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3-Diethylaminoacrylonitrile (**1**) reacts with hydrazone halides (**2a-d**) to yield 1,3-disubstituted pyrazole-4-carbonitriles **5a-d**. The acetyl 1-*p*-chlorophenylpyrazole-4-carbonitrile (**5a**) condensed with hydrazine hydrate to yield the bishydrazone **10** and with dimethylformamide dimethylacetal to yield 1-aryl-3-(3-dimethylamino)acryloyl pyrazole-4-carbonitrile (**11**). This enamine reacts with hydrazine hydrate to yield the pyrazolylpyrazole (**12**) and with naphthoquinone to yield the 3-naphthofuranoyl pyrazole **13**. The pyrazolyl pyridine derivative **14** was obtained upon treatment of **11** with acetylacetone in the presence of ammonium acetate. Compound **11** was coupled with *p*-chlorobenzene diazonium chloride to yield the hydrazone **16** that was coupled further with *p*-chlorobenzene diazonium chloride to yield the formazane **18**.

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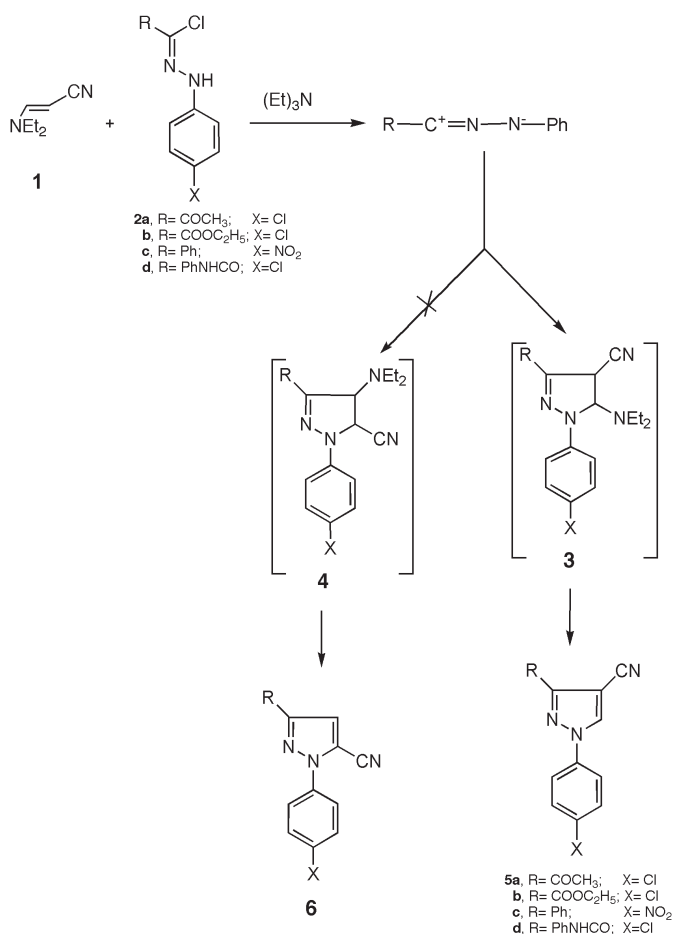
## Introduction.

Functionally substituted enamines are versatile reagents and their chemistry has received in the last fifteen years considerable attention [1-4]. In our previous work aimed at exploring synthetic potentialities of enaminones [5-12] we have reported 1,3-dipolar cycloaddition of nitrileimines to enaminones to yield pyrazoles [13,14]. This reaction was then utilized to prepare several novel pyrazoles and tetrazines [15].

In conjunction of this work we investigated the reaction of enaminonitriles with nitrileimines. We have found that 3-diethylaminoacrylonitrile **1**, the preparation of which has been described in the literature [16], reacts readily with nitrileimines, generated *in situ* from hydrazone halides **2a-e** and triethylamine, to yield products of addition across the double bond affording cycloadducts that subsequently aromatized *via* diethylamine elimination to yield pyrazoles. Two structures seemed possible for these pyrazoles (*cf.* **5** and **6**) depending on regioorientation of the cycloaddition. Thus cycloadduct **3** would afford **5** while cycloadduct **4** would yield **6**.

