STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: ARYLHYDRAZONONITRILES FOR THE SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED AZINES

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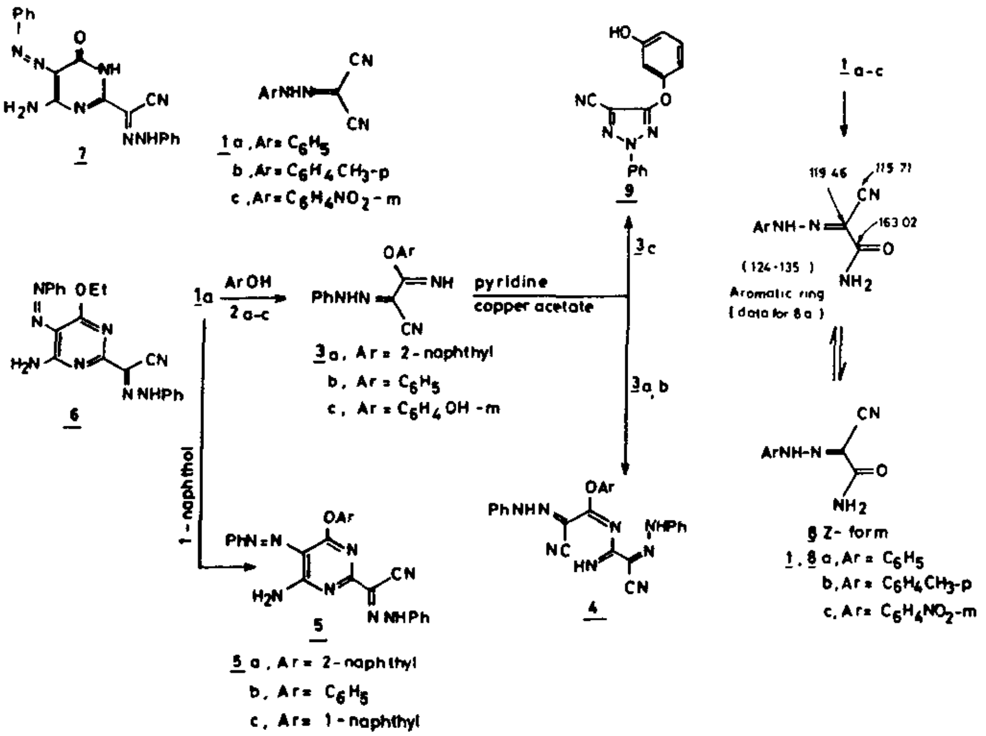
Abstract- The reaction of arylhydrazononitriles with naphthols, phenols and glycine is reported.

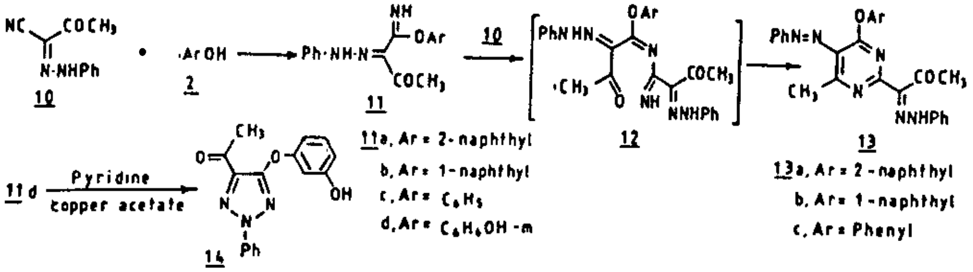
Polyfunctionally substituted heteroaromatics are interesting as potential biodegradable agrochemicals and as intermediates in dye industry.[1] The chemistry of these compounds has recently received considerable interest.[2-4] Although synthetic approaches to azoles and azines are now well documented only very few of such approaches can be adopted for synthesis of polyfunctional heteroaromatics. As a part of our program aimed to developing simple and efficient approaches for synthesis of polyfunctionally substituted heteroaromatics *we have previously developed* several syntheses of polyfunctional azoles and azines utilizing α-arylhydrazononitriles as starting materials.[5-10] In conjunction of this work we report here results of our further investigation on α-arylhydrazononitriles. Thus it has been found that phenylazomalononitrile (**1a**) reacts with 2-naphthol in ethanol, in the presence *of piperidine, to yield the adduct* 1-(2-Naphthyloxy)-2- cyano-2-phenylhydrazonoiminoglyoxalte (**3a**). That is when refluxed in pyridine in presence of copper acetate afforded a product of molecular formula $C_{19}H_{14}N_4O$. Structure **5a** was considered for this product. Compound **5a** is assumed to be formed *via* intermediacy of **4a** which results from condensation of two molecules of **3a** *via* 2-naphthol elimination. However, the reaction of **1a** with 1-naphthol has lead directly to the formation of **5c**. Trials to isolate the corresponding intermediate (**3**) failed. We assumed that the intermediate (**3**) is formed in this reaction, however, it reacts readily further with other molecule of **1a** to yield **5c**. Attempts to effect addition of phenol in ethanolic triethylamine resulted in formation of **6**. Compound (**6**) has been also obtained on refluxing **1a** in ethanolic triethylamine in absence of phenol and its structure has recently been established by Gewald.[11] Attempted addition of phenol to **1a** in refluxing aqueous pyridine resulted in formation of the pyrimidine derivative (**7**). Compound (**7**) is assumed to be formed *via* hydrolysis of the cyano function in **1a** to yield intermediate amide (**8a**). Compound (**8a**) reacts further with **1a** to yield **7**. In absence of solvent, phenol reacts with **1a** at 160°C to yield **3b**. This on reflux in pyridine in presence of copper acetate afforded the pyrimidine derivative (**5b**).

