# Functionally substituted enamines as building blocks in heterocyclic synthesis: reactivity of glyoxal diphenylhydrazone toward electrophilic reagents

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Glyoxalbis(phenylhydrazone) **1a** reacts with aromatic aldehydes and secondary amines to yield either propan-1,2-dialdiphenylhydrazones **2** or arylazopyrazoles **7** depending on the nature of utilised aldehyde. The reactivity of **1a** with phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF) (Vilsmeier reaction) afforded the cinnolin-3-carbaldehyde phenylhydrazone **11**. Compound **1a** afforded also the tribenzoyl derivative **16** on treatment with benzoyl chloride. Only the diacetyl derivative **17** was produced on refluxing **1a** in acetic anhydride. The diphenylhydrazone **20** was produced on treatment of **19**, prepared *via* coupling **18** with benzenediazonium chloride followed by phenylhydrazine. This cyclised into pyrazole **21** on reflux in acetic acid.

**Keywords:** glyoxalbis(phenylhydrazone), phenylazopyrazole, aminocinnoline, Vilsmeier–Haack reaction

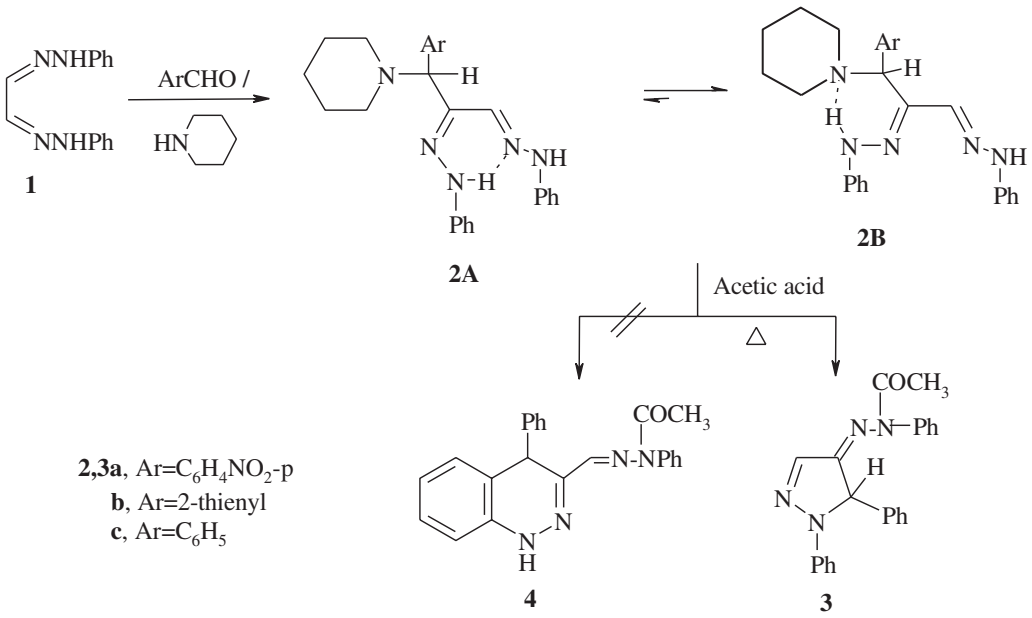
In 1954 Stork[1] reported that cyclohexanone reacted with pyrrolidine to give condensation products that were termed 'enamines' by Wittig and Blumenthal.[2] They readily reacted with electrophiles at β-carbon a reactivity pattern that found extensive the organic synthesis.[3] In previous work from our laboratories we have explored utility of reactivity of several functionally substituted enamines toward electrophiles and nucleophiles as a route to heteroaromatics.[4-8] Aldehyde hydrazones are azaenamines and the aldehydic CH is thus electron rich. Reactivity of aldehyde hydrazones toward electrophiles has only recently been investigated.[9-12]