<sup>1</sup>H NMR and <sup>13</sup>C NMR enabled assignment of structure **5** for these reaction products. Thus <sup>1</sup>H NMR, taking **5a** as a typical example, showed pyrazole ring proton signal at  $\delta$  9.42 ppm, which can only be interpreted for pyrazole H-5. Pyrazole H-4 should appear at a much higher field. Simulated spectra for both structures proposed H-4 in compound **6** to appear at  $\delta$  7.35 ppm while H-5 in compound **5** at 8.17 ppm. <sup>13</sup>C NMR adds further evidence. Thus taking again **5a** as typical example pyrazole C-4 appeared at  $\delta$  92.9 ppm. If the reaction product was **6** again the carbon should appear at much lower field. Spectral simulation for **5** and **6** showed C-4 in **5** to be expected at  $\delta$  98.33 ppm while in isomeric **6** this carbon would be expected at  $\delta$  108.69 ppm. In an attempt to convert **5a** into amino pyrazolo[3,4-*c*]pyrimidine **9** *via* intermediate **8a**, only the bishydrazone **10** was obtained.

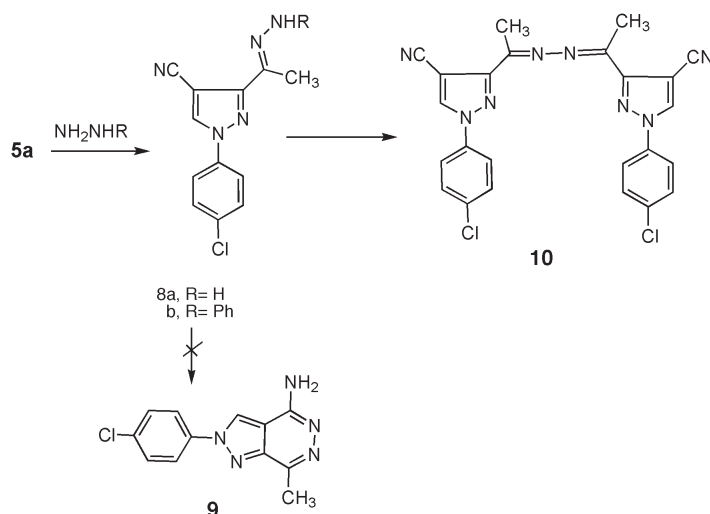
Scheme 1



Condensation with phenylhydrazine afforded only the phenylhydrazone **8b**, which could not be further cyclised.

Compound **5a** condensed with dimethylformamide dimethylacetal to yield the *trans* enaminone **11** as <sup>1</sup>H NMR revealed *trans* olefinic protons at  $\delta$  5.86 and  $\delta$  7.71

