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ß-Enaminonitriles in Heterocyclic Synthesis: A Novel Synthesis and Transformations of α-Substituted-ß-enaminonitriles

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Abstract : Novel synthesis of α-substituted-ß-enaminonitriles could be obtained from reaction of ß-enaminonitriles with paraformaldehyde and dimethylamine. Such compounds reacted readily with a wide variety of reagents to give unique heterocyclic systems.

The N-1 substituted-2(IH)-pyrimidinones and their analogous reversibly arrest the mitosis of cells in metaphase and are useful in the treatment of diseases caused by uncontrolled rapidly proliferating cells.[1-3] Extensive work has been prompted on the synthesis and chemistry of pyrimidines and their condensed derivatives.[1-4] Although ß-enaminonitriles has been extensively utitized in organic synthesis,[5-11] little have been reported on the utility of these versatile reagents for building up N-substituted pyrimidines and their condensed derivatives. Now, we report on the reaction of ß-enaminonitriles[5,12-14] **1a-c** with paraformaldehyde / dimethylamine in a novel synthesis of α-substituted-ß-enaminonitriles together with some of their transformations into pyrimidines, quinazolines, pyridines, quinolines and their fused ring systems.

Treatment of ß-N-substituted-aminocrotononitriles **1a-c** with paraformaldehyde/dimethylamine in ethanol afforded exclusively and in excellent yields the corresponding α-N,N-dimethylmethylamino-ß-N-substituted-aminocrotononitriles **2a-c**, the structure of which were established by elemental analyses and spectroscopic methods. Thus, for example, the mass spectral data of **2a** revealed a molecular formula $C_{14}H_{19}N_3$ (m/z=229), Its ^1H NMR spectrum showed in addition to the methyl groups and aromatic bands, a signal at δ =3.05 ppm for the methylene protons and a broad band at δ= 9.03 ppm assigned for the NH unit; this signal underwent a facile hydrogen deuterium exchange and disappeared upon addition of deuterium oxide to the NMR sample. Also, its

^{13}C NMR spectrum data is in support of the proposed structure as it revealed five sp^3 carbons at δ= 19.7, 22.57, 45.81, 45.86 and 60.50 ppm (cf. Experimental).

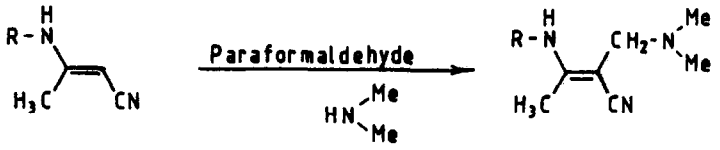
The Mannich compounds **2** exhibited high reactivity towards various reagents and underwent numerous chemical transformations, which led to a wide range of certain polyfunctionally substituted heterocycles. Thus, the N-substituted-pyrimidinethione **6** was obtained, in one pot reaction, on treatment of **2a** with benzoyl isothiocyanate (**3**) in acetonitrile. Compound **6** is assumed to be formed via intermediacy of the acyclic adduct **4** followed by cyclization via loss of dimethylamine to give the intermediate **5** which, in turn, aromatized by loss of benzaldehyde. (cf. Scheme 1). The proposed structure **6** was established on the basis of its correct elemental analysis and compatible spectroscopic data. Alternatively, the pyrimidinethione **6** could also be prepared via an independent route involving the reaction of **2a** with potassium thiocyanate in boiling dioxane to give the acyclic intermediate **7**. The latter cyclized and aromatized via loss of hydrogen molecule into the final isolable product **6**. Similar autoxidation of **8** into **6**, under the reaction conditions, have been reported by Soto et al[15] and by others[16-18] (cf. Scheme 1). The methyl group in compound **6** proved to be highly active towards electrophilic reagents. Thus, it reacted with benzylidenemalononitrile (**9**) to give the quinazolinethione derivative **11**. Compound **11** is believed to be formed via anticipated Michael addition of the activated methyl group in **6** to the double bond in **9** followed by cyclization and aromatization by loss of hydrogen cyanide (cf. Scheme 1).

Coupling of **2a** with benzenediazonium chloride give **13**. Formation of **13** from **2a** and benzenediazonium chloride is assumed to proceed via Japp-Klingemann CN-group cleavage from intermediately formed coupling reactant **12**.

