Synthesis of bipyrazole and 1,3,4-thiadiazole derivatives

Kamal M. Dawood*, Eman A. Ragab and Ahmad M. Farag

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

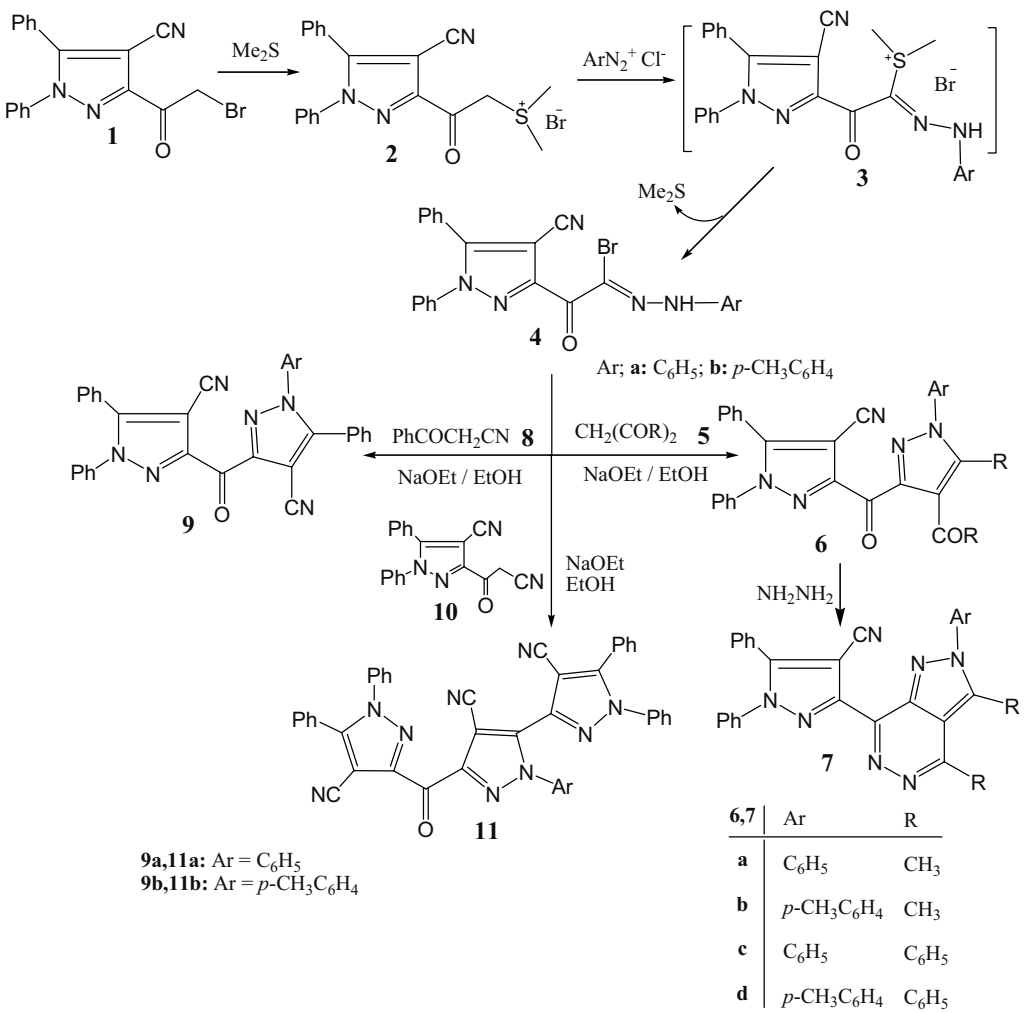
New hydrazonoyl bromides reacted with several C-nucleophiles to give the corresponding bipyrazoles. Treatment of 3-cyanoacetylpyrazole derivatives with phenyl isothiocyanate in potassium hydroxide followed by hydrazonoyl bromides gave the corresponding pyrazolyl-1,3,4-thiadiazoles.

Keywords: pyrazoles, thiophenes, 1,3,4-thiadiazoles, hydrazonoyl bromides

The considerable pharmacological importance of pyrazole derivatives[1-3] has attracted a great deal of attention. In addition, bis-pyrazole derivatives are involved in wide variety of medical and pharmaceutical applications.[4,5] 1,3,4-Thiadiazoles are also reported as highly anti-inflammatory,[6,7] anticonvulsant[6,8] and antimicrobial[9] agents. Furthermore, thiophene derivatives are known to have antiamoebic,[10] molluscicidal[11] and anti-inflammatory[12,13] activity On the other hand, the synthesis of combinatorial libraries of heterocyclic compounds permits the testing of the biological properties of a vast array of compounds. Routes to novel skeletons, which could be synthesised using combinatorial methods, are presently a major research objective. Hydrazonoyl halides are key intermediates in the synthesis of several heterocyclic systems.[14] In continuation of our recent work aiming at the synthesis of biologically active heterocyclic systems,[15-26] we report here a general route to several new polyheterocyclic skeletons having pyrazole, and 1,3,4-thiadiazole moieties, which could be adapted to the synthesis of small libraries. Anal. for this purpose, 3-bromoacetylpyrazole **1** and 3-cyanoacetylpyrazole **10** were found to be versatile substrates for the achievement of our target.

