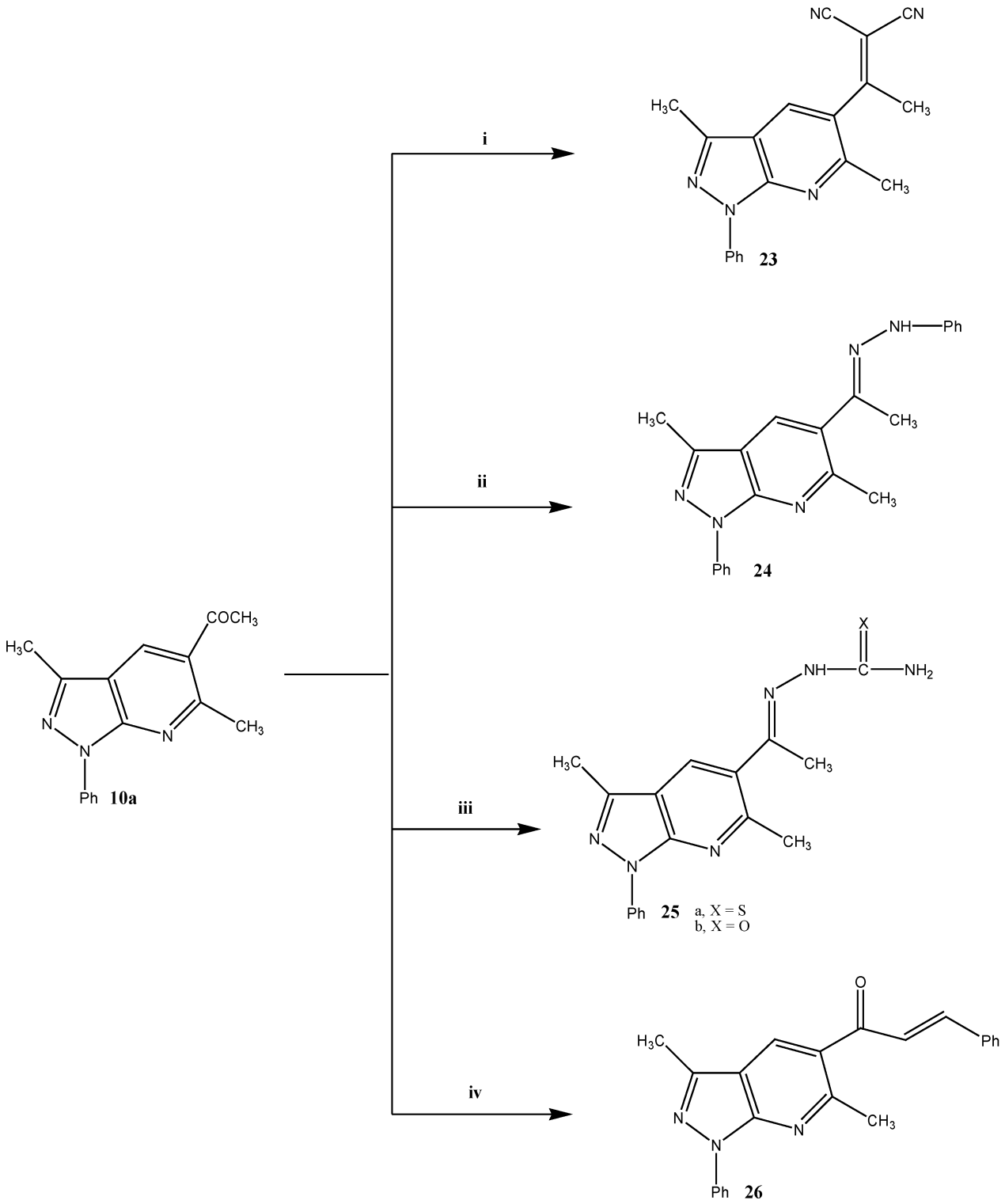
Scheme III



i = $CH_2(CN)_2$ ii = $NH_2NHCSNH_2$ iii = $PhNHNH_2$

iv = $PhCOCH_3$ / NaOH v = $CH_2(CN)_2$

Scheme IV



i = $CH_2(CN)_2$ ii = $PhNHNH_2$ iii = $NH_2NHC(X)NH_2$ iv = PhCHO / NaOH

a, X = S
b, X = O

Table 1. Spectral data of the new compounds

Compd. No	IR, ν (cm^{-1})	^{1}H NMR (δ)
2	3330 (NH), 3050 (CH arom.), 2990 (CH aliph.)	2.35 (s, 3H, CH_3), 6.55 (s, 1H, CH-pyrazole), 7.35-7.85 (m, 10H, arom), 10.5 (s, 1H, NH)
3a	3300-3180 (NH_2), 3040 (CH arom.), 2980 (CH aliph.)	2.40 (s, 3H, CH_3), 5.6 (s, 2H, NH_2), 7.03-7.55 (m, 10H, arom.)
3b	3320-3220 (NH_2), 3060 (CH arom.), 2990 (CH aliph.)	2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.50 (s, 2H, NH_2), 7.2-7.65 (m, 9H, arom.)
3c	3310-3190 (NH_2), 3050 (CH arom.), 2980 (CH aliph.)	2.40 (s, 3H, CH_3), 2.60 (s, 3H, -OCH_3), 4.90 (s, 2H, NH_2), 7.10-7.75 (m, 9H, arom.)
4	3250 (NH), 3050 (CH arom.), 2980, 2990 (CH aliph.), 1710 (CO)	2.30 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 6.5 (s, 1H, CH-pyrazole), 7.55-8.05 (m, 5H, arom.), 8.6 (1H, NH)
5a	3330 (NH), 3050 (CH arom), 2990 (CH aliph.), 2200 (CN)	2.40 (s, 3H, CH_3), 6.55 (s, 1H, CH-pyrazole), 7.35-7.60 (m, 5H, arom.), 7.75 (s, 1H, CH), 10.60 (s, H, NH)
5b	3260 (NH), 3050 (CH arom.), 2990, 2980 (CH aliph.), 2210 (CN), 1690 (CO)	1.30 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 6.75 (s, 1H, CH-pyrazole), 7.30-7.60 (m, 5H, arom.), 7.73 (s, 1H, CH-ethylenic), 10.6 (s, 1H, NH)