## Results and discussion

In conjunction with our interest in developing simple routes to heterocycles utilising inexpensive starting materials *via* simple high yield routes[13,14] we report here on reactivity of glyoxal bis(phenylhydrazone) **1a** toward electrophiles as a route to functionally substituted heteroaromatics. Thus, compound **1a** readily reacted with benzaldehyde and piperidine to yield the alkylated product, which was shown from $^1$H NMR to exist, at least in DMSO solution as a mixture of **2A** and **2B** respectively. Thus the $^1$H NMR showed two signals at δ 4.00 and 5.01 where the high field signal was attributed to the hydrogen at C-3 of **2A** and the low field signal for **2B**. Again four low field NH signals were observed at δ 10.24, 10.74 12.13 and 12.37. The low field signals are attributed to hydrogen bonded NH in **2A** and **2B** while the high fields are attributed to the non bonded one in **2A** and two weakly bonded in **2B** (Scheme 1).

Prolonged reflux of **2** in acetic acid resulted in conversion into **3** while reflux in pyridine afforded **7c**. In contrast, *p*-nitrobenzaldehyde and piperidine reacted with **1a** to yield directly **7a**. It is believed that the formed Mannich base initially undergoes elimination of piperidine to yield the enazo derivative **5**. This then is cyclised into the dihydropyrazole **6** that is auto-oxidised to **7**. Similarly, **1a** reacted with thiophene-2-carbaldehyde and piperidine to yield **7b.** Possible conversion of **2** into the cinnoline **8** was also considered but readily ruled out based on $^1$H NMR which revealed the absence of NH absorption in **7a–c** (Scheme 2).

Compound **1a** reacted with $POCl_3$/DMF (Vilsmeier–Haack reaction) to yield a product that may be formulated as the phenylazopyrazole **10** or cinnoline **11**. Both can be formed




**Scheme 1**

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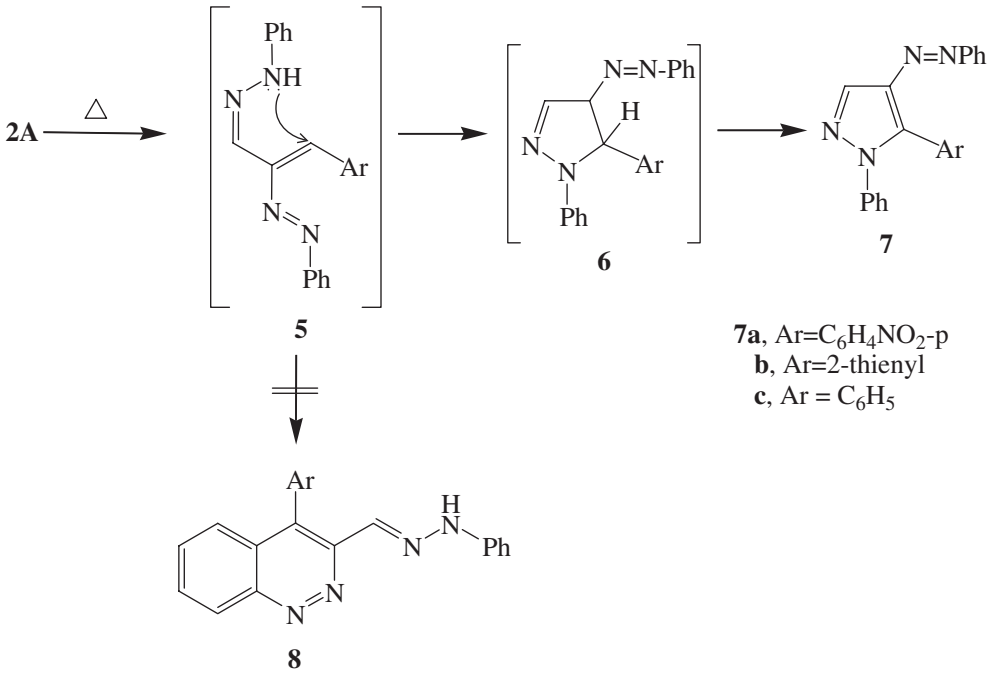



