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The reaction of ethyl benzoylacetate with malononitrile: a novel synthesis of some pyridazine, pyridazino[2,3-*a*]quinazoline and pyrrole derivatives

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Abstract—Ethyl benzoylacetate undergoes Claisen condensation reaction with malononitrile to afford 2-cyano-5-phenyl-3,5-dioxopentanitrile which could be cyclized into 2-aminopyran and coupled with diazonium salts to afford azo derivatives. These azo derivatives and those of ethyl benzoylacetate could be cyclized into 4-oxo-, 6-oxo- and 6-iminopyridazines and pyridazino[2,3-*a*]quinazolines, respectively. The 6-iminopyridazines could be transformed into the 6-oxopyridazines. The imino- and oxopyridazines could be transformed into pyrrole derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

In the last few years we have been involved in a program aimed at the synthesis of new heterocyclic systems of biological interest to be tested as biodegradable agrochemicals.^{1–3} In the context of this program, some new functionally substituted pyridazine derivatives were required. Ethyl 4,4-dicyano-3-phenyl-3-butenolate **3** seemed a good candidate to fulfil this objective via its coupling with the diazotized aromatic amines **4a–d** to afford the azo derivatives **5a–d**, followed by cyclization to the pyridazines **6a–d** (Scheme 1) similar to the previously reported work on related systems.^{3,4} This prompted us to investigate the reaction of ethyl benzoylacetate **1** with malononitrile **2** aiming to obtain the Knoevenagel condensation product **3**. To our knowledge this compound has been mentioned twice as an intermediate which afforded a pyridine derivative on cyclization in very low yield.^{5,6}

In our hands ethyl benzoylacetate **1** reacted with malononitrile **2** in refluxing ethanol catalyzed by piperidine to afford a viscous brown oil. Heating of this oil in toluene led to a crystalline product, mp 286°C. Mass spectrum of this product showed *m/e* 212. The IR spectrum showed absorption bands at 3400–3300, 2216 and 1650 cm⁻¹. ¹H NMR spectrum revealed a singlet (1H) at δ 5.66⁷, a singlet (2H) at δ 7.35 and an aromatic multiplet (5H) at δ 7.59–7.82. On the basis of these data, the pyran-4-one structure **8** was assigned to this product. This result gave us the impression that the oily product should be 2-cyano-5-phenyl-3,5-dioxopentanitrile **7**. The ¹H NMR spectrum of this oil did not reveal any signals due to the ester

