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Facile and Simple Syntheses of Heterocyclic Compounds Based on Pyridine and Pyrazolopyridine Derivatives

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Abstract: In one pot synthesis, cyanopyridone **4** was achieved upon refluxing of p-methoxybenz- aldhyde, 2-butanon, ethyl cyanoacetate and ammonium acetate in ethanol. The chloro- derivative **5** was obtained, **5** under went neocleophilic substitution reaction with morpholine, and piprazine to give **6, 7** respectively. Cyclocondensation reactions of **9** with active methylene compounds afforded 1,5,8a,9-tetraaza-fluorene derivatives (**10a,b,11,12**). Compound **13** obtained upon heating of compound **9** with benzoin in presence of phosphorous oxychloride. Synthesis of **14** was also achieved. Diazotization of **9** and its reactions with cyano compounds, α-haloketones and benzensulphonylacetophenone gave compounds **16,17,18a,b and 19**,respectively. When diazonium salt **15** reacted with phenacyl bromide in pyridine gave the corresponding indene derivative **21.**

Key words: cyanopyridone, active methylene, neocleophilic substitution, phenacyl bromide

Introduction

Pyrazole derivatives have attracted particular interests during the last twenty-five years due to use of such ring system as the core structure in many drug substances, covering wide range of pharmacological applications.[1-7]

Pyrazolopyridines (**PZP's**) in general represent a chemically unique class of non-sedative anoxiolytic agents. Tracazolate (**ICI136, 753**) is member of pyrazolopyridine series that has shown anxiolytic properties in animal models.

Pyrazolopyridines cause enhancement of both 3H-flunitrazepam **(3H-FLU)** and 3H-GABA to their binding sites in brain. [8]

In addition, combinatorial parallel synthesis has become firmly established within the pharmaceutical industry as a mean of rapidly producing large members of compounds for biological assays in a time and resource- effective manner. [9, 10]

In continuation of our previous work, [11-17] and the reported biological activities of pyridine and pyrazolopyridines, we were interested in synthesis of new derivatives build on pyridine moiety.

Experimental

The purity of the synthesized compounds was evidenced by TLC and their elemental analyses were generally found to be within ± 0.04% of the theoretical values.

IR spectra (KBr, νcm $^{-1}$) were recorded on Perkin Elmer 580 spectrophotometer.

^{1}H-NMR and ^{13}C NMR were carried on JNM, FT-NMR-EX270, run ^{1}H-NMR 270 MHz, in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ. ppm. Mass spectra were recorded on Varian Mat 112 spectrometer.

Synthesis of 3-cyano-4-(4-methoxyphenyl)-5,6-dimethyl-2(1*H*)-pyridone (4).

A mixture of ethyl cyanoacetate (1.7 g, 15mmol), 2-butanone (1.08g, 15mmol), 4-methoxybenzaldehyde (2.04 g, 15mmol) and ammonium acetate (6.93 g, 9 mmol) in (40 ml) absolute ethanol was heated under reflux for 10 hs, where a crystalline yellow solid formed. The formed precipitate cooled, collected by filtration, washed with cold Benzene, dried and crystallized from ethanol to give yellow crystals of **4.**

(60% yield), m.p= 290 -293 ^{o}C.
IR (ν/cm^{-1}): 2215 (CN).
^{1}H-NMR (DMSO-d_6): δ/ppm= 2.07(s,3H, CH_3), 2.25 (s,3H,CH_3), 3.85 (s,3H,OCH_3), 4.06 (s, 1H, NH, exchangeable with D_2O), 7.07(d, 2H, *j* = 8.2Hz, Ar-H), 7.35 (d,2H, *j*=8.2Hz, Ar-H).
M.S (E.I) m/z% =245(M^{+}, 56%), 91 (100).
Anal. calcd. for $C_{15}H_{14}N_2O_2$ (245.28): C, 70.85; H, 5.55; N, 11.02, found%: C, 70.93; H, 5.62; N, 10.94.

Synthesis of 2-chloro-3-cyano-4-(4-methoxyphenyl)-5,6-dimethylpyridine (5):
A solution of compound **4** (1.27g, 5 mmol) in phosphorous oxychloride (10ml) was refluxed for 4 hs., on a water bath. Then after cooling it was poured gradually onto crushed ice with vigorous stirring to obtain a yellow solid product. It was filtered off, washed with water, dried and finally crystallized from petroleum ether 60-80 to give pale yellow crystals of **5.**
(95% yield), m.p.= 115-116 ^{0}C.
IR (ν/cm^{-1}): 2215 (CN).
^{1}H-NMR (DMSO-d_6): δ/ppm = 2.02(s,3H,CH_3), 2.15 (s,3H,CH_3), 3.92 (s,3H,OCH_3), 7.07(d, 2H, *j* = 8.2Hz,Ar-H),7.35 (d,2H, *j*=8.2Hz Ar-H).
M.S (E.I) m/z % =272(M^{+}, 65%), 91(100).
Anal. calcd. for $C_{15}H_{13}Cl\ N_2O$ (272.73): C, 66.05; H, 4.80; Cl; 13.00; N, 10.27; found %: C; 66.12; H, 5.02, Cl, 12.85; N, 10.02.

Synthesis of 3-cyano-5,6-dimethyl-4-(4-methoxyphenyl)-2-substituted-pyridine:
General procedure:
An equimolecular amounts of **5** and morpholine or piprazine in absolute ethanol (30ml) in presence of pipridine (1ml) as catalyst was refluxed for 15hs. The reaction mixture was poured onto cold water (250ml), filtered off, washed with petroleum ether 60-80 and finally crystallized from the appropriate solvent.

4-(4-methoxyphenyl)-5,6-dimethyl-2-morpholinopyridine-3-carbonitrile (6):
Crystallized from cyclohexane to give colorless needle crystals. (80% yield), m.p. = 141- 3^{0}C.
IR (ν/cm^{-1}): 2211 (CN).
^{1}H-NMR (DMSO-d_6): δ/ppm= 2.07(s,3H,CH_3), 2.16 (s,3H,CH_3), 2.75, 3.35(2m, 8H, morph- en ring), 3.85 (s,3H,OCH_3), 7.07(d, 2H, *j* = 8.26Hz,Ar-H),7.35 (d,2H, *j*=8.26Hz Ar-H).
M.S (E.I) m/z% = 323(M^{+}, 65%), 322 (M^{-1}, 100).
Anal. calcd for $C_{19}H_{21}N_3O_2$ (323.16): C, 70.57; H, 6.55; N, 12.99; found %: C; 71.07; H, 6.82; N, 13.41.

