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STUDIES ON ENAMINES AND AZAENAMINES: 2-OXOARYLHYDRAZONALS AS C-1 NUCLEOPHILES

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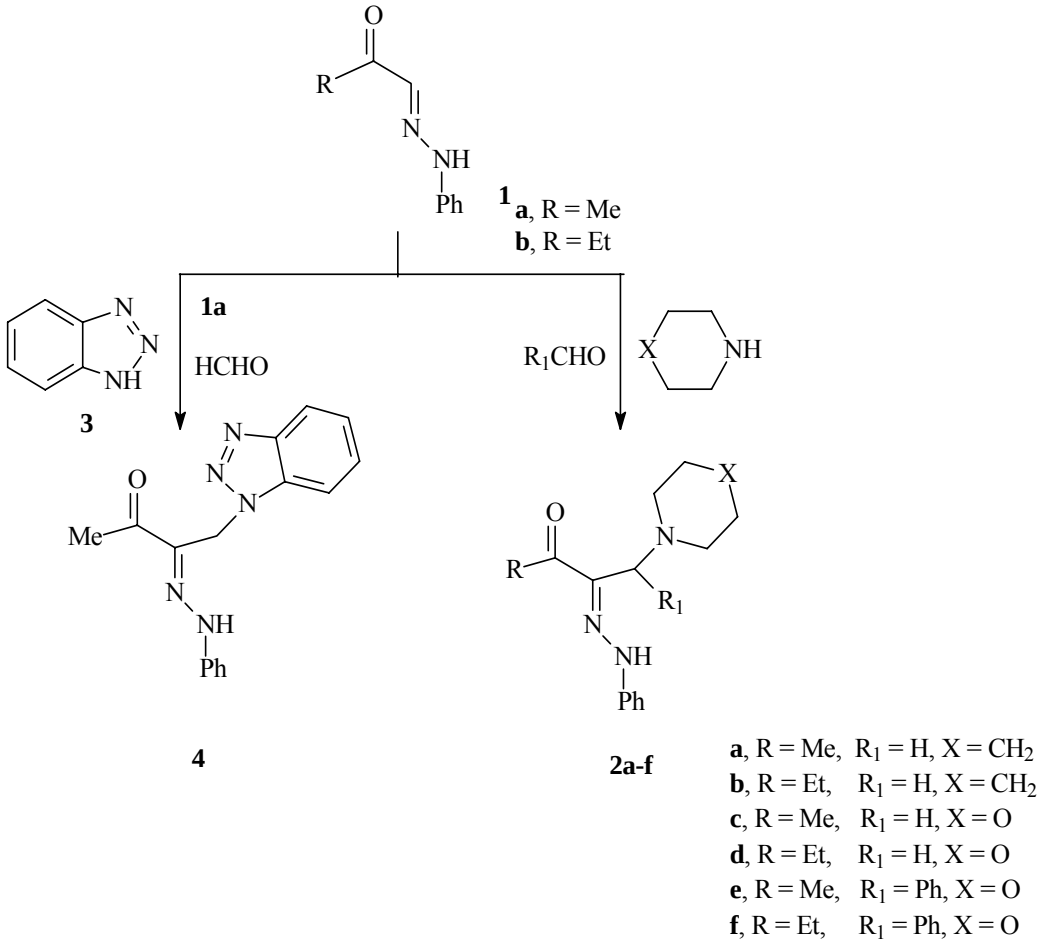
Abstract – 2-Oxoarylhydrazonals **1a**,**b** react with aldehydes; piperidine; morpholine and benzotriazole to yield the corresponding Mannich bases **2a**,**f**, and **4**. Formaldehyde reacts with **1a**,**b** to yield the hydroxymethylarylhyrazons **5a**,**b** together with bisarylhydrazones **6**. The hydroxymethyl derivatives **5a** are converted to arylhydrazonal **7** upon oxidation in refluxing nitrobenzene. The reaction of aldehydes and malononitrile with **1a,b** in ethanolic solution in presence of chitozan as heterogeneous catalyst afforded 6-amino-1,4-dihydropyridazins **14a**,**b**.

INTRODUCTION

Enamines are versatile reagents and their chemistry is receiving considerable recent interest.[1-3] Recently we recognized that aldehyde hydrazones are azaenamines as hydrazone lone pair resonance renders C-1 quite nucleophilic.[4-6] In conjunction of this work we report on the reactivity of 2-oxo-1-arylhydrazonals **1a,b** toward α,β-unsaturated nitriles and Mannich bases.

RESULTS AND DISCUSSION

Thus **1a** or **1b** reacted with a mixture of formaldehyde or benzaldehyde and piperidine or morpholine to yield Mannich bases **2a-f** in 60-85 % yields. Benzotriazole reacted also as a secondary amine. Thus mixing **1a,b** with formaldehyde and benzotriazole **3** gave a corresponding Mannich products together with products of molecular formula $C_{19}H_{20}N_4O_2$ (336.39) and $C_{21}H_{24}N_4O_2$ (364.45) respectively corresponding to the condensation of the latter with **1a**,**b** *via* water elimination together with other product. Although either alkylation at benzotriazole N-1 or N-2 may take place, the ^{1}H NMR of the reaction product indicated that only N-1 alkylated products **4** were formed (Scheme 1).

