Heteroatom Chemistry
Volume 15, Number 7, 2004

A Convenient Route to Pyridones, Pyrazolo[2,3-a]pyrimidines and Pyrazolo[5,1-c]triazines Incorporating Antipyrine Moiety

Ahmad M. Farag, Kamal M. Dawood, and Hanan A. Elmenoufy

Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt

Received 16 March 2004

ABSTRACT: *Condensation of 4-aminoantipyrine with ethyl acetoacetate, ethyl benzoylacetate, and ethyl cyanoacetate furnished the corresponding ethyl 3-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)aminoacrylate and 2-cyano-*N*-[(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)]acetamide derivatives. The aminoacrylates derivatives react with acetonitrile and sodium hydride to give 2-amino-6-methyl-1-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)-4-pyridone. Reaction of the cyanoacetamide derivative with dimethylformamide-dimethylacetal (DMF-DMA) afforded 2-cyano-*N*-[1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-pyrazol-4-yl]-2-(*N*,*N*-dimethylamino)methylene acetamide in high yield. Treatment of the latter with 5-aminopyrazole derivatives afforded the corresponding pyrazolo[2,3-a]pyrimidines. 2-cyano-*N*-[(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)]acetamide also reacts with heterocyclic diazonium salts to give the corresponding pyrazolo[5,1-c]-1,2,4-triazine derivatives*. © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:508–514, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20046

Correspondence to: Ahmad M. Farag; e-mail: afarag@main-ssc.cairo.edu.eg.

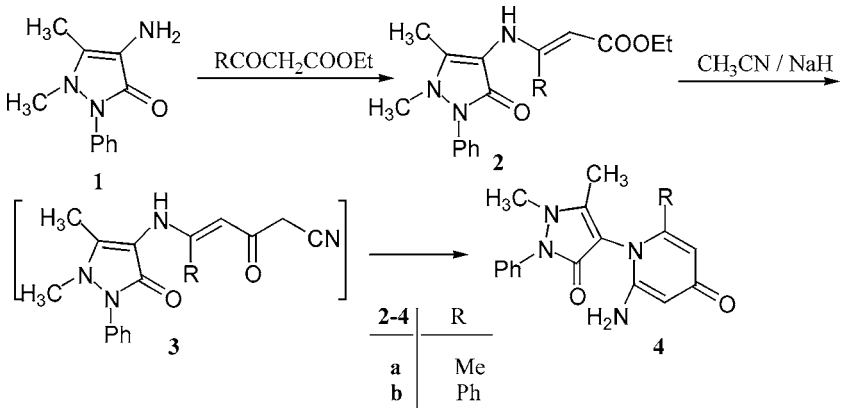
INTRODUCTION

The synthesis of 1,2-dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one (antipyrine) derivatives has attracted a great deal of attention in view of their potent biological and pharmacological importance [1–4]. In continuation of our interest in the synthesis of heteroatom compounds for biological screening [5–8], this study was undertaken to utilize 4-aminoantipyrine in the synthesis of a number of pyridone, thiazole, pyrazolo[2,3-a]-pyrimidine, and pyrazolo[5,1-c]-1,2,4-triazine derivatives having an antipyrine moiety.

RESULTS AND DISCUSSION

Condensation of 4-aminoantipyrine (**1**) with ethyl acetoacetate and ethyl benzoylacetate at refluxing temperature afforded products that were characterized as ethyl 3-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)aminoacrylate derivatives **2a** and **2b**, respectively (Scheme 1). Both products showed ethyl ester protons as triplet and quartet signals around δ 1.3 and 4.2, in addition to an olefinic CH singlet near δ 4.9 in their ^{1}H NMR spectra. Their IR spectra revealed absorption bands due to ester NH functions and carbonyl near 3274 and 1674 cm^{-1}, respectively.