4-(4-methoxyphenyl)-5,6-dimethyl-2-piprazinyl-pyridine-3-carbonitrile (7) :
Crystallized from ethanol to give colorless needle crystals. (92% yield), m.p. = 243-246 ^{0}C.
IR (ν/cm^{-1}): 3211 (NH of piprazine), 2211 (CN).
^{1}H-NMR (DMSO-d_6): δ/ppm= 2.07(s,3H,CH_3), 2.5 (s,3H,CH_3), 2.67, 3.18 (m, 8H, piprazine ring), 3.85 (s,3H,OCH_3), 4.06 (s, 1H, NH, exchangeable with D_2O), 7.07(d, 2H, *j* = 8.22Hz, Ar-H),7.35 (d,2H, *j*=8.22Hz Ar-H).
M.S (E.I) m/z% = 322(M^{+}, 11%), 320 (M^{-2},100).
Anal. calcd for $C_{19}H_{22}N_4O$ (322.41): C, 70.78; H, 6.88; N, 17.38; found %: C, 70.92; H, 6.75; N, 17.61.

Synthesis of 3-amino-4-(4-methoxyphenyl)-5,6-dimethyl-*1H*-pyrazolo[3,4-*b*]- pyridine (9):
To a solution of compound **5** (5.45 g, 20 mmol) in absolute ethanol (20 ml), hydrazine hydrate (0.8g, 85%) was added. The reaction mixture was heated under refluxing temperature for 12 hs. The reaction mixture cooled and poured onto crushed ice with stirring. A yellow precipitate separated, filtered off and washed with water, dried and crystallized from ethanol /DMF mixture(1:1) to give yellow crystals of **9** (75% yield), m.p. = 332-334 ^{0}C.
^{1}H-NMR (DMSO-d_6): δ/ppm= 2.07(s,3H,CH_3), 2.59 (s,3H,CH_3), 3.85 (s,3H,OCH_3), 4.06 (s, 2H, NH_2 exchangeable with D_2O),7.07(d, 2H, *j* = 8.2Hz,Ar-H),7.35 (d,2H, *j*=8.2Hz Ar-H), 11.85(bs,1H,NH exchangeable with D_2O, pyrazole).
^{13} C-NMR (DMSO-d_6): δ/ppm = 14.6, 24.3 (2CH_3), 55.8 (OCH_3), 119.5-129.3, 146.9, 162.7 (6C-phenyl ring),142.2 (C_3, pyrazole ring), 150.0, 157.0, 158.0,134.6,125.8 (5C , pyridine ring).
MS (EI): m/z (%): = 268 (M^{+}, 100).
Anal. calcd for $C_{15}H_{16}N_4O$ (268.13): C, 67.15; H, 6.01; N, 20.88; found %: C, 67.21; H, 5.87; N, 20.80.

Synthesis of 2,3, 8-trimethyl-4-(4-methoxyphenyl)-1,5,8a,9-tetraaza-fluorene derivatives (10a,b) :
General procedure:
An equimolecular amounts of **9** with acetyl acetone or ethyl acetoacetate, respectively in glacial acetic acid. (15ml) was heated under reflux for 10 hs. The excess solvent evaporated under vacuum, the resulted solid filtered off, washed with petroleum ether 40-60 and crystallized from appropriate solvent to give **10a-b.**
10a: Crystallized from cyclohexane to give orange crystals, (62% yield), m.p. 197-201 ^{0}C.
^{1}H-NMR($CDCl_3$): δ/ppm = 2.23(s, 3H, CH_3), 2.45(s, 3H, CH_3), 2.70(s, 3H, CH_3), 2.88(s, 3H, CH_3), 3.90 (s, 3H,-OCH_3), 6.80(s, 1H, CH of pyrimidine ring), 7.05(d, 2H, d, 2H, *j* = 8.2Hz,Ar-H), 7.30 (d, 2H, d, 2H, *j* = 8.2Hz,Ar-H).
MS (EI): m/z (%): = 332 (M^{+}, 32), 331 (M^{-1},100).
Anal. calcd for $C_{20}H_{20}N_4O$ (332.41): C, 72.26, H, 6.10; N, 16.82; found %: C, 72.04; H, 5.89; N, 17.05.
10b Crystallized from cyclohexane, (92% yield), m.p. =160-2 ^{0}C.
IR (ν/cm^{-1}): 1640 (C=O).
^{1}H-NMR ($CDCl_3$): δ/ppm = 1.80(s, 3H, CH_3), 2.10(s, 3H, CH_3), 2.31(s, 3H, CH3), 3.90(s, 3H,-OCH_3), 5.90 (s, 1H, CH of pyrimidine ring), 6.91(d, 2H, *j* = 8.31Hz, Ar-H), 7.30 (d, 2H,*j* = 8.31Hz, Ar-H), 7.7 (s, 1H, NH exchangeable with D_2O).
MS (EI): m/z (%): = 334 (M^{+}, 20), 332 (M^{-2},100).

Anal. calcd. for $C_{19}H_{18}N_4O_2$ (334.38): C, 68.25; H, 5.43; N, 16.76, found%: C, 68.12, H, 5.38; N, 16.83.

Synthesis of 8-amino-2,3-dimethyl -4-(4-methoxyphenyl)-*5H*- 1,5-8a,9-tetraaza-fluoren-6-one (11) :

A solution of compound **9** (2.68g, 10mmol) and ethyl cyanoacetate (1.47g, 13 mmol) in absolute ethanol (20 ml) containing (1ml) of pipredine was heated under reflux for 12 hs. The solid product collected by filtration and crystallized from ethanol to give an orange powder of the product. (73% yield), m.p. = 222- 225 ^{0}C.
IR (ν/cm^{-1}): 3478-3379 (NH_2), 1660 (C=O).
^{1}H-NMR ($CDCl_3$): δ/ppm= 2.1(s,3H,CH_3), 2.6(s,3H,CH_3), 3.86 (s,3H,OCH_3), 5.82 (s, 1H, CH of pyrimidine ring),7.05(d, 2H, *j* = 8.24Hz, Ar-H),7.30 (d, 2H, *j* = 7.63Hz,Ar-H), 7.82 (s, 2H, NH_2 exchangeable with D_2O). 10.85(bs, 1H, NH exchangeable with D_2O).
^{13} C-NMR ($CDCl_3$): δ/ppm = 15.9 (CH_3),25.0 (CH_3), 55.6 (OCH_3), 66.9,79.1 (2 C of pyrimidine ring), 114.5-129.3, 149.9, 162.7 (6C-phenyl ring), 143.2 (C of the pyrazole ring) ,134.6,125.8, 150.0, 157.0, 158.0 (5C , pyridine ring). 163.0 (C=O).
MS (EI): m/z (%): = 335 (M^+, 35), 91 (100).
Anal. calcd for $C_{18}H_{17}N_5O_2$ (335.37): C, 64.47; H, 5.11; N, 20.88, found % C, 64.41, H, 5.02, N, 20.94.