When **2a** was heated with malononitrile (**14a**) or ethyl cyanoacetate (**14b**) under reflux in ethanol with a few drops of piperidine, it readily reacted to afford the N-tolylpyridine derivative **15**. Structure **15** was preferred for the reaction product on the basis of its elemental and spectroscopic data. Compound **15** underwent a wide variety of further transformations. It reacted readily with benzylidenemalononitrile (**9**) to afford a condensation product, formulated as the quinoline **16**, via elimination of hydrogen cyanide. Moreover, compound **16** could be obtained via an independent route involving the condensation of the pyridine **15** with benzaldehyde, which afforded the styryl derivative **17** followed by reaction with malononitrile.

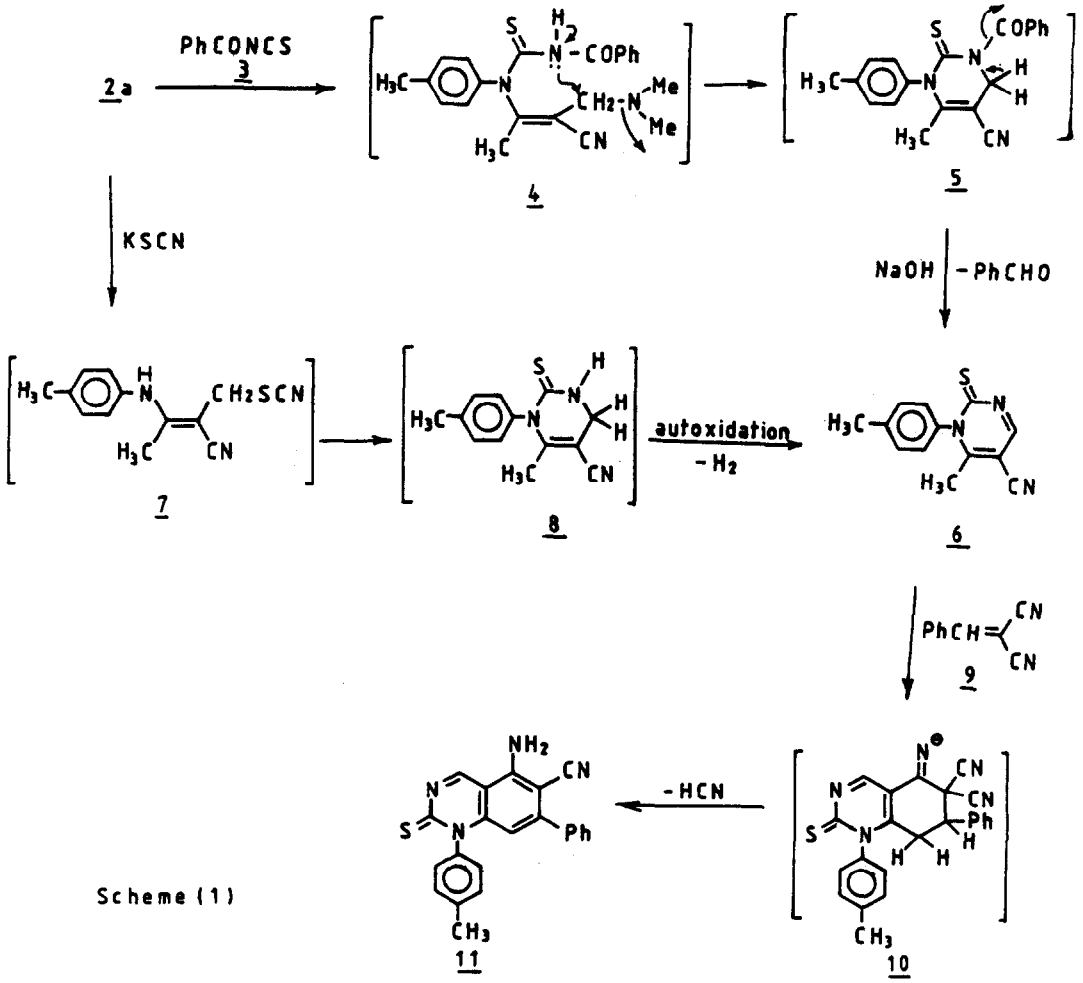
A novel synthesis of a pyridopyridine from methylpyridines and carbon disulphide was obtained. Thus compound **15** reacted with carbon disulphide in the presence of sodium hydride followed by methyl iodide treatment, to afford the pyrido[4,3-b]pyridine **19**. The reaction is believed to proceed via the intermediate **18** (cf. Scheme 2). To our knowledge, this is the first reported formation of pyridines from the reaction of alkylheterocycles with carbon disulphide.