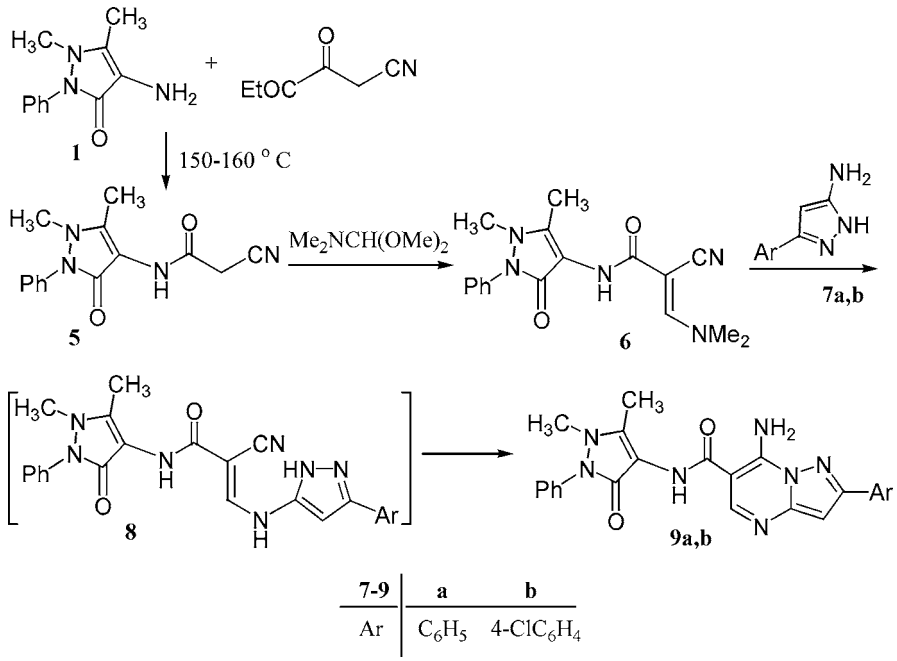
When ethyl acrylate derivative **2a** was treated with acetonitrile in the presence of sodium hydride by the Claisen condensation condition, it furnished a single product identified as 2-amino-6-methyl-1-



SCHEME 1

(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)-4-pyridone (**4a**), which is assumed to be formed through the in situ intramolecular cyclization of the nonisolable β-ketonitrile **3** (Scheme 1). The structure of 4-pyridone derivative **4** was established on the basis of its elemental analyses and spectral data. For example, its IR spectrum showed absorption bands at 3246, 3124, 1678, 1660 cm^{-1} due to amino and two carbonyl functions, respectively, and its mass spectrum showed a molecular ion peak at *m/z* 310.

Treatment of 4-aminoantipyrine (**1**) with ethyl cyanoacetate afforded a single product that was identified as 2-cyano-*N*-[(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)]acetamide (**5**) on the basis of its elemental and spectral analyses in addition to its chemical transformations outlined in Scheme 2. The ^{1}H NMR spectrum of compound **5** revealed a singlet signal at δ 3.24 due to methylene protons. Reaction of the cyanoacetamide derivative **5** with dimethylformamide-dimethylacetal (DMF-DMA), afforded the corresponding enaminonitrile derivative **6** in a good yield (Scheme 2). Treatment of the enaminonitrile derivative **6** with 5-aryl-3-aminopyrazoles **7a,b** resulted in the formation of the pyrazolo[2,3-a]pyrimidine derivatives **9a,b**. The ^{1}H NMR spectrum of the enaminonitrile **6** exhibited a singlet signal at δ 3.03 due to NMe_2 protons, however,



SCHEME 2

this signal disappeared in the ^{1}H NMR spectra of compounds **9a,b**. The formation of the pyrazolo[2,3-a]pyrimidine **9** from the enaminonitrile **6** is assumed to take place through an intramolecular cyclization of the nonisolable intermediate **8** as shown in Scheme 2.

