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NEW SYNTHESIS OF 1,4-DIARYLPIPERAZINE-2,5-DIONE AND 3,4,5-TRISUBSTITUTEDPYRIDINE-2(1H)-ONE

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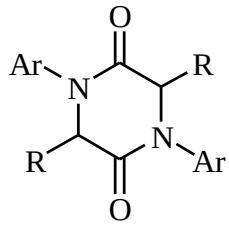
Abstract

Treatment of *N*-aryl 2-chloroacetamides (**2a-f**) with sodium isopropoxide in isopropyl alcohol afforded 1,4-diarylppiperazine-2,5-dione (**3a-f**). Treatment of malononitrile dimer (**9**), ethyl cyanoacetate (**11**) and the arylidines of cyanothioacetamide (**13**) with DMFDMA afforded the corresponding enamines (**10, 12 and 14**) respectively. Reaction of **14** with either sodium ethoxide or sodium methoxide affords 5-cyano-4-ethoxy-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid amide (**15**) and 5-cyano-4-methoxy-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid amide (**16**) respectively.

Introduction

Okawara *et al,*[1] describes the synthesis of various 1,4-disubstituted-2,5-diketopiperazines by intermolecular condensation of halocarboxamides using a reaction system comprising a mixture of dichloromethane and 50% aqueous sodium hydroxide solution in the presence of a solid phase transfer catalyst. Among the compounds whose synthesis are 1,4-dibenzylpiperazine-2,5-dione (**1a**), 1,4-diphenylpiperazine-2,5-dione (**1b**) and 1,4-diphenyl-3,6-dimethylpiperazine-2,5-dione (**1c**).



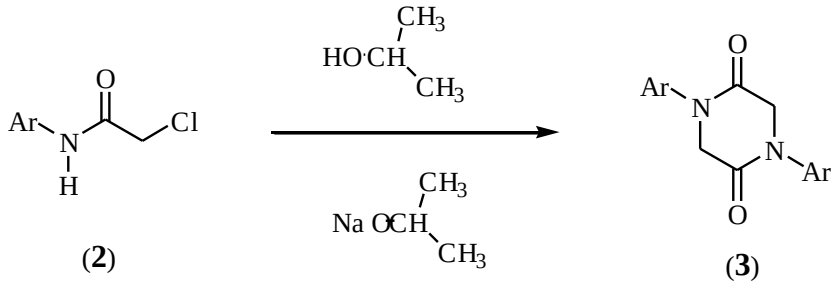
(**1**)

a, Ar = $PhCH_2$ R = H
b, Ar = Ph R = H
c, Ar = Ph R = CH_3

Cavicchioni et al,[2] reports the preparation of both N,N'-dialkylpiperazines and 2-amino-2-haloalkyloxazolidones by intermolecular condensations of the same reactants used in the synthesis described by Okawara. They do not give much detail on the reaction system utilized but apparently employed a polar organic solvent system rather than a two-phase system comprising a phase transfer catalyst. It is reported that[3-7] 1,4-disubstitued 2,5-diketopiperazines were used in a synthesis scheme leading to the preparation of N-phosphonomethylglycine. N-phosphonomethylglycine, known also by its common name, glyphosate, is a highly effective and commercially important phytotoxicant useful in controlling a large variety of weeds. It is applied to the foliage of a very broad spectrum of perennial and annual grasses and broadleaf plants. Industrial uses include control of weeds along roadsides, waterways, transmission lines, storage areas, and other non-agricultural areas.

Results and Discussion

From the biological point of view we concentrate our effort for synthesis of 1,4-diarylpiperazine-2,5-diones. We repot the synthesis of 1,4-diarylpiperazine-2,5-diones (3a-f), from the reaction of N-aryl 2-chloroacetamides (2a-f) in 2-propanol and sodium isopropoxide. N-aryl 2-chloroacetamides (2a-f) in 2-propanol were added to sodium isoproxoide in 2-propanol with stirring at room temperature. After stirring at room temperature for 12 h, the reaction was left under reflux for 1h. Then left stirring again at room temperature for another 12 h. The solid obtained in good yield after working up the reaction was formulated as (3).



