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

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Abstract: Pyrazolo[3,4-b]pyridines (4) and (5) have been obtained by the condensation of 3-(alkyl/aryl)-5-amino-1-phenyl-1H-pyrazole-4-carboxaldehydes (3) with active methylene compounds viz: diethyl malonate and malononitrile.

The discovery that pyrazolo[3,4-b]pyridines are involved in various pharmacological applications[1,2,3] as good vasodialators, hypotensive, hypoglycemic, antiinflammatory, analgesic and antipyretic agents have promoted a great current interest in facile and general routes to these molecules in synthetically useful yields. The earlier method of synthesis of such systems involve the cyclisation[4,5] of 4-substituted pyrazolinones with NH_4OAc and PPA.

We now report a novel synthetic route to the synthesis of pyrazolo[3,4-b]pyridines which involve annulation of a pyridine ring onto the preformed pyrazole ring. The reaction involves the condensation of 3-(alkyl/aryl)-5-amino-1-phenyl-1H-pyrazole-4-carboxaldehydes (3) with active methylene compounds viz: diethyl malonate and malononitrile (Scheme-1).

o-Aminoaldehyde derivatives are the key intermediates for the synthesis of various biologically active heterocycles.[6-9] The essential intermediate 3-(alkyl/aryl)-5-amino-1-phenyl-1H-pyrazole-4-carboxaldehydes (3) has been prepared as follows:

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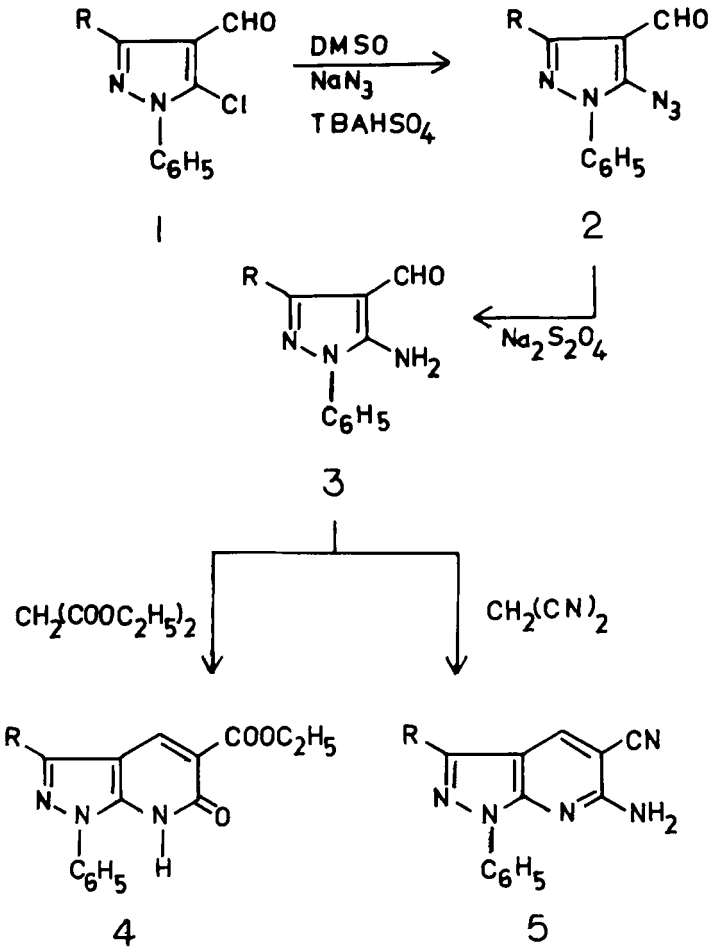

1 2 3 4 5

SCHEME :- 1

1 – 5	R
a	$-CH_3$
b	$-C_6H_5$
c	$n\text{-}C_3H_7$

Table : 1

Physical, IR, ^1H NMR and Mass Spectral data of compounds (2)

2	R	Yield [%]	m.p. [°C]	Molecular Formulae[(a)] [Mol. Wt.]	IR (Nujol) [cm^{-1}]	^1H NMR ($CDCl_3$ / TMS) [δ / ppm]
a*	$-CH_3$	75	42-43 Lit[11] 42	$C_{11}H_9N_5O_1$ (227)	2140 [Azide] 1690 [-C=O] 2750 [-CH=O]	2.4(s, 3H, CH_3), 7.1-7.7(m, 5H, C_6H_5), 9.8(s, 1H, CHO)
b	$-C_6H_5$	80	54-55	$C_{16}H_{11}N_5O_1$ (289)	2160 [Azide] 1710 [-C=O] 2780 [-CH=O]	7.0-7.9(m, 10H, 2xC_6H_5), 9.9(s, 1H, CHO)
c	n-C_3H_7	70	37	$C_{13}H_{13}N_5O_1$ (255)	2140 [Azide] 1700 [-C=O] 2770 [-CH=O]	1.0(t, 3H, CH_3), 1.7(m, 2H, CH_2), 2.8(t, 2H, CH_2), 7.5(m, 5H, C_6H_5), 9.9(s, 1H, CHO)