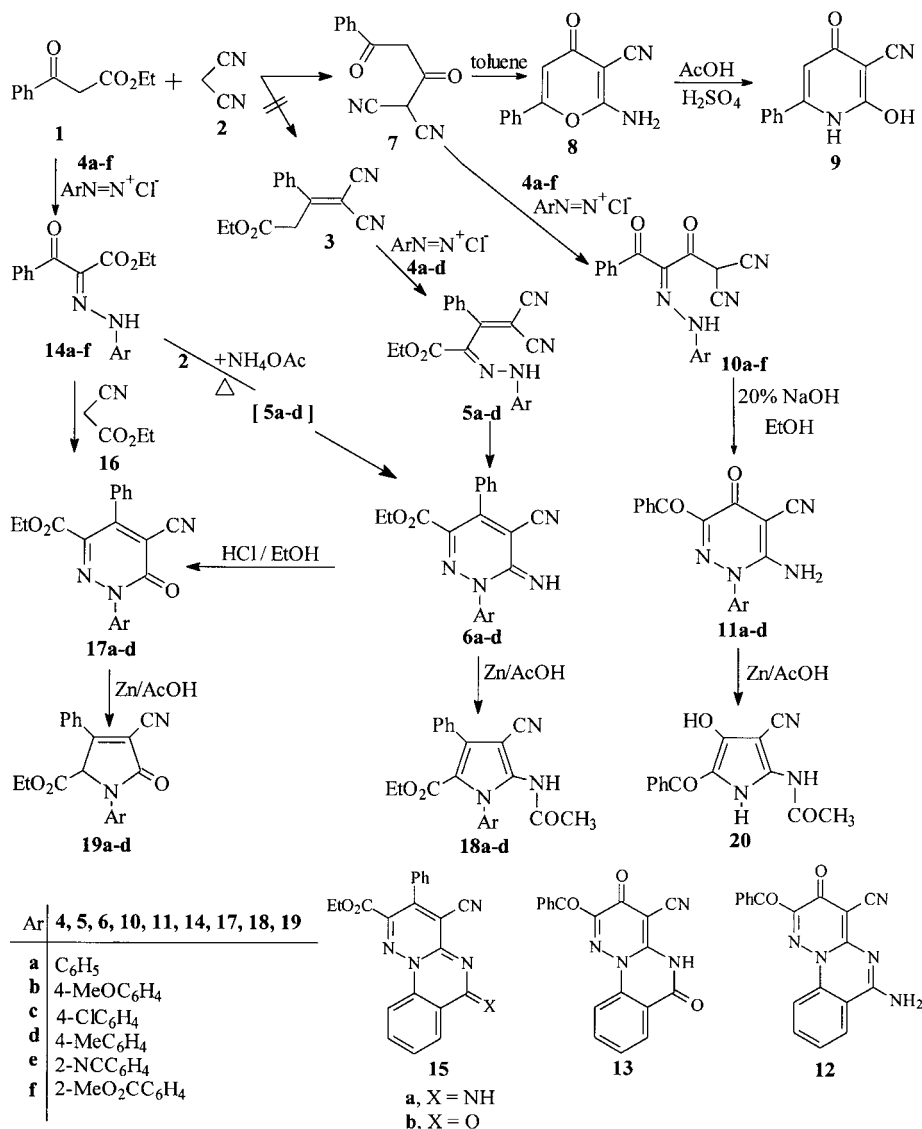
group, but two singlets at δ 4.1 (2H) and 4.6 (1H) corresponding to methylene and methyne protons, respectively, besides an aromatic multiplet at δ 7.25–7.8. It is assumed that the reaction of **1** and **2** took place via a Claisen condensation with elimination of ethanol to afford **7** rather than the expected Knoevenagel-type condensation to afford **3**. Refluxing the pyran derivative **8** in acetic/sulfuric acid mixture leads to another crystalline product, mp 256°C. The elemental analysis of this product was consistent with the same formula as that of **8**. IR and ¹H NMR spectra suggested the 4-pyridone structure **9**, which was assigned to this product. The conversion of 2-aminopyrans into functionalized pyridines is well known.^{8,9} Furthermore, the synthesis of phenyl substituted pyridines by different methods has been widely investigated¹⁰ and this is one simple method to 2-phenylpyridine. The formation of pyrans and pyridines from active methylene compounds and malononitrile or its derivatives is also well known in the literature.^{6,11,12}

The structure of the oily product **7** was further confirmed from the following behavior. It undergoes the coupling reaction with the diazonium salts **4a–f** to afford the colored hydrazo products **10a–f**, respectively. Elemental analysis and spectral data are in favor of these proposed hydrazo structures (see Section 1). Refluxing compounds **10a–d** in ethanolic sodium hydroxide (20% water solution) accomplished their cyclization to the pyridazine derivatives **11a–d**, while the same treatment of compounds **10e** and **10f** led to the pyridazino[2,3-*a*]quinazoline derivatives **12** and **13**, respectively. The IR spectra of compounds **11a–d**, **12** and **13** show absorption bands due to amino, cyano and two carbonyl groups, except in **13** where an NH and three carbonyl absorptions were observed (see Section 1).

Keywords: pyridazines; pyridazinoquinazolines; pyrroles.

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[†] This work is abstracted in part from the M.Sc. thesis of A. E. Mekky.



Scheme 1.

On the other hand, the initially desired iminopyridazines **6a-d** were successfully obtained by fusing the hydrazo derivatives **14a-d** (obtained from coupling of **1** with the diazonium salt of the appropriate aromatic amine according to literature methods^{13,14}) with malononitrile **2** in the presence of ammonium acetate. The IR spectra of **6a-d** showed absorption bands at 3400–3330, 2200–2210 and 1710 cm⁻¹ corresponding to NH, CN and ester carbonyl, respectively. The formation of the pyridazines **6a-d** apparently took place via the intermediacy of **5a-d**, which could not be separated. Compounds **14e,f** were cyclized in the same way to afford the pyridazino[2,3-*a*]-quinazoline derivatives **15a** and **15b**, respectively. The cyclization took place presumably via an internal addition of the NH group in the 6-imino pyridazine to the neighboring CN group in the hypothetical **6e** (Ar=2-NC-C₆H₄) to afford **15a** or an internal reaction of the imine with the ester group in the case of **6f** (Ar=2-MeO₂CC₆H₄) to afford **15b**.