(2-Mercapto-7,8-dimethyl-9-(4-methoxyphenyl)-[1,2,4]triazolo[1`,5`:1,5]pyrazolo[3,4-*b*]pyridin-3-*yl*)-phenyl-methanone (12):

To a solution of benzoylisothiocyanate (0.16g, 1mmol) in hot and dry acetone, a hot solution of **9** (0. 268g, 1mmol) in acetone / DMF was added drop wise and the reaction mixture was heated under refluxing temperature for 5 hs. The reaction mixture poured onto ice cold water where the solid product formed and collected by filtration, washed with water several times and crystallized from acetone afforded **12**, (78% yield), m.p.=250-252 ^{0}C.
^{1}H-NMR (DMSO-d_6): δ/ppm= 2.14 (s, 3H, CH_3), 2.60 (s 3H, CH_3)), 3.41 (s,1H,SH, exchangeable with D_2O), 3.84(s, 3H,-OCH_3), 6.80(d, 2H, *j*=8.53Hz, Ar-H), 7.26(d, 2H, *j*=8.53Hz, Ar-H) , 7.7(t,1H, *j*=9.23Hz, Ar-H) ,7.85(d,2H, *j*=8.02Hz, Ar-H).7.75(d,2H, *j*=8.02Hz, Ar-H).
MS (EI): m/z (%): = 429 (M^+, 35), 91 (100).
Anal. calcd. for $C_{23}H_{19}N_5O_2S$ (429.50): C, 64.32; H, 4.46; N,16.31; S, 7.47, found%: C, 64.06, H, 4.31; N, 16.20; S, 7.31.

2,3-Dimethyl-4-(4-methoxyphenyl)*1H*-2,3,7,8,8a-pentaaza-cyclopenta[*a*]indene (13):

A mixture of compound **9** (0.536g, 2mmol) and benzoin (0.458g, 2.2mmol) was refluxed in phosphorous oxychloride (20mL) for 8 hs on a water bath. It poured gradually onto crushed ice with vigorous stirring to obtain a yellow solid product, filtered off, washed with water, dried and finally crystallized from acetone to give orange crystals, (74% yield), m.p=293-295^{0}C.
IR (ν/cm^{-1}): 3197(NH).
^{1}H-NMR (DMSO-d_6): δ/ppm 2.23(s, 3H, CH_3), 2.45(s, 3H, CH_3), 3.90 (s, 3H,-OCH_3), 6.88-7.65 (m,14H, Ar-H), 11.23(1H,exchangeable with D_2O).
MS (EI): m/z (%): = 444 (M^+, 32), 91 (100).
Anal. calcd. for $C_{29}H_{24}N_4O$ (444.20): C, 78.36; H, 5.44; N, 12.60, found%: C, 78.21; H, 5.52; N,12.75.

Synthesis of N-[4-(4-methoxyphenyl)-5, 6-dimethyl-*2H*-pyrazolo[3, 4-*b*]pyridin-3-*yl*] formamide (14).

A solution of compound **9** (0.53g, 2mmol) in formic acid (20 ml) and acetic anhydride (20ml) was heated under refluxing temperature for 10 hs. Then the reaction mixture poured onto ice cold water and neutralized with ammonia solution, the solid separated, collected by filtration, washed with water several times and crystallized from acetonitrile to give colorless crystals of product **14**. (95% yield), m.p. = 215-218 ^{0}C.
IR (ν/cm^{-1}):3245 (NH), 1705 (C=O).
^{1}H-NMR ($CDCl_3$): δ/ppm= 2.06 (s, 3H, CH3), 2.4 (s, 3H, CH3),), 3.84(s, 3H,-OCH3), 4.0 (s,1H,NH exchangeable with D_2O), 7.01(d, 2H, *j*=8.53Hz, Ar-H), 7.15(d,2H, *j*=8.53Hz, Ar-H), 7.8 (s,1H,C-H) , 9.1 (bs,1H,NH exchangeable with D_2O).
MS (EI): m/z (%): = 296 (M^+, 25), 268 (100).
Anal. calcd. for $C_{16}H_{16}N_4O_2$ (296.33): C, 64.85; H, 5.44; N, 18.91, found%: C, 64.71; H, 5.07; N, 19.02.

Synthesis of 4-(4-methoxyphenyl)-5,6-dimethyl-2(*H*)-pyrazolo[3,4-b]pyridine-3-diazoniumhydrochloride (15):

Amine hydrochloride salt solution of compound **9** prepared from (0.536gm, 2mmol of **9**in 5 mL Conc. HCl and the solution was kept in an ice bath at 0-5 ^{0}C for10 mins. Sodium nitrite solution prepared from (0.145 gm, 2.1mmol, 5ml water) was added drop wise with stirring to the amine hydrochloride salt solution over a period of 20- 25 mins at 0^{0}C.where a yellow precipitate of diazonium hydrochloride salt was formed. The reaction mixture was stirred for additional 15 mints while maintaining the temperature at 0 ^{o}C.

Syntheses of 2,3-dimethyl-4-(4-methoxyphenyl)-1,5,6,8a,9-pentaaza-fluorene derivatives (16,17,18a,b, 19)

To a well cold and stirred solution of amine hydrochloride salt **15** and sodium acetate anhydrous (5 gm) in ethanol (100ml), malononitrile (0.145 gm, 2mmol) or ω-cyanoacetophenone or of α-chloroacetyl acetone (0.273g ,0.022 mol) or α-chloroethylaceto-acetate (0.344g ,2.2mmol) or benzene sulphonylacetophenone (0.572g,2.2mmol) was added with stirring at (0-5 ^{0}C). Stirring was continued for additional 2 hs. It left overnight in the refrigerator. Water (250 ml) added to the reaction mixture and the solid product formed and collected by filtration. It crystallized from the appropriate solvent.