In support of this view compounds (**8a-c**) were prepared *via* refluxing **1a-c** in aqueous acetic acid respectively. The structure of these products was established from spectral data. ^{13}C nmr data revealed existence of these compounds as an equilibrium of E and Z forms. However, both forms could not be separated in pure form.

Similar to the behavior of 1a toward 2- naphthol, 1- naphthol and phenol, compound (1a) reacted with resorcinol to yield adduct (3c). Which on reflux in pyridine in presence of copper acetate afforded the 1,2,3-triazole derivative (9). Cyclization of 3c by this way finds, thus, parallelism to recently reported under the same conditions.[9]

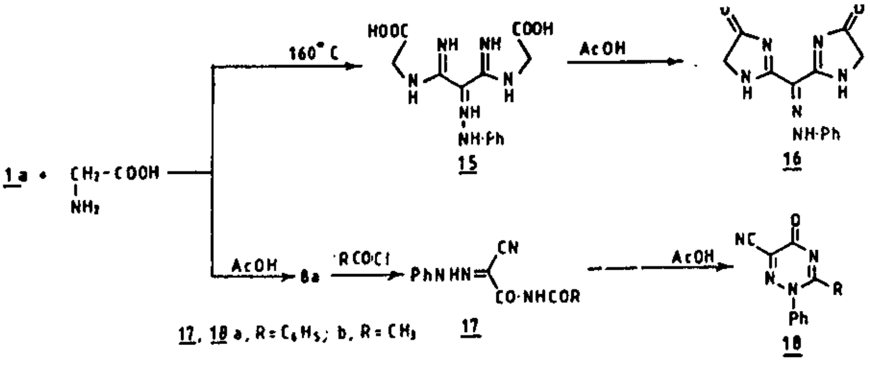


The arylhydrazononitrile derivative (10) also reacted with 2-naphthol, 1-naphthol and phenol to yield the pyrimidine derivatives (13a-c). Compounds (13a-c) are assumed to be formed *via* intermediacy of adducts (11a-c) which readily adds 10 to yield 12a-c. The latter intermediates (12a-c) then cyclize into the final isolable 13a-c. Similar to the behavior of 10 toward 2-*naphthol, 1-naphthol and phenol, compound (10) reacted with resorcinol to* yield the adduct (11d), which on refluxing pyridine in presence of copper acetate afforded the 1,2,3-triazole derivative (14).