Treatment of **2a** with 3-aminopyrazole derivative **20** resulted in the formation of a condensation product having the molecular formula $C_{14}H_{10}N_4$ in which a molecule of p-toluidine has been lost. Two isomeric forms **21** and **22** are possible for this product which are expected to have almost the same spectral data. Pyrazolo-

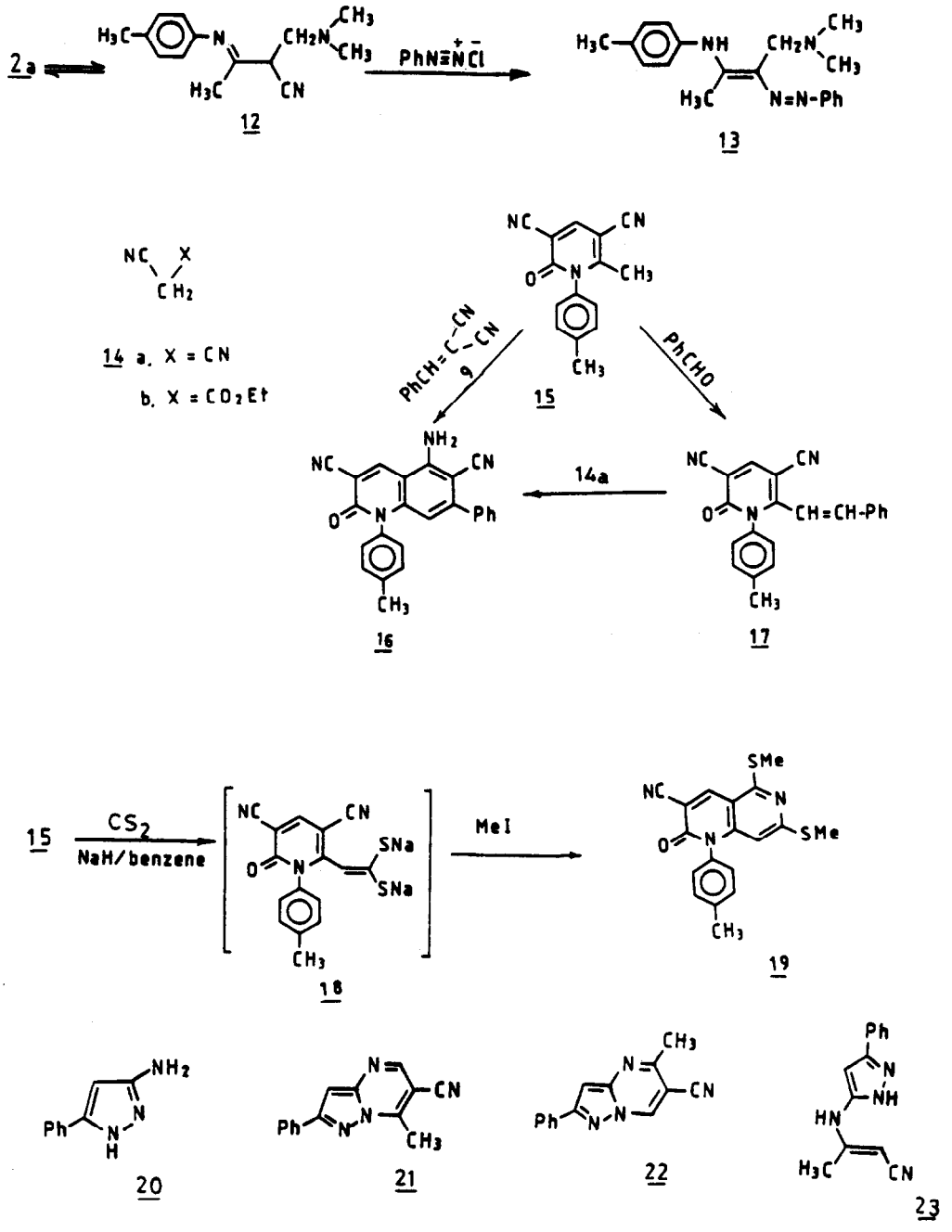


1a, R = $C_6H_4CH_3$-p
b, R = $C_6H_4OCH_3$-p
c, R = H

2a, R = $C_6H_4CH_3$-p
b, R = $C_6H_4OCH_3$-p
c, R = H



Scheme (1)