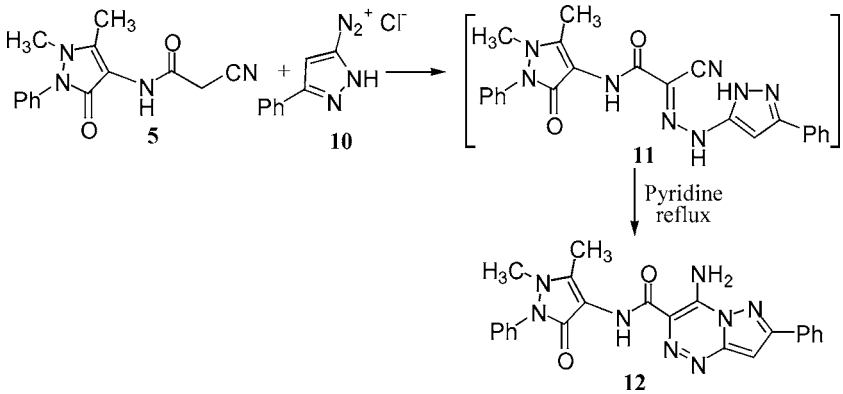
In continuation of our interest in the synthesis of bridged-head nitrogen heterocyclic systems [9–11], we have found that diazotized heterocyclic amines are excellent building blocks for the synthesis of the target compounds. Thus, coupling of compound **5** with 3-phenylpyrazol-5-diazonium chloride (**10**), afforded the corresponding pyrazolo[5,1-c]-1,2,4-triazine derivative **12** *via* the nonisolable hydrazone intermediate **11** (Scheme 3). The IR spectrum of the isolated product showed three absorption bands at 3392, 3339, 3281 due to NH and NH_2 functions besides two carbonyl absorption bands at 1670 and 1618 cm^{-1}. Its ^{1}H NMR spectrum revealed two D_2O-exchangeable singlets at δ 9.1 and 10.9 due to NH and NH_2 protons, in addition to the two methyl protons of the antipyrine ring at δ 2.26 and 3.12.

Compound **5** also reacted with some aromatic aldehydes to afford the corresponding benzylidene derivatives **13a–c** (Scheme 4). Treatment of the latter compounds with malononitrile furnished the aminopyridone derivatives **15a–c** (Scheme 4). The IR spectrum of compound **15a** revealed absorption bands at 3438, 3410, 2212, 1681, and 1651 cm^{-1}due to amino, nitrile, and two carbonyl functions, respectively. The ^{1}H NMR spectrum of **15a** exhibited singlet signals at δ 2.16 and 3.26 due to two methyl protons in addition to a broad D_2O-exchangeable signal at δ 8.47 due to amino protons. Formation of **15** is supposed to proceed through the Michael type addition followed by auto-oxidation of the intermediate **15c**. Additionally, the elucidation of structures of **15a–c** was supported chemically through their alternative synthesis from the reaction of **5** with the benzylidenemalononitriles **14a–c** under similar reaction conditions to give products identical in all respects (mp, mixed mp, and spectra) with the obtained aminopyridone derivatives **15a–c**.

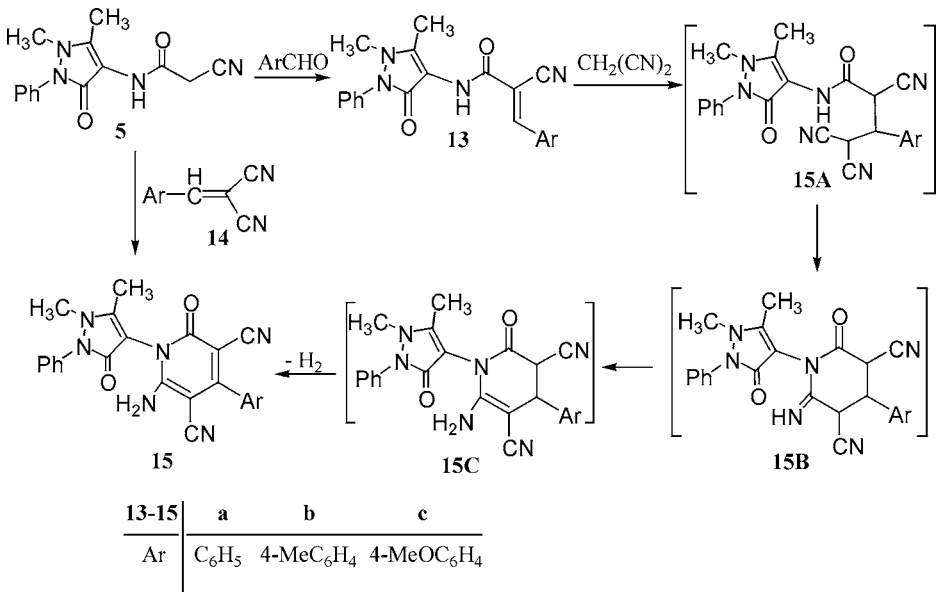
Treatment of compound **5** with phenyl isothiocyanate, in dimethylformamide, and in the presence of potassium hydroxide, at room temperature, followed by treatment with dilute hydrochloric acid, afforded a yellow-colored product that was identified as 2-cyano-2-[carboxamido-*N*-[4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)-2-yl] thioacetanilide (**16**) (Scheme 5). The structure of the latter was established on the basis of its elemental analyses and spectral data. Its IR spectrum showed absorption bands at 3346 and 2199 cm^{-1} due to NH group and a nitrile functions, respectively. The mass spectrum of the reaction product showed the molecular ion peak at *m/z* 405.