**Scheme 2**

from common intermediate **9** (Scheme 3). Structure **11** was confirmed based on IR and $^1$H NMR spectra. Thus, IR of the reaction product revealed NH band at 3301 cm$^{-1}$. Also $^1$H NMR revealed a $D_2O$ exchangeable signal at δ 3.33 ppm. Cyclisation of arylhydrazones in acid media into cinnolines has been reported from our laboratories[15] (Scheme 3).

Attempts to acylate **1b** resulted in formation of aminocinnoline **14** formed *via* initial conversion of **1b** into acetyl derivative **12** that then undergo thermal elimination of *p*-nitroacetanilide to yield nitrile **13** that cyclised into **14**. Similar conversion of hydrazones to nitriles has been recently reported by one of us[16] (Scheme 4).

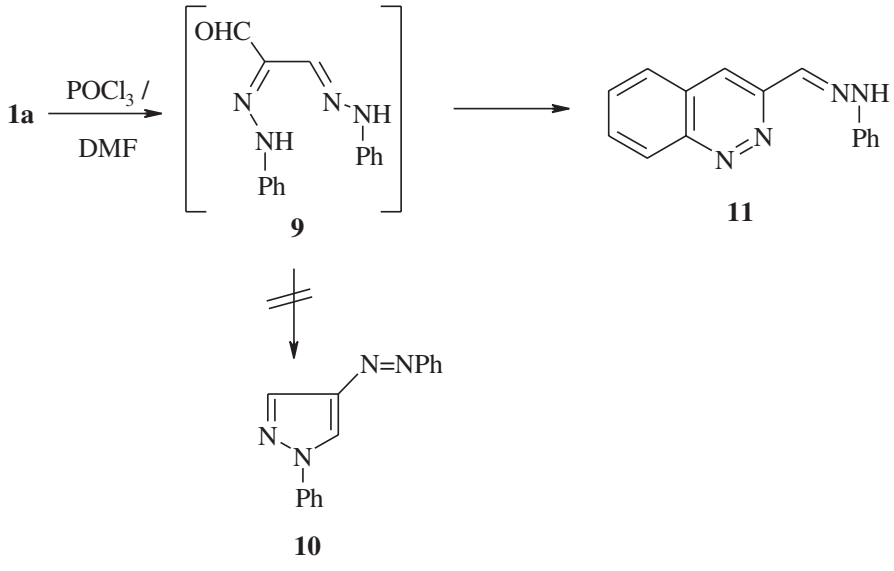
Compound **1a** afforded a tribenzoyl derivative on benzoylation with excess of benzoyl chloride. This was formulated as **16**, rather than **15** on basis of $^1$H NMR and IR that revealed the absence of NH signal and band. Refluxing **1a** in acetic anhydride afforded the diacetyl derivative **17** whose structure was inferred from spectral data.

The C-acetylated derivative **20** was prepared *via* coupling **18** with benzenediazonium chloride and subsequent treatment of the reaction product with phenylhydrazine to yield **20**. This cyclised into **21** on reflux in acetic acid (Scheme 5).

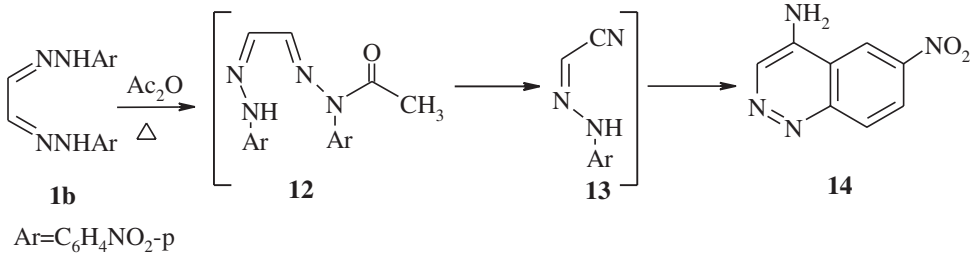
In conclusion, aldehyde hydrazones are reactive toward electropiles. When the aromaticity of the formed product is a driving force, no special substitution pattern is required, as with previous studies on aldehyde hydrazones.