Results and discussion

Treatment of the bromoacetylpyrazole **1** with dimethylsulfide in refluxing methanol afforded the corresponding 1-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-1-ethanone-2-dimethyl sulfonium bromide (**2**) (Scheme 1). The sulfonium bromide **2** reacted with diazotised aromatic amines, in ethanol



6,7	Ar	R
a	C_6H_5	CH_3
b	p-$CH_3C_6H_4$	CH_3
c	C_6H_5	C_6H_5
d	p-$CH_3C_6H_4$	C_6H_5

Scheme 1

* Correspondent. E-mail: dr_dawood@yahoo.com

buffered with sodium acetate, at 0–5 °C to give the new pyrazolylhydrazonoyl bromides **4a,b** in good yields via loss of dimethylsulfide from the non-isolable hydrazone sulfonium bromide **3** (Scheme 1). The IR spectra of **4a,b** revealed, in each case, three characteristic absorptions near 3200, 2230 and 1650 cm^{-1} due to hydrazone-NH, nitrile and carbonyl functions, respectively. The ^1H NMR spectrum of **4b** for example, displayed a singlet signal at δ 2.23 due to methyl protons and a broad singlet signal (D_2O-exchangeable) at δ 8.71, due to NH proton, in addition to a multiplet at δ 7.01–7.32 corresponding to the aromatic protons.

The reactivity of the new hydrazonoyl bromides **4a,b** towards various *C*-nucleophiles were investigated. Thus, reaction of **4a,b** with acetylacetone **5a** in ethanolic sodium ethoxide solution, afforded products identified as 3-(4-acetyl-1-aryl-5-methyl-1H-pyrazol-3-carbonyl)-1,5-diphenyl-1H-pyrazole-3-carbonitrile derivatives **6a,b** (Scheme 1). Similarly, when the hydrazonoyl bromides **4a,b** were treated with dibenzoylmethane **5b** under the same reaction conditions, they afforded 3-(4-benzoyl-1-aryl-5-phenyl-1H-pyrazol-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile derivatives **6c,d,** respectively (Scheme 1). The structures of the isolated products **6a–d** were established on the basis of their elemental analyses and spectral data, as well as their chemical transformations as outlined in Scheme 1. The IR spectra of the reaction products showed, in each case, two absorption bands in the region 1650–1690 cm^{-1} due to two carbonyl groups. The ^1H NMR spectrum of compound **6a** revealed two singlet signals at δ 2.45 and 3.31 corresponding to methyl and acetyl protons, respectively, in addition to a multiplet in the region δ 7.34–7.62 due to aromatic protons, also the ^1H NMR spectrum of **6d** revealed one singlet at δ 2.39 due to methyl protons in addition to a multiplet in the region 7.30–7.53 due to aromatic protons. Treatment of the pyrazoles **6a–d** with hydrazine hydrate in refluxing ethanol afforded products identified as the pyrazolo[3,4-d]pyridazine derivatives **7a–d** (Scheme 1). The IR spectra of the isolated products **7a–d** were free of carbonyl absorptions.

In a similar manner, the hydrazonoyl bromides **4a,b** react with benzoylacetonitrile (**8**) in ethanolic sodium ethoxide solution, at room temperature to afford products that were identified as 3-(4-cyano-1-aryl-5-phenyl-1H-pyrazol-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile derivatives **9a,b** (Scheme 1). The IR spectra of compounds **9a,b** revealed, in each case, two nitrile bands and one carbonyl absorption band near 2230 and 1650 cm^{-1}, respectively. Their mass spectra revealed, in each case, a peak corresponding to molecular ion. The ^1H NMR spectrum of **9b** displayed singlet signal at δ 2.32 characteristic for methyl protons, in addition to a multiplet signals at δ 7.25–7.53 due to aromatic protons.

In a similar fashion, the hydrazonoyl bromides **4a,b** reacted with cyanoacetylpyrazole derivative **10** in ethanolic sodium ethoxide solution at room temperature and furnished, in each case, one isolable product. On the basis of their spectral analyses, the structures of the reaction products were identified as 3'-(4-cyano-1,5-diphenyl-1H-pyrazol-3-carbonyl)-1,5-diphenyl-1'-aryl-1H,1'H-3,5'-bipyrazol-4,4'-dicarbonitrile **11a,b** (Scheme 1). The IR spectra of the isolated products showed, in each case, two bands near 2225 cm^{-1} due to two nitrile functions and a strong band near 1660 cm^{-1} due to carbonyl group. The ^1H NMR spectrum of compound **11b** displayed a singlet signal at δ 2.33 and a multiplet at 7.17–7.67 characteristic for *p*-tolyl and aromatic protons, respectively.