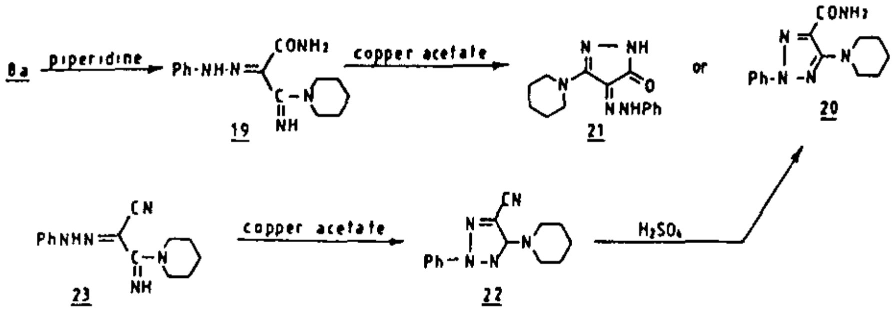


Attempts to add glycine to 1a in refluxing acetic acid resulted only in the formation of the amide 8a. However, when 1a was heated with glycine at 160°C, the diadduct (15) was formed in good yield. Attempts to control the reaction to obtain a monoadduct failed. Similar observation has been recently reported by Gewald[11] on attempted addition of malononitrile to 1a. The diadduct (15) cyclized readily on reflux in glacial acetic acid into the imidazolone derivative (16).

The amide (8a) reacted with benzoyl chloride to yield the benzoyl derivative (17a). This could be cyclized into the 1,2,4-triazine derivative (18a). Similarly, the acetyl derivative (17b) was obtained on acylating 8a with acetyl chloride. This could be smoothly cyclized into the 1,2,4-triazine-3-carbonitrile (18b) on refluxing glacial acetic acid.



The amide (8a) reacted with piperidine to yield the piperidine (19). This cyclized into the 1,2,3-triazole derivative (20) or (21) on refluxing pyridine in presence of copper acetate. Structure (20) was established by synthesis of the same compound *via* cyclizing (23) into (22) and treatment of latter product with H_2SO_4.



EXPERIMENTAL

All melting points are uncorrected. ir spectra were obtained in KBr discs on Pye Unicam SP 1100 spectrophotometer. ^{1}H-nmr spectra were measured in DMSO, TMS as internal standard on Varian EM 360 nmr spectrometer (90 MHz). Microanalysis were performed by the Microanalytical Units at Cairo University.

Reaction of Ia with 2-naphthol, 1-naphthol and resorcinol: formation of 3a, 3c and 5b. General procedure:

Equimolecular amounts of 1a (1.7g, 0.01 mol) and each of the corresponding arylols (0.01 mol) in ethanol (50 ml) were treated with few drops of piperidine. The reaction mixture was refluxed for 3h. The product so formed on cooling was collected by filtration and recrystallized from the proper solvent.

1-[2-Naphthyloxy]-2-cyano-2-phenylhydrazonoiminoglyoxalate (3a).

Yield black crystals from dioxane, 80% yield, mp 205°C; ir 3350-2240 cm^{-1} (NH) and 2220 cm^{-1} (CN). Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.83. Found: C, 72.70; H, 4.62; N, 17.25.

Resorcinyl-2-cyano-2-phenylhydrazonoiminoglyoxalate (3c).

Yield black crystals from dioxane, 75% yield, mp > 300°C; ir 3550-3500 cm^{-1} (OH) 3340-3250 cm^{-1} (NH) and 2200 cm^{-1} (CN). Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 54.30; H, 4.30; N, 20.00.

2-Phenylhydrazono-2-[4-amino-5-phenylazo-6-(1-naphthyloxy)pyrimidin]-2-ylglyoxalonitrile (5b).

Yield green crystals from ethanol, 75% yield, mp 215°C; ir 3340-2260 cm^{-1} (NH) and 2200 cm^{-1} (CN). Anal. Calcd for $C_{28}H_{20}N_8O$: C, 69.40; H, 4.16; N, 23.12. Found: C, 69.66; H, 4.26; N, 23.22.

Phenyloxy-2-cyano-2-phenylhydrazononiminoglyoxalate (3b).

A mixture of equimolecular amounts of **1a** (1.7 g, 0.01 mol) and phenol (0.94 g, 0.01 mol) was heated in oil bath at 160°C for 1h. The reaction mixture was poured into water and the solid product so formed was collected by filtration and recrystallized from ethanol to yield green crystals, 1.8 g, 70% yield, mp 260°C, ir 3420-2250 cm^{-1} (2NH) and 2210 cm^{-1} (CN). Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.18; H, 4.54; N, 21.21. Found: C, 68.20; H, 4.60; N, 21.41.