When compounds **14a-d** were fused with ethyl cyanoacetate under the same reaction conditions, the 6-oxo-

pyridazine derivatives **17a-d** were obtained, respectively. Compounds **6a-d** could be quantitatively transformed into **17a-d** on reflux in ethanolic HCl. The identity of the compound pairs was inferred from mp and TLC analysis. In the same way compound **15a** was quantitatively transformed into **15b**.

Refluxing the 6-iminopyridazine derivatives **6a-d** in acetic acid in the presence of zinc dust, they were transformed into the pyrrole derivatives **18a-d**, respectively. The 6-oxopyridazine derivatives **17a-d** underwent the same reaction to afford the dihydropyrrole derivatives **19a-d**, respectively. IR, ¹H NMR and elemental analyses are in agreement with the proposed structures. The formation of the pyrrole derivatives **18a-d** and **19a-d** from the pyridazines **6a-d** and **17a-d**, respectively, is assumed to take place via reductive cleavage of the N–N bond in the pyridazines followed by recyclization with loss of ammonia.^{3,4}

It should be mentioned that the 4-oxopyridazines **11a-d** undergo the same reaction to afford only one product in

all cases. Structure **20** was assigned to this product and the identity was inferred from mp, TLC and IR spectra. It is assumed that compounds **11a–d** undergo a reductive cleavage of the N–N bond followed by recyclization via the attack of the NH₂ on the enamine carbon atom with elimination of the aromatic amine residue.

1. Experimental

1.1. General procedure

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ¹H NMR spectra were taken on a Varian Gemini 200 MHz spectrometer in DMSO-d₆ using TMS as internal standard. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out by the Microanalytical Centre at Cairo University.

1.1.1. 2-Cyano-5-phenyl-3,5-dioxopentanitrile 7. To a mixture of ethyl benzoylacetate **1** (19.2 g, 100 mmol) and malononitrile **2** (6.6 g, 100 mmol) in 50 mL of absolute ethanol was added 1 mL of piperidine. The reaction mixture was refluxed for 3 h, then left to cool to room temperature, then poured on ice cold water and neutralized by HCl. The water layer was decanted and the remaining oil was washed several times with cold water and extracted with ether. The ether layer was dried over anhydrous CaCl₂ overnight. The solvent was removed under vacuum to leave a brown viscous oil (18 g, 85%). ν_{\max} 2250 (CN), 1690 and 1675 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 4.1 (s, 2H), 4.6 (s, 1H), 7.25–7.80 (m, 5H, arom.).

1.1.2. 2-Amino-6-phenyl-4-oxo-4H-pyran-3-carbonitrile 8. A solution of the brown oil **7** (4.2 g, 20 mmol) in 30 mL toluene was refluxed for 3 h, and left to cool overnight. The solid precipitate that appeared was filtered off and recrystallized to afford 3.8 g (90%) of **8**. Mp 286°C (toluene); [Found: C, 67.90; H, 3.70; N, 13.20. C₁₂H₈N₂O₂ requires C, 67.92; H, 3.80; N, 13.20; ν_{\max} (KBr) 3398–3300 (NH₂), 2216 (CN), 1650 (C=O); δ_{H} (200 MHz, DMSO-d₆) 5.66 (s, 1H, pyran 5-H), 7.35 (s, 2H, NH₂), 7.59–7.82 (m, 5H, arom.).

1.1.3. 2-Hydroxy-6-phenyl-4-oxo-1,4-dihydropyridine-3-carbonitrile 9. To a solution of the pyran **8** (2.1 g, 10 mmol) in 30 mL of glacial acetic acid was added 1 mL of concentrated sulfuric acid and the mixture was refluxed for 1 h, then left to cool. The precipitated solid was filtered off and recrystallized to afford (1.8 g, 85%) of **9** mp 256°C (EtOH); [Found: C, 67.90; H, 3.80; N, 13.30. C₁₂H₈N₂O₂ requires C, 67.92; H, 3.80; N, 13.20; ν_{\max} (KBr) 3450–3200 (br, NH and OH), 2210 (CN), 1655 (C=O); δ_{H} (200 MHz, DMSO-d₆) 4.2 (br.s, 1H, OH), 5.70 (s, 1H, pyridine 5-H), 7.45 (s, 1H, NH), 7.48–7.60 (m, 5H, arom.).