Scheme 2

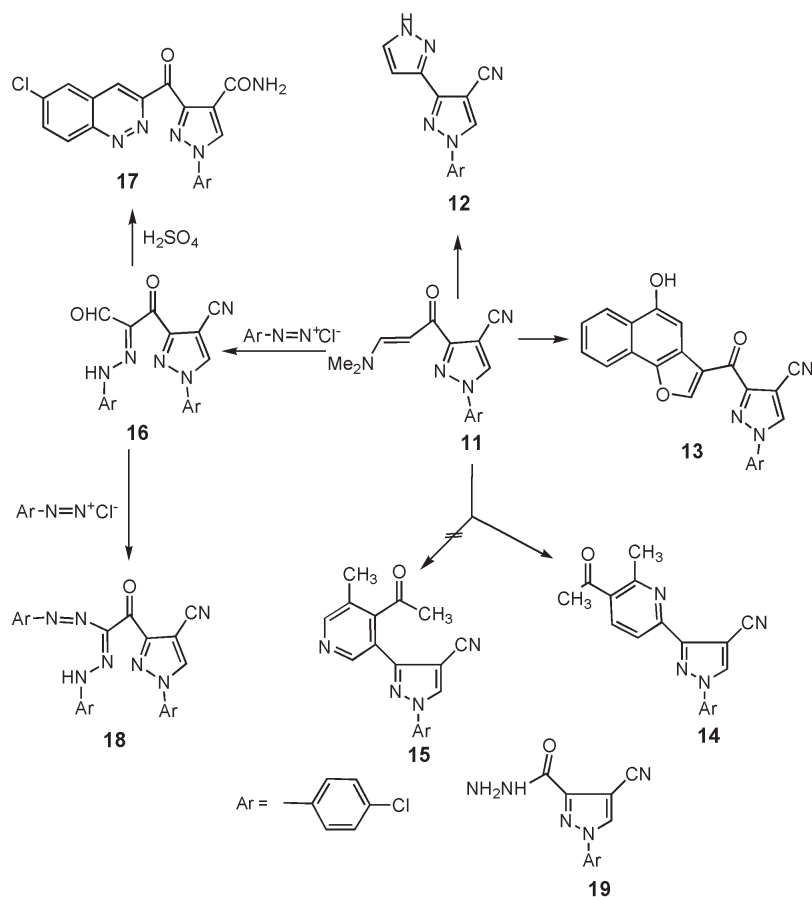


ppm as two doublets with  $J = 16$  Hz. The enaminone **11** reacted readily with hydrazine hydrate to yield the pyrazolopyridine **12**. Typical for the recently reported behavior of enaminones, Compound **11** reacted with naphtho-

quinone to yield naphthofuranylpyrazole **13**.

Reaction of **11** with acetylacetone in refluxing acetic acid and in presence of ammonium acetate has afforded a pyrazolopyridine derivative that may be formulated

Scheme 3



as **14** or isomeric **15**. Structure **14** is assigned for the product based on presence of pyridyl ring protons as doublets at  $\delta$  8.36 and  $\delta$  9.56 ppm with  $J = 8$  Hz. If the reaction product is **15** one would expect [17,18] pyridyl ring protons to have much smaller coupling constant ( $J = 3-4$  Hz).

Similar to reported behavior of enaminones [19] compound **11** also coupled with benzenediazonium chloride to yield the arylhydrazono derivative **16** that could be cyclised into pyrazolylcinnoline **17** on heating with concentrated sulphuric acid. Further coupling with **16** gave the coupling product **18**. Attempts to convert **5b** into a pyrazolopyridazine derivative *via* reaction with hydrazine hydrate afforded only hydrazide **19**.

## EXPERIMENTAL

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-vector 22 spectrophotometer. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in DMSO- $d_6$  and  $\text{CDCl}_3$  as solvent at 200 or 300 MHz on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in  $\delta$  units (ppm). Mass spectra were measured on a Shimadzu GMMS - QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the microanalytical center, Cairo University.

### General Procedure for Preparation of **5a-d**.

A mixture of enaminonitrile **1** (10 mmol), hydrazonyl halide **2a-d** (10 mmol),  $\text{Et}_3\text{N}$  (10 mmol) in ethanol (20 ml) was refluxed for 4 h. The solvent was evaporated under *vacuo* and the crude product was collected and crystallized from ethanol.

### 3-Acetyl-1-(4-chlorophenyl)-1H-pyrazole-4-carbonitrile (**5a**).

This compound was obtained in 72 % yield, mp: 207 °C; IR (KBr):  $\nu$  2238 (CN), 1688  $\text{cm}^{-1}$  (CO); MS (EI):  $m/z$  (%) = 245/247 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 2.57 (s, 3H,  $\text{CH}_3\text{CO}$ ), 7.62- 7.93 (m, 4H, Ar-H), 9.42 ppm (s, 1H, pyrazole H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 26.5 ( $\text{CH}_3$ ), 92.9 (C-4 pyrazole), 112.6 (CN), 121.57, 129.9, 133.1, 136.9, (CH aromatic), 137.5 (C-5 pyrazole), 151.2 (C-3 pyrazole), 191.6 (CO) ppm.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_8\text{ClN}_3\text{O}$  (245.67): C, 58.67; H, 3.28; N, 17.10. Found: C, 58.62; H, 3.30; N, 17.08.