The thioacetanilide derivative **16** reacts with phenacyl bromide (**17**) to afford the corresponding thiazole derivative **18** (Scheme 5). The IR spectrum of the isolated product showed absorption bands at 3408 and 2169 cm^{-1} characteristic for NH and nitrile groups, respectively. Its ^{1}H NMR spectrum showed two singlet signals at δ 2.14, 3.05 due to two methyl protons and thiazole-5-CH proton at δ 7.71. The foregoing spectral data supported the proposed structure **18** and ruled out the other possible thiophene structure **19** (Scheme 5).

Similarly, compound **16** reacted with ethyl chloroacetate under similar reaction conditions and afforded the thiazolidinone derivative **21** as shown in Scheme 5. Compound **21** was alternatively synthesized by the reaction of the cyanothioacetanilide derivative **16** with chloroacetonitrile, which afforded the thiazolidinimine intermediate **20**. The intermediate was readily converted into thiazolidinone **21**



SCHEME 3

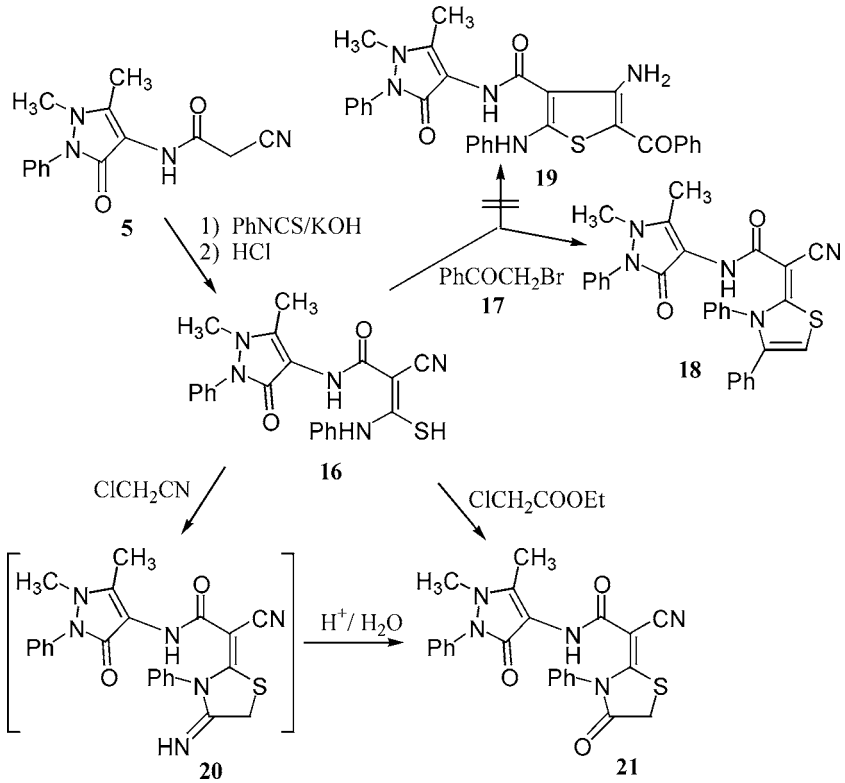


SCHEME 4

under the reaction condition (Scheme 5). The IR spectrum of compound **21** showed absorption bands at 3311 and 2194 cm^{-1} due to amide-NH and nitrile functions in addition to three carbonyl absorption bands at 1660, 1637, and 1625 cm^{-1}.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared



SCHEME 5

spectrophotometer. ^{1}H NMR spectra were determined at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 3-Aryl-5-amino-(1H)-pyrazoles **7a,b** [12], 3-phenyl-(1H)-pyrazole-5-diazonium chloride (**10**) [13], benzylidenemalononitriles **14a–c** [14,15], and phenacyl bromide (**17**) [16] were prepared according to the procedures reported in the literature.