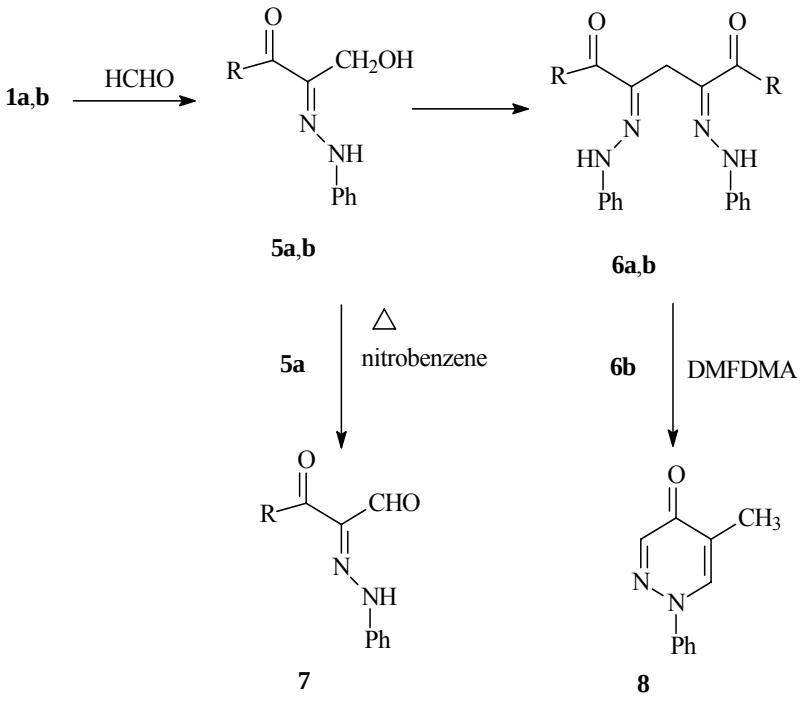


Scheme 1

The other product in this reaction could also be obtained by treatment of **1a,b** with formaldehyde and was thus assigned structure **6a**,**b** and are assumed to be formed *via* initial formation of adduct the **5a**,**b** which then condense with another molecule of **1a,b** to yield the final isolable **4**. Intermediate **5a**,**b** has been isolated in 50 and 53 % yields respectively. It is of value to report here that **2a** has been obtained earlier by Mustafa *et al*. *Via* reacting 2-phenylhydrazonopenta-2,3,4-trione with Mannich bases.[7]

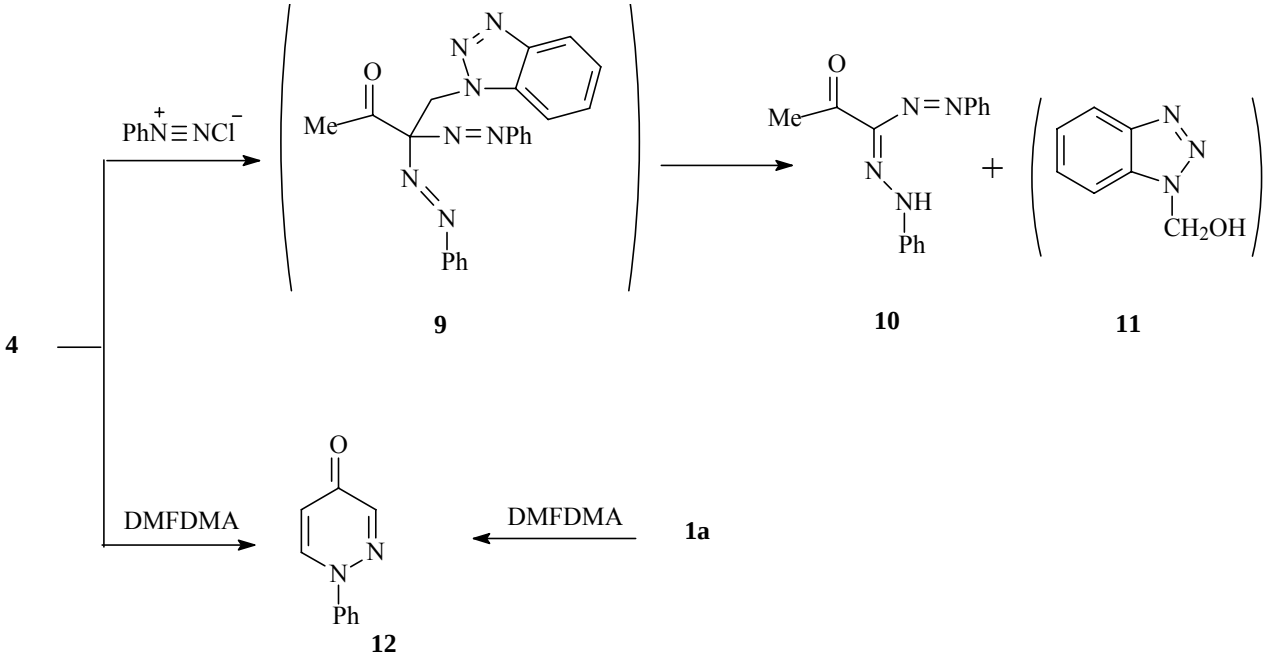
Compound **5a** could be readily oxidized into arylhydrazonal **7** upon reflux in nitrobenzene. Although the chemistry of arylhydrazonals have been explored recently by Elnagdi *et al.*[8-11] Utilizing these arylhydrazonals as precursors to a wide number of heterocycles they utilized expensive functionally substituted enamines as precursor to those arylhydrazonals. The formation of **5a** from 2-oxo-1-arylhydrazonals may thus provide a quite inexpensive route to arylhydrazonals.