### Ethyl 1-(4-Chlorophenyl)-4-cyano-1H-pyrazole-3-carboxylate (**5b**).

This compound was obtained in 66 % yield, mp: 178- 180 °C; IR (KBr):  $\nu$  2236 (CN), 1725.4  $\text{cm}^{-1}$  (CO); MS (EI):  $m/z$  (%) = 275/277 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 2.26 (t, 3H,  $\text{CH}_3$ ,  $J=7$  Hz), 4.34 (q, 2H,  $\text{CH}_2$ ,  $J=7$  Hz) 7.61- 7.85 (m, 4H, Ar H), 9.48 ppm (s, 1H, pyrazole H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 14.0 ( $\text{CH}_3$ ), 61.72 ( $\text{CH}_2$ ), 95.4 (C-4 pyrazole), 112.1 (CN), 121.5, 129.8, 133.1, 136.7, (CH aromatic), 137.0 (C-5 pyrazole), 144.7 ppm (C-3 pyrazole), 159.2 (CO).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{10}\text{ClN}_3\text{O}_2$  (275.70): C, 56.64; H, 3.66; N, 15.24. Found: C, 56.65; H, 3.61; N, 15.28.

### 1-(4-Nitrophenyl)-3-phenyl-1H-pyrazole-4-carbonitrile (**5c**).

This compound was obtained in 70 % yield, mp: 168 -170 °C; IR (KBr):  $\nu$  2224  $\text{cm}^{-1}$  (CN); MS (EI):  $m/z$  (%) = 290 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 8.47 (d, 2H, H o- to  $\text{NO}_2$ ), 8.23 (d, 2H, H m- to  $\text{NO}_2$ ), 7.58-7.60 (m, 2H, Ph H-3), 7.6-8.3 (m, 3H, Ph H-2,H4), 9.66 (pyrazole H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 94.6 (C-4 pyrazole), 115.7 (CN), 120.1, 121.5, 126.5, 128.8, 129.5, 133.6, 135.2 (C-5 pyrazole), 147.8, 155.2 ppm (C-3 pyrazole).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}_2$  (290.28): C, 66.20; H, 3.47; N, 19.30. Found: C, 66.19; H, 3.42; N, 19.32.

### 1-(4-Chlorophenyl)-4-cyano-1H-pyrazole-3-carboxylic Acid Phenylamide (**5d**).

This compound was obtained in 55 % yield, mp: 236-238 °C; IR (KBr):  $\nu$  3300 (NH), 2241.1  $\text{cm}^{-1}$  (CN); MS (EI):  $m/z$  (%) = 322/324 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 7.15-8.09 (m, 9H, Ar H), 9.491 (s, 1H, pyrazole H), 10.46 (s, 1H, NH,  $\text{D}_2\text{O}$  exhaige).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{11}\text{N}_4\text{ClO}$  (322.76): C, 63.26; H, 3.44; N, 17.36. Found: C, 63.23; H, 3.45; N, 17.38.

### General Procedure for Preparation of Compounds **8b** and **10**.

A mixture of 3-acetyl-1-(4-chloro-phenyl)-1H-pyrazole-4-carbonitrile **5a** (10 mmol) and phenylhydrazine and/or hydrazine hydrate (10 mmol) is refluxed in DMF for 2 hrs. The reaction mixture is then poured on water. The crude product was collected and crystallized from an ethanol/DMF mixture.