6	3280 (NH), 3050 (CH arom), 2995 (CH aliph.), 2210 (CN), 1700 (CO)	2.35 (s, 3H, CH_3), 7.35-7.60 (m, 5H, arom), 7.95 (s, 1H, CH-pyridine), 10.10 (s, H, NH)
7	3050 (CH arom.), 2990 (CH aliph.), 2200 (CN)	2.3 (s, 3H, CH_3), 7.55-8.25 (m, 5H, arom.), 8.10 (s, 1H, CH-pyridine)
10b	3050 (CH arom.), 2990, 2980 (CH aliph.)	2.35 (s, 3H, CH_3), 7.55-8.25 (m, 12H, 10H arom. + 2H, CH-pyridine)
11	3350-3250 (NH_2), 3050 (CH arom.), 2990 (CH aliph.), 2200 (CN)	2.40 (s, 3H, CH_3), 6.5 (s, 2H, NH_2), 7.64-8.24 (m, 10H, arom)
13	3050 (CH arom.), 2980, 2990 (CH aliph.), 1690 (CO)	2.45 (s, 3H, CH_3), 7.55-8.25 (m, 5H, arom.), 8.5 (s, 1H, CH-pyridine), 9.62 (s, 1H, CHO)
14	3400 (OH), 3050 (CH arom.), 2990, 2980 (CH aliph.)	2.35 (s, 3H, CH_3), 6.9 (s, 1H, CH, aldoxime), 7.60-8.24 (m, 5H, arom.), 8.47 (s, 1H, CH-pyridine), 11.20 (s, 1H, OH)
18	3050 (CH arom.), 2990 (CH aliph.), 2210 (CN)	2.40 (s, 3H, CH_3), 2.52 (s, 6H, $2CH_3$), 7.55-8.05 (m, 7H, (5H, arom + 2H, 2CH.))
19	3350-3150 (NH_2 + NH), 3050 (CH arom.), 2990 (CH aliph.)	2.30 (s, 3H, CH_3), 2.48 (s, 6H, $2CH_3$), 7.5 (s, 1H, CH), 7.1 (s, 1H, CH), 7.5 (s, CH), 7.55-8.05 (m , 5H, arom), 9.5 (s, 2H, NH_2), 10.9 (s, 1H, NH)
20	3300 (NH), 3040 (CH arom.), 2990, 2980 (CH aliph.)	2.36 (s, 3H, CH_3), 2.47 (s, 6H, $2CH_3$), 6.98-8.05 (m, 12H, (10H, arom + 2H, 2CH.)), 11.10 (s, 1H, NH)