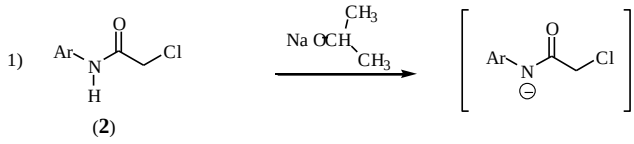
(**2**) (**3**)

a, Ar = ph
b, Ar = C_6H_4-*p*CH_3
c, Ar = C_6H_4-*p*Cl
d, Ar = C_6H_4-*p*Br
e, Ar = C_6H_4-*p*NO_2
f, Ar = C_6H_4-*p*$COCH_3$

a, Ar = ph
b, Ar = C_6H_4-*p*CH_3
c, Ar = C_6H_4-*p*Cl
d, Ar = C_6H_4-*p*Br
e, Ar = C_6H_4-*p*NO_2
f, Ar = C_6H_4-*p*$COCH_3$

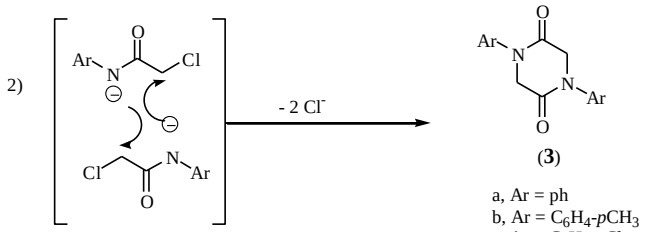
The reaction proceed by intermolecular cyclization as in Scheme (**1**).

Scheme (**1**)



(**2**)

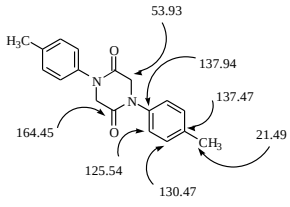
a, Ar = ph
b, Ar = C_6H_4-*p*CH_3
c, Ar = C_6H_4-*p*Cl
d, Ar = C_6H_4-*p*Br
e, Ar = C_6H_4-*p*NO_2
f, Ar = C_6H_4-*p*$COCH_3$



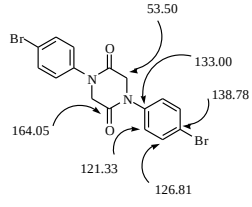
(**3**)

a, Ar = ph
b, Ar = C_6H_4-*p*CH_3
c, Ar = C_6H_4-*p*Cl
d, Ar = C_6H_4-*p*Br
e, Ar = C_6H_4-*p*NO_2
f, Ar = C_6H_4-*p*$COCH_3$

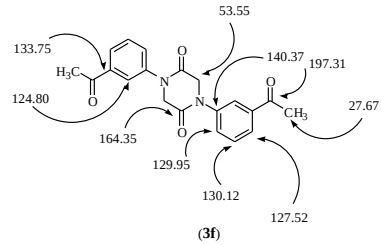
The structure of the products was established by elemental analysis and spectral data. The mass spectra of the products show a molecular ion peak fit to the structure (**3a-f**). Also the ^{1}H NMR spectra of the products show beside the aromatic protons a singlet signal at $\delta_H \approx 4.4$ ppm corresponding to the CH_2 of piperazine ring. Also the ^{13}C NMR products (**3b,d,f**) give strong evidence of the isolated products as shown on the structures **3b,d,f**.



(**3b**)



(**3d**)



(**3f**)

For further confirmation of the structure we did the DEPT 135, 90, 45 of ^{13}C NMR spectra of compounds **3b,d,f**. in which the methylene group of the piperazine appears at $\delta_C \approx -53$ ppm. The number of signals in ^{13}C NMR spectra is half the number of the carbon atoms in the molecule, this attributed to the symmetry of the molecule as well as its non-planarity as shown in the molecular modeling of compound **3a** fig. (**1**).

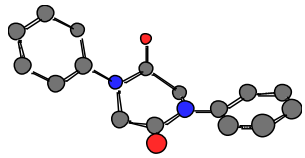
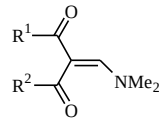
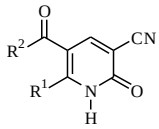


Fig. (1): The molecular modeling of compound 3a showing the non-planarity of the molecule.