Scheme (2)

[1,5-a]pyrimidine derivative **21** is proved to represent the reaction product based on chemical evidence. The isomeric form **22** could be prepared via an independent route involving the reaction of ß-aminocrotonitrile **1c** with **20**, which gave the novel ß-enaminonitrile **23**, followed by reaction with paraformaldeyde. To our knowledge this is the first reported synthesis of ß-enaminonitriles having an heterocyclic moiety.[9]

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 Spectrophotometer. ^{1}H NMR spectra were recorded on a Perkin - Elmer R32 90 MHz and a Varian EM-300 MHz Spectrometers with DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed as δ units (ppm). Analytical data were obtained from the Microanalyical Data Center at Cairo University, Egypt.

ß-N-Substituted-aminocrotononitriles **1a,b**[12,13] and 3-aminocrotononitrile **1c**[5] were prepared according to Literature procedures.

α-N,N-Dimethylmethylamino-ß-N-substituted-aminocrotononitriles 2a-c. General procedure : To a solution of **1a-c** (0.01 mol) in absolute ethanol (20 ml) paraformaldehyde (0.3 g) and dimethylamine (1 g, 0.01 mol) were added. The reaction mixture was left at room temperature overnight for 24 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Compound **2a** : yield 2 g (87%), m.p. 110°C.-IR : $\bar{\nu}$= 3340 (NH), 2950 (CH_3), 2220 (CN). - ^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.09 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.05 (s, 2H, CH_2), 7.01 (d, 2H, arom. protons) 7.09 (d, 2H, arom. protons), 9.03 (s, br, 1H, NH, exchangeable). ^{13}C NMR (DMSO) δ (ppm) = 19.7 (CH_3), 22.57 (p-tolyl CH_3), 45.81, 45.86 [$N(CH_3)_2$]; 60.50 (CH_2), 125.43 (CN), 125.69-136.37 (arom. carbons), 139.69 (C-2) and 160.73 (C-3). Found C 73.2 H 8.3 N 18.2 Calcd. for $C_{14}H_{19}N_3$ (229.30) C 73.33 H 8.43 N 18.32.

Compound **2b** : yield 2.1g (88%), m.p. 130°C. -IR : $\bar{\nu}$= 3350 (NH), 2950 (CH_3), 2219 (CN). Found C 68.4 H 7.7 N 17.2 Calcd. for $C_{14}H_{19}N_3O$ (245.31) C 68.57 H 7.75 N 17.14.

Compound **2c**; yield 1g (70%), m.p. 45°C. -IR: $\bar{\nu}$ cm^{-1} = 3400 - 3320 (NH, NH_2), 2970 (CH_3); 2217 (CN). Found C 60.51 H 9.3 N 30.4. Calcd. for $C_7H_{13}N_3$ (139.1) C 60.43 H 9.35 N 30.21.

1,2-Dihydro-6-methyl-2-thioxo-1-p-tolylpyrimidine-5-carbonitrile (6)

Method A. To a suspension of ammonium thiocyanate (3g, 0.04 mol) in acetonitrile (100 ml), benzoyl chloride (4.2 g, 0.03 mol) was added. The reaction mixture was refluxed for 5 min. then treated with **2a** (6.6g, 0.03 mol). The reaction mixture was refluxed for 30 min. and then treated with NaOH (1g). The mixture was boiled under reflux for an additional 30 min.. and then poured onto ice/water. The solid product was collected by filtration and crystallized from ethanol as buff crystals, m.p. 144 °C.