21	3060 (CH arom.), 2990, 2980 (CH aliph.), 1690 (CO)	2.40 (s, 3H, CH_3), 2.45 (s, 6H, $2CH_3$), 7.53-8.05 (m, 12H, (10H, arom + 2H, 2CH.))
22	3350-3250 (NH_2), 3050 (CH arom.), 2990 (CH aliph.), 2210 (CN)	2.35 (s, 3H, CH_3), 2.49 (s, 6H, $2CH_3$), 3.79 (s, 1H, CH-pyran), 5.6 (s, 2H, NH_2), 6.53 (s, 1H, CH-pyran), 7.53-8.05 (m, 11H, (10H, arom + 1H, 1CH))
23	3060 (CH arom.), 2990, 2980 (CH aliph.), 2200 (CN)	2.2 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.57-8.25 (m, 6H, (5H, arom. + 1H, CH-pyridine))
24	3290 (NH), 3040 (CH arom.), 2990, 2980 (CH aliph.)	2.01 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.53-8.38 (m, 11H, (10H, arom. + 1H, CH-pyridine)), 11.1 (s, 1H, NH)
25a	3360-3230 (NH_2 + NH), 3050 (CH arom.), 2980 (CH aliph.)	2.2 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.53-8.38 (m, 6H (5H, arom) + 1H, CH-pyridine), 9.35 (s, 2H, NH_2), 11.12 (s, 1H, NH)
25b	3350-3220 (NH_2 + NH), 3050 (CH arom.), 2990 (CH aliph.), 1655 (CO)	2.1 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.35 (s, 2H, NH_2), 7.53-8.38 (m, 6H, (5H, arom. +1H, CH-pyridine), 10.55 (s, 1H, NH)
26	3050 (CH arom.), 2990, 2980 (CH aliph.), 1690 (CO)	2.40 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.7 (s, 1H, CH-ethylenic), 7.53-8.28 (m, 12H, (10H, arom. + 1H, CH-ethylenic + 1H, CH, pyridine))