Compound **6b** was reacted with dimethylformamide dimethyl acetal (DMFDMA) to afford **8** (Scheme 2). We have investigated the behavior of **4** toward electrophiles and found that hydrazone carbon is still nucleophilic in this compound as it coupled with benzenediazonium chloride to yield formazane **10** *via* intermediate **9** that readily underwent Japp-Kilingemann reaction to yield **10**.[12]



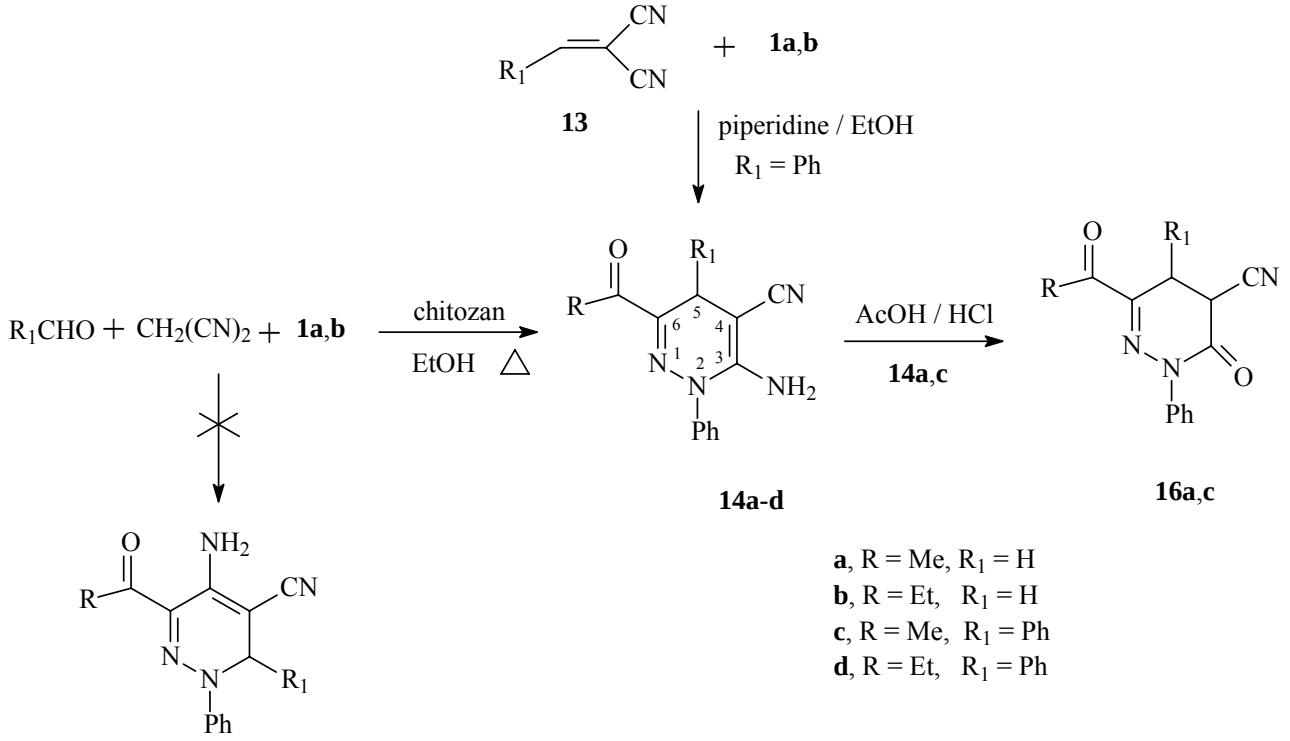
Scheme 2

It is assumed that hydroxylmethylbenzotriazole **11** is formed in this reaction but could not be isolated. Reacting **4** with DMFDMA afforded **12** which are formed *via* initial protonation of **4** to yield **1a** that then condensed with DMFDMA to yield **12** (Scheme 3). Compound **12** could be also obtained, in better yield, *via* reacting **1a** with DMFDMA.