1.1.4. 4-Arylazo/hydrazo-2-cyano-5-phenyl-3,5-dioxopentanitriles 10a–f (general procedure). To a cold solution of **7** (2.1 g, 10 mmol) and sodium acetate 1.5 g in 35 mL of ethanol was added dropwise a cold solution of a

diazotized amine (aniline, *p*-anisidine, *p*-chloroaniline, *p*-toluidine, anthranilonitrile or methyl anthranilate, 10 mmol) while stirring. The addition took about 30 min, after which stirring was continued for further 1 h. The colored solid precipitates were collected by filtration, washed with cold water, and recrystallized from ethanol to afford the title compounds, respectively.

10a. (2.84 g, 90%), mp 203°C (EtOH); [Found: C, 68.40; H, 3.90; N, 17.80. C₁₈H₁₂N₄O₂ requires C, 68.35; H, 3.82; N, 17.71; ν_{\max} (KBr) 3400–3250 (NH), 2224 and 2210 (2 CN), 1695 and 1680 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 4.5 (s, 1H), 7.20–7.80 (m, 10H, arom.), 8.21 (br, s, 1H, NH).

10b. (3.18 g, 92%), mp 163°C (EtOH); [Found: C, 66.00; H, 3.90; N, 16.10. C₁₉H₁₄N₄O₃ requires C, 65.89; H, 4.07; N, 16.18; ν_{\max} (KBr) 3440–3310 (NH), 2245 and 2200 (2 CN), 1705 and 1675 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 3.8 (s, 3H, OCH₃), 4.45 (s, 1H), 7.25–7.85 (m, 9H, arom.), 8.25 (br, s, 1H, NH).

10c. (2.8 g, 80%), mp 202°C (EtOH); [Found: C, 61.70; H, 3.30; N, 15.80; Cl, 10.20. C₁₈H₁₁N₄O₂Cl requires C, 61.64; H, 3.16; N, 15.97; Cl, 10.11; ν_{\max} (KBr) 3410–3350 (NH), 2235 and 2210 (2 CN), 1690 and 1670 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 4.50 (s, 1H), 7.30–7.75 (m, 9H, arom.), 8.15 (br, s, 1H, NH).

10d. (2.48 g, 75%), mp 238°C (EtOH); [Found: C, 68.90; H, 4.20; N, 17.10. C₁₉H₁₄N₄O₂ requires C, 69.08; H, 4.27; N, 16.98; ν_{\max} (KBr) 3420–3310 (NH), 2225 and 2205 (2 CN), 1700 and 1670 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 2.35 (s, 3H, CH₃), 4.35 (s, 1H), 7.15–7.85 (m, 9H, arom.), 8.30 (br, s, 1H, NH).

10e. (2.70 g, 79%), mp 122°C (EtOH); [Found: C, 66.80; H, 3.30; N, 20.60. C₁₉H₁₁N₅O₂ requires C, 66.86; H, 3.25; N, 20.52. ν_{\max} (KBr) 3420–3350 (NH), 2235 and 2220 and 2210 (3 CN), 1710 and 1680 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 4.41 (s, 1H), 7.28–7.95 (m, 9H, arom.), 8.15 (br, s, 1H, NH).

10f. (3.01 g, 81%), mp 221°C (EtOH); [Found: C, 64.20; H, 3.90; N, 14.90. C₂₀H₁₄N₄O₄ requires C, 64.17; H, 3.77; N, 14.97. ν_{\max} (KBr) 3405–3310 (NH), 2216 and 2195 (2 CN), 1720 (C=O ester) 1710 and 1675 (2 C=O); δ_{H} (200 MHz, DMSO-d₆) 3.95 (s, 3H, CH₃), 4.44 (s, 1H), 7.25–8.1 (m, 9H, arom.), 8.25 (br, s, 1H, NH).

1.1.5. 6-Amino-1-aryl-3-benzoyl-4-oxo-1,4-dihydropyridazine-5-carbonitriles 11a–d, 6-amino-2-benzoyl-3-oxopyridazino [2,3-*a*] quinazoline-4-carbonitrile 12 and 2-benzoyl-3,6-dioxo-5,6-dihydropyridazino[2,3-*a*]quinazoline-4-carbonitrile 13 (general procedure). To a solution of each of **10a–f** (10 mmol) in 20 mL ethanol was added 5 mL of 20% aq. NaOH solution. The reaction mixture was refluxed for 2 h in each case, then left to cool overnight. The precipitated solid products formed were filtered off, washed several times with cold water and recrystallized from the proper solvent to afford the corresponding cyclized products:

11a. (2.81 g, 89%), mp 300°C (EtOH/DMF); [Found: C,

68.30; H, 3.70; N, 17.80. $C_{18}H_{12}N_4O_2$ requires C, 68.35; H, 3.82; N, 17.71: ν_{\max} (KBr) 3400–3300 (NH₂), 2210 (CN), 1710 and 1650 (2 C=O); δ_H (200 MHz, DMSO-d₆) 7.05 (s, 2H, NH₂), 7.35–8.10 (m, 10H, arom.).