Treatment of a solution of the cyanoacetylpyrazole **10** in DMF with phenyl isothiocyanate, in the presence of potassium hydroxide, at room temperature followed by the addition of an equimolar amount of the appropriate hydrazonoyl bromide **4a,b** afforded, in each case, only one isolable product as examined by TLC. The elemental analyses and spectral data are compatible with the 1,3,4-thiadiazole structures **14a,b**. Anal. for example, the IR spectra of the isolated products **14a,b** revealed, in each case, three absorption bands near 2210 cm^{-1} corresponding to nitrile functions and two carbonyl groups near 1675 cm^{-1}. The ^1H NMR of compound **14b** displayed a singlet at δ 2.29 and a multiplet at δ 7.15–7.67 due to methyl and aromatic protons, respectively. The mass spectrum of compound **14b** for example, exhibited a molecular ion peak at *m/z* 757. These results indicated that the reaction of **10** with the hydrazonoyl bromides **10a,b** proceeded, in each case, *via* the loss of hydrogen bromide followed by elimination of aniline molecule from the non-isolable intermediate **13** (Scheme 2) similar to our analogous reports.[19,23]

Treatment of the intermediate **13** with methyl iodide afforded a single product identified as 3-(2-cyano-3-methylthio-3-phenylaminoacryloyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**15**) (Scheme 2) based on its elemental analysis and spectral data. The IR spectrum of **15** exhibited four strong absorption bands at 3340, 2230, 2199 and 1710 cm^{-1} characteristic for one NH, two C≡N and one C=O functions, respectively. The ^1H NMR spectrum of **15** revealed two singlet signals at δ 2.25 and 13.71 due to SCH_3 and NH protons besides a multiplet at δ 7.27–7.33 due to aromatic protons.

When compound **15** was treated with hydrazine hydrate in refluxing ethanol it afforded a single product that was identified as 1,5-diphenyl-5'-phenylamino-1H,2'H-3,3'-bipyrazolyl-4,4'-dicarbonitrile (**17**) as shown in Scheme 2. The structure of the latter product **17** was established according to its elemental and spectral analyses.

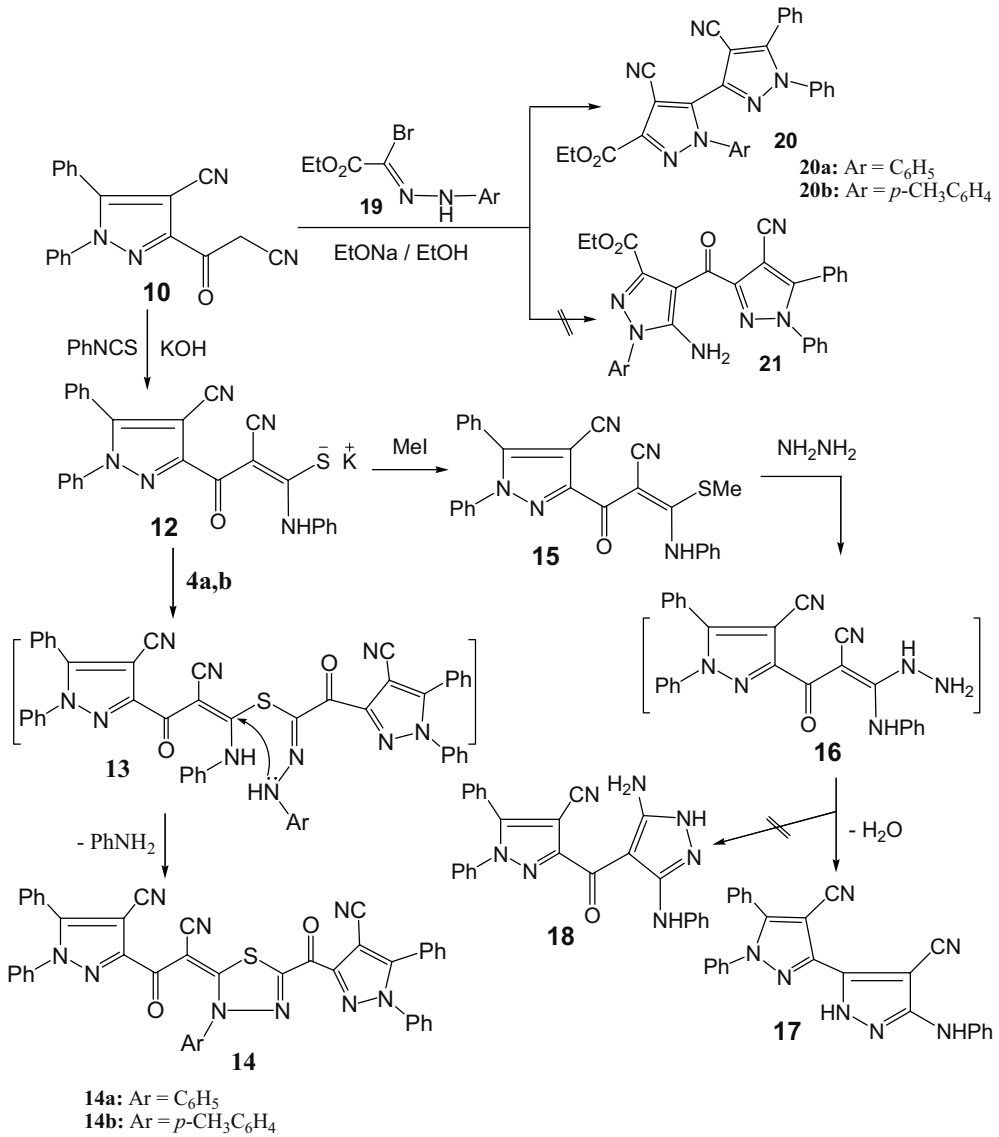
The reaction of cyanoacetylpyrazole **10** with hydrazonoyl chlorides **19a,b** in ethanolic sodium ethoxide solution at room temperature afforded, in each case, a single product based on TLC analysis. The isolated products were assigned as *1H,1'H*-3,5'-bipyrazole derivatives **20a,b** (Scheme 2) on the basis of their elemental analyses and spectral data. The IR spectra of compounds **20a,b** showed in all cases the presence of two nitrile absorption bands near 2230 and 2180 cm^{-1} and the lack of amino and carbonyl functions as an evidence for ruling out the structure **21**.