*Synthesis of Ethyl 3-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)-aminoacrylate Derivatives* **2a,b**

To hot neat ethyl acetoacetate or ethyl benzoylacetate (10 mmol) was added 4-aminoantipyrine (**1**) (2.03 g, 10 mmol) portionwise over a period of 1 h, keeping the reaction temperature at 150–160°C. After the addition was complete, the reaction mixture was left to cool to room temperature then triturated with methanol. The solid product was collected by filtration, washed with cold ethanol, and finally recrystallized from ethanol to give the corresponding ethyl acrylates **2a,b**, respectively.

2a, yield (58%); mp 128–130°C (Lit. mp 130°C) [17].

2b, yield (69%); mp 148–150°C; IR (KBr) ν 3274 (NH), 1674, 1632 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.25 Hz), 1.87 (s, 3H), 2.79 (s, 3H), 4.17 (q, 2H, J = 7.25 Hz), 4.95 (s, 1H), 7.21–7.39 (m, 10H), 9.25 (s, 1H); MS *m/z*, 378 ($M^+ + 1$), 377 (M^+) , 331, 304, 274, 105, 77, 56. For $C_{22}H_{23}N_3O_3$Calcd: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.32; H, 6.42; N, 11.50%.

*2-Amino-6-methyl-1-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)-4-pyridone (***4a***)*

To a solution of the ethyl acrylate derivative **2a** (0.63 g, 2 mmol) in a mixture of dry benzene (30 mL), acetonitrile (0.3 mL), and dimethylformamide (1 mL) was added sodium hydride (0.15 g) portion-wise with stirring. After complete addition, the reaction mixture was heated at refluxing temperature for 2 h, then left to cool. The reaction mixture was treated with water and the aqueous layer was collected, then treated with dilute solution of HCl (10%) to give the pyridone derivative **4a** in 67% yield, mp > 300°C; IR (KBr) ν 3246, 3124 (NH_2), 1678, 1660 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 7.25–7.47 (m, 7H), 9.38 (br, s, 2H, NH_2); MS *m/z*, 311 ($M^+ + 1$), 310 (M^+), 269, 123, 56. For $C_{17}H_{18}N_4O_2$ Calcd: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.53; H, 5.75; N, 18.30%.

*2-Cyano-*N*-[1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl]acetamide (***5***)*

In a 250 mL three-necked round-bottomed flask, fitted with an air condenser and a thermometer, ethyl cyanoacetate (22.6 g, 21.26 mL, 200 mmol) was placed. The flask was immersed in an oil bath heated to 145–150°C, then 4-aminoantipyrine (**1**) (40.6 g, 200 mmol) was added portionwise over a period of 30 min and heating was continued for an additional 15 min. The reaction flask was removed from the oil bath, left to cool, and the product was triturated with water. The solid product was filtered off, washed with ethanol several times, dried, and finally recrystallized from ethanol to afford the cyanoacetamide derivative **5** in 60% yield, mp 218–220°C, IR (KBr) 3188 (NH), 2360 (C≡N), 1701, 1639 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm 2.21 (s, 3H, CH_3), 3.15 (s, 3H, NCH_3), 3.24 (s, CH_2), 7.27–7.57 (m, 5H, ArH), 9.91 (br s, 1H, D_2O-exchangeable, NH); MS *m/z*, 271 ($M^+ + 1$), 270 (M^+), 231, 230, 202, 83, 68, 56. For $C_{14}H_{14}N_4O_2$ Calcd: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.52; H, 5.01; N, 20.53%.

*Synthesis of 2-Cyano-*N*-[1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl]-2-(*N,N*-dimethylamino)methylene Acetamide (***6***)*

A mixture of the cyanoacetamide derivative **5** (3.5 g, 13 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (1.7 mL, 13 mmol) in dry xylene (30 mL) was refluxed for 4 h, then allowed to cool. The precipitated product was filtered off, washed with petroleum ether (60/80°C), and dried. Recrystallization from ethanol gave the enaminonitrile derivative **6** in 77% yield. mp 157–159°C; IR (KBr) ν 3325 (NH), 2183 (C≡N), 1660, 1612 (2C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.33 (s, 6H, NMe_2), 7.30–7.49 (m, 5H, ArH), 8.61 (s, 1H), 10.07 (br s, 1H, NH); MS *m/z*, 325 (M^+), 229, 123, 56. For $C_{17}H_{19}N_5O_2$ Calcd: C, 62.75; H, 5.89; N, 21.52. Found: C, 62.51; H, 6.01; N, 21.71%.