Scheme 3

Recently Elnagdi *et al.*[4-6] reported that **1a,b** react with benzylidenemalononitrile **13** to yield the dihydropyridazines **14c,d**. We have now found that an equimolar mixture of benzaldehyde and malononitrile react in refluxing ethanol in the presence piperidine to yield **14a,b** in almost same yields reported earlier for reaction of **1a,b** and **13**. Attempts to extend this methodology replacing benzaldehyde by formaldehyde resulted only in the formation of the hydroxymethylarylhydrazone **5**. We looked for an alternate catalyst for this multicomponent reaction. The chitozan has been recently employed efficiently as a mild basic heterogeneous catalysis. When formaldehyde, malononitrile and **1a** were mixed in ethanolic solution in presence of chitosan, a product of molecular formula $C_{13}H_{12}N_4O$ (240.26) was formed. Although, it seemed quite logical to assign structure **14a** for this product, but there is a slim possibility that this product is really **15** remained. HMBC indicated that, methylene H at δ = 3.17 ppm is coupled ^4J with carbonyl carbon at δ = 196.3 ppm; thus excluding completely possible formation of **15** in which methylene protons are far from carbonyl carbon. To establish the structure of this product, **14a**,**c** were hydrolysed by acetic acid in presence of hydrochloric acid to yield a dihydropyridazinone **16a**,**c** (cf. scheme 4). Moreover, ^{15}NNMR and ^{15}NHMBC were run and inspected ^{15}N spectrum of **14a** revealed four nitrogen signals at δ = 67, 159, 259 and 345 ppm for an amino group, pyridazine N-1, CN group, and pyridazine N-2 respectively. ^{1}H HMBC-^{15}N indicated an amino protons showing coupled ^4J with N at δ = 159 ppm, while 5-CH_2 with N at δ = 345 ppm. This further established proposed structure **14a-d**.



Scheme 4

CONCLUSION

It could thus be revealed that the title compounds react as C-1 nucleophiles as would be expected for an azaenamines. A novel route to arylhydrazonals could be achieved. Moreover, the route to the 6-amino-1,4-dihydropyridazines *via* multicomponent reaction in presence of chitozan could be further explored.

EXPERIMENTAL

All melting points are uncorrected and were determined with Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded in KBr and were determined on a Perkin-Elmer 2000 FT–IR system. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker DPX at (100 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometer in $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI 70 EV. Elemental analyses were measured by means of LEOCHNS-932 Elemental Analyzer.

General procedure to syntheses of compounds (2a-f)

A mixture of **1a**,**b** (0.01 mol) and formaldehyde (0.30 g, 0.01 mol) or benzaldehyde (1.06 g, 0.01 mol) in presence of piperidine (8 mL) or morpholin (8 mL), were refluxed for 1-2 h (monitored by TLC). The reaction mixture was evaporated under reduced pressure in vacuum. The solid product, so formed, was recrystallized from EtOH.

3-(2-Phenylhydrazono)-4-(piperidin-1-yl)butan-2-one (2a)

Yellow crystals; yield 85 %; mp 113-115 ^{o}C. *Anal*. Calcd for $C_{15}H_{21}N_3O$ (259.3): C, 69.47; H, 8.16; N, 16.20. Found: C, 69.59; H, 8.16; N, 16.36. IR (cm^{-1}): 2938 (NH), 1661 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 1.40-1.51 (m, 6H, pip-H), 2.20-2.50 (m, 7H, pip-H and Me), 3.56 (s, 2H, CH_2), 6.95-7.35 (m, 5H, Ar-H), 12.11 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6):δ, ppm = 196.7 (CO), 144.3, 139.5, 130.5 (2C), 122.8, 114.6 (2C), 54.1 (2C), 53.2, 26.7 (2C), 24.9, 24.6. MS: *m/z* (%) 259 (M^+, 45), 167 (100), 123 (65), 98 (95), 77 (80).

2-(2-Phenylhydrazono)-1-(piperidin-1-yl)pentan-3-one (2b)

Yellow crystals; yield 82 %; mp 102-103 ^{o}C. *Anal*. Calcd for $C_{16}H_{23}N_3O$ (273.3): C, 70.30; H, 8.48; N, 15.37. Found: C, 70.38; H, 8.67; N, 15.47. IR (cm^{-1}): 2943 (NH), 1664 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 1.02 (t, 3H, J = 8, Me) 1.39-1.51 (m, 6H, pip-H), 2.30 (m, 4H, pip-H), 2.88 (q, 2H, J = 8, CH_2), 3.57 (s, 2H, CH_2), 6.94-7.35 (m, 5H, Ar-H), 12.08 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ, ppm = 199.4 (CO), 144.4, 138.8, 130.5 (2C), 122.7, 114.5 (2C), 54.2 (2C), 53.4, 29.6, 26.7 (2C), 24.6, 9.9. MS: *m/z* (%) 273 (M^+, 25), 187 (60), 122 (50), 104 (85), 77 (100).

4-Morpholino-3-(2-phenylhydrazono)butan-2-one (2c)

Yellow crystals; yield 90 %; mp 117-119 ^{o}C. *Anal*. Calcd for $C_{14}H_{19}N_3O_2$ (261.3): C, 64.35; H, 7.33; N,

16.08. Found: C, 64.39; H, 7.65; N, 15.89. IR (cm^{-1}): 2964 (NH), 1662 (CO); ^{1}H NMR ($CDCl_3$): δ, ppm = 2.49 (m, 7H, morpholin-H, Me), 3.72 (m, 6H, morpholin-H, CH_2), 7.02-7.38 (m, 5H, Ar-H), 11.88 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ, ppm = 197.5 (CO), 143.8, 138.1, 130.1 (2C), 122.9, 114.4 (2C), 67.7 (2C), 53.4, 53.2 (2C), 24.9. MS: *m/z* (%) 261 (M^+, 15), 169 (55), 105 (50), 100 (60), 77 (100).

