Res Chem Intermed
DOI 10.1007/s11164-014-1551-7

Efficient synthesis of some new functionalized 3-amino- and 5-aminopyrazoles derivatives

Ehab Abdel-Latif · Abdel-Galil M. Khalil

Received: 14 November 2013 / Accepted: 30 January 2014
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Abstract Cyanoacetic acid hydrazide derivatives were utilized as key intermediates for the synthesis of some new 3-amino- and 5-aminopyrazole derivatives. Coupling of *N*′-phenylsulfonyl-2-cyanoacetohydrazide (**1**) and 1-(2-cyanoacetyl)-4-phenyl thiosemicarbazide (**4**) with different aryl diazonium chlorides afforded the corresponding 5-amino-1-substituted-4-pyrazolin-3-one derivatives **3** and **6**, respectively. Treatment of ketene dithioacetal **9** and ketene-N,S-acetal **13** with hydrazine and/or benzenesulfonyl hydrazide furnished the corresponding 3-amino-5-1*H*-pyrazole-4-carbohydrazide derivatives **10**, **11**, and **14**. The structures of the new synthesized compounds were elucidated and confirmed by elemental analyses and spectral data.

Keywords Hydrazides · Benzenesulphonyl chloride · Carbon disulfide · Ketene dithioacetal · 5-Aminopyrazole

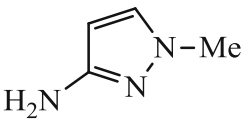
Introduction

Pyrazole and its derivatives are very interesting heterocyclic compounds with wide-ranging biological activities [1, 2]. In particular, 3-aminopyrazole derivatives have been reported as protein β-sheet stabilizers [3] and are much used as ideal precursors for the synthesis of biologically active fused heterocyclic compounds [4–7]. Some of the 3-aminopyrazole analogues (e.g., H30935) are used as building blocks to more complex moieties, such as potential drug candidates [8–11] and others (e.g., H32918) as selective-based MK2-inhibitors [12]. Moreover, they are used as intermediates in the dyestuff industry [13–17].

E. Abdel-Latif (✉) · A.-G. M. Khalil
Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt
e-mail: ehabattia00@gmx.net

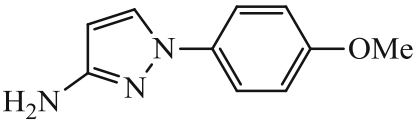
Published online: 19 February 2014

The chemistry of 3(5)-aminopyrazoles has been recently reviewed and has received considerable attention not only from the point of pharmaceutical and medicinal applications but also because of their synthetic importance as versatile precursors for the synthesis of azoloazines [18–21]. A literature survey revealed that the synthetic strategy required to prepare 3(5)-aminopyrazoles involves either the reactions of hydrazine hydrate with each of the α,β-unsaturated nitriles [22–25] and 3-oxoalkanenitriles [26–29], or the reactions of hydrazonyl halides with active methylene nitriles [30]. In the light of these facts, we report here an efficient synthesis of novel substituted 3-amino- and 5-aminopyazole derivatives, which have not previously been reported.



H30935

3-Amino-1-methyl-1*H*-pyrazole



H32918

3-Amino-1-(4-methoxyphenyl)-1*H*-pyrazole

Experimental

The chemicals used for the synthesis of the compounds were obtained from Aldrich and Sigma Chemical without further purification. The solvents used were of analytical grade. Melting points were measured on an electrothermal Gallenkamp melting point apparatus. Elemental analyses were carried out at the Microanalytical Unit, Cairo University, Giza, Egypt; the results were in satisfactory agreement with the calculated values. The IR spectra were recorded in KBr disks on a Mattson 5000 FTIR spectrometer (not all frequencies are reported). The NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz using *TMS* as an internal standard and $CDCl_3$ and/or DMSO-d_6 as solvent. The mass spectra were performed using a Varian MAT 311 mass spectrometer at 70 eV.

Synthesis of *N*′-phenylsulfonyl-2-cyanoacetohydrazide (1), 1-cyanoacetyl-4-phenylthiosemicarbazide (4) and *N*′-arylidene-2-cyanoacetohydrazides 7

The starting materials *N*′-phenylsulfonyl-2-cyanoacetohydrazide (**1**) [31], 1-cyanoacetyl-4-phenylthiosemicarbazide (**4**) [35], and *N*′-arylidene-2-cyanoacetohydrazide derivatives **7** [36] were prepared according to the previous literature.

General synthesis of 5-amino-4-arylazo-1-phenylsulfonyl-4-pyrazolin-3-ones 3**a–c** and 5-amino-4-arylazo-1-phenylthiocarbamoyl-4-pyrazolin-3-ones **6a–c**

A cold solution of sodium nitrite (5 mmol) in 30 mL of water was added gradually to a cold suspension of desired aromatic amine (5 mmol) in 1.5 mL of concentrated

HCl. The diazonium salt thus obtained was added by continuous stirring to a cold solution of compound **1** and/or compound **4** (5 mmol) in 20 mL of pyridine. The reaction mixture was stirred at 0–5 °C for 2 h and diluted with water. The solid was then filtered, dried, and recrystallized from ethanol to afford the corresponding pyrazoline derivatives **3** and/or **6**, respectively.