Reaction of the Enaminonitrile **6** *with 5-aminopyrazoles* **7a,b**

To a mixture of the enaminonitrile **6** (0.5 g, 1.5 mmol) and 5-aminopyrazoles **7a,b** (1.5 mmol) in ethanol (20 mL) was added few drops of piperidine as a catalyst. The mixture was refluxed for 3 h, then left to cool to room temperature. The solid that formed was collected by filtration, washed with ethanol dried, and finally recrystallized from ethanol to give the corresponding pyrazolo[2,3-a]pyrimidine derivative **9a,b** in 62 and 68% yield, respectively.

9a: mp 252–253°C; IR (KBr) ν 3222, 3136 (NH_2), 1662, 1627 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.22 (s, 3H), 3.10 (s, 3H), 6.82 (s, 1H), 7.03 (s, 1H), 7.21–7.66 (m, 10H), 8.64 (br. s, 2H, NH_2), 9.39 (s, 1H, NH); MS *m/z,* 439 (M^+), 348, 256, 159, 77, 56. For $C_{24}H_{21}N_7O_2$Calcd: C, 65.59; H, 4.82; N, 22.31. Found: C, 65.41; H, 4.57; N, 22.11%.

9b: mp 269–270°C; IR (KBr) ν 3209, 3132 (NH_2), 1651, 1630 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.21 (s, 3H), 3.11 (s, 3H), 6.86 (s, 1H), 7.05 (s, 1H), 7.38–8.13 (m, 9H), 8.68 (br. s, 2H, NH_2), 9.48 (s, 1H, NH); MS *m/z*, 475 ($M^+ + 2$), 474 ($M^+ + 1$), 473 (M^+), 270, 203, 84, 56. For $C_{24}H_{20}ClN_7O_2$Calcd: C, 60.82; H, 4.25; N, 20.69. Found: C, 60.63; H, 4.51; N, 20.46%.

Reaction of Cyanoacetamide Derivative **5** *with Pyrazole Diazonium Salt* **7**

To a stirred cold solution of cyanoacetamide derivative **5** (0.54 g, 2 mmol) in pyridine (25 mL) was added the pyrazole diazonium salt **7** (2 mmol) portionwise over a period of 30 min. The reaction mixture was kept in an icebox overnight then diluted with water. The solid that precipitated was filtered off, washed with water, and dried. Recrystallization from DMF gave 4-amino-3-[(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl)-carboxamido]-7-phenylpyrazolo[5,1-c]-1,2,4-triazine (**12**) in 61% yield, mp 254–256°C; IR (KBr) ν 3392 (NH), 3339, 3281 (NH_2), 1670, 1618 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 7.40–7.56 (m, 11H, ArH), 9.10 (s, 2H, NH_2), 10.90 (s, 1H, NH); MS *m/z*, 440 (M^+), 329, 159, 130, 104, 77, 56. For $C_{23}H_{20}N_8O_2$ Calcd: C, 62.72; H, 4.58; N, 25.44. Found: C, 63.01; H, 4.56; N, 25.38%.

Reaction of Cyanoacetamide Derivative **5** *with Aromatic Aldehydes*

General Procedure. To a solution of the cyanoacetamide derivative **5** (0.54 g, 2 mmol) and the appropriate aromatic aldehyde (2 mmol), in ethanol (20 mL), was added few drops of piperidine and the reaction mixture was refluxed for 4 h then allowed to cool. The precipitate that formed was filtered off, washed with ethanol, and purified by recrystallization from ethanol to afford the corresponding 2-cyano-2-arylmethylene-*N*-[1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl]-acetamide derivatives **13a–c**.

13a:Yield (63%), mp 223–224°C; IR (KBr) ν 3202 (NH), 2225 (C≡N), 1708, 1675 (2C=O) cm^{-1}; MS *m/z*, 358 (M^+), 281, 271, 231, 230, 229, 83, 77, 56. For $C_{21}H_{18}N_4O_2$ Calcd: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.01; H, 5.41; N, 15.23%.