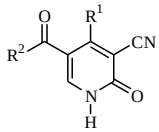
We have reported that the enamines (**4**) were used as precursors in the synthesis of 3,5,6-trisubstitutedpyridine-2(1*H*)-one (**5,7**) and 3,4,5-trisubstitutedpyridine-2(1*H*)-one (**6,8**)[8,9,12].



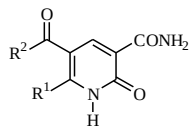
(**4**)



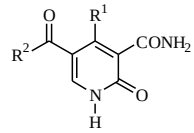
(**5**)



(**6**)



(**7**)



(**8**)

The structure of these compounds was confirmed by X-ray crystallography[8,9] fig.(**2**)[11].

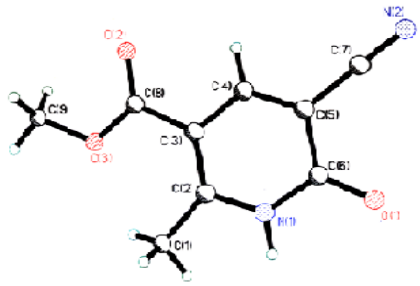
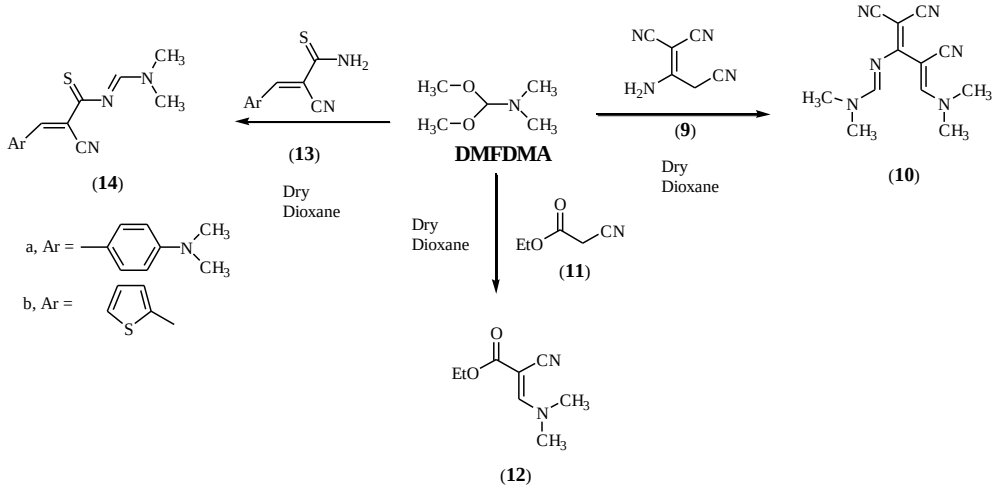


Fig. (2): X-ray crystallography of Methyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate[11].

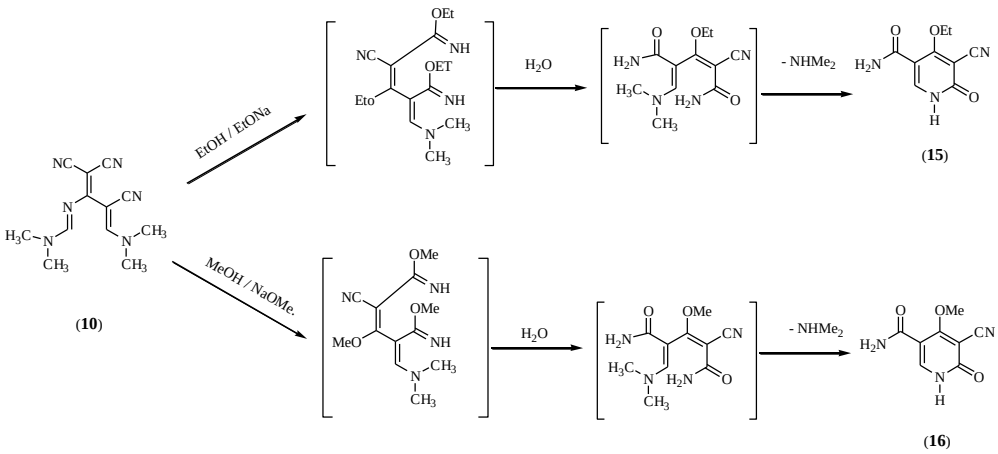
In conjunction with our studies we report the reaction of malononitrile dimer (**9**) with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (1:2) to give *N*-[2,2-dicyano-1-(1-cyano-2-dimethylamino-vinyl)-vinyl]-*N*,*N*-dimethyl-formamidine(**10**) and the reaction with ethyl cyanoacetate (**11**) with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) affords ethyl 3-cyano-3-dimethylamino-acrylate (**12**). Also it was found that, the reaction of 3-aryl-2-cyanothioacrylamides (**13a,b**) with the same reagent (*N*,*N*-dimethylformamide dimethyl acetal (DMFDMA)) afforded a violet crystalline substance which is formulated as 3-aryl-2-cyano-N-dimethylaminomethylenethio-acrylamides (**14a,b**) as shown in Scheme (**2**).