(a) : Microanalysis was found to be in agreement with the expected values

• : MS (m/z) : 227 (M^+)

The reaction of 3-(alkyl/aryl)-5-chloro-1-phenyl-1H-pyrazole-4-carboxaldehydes[10] (1) with sodium azide and DMSO in presence of phase transfer catalyst viz: tetrabutylammonium hydrogen sulfate gave the corresponding 3-(alkyl/aryl)-5-azido-1-phenyl-1H-pyrazole-4-carboxyldehyde (2) derivatives in good yields (70-80 %). One of the azido compound 2a, was obtained earlier[11] in 67 % yields without the use of phase tranafer catalyst. The 3-(alkyl/aryl)-5-azido-1-phenyl-1H-pyrazole-4-carboxaldehydes (2) on reduction with sodium dithionite in alcoholic medium gave the required intermediate (3) in 70-75 % yields. This reduction was earlier carried out by hydrogen sulfide in alcoholic medium[12] in comparatively low yields (60 %).

Compounds (3) on reaction with diethyl malonate gave the corresponding 3-(alkyl/aryl)-5-carbethoxy-6,7-dihydro-6-oxo-1-phenyl-1H-pyrazolo[3,4-b]pyridine derivatives (4) in (80-85 %) yields. However, the

Table : 2

Physical, IR, ^{1}H NMR and Mass Spectral data of compounds (3)

3	R	Yield [%]	m.p. [°C]	Molecular Formulae[(a)] [Mol. Wt.]	I R (Nujol) [cm^{-1}]	^{1}H NMR ($CDCl_3$ / TMS) [δ / ppm]
a*	$-CH_3$	70	66-67	$C_{11}H_{11}N_3O_1$ (201)	3350 [NH_2] 1660 [-C=O] 2770 [-CH=O]	2.4(s, 3H, CH_3), 6.1(s, 2H, NH_2), 7.3-7.8(m, 5H, C_6H_5), 9.8(s, 1H, CHO)
b	$-C_6H_5$	75	50-52	$C_{16}H_{13}N_3O_1$ (278)	3350 [NH_2] 1660 [-C=O] 2790 [-CH=O]	6.0(s, 2H, NH_2), 7.3-7.8(m,10H, 2xC_6H_5), 9.8(s, 1H, CHO)
c	n-C_3H_7	70	41-42	$C_{13}H_{15}N_3O_1$ (229)	3350 [NH_2] 1660 [-C=O] 2780 [-CH=O]	1.1(t, 3H, CH_3), 1.8(m, 2H, CH_2), 2.8(t, 2H, CH_2), 6.1(s, 2H, NH_2), 7.6(m, 5H, C_6H_5), 9.8(s, 1H, CHO)

(a) : Microanalysis was found to be in agreement with the expected values

* : MS (m/z): 201 (M^+)

reaction of (3) with malononitrile in presence of triethylamine gave the corresponding 3-(alkyl/aryl)-6-amino-5-cyano-1-phenyl-1H-pyrazolo[3,4-b] pyridines (5) in good yields (70-80 %).

The structures of compounds 2,3,4 and 5 were assigned on the basis of their microanalysis, ^{1}H NMR, IR and Mass spectral data.

Experimental

Melting points were uncorrected. IR spectra were recorded on a Shimadzu infrared spectrophotometer IR-435 ($\nu_{max.}$ in cm^{-1}). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Perkin-Elmer R-32 (90 MHz) spectrometer, using TMS as an internal standard (chemical shifts in δ, ppm).

Table : 3

Physical, IR, ^1H NMR and Mass Spectral data of compounds (4)

4	R	Yield [%]	m.p. [°C]	Molecular Formulae[(a)] [Mol. Wt.]	I R (Nujol) [cm^{-1}]	^1H NMR ($CDCl_3$ / TMS) [δ / ppm]
a*	$-CH_3$	85	285	$C_{16}H_{15}N_3O_3$ (297)	3320 [-NH] 1670 [-COOEt]	1.4(t,3H,CH_3), 2.6(s, 3H,CH_3), 4.4(q, 2H, CH_2), 7.4(m, 3H, C_6H_5), 8.2(d, 2H, C_6H_5), 8.6(s, 1H, CH = C), 12.2(br., 1H, NH, D_2O exch.)
b	$-C_6H_5$	75	270	$C_{21}H_{17}N_3O_3$ (369)	3330 [-NH] 1660 [-COOEt]	1.4(t,3H,CH_3), 4.4(q, 2H, CH_2), 7.4(m, 6H, 2xC_6H_5), 8.0(d, 4H, 2xC_6H_5), 8.8(s, 1H, CH = C), 12.1(br., 1H, NH, D_2O exch.)
c	$n\text{-}C_3H_7$	75	185-186	$C_{18}H_{19}N_3O_3$ (325)	3320 [-NH] 1670 [-COOEt]	1.0(t,3H,CH_3), 1.4(t, 3H,CH_3), 1.8(m, 2H, CH_2),2.8(t,2H,CH_2), 4.6(q,2H,OCH_2), 7.4(m, 3H, C_6H_5), 8.3(d, 2H, C_6H_5), 8.6(s, 1H, CH = C), 12.2(br., 1H, NH, D_2O exch.)