## Experimental

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Pye Unicam SP-3000 IR spectrophotometer and Testscan Shimadzu FT-IR 8000 series. $^1$H and $^{13}$C NMR spectra were recorded on Varian EM 390 spectrometers with DMSO-$d_6$ as solvent and TMS as an internal standard; chemical shifts (δ) are reported in ppm. Mass spectra were measured on a GCMS-QP 1000-EX Shimadzu. Elemental analyses were carried out at the microanalytical center, University of Cairo, Giza, Egypt.




**Scheme 3**




**Scheme 4**

*2-Oxo-3-phenyl-3-(piperidin-1-yl)propanal bis(phenylhydrazone)* (**2**): A mixture of gloxal bis(phenylhydrazone) (2.38 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and piperidine (2.55 g, 30 mmol) was refluxed for 2h. The reaction mixture was then poured into water, and then triturated with dilute HCl. The solid product, so formed, was collected by filtration and crystallised from ethanol. Yield: 2.72 g (66%), m.p. 176–177 °C. IR (KBr): $\nu_{max}$/cm$^{-1}$ 3301 (NH), 3447 (NH). MS: *m/z* = 411 ($M^+$). $^1$H NMR (DMSO-$d_6$) (there are extra hydrogen indicating the presence of more than one isomer; signals for the hydrogen of the predominant isomer are underlined): δ = 1.75–1.85 (m, 10H, piperidine-H), 2.38–2.46 (m, 10H, piperidine-H), 4.00 (s, 0.2H, CH-3), 5.01 (s, 0.8H, CH-3), 7.03–7.54 (m, 30H, 2Ar–H), 7.55 (s, 0.8H, CH-1), 8.23 (s, 0.2H, CH-1), 10.24 (s, 0.8H, NH), 10.74 (s, 0.2H, NH), 12.13 (s, 0.8H, NH), 12.36 (s, 0.2H, NH). $^{13}$C NMR (DMSO-$d_6$): (there are extra carbon indicating the presence of more than one isomer; signals for the carbon of the predominant isomer are underlined): δ = 24.55, 26.43, 26.54, 27.09, 47.32, 52.81, 53.16, 69.98, 112.59, 112.75, 113.41, 119.48, 120.31, 120.65, 120.96, 122.64, 125.97, 128.15, 128.28, 128.99, 129.08, 129.30, 129.90, 130.03, 130.09, 130.22, 131.14, 138.45, 138.66, 141.33, 144.96, 145.77. Anal. Calcd for $C_{26}H_{29}N_5$ (411.49): C, 75.88; H, 7.10; N, 17.02. Found: C, 75.85; H, 7.10; N, 17.00 %.

*1,5-Diphenyl-2-pyrazolin-4-one acetyl(phenyl)hydrazone* (**3**): A suspension of **2** (4.11 g, 10 mmol) in glacial acetic acid (30 ml) was refluxed for 24 h. The reaction mixture was left to cool, and then poured into cooled water. The solid product, so formed, was collected by filtration and crystallised from dimethylformamide. Yield: 2.06 g (56%), m.p. 287–289 °C**.** IR (KBr): $\nu_{max}$/cm$^{-1}$ 1669 (C=O). MS: *m/z* = 368 ($M^+$). Insoluble in common $^1$H NMR solvents**.** Anal. Calcd for $C_{23}H_{20}N_4O$ (368.39): C, 74.98; H, 5.47; N, 15.21. Found: C, 74.95; H, 5.45; N, 15.22 %.