### 1-(4-Chlorophenyl)-3-[1-(phenylhydrazono)-ethyl]-1H-pyrazole-4-carbonitrile (**8b**).

This compound was obtained in 79 % yield, mp: 190 °C; IR (KBr):  $\nu$  3348.4 (NH), 2232.2 (CN); MS (EI):  $m/z$  (%) = 335/337 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 2.28 (s, 3H,  $\text{CH}_3$ ), 6.72-7.84 (m, 9H, Ar H), 9.26(s, 1H, pyrazole H), 9.61 (s, 1H, NH);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\nu$  = 12.06 ( $\text{CH}_3$ ), 90.1 (C-4 pyrazole), 113.2 (C-3 pyrazole), 114.7 (CN), 119.7, 120.5, 128.9, 129.6, 131.8, 133.8, 136.4 (CH aromatic), 137.2 (C-5 pyrazole), 145.3 (CH aromatic), 153.8 (C=N).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{14}\text{N}_5\text{Cl}$  (335.80): C, 64.38; H, 4.20; N, 20.86. Found: C, 64.41; H, 4.23; N, 20.83.

### Preparation of 1-[1-(4-Chlorophenyl)-3-cyano-1H-pyrazol-4-yl]-ethanone Azine (**10**).

This compound was obtained in 70 % yield, mp: 320 °C; IR (KBr):  $\nu$  = 2230.3 (CN); MS (EI):  $m/z$  (%) = 487.35/489 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 2.5 (s, 6H,  $2\text{CH}_3$ ), 7.90 – 8.12 (m, 8H, Ar H), 9.70 (s, 2H, CH pyrazole).

*Anal.* Calcd. for  $\text{C}_{24}\text{H}_{16}\text{N}_8\text{Cl}_2$  (487.35): C, 59.15; H, 3.31; N, 22.99. Found: C, 59.20; H, 3.28; N, 22.89.

### Preparation of 1-(4-Chlorophenyl)-3-((E)-3-dimethylaminoacryloyl)-1H-pyrazole-4-carbonitrile (**11**).

A mixture of **5a** and DMFDMA was refluxed in xylene for 3 hrs. The solvent was removed by evaporation under *vacuo*. The solid product was then crystallized from ethanol to give **5a** in 75 % yield, mp: 190 °C; IR (KBr):  $\nu$  = 3092, 3031 (CH olefinic), 2234 (CN), 1642 (CO); MS (EI):  $m/z$  (%) = 300/302 ( $\text{M}^+$ );  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 2.92 (s, 6H,  $2\text{CH}_3$ ), 5.86 (d, 1H, olefinic H,  $J=16$  Hz), 7.61-7.95 (m, 4H, Ar H), 7.71 (d, 1H, olefinic H,  $J=16$  Hz), 9.34 (s, 1H, CH pyrazole);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 45.6 ( $\text{CH}_3$ ), 93.2, 94.1 (C-4 pyrazole), 114.7 (CN), 119.7, 122.2, 130.6, 133.3 (C-5 pyrazole), 137.4, 137.4, 138.1, (C-3 pyrazole), 155.2 (N-C=C), 180.5 (CN).

*Anal.* Calcd. for  $C_{15}H_{13}N_4ClO$  (300.75): C, 59.91; H, 4.36; N, 18.63. Found: C, 59.89; H, 4.33; N, 18.65.

Preparation of 1-(4-Chlorophenyl)-1*H*,1'*H*-[3,3]bipyrazolyl-4-carbonitrile (**12**).

A mixture of enaminone (**11**) with hydrazine hydrate was refluxed in DMF (25 mL) for 3 h. The reaction mixture was then poured on water. The solid that formed was collected by filtration and crystallized from ethanol and DMF to give **12** in 78 % yield, mp: 310 °C; IR (KBr):  $\nu$  2232 (CN); MS (EI):  $m/z$  (%) = 269/271 ( $M^+$ );  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 7.60-8.10 (m, 4H, aromatic H), 8.28 (m, 1H, CH pyrazole), 8.98 (d, 1H, CH pyrazole), 9.38 (s, 1H, CH pyrazole), 13.27 (s, 1H, NH,  $D_2O$  exchange).