Scheme (**2**)



The structures of the isolated products were confirmed by elemental analysis and spectral data where ^{1}H NMR spectrum of compound (**10**) shows two singlet signals at δ_H = 7.671 and 8.066 ppm corresponding to the vinyl proton and the proton of the formamidine moiety respectively. Compound (**12**) shows a singlet signal at δ_H = 8.1 ppm corresponding to the vinyl proton. Also compound (**14a**) shows two singlet signals at δ_H = 8.576 and 8.745 ppm and compound (**14b**) shows two singlet signals at δ_H = 8.658 and 8.786 ppm corresponding to the vinyl proton and the proton of the formamidine moiety respectively. These enamines (**10, 12 and 14**) are useful as precursor for the preparation of heterocyclic compounds. Therefore there are some illustrative reactions, designed to demonstrate the potential usefulness of the products described above for further heterocyclic synthesis, are represented in Scheme 3. Thus, reaction of *N*-[2,2-dicyano-1-(1-cyano-2-dimethylamino-vinyl)-vinyl]-*N*,*N*-dimethyl-formamidine(**10**) with either sodium ethoxide in ethanol or sodium methoxide in methanol afforded a products that formulated as 5- cyano-4-ethoxy-6-oxo-1,6-dihydropyridine-3-carboxamide (**15**) and 5- cyano-4-methoxy-6-oxo-1,6-dihydropyridine-3-carboxamide (**16**).

Scheme (**3**)



The structures of the isolated products were confirmed by elemental analysis and spectral analysis where the ^{1}H NMR spectra of compounds **15** and **16** show singlet signals at δ_H = 8.5 ppm for one proton corresponding to ring proton beside two deuterable broad signals at δ_H = 7.49 ppm for one proton and δ_H = 8.05 ppm for two protons corresponding to the ring NH and the amide NH_2 group respectively.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer as KBr disks. NMR spectra were recorded on Bruker AC300 spectrometer at 200 MHz for solutions of $[^2H_6]$dimethyl sulfoxide with tetramethylsilane (TMS) as an internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometer using electron impact (EI). N-aryl-2-Chloro-acetamide (**2a-f**) [9] and the malononitrile dimmer were prepared by the literature method [10].

General Procedure 1,4-Diarypiperazine-2,5-dione (3a-f): In a dry flask a mixture of 2-propanol (20 ml) and sodium metal (0.23g 0.01mol) was left under stirring till all sodium dissolved, then N-aryl-2-Chloro-acetamide (**2a-f**) (0.01mol) in 5 ml of 2-propanol was added drop-wise with stirring and left stirring overnight. A white precipitate is formed, then the mixture was left under reflux for 1h after this the mixture was left with stirring at room temperature overnight. Then 5 ml of 10% ammonium chloride was added the solid obtained was collected by filtration and purified by recrystallisation.

1,4-Diphenylpiperazine-2,5-dione (3b): This compound was prepared by the method described above using 2-Chloro- N-phenyl-acetamide (**2a**) (1.7g, 10mmol). The solid obtained in yield (1g, 75.2%) as colorless crystals (EtOH), m.p. 276-8˚C, ir**:** C=O 1664 cm^{-1}, ^1H nmr ($CDCl_3$) δ 4.48 (s, 4H, $2CH_2$), 7.30-7.47 (m, 10H, phenyl protons), ms: m/z 266 (M^+).

Anal.Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.9; H, 5.5; N, 10.4.