Method B. To a solution of **2a** (2.2 g, 0.01 mol) in dioxane (20 ml), potassium thiocyanate (1g) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water was collected by filtration and crystallized from ethanol: yield 2 g (80%), m.p. 142°C. -IR: $\bar{\nu}$= 3050 (CH_3), 2219 (CN). - ^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.21 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 6.71 (s, 1H, CH), 7.06 (d, 2H, arom. protons), 7.09 (d, 2H, arom. protons). Found C 64.7 H 4.4 N 17.4 S 13.2. Calcd. for $C_{13}H_{11}N_3S$ (241.29) C 64.70 H 4.59 N 17.41 S 13.28.

5-Amino-1,2-dihydro-7-phenyl-2-thioxo-1-p-tolylquinazoline-6-carbonitrile (11). To a solution of **6** (2.3 g, 0.01 mol) in dioxan (30 ml) containing piperidine (5 drops) benzylidenemalononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product was collected by filtration and crystallized from dioxane: yield 2 g (51%), m.p. 189°C. - IR: $\bar{\nu}$= 3450-3380 (NH_2), 3025 (CH_3), 2218 (CN). -^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.29 (s, 3H, CH_3), 3.41 (br, 2H, NH_2), 6.85 - 7.1 (m, 11H, arom. protons). Found C 71.6 H 4.3 N 15.0 S 8.6. Calcd. for $C_{22}H_{16}N_4S$ (386.43) C 71.71 H 4.37 N 15.20 S 8.70.

Coupling of 2a with benzenediazonium salt (13). To a cold solution of **2a** (2.2 g, 0.01 mol) in ethanol (20 ml) containing sodium acetate (3.0 g), benzenediazonium chloride (0.01 mol) was added with continuous stirring. The reaction mixture was left at 4°C for 2 h. The solid product so formed, was collected by filtration and crystallized from ethanol: yield 1.5 g (49%), m.p. 201°C. -IR : $\bar{\nu}$ = 3025 - 2950 (CH_3). -^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.01 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 7.0 (br, 1H, NH), 7.20 = 7.71 (m, 9H, arom. protons). Found C 73.8 H 7.8 N 18.0. Calcd. for $C_{19}H_{24}N_4$ (308.40). C 73.99 H 7.83 N 18.16.

1,2-Dihydro-6-methyl-2-oxo-1-p-tolylpyridine-3,5-dicarbonitrile (15). To a solution of **2a** (4.4 g, 0.02 mol) in absolute ethanol (20 ml) containing 3 drops of piperidine each of malononitrile or ethyl cyanoacetate (0.02 mol) was added. The reaction mixture was heated under reflux for 1 h. The solid product, so formed, was collected by filtration and crystallized from dioxane: yield 3 g (60%), m.p. 210°C. -IR: $\bar{\nu}$= 3050 (CH_3), 2221, 2219 (CN), 1690 (CO). -^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.80 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.0 - 7.59 (m, 5H, arom. protons). Found C 72.0 H 4.3 N 16.7 Calcd. for $C_{15}H_{11}N_3O$ (249.25) C 72.28 H 4.44 N 16.85.

5-Amino-1,2-dihydro-2-oxo-7-phenyl-1-p-tolylquinoline-3,6-dicarbonitrile (16).

Method A. To a solution of **15** (2.4 g, 0.01 mol) in dioxan (20 ml) containing piperidine (5 drops) benzylidenemalononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water was collected by filtration and crystallized from ethanol: yield 1.2 g (31%), m.p. 232°C. -IR: = 3450, 3300 (NH_2), 2221 (CN), 1710 (CO). - ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.91 (s, 3H, CH_3), 3.50 (br, 2H, NH_2), 6.92 - 7.35 (m, 11H, arom. protons). Found C 76.5 H 4.0 N 14.8 Calcd. for $C_{24}H_{16}N_4O$ (376.39) C 76.58 H 4.28 N 14.88.

Method B. 1,2-Dihydro-2-oxo-6-styryl-1-p-tolylpyridine-3,5-dicarbonitrile (17). To a solution of **15** (2.4 g, 0.01 mol) in dioxan (30 ml) containing piperidine (5 drops), benzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed was collected by filtration and crystallized from ethanol: yield 1 g (29%), m.p. 170°C. -IR: $\bar{\nu}$= 2220 - 2218 (CN), 1695 (CO). Found C 78.2 H 4.4 N 12.3. Calcd. for $C_{22}H_{15}N_3O$ (337.36) C 78.32 H 4.47 N 12.45.