When the bromoacetylpyrazole **1** was treated with 2-aminobenzimidazole, in refluxing ethanol it afforded a single product that was identified as 2-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-1H-imidazo[1,2-a]benzimidazole **(22),** as shown in Scheme 3. The IR spectra of the isolated product was free of absorption band characteristic for carbonyl group and showed only one absorption band at 3380–3387 cm^{-1} due to NH stretching. Moreover, the mass spectrum showed a peak corresponding to its molecular ion.

Experimental

Melting points were measured with a Gallenkamp apparatus. The IR spectra were recorded on a Shimadzu FT-IR 8101 PC IR spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^1H NMR spectra were run at 300 MHz and ^{13}C NMR spectra were run at 75.46 MHz in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. Chemical shifts were related to that of the solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University. Bromoacetylpyrazole **1,**[23] benzoylacetonitrile (**7**),[27] and cyanoacetylpyrazole derivative **10**[24] were prepared according to the literature procedures.

1-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-1-ethanone-2-dimethylsulfonium bromide **(2):** A mixture of 3-bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile **(1)** (18.31 g, 50 mmol) and dimethyl sulfide (6 mL) in absolute methanol (75 mL) was refluxed for 30 min. The reaction mixture was allowed to cool and the solid product was collected by filtration, washed with methanol and finally recrystallised from ethanol to give the dimethylsulfonium bromide **2** as colourless crystals in 75% yield; m.p. 150–152 °C; IR (KBr)



Scheme 2

ν_{max} cm^{-1} 2228 (C≡N), 1700 (C=O); ^1H NMR (DMSO-d_6) δ 4.07 (s, 6H, $2CH_3$), 5.91 (s, 2H, CH_2), 7.33–7.50 (m, 10H, ArHs); ^{13}C NMR (DMSO-d_6) δ 64.8, 86.5, 112.8, 125.7, 125.9, 126.0, 128.9, 129.3, 129.6, 130.6, 137.8, 148.3, 150.4, 189.9. Anal. for $C_{20}H_{18}BrN_3SO$ Calcd C, 56.08; H, 4.24; N, 9.81; S, 7.49. Found: C, 56.20; H, 4.35; N, 9.8; S, 7.31%.

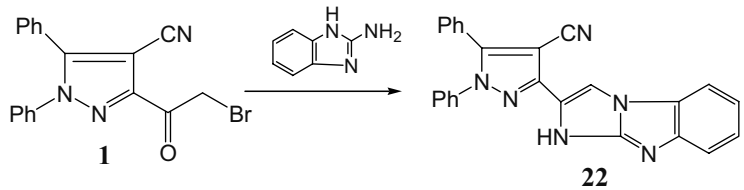
4-Cyano-α-oxo-1,5-diphenyl-N-aryl-1H-pyrazol-3-ethane-hydrazonoyl bromides **4a,b**: To a solution of the sulfonium bromide **2** (12.85 g, 30 mmol) in ethanol (50 mL) was added sodium acetate trihydrate (5 g) and the reaction mixture was cooled at 0 °C then treated with the appropriate arene diazonium chloride (30 mmol) with stirring over a period of 30 min. After the addition was complete, the reaction mixture was stirred for further 3 h at 0–5 °C and left to stand in an ice box for 12 h then diluted with water. The solid that precipitated was filtered off, washed with water and dried. Recrystallisation from acetic acid afforded the corresponding hydrozonoyl bromides **4a,b** in 65 and 70% yields, respectively.

4-Cyano-α-oxo-N,1,5-triphenyl-1H-pyrazole-3-ethanehy-drazonoyl bromide (**4a**): Yield (65%); m.p. 176–178 °C; IR (KBr) ν_{max} cm^{-1} 3209 (NH), 2237 (C≡N), 1651 (C=O), 1543 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11–7.40 (m, 15H, ArH), 8.80 (br.s, 1H, NH); *m/z* 470 (M^+). $C_{24}H_{16}BrN_5O$ Calcd. C, 61.29; H, 4.43; N, 14.89. Found: C, 61.33; H, 4.56; N, 14.92%.

4-Cyano-α-oxo-N-(4-tolyl)-1,5-diphenyl-1H-pyrazole-3-ethane-hydrazonoyl bromide (**4b**): Yield (10.16 g, 70%); m.p. 220–222 °C; IR (KBr) ν_{max} cm^{-1} 3237 (NH), 2230 (C≡N), 1651 (C=O). ^1H NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 7.01–7.32 (m, 14H, ArHs), 8.71 (s, br, 1H, NH); *m/z* 484 (M^+). Anal. for $C_{25}H_{18}BrN_5O$ Calcd C, 61.99; H, 3.75; N, 14.46. Found: C, 62.11; H, 3.84; N, 14.37%.