Synthesis of 8-amino-2,3-dimethyl-4-(4-methoxyphenyl)1,5,6,8a,9-pentaaza-fluorene-7-carbonitrile(16).
Crystallized from toluene (67%), m.p. = 215-7 ^{0}C.
IR (ν/cm^{-1}): 3455-3325 (NH_2), 2225 (CN).
^{1} H-NMR ($CDCl_3$): δ/ppm =2.43(s,3H,CH3),2,88 (s,3H,CH_3), 3.73 ((s,3H, OCH_3) , 7.09(d, 2H, d, *j*=8.53Hz, Ar-H), 7.45 (d, 2H, d, *j*=8.53Hz, Ar-H), 3.15(s,2H,NH exchangeable with D_2O).
MS (EI): m/z (%): = 345(M^+, 71), 344 (M^{-1}, 100).
Anal. calcd. for $C_{18}H_{15}N_7O$ (345.37): C, 62.60; H, 4.38; N, 28.39, found %: C, 62.67; H, 4.23; N, 28.46.

8-Amino-2,3-dimethyl-4(4-methoxyphenyl)-1,5,6,8a,9-pentaaza-fluorene-7-yl)-phenyl-1-methanone (17)
Crystalised from n-hexane (67%), m.p. = 163-5 ^{0}C.
IR (ν/cm^{-1}): 3485-3353 (NH_2), 1668 (CO).
^{1}H-NMR (DMSO-*d_6*): δ/ppm= 2.07(s,3H,CH_3), 2.5(s,3H,CH_3),3.85 (s,3H,OCH_3), 4.06 (s, 2H, NH_2 exchangeable with D_2O), 6.88(d, 2H, *j*=8.53Hz, Ar-H), 7.4 (d, 2H, *j*=8.53Hz, Ar-H),7.5(t,1H, *j*=10.21Hz, Ar-H), 8.6 (d,2H, *j*=9.23Hz, Ar-H), 7.45 (d, 2H, *j*=8.53Hz, Ar-H).
^{13} C-NMR (DMSO-*d_6*): δ/ppm = 14.9 (CH_3),24,0 (CH_3), 55.1 (OCH_3), 66.9,79.1 (2 C of pyrimidine ring), 119.5-129.3, 146.8, 150.9-162.7 (12C-phenyl ring), 142.2 (C of the pyrazole ring) , 134.6,125.8150.0, 157.0, 158.0, (5C , pyridine ring). 163.0 (C=O).
MS (EI): m/z (%): = 268 (M, 100), 253 (19).
Anal. calcd. for $C_{24}H_{20}N_6O_2$ (424.47): C, 67.94; H, 4.75; N, 19.80, found %: C, 67.82; H, 4.82; N,19.54.

1-(2,3,8-Trimethyl-4-(4-methoxyphenyl)-1,5,6,8a,9-pentaaza-fluoren-7-*yl)*-ethanone (18a)
Crystallized from methanol, (84.5% yield), m.p = 165-168^{0}C.
IR (ν/cm^{-1}): 1716 (C=O).
^{1}H-NMR ($CDCl_3$): δ/ppm = 2.04(s, 3H, $COCH_3$), 2.03,2,88 (2s,6H,CH_3), 2.40 (s,3H, CH3), 3.98 ((s,3H, OCH_3) , 7.09(d, 2H, d, *j*=8.53Hz, Ar-H), 7.45 (d, 2H, d, *j*=8.53Hz, Ar-H),
MS (EI): m/z (%) = 361(M^+, 100).
Anal. Calcd. for: $C_{20}H_{19}N_5O_2$ (361.41). C, 66.47; H, 5.30, N, 19.38; found %: C, 66.59; H, 4.90; N, 19.46.

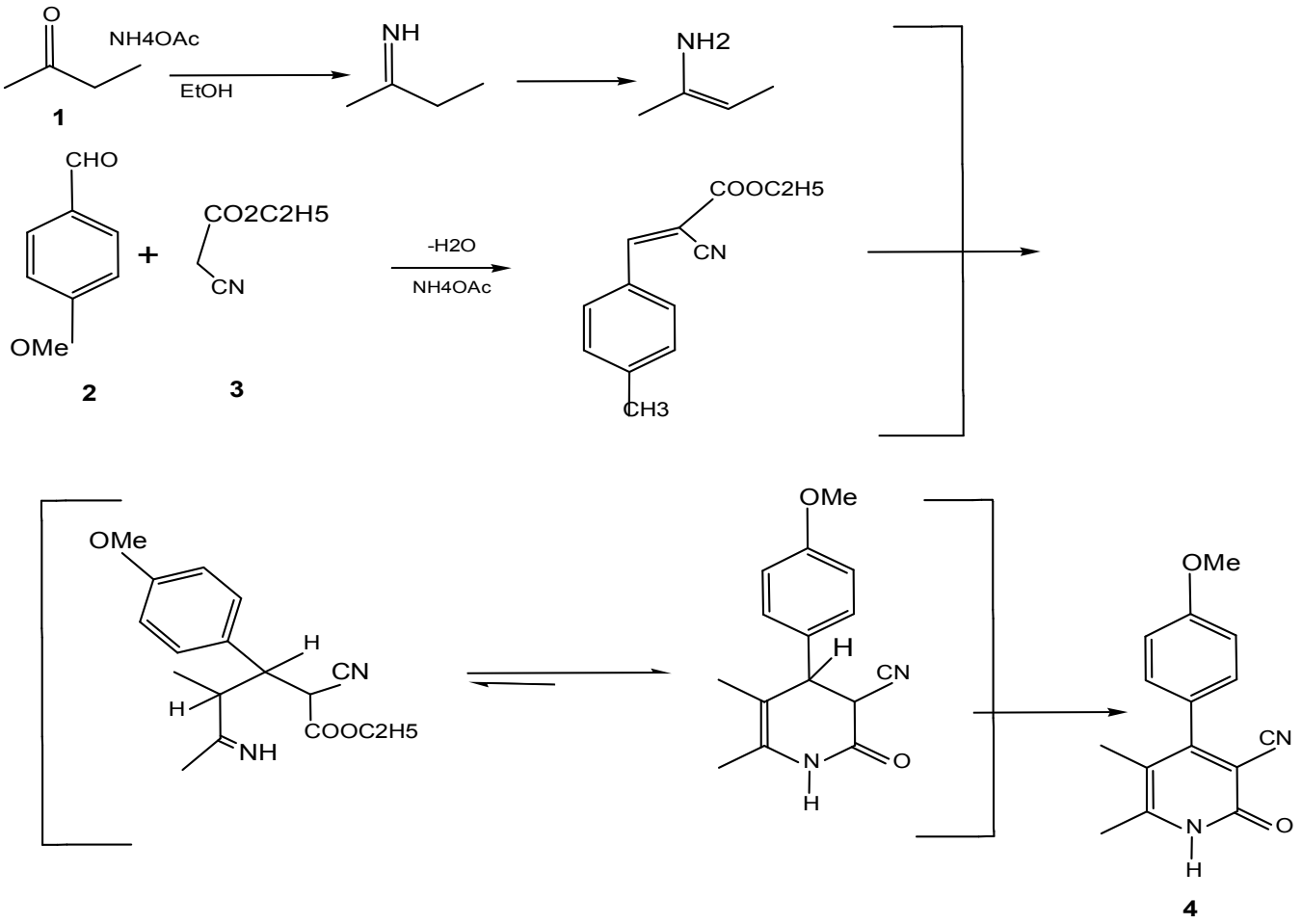
2,3,8-Trimethyl-4-(4-methoxyphenyl)-1,5,6,8a,9-pentaaza-fluorene-7-carboxylic acid ethylester (18b)
Crystallized from methanol, (65% yield), m.p =210-2 ^{0}C.
IR (ν/cm^{-1}): 1720 (C=O, ester).
^{1}H-NMR ($CDCl_3$): δ/ppm = 1.89 (t, 3H, CH_3), 2.04, 2.14, (2s, 6H, CH_3), 2.60 (s 3H, CH_3), 3.65(q, 2H,CH_2) 3.84(s, 3H, OCH_3), 6.80(d, 2H, *j*=8.53Hz, Ar-H), 7.26(d, 2H, *j*=8.53Hz, Ar-H) .
MS (EI): m/z (%): = 391(M^+, 85.7), 390 (M^{-1},100).
Anal. calcd. for $C_{21}H_{21}N_5O_3$ (391.43): C, 64.44; H, 5.41; N, 17.89; found %: C, 64.51; H, 6.02; N, 18.21.