11b. (2.94 g, 85%), mp 302°C (EtOH/DMF); [Found: C, 66.00; H, 4.20; N, 16.20. $C_{19}H_{14}N_4O_3$ requires C, 65.89; H, 4.07; N, 16.18. ν_{\max} (KBr) 3410–3320 (NH₂), 2215 (CN), 1710 and 1655 (2 C=O); δ_H (200 MHz, DMSO-d₆) 2.85 (s, 3H, OCH₃), 6.95 (s, 2H, NH₂), 7.25 (d, 2H), 7.35 (d, 2H), 7.55–8.05 (m, 5H, arom.).

11c. (2.98 g, 85%), mp >330°C (EtOH/DMF); [Found: C, 61.70; H, 3.20; N, 16.10; Cl, 10.20. $C_{18}H_{11}N_4O_2Cl$ requires C, 61.64; H, 3.16; N, 15.97; Cl, 10.11. ν_{\max} (KBr) 3390–3330 (NH₂), 2205 (CN), 1705 and 1660 (2 C=O); δ_H (200 MHz, DMSO-d₆) 6.99 (s, 2H, NH₂), 7.15–7.85 (m, 9H, arom.).

11d. (2.77 g, 84%), mp >330°C (EtOH/DMF); [Found: C, 69.10; H, 4.30; N, 16.90. $C_{19}H_{14}N_4O_2$ requires C, 69.08; H, 4.27; N, 16.98. ν_{\max} (KBr) 3400–3300 (NH₂), 2210 (CN), 1695 and 1650 (2 C=O); δ_H (200 MHz, DMSO-d₆) 2.80 (s, 3H, OCH₃), 6.90 (s, 2H, NH₂), 7.25–8.15 (m, 9H, arom.).

12. (2.56 g, 75%), mp >330°C (EtOH/DMF); [Found: C, 66.80; H, 3.40; N, 20.60. $C_{19}H_{11}N_5O_2$ requires C, 66.86; H, 3.25; N, 20.52. ν_{\max} (KBr) 3340–3320 (NH₂), 2220 (CN), 1715 and 1650 (2 C=O); δ_H (200 MHz, DMSO-d₆) 7.15–7.79 (m, 9H, arom.), 8.10 (s, 2H, NH₂).

13. (2.46 g, 72%), mp >330°C (EtOH/DMF); [Found: C, 66.80; H, 3.10; N, 16.40. $C_{19}H_{10}N_4O_3$ requires C 66.67; H, 2.94; N, 16.37. ν_{\max} (KBr) 3410–3350 (NH₂), 2215 (CN), 1710 and 1680 and 1650 (3 C=O); δ_H (200 MHz, DMSO-d₆) 6.80 (s, 1H, NH), 7.15–7.90 (m, 9H, arom.).

1.1.6. Ethyl 1-aryl-5-cyano-6-imino-4-phenyl-1,6-dihydropyridazine-3-carboxylates 6a–d, ethyl 4-cyano-6-imino-3-phenyl-6H-pyridazino[2,3-a]quinazoline-2-carboxylate 15a and ethyl 4-cyano-6-oxo-3-phenyl-6H-pyridazino[2,3-a]quinazoline-2-carboxylate 15b (general procedure). A mixture of 10 mmol of each of the azo derivatives **14a–f** (prepared from ethyl benzoyl acetate **1** by coupling with aromatic diazonium salts according to the literature methods^{13,14}), malononitrile **2** (10 mmol) and 1 g of ammonium acetate (15 mmol) was fused on an oil bath at 200°C for 2 h. The melt was left to cool to room temperature and triturated with ethanol. The solid precipitates were filtered off and recrystallized from acetic acid to afford:

6a. (2.58 g, 75%), mp 279°C (EtOH); [Found: C, 69.60; H, 4.50; N, 16.20. $C_{20}H_{16}N_4O_2$ requires C, 69.76; H, 4.68; N, 16.27. ν_{\max} (KBr) 3390–3310 (NH), 2207 (CN), 1712 (C=O); δ_H (200 MHz, DMSO-d₆) 1.45 (t, $J=7$ Hz, 3H, CH₃), 3.8 (q, $J=7$ Hz, 2H, CH₂), 7.3–7.85 (m, 10H, arom.), 8.25 (b, s, 1H, NH).