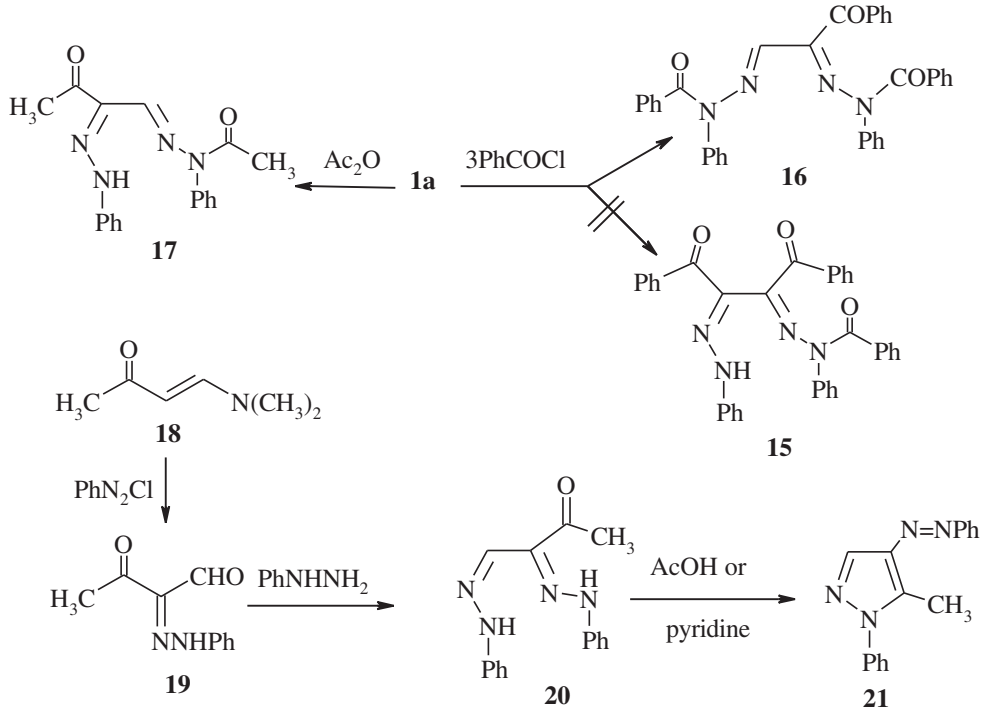
*General procedure for the preparation of [5-Aryl-1-phenyl-1H-pyrazol-4-yl]-phenyldiazene* **7a,b**: A mixture of glyoxalbis(phenylhydrazone) **1a** (2.38 g, 10 mmol), aldehydes derivatives (10 mmol), and piperidine (2.55 g, 30 mmol) was refluxed for 2h, The reaction mixture was then poured into water, and then triturated with dilute HCl. The solid product, so formed, was collected by filtration and crystallized from ethanol.

*[5-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl]-phenyldiazene* (**7a**): Yield: 2.32 g (63%), m.p. 191–193 °C. MS: *m/z* = 369 ($M^+$). Insoluble in common $^1$H NMR solvents. Anal. Calcd for $C_{21}H_{15}N_5O_2$ (369.34): C, 68.29; H, 4.09; N, 18.96. Found: C, 68.25; H, 4.03; N, 18.96 %.

Phenyl(1-phenyl-5-thiophen-2-yl-1*H*-pyrazol-4-yl)diazene (**7b**): Yield: 2.08 g (63%), m.p. 122–124 °C. MS: *m/z* = 330 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ = 7.07–7.85 (m, 13H, Ar–H), 8.16 (s, 1H, pyrazole-3-H). $^{13}$C NMR (DMSO-$d_6$): δ = 122.19, 122.30, 126.58, 127.51, 127.65, 128.97, 129.50, 129.55, 129.93, 130.73, 130.85, 137.69, 138.27, 139.27, 152.70. Anal. Calcd for $C_{19}H_{14}N_4S$ (330.31): C, 69.08; H, 4.27; N, 16.96. Found: C, 69.05; H, 4.25; N, 16.95 %.