7-Benzensulphonyl-2,3-dimethyl-4-(4-methoxyphenyl)-8-phenyl-1,5,6,8a,9-pentaaza-fluorene (19)
Crystallized from methanol, (70%yield), m.p=220-2^{0}C.
^{1}H-NMR (DMSO-*d_6*): δ/ppm= 2.14 (s, 3H, CH_3), 2.60 (s 3H, CH_3)), 3.84(s, 3H, OCH_3), 6.80- 7.66(m, 14H,9Ar-H).
MS (EI): m/z % =521(M^+, 23), 77(100%).
Anal. calcd for $C_{29}H_{23}N_5$ O_3S (521.60): C, 66.78; H, 4.44; N, 13.43; S, 6.15, found %: C, 67.35; H, 4.62; N, 14.21: S, 6.25.

(5,6-Dimethyl-4-(4-methoxyphenyl)- *1H*-2,3,7,8,8a-pentaaza-cyclopenta[*a*]inden-1-yl)-7-methanone (21)
To a well cold and stirred solution of amine hydrochloride salt **15** and sodium acetate anhydrous (5 gm) in pyridine**,** phenacyl bromide (0.396g, 2mmol) was added drop wise at (0-5 ^{0}C). Stirring was continued for additional 2 hs. A yellow precipitate formed and left overnight in the refrigerator. Water(250ml) added to the reaction mixture and the solid product so formed collected by filtration, washed with water several times and crystallized from chloroform to give yellow product of **21**,(75% yield). m.p.= 334-336 ^{0}C., Sharing.
IR (ν/cm^{-1}): 1638(CO).
^{1}H-NMR ($CDCl_3$): δ/ppm =1.8(s,3H,CH_3),2.52 (s, 3H,CH_3), 3.97 ((s,3H, OCH3) , 6.02 (s, 1H, triazol), 6.88(d, 2H, *j*=8.53Hz, Ar-H), 7.4 (d, 2H, *j*=8.53Hz, Ar-H),7.5(t,1H, *j*=10.21Hz, Ar-H), 7.54(t, 2H, *j*=7.45Hz, Ar-H),8.6 (d,2H, *j*=10.23Hz, Ar-H).
MS (EI): m/z (%): = 397 (M^+, 80), 398 (M^{+1}, 100).
Anal. calcd. for $C_{23}H_{19}N_5O_2$ (397.44): C, 69.51; H, 4.82; N; 17.62 ; found %: C, 69.41; H, 4.91; N, 17.49.

Results and Discussion

The present investigation deals with the synthesis of cyanopyridone as starting material required to carry up a synthetic course for the preparation of some pyrazolopyridine derivatives.
The one pot synthesis of cyanopyridone was achieved upon refluxing of *p*-methoxybenz- aldhyde, 2-butanon, ethyl cyanoacetate and ammonium acetate in ethanol
The reaction proceeded through a Michael type addition of the ethyl cyanoacetate to the unsaturated system, followed by cycllization under the reaction condition (c. f. exp. Scheme 1,)