Reaction of the hydrazonoyl bromides **4a,b** *with the active methylenes* **5, 8** *and* **10**

The appropriate active methylene compound (acetylacetone **5a**, dibenzoylmethane **5b**, benzoylacetonitrile **8** or cyanoacetylpyrazole **10**)



Scheme 3

(2 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute ethanol (20 mL)] with stirring. After stirring for 15 min, the appropriate hydrazonoyl bromide **4a,b** (2 mmol) was added portion-wise to the resulting solution over a period of 30 min. and the reaction mixture was left to stir for further 12 h at room temperature. The solid product that formed was filtered off, washed with water and dried. Recrystallisation from ethanol/DMF mixture afforded the pyrazole derivatives **6a,b, 6c,d, 9a,b,** and **11a,b**, respectively in 70–95% yields.

3-(4-Acetyl-1-phenyl-5-methyl-1H-pyrazol-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**6a**): Yield (0.67 g, 71%); m.p. 198–199 °C; IR (KBr) ν_{max} cm^{-1} 2230 (C≡N), 1682, 1651 (2C=O). ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.34–7.62 (m, 15H, ArHs); *m/z* 471 (M^+). Anal. for $C_{29}H_{21}N_5O_2$ Calcd C, 73.87; H, 4.49; N, 14.85. Found: C, 73.90; H, 4.30; N, 14.98%.

3-(4-Acetyl-5-methyl-1-(p-tolyl)-1H-pyrazol-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**6b**): Yield (0.73 g, 75%); m.p. 204–206 °C; IR (KBr) ν_{max} cm^{-1} 2229 (C≡N), 1685, 1650 (2C=O). ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.40–7.48 (m, 14H, ArHs); *m/z* 485 (M^+). Anal. for $C_{30}H_{23}N_5O_2$ Calcd C, 74.21; H, 4.77; N, 14.42. Found: C, 74.05; H, 4.82; N, 14.58%.

3-(4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**6c**): Yield (1.01 g, 85%); m.p. 232–234 °C; IR (KBr) ν_{max} cm^{-1} 2230 (C≡N), 1690, 1651 (2C=O). ^{1}H NMR (DMSO-d_6) δ 7.17–7.66 (m, ArHs); *m/z* 595 (M^+). Anal. for $C_{39}H_{25}N_5O_2$: Calcd C, 78.64; H, 4.23; N, 11.76. Found: C, 78.77; H, 4.41; N, 11.60%.

3-(4-Benzoyl-1-(p-tolyl)-5-phenyl-1H-pyrazole-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**6d**): Yield (1.15 g, 95%); m.p. 240–242 °C; IR (KBr) ν_{max} cm^{-1} 2237 (C≡N), 1690, 1659 (2C=O); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 7.17–7.65 (m, 24H, ArHs); *m/z* 609 (M^+). Anal. for $C_{40}H_{27}N_5O_2$ Calcd C, 78.80; H, 4.46; N, 11.49. Found: C, 78.92; H, 4.52; N, 11.36%.

3-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**9a**): Yield (0.74 g, 72%); m.p. 260–262 °C; IR (KBr) ν_{max} cm^{-1} 2230 (2C≡N), 1655 (C=O); ^{1}H NMR (DMSO) δ 7.23–7.51 (m, ArH); *m/z* 516 (M^+). Anal. for $C_{33}H_{20}N_6O$ Calcd C, 76.73; H, 3.90; N, 16.27. Found: C, 76.86; H, 4.14; N, 16.44%.

3-(4-Cyano-1-(p-tolyl)-5-phenyl-1H-pyrazole-3-carbonyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**9b**): Yield (0.8 g, 76%); m.p. 270–272 °C; IR (KBr) ν_{max} cm^{-1} 2228 (2C≡N), 1659 (C=O); ^{1}H NMR (DMSO) δ 2.32 (s, 3H, CH_3), 7.25–7.53 (m, 19H, ArH); *m/z* 530 (M^+). Anal. for $C_{34}H_{22}N_6O$ Calcd C, 76.97; H, 4.18; N, 15.84. Found: C, 77.01; H, 4.33; N, 15.94%.

3′-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-1,5,1′-triphenyl-1H,1′H-3,5′-bipyrazolyl-4,4′-dicarbonitrile (**11a):** Yield (0.92 g, 72%); m.p. 293–295 °C. IR: ν_{max} cm^{-1} 2231, 2222 (3≡N), 1643 (C=O). ^{1}H NMR (DMSO-d_6) δ 7.33–7.53 (m, ArHs); *m/z* 683 (M^+). Anal. for $C_{43}H_{25}N_9O$ Calcd C, 75.54; H, 3.69; N, 18.44. Found: C, 75.43; H, 3.84; N, 18.66%.