*Anal.* Calcd. for  $C_{13}H_8CIN_5$  (269.70): C, 57.90; H, 2.99; N, 25.97. Found: C, 57.81; H, 2.86; N, 26.13.

1-(4-Chlorophenyl)-3-(5-hydroxynaphtho[1,2-*b*]furan-3-carbonyl)-1*H*-pyrazole-4-carbonitrile (**13**).

A mixture of enaminone (**11**) and naphthoquinone was stirred in acetic acid and left over night at room temperature. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from ethanol and DMF. This compound was obtained as brown crystals in 83 % yield, mp: 312 °C; IR (KBr):  $\nu$  3415 (OH), 2239 (CN), 1705.7 (CO); MS (EI):  $m/z$  (%) = 413/415 ( $M^+$ );  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 7.58-8.28 (m, 9H, Ar H), 9.41 (s, 1H, pyrazole), 9.56 (s, 1H, furan H), 10.34 (s, 1H, OH);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  = 95.4 (C-4 pyrazole), 101.1, 114.5 (CN), 120.2, 120.8, 121.7, 122.7, 124.2, 124.6, 125.9, 128.4, 130.6, (CH aromatic), 133.9 (C-5 pyrazole), 137.8, 138.1 (C-3 pyrazole), 145.1, 151.9, 152.9, 155.4, 180.1 (CO).

*Anal.* Calcd. for  $C_{23}H_{12}CIN_3O_3$  (413.82): C, 66.76; H, 2.92; N, 10.15. Found: C, 66.82; H, 2.96; N, 10.09.

Preparation of 3-(5-Acetyl-6-methylpyridin-2-yl)-1-(4-chlorophenyl)-1*H*-pyrazole-4-carbonitrile (**14**).

A mixture of enaminone (**11**) and acetyl acetone was refluxed in acetic acid and ammonium acetate for 2 hrs. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from ethanol. This compound was obtained as yellow crystals in 82 % yield, mp: 220-222 °C; IR (KBr):  $\nu$  2236.2 (CN), 1679.7 (CO); MS (EI):  $m/z$  (%) = 336/338 ( $M^+$ ),  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 2.63 (s, 3H,  $CH_3$ ), 3.30 (s, 3H,  $CH_3$ ), 7.64-8.04 (m, 4H, Ar H), 8.36 (d, 1H, pyridine H,  $J=8$ ), 9.47 (s, 1H, pyrazole H), 9.56 (d, 1H, pyridine H,  $J=8$ );  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  = 25.1 ( $CH_3$ ), 30.4 ( $CH_3$ ), 93.7 (C-4 pyrazole), 114.5 (CN), 118.6, 121.1, 122.4, 130.6, 133.3 (C-5 pyrazole), 138.1, 139.6, 150.4 (C-3 pyrazole), 152.3, 158.1, 201.1 (C=O).

*Anal.* Calcd. for  $C_{18}H_{13}CIN_4O$  (336.78): C, 64.20; H, 3.89; N, 16.64. Found: C, 64.29; H, 3.91; N, 16.72.

Preparation of 1-(4-Chlorophenyl)-3-{2-[(4-chlorophenyl)hydrazono]-3-oxo-propionyl}-1*H*-pyrazole-4-carbonitrile (**16**).

A cold solution of aryldiazonium salt (10 mmol) was prepared by adding a solution of sodium nitrite (0.7 g into 10 mL  $H_2O$ ) to a cold solution of arylamine hydrochloride (10 mmol of arylamine in 5 mL concentrated HCl) with stirring. The resulting solution of aryldiazonium salt was then added to a cold solution of enaminone (**11**) in ethanol (50 mL) containing sodium acetate (1 g). The mixture was stirred and the solid product was collected by filtration and crystallized from ethanol to yield 82 % of **16**,

mp: 217 °C; IR (KBr):  $\delta$  3420 (NH), 2238 (CN), 1704 (CO), 1643 (CHO); MS (EI):  $m/z$  (%) = 411 ( $M^+$ );  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 7.38-7.95 (m, 8H, Ar H), 7.79 (s, 1H, pyrazole H), 9.52 (s, 1H, CHO), 9.93 (s, 1H, NH,  $D_2O$  exchange).