6b. (2.84 g, 76%), mp 265°C (EtOH); [Found: C, 67.20; H, 4.90; N, 15.10. $C_{21}H_{18}N_4O_3$ requires C, 67.37; H, 4.85; N, 14.96. ν_{\max} (KBr) 3400–3300 (NH), 2200 (CN), 1710 (C=O); δ_H (200 MHz, DMSO-d₆) 1.35 (t, $J=7$ Hz, 3H,

CH₃), 3.7 (s, 3H, CH₃), 3.85 (q, $J=7$ Hz, 2H, CH₂), 7.25 (d, 2H), 7.35 (d, 2H), 7.50–8.0 (m, 5H, arom.), 8.20 (br, s, 1H, NH).

6c. (2.64 g, 70%), mp 224°C (EtOH); [Found: C, 63.30; H, 4.10; N, 14.80; Cl, 9.30. $C_{20}H_{15}N_4O_2Cl$ requires C, 63.41; H, 3.99; N, 14.79; Cl, 9.37. ν_{\max} (KBr) 3390–3320 (NH), 2207 (CN), 1710 (C=O); δ_H (200 MHz, DMSO-d₆) 1.38 (t, $J=7$ Hz, 3H, CH₃), 3.9 (q, $J=7$ Hz, 2H, CH₂), 7.3–8.10 (m, 9H, arom.), 8.23 (b, s, 1H, NH).

6d. (2.83 g, 79%), mp 233°C (EtOH); [Found: C, 70.30; H, 4.90; N, 15.60. $C_{21}H_{18}N_4O_2$ requires C, 70.38; H, 5.06; N, 15.63. ν_{\max} (KBr) 3385–3300 (NH), 2210 (CN), 1715 (C=O); δ_H (200 MHz, DMSO-d₆) 1.43 (t, $J=7$ Hz, 3H, CH₃), 2.43 (s, 3H, CH₃), 3.80 (q, $J=7$ Hz, 2H, CH₂), 7.25–7.85 (m, 9H, arom.), 8.30 (br,s, 1H, NH).

15a. (2.93 g, 80%), mp 242°C (EtOH); [Found: C, 68.30; H, 3.90; N, 18.80. $C_{21}H_{15}N_5O_2$ requires C, 68.28; H, 4.09; N, 18.96. ν_{\max} (KBr) 4090–3300 (NH), 2225 (CN), 1715 (C=O); δ_H (200 MHz, DMSO-d₆) 1.30 (t, $J=7$ Hz, 3H, CH₃), 3.90 (q, $J=7$ Hz, 2H, CH₂), 7.30–7.90 (m, 9H arom.), 8.25 (br,s, 1H, NH).

15b. (3.03 g, 82%), mp 223°C (EtOH); [Found: C, 68.20; H, 3.70; N, 15.20. $C_{21}H_{14}N_4O_3$ requires C, 68.10; H, 3.81; N, 15.13. ν_{\max} (KBr) 2223 (CN), 1710 and 1680 (2 C=O); δ_H (200 MHz, DMSO-d₆) 1.35 (t, $J=7$ Hz, 3H, CH₃), 3.85 (q, $J=7$ Hz, 2H, CH₂), 7.35–7.90 (m, 9H arom.).

1.1.7. Ethyl 1-aryl-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridazine-3-carboxylates 17a–d. A mixture of 10 mmol of each of the azo derivatives **14a–d**, ethyl cyanoacetate **16** (10 mmol) and 1 g of ammonium acetate (15 mmol) was fused on an oil bath at 200°C for 2 h and treated as mentioned above to afford:

17a. (2.6 g, 75%), mp 185°C (EtOH); [Found: C, 69.60; H, 4.50; N, 12.30. $C_{20}H_{15}N_3O_3$ requires C, 69.56; H, 4.38; N, 12.17. ν_{\max} (KBr) 2225 (CN), 1710 and 1670 (2 C=O); δ_H (200 MHz, DMSO-d₆) 1.29 (t, $J=7$ Hz, 3H, CH₃), 4.10 (q, $J=7$ Hz, 2H, CH₂), 7.30–7.85 (m, 10H, arom.).