3′-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-1,5-diphenyl-1′-(p-tolyl)-1H,1′H-[3,5′]bipyrazolyl-4,4′-dicarbonitrile (**11b):** Yield (0.99 g, 71%); m.p. 265–267 °C; IR (KBr) ν_{max} cm^{-1} 2230, 2223 (2 C≡N), 1659 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H, CH_3), 7.29-7.52 (m, 24H, ArHs); *m/z* 697 (M^+). Anal. for $C_{44}H_{27}N_9O$: Calcd C, 75.74; H, 3.90; N, 18.07. Found: C, 75.82; H, 4.01; N, 18.25%.

Synthesis of pyrazolo[3,4-d]pyridazine derivatives **7a–d.**

A mixture of the appropriate pyrazole derivative **6a–d** (1 mmol) and hydrazine hydrate (0.4 mL, 80%), in ethanol (20 mL) was refluxed for 1 h, then allowed to cool. The solid product that formed was collected by filtration, washed with water, dried and finally recrystallised from ethanol/DMF mixture to afford the pyrazolo[3,4-d]-pyridazines **7a–d**, respectively in 75-97% yields.

7-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-3,4-dimethyl-2-phenyl-2H-pyrazolo[3,4-d]-pyridazine (**7a**): Yield (0.35 g, 76%); m.p. 275–277 °C. IR: ν_{max} cm^{-1} 2230 (C≡N). ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 7.40–7.69 (m, 15H, ArHs); *m/z* 467 (M^+). Anal. for $C_{29}H_{21}N_7$ Calcd C, 74.50; H, 4.53; N, 20.97. Found: C, 74.71; H, 4.43; N, 21.07%.

7-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-3,4-dimethyl-2-(p-tolyl)-2H-pyrazolo[3,4-d] pyridazine (**7b**): Yield (79%); m.p. 297–299 °C; IR (KBr) ν_{max} cm^{-1} 2230 (C≡N); ^{1}H NMR (DMSO-d_6) δ 2.78 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 7.43–7.56 (m, 14H, ArHs); *m/z* 481 (M^+). Anal. for $C_{30}H_{23}N_7$ Calcd C, 74.83; H, 4.81; N, 20.36. Found: C, 75.04; H, 4.73; N, 20.59%.

7-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-2,3,4-triphenyl-2H-pyrazolo[3,4-d]pyridazine (**7c**): Yield (0.53 g, 90%); m.p. > 300 °C; IR (KBr) ν_{max} cm^{-1} 2230 (C≡N); ^{1}H NMR (DMSO-d_6) δ 7.01–7.39 (m, 6H, ArHs), 7.45–7.52 (m, 19H, ArHs); *m/z* 591 (M^+). Anal. for $C_{39}H_{25}N_7$: Calcd C, 79.17; H, 4.26; N, 16.57. Found: C, 80.01; H, 4.33; N, 16.79%.

7-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-3,4-diphenyl-2-(p-tolyl)-2H-pyrazolo[3,4-d]pyridazine (**7d**): Yield (0.57 g, 95%); m.p. > 300 °C; IR (KBr) ν_{max} cm^{-1} 2230 (C≡N); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 7.07–7.52 (m, 24H, ArHs); *m/z* 605 (M^+). Anal. for $C_{40}H_{27}N_7$: Calcd C, 79.32 H, 4.49 N, 16.19. Found: C, 79.4; H, 4.5; N, 16.05%.

Synthesis of 1,3,4-thiadiazole derivatives **14a,b**

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) was added the cyanoacetylpyrazole **10** (0.6 g, 2 mmol). After stirring for 30 minutes, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, then the appropriate hydrazonoyl bromide **4** (2 mmol) was added. The mixture was stirred for further 12 h at room temperature. The solid product was filtered off, washed with ethanol and recrystallised from DMF to afford the corresponding 1,3,4-thiadiazole derivatives **14a,b**.

5-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-2-(4-cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-3-phenylcyanomethylene-2,3-dihydro[1,3,4]thiadiazole **(14a):** Yield (1.11 g, 75%); m.p. 290–292 °C; IR (KBr) ν_{max} cm^{-1} 2235, 2205 (C≡N), 1674 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.27–7.80 (m, ArHs); m/z 743 (M^+). Anal. for $C_{44}H_{25}N_9O_2S$ Calcd C, 71.05; H, 3.39; N, 16.95; S, 4.31. Found: C, 71.23; H, 3.41; N, 17.01; S, 4.43%.

5-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-2-(4-cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-3-(p-tolyl)cyanomethylene-2,3-dihydro[1,3,4]thiadiazole **(14b):** Yield (1.2 g, 79%); m.p. 286–288 °C; IR (KBr) ν_{max} cm^{-1} 2235, 2208 (3 C≡N), 1678 (2 C=O). ^{1}H NMR (DMSO-d_6) δ 2.99 (s, 3H, CH_3), 7.15–7.67 (m, 24H, ArHs); m/z 757 (M^+). Anal. for $C_{45}H_{27}N_9O_2S$: Calcd C, 71.32; H, 3.59; N, 16.63; S, 4.23. Found: C, 71.40; H, 3.68; N, 16.52; S, 4.19%.