1-Morpholino-2-(2-phenylhydrazono)pentan-3-one (2d)

Yellow crystals; yield 87 %; mp 108-110 ^{o}C. *Anal*. Calcd for $C_{15}H_{21}N_3O_2$ (275.3): C, 65.43; H, 7.69; N, 15.26. Found: C, 65.62; H, 7.90; N, 15.43. IR (cm^{-1}): 2938 (NH), 1661 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 1.16 (t, 3H, J = 8, Me) 2.48 (m, 4H, morpholin-H), 2.99 (q, 2H, J = 8, CH_2), 3.72 (m, 6H, morpholin-H, and CH_2), 7.01-7.38 (m, 5H, Ar-H), 11.82 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ, ppm = 200.4 (CO), 143.9, 137.4, 130.1 (2C), 122.8, 114.4 (2C), 67.7 (2C), 53.4, 53.5 (2C), 29.9, 9.6. MS: *m/z* (%) 275 (M^+, 25), 183 (85), 105 (85), 100 (90), 77 (100).

4-Morpholino-4-phenyl-3-(2-phenylhydrazono)butan-2-one (2e)

Yellow crystals; yield 80 %; mp 149-150 ^{o}C. *Anal*. Calcd for $C_{20}H_{23}N_3O_2$ (337.42): C, 71.19; H, 6.87; N, 12.45. Found: C, 70.93; H, 7.20; N, 12.66. IR (cm^{-1}): 2974 (NH), 1662 (CO); ^{1}H NMR ($CDCl_3$): δ, ppm = 2.36 (m, 7H, morpholin-H and Me), 3.74 (m, 4H, morpholin-H), 4.93 (s, 1H, CH), 6.99-7.45 (m, 10H, Ar-H), 12.68 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ, ppm = 195.4 (CO), 14.86, 13.78, 136.5, 129.5 (2C), 128.7 (2C), 128.2, 127.7 (2C), 122.2, 113.8 (2C), 67.5, 66.2 (2C), 51.7 (2C), 24.3. MS: *m/z* (%) 337 (M^+, 85), 250 (100), 207 (20), 176 (20), 105 (20), 77 (10).

1-Morpholino-1-phenyl-2-(2-phenylhydrazono)pentan-3-one (2f)

Yellow crystals; yield 83 %; mp 133-135 ^{o}C. *Anal*. Calcd for $C_{21}H_{25}N_3O_2$ (351.45): C, 71.77; H, 7.17; N, 11.96. Found: C, 71.64; H, 7.38; N, 11.96. IR (cm^{-1}): 2976 (NH), 1668 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 0.94 (t, 3H, J = 8, Me) 2.50-3.54 (m, 10H, morpholin-H and CH_2), 4.93 (s, 1H, CH), 6.99-7.45 (m, 10H, Ar-H), 12.68 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ, ppm = 198.2 (CO), 142.9, 138.1, 136.6, 129.5 (2C), 129.2 (2C), 128.3, 127.7 (2C), 122.1, 113.7 (2C), 67.7, 66.2 (2C), 51.7 (2C), 28,9, 8.7. MS: *m/z* (%) 351 (M^+, 25), 264 (100), 259 (35), 207 (25), 176 (15), 105 (20), 77 (30).

Synthesis of 4-(1*H*-benzo[1,2,3]triazol-1-yl)-3-(2-phenylhydrazono)butan-2-one (4)

A mixture of **1a** (1.62 g, 0.01 mol), formaldehyde (0.30 g, 0.01 mol) and benzotriazole (1.19 g, 0.01 mol) in dioxane (10 mL) were refluxed for 1-2 h (monitored by TLC). The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product. This crude product contains compounds **4** and **6a**. These were separated by long column chromatography using a mixture of petroleum ether (bp 60-80) and EtOAc (3:1) as an eluent. Compound **4** when separated from column chromatography was recrystallized from petroleum ether (bp 60-80) and gave yellow crystals; yield 55 %; mp 127-129 ^{o}C. *Anal*. Calcd for $C_{16}H_{15}N_5O$ (293.33): C, 65.52; H, 5.15; N, 23.88. Found: C65.55; H, 5.44; N, 23.59. IR

(cm^{-1}): 3289 (NH), 1664 (CO); ^{1}H NMR ($CDCl_3$): δ, ppm = 2.53 (s, 3H, Me), 5.84 (s, 2H, CH_2), 7.09-8.05 (m, 9H, Ar-H), 10.28 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ, ppm = 196.1 (CO), 145.7, 142.4, 135.1, 132.7, 129.5 (2C), 128.4, 124.7, 123.7, 119.8, 114.8 (2C), 110.4, 38.4, 24.1. MS: *m/z* (%) 293 (M^+, 90), 222 (65), 195 (50), 174 (30), 118 (70), 105 (90), 91 (60), 77 (100), 65 (50).

General procedure to syntheses of compounds (5a,b) and (6a,**b)**

A mixture of **1a**,**b** (0.01 mol) and formaldehyde (0.30 g, 0.01 mol), in dioxane (10 mL) were refluxed for 5-7 h (monitored by TLC). The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product. This crude product contains two compounded **5a-b** and **6a**,**b**. The crude product was washed with petroleum ether (60-80) to extract the adduct **5a,b** as yellow crystals and the remaining product **6a**,**b** was recrystallized from EtOH giving orange crystals.