*(1,5-Diphenyl-1H-pyrazol-4-yl)phenyldiazene* (**7c**): A suspension of compound **2** (4.11 g,10 mmol) in pyridine (30 ml) was refluxed for 3 h, then poured onto cooled water and triturated with dil HCl. The solid product, so formed was collected by filtration and crystallised from ethanol. Yield: 2.04 g (63%), m.p. 124–126 °C. MS: *m/z* = 324 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ = 7.17–7.80 (m, 15 H, Ar–H), 8.06 (s, 1H, pyrazole-3-H). Anal. Calcd for $C_{21}H_{16}N_4$ (324.33): C, 77.76; H, 4.96; N, 17.27. Found: C, 77.75; H, 4.95; N, 17.25 %.

*Cinnoline-3-carbaldehyde phenylhydrazone* (**11**): A mixture of **1a** (15 mmol) in anhydrous dimethylformamide (10 ml) and the Vilsmeier-Haack reagent (9.0 g, 30 mmol) was refluxed at 70 °C for 1h. After cooling, the mixture was pour onto ice. Then to the clear solution was add carefully dilute aqueous sodium hydroxide solution under cooling until a pH value of 8–9 was reached the precipitated




**Scheme 5**

and crystallised from ethanol. Yield: 1.97 g (53%), m.p. 150–152 °C. IR (KBr): $\nu_{max}$/cm$^{-1}$ 3301 (NH). MS: *m/z* = 248 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ = 3.33 (s, 1H, NH), 7.37–7.99 (m, 9H, Ar–H), 8.27 (s, 1H, CH), 9.35 (s, 1H, cinnolin-4-H). $^{13}$C NMR (DMSO-$d_6$): δ = 118.74, 122.01, 126.29, 127.25, 129.48, 129.71, 130.84, 133.39, 139.17, 142.48, 152.35. Anal. Calcd for $C_{15}H_{12}N_4$ (248.28): C, 72.56; H, 4.87; N, 22.56. Found: C, 72.55; H, 4.83; N, 22.55 %.

*6-Nitrocinnolin-4-ylamine* (**14**): A solution of **1b** (3.28 g, 10 mmol), in acetic anhydride (20 ml) was refluxed for 3 h. The reaction mixture was cooled and the solid that separated was collected and crystallised from dimethylformamide. Yield: 1.06 g (56%), m.p. 302–303 °C. IR (KBr): $\nu_{max}$/cm$^{-1}$ 3309, 3269 ($NH_2$). MS: *m/z* = 190 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ = 3.55 (br., 2H, $NH_2$), 7.11 (d, 1H, *J*=9Hz, cinnolin-8-H), 7.82 (s, 1H, cinnolin-3-H), 8.13 (d, 1H, *J*=9Hz, cinnolin-7-H), 11.51 (s, 1H, cinnolin-5-H). $^{13}$C NMR (DMSO-$d_6$): δ =111.68, 126.14, 126.17, 139.04, 139.08, 140.61, 140.65, 149.77. Anal. Calcd for $C_8H_6N_4O_2$ (190.15): C, 50.53; H, 3.18; N, 29.46. Found: C, 50.55; H, 3.15; N, 29.44 %.

*2,3-Bis[benzoyl(phenyl)hydrazono]-1-phenylpropan-1-one* (**16**): To a solution of **1a** (2.38 g, 10 mmol) in pyridine (10 ml) benzoyl chloride (1.4 g, 30 mmol) was added. The reaction mixture was refluxed for 2 h, then cooled and poured onto cold hydrochloric acid (10 ml, 10%) with stirring. The solid that precipitated was collected, washed with cold water and finally crystallised from dimethylsulfoxide. Yield: 3.47 g (63%), m.p. 314–316 °C. IR (KBr): $\nu_{max}$/cm$^{-1}$ 1670 (C=O). MS: *m/z* = 551 ($M^+$). Insoluble in common $^1$H NMR solvents. Anal. Calcd for $C_{35}H_{26}N_4O_3$ (550.56): C, 76.35; H, 4.76; N, 10.18. Found: C, 76.35; H, 4.72; N, 10.17 %.