(a) : Microanalysis was found to be in agreement with the expected values

* : MS (m/z) : 297 (M^+)

3-(Alkyl/aryl)-5-azido-1-phenyl-1H-pyrazole-4-carboxaldehydes (2) from 3-(alkyl/aryl)-5-chloro-1-phenyl-1H-pyrazole-4-carboxaldehydes (1) : General Procedure:

A mixture of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde[10] (**1a**; 1.0 g; 5 mmol), sodium azide (0.4 g; 6 mmol), tetrabutylam-

Table : 4

Physical, IR, ^1H NMR and Mass Spectral data of compounds (5)

5	R	Yield [%]	m.p. [°C]	Molecular Formulae[(a)] [Mol. Wt.]	I R (Nujol) [cm^{-1}]	^1H NMR (Py-d_5 / TMS) [δ / ppm]
a*	$-CH_3$	70	225-26	$C_{14}H_{11}N_5$ (249)	3350 [$-NH_2$] 2200 [$-C\equiv N$]	2.5(s, 3H, CH_3), 4.7(s, 2H, NH_2), 7.3(m, 3H, C_6H_5), 8.4(d, 2H, C_6H_5), 8.6(s, 1H, CH=C)
b	$-C_6H_5$	70	305	$C_{19}H_{13}N_5$ (311)	3360 [$-NH_2$] 2200 [$-C\equiv N$]	4.4(s, 2H, NH_2), 7.5(m, 6H, $2xC_6H_5$), 8.6(d, 4H, $2xC_6H_5$), 8.8(s, 1H, CH=C)
c	$n\text{-}C_3H_7$	65	130-132	$C_{16}H_{15}N_5$ (277)	3340 [$-NH_2$] 2200 [$-C\equiv N$]	1.0(t, 3H, CH_3), 1.8(m, 2H, CH_2), 4.7(s, 2H, NH_2), 7.3(m, 3H, C_6H_5), 8.5(d, 2H, C_6H_5), 8.7(s, 1H, CH=C)

(a) : Microanalysis was found to be in agreement with the expected values

* : MS (m/z) : 249 (M^+)

monium hydrogen sulfate (0.2 g; 0.6 mmol) and DMSO (4 ml) was stirred at 45-50 °C for 1.5 h and then poured over the crushed ice. The resultant solid product was filtered, washed with water, dried and recrystallised from benzene-petroleum ether. The characterisation data of compounds prepared are given in Table-1.

3-(Alkyl/aryl)-5-amino-1-phenyl-1H-pyrazole-4-carboxaldehydes (3) :
General Procedure:

A mixture of (**2a**; 0.6 g; 2.6 mmol), sodium dithionite (0.35 g; 2.7 mmol) and methanol (6 ml) was refluxed for 3.5 h. The reaction mixture was filtered, inorganic residue washed with methanol (5 ml) and the combined

methanolic solution was distilled and poured over crushed ice. The resultant solid product was filtered, washed with water, dried and recrystallised from benzene-petroleum ether. The characterisation data of compounds prepared are given in Table-2.

3-(Alkyl/aryl)-5-carbethoxy- 6,7-dihydro-6-oxo-1-phenyl-1H-pyrazolo[3,4-b] pyridines (4) : General Procedure:

A mixture of 5-amino-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde (**3a**; 0.5 g; 2.5 mmol) and diethyl malonate (2.5 g; 2.4 ml; 15 mmol), was heated for 6 h at 150-60 ^{o}C. The reaction mixture was macerated with petroleum ether and seperated yellow solid product was filtered, dried and recrystallised from methanol. The characterisation data of compounds prepared are given in Table-3.

3-(Alkyl/aryl)-6-amino-5-cyano-1-phenyl-1H-pyrazolo[3,4-b]pyridines (5): General Procedure:

A mixture of **3a** (0.5 g; 2.5 mmol), malononitrile (0.17 ml; 2.6 mmol), triethylamine (6 drops) and methanol (15 ml) was refluxed on steam bath for 2 h. The white coloured product obtained on cooling was filtered and recrystallised from methanol. The characterisation data of compounds prepared are given in Table 4.

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