4-Hydroxy-3-(2-phenylhydrazono)butan-2-one (5a)

Yellow crystals; yield 50 %; mp 117-119 ^{o}C. *Anal*. Calcd for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.24; H, 6.52; N, 14.31. IR (cm^{-1}): 3305 (OH), 3280 (NH), 1646 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 2.36 (s, 3H, Me), 4.45 (s, 2H, CH_2), 5.25 (br, 1H, OH) D_2O exchangeable, 6.95-7.36 (m, 5H, Ar-H), 10.51 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ, ppm = 196.1 (CO), 144.0, 142.2, 129.7 (2C), 122.2, 114.5 (2C), 51.6, 24.7. MS: *m/z* (%) 192 (M^+, 90), 174 (30), 162 (10), 105 (95), 92 (85), 77 (100), 65 (75).

1-Hydroxy-2-(2-phenylhydrazono)pentan-3-one (5b)

Yellow crystals; yield 53 %; mp 110-112 ^{o}C. *Anal*. Calcd for $C_{11}H_{14}N_2O_2$ (206.24): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.20; H, 6.62; N, 13.81. IR (cm^{-1}): 3303 (OH), 3277 (NH), 1652 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 1.38 (t, 3H, J = 8, Me), 3.10 (q, 2H, J = 8, CH_2), 4.24 (s, 2H, CH_2), 5.58 (br, 1H, OH) D_2O exchangeable, 7.01-7.38 (m, 5H, Ar-H), 10.51 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ, ppm = 198.1 (CO), 146.2, 142.2, 130.7 (2C), 122.3, 115.5 (2C), 51.6, 28,9, 8.7. MS: *m/z* (%) 206 (M^+, 85), 188 (45), 174 (25), 105 (95), 91 (70), 77 (95).

3,5-Bis(2-phenylhydrazono)heptane-2,6-dione (6a)

Orange crystals; yield 40 %; mp 204-205 ^{o}C. *Anal*. Calcd for $C_{19}H_{20}N_4O_2$ (336.39): C, 67.84; H, 5.99; N, 16.66. Found: C, 67.88; H, 6.19; N, 16.74. IR (cm^{-1}): 3026 (2NH), 1639 (2CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 2.44 (s, 6H, 2Me), 3.73 (s, 2H, CH_2), 7.00-7.40 (m, 10H, Ar-H), 10.96 (br, 2H, 2NH) D_2O exchangeable; ^{13}C NMR ($CDCl_3$): δ, ppm = 196.3 (CO), 143.2, 134.7, 129.3 (2C), 121.6, 113.4 (2C), 24.1, 7.6. MS: *m/z* (%) 338 (M^{+2}, 15), 337 (M^{+1}, 70), 336 (M^+, 85), 319 (15), 229 (30), 202 (45), 108 (100), 93 (15).

4,6-Bis(2-phenylhydrazono)nonane-3,7-dione (6b)

Orange crystals; yield 40 %; mp 137-139 ^{o}C. *Anal*. Calcd for $C_{21}H_{24}N_4O_2$ (364.45): C, 69.21; H, 6.64; N, 15.34. Found: C, 68.98; H, 6.89; N, 15.39. IR (cm^{-1}): 3253 (2NH), 1658 (2CO); ^{1}H NMR (DMSO-d_6): δ,

ppm = 1.05 (t, 6H, *J* = 8, 2Me), 2.79 (q, 4H, *J* = 8, $2CH_2$), 3.41 (s, 2H, CH_2), 6.92-7.33 (m, 10H, Ar-H), 11.28 (br, 2H, 2NH) D_2O exchangeable; ^{13}C NMR ($CDCl_3$): δ, ppm = 199.6 (CO), 143.7 134.4, 129.8 (2C), 121.9, 113.8 (2C), 29.6, 8.9, 7.6. MS: *m/z* (%) 364 (M^+, 40), 275 (95), 201 (60), 189 (40), 108 (100), 93 (70), 77 (55), 56 (90).

Synthesis of 3-oxo-2-(2-phenylhydrazono)butanal (7)

A mixture of **5a** (1.92 g, 0.01 mol) and nitrobenzene (1 mL) were refluxed for 30 min in an oil bath at 150 ^oC. After cooling the mixture was poured onto cold petroleum ether (bp 60-80). The solid, so formed, was collected by filtration and recrystallized from petroleum ether (bp 60-80) to give yellow product; yield 75 %; mp 127-129 ºC. *Anal*. Calcd for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.04; H, 5.52; N, 14.51. IR (cm^{-1}): 3273 (NH), 1746 (CO), 1691 (CHO); ^1H NMR (DMSO-d_6): δ, ppm = 2.41 (s, 3H, Me), 7.25-7.67 (m, 5H, Ar-H), 9.93 (br, 1H, CHO), 14.14 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ, ppm = 196.9 (CO), 187.5 (CHO), 141.8, 132.7, 132.7 (2C), 130.1, 117.3 (2C), 25.1. MS: *m/z* (%) 190 (M^+, 90), 161 (60), 118 (70), 105 (95), 92 (85), 77 (100).