2-(2-Cyano-3-methylthio-3-phenylaminoacryloyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**15**)

To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide (30 mL), cyanoacetylpyrazole **10** (3.12 g, 10 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (1.35 g, 10 mmol) was added to the resulting mixture and stirring was continued for 2 h at room temperature. To the resulting mixture, methyl iodide (1.41 g, 10 mmol) was added and the mixture was left to stir for further 6 h till all the starting materials were completely consumed. The precipitated solid was filtered off, washed with water, dried and finally recrystallised from ethanol to afford 3.95 g of **15** (86% yield); m.p. 210–212 °C; IR (KBr) ν_{max} cm^{-1} 3340 (NH), 2230, 2199 (2 C≡N), 1710 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H, SCH_3), 7.27–7.33 (m, 15H, ArH), 13.71 (br.s, 1H, D_2O-exchangeable, NH); *m/z* 461 (M^+). Anal. for $C_{27}H_{19}N_5OS$ Calcd. C, 70.26; H, 4.15; N, 15.17; S, 6.95. Found: C, 70.39; H, 4.04; N, 15.35; S, 7.18%.

Synthesis of 1,5-diphenyl-5′-phenylamino-1H,2′H-3,3′-bipyrazol-4,4′-dicarbonitrile (**17**)

To a solution of **15** (0.92 g, 2 mmol) in ethanol (20 mL), hydrazine hydrate (80%, 0.2 mL) was added. The mixture was refluxed for 4 h, then allowed to cool to room temperature. The solid product that formed was filtered off, washed with ethanol and dried. Recrystallisation from ethanol/DMF mixture afforded 0.74 g of **17** (87% yield); m.p. 278–280 °C; IR (KBr) ν_{max} cm^{-1} 3294, 3240 (2 NH), 2232, 2222 (2 C≡N); ^{1}H NMR (DMSO-d_6) δ 7.39–7.51 (m, 15H, ArH), 9.24 (br.s, 1H, D_2O-exchangeable, NH), 9.67 (br.s, 1H, D_2O-exchangeable, NH); *m/z* 427 (M^+). Anal. for $C_{26}H_{17}N_7$ Calcd C, 73.05; H, 4.01; N, 22.94. Found: C, 72.90; H, 4.28; N, 23.22%.

Synthesis of 1′-acetyl-1,5-diphenyl-1H,1′H[3,5′]bipyrazolyl-4,4′-dicarbonitriles **20**

General procedure: To an ethanolic sodium ethoxide solution [prepared by dissolving sodium metal (0.046 g, 2 mmol) in absolute ethanol (20 mL)] was added cyanoacetylpyrazole **10** (0.62 g, 2 mmol) with stirring. To the resulting solution, the appropriate hydrazonoyl chloride **19a,b** (2 mmol) was added portionwise with stirring over a period of 30 min. The reaction mixture was left to stir for further 12 h at room temperature. The resulting solid product was filtered off, washed with water, dried and finally recrystallisation from DMF/ethanol mixture (1 : 1) to afford the corresponding bipyrazole derivatives **20a,b** in good yields.

Ethyl 4-cyano-5-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-1-phenyl-1H-pyrazol-3-carboxylate (**20a**): Yield (65%); m.p. 221–223 °C; IR (KBr) ν_{max} cm^{-1} 2233, 2185 (2 C≡N), 1720 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.36 (t, 3H, CH_3, *J* = 7.2 Hz), 4.44 (q, 2H, CH_2, *J* = 7.2 Hz), 7.23–7.31 (m, 3H, ArH), 7.32-7.56 (m, 12H, ArH); ^{13}C NMR (DMSO) δ 13.4, 61.8, 93.9, 96.5, 111.3, 111.5, 125.1, 125.2, 128.8, 129.1, 129.3, 129.7, 130.5, 137.4, 139.1, 139.4, 144.6, 146.6, 146.8, 149.3, 158.8; *m/z* 484 (M^+). Anal. for $C_{29}H_{20}N_6O_2$ Calcd C, 71.89; H, 4.16; N, 17.35. Found: C, 71.65; H, 4.03; N, 17.12%.

Ethyl 4-cyano-5-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-1-(p-tolyl)-1H-pyrazole-3-carboxylate (**20b**): Yield (66%); m.p. 208–210 °C; IR (KBr) ν_{max} cm^{-1} 2235, 2189 (2 C≡N), 1743 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.35 (t, 3H, CH_2CH_3, *J* = 7.2 Hz), 2.38 (s, 3H, CH_3), 4.44 (q, 2H, CH_2CH_3, *J* = 7.2 Hz), 7.25–7.50 (m, 14H, ArH); *m/z* 498 (M^+). Anal. for $C_{30}H_{22}N_6O_2$ Calcd C, 72.28; H, 4.45; N, 16.86. Found: C, 72.49; H, 4.33; N, 16.78%.

Reaction of bromoacetylpyrazole **1** *with 2-aminobenzimidazole*

A mixture of 3-bromoacetylpyrazole **1** (0.73 g, 2 mmol) and 2-aminobenzimidazole (0.29 g, 2.2 mmol) in ethanol (20 mL) was refluxed for 3 h, then allowed to cool. The solid that formed was filtered off, washed with water and dried. Recrystallisation from dimethylformamide afforded 2-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-1H-imidazo[1,2-a]benzimidazole (**22**). Yield (76%); m.p. 270–272 °C; IR (KBr) ν_{max} cm^{-1} 3387 (NH), 2230 (C≡N); ^{1}H NMR (DMSO-d_6) δ 6.0 (s, 1H, pyrazole-CH), 7.27–7.67 (m, 13H, ArHs), 8.0 (d, 1H, ArH, *J* = 7.8 Hz), 8.43 (br.s, 1H, NH); *m/z* 400 (M^+). Anal. for $C_{25}H_{16}N_6$ Calcd C, 74.99; H, 4.03; N, 20.99. Found: C, 75.14; H, 3.88; N, 20.80%.