5-Amino-4-phenylazo-1-phenylsulfonyl-4-pyrazoline-3-one (**3a**)

Yield 67 %, m.p. 220–221 °C. IR (KBr, cm^{-1}): 3,307, 3,190 (NH_2 and NH), 1,624 (C=O). ^1H NMR (DMSO-d_6, δ ppm): 7.25–7.75 (m, 10H, Ar–H), 8.20 (s, 2H, NH_2), 10.45 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{13}N_5O_3S$ (343.36): C, 52.47; H, 3.82; N, 20.40. Found: C, 52.58; H, 3.76; N, 20.51.

5-Amino-1-phenylsulfonyl-4-(p-tolylazo)-4-pyrazoline-3-one (**3b**)

Yield 78 %, m.p. 241–241 °C. IR (KBr, cm^{-1}): 3,316, 3,233, 3,193 (NH_2 and NH), 1,629 (C=O). ^1H NMR (DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3), 7.10–7.85 (m, 9H, Ar–H), 8.78 (s, 2H, NH_2), 11.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 21.52, 105.28, 116.88, 122.65, 128.82 (2C), 129.68 (2C), 132.41 (2C), 133.16 (2C), 139.30, 141.08, 142.92, 161.62. MS (*m/z*, relative intensity): 358 (M^++1, 100). Anal. Calcd. for $C_{16}H_{15}N_5O_3S$ (357.39): C, 53.77; H, 4.23; N, 19.60. Found: C, 53.96; H, 4.29; N, 19.51.

5-Amino-4-(p-anisylazo)-1-phenylsulfonyl-4-pyrazoline-3-one (**3c**)

Yield 58 %, m.p. 234–235 °C. IR (KBr, cm^{-1}): 3,442, 3,335, 3,208 (NH_2 and NH), 1,638 (C=O). ^1H NMR (DMSO-d_6, δ ppm): 3.85 (s, 3H, OCH_3), 6.90 (d, 1H, Ar–H), 7.20–7.75 (m, 7H, Ar–H), 8.55 (s, 2H, NH_2), 10.85 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{15}N_5O_4S$ (373.39): C, 51.47; H, 4.05; N, 18.76. Found: C, 51.39; H, 4.11; N, 18.84.

5-Amino-4-phenylazo-1-phenylthiocarbamoyl-4-pyrazolin-3-one (**6a**)

Yield 64 %, m.p. 181–182 °C. IR (KBr, cm^{-1}): 3,382, 3,344, 3,268 (NH_2 and NH), 1,634 (C=O). ^1H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 6.85.7.60 (m, 10H, Ar–H), 8.85 (s, 2H, NH_2), 10.70 (s, 1H, NH), 12.15 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{14}N_6OS$ (338.39): C, 56.79; H, 4.17; N, 24.84. Found: C, 56.63; H, 4.22; N, 24.76.

5-Amino-1-phenylthiocarbamoyl-4-(p-tolylazo)-4-pyrazolin-3-one (**6b**)

Yield 71 %, m.p. 208–209 °C. IR (KBr, cm^{-1}): 3,417, 3,366, 3,305, 3,186 (NH_2 and NH), 1,631 (C=O). ^1H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 6.75–7.40 (m, 9H, Ar–H), 9.05 (s, 2H, NH_2), 11.10 (s, 1H, NH), 13.15 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 21.65, 104.05, 118.96, 124.32, 128.37 (2C), 130.23 (2C), 132.69 (2C), 133.52 (2C), 139.75, 141.51, 143.55, 162.14, 184.15. MS (*m/z*, relative intensity): 353 (M^++1, 100). Anal. Calcd. for $C_{17}H_{16}N_6OS$ (352.41): C, 57.94; H, 4.58; N, 23.85. Found: C, 57.82; H, 4.50; N, 23.77.

5-Amino-4-(p-anisylazo)-1-phenylthiocarbamoyl-4-pyrazolin-3-one (**6c**)

Yield 66 %, m.p. 214–216 °C. IR (KBr, cm^{-1}): 3,405, 3,374, 3,272, 3,218 (NH_2 and NH), 1,636 (C=O). ^1H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 3.90 (s, 3H, OCH_3), 6.80–7.70 (m, 9H, Ar–H), 8.90 (s, 2H, NH_2), 10.80 (s, 1H, NH), 12.65 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{16}N_6O_2S$ (368.41): C, 55.42; H, 4.38; N, 22.8. Found: C, 55.64; H, 4.33; N, 22.70.