13b: Yield (75%), mp 230–231°C; IR (KBr) ν 3193 (NH), 2252 (C≡N), 1690, 1674 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.19 (s, 3H, NCH_3), 7.19–7.63 (m, 10H, ArH), 9.37 (s, 1H, NH). For $C_{22}H_{20}N_4O_2$ Calcd: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.62; H, 5.18; N, 15.24%.

13c: Yield (88%), mp 214–216°C; IR (KBr) ν 3192 (NH), 2255 (C≡N), 1701, 1668 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.95 (s, 3H, CH_3), 3.20 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 7.23–7.57 (m, 10H, ArH), 9.38 (s, 1H, NH, D_2O exchangeable). For $C_{22}H_{20}N_4O_3$ Calcd: C, 68.03; H, 5.19; N, 14.42. Found: C, 68.30; H, 5.30; N, 14.11%.

*Synthesis of 6-Amino-2-oxo-4-aryl-1-[1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl]pyridine-3,5-dicarbonitrile (***15a–c***)*

Method A. To a solution of the appropriate benzylidenemalononitrile **14a–c** (5 mmol) in ethanol (20 mL) was added an equimolar amount of the 2-cyano-*N*-[1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3*H*-pyrazol-4-yl]acetamide (**5**) (1.36 g, 5 mmol) and few drops of piperidine and the reaction mixture was heated under reflux for 2 h, then left to cool to room temperature. The solid product that formed was collected by filtration, washed with ethanol, and then recrystallized from the EtOH/DMF to give the corresponding pyridin-2-one derivatives **15a–c**.

15a: Yield (76%), mp 210–211°C; IR (KBr) ν 3438, 3410 (NH_2), 2212 (C≡N), 1681, 1651 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.16 (s, 3*H*, CH_3), 3.26 (s, 3H, NCH_3), 7.41–7.58 (m, 10H, ArH), 8.47 (s, 2H, NH_2); MS *m/z*, 422 (M^+), 303, 302, 77, 56. For $C_{24}H_{18}N_6O_2$ Calcd: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.46; H, 4.50; N, 20.01%.

15b: Yield (75%), mp >300°C; IR (KBr) ν 3471, 3307 (NH_2), 2185 (C≡N), 1682, 1662 (2C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.16 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.28 (s, 3H, NCH_3), 7.40–7.46 (m, 9H, Ar-H), 8.53 (s, 2H, NH_2); MS *m/z*, 437 ($M^+ + 1$), 436 (M^+), 316, 302, 179, 122, 83, 56. For $C_{25}H_{20}N_6O_2$ Calcd: C, 68.80; H, 4.62; N, 19.25. Found: C, 68.31; H, 4.91; N, 19.41%.

15c: Yield (63%), mp >300°C; IR (KBr) ν 3278, 3194 (NH_2), 2212 (C≡N), 1666 (C=O), 1640 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.15 (s, 3H, CH_3), 3.26 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 7.10–7.58 (m, 9H, ArH), 8.40 (s, 2H, NH_2, D_2O exchangeable). For $C_{25}H_{20}N_6O_3$ Calcd: C, 66.36; H, 4.46; N, 18.57. Found: C, 66.61; H, 4.61; N,18.27%.

Method B. To a solution of the appropriate 2-cyano-2-arylmethylene-*N*-(1,2-dihydro-1,5-dimethyl-2-phvenyl-3-oxo-3*H*-pyrazol-4-yl]acetamide **13a–c**

(5 mmol) in ethanol (20 mL) was added malononitrile (1.36 g, 5 mmol) and few drops of piperidine. The reaction mixture was heated under reflux for 2 h then left to cool. The precipitated product was collected by filtration, washed with ethanol, and then recrystallized from the EtOH/DMF to give products identical in all respects ([m.p, mixed mp and spectra]) with those **15a–c** obtained from method A above.

Synthesis of the Thioacetanilide Derivative **16**

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) was added the cyanoacetamide derivative **5** (0.544 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, then the reaction mixture was poured over a cold solution of 0.5 N hydrochloric acid. The solid product that formed was filtered off, washed with water, dried, and finally recrystallized from ethanol to afford compound **16** in 64% yield, mp 154–155°C; IR (KBr) ν 3263, 3067 (2NH), 2174 (C≡N), 1724, 1686 (2C=O) cm^{-1}; MS *m/z*, 405 (M^+), 391, 372, 312, 229, 169, 105, 77. For $C_{21}H_{19}N_5O_2S$ Calcd: C, 62.20; H, 4.72; N, 17.27. Found: C, 62.51; H, 4.62; N, 17.43%.