17b. (2.96 g, 79%), mp 130°C (EtOH); [Found: C, 67.30; H, 4.60; N, 11.10. $C_{21}H_{17}N_3O_4$ requires C, 67.19; H, 4.56; N, 11.19. ν_{\max} (KBr) 2220 (CN), 1710 and 1660 (2 C=O); δ_H (200 MHz, DMSO-d₆) 1.25 (t, $J=7$ Hz, 3H, CH₃), 3.85 (s, 3H, CH₃), 4.14 (q, $J=7$ Hz, 2H, CH₂), 7.15–7.75 (m, 9H, arom.).

17c. (2.6 g, 68%), mp 148°C (EtOH); [Found: C, 63.30; H, 3.70; N, 10.90; Cl, 9.30. $C_{20}H_{14}N_3O_3Cl$ requires C, 63.25; H, 3.72; N, 11.06; Cl, 9.33. ν_{\max} (KBr) 2210 (CN), 1710 and 1665 (2 C=O); δ_H (200 MHz, DMSO-d₆) 1.29 (t, $J=7$ Hz, 3H, CH₃), 4.10 (q, $J=7$ Hz, 2H, CH₂), 7.30–7.85 (m, 9H, arom.).

17d. (2.7 g, 75%), mp 176°C (EtOH); [Found: C, 70.20; H, 4.70; N, 11.50. $C_{21}H_{17}N_3O_3$ requires C, 70.18; H, 4.77; N, 11.69. ν_{\max} (KBr) 2215 (CN), 1715 and 1660 (2 C=O); δ_H (200 MHz, DMSO-d₆) 1.24 (t, $J=7$ Hz, 3H, CH₃), 2.45 (s, 3H, CH₃), 4.12 (q, $J=7$ Hz, 2H, CH₂), 7.25–7.78 (m, 9H, arom.).

1.1.8. Transformation of 15a into 15b and 6a–d into 17a–d, respectively (general procedure). To a solution of **15a** or each of **6a–d** (50 mmol) in 20 mL ethanol was added 5 mL of concentrated hydrochloric acid and the mixture was refluxed for 1 h. After cooling to room temperature, the reaction mixture was diluted with cold water and neutralized with ammonia. The solid precipitates were collected by filtration and recrystallized from acetic acid to afford products identical in all respect (mp, mixed mp, TLC) with **15b** and **17a–d**, respectively.

1.1.9. Ethyl 1-aryl-5-acetylamino-4-cyano-3-phenylpyrrole-2-carboxylates 18a–d, ethyl 1-aryl-4-cyano-5-oxo-3-phenyl-2,5-dihydropyrrole-2-carboxylates 19a–d and 2-acetylamino-5-benzoyl-4-hydroxy-1H-pyrrole-3-carbonitrile 20 (general procedure). To a solution of **6a–d**, **11a–d** or **17a–d** (10 mmol) in 25 mL glacial acetic acid was added 2 g of Zn dust. The reaction mixture was refluxed for 2 h during which time the color turns to pale yellowish green. The reaction mixture was filtered in each case while hot and left to cool to room temperature. The precipitated solids were collected by filtration and recrystallized to afford:

18a. (2.42 g, 65%), mp 245°C (AcOH); [Found: C, 70.70; H, 5.20; N, 11.30. $C_{22}H_{19}N_3O_3$ requires C, 70.76; H, 5.13; N, 11.25. ν_{\max} (KBr) 3420–3340 (NH), 2225 (CN), 1715 and 1680 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.21 (t, $J=7$ Hz, 3H, CH₃), 2.21 (s, 3H, CH₃), 3.94 (q, $J=7$ Hz, 2H, CH₂), 7.10 (s, 1H, NH), 7.25–7.85 (m, 10H, arom.).

18b. (2.26 g, 56%), mp 238°C (AcOH); [Found: C, 68.60; H, 5.20; N, 10.30. $C_{23}H_{21}N_3O_4$ requires C, 68.47; H, 5.25; N, 10.42. ν_{\max} (KBr) 3400–3310 (NH), 2215 (CN), 1725 and 1685 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.15 (t, $J=7$ Hz, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.79 (s, 3H, OCH₃), 3.98 (q, $J=7$ Hz, 2H, CH₂), 7.04 (s, 1H, NH), 7.24 (d, 2H), 7.35 (d, 2H), 7.45–7.80 (m, 5H, arom.).