*4-[Acetyl(phenyl)hydrazono]-3-(phenylhydrazono)butan-2-one* (**17**): A solution of **1a** ( 2.38 g, 10 mmol), in acetic anhydride (20 ml) was refluxed for 3 h. the reaction mixture was cooled and the solid that separated was collected and crystallised from acetic acid. Yield: 1.80 g (56%), m.p. 314–316 °C. IR (KBr): $\nu_{max}$/cm$^{-1}$ 1690 (C=O), 3366 (NH). MS: *m/z* = 322 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ = 2.27 (s, 3H, $CH_3CO$), 2.38 (s, 3H, $CH_3CO$), 6.84 (s, 1H, CH-4), 7.14–7.22 (m, 5H, Ar–H), 7.52–7.63 (m, 5H, Ar–H), 10.71 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$): δ 22.63, 24.33, 112.99, 120.53, 129.68, 129.79, 129.91, 130.18, 130.79, 130.92, 135.09, 138.78, 138.95, 139.19, 139.28, 144.56. Anal. Calcd for $C_{18}H_{18}N_4O_2$ (322.33): C, 67.07; H, 5.62; N, 17.38. Found: C, 67.06; H, 5.60; N, 17.35 %.

*3,4-Bis(phenylhydrazono)butan-2-one* (**20**): A mixture of **19** (1.90 g, 10 mmol), phenylhydrazine (1.08 g, 10 mmol) in ethanol (30 ml) was refluxed for 1h. The reaction mixture was allowed to cool and the solid product, so formed, was collected by filtration and crystallised from acetic acid. Yield: 2.69 g (69%), m.p. 231–233 °C. IR (KBr): $\nu_{max}$/cm$^{-1}$ 1651 (C=O), 3274, 3344 (2NH). MS: *m/z* = 280 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ =2.45 (s, 3H, $CH_3$), 6.89–7.44 (m, 10H, Ar–H), 8.26 (s, 1H, CH-4), 10.82 (s, 1H, NH), 13.18 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$): δ = 24.39, 112.20, 144.69, 120.25, 123.35, 129.63, 129.81, 131.06, 132.89, 142.60, 143.70, 196.157. Anal. Calcd for $C_{16}H_{16}N_4O$ (280.32): Calc C, 68.55; H, 5.75; N, 19.99. Found: C, 68.54; H, 5.74; N, 19.96 %.

*(5-Methyl-1-phenyl-1-H-pyrazol-4-yl)phenyldiazene* (**21**): A suspension of **20** (2.80 g, 10 mmol) in glacial acetic acid (30 ml) was refluxed for 4 h. The reaction mixture was left to cool, then poured onto cooled water. The solid product, so formed, was collected by filtration and crystallised from ethanol. Yield: 1.47 g (56%), m.p. 112–114 °C. MS: *m/z* = 262 ($M^+$). $^1$H NMR (DMSO-$d_6$): δ = 2.69 (s, 1H, $CH_3$), 7.48–7.83 (m, 10H, Ar–H), 8.07 (s, 1H, pyrazol-3-H). $^{13}$C NMR (DMSO-$d_6$): δ 10.62, 121.86, 124.59, 128.38, 129.36, 129.42, 130.05, 130.30, 138.78, 139.06, 140.96, 152.64. Anal. Calcd for $C_{16}H_{14}N_4$ (262.28): C, 73.26; H, 5.38; N, 21.36. Found: C, 73.25; H, 5.38; N, 21.35 %.

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