Received 31 July 2009; accepted 10 September 2009
Paper 09/0716 doi: 10.3184/030823409X12528547964044
Published online: 9 October 2009

References

1 J. Kleemann, B. Engel, Kutscher and D. Reichert, *Pharmaceutical substances*, Thieme, New York, 1999.
2 S.R. Stauffer, C.J. Coletta, R. Tedesco, G. Nishiguchi, K. Carlson, J. Sun, B.S. Katzenellenbogen and J.A. Katzenellenbogen, *J. Med. Chem*., 2000, **43**, 4934.
3 F. Manna, F. Chimenti, A. Bolasco, M.L. Cenicola and M.D. Amico, *Eur. J. Med. Chem. Chim. Ther.,* 1992, **27**, 633.
4 O. Bruno, A. Ranise, F. Bondavalli, P. Schenone, M. D'Amico, A. Filippelli, W. Felippelli and S. Rossi, *Farmaco,* 1993, **48**, 949.
5 A.M. Cuadro, J. Elguero and P. Navarro, *Chem. Pharm. Bull.,* 1985, **33**, 2535.
6 K.M. Dawood, H. Abdel-Gawad E.A. Ragab, M. Ellithey and H.A. Mohamed, *Bioorg. Med. Chem.,* 2006, **14**, 3672.
7 S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, W. Filippelli, G. Falcone, L. Giordano and M.R. Vitelli, *Bioorg. Med. Chem.,* 2001, **9**, 2149.
8 M.A. Ilies, B. Masereel, S. Rolin, A. Scozzafava, G. Campeanu, V. Cimpeanu and C.T. Supuran, *Bioorg. Med. Chem.,* 2004, **12**, 2717.
9 H.N. Dogan, A. Duran, S. Rollas, G. Sener, M.K. Uysal and D. Gulen, *Bioorg. Med. Chem.,* 2002, **10**, 2893.
10 S. Sharma, F. Athar, M.R. Maurya and A. Azam, *Eur. J. Med. Chem.,* 2005, **40**, 1414.
11 A.A. Fadda, E. Abdel-Latif and R.E. El-Mekawy, *Eur. J. Med. Chem.,* 2009, **44**, 1250.
12 A.D. Pillai, P.D. Rathod, F.P. Xavier, H. Padh, V. Sudarsanam and K.K. Vasu, *Bioorg. Med. Chem.,* 2005, **13**, 6685.
13 P.R. Kumar, S Raju, P.S. Goud, M Sailaja, M.R. Sarma, G. Om Reddy, M.P. Kumar, V.V.R.M.K. Reddy, T Suresh and P. Hegde, *Bioorg. Med. Chem.,* 2004, **12**, 1221.
14 A.S. Shawali and M.A. Abdalla, *Adv. Heterocycl. Chem.,* 1995, **63**, 277.
15 K.M. Dawood, E.A. Ragab and S.N. Mohamed, *Z. Naturforschung*,, 2009, **64B**, 43.
16 N.A. Kheder, E.S. Darwish and K.M. Dawood, *Heterocycles,* 2009, **78**, 177.
17 A.M. Farag, A.S. Mayhoub, S.E. Barakat and A.H. Bayomi, *Bioorg. Med. Chem.,* 2008, **16**, 881.
18 A.M. Farag, A.S. Mayhoub, S.E. Barakat and A.H. Bayomi, *Bioorg. Med. Chem.,* 2008, **16**, 4569.
19 K.M. Dawood and M.A. Raslan, *J. Heterocycl. Chem.,* 2008, **45**, 137.
20 K.M. Dawood, H. Abdel-Gawad, M. Ellithey, H.A. Mohamed and B. Hegazi, *Arch. Pharm. Chem. Life Sci.,* 2006, **339**, 133.
21 K.M. Dawood, *J. Heterocycl. Chem.*, 2005, **42**, 221.
22 K.M. Dawood, *Tetrahedron,* 2005, **61**, 5229.
23 K.M. Dawood, E.A. Ragab and A.M. Farag, *J. Chem. Res.,* 2003, *(S)* 685 *(M)* 1151.
24 K.M. Dawood, A.M. Farag and E.A. Ragab, *J. Chin. Chem. Soc.,* 2004, **51**, 853.
25 Z.E. Kandeel, K.M. Dawood, E.A. Ragab and A.M. Farag. *Heteroatom Chem.,* 2002, **13**, 248.
26 K.M. Dawood, A.M. Farag, E.A. Ragab and Z.E. Kandeel, *J. Chem. Res.,* 2000, *(S)* 206, *(M)* 622.
27 A. Obregia, *Liebigs Ann. Chem.*, 1898, **266**, 324.