18c. (2.44 g, 60%), mp 241°C (AcOH); [Found: C, 64.90; H, 4.40; N, 10.20; Cl, 8.80. $C_{22}H_{18}N_3O_3Cl$ requires C, 64.79; H, 4.45; N, 10.30; Cl, 8.69. ν_{\max} (KBr) 3415–3310 (NH), 2210 (CN), 1710 and 1690 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.14 (t, $J=7$ Hz, 3H, CH₃), 2.18 (s, 3H, CH₃), 3.90 (q, $J=7$ Hz, 2H, CH₂), 6.98 (s, 1H, NH), 7.16–7.82 (m, 9H, arom.).

18d. (2.4 g, 62%), mp 244°C (AcOH); [Found: C, 71.40; H, 5.50; N, 10.50. $C_{23}H_{21}N_3O_3$ requires C, 71.30; H, 5.46; N, 10.39. ν_{\max} (KBr) 3405–3310 (NH), 2220 (CN), 1715 and 1685 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.12 (t, $J=7$ Hz, 3H, CH₃), 2.16 (s, 3H, CH₃), 2.30 (s, 3H, *p*-CH₃), 3.94 (q, $J=7$ Hz, 2H, CH₂), 7.00 (s, 1H, NH), 7.20–7.80 (m, 9H, arom.).

19a. (1.8 g, 55%), mp 239°C (AcOH); [Found: C, 72.40; H, 4.90; N, 8.50. $C_{20}H_{16}N_2O_3$ requires C, 72.28; H, 4.85; N, 8.43. ν_{\max} (KBr) 2225 (CN), 1735 and 1685 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.15 (t, $J=7$ Hz, 3H, CH₃), 3.94 (q, $J=7$ Hz, 2H, CH₂), 5.68 (s, 1H, Pyrrole-H), 7.15–7.85 (m, 10H, arom.).

19b. (2.1 g, 58%), mp 217°C (AcOH); [Found: C, 69.80; H, 4.90; N, 7.60. $C_{21}H_{18}N_2O_4$ requires C, 69.60; H, 5.01; N, 7.73. ν_{\max} (KBr) 2222 (CN), 1738 and 1690 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.12 (t, $J=7$ Hz, 3H, CH₃), 3.82 (s, 3H, OCH₃), 4.06 (q, $J=7$ Hz, 2H, CH₂), 5.56 (s, 1H, Pyrrole-H), 7.05 (d, 2H), 7.25 (d, 2H), 7.35–7.65 (m, 5H, arom.).

19c. (1.9 g, 52%), mp 234°C (AcOH); [Found: C, 65.60; H, 4.20; N, 7.60; Cl, 9.70. $C_{20}H_{15}N_2O_3Cl$ requires C, 65.49; H, 4.12; N, 7.64; Cl, 9.67. ν_{\max} (KBr) 2215 (CN), 1732 and 1693 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.11 (t, $J=7$ Hz, 3H, CH₃), 3.98 (q, $J=7$ Hz, 2H, CH₂), 5.59 (s, 1H, Pyrrole-H), 7.05–7.55 (m, 9H, arom.).

19d. (1.73 g, 50%), mp 243°C (AcOH); [Found: C, 72.80; H, 5.30; N, 7.90. $C_{21}H_{18}N_2O_3$ requires C, 72.82; H, 5.24; N, 8.09. ν_{\max} (KBr) 2226 (CN), 1735 and 1684 (2C=O); δ_H (200 MHz, DMSO- d_6) 1.14 (t, $J=7$ Hz, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.95 (q, $J=7$ Hz, 2H, CH₂), 5.49 (s, 1H, Pyrrole-H), 7.0–7.68 (m, 9H, arom.).

20. (1.45 g, 54%), mp 253°C (AcOH); [Found: C, 62.50; H, 4.10; N, 15.40. $C_{14}H_{11}N_3O_3$ requires C, 62.45; H, 4.12; N, 15.61. ν_{\max} (KBr) 3410–3300 (br, OH and NH) 2222 (CN), 1700 and 1680 (2C=O); δ_H (200 MHz, DMSO- d_6) 2.30 (s, 3H, CH₃), 4.21 (s, 1H, OH), 6.85–7.42 (m, 5H, arom.), 7.62 (s, 1H, NH), 8.5 (s, 1H, pyrrole-NH).

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