Preparation of compounds (5a,c and 9). General Procedure:

2 gm of **3a-c** were refluxed in pyridine (20 ml) in presence of copper acetate (0.2 g) for 2 h. The reaction mixture was poured on ice water and neutralized by HCl. The solid product so formed was crystallized from the proper solvent.

2-Phenylhydrazono-2-[4-amino-5-phenylazo-6-(2-naphthoxy)pyrimidin]-2-ylglyoxalonitrile (5a).

Black crystals from dioxane; 57% yield, mp 235°C ; ir 3450-2250 cm^{-1} (NH) and 2200 cm^{-1} (CN). Anal. Calcd for $C_{28}H_{20}N_8O$: C, 69.40; H, 4.16; N, 23.12. Found: C, 69.52; H, 4.21; N, 23.22.

2-Phenylhydrazono-2-(4-amino-5-phenylazo-6-phenoxypyrimidin)-2-ylglyoxalonitrile (5c).

Green crystals from ethanol, 90% yield, mp 290°C; ir 3400-3300 cm^{-1} (NH_2); 3300-3220 cm^{-1} (NH_2) ; 2215 cm^{-1} (CN). Anal. Calcd for $C_{24}H_{18}N_8O$: C, 66.14; H, 4.17; N, 25.79. Found: C, 66.40; H, 4.20; N, 25.85.

2-Phenyl-5-resorcinolyloxy-1,2,3-triazol-3-carbonitrile (9).

Black crystals from ethanol 80% yield, mp 260°C; ir 2210 cm^{-1} (CN). Anal. Calcd for $C_{15}H_{10}N_4O_2$. C, 64.74; H, 3.62; N, 20.14. Found: C, 64.76; H, 3.65; N, 20.31.

2-Phenylhydrazono-2-(4-amino-5-phenylazo-6-ethoxypyrimidin)-2-ylglyoxalonitrile (6).

A solution of equimolecular amounts of **1a** (1.7 g, 0.01 mol) and phenol (0.94 g, 0.01 mol) in ethanol (50 ml) was treated with little amount of triethylamine, then refluxed for 3 h. The solid product so formed was collected by filtration and recrystallized from ethanol to yield brown crystals (mp and mixed mp). This product proved identical with a sample of 6 prepared after procedure reported by Gewald[11] (identified was made by mp and mixed mp).

2-Phenylhydrazono-2-(4-amino-5-phenylazo-6-oxo-1,6-dihydropyrimidin)-2-ylglyoxalonitrile (7).

A solution of equimolecular amounts of **1a** (1.7 g, 0.01 mol) and phenol (0.94, 0.01 mol) was refluxed in aqueous pyridine for 3h. The reaction mixture was poured on ice water and the solid product so formed was collected by filtration and crystallized from dioxane to yield brown crystals, 80% yield, mp 240°C, ir 3450-3350 cm^{-1} (NH_2) ; 3300-3250 cm^{-1} (NH) ; 2200 cm^{-1} (CN) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{18}H_{14}N_8O$: C,60.32 ; H, 3.93; N, 31.27. Found: C, 60.40; H, 4.10; N, 31.35.

Preparation of compounds (8a-c).

2 g of each of the corresponding arylhydrazononitriles (1a-c) in aqueous acetic acid (30 ml) were refluxed for 2 h. The solid product so formed on cooling was collected by filtration and recrystallized from the proper solvent to give the corresponding amides (8a-c).

2-cyano-2-phenylhydrazonoglyoxalic acid amide (8a).

Brown crystals from ethanol, 95% yield, mp 245°C; ir 3490-3380 cm^{-1} (NH_2); 3300-3150 cm^{-1} (NH), 2200 cm^{-1} (CN) and 1650 cm^{-1} (CO); ^{13}C nmr (cf.formula).

Anal. Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.29; N, 29.77. Found: C, 57.52; H, 4.41; N, 30.00.

2-Cyano-2-*p*-tolylhydrazonoglyoxalic acid amide (8b).