Reaction of Thioacetanilide Derivative **16** *with* α*-Haloketones*

General Procedure. To a solution of the thioacetanilide derivative**16** (0.81 g, 2 mmol) in ethanol (20 mL), the appropriate α-haloketone, phenacyl bromide (**17**), ethyl chloroacetate or chloroacetonitrile (2 mmol) were added. Triethylamine (0.2 mL) was added dropwise and the reaction mixture was refluxed for 1 h then allowed to cool. The formed solid was filtered off, washed with ethanol, and recrystallized from EtOH/DMF to afford the corresponding 2-cyano-2-(3,4-diphenyl-2-thiazolylidene)-*N*-(antipyrin-4-yl)methylene acetamide (**18**) and 2-cyano-2-(4-oxo-3-phenyl-2-thiazolylidene)-*N*-(antipyrin-4-yl)methylene acetamide (**21**) derivatives respectively.

18: Yield (64%), mp 255–257°C; IR (KBr) ν 3408 (NH), 2169 (C≡N), 1652, 1623 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H, CH_3), 3.05 (s, 3H, NCH_3), 7.18–7.50 (m, 15H, ArH), 7.71 (s, 1H, thiazole-H); MS *m/z*, 506 ($M^+ + 1$), 505 (M^+), 276, 229, 134, 91, 56. For $C_{29}H_{23}N_5O_2S$ Calcd: C, 68.89; H, 4.59; N, 13.85. Found: C, 68.90; H, 4.50; N, 13.91%.

21: Yield (69%), mp 268–269°C; IR (KBr) ν 3244 (NH), 2210 (C≡N), 1724, 1655 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H, CH_3), 3.08 (s, 3H, NCH_3), 3.85 (s, 2H, CH_2), 7.25–7.61 (m, 10H, ArH); MS *m/z*, 446 ($M^+ + 1$), 445 (M^+), 230, 229, 202, 83, 82, 56. For $C_{23}H_{19}N_5O_3S_2$ Calcd: C, 62.01; H, 4.30; N, 15.72. Found: C, 61.90; H, 4.01; N, 15.46%.

REFERENCES

[1] Giraldez, A.; Nievees, R.; Ochoa, C.; Vara de Rey, C.; Cenarruzabeitia, E.; Lasheras, B. Eur J Med Chem 1989, 24, 497.
[2] Svensson, C. K.; Dorbitch, R. K.; Kloss, K. A. J Pharm Sci 1991, 80, 225.
[3] Baggott, J. E.; Morgan, S. L.; Ha, T.; Vaughn, W.; Hine, R. J. Biochem J 1992, 282, 197.
[4] Schillaci, D.; Maggio, B.; Raffa, D.; Daidone, G. Farmaco 1992, 47, 127.
[5] Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. J Chem Res, Synop 1998, 208.
[6] Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. Heteroatom Chem 1999, 10, 417.
[7] Dawood, K. M. Synth Commun 2001, 31, 1647.
[8] Kandeel, Z. E.; Dawood, K. M.; Ragab, E. A.; Farag, A. M Heteroatom Chem 2002, 13, 248.
[9] Farag, A. M. J Chem Res, Synop 1994, 432.
[10] Farag, A. M. J Chem Res, Synop 1995, 96.
[11] Dawood, K. M.; Farag, A. M.; Ragab, E. A.; Kandeel, Z. E. J Chem Res, Synop 2000, 206, Miniprint 2000, 0622.
[12] Joshi, K. C.; Pathak, V. N.; Garg, U. J Heterocycl Chem 1979, 16, 1141.
[13] Elnagdi, M. H.; Elmoghayer, M. R. H.; Fleita, D. H.; Hafez, E. A.; Fahmy, S. M J Org Chem 1976, 41, 3781.
[14] Gabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. J Org Chem 1984, 49, 5195.
[15] Angeletti, I.; Canepa, C.; Marcinetti, G.; Venturello, P. Tetrahedron Lett 1988, 29, 2261.
[16] Cowper, R. M.; Davidson, L. H. Org Synth Coll 1943, 2, 480.
[17] Maquestiau, A.; Vanden Eynde. J. J Bull Soc Chim Belg 1986, 95, 641–648.