Table 2. Physical and analytical data of the new compounds

Compd. No	Mp (°C) (Solvent)	Yield (%)	Mol. Formula (MW)	Analysis% Calcd./Found		
				C	H	N
2	180 (diluted ethanol)	79	$C_{16}H_{15}N_3O_2S$ (313.4)	61.32 61.51	4.82 4.70	13.41 13.44
3a	165 (ethanol)	86	$C_{16}H_{15}N_5$ (277.3)	69.29 69.50	5.45 5.30	25.25 25.20
3b	153 (ethanol)	78	$C_{17}H_{17}N_5$ (291.3)	70.09 70.25	5.88 5.90	24.05 24.15
3c	145 (benzene-pet.ether)	71	$C_{17}H_{17}N_5O$ (307.3)	66.44 66.70	5.58 5.40	22.79 22.90
4	112 ($CHCl_3$-pet.ether)	67	$C_{12}H_{12}ClN_3O$ (249.7)	57.72 57.47	4.84 4.87	16.83 16.66
5a	190 (ethanol)	93	$C_{14}H_{11}N_5$ (249.3)	67.46 67.41	4.45 4.35	28.10 28.23
5b	180 (ethanol)	87	$C_{16}H_{16}N_4O_2$ (296.3)	64.85 64.77	5.44 5.43	18.91 18.70
6	> 350 dioxan	38	$C_{14}H_{10}N_4O$ (250.3)	67.19 67.33	4.03 4.17	22.39 22.26
7	185 (diluted ethanol)	41	$C_{14}H_9ClN_4$ (268.7)	62.58 62.51	3.38 3.12	20.85 20.94
10b	190 (ethanol)	92	$C_{19}H_{15}N_3$ (285.3)	79.98 80.12	5.30 5.32	14.73 14.61
11	225 (ethanol)	52	$C_{20}H_{15}N_5$ (325.4)	73.82 73.85	4.65 4.61	21.53 21.64
13	170 (ethanol)	61	$C_{14}H_{10}ClN_3O$ (271.7)	61.89 61.66	3.71 3.75	15.47 15.28
14	195 (ethanol)	67	$C_{14}H_{11}ClN_4O$ (286.8)	58.65 58.78	3.87 3.86	19.54 19.67
18	155 (ethanol)	83	$C_{17}H_{16}N_6$ (304.4)	67.09 67.19	5.30 5.28	27.61 27.83
19	130 (diluted ethanol)	81	$C_{15}H_{19}N_7S$ (329.4)	54.69 54.54	5.81 5.80	29.76 29.71
20	110 (diluted ethanol)	47	$C_{20}H_{22}N_6$ (346.4)	69.34 69.39	6.40 6.59	24.26 24.58
21	118 (diluted ethanol)	78	$C_{22}H_{22}N_4O$ (358.4)	73.72 73.78	6.19 6.31	15.63 15.56
22	145 ($CHCl_3$-pet.ether)	46	$C_{25}H_{24}N_6O$ (424.5)	70.73 70.89	5.70 5.70	19.80 20.08
23	110 (diluted ethanol)	73	$C_{19}H_{15}N_5$ (313.4)	72.83 72.79	4.82 4.88	22.35 22.51
24	122 (diluted ethanol)	52	$C_{22}H_{21}N_5$ (355.4)	74.34 74.09	5.96 5.83	19.70 19.66
25a	157 (diluted ethanol)	71	$C_{17}H_{18}N_6S$ (338.4)	60.33 60.18	5.36 5.21	24.84 25.11
25b	140 (diluted ethanol)	53	$C_{17}H_{18}N_6O$ (322.4)	63.34 63.68	5.63 5.69	26.07 26.16
26	138 (ethanol)	74	$C_{23}H_{19}N_3O$ (353.4)	78.16 78.28	5.42 5.57	11.89 11.93

malononitrile (0.34 g, 3 mmol) in ethanol (25 mL) was heated at reflux for 2 h and then allowed to cool at room temperature. The solid product was filtered off and crystallized from the proper solvent to give **5a** as pale yellow needles (cf. Tables 1 and 2).

Ethyl-2-cyano-3-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl-amino)methylene)acrylate (5b)

A mixture of **1** (0.52 g, 3 mmol) and ethyl 2-cyano-3-ethoxyacrylate (0.51 g, 3 mmol) in ethanol (20 mL) was heated at reflux for 2 h and then allowed to cool at room temperature. The solid product was filtered off and crystallized from the proper solvent to give **5b** as pale yellow needles (cf. Tables 1 and 2).

3-Methyl-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboitrile (6)

A mixture of **5b** (0.0025 mol), and anhydrous $AlCl_3$ (0.6 g, 5 mmol) in nitrobenzene (25 mL) was heated at reflux for 10 h and then the solvent was removed under reduced pressure. The solid residue was triturated with conc. HCl (20 mL) and poured into crushed ice with stirring for some time. The product was filtered off and crystallized from the proper solvent to give **6** as pale yellow needles (cf. Tables 1 and 2).