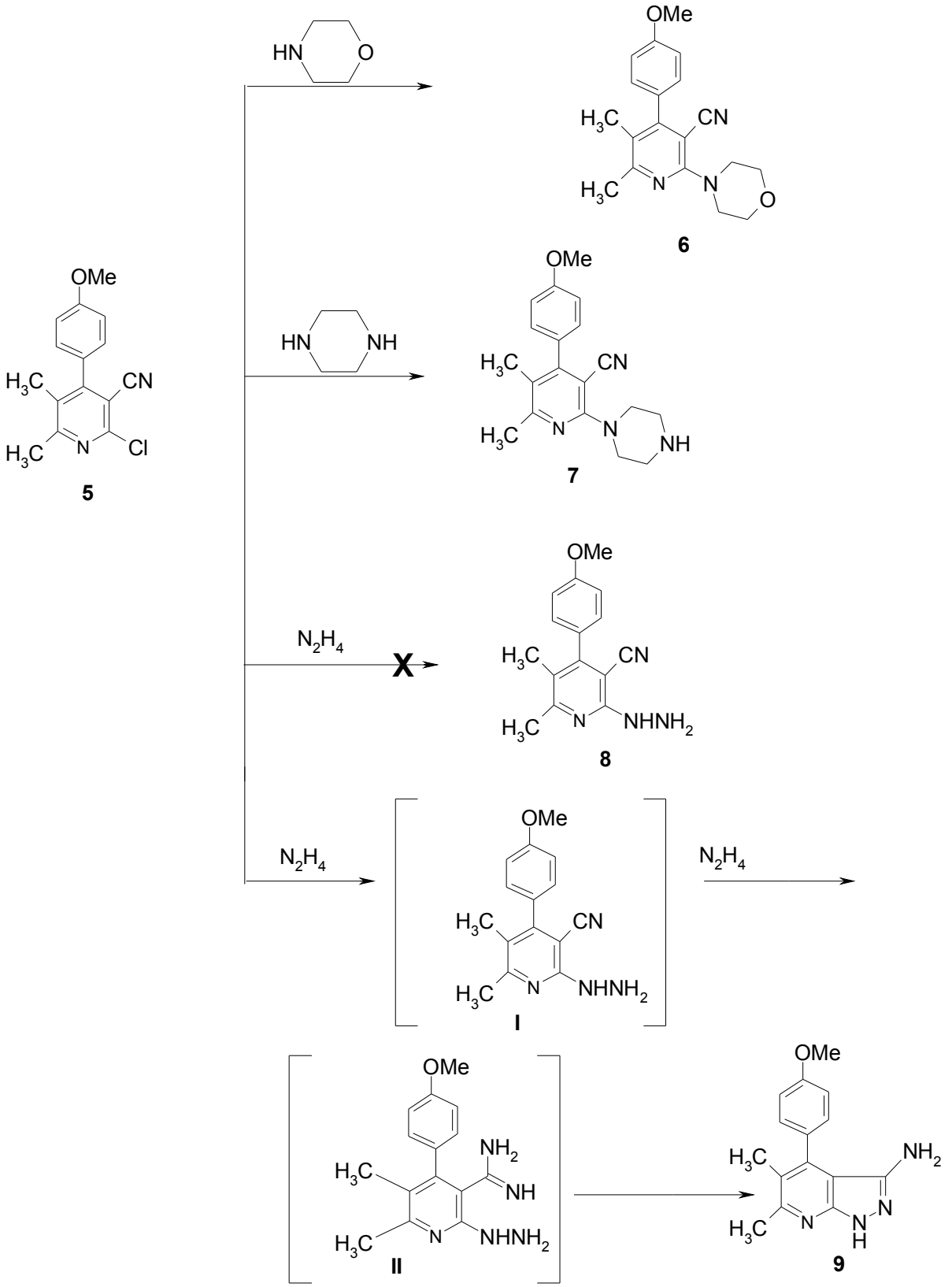
Scheme 1

The chloro- derivative **5** was obtained upon gentle heating of compound **4** in phosphorous oxychloride. It is known that position 2- in chloropyridine derivatives show distinct activities toward neucleophiles. Therefore, **5** was reacted with morpholine, piprazine and hydrazine hydrate to give 3-cyano-5,6-dimethyl-4-(4-methoxyphenyl)-2-morphenylpyridine(**6)** and 3-cyano-5,6-dimethyl-4-(4-methoxyphenyl)-2-piprazinylpyridine (**7**).The structure of (**6,7**) was confirmed from its spectral data, IR (KBr, ν cm^{-1}) showed characteristic peak for CN at 2211 (c. f. exp, scheme 2).

It was reported that neocleophilic substitution of **5** with hydrazine hydrate afforded the hydrazide derivative (**8**), [14] In contrary, we obtained 3-amino-5,6-dimethyl-4-(4-methoxy- phenyl)-pyrazolo[3,4-*b*]pyridine(**9**) depending on the reaction condition (c. f. exp, scheme 2).

The structure of **9** was elucidated from its correct values in its elemental analyses and its agreeable data with its spectral feature, i.e. IR(KBr, ν cm^{-1}) showed the absence of peak characteristic for CN, ^{1}H-NMR (δ ppm) showed resonance at 4.o6 (s, 2H, exchangeable with D_2O, NH_2) and at 11.85 (bs, 1H, NH, exchangeable with D_2O, pyrazol), ^{13}C-NMR(δ ppm) represent characteristic signal at 142.2 C_3 pyrazol. MS (EI); m/z at 268(100%).

In addition to its chemical conformational chemical reactions (c. f. exp, scheme 2).



Scheme 2

Cyclocondensation reactions of **9** with active methylene compounds, namely, acetyl acetone, ethylacetoacetate and ethyl cyanoacetate) afforded 4-(4-methoxyphenyl)-1, 5,8a,9-tetraaza-fluorene derivatives(**10a,b,11**) (c. f. Exp., scheme 3).