1,4-Di-p-tolyl-piperazine-2,5-dione (3a): The title compound was prepared by the method described above using 2-Chloro- N-p-tolyl-acetamide (**2b**) (1.84g, 10mmol). The solid obtained in yield (1.2g, 81.63%), as colorless crystals m.p. 206-208˚C (EtOH), ir: C=O 1660 cm^{-1}. ^1H nmr($CDCl_3$): δ 2.60 (s, 6H, $2CH_3$), 4.56 (s, 4H, $2CH_2$), 7.47- 7.61, 7.81-7.95 (m, 8H-Ar), ^{13}C nmr($CDCl_3$): δ 21.49 (CH_3), 53.93 (CH2), 125.54130.47, 137.47, 137.94 (CH-Ar), 164.45 (CO), DEPT135: δ 21.06 (CH_3), -53.49 (CH_2), 124.86, 130.04 (CH-Ar), 125.17, 129.77(CH-Ar), ms: m/z 294(M^+).

Anal.Calcd. for $C_{18}H_{18}N_2O_2$, C, 73.45; H, 6.16; N, 9.52. Found, C, 73.2; H, 6.3; N, 9.7.

1,4-Bis-(4-chlorophenyl)-piperazine-2,5-dione (3c): This compound was prepared by the method described above using 2-Chloro- N-p-chloro-phenyl-acetamide (2c) (2g, 10mmol). The solid obtained in yield (1.4g, 85.36%) as colorless crystals (EtOH), m.p. 244-246˚C, ir: C=O 1668 cm^{-1},^{1}H nmr ($CDCl_3$) δ 4.43 (s, 4H, $2CH_2$), 7.22-7.24 (d, 4H, J=7.1Hz), 7.35-7.37 (d, 4H-Ar AB, J= 7.2Hz), ^{13}C nmr ($CDCl_3$), ms: m/z 256 (M^+)

Anal.Calcd. for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; N, 21.15. Found: C, 57.1; H, 3.4; N, 21.3.

1,4-Bis-(4-bromophenyl)-piperazine-2,5-dione (3d): This compound was prepared by the method described above using 2-Chloro- N-p-bromo-phenyl-acetamide (2d) (2.5g, 10mmol). The solid obtained in yield (1.8g, 84.5%) as colorless crystals (EtOH), m.p. 148-150˚C, ir: C=O 1658 cm^{-1},^{1}H nmr ($CDCl_3$) δ 4.42 (s, 4H, $2CH_2$), 7.15-7.22 (d, 4H-Ar, J=7Hz), 7.50-7.52 (d, 4H-Ar AB, J= 7Hz), ^{13}C nmr ($CDCl_3$) δ53.50 9 (CH_2), 120.53, 126.81, 133, 138.78 (CH-Ar), 164.05 (CO), DEPT135, δ -53.06(CH_2), 126.38, 132.56 (CH-Ar), DEPT90, δ 126.43, 132.62 (CH-Ar), DEPT45, 53.50(CH_2), 133, 126.81 (CH-Ar), ms: m/z 422 (M^+), m/z 424 (M^++2)

Anal.Calcd. for $C_{16}H_{12}Br_2N_2O_2$: C, 45.31; H, 2.85; N, 6.61. Found: C, 45.1; H, 3.0; N, 6.8.

1,4-Bis-(4-nitrophenyl)-piperazine-2,5-dione (3e): This compound was prepared by the method described above using 2-Chloro- N-p-nitro-phenyl-acetamide (2e) (1.15g, 10mmol). The solid obtained in yield (1.4g, 71.43%) as colorless crystals (EtOH), m.p. 215-217˚C, ir: C=O 1665 cm^{-1},^{1}H nmr ($CDCl_3$) δ 4.46 (s, 4H, $2CH_2$), 7.46-7.48 (d, 4H, J=6.9Hz), 8.52-8.54 (d, 4H-Ar AB, J= 6.9Hz), ms: m/z 356 (M^+)

Anal.Calcd. for $C_{16}H_{12}N_4O_6$: C, 53.31; H, 3.39; N, 15.73. Found: C, 53.1; H, 3.5; N, 15.9.