*Anal.* Calcd. for  $C_{19}H_{11}Cl_2N_5O_2$  (412.24): C, 55.36; H, 2.69; N, 16.99. Found: C, 55.25; H, 2.73; N, 17.12.

Preparation of 3-(6-Cinnoline-3-carbonyl)-1-(4-chlorophenyl)-1*H*-pyrazole-4-carboxylic Acid Amide (**17**).

Hydrazonal **16** was heated in  $H_2SO_4$  for 15 minutes. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from ethanol. This compound was obtained as yellow powders in a yield of 80%, mp: 265 °C; IR (KBr):  $\nu$  3420.2, 3331.7 (NH), 1659.8, 1621 (CO); MS (EI):  $m/z$  (%) = 411/413 ( $M^+$ );  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 7.41-8.13 (m, 7H, Ar H), 9.12 (s, 1H, pyrazole H), 9.14 (s, 1H, cinnoline H), 13.61 (s, 2H, NH).

*Anal.* Calcd. for  $C_{19}H_{11}Cl_2N_5O_2$  (412.24): C, 55.36; H, 2.69; N, 16.99. Found: C, 55.45; H, 2.81; N, 16.85.

Preparation of 3-{2-(4-Chlorophenylazo)-2-[(4-chlorophenyl)hydrazono]-acetyl}-1-(4-chloro-phenyl)-1*H*-pyrazole-4-carbonitrile (**18**).

A cold solution of aryldiazonium salt (20 mmol) was prepared by adding a solution of sodium nitrite (1.5 g into 10 mL  $H_2O$ ) to a cold solution of arylamine hydrochloride (20 mmol of arylamine in 10 mL concentrated HCl) with stirring. The resulting solution of aryldiazonium salt was then added to a cold solution of pyrazole (**11**) in ethanol (50 mL) containing sodium acetate (2 g). The mixture was stirred and the solid product was collected by filtration and crystallized from ethanol to give 82 % yield of **18**, mp: 282 °C; IR (KBr):  $\nu$  3448 (NH), 2239 (CN), 1711 (CO); MS (EI):  $m/z$  (%) = 521/523/525 ( $M^+$ );  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 6.53-7.98 (m, 12H, Ar H), 8.80 (s, 1H, CH pyrazole), 9.51 (s, 1H, NH).

*Anal.* Calcd. for  $C_{24}H_{14}Cl_2N_7O$  (522.78): C, 55.14; H, 2.70; N, 18.75. Found: C, 55.23; H, 2.79; N, 18.63.

Preparation of 1-(4-Chlorophenyl)-4-cyano-1*H*-pyrazole-3-carboxylic Acid Hydrazide (**19**).

A mixture of pyrazole ester **5b** and hydrazine hydrate was refluxed in dimethylformamide (DMF) for 3 hr. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from an ethanol-DMF mixture. This compound was obtained as yellow powders in 85% yield, mp: 322 °C; IR (KBr):  $\nu$  3290-3131.6 ( $NH_2$ ), 2244.8(CN), 1704.9 (CO); MS (EI):  $m/z$  (%) = 261/263 ( $M^+$ );  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  = 5.96 (s, 2H,  $NH_2$ ) 7.66-7.96 (m, 4H, Ar H), 9.48 (s, 1H, pyrazole H), 11.190 (s, 1H, NH).

*Anal.* Calcd. for  $C_{11}H_8CIN_5O$  (261.67): C, 50.49; H, 3.08; N, 26.76. Found: C, 50.41; H, 3.18; N, 26.81.

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