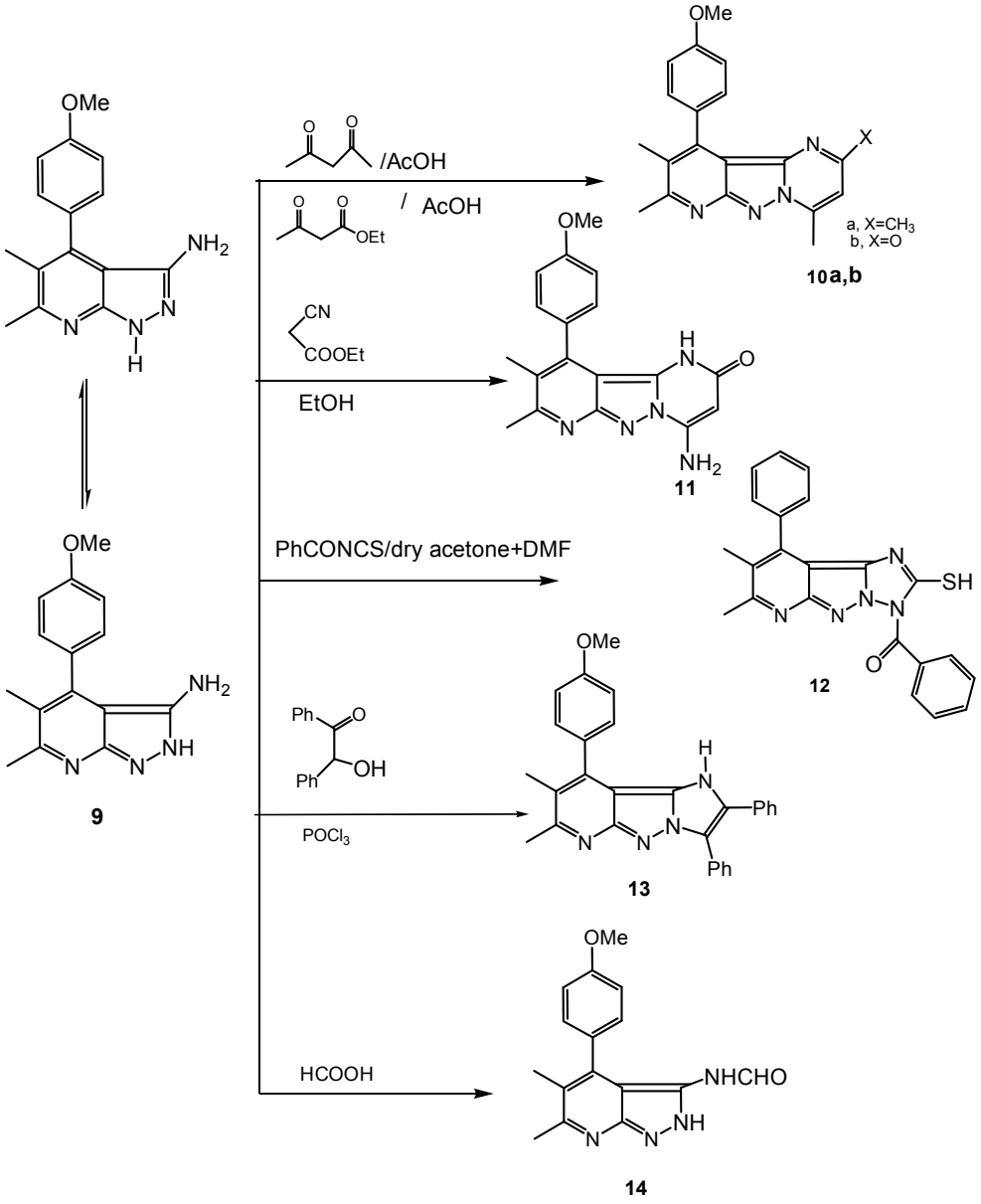
The structure of the formed compounds was coinciding with their correct values in elemental analyses and their

agreeable spectral features. ^{1}H-NMR (δ ppm) showed characteristic signals for pyrimidine moieties at 6.80 (10a), 5.90 (10b), 5.82(11).

The reaction of **9** with benzoylisithiocyanate afforded compound **12**. The structure of (2-mercapto-7,8-dimethyl-9-(4-methoxyphenyl)-[1,2,4]triazolo[1`,5`:1,5]pyrazolo[3,4-*b*]pyridin-3-*yl*)-phenyl-methanone **(12)** confirmed from its correct values in its elemental analyses values and its agreeable spectral data. ^{1}H-NMR (DMSO-d_6): δ/ppm showed characteristic signal for SH at= 3.41 (s, 1H, SH, exchangeable with D_2O) (c. f. exp. Scheme 3).

Upon the fact that phosphorous oxychloride consider as a good cyclizing agent, therefore, was obtained 5,6-dimethyl-1,2-diphenyl-4-(4-methoxyphenyl)-3*H*-3,7,8,8a-tetraaza-cyclo- penta[a]indene **13** upon heating of compound **9** with benzoin in presence of phosphorous oxychloride .The structure of indene derivative was confirmed from its correct values in its elemental analyses values in addition to its agreeable spectral data, therefore, IR (ν/cm^{-1}): 3197(NH). ^{1}H- NMR (DMSO-d_6) revealed resonating signal at 11.23(1H, exchangeable by D_2O, NH).

Synthesis of N-[4-(4-methoxyphenyl)-5, 6-dimethyl-*2H*-pyrazolo[3, 4-b]pyridine-3- *yl*]- formamide (**14**) was also achieved upon heating of **9** with formic acid in acidic medium.



Scheme3

Heterocyclic diazonium salts represent an interesting class of reactive substrates and their synthetic potentialities have received recent attention. Moreover, several heterocyclic diazo compounds possess biological activities.

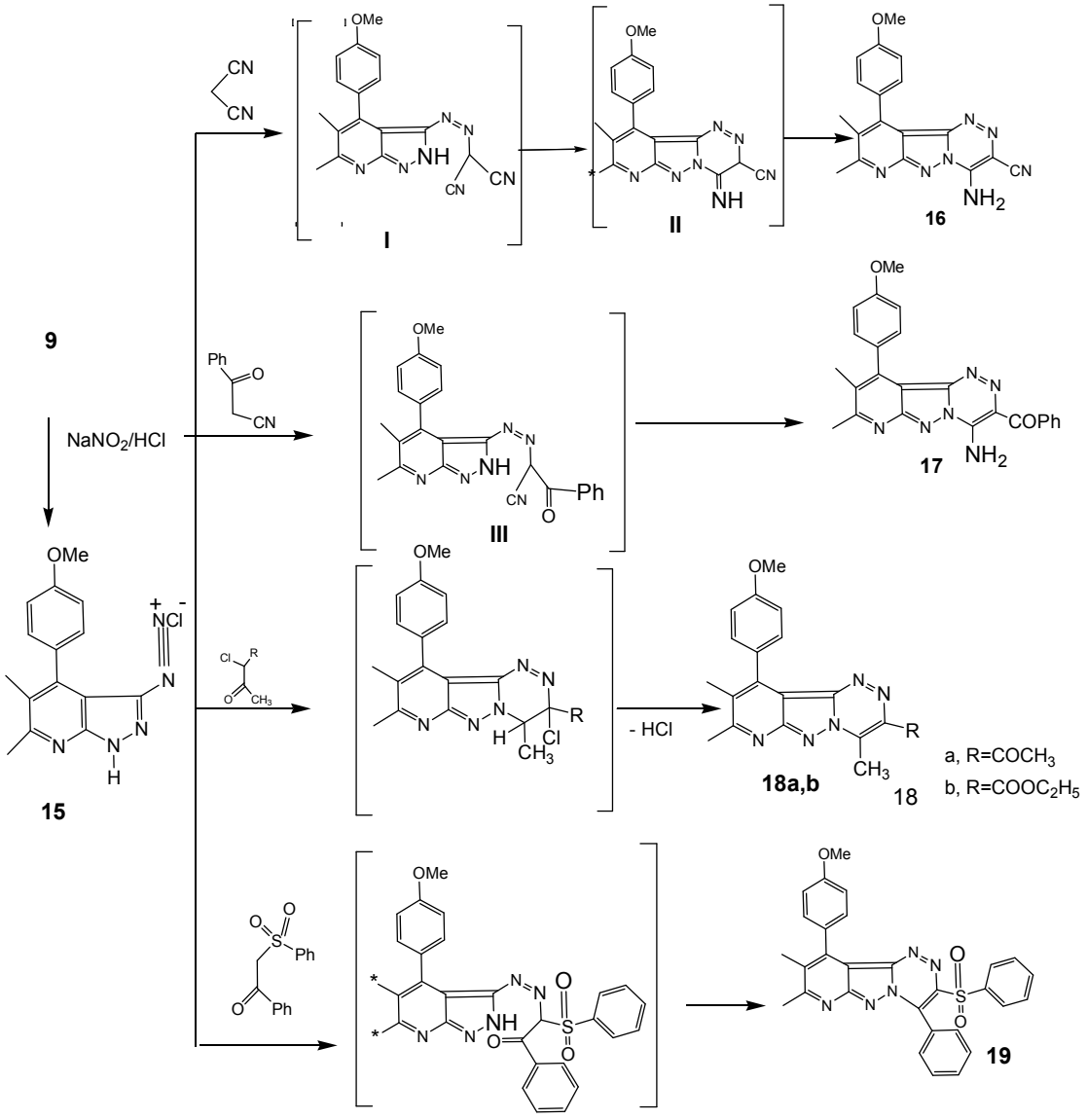
The diazotization of 3-amino-4-(4-methoxyphenyl)-5, 6-dimethyl-*1H*-pyrazolo [3, 4-*b*] pyridine (**9)** and its reactions with active methylene reagents have been studied to develop a synthetic approach to polyfunctionality substituted fused heterocycles.