4-Chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7)

Method A

A mixture of **5b** (0.6 g, 2 mmol) and $POCl_3$ (15 mL) was heated under reflux for 10 h. The reaction mixture was then poured into crushed ice. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **7** as pale yellow needles (cf. Tables 1 and 2).

Method B

A mixture of **6** (0.62 g, 2 mmol), $POCl_3$ (15 mL) and PCl_5 (1.25 g, 7.5 mmol) was heated under reflux for 8 h. The reaction mixture was then poured into crushed ice. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **7** as pale yellow needles (cf. Tables 1 and 2).

3-Methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (10b)

A mixture of **9** (0.5 g, 2.5 mmol) and acetophenone (0.3 g, 2.5 mmol) in ethanol (25 mL) was heated under reflux for 2 h. The reaction mixture was left to cool. The product was filtered off and crystallized from the proper solvent to give **10b** as pale yellow needles (cf. Tables 1 and 2).

6-Amino-3-methyl-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (11)

A mixture of **1** (0.7 g, 4 mmol) and benzylidine-malononitrile (0.62 g, 4 mmol) in pyridine (30 mL) containing piperidine (2 mL) was heated under reflux for 8 h. The solvent was removed under reduced pressure. The residue was extracted in portions with diluted ethanol to give **11** as buff coloured crystals (cf. Tables 1 and 2).

6-Chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (13)

A solution of compound **12** (1.1 g, 5 mmol) in DMF (20 mL) was added portionwise to a cold Vilsmeier-Haack mixture prepared by adding $POCl_3$ (4.6 g, 30 mmol) to DMF (15 mL) dropwise at 0-5 °C over a period of 1 h. After a completion of the addition, the mixture was heated at 80 °C for 2 h. After cooling, the reaction mixture was poured into crushed ice (100 g). The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **13** as buff coloured crystals (cf. Tables 1 and 2).

6-Chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehydeoxime (14)

A mixture of **13** (0.68 g, 2.5 mmol) hydroxyl amine hydrochloride (0.17 g, 2.5 mmol) and sodium acetate (0.33 g, 4 mmol) in ethanol (30 mL) was heated under reflux for 6 h. After cooling, the reaction mixture was poured into crushed ice (100 g). The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **14** as buff coloured crystals (cf. Tables 1 and 2).

6-Chloro-5-cyano-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine (15)

A mixture of **14** (0.72 g, 2.5 mmol) and acetic anhydride (25 mL) was heated under reflux for 6 h. After cooling, the reaction mixture was poured into crushed ice (100 g). The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **15** as pale

yellow crystals. Both mp and mixed mp were identical with the authentic sample of compound **15** prepared by our method.[11]

6,7-Dihydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (16)

To a stirred solution of **17** (0.62 g, 2.5 mmol) in conc. HCl (10 mL) and water (10 mL) was added a cold solution of sodium nitrite (0.21 g, 3 mmol in 5 mL water) at 0-5 °C over a period of 30 min. After the completion of the addition, the reaction mixture was heated at 60-70 °C for 1 h. and then poured onto water. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **16** as buff coloured crystals. Both mp and mixed mp were identical with the authentic sample of compound **16** prepared according to the literature.[12]

5-[(N,N-Dimethylamino)methyleneamino]-3-methyl-4-(2-methylenemalononitrile)-1-phenylpyrazole (18)

A mixture of **8** (0.64 g, 2.5 mmol) and malononitrile (0.17 g, 2.5 mmol) in ethanol (30 mL) was heated under reflux for 6 h. After cooling, the reaction mixture was poured onto water acidified with acetic acid. The precipitate was filtered off, washed with water, dried and crystallized from the proper solvent to give **18** as yellow needles (cf. Tables 1 and 2).