Synthesis of 5-methyl-1-phenylpyridazin-4(1*H*)-one (8)

A mixture of compound **6b** (3.64 g, 0.01 mol) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (1.19 g, 0.01 mol) in xylene (10 mL) was refluxed for 6 h. The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product, which was crystallized from petroleum ether (bp 60-80) to give colorless product; yield 75 %; mp 130-131^oC. *Anal*. Calcd for $C_{11}H_{10}N_2O$ (186.21): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.70; H, 5.59; N, 15.37. IR (cm^{-1}): 1628 (CO); ^1H NMR (DMSO-d_6): δ, ppm = 2.16 (s, 3H, Me), 7.28-7.60 (m, 5H, Ar-H), 8.00 (s, 1H, CH), 8.21 (s, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 170.9 (CO), 146.6, 143.5, 138.7, 130.1 (2C), 128.1, 127.5, 121.1 (2C), 13.2. MS: *m/z* (%) 186 (M^+, 100), 158 (15), 130 (95), 104 (15), 77 (55).

Synthesis of 3-acetyl-1,5-diphenylformazan (10)

A solution of compound **4** (2.93 g, 0.01 mol) in EtOH (10 mL) was treated with sodium acetate (2 g). Benzenediazonium chloride was then added gradually, with stirring, to the mixture. The diazonium salt being prepared according to the standard literature procedures from aniline (0.93 g, 0.01 mol), concentrated hydrochloric acid (2.5 mL), and sodium nitrite (0.69 g, 0.01 mol). After complete addition of the diazonium salt, the reaction mixture was kept at rt for 1 h. The solid, so formed, was collected by filtration and recrystallized from benzene to give red crystals; yield 87 %; mp 119-121 ^oC. *Anal*. Calcd for $C_{15}H_{14}N_4O$ (266.30): C, 67.65; H, 5.30; N, 21.04. Found: C, 67.69; H, 5.62; N, 20.95. IR (cm^{-1}): 3290 (NH), 1680 (CO); ^1H NMR (DMSO-d_6):δ, ppm = 2.69 (s, 3H, Me), 7.28-7.72 (m, 10H, Ar-H), 15.94 (s, 1H, NH) D_2O exchangeable; ^{13}C NMR ($CDCl_3$): δ, ppm = 193.1, 147.4, 141.5, 130.2 (2C), 130.0 (2C), 129.2, 120.1 (2C), 114.8, 26.9. MS: *m/z* (%) 266 (M^+, 85), 222 (15), 195 (25), 161 (35), 119 (30), 105 (70), 92 (100), 77 (90).

Synthesis of 1-phenylpyridazin-4(1*H*)-one (12)

A mixture of compound **4** (2.93 g, 0.01 mol) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (1.19 g, 0.01 mol) in xylene (10 mL) was refluxed for 4-6 h (monitored by TLC). The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product, which was crystallized from petroleum ether (bp 60-80) to give colorless product; yield 68 %; mp 90-92 °C. *Anal*. Calcd for $C_{10}H_8N_2O$ (172.19): C, 69.76; H, 4.68; N, 16.27. Found: C, 69.76; H, 4.87; N, 16.55; IR (cm^{-1}): 1614 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 6.64 (d, 1H, CH), 7.28-7.58 (m, 5H, Ar-H), 8.07 (s, 1H, CH), 8.24 (d, 1H, CH); ^{13}C NMR ($CDCl_3$): δ, ppm = 169.8 (CO), 149.3, 142.8, 140.5, 129.6 (2C), 127.7, 120.6 (2C),116.6. MS: *m/z* (%) 172 (M^+, 85), 145 (15), 45 (25), 117 (100), 104 (50), 90 (30), 77 (85), 63 (20).

General procedure to syntheses of compounds (14a-d)

A mixture of **1a**,**b** (0.01 mol), formaldehyde (0.30 g, 0.01 mol) or benzaldehyde (1.06 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in presence of chitozan (1.5 g) and EtOH (10 mL) as a solvent, were refluxed for 2-4 h (monitored by TLC using a mixture from petroleum ether (bp 60-80): EtOAc 2:1). The reaction mixture was evaporated under reduced pressure in vacuum. The solid product, so formed, was recrystallized from EtOH to give yellow crystals.

6-Acetyl-3-amino-2-phenyl-2,5-dihydropyridazine-4-carbonitrile (14a)

Yield 70 %; mp 154-155 °C. *Anal*. Calcd for $C_{13}H_{12}N_4O$ (240.26): C, 64.99; H, 5.03; N, 23.32. Found: C, 64.75; H, 5.30; N, 23.00; IR (cm^{-1}): 3358, 3314 (NH_2), 2186 (CN), 1678(CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 2.41 (s, 3H, Me), 3.17 (s, 2H, CH_2), 5.68 (br, 2H, NH_2) D_2O exchangeable, 7.28-7.54 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ, ppm = 196.6 (CO), 150.3, 143.7, 139.7, 129.7 (2C), 128.4, 125.7 (2C), 120.3, 52.7, 24.5, 20.2. MS: *m/z* (%) 240 (M^+, 70), 197 (100), 180 (30), 170 (75), 119 (50), 77 (85), 65 (15).