1,4-Bis-(3-acetylphenyl)-piperazine-2,5-dione (3f): This compound was prepared by the method described above using 2-Chloro- N-p-bromo-phenyl-acetamide (2f) (2.1g, 10mmol). The solid obtained in yield (1.4g, 80.46%) as colorless crystals (EtOH), m.p. 170-172˚C, ir: C=O 1690,1655 cm^{-1},^{1}H nmr ($CDCl_3$) δ 2.63(s, 6H, $2CH_3$), 4.49(s, 4H, 2CH2), 7.27-7.95 (m, 8H- Ar), ^{13}C nmr ($CDCl_3$) δ27.07 (CH_3), 53.55 (CH_2), 12470, 127.79, 129.98, 130.12, 133.75140.47 (Ar), 164.35(CO), 197.31(CO), DEPT135, δ 26.66 (CH_3), -53.15 (CH_2) 124.34, 127.40, 129.66129.70 (CH–Ar), DEPT90, δ 124.32, 127.45, 129.71, 129.75 (CH-Ar),

DEPT45, 27.09 (CH_3), 53.58(CH_2), 124.70, 127.8129.99, 130.13 (CH- Ar), ms: m/z 350 (M^+).

Anal.Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.3; H, 4.9; N, 7.8.

Preparation of N-[2,2-Dicyano-1-(1-cyano-2-dimethylamino-vinyl)-vinyl]-N,N-dimethyl-formamidine (10): In a dry flask a mixture of malononitrile dimmer (9) (1.32g, 10 mmol), dry dioxane (20 mL) and N,N-dimethylformamide dimethyl acetal (DMFDMA) (1.19g, 10 mmol) was left stirring at room temperature for 24h, the solution turn yellow gradually, and then refluxed for 2h. The solid obtained after cooling in yield (2.4g, 95%) as colorless crystals (EtOH), m.p.86-87˚C, ir: CN 2230, 2200, 2180, C=C 1621 cm^{-1},^{1}H nmr (DMSO-d_6) δ 3.06 (s, 3H, CH_3), 3.192 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.337 (s, 3H, CH_3), 7.671 (s, 1H, CH), 8.066 (s, 1H, CH), ms: m/z 242 (M^+)

Anal.Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.2; H, 5.9; N, 34.8.

Preparation of Ethyl 2-cyano-2-dimethylaminoacrylate (12): In a dry flask a mixture of ethyl cyanoacetate (11) (1.13g, 10 mmol), dry dioxane (20 mL) and N,N-dimethylformamide dimethyl acetal (DMFDMA) (1.19g, 10 mmol) was left stirring at room temperature for 24h, the solution turn yellow gradually. The solid obtained after evaporation of solvent in yield (2.4g, 95%) as colorless crystals (EtOH), m.p. 75-6˚C, ir: CN 2230, C=0 1989 cm^{-1},^{1}H nmr ($CDCl_3$) δ 1.48 (t, 3H, CH_3, J=7.5Hz), 3.38 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 4.4 (q, 2H, CH_2, J=7.4Hz), 8.038 (s, 1H, CH),ms: m/z 242 (M^+)

Anal.Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.2; H, 6.9; N, 16.8

General Procedure for the Preparation of 3-Aryl-2-cyano-N-dimethylaminomethylenethioacrylamide (14a,b): In a dry flask a mixture of 3-aryl-2-cyanothioacrylamide (13) (10 mmol), dry dioxane (20 mL) and N,N-dimethylformamide dimethyl acetal (DMFDMA) (1.19g, 10 mmol) was left under refluxed for 2h, The solution turn violet. The solid product obtained after cooling was recovered by filtration and recrystallized from ethanol.

2-Cyano-N-dimethylaminomethylene-3-(4-dimethylaminophenyl)-thioacrylamide (14a): The title compound was prepared by the method described above using 2-cyano-3-(4-dimethylaminophenyl-thioacrylamide (13a) (2.31g,

10mmol). The solid obtained in yield (2.5g, 87.41%) as violet crystals, m.p. 270-2˚C (EtOH). ir: CN 2218, C=C 1630, 1605 cm^{-1}. ^1H nmr (DMSO-d_6) δ 3.086 (s, 6H, $2CH_3$), 3.229 (s, 3H, CH_3), 3.356 (s, 3H, CH_3), 6.846 (d, 2H, AB-Ar), 8.665 (d, 2H, AB-Ar), 8.576 (s, H, CH), 8.745 (s, H, CH), ms: m/z 286 (M^+).

Anal.Calcd. for $C_{15}H_{18}N_4S$, C, 62.91; H, 6.33; N, 19.56, Found, C, 62.8; H, 6.1; N, 19.4.