Green crystals from ethanol, 92.5% yield, mp 240°C; ir 3450-3370 cm^{-1} (NH_2); 3350-3200 cm^{-1} (NH); 2200 cm^{-1} (CN) and 1660 cm^{-1} (CO), Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.39; H,6 4.98; N, 27.71. Found: C, 59.46; H, 5.00; N, 27.92.

2-Cyano-2-(*m*-nitrophenyl)hydrazonoglyoxalic acid amide (8c).

Green crystals from ethanol; 85% yield; mp 225°C; ir 3460-3380 cm^{-1} (NH_2); 3350-3300 cm^{-1} (NH); 2210 cm^{-1} (CN) and 1645 cm^{-1} (CO). ^1H nmr 7.5-8.5 ppm (m, 6H, aromatic H and NH_2); 12.2 ppm (s, 1H, NH). Anal. Calcd for $C_9H_7N_5O_3$: C, 46.35 ; H, 3.03 ; N, 30.04. Found: C, 46.41; H, 3.00; N, 30.20.

Reaction of 10 with 2-naphthol, 1-naphthol, phenol and resorcinol.

A solution of equimolecular amounts of 10 (0.01 mol) and each of the corresponding naphthols, phenol and resorcinol (0.01 mol) were heated in oil bath at 120°C for 1 h. The reaction mixture was poured on water and the solid product so formed was collected by filtration and crystallized from the proper solvent to give **11a-d**

(2-Naphthyl)-2-acetyl-2-phenylhydrazonoiminobutyroate (11a).

Green crystals from dioxane, 78% yield, mp >300°C; ir 3320-3250 cm^{-1} (2NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.60; H, 5.25; N, 12.70.

(1-Naphthyl)-2-acetyl-2-phenylhydrazonoiminobutyroate (11b).

Green crystals from ethanol 70% yield, mp 282°C, ir 3320-3250 cm^{-1} (2NH) and 1650 cm^{-1} (CO). Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.55; H, 5.32; N, 12.51.

Phenyl-2-acetyl-2-phenylhydrazonoiminobutyroate (11c).

Dark green crystals from dioxane,80% yield mp 300°C, ir 3380-3300 cm^{-1} (2NH) and 1660 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.40; H, 5.50; N, 15.00.

Resorcinyl-2-acetyl-2-phenylhydrazonoiminobutyroate (11d).

Black crystals from ethanol, 80% yield, mp 240°C, ir 3550 cm^{-1} (OH), 3340-3290 cm^{-1} (2NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.08; N, 14.13. Found: C, 64.75; H, 5.12; N, 14.26.

Preparation of 13a-*c* and 14.

2 gm of 11a-d were refluxed for 2h in pyridine (20 ml) in presence of copper acetate (0.2 g). The reaction mixture was poured on cold water and neutralized by dil. HCl. The solid product so formed was collected by filtration and crystallized from the proper solvent.

1-[4-Methyl-5-phenylazo-6-(2-naphthyloxy)pyrimidin]-2-yl-2-oxobutanol-1-phenylhydrazone (13a):

Black crystals from DMF, 76% yield, mp >300°C; ir 3250-3150 cm^{-1} (NH) and 1655 cm^{-1} (CO). Anal. Calcd for $C_{30}H_{24}N_6O_2$: C, 71.98; H, 4.83; N, 16.79. Found: C, 72.20; H, 5.00; N, 16.94.

1-[4-Methyl-5-phenylazo-6-(1-naphthyloxy)pyrimidin]-2-yl-2-oxobutanol-1-phenylhydrazone (13b).

Green crystals from dioxane, 79% yield, mp 280°C; ir 3350-3280 cm^{-1} (2NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{30}H_{24}N_6O_2$: C, 71.98; H, 4.83; N, 16.79. Found: C,72.20; H, 5.00; N, 16.94.

1-(4-Methyl-5-phenylazo-6-phenyloxypyrimidin)-2-yl-1-phenylhydrazone (13c).

Red crystals from ethanol, 85% yield, mp 250°C, ir 3350-3300 cm^{-1} (NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{26}H_{20}N_6O_2$: C, 69.63; H, 4.50; N, 18.74. Found: C, 69.81; H, 4.50; N, 18.85.

2-Phenyl-5-Resorcinyloxy-1,2,3-triazole-3-acetylate (14).