5-[(N,N-Dimethylamino)methyleneamino]-3-methyl-4-(2-methylenehydrazinecarbothioamide)-1-phenylpyrazole (19)

A mixture of **8** (0.5 g, 2 mmol) and thiosemicarbazide (0.15 g, 2 mmol) in ethanol (25 mL) was heated under reflux for 6 h. After cooling, water was added to the reaction mixture. The precipitate was filtered off, dried and crystallized from the proper solvent to give **19** as white needles (cf. Tables 1 and 2).

5-[(N,N-Dimethylamino)methyleneamino]-3-methyl-4-(1-methylene-2-phenylhydrazine)-1-phenylpyrazole (20)

A mixture of **8** (0.5 g, 2 mmol) and phenyl hydrazine (0.2 g, 2 mmol) in ethanol (25 mL) was heated under reflux for 8 h. After cooling, the reaction mixture was poured onto ice water acidified with acetic acid (5 mL). The precipitate formed after some time was filtered off, dried and crystallized from the proper solvent to give **20** as pale yellow crystals (cf. Tables 1 and 2).

5-[(N,N-Dimethylamino)methyleneamino]-3-methyl-4-(1-phenylprop-2-en-1-one)-1-phenylpyrazole (21)

A mixture of **8** (0.5 g, 2 mmol) and acetophenone (0.24 g, 2 mmol) and sodium hydroxide solution (10 mL, 20%) in ethanol (25 mL) was stirred at room temperature overnight. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **21** as yellow crystals (cf. Tables 1 and 2).

4-(2-Amino-6-phenyl-4*H*-pyran-3-carbonitrile)-5-[(N,N-dimethylamino)methyleneamino]-3-methyl-1-phenylpyrazole (22)

A mixture of **21** (0.45 g, 1.25 mmol) and malononitrile (0.08 g, 1.25 mmol) and few drops of morpholine in ethanol (25 mL) was heated under reflux for 8 h. After cooling, the reaction mixture was poured onto ice water acidified with acetic acid (5 mL) and stirred for several hours. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **22** as yellow crystals (cf. Tables 1 and 2).

2-(1-(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethylidene)malononitrile (23)

A mixture of **10a** (0.53 g, 2 mmol) and malononitrile (0.13 g, 2 mmol) in ethanol (25 mL) was heated under reflux for 8 h. The product was filtered off and crystallized from the proper solvent to give **23** as buff coloured needles (cf. Tables 1 and 2).

3,6-Dimethyl-1-phenyl-5-(1-(2-phenylhydrazono)ethyl-1*H*-pyrazolo[3,4-*b*]pyridine (24)

A mixture of **10a** (0.53 g, 2 mmol), and phenyl hydrazine (0.2 g, mmol) in ethanol (25 mL) containing acetic acid (1 mL) was heated under reflux for 4 h. The reaction mixture was poured onto water and stirred for some time. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **24** as harvested crystals (cf. Tables 1 and 2).

2-(1-(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethylidene)hydrazinecarbothioamide (25a)

A mixture of **10a** (0.53 g, 2 mmol) and thiosemi-

carbazide (0.15 g, 2 mmol) in ethanol (25 mL) was heated under reflux for 8 h. The reaction mixture was concentrated to one-half volume and left to cool. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **25a** as buff coloured needles (cf. Tables 1 and 2).

2-(1-(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethylidene)hydrazinecarboxamide (25b)

A mixture of **10a** (0.53 g, 2 mmol), semicarbazide hydrochloride (0.22 g, 2 mmol) and sodium acetate (0.41 g, 5 mmol) in ethanol (25 mL) was heated under reflux for 8 h. Water (10 mL) was added to the reaction mixture. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **25b** as yellowish-orange crystals (cf. Tables 1 and 2).

1-(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-phenylpro-2-en-1-one (26)

A mixture of **10a** (0.53 g, 2 mmol), benzaldehyde (0.2 g, 2 mmol) and sodium hydroxide solution (5 mL, 25%) in ethanol (25 mL) was stirred overnight. The product was filtered off, washed with water, dried and crystallized from the proper solvent to give **26** as yellow needles (cf. Tables 1 and 2).

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