2-Cyano-N-dimethylaminomethylene-3-thiophen-2-yl-thioacrylamide (14b): The title compound was prepared by the method described above using 2-cyano-3-thiophen-2-yl-thioacrylamide (13b) (1.94g, 10mmol). The solid obtained in yield (2.2g, 88.35%) as violet crystals, m.p. 143-4˚C (EtOH). ir: CN 2218, C=C 1625, 1602 cm^{-1}. ^1H nmr (DMSO-d_6) δ 3.194 (s, 3H, CH_3), 3.270 (s, 3H, CH_3), 7.278 (s, 1H, CH-Ar), 7.91 (d, 2H, CH-Ar), 8.05 (d, 2H, CH-Ar), 8.658 (s, H, CH), 8.786 (s, H, CH), ms: m/z 249 (M^+).

Anal.Calcd. for $C_{11}H_{11}N_3S_2$, C, 52.98; H, 4.45; N, 16.85, Found, C, 52.8; H, 4.3; N, 17.

5-Cyano-4-ethoxy-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid amide (15): A mixture of N-[2,2-dicyano-1-(1-cyano-2-dimethylamino-vinyl)-vinyl]-N,N-dimethyl-formamidine (10) (2.42g, 10mmol), and sodium ethoxide (30mL ethanol, 0.5g sodium metal) was heated under reflux for about 2h. The reaction mixture was poured on cold water; the solid product was recovered by filtration to give the title compound (15) in yield (1.8, 86.95%) as yellow powder, m.p.210-11 (EtOH), ir: NH, NH_2 3435, 3317, 3203, C=O 1666, 1643 cm^{-1}, ,^1H nmr (DMSO-d_6) δ 1.318 (t, 3H, CH_3, J=7Hz), 3.47 (s, 3H, CH_3), 4.412 (q, 2H, CH_2, J=7Hz), 7.49 (broad exch., 1H, NH), 8.05 (broad exch., 2H, NH_2) 8.468 (s, 1H, ring-H), ms: m/z 207(M^+).

Anal.Calcd. for $C_9H_9N_3O_3$, C, 52.17; H, 4.38; N, 20.28. Found, C, 52.3; H, 4.6; N, 20.4.

5-Cyano-4-methoxy-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid amide (16): A mixture of N-[2,2-dicyano-1-(1-cyano-2-dimethylamino-vinyl)-vinyl]-N,N-dimethyl-formamidine (10) (2.42g, 10mmol), and sodium methoxide (30mL methanol, 0.5g sodium metal) was heated under reflux for about 2h. The reaction mixture was poured on cold water; the solid product was recovered by filtration to give the title compound (16) in yield (1.8, 86.95%) as yellow powder, m.p. 196-8^{o}C (EtOH), ir: NH, NH_2 3430, 3314, 3208, C=O 1664, 1642 cm^{-1}, ,^1H nmr (DMSO-d_6) δ 4.81 (s, 3H, CH_3), 7.47 (broad exch., 1H, NH), 8.10 (broad exch., 2H, NH_2) 8.512 (s, 1H, CH), ms: m/z 207(M^+).

Anal.Calcd. for $C_8H_7N_3O_3$, C, 49.74; H, 3.65; N, 21.75. Found, C, 49.9; H, 3.5; N, 21.9.

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11. X-ray crystal data for methyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate: $C_9H_8N_2O_3$, M = 192.2 pale yellow monoclinic, space group P2/c, a = 6.960 (2), *b* = 13.150 (3), *c* = 9.900 (5) Å, β = 110.339 (3)^o, *V* = 849.3 (5) Å ^{3}, Z = 4, F (000) = 400, D_c = 1.503 Mg m^{-3}, Mo-K□ radiation (graphite monochromator), λ = 0.71073 Å, μ = 0.108 mm^{-1}. The structure was solved by direct methods [SHELXTL PLUS (VMS)] and refined by full matrix least squares to R = 0.0432, wR = 0.0513 for1131 observed [F>4.0σ□(F)] reflections collected using a Siemens R3m/Vdiffractometer operating in the 2 θ range 3.0 to 50.0^o at 233K. Complete listings of atomic coordinates, bond angles and lengths, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England, and are available from there.
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