Black crystals from ethanol, 75% yield, mp 260°C; ir 3300-3200 cm^{-1} (NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.81; H, 4.27; N, 15.12.

Reaction of 1a with glycine: Formation of 15.

A solution of equimolecular amounts of **1a** (1.7 g, 0.01 mol) and glycine (0.01 mol)was heated *in oil* bath at 160°C for 1 hour. The reaction mixture was poured on water and the solid product so formed was collected by filtration and crystallized from DMF to yield brown crystals; 80% yield, mp >300°C; ir 3550 cm^{-1} (OH); 3350-3200 (NH) and 1620 cm^{-1} (CO). Anal. Calcd for $C_{13}H_{16}N_6O_4$: C, 48.74; H, 5.04; N, 26.24. Found: C, 48.91; H, 5.22; N,26.35.

Preparation of imidazolone derivative (16).

2.0 g of **15** in acetic acid were refluxed for 3h. The reaction mixture was poured on ice water and the solid product so formed was collected by filtration and crystallized from dioxane to yield black crystals in 90% yield, mp >300°C, ir 3350-3200 cm^{-1} (NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{13}H_{12}N_6O_2$: *C, 54.92; H, 4.26; N, 29.57. Found: C, 55.00; H, 4.35; N, 29.81.*

Reaction of 8a with acid chlorides: Formation of 17a,b. General procedure:

A mixture of equimolecular amounts of **8a** 1.88 g (0.01 mol) was refluxed in pyridine for 3h. The reaction mixture was poured on ice water and neutralized by dil. HCl. The solid product so formed was collected by filtration and crystallized from the proper solvent.

Compound (17a).

Red crystals from ethanol, 80% yield, mp 260°C, ir 3300-3200 cm^{-1} (NH) and 1600 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.82; H, 4.21; N, 19.13.

Compound (17b).

Brown crystals from ethanol, 82% yield mp 275°C;ir 3350-3260 cm^{-1} (NH) and 1655 cm^{-1} (CO). Anal. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.42; H, 4.50; N, 24.48.

Preparation of triazinone derivative (18a,b). General procedure:

2 g of each of **17a,b** in acetic acid were refluxed for 3 h. The reaction mixture was poured on ice water and the solid product so formed was collected by filtration and crystallized from the proper solvent.

2,3-Diphenyl-6-oxo-1,3,4-triazine-5-carbonitrile (18a).

Buff crystals, 85% yield; mp 300°C;ir 2210 cm^{-1} (CN) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.68; N, 20.43. Found: C, 70.20; H, 3.80; N, 20.50.

2-Methyl-6-oxo-3-phenyl-1,3,4-triazine-5-carbonitrile (18b).

Red crystals, 80% yield; mp 295°C; ir 2200 cm^{-1} (CN) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.40; H, 4.00; N, 26.55.

1-Imino-1-piperidyl-2-phenylhydrazonoglyoxalic acid amide (19).

A mixture of **8a** (1.88 g, 0.01 mol) and piperidine (x ml, 0.01 mol) in methanol (50 ml) was refluxed for 30 min. The solid product so formed was collected by filtration and crystallized from ethanol to yield brown crystals, 75% yield, mp 280°C, ir 3400-3350 cm^{-1} (NH) and 1650 cm^{-1} (CO). Anal. Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.70; H, 6.91; N, 25.91.

2-Phenyl-5-piperidyl-1,2,3-triazol-4-carboxylic acid amide (20).

Method (A) 2.0 g of **19** was refluxed in pyridine in the presence of copper acetate for 30 min. The reaction mixture was poured on ice water and neutralized by dil. HCl. The solid product so formed was collected by filtration and crystallized from ethanol to yield black crystals, 1.6 g; 80% yield, mp >300°C; ir 1640 cm^{-1} (CO). Anal. Calcd for $C_{14}H_{17}N_5O$: C, 61.77; H, 5.60; N, 25.64. Found: C, 61.77; H, 5.60; N, 25.64.

Method (B): 2.0 g of compound (**22**) was dissolved in sulfuric acid and heated gently for 15 min. The reaction mixture was poured on water. The solid product so formed was collected by filtration and crystallized from ethanol to yield

20 as black crystals; (mp and mixed mp).

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