3-Amino-2-phenyl-6-propionyl-2,5-dihydropyridazine-4-carbonitrile (14b)

Yield 75 %; mp 125-126 °C. *Anal*. Calcd for $C_{14}H_{14}N_4O$ (254.29): C, 66.13; H, 5.55; N, 22.03. Found: C, 66.28; H, 5.83; N, 21.70; IR (cm^{-1}): 3400, 3327 (NH_2), 2181 (CN), 1682 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 1.14 (t, 3H, J = 8, Me), 2.86 (q, 2H, J = 8, CH_2), 3.27 (s, 2H, CH_2), 4.27 (br, 2H, NH_2) D_2O exchangeable, 7.41-7.54 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ, ppm = 199.3 (CO), 150.3, 143.3, 139.8, 129.7 (2C), 128.3, 125.6 (2C), 120.3, 52.7, 29.9, 20.4, 8.2. MS: *m/z* (%) 254 (M^+, 80), 197 (100), 170 (30), 119 (25), 77 (35).

6-Acetyl-3-amino-2,5-diphenyl-2,5-dihydropyridazine-4-carbonitrile (14c)

Yield 85 %; mp 236-238 ºC. *Anal*. Calcd for $C_{19}H_{16}N_4O$ (316.36): C, 72.14; H, 5.10; N, 17.7. Found: C, 71.80; H, 5.44; N, 17.42; IR (cm^{-1}): 3411, 3311 (NH_2), 2192 (CN), 1677 (CO); ^{1}H NMR (DMSO-d_6): δ, ppm = 2.33 (s, 3H, Me), 3.33 (s, 1H, CH), 6.05 (br, 2H, NH_2) D_2O exchangeable, 7.18-7.56 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$): δ, ppm = 196.3 (CO), 150.7, 144.4, 142.5, 140.6, 129.8 (2C), 129.5 (2C),

128.3, 127.7, 127.3 (2C), 126.2 (2C), 121.1, 57.2, 36.5, 25.2. MS: *m/z* (%) 316 (M^+, 15), 273 (90), 246 (30), 239 (100), 197 (15), 180 (10), 119 (25), 77 (45), 65 (15).

3-Amino-2,5-diphenyl-6-propionyl-2,5-dihydropyridazine-4-carbonitrile (14d)

Yield 88 %; mp 250-252 ^oC. *Anal*. Calcd for $C_{20}H_{18}N_4O$ (330.39): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.59; H, 5.70; N, 16.68; IR (cm^{-1}): 3464, 3316 (NH_2), 2186 (CN), 1688 (CO); ^1H NMR (DMSO-d_6): δ, ppm = 1.04 (t, 3H, J = 8, Me), 2.94 (q, 2H, J = 8, CH_2), 4.76 (s, 1H, CH), 6.06 (br, 2H, NH_2) D_2O exchangeable, 7.18-7.55 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$): δ, ppm = 198.4 (CO), 150.3, 143.3, 142.1, 140.1, 129.5 (2C), 128.9 (2C), 127.8, 127.2, 126.7 (2C), 125.6 (2C), 120.4, 56.8, 36.2, 29.5, 7.9. MS: *m/z* (%) 330 (M^+, 50), 273 (100), 253 (95), 246 (60), 197 (25), 170 (15), 156 (15), 118 (25), 93 (15), 77 (75), 56 (75).

General procedure to the syntheses of compounds (16a,**c)**

A mixture of **14a**,**c** (0.01 mol), acetic acid (10 mL) and 37% hydrochloric acid (3.5 mL), were refluxed for 15 min. The mixture was cooled and then poured onto ice-water. The solid, so formed, was collected by filtration and crystallized from petroleum ether (bp 60-80) to give yellow crystals.

6-Acetyl-3-oxo-2-phenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile (16a)

Yield 80 %; mp 145-157 ^oC. *Anal*. Calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.73; H, 4.86; N, 17.10; IR (cm^{-1}): 2261 (CN), 1708 (CO), 1692 (CO); ^1H NMR (DMSO-d_6): δ, ppm = 2.51 (s, 3H, Me), 3.16-3.90 (m, 3H, CH, CH_2), 7.38-7.64 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ, ppm = 195.1, 157.5, 147.5, 139.6, 129.3 (2C), 128.2, 124.7 (2C), 112.6, 31.3, 24.5, 23.6. MS: *m/z* (%) 241 (M^+, 100), 239 (50), 216 (20), 198 (35), 170 (20), 145 (15), 120 (25), 91 (30), 77 (85).

6-Acetyl-3-oxo-2,5-diphenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile (16c)

Yield 75 %; mp 165-166 ^oC. *Anal*. Calcd for $C_{19}H_{15}N_3O_2$ (317.35): C, 71.91; H, 4.76; N, 13.24. Found: C, 72.04; H, 5.11; N, 13.46; IR (cm^{-1}): 2262 (CN), 1699 (CO), 1690 (CO); ^1H NMR (DMSO-d_6): δ, ppm = 2.48 (s, 3H, Me), 4.29 (d, 1H, J = 8, CH), 4.94 (d, 1H, J = 8, CH), 7.25-7.59 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$): δ, ppm = 194.6, 157.5, 157.4, 149.4, 139.5, 131.7, 129.9 (2C), 129.2 (2C), 128.4, 127.8 (2C), 124.4 (2C), 112.9, 39.4, 39.1, 24.8. MS: *m/z* (%) 317 (M^+, 100), 290 (20), 246 (20), 220 (15), 180 (10), 156 (35), 129 (15), 116 (25), 91 (15), 77 (35).

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