It has been found that diazotization of **9** in presence of nitrous acid and concentrated hydrochloric acid afforded the diazonium salt **15**. On the treatment of diazonium salt **15** with malononitrile, ω- cyanoacetophenone, α-chloroacetylacetone, α- chloroethyl aceto- acetate and benzensulphenylacetophenone, respectively, 2,3-dimethyl-4-(4-methoxyphenyl)-1,5, 6, 8a,9-pentaaza-fluorene derivatives (**16,17,18a,b, 19**). Beside the correct values in elemental analyses, the IR, ^{1}H-NMR and ^{13}C-NMR and MS spectra of **16,17,18a,b, 19** showed agreeable data with the proposed structures **(**c. f. exp**.)**. Compound **16** showed the following characteristic spectral features, IR (ν/cm^{-1}): 3455-3325 (NH_2), 2225 (CN). ^{1} H-NMR ($CDCl_3$): δ/ppm 3.15(s,2H,NH exchangeable with D_2O) and MS (EI): m/z (%): = 345(M^+, 71).

Compound 17 gave significant peak in IR (ν/cm^{-1}): 3485-3353 (NH_2) and 1668 (CO) and in

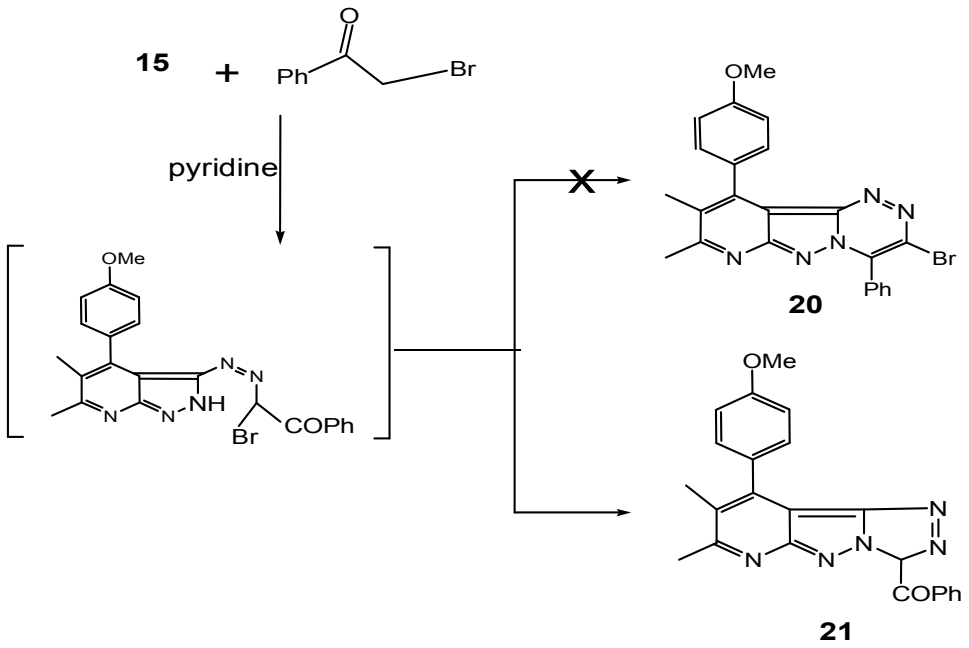
^{13} C-NMR (DMSO-d_6): δ/ppm = 66.9, 79.1 (2 C of pyrimidine ring), 163.0 (C=O).

IR(KBr, ν cm^{-1}) for compounds 18a,b represented signals at 1670 (C=O) and 1720 (C=O, ester) and 18b gave characteristic signals for ester in ^{1}H-NMR ($CDCl_3$): δ/ppm = 1.89 (t, 3H, CH_3) and 3.65(q, 2H,CH_2).



Scheme 4

Thus, when diazonium salt **15** reacted with phenacyl bromide in pyridine gave the corresponding indene derivative **21** indicating condensation with elimination of HBr (c. f. exp., scheme 4). The structure of **21** was assigned on the basis of IR, ^{1}H-NMR and elemental analyses. IR (KBr, ν cm$^{-1)}$ represent peak at 1674 for (CO) and ^{1}H-NMR ($CDCl_3$): δ/ppm gave significant signal at 6.02 (s, 1H, triazol).



Scheme 5

Conclusion

We can conclude that the one pot synthesis of cyanopyridone was achieved. Neocleophilic substitution of **5** with hydrazine hydrate gave **9** depending on the reaction condition. Cyclocondensation reactions of **9** with active methylene reagents gave compounds **10a, b, 11.**Diazotization of 9 and its reactions with active methylene reagents have been studied. Treatment of diazonium salt **15** with active methylene reagents afforded **16, 17, 18a, b, 19** and **21**.

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