To a solution of **17** (1.6 g, 0.05 mol) in dioxan (30 ml) containing piperidine (5 drops) malononitrile (0.33 g, 0.005 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution by water, was collected by filtration and crystallized from ethanol to give 0.7 g (50%) of compound identical in all respects (m.p., mixed m. p. and IR spectrum) with **16** prepared according to method A.

1,2-Dihydro-5,7-dimethylmercapto-2-oxo-1-p-tolylpyrido[4,3-b]pyridine-3-carbonitrile (19). To a solution of **15** (2.2 g, 0.01 mol) in dry benzene (20 ml) and DMF (5ml) containing sodium hydride (0.02 mol) carbon disulphide (0.01 mol) was added. The reaction mixture was heated under reflux, in water bath, for 2 h. After cooling at room temperature methyl iodide (0.02 mol) was added and the reaction mixture was boiled under reflux for an additional 30 min. The solid product formed, on evaporation under vacuum, was neutralized with ethanol/HCl. The solid product obtained on dilution with water was collected by filtration and crystallized from ethanol:yield 1 g (28%), m.p. 256°C. -IR: $\bar{\nu}$= 2220 - 2218 (CN), 1680 (CO). -^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.02 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.91 - 7.22 (m, 6H, arom. protons). Found C 61.1 H 4.2 N 11.8 S 18.0 Calcd. for $C_{18}H_{15}N_3OS_2$ (353.44) C 61.16 H 4.27 N 11.88 S 18.14.

7-Methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (21). A solution of **2a** (2.2 g, 0.01 mol) and aminopyrazole **20** (1.6 g, 0.01 mol) in glacial acetic acid (20 ml) was heated at reflux for 30 min., then left to cool to room temperature, poured into cold water. The solid product was collected by filtration and crystallised from dioxane/H_2O 3:1 to give **21:** yield 1.8 g (78%), m.p. 175°C. -IR : $\bar{\nu}$ = 2970 (CH_3). 2219 (CN). - ^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.32 (s, 3H, CH_3), 6.81-7.20 (m, 7H, arom. protons). Found C 71.7 H 4.1 N 23.7. Calcd. for $C_{14}H_{10}N_4$ (234.24) C 71.78 H 4.29 N 23.91.

3-(3'-Phenylpyrazole-5'-yl)-3-aminobutenonitrile (23). A solution of 3-aminocrotonitrile **1c** (0.8 g, 0.01 mol) and **20** (1.6 g, 0.01 mol) in acetic acid (20 ml), was stirred at room temperature for 15 min., then poured into ice-cold water. The solid product was collected by filtration and washed three time with cold water. Purified by dioxane (cold) then precipitate by dilution (to avoid cyclization), to give **23:** yield (2 g, 89%), m.p. 125°C.- IR: $\bar{\nu}$= 2950 (CH_3), 2221 (CN).-^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.09 (s, 3H, CH_3), 3.92 (s, 1H, CH), 6.71 (s, 1H, pyrazole H), 7.12-7.23 (m, 5H, arom. protons), 8.01 (s, br, 1H, pyrazole NH), 9.02 (s, br, 1H, NH; exchangeable). Found C 69.6 H 5.2 N 24.9 Calcd for $C_{13}H_{12}N_4$ (224.25) C 69.62 H 5.38

N 24.98.

5-Methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (22). To a solution of **23** (2.2 g, 0.01 mol) in absolute ethanol (20 ml) paraformaldehyde (0.3 g) with few drops of triethylamine were added. The reaction mixture was stirred overnight. The solid product formed on dilution with water was collected by filtration and recrystallized from dioxane/ethanol 2:2 to give **22**; yield 1.4 g (60%), m.p. 161°C. -IR: $\bar{\nu}$= 2960 (CH_3), 2221 (CN). ^{1}H-NMR (DMSO-d_6) : δ (ppm) = 2.40 (s, 3H, CH_3), 6.82 - 7.20 (m, 7H, arom. protons). Found C 71.8 H 4.1 N 23.8. Calcd. for $C_{14}H_{10}N_4$ (234.24) C 71.78 H 4.29 N 23.91.

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