General synthesis of *N*′-arylidene-2-cyano-3,3-bis-(methylthio)-acrylohydrazides **9a–c**

To a stirred suspension of finely powdered potassium hydroxide (20 mmol) in dry dimethyl formamide (20 mL) cooled to 0 °C, first the cyanoacetic acid arylidene-hydrazide **7** (10 mmol) and then carbon disulfide (10 mmol) were added gradually. The reaction mixture was stirred at room temperature for 3 h, treated with methyl iodide, and stirred at room temperature for an additional 6 h. Then, it was poured into ice-water; the resulting precipitate was filtered off, dried, and recrystallized from ethanol to give **9**.

N′-Benzylidene-2-cyano-3,3-bis-(methylthio)-acrylohydrazide (**9a**)

Yield 54 %, m.p. 176–177 °C. IR (KBr, cm^{-1}): 3,163 (NH), 2,111 (C≡N), 1,640 (C=O). ^1H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 2.45 (s, 3H, SCH_3), 2.55 (s, 3H, SCH_3), 7.25–7.60 (m, 5H, Ar–H), 8.15 (s, 1H, CH=N), 10.65 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{13}N_3OS_2$ (291.39): C, 53.58; H, 4.50; N, 14.42. Found: C, 53.47; H, 4.53; N, 14.49.

2-Cyano-*N*′-(*p*-methylbenzylidene)-3,3-bis-(methylthio)-acrylohydrazide (**9b**)

Yield 66 %, m.p. 193–194 °C. IR (KBr, cm^{-1}): 3,178 (NH), 2,110 (C≡N), 1,638 (C=O). ^1H NMR (DMSO-d_6, δ ppm): 2.40 (s, 6H, Ar–CH_3 and SCH_3), 2.55 (s, 3H, SCH_3), 7.20 (d, 2H, Ar–H), 7.50 (d, 2H, Ar–H), 8.20 (s, 1H, CH=N), 11.20 (s, 1H, NH). Anal. Calcd. for $C_{14}H_{15}N_3OS_2$ (305.42): C, 55.06; H, 4.95; N, 13.76. Found: C, 55.14; H, 4.98; N, 13.68.

2-Cyano-*N*′-(*p*-methoxybenzylidene)-3,3-bis-(methylthio)-acrylohydrazide (**9c**)

Yield 62 %, m.p. 198–200 °C. IR (KBr, cm^{-1}): 3,183 (NH), 2,108 (C≡N), 1,641 (C=O). ^1H NMR (DMSO-d_6, δ ppm): 2.45 (s, 3H, SCH_3), 2.55 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3), 6.90 (d, 2H, Ar–H), 7.50 (d, 2H, Ar–H), 8.20 (s, 1H, CH=N), 11.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 16.35 (2C), 55.48, 78.66, 116.66, 126.86 (2C), 130.24 (2C), 132.18, 153.90, 158.62, 163.08, 179.95. MS (*m/z*, relative intensity): 322 (M^+, 52.4 %). Anal. Calcd. for $C_{14}H_{15}N_3O_2S_2$ (321.42): C, 52.32; H, 4.70; N, 13.07. Found: C, 52.15; H, 4.76; N, 13.18.

General synthesis of 3-amino-*N*′-arylidene-5-methylthio-1*H*-pyrazole-4-carbohydrazides **10a–c**

A mixture of ketene dithioacetal **9** (3 mmol) and hydrazine hydrate 80 % (6 mmol) in ethanol (25 mL) was heated under reflux for 2 h, then left to cool to room temperature and further left overnight. The precipitated solid was filtered off and dried, and then recrystallized from ethanol/DMF mixture (3:1) to yield compounds **10a–c** as yellow crystals.

3-Amino-*N*′-benzylidene-5-methylthio-1*H*-pyrazole-4-carbohydrazide (**10a**)

Yield 67 %, m.p. 223–224 °C. IR (KBr, cm^{-1}): 3,342, 3,227, 3,155 (NH_2 and NH), 1,648 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.50 (s, 3H, SCH_3), 7.30–7.70 (m, 5H, Ar–H), 8.10 (s, 2H, NH_2), 8.25 (s, 1H, CH=N), 10.30 (s, 1H, NH), 12.45 (s, 1H, NH). Anal. Calcd. for $C_{12}H_{13}N_5OS$ (275.33): C, 52.35; H, 4.76; N, 25.44. Found: C, 52.56; H, 4.84; N, 25.33.

3-Amino-*N*′-(*p*-methylbenzylidene)-5-methylthio-1*H*-pyrazole-4-carbohydrazide (**10b**)

Yield 73 %, m.p. 246–247 °C. IR (KBr, cm^{-1}): 3,368, 3,212 (NH_2 and NH), 1,652 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 7.30–7.60 (m, 4H, Ar–H), 8.05 (s, 2H, NH_2), 8.20 (s, 1H, CH=N), 9.80 (s, 1H, NH), 12.30 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{15}N_5OS$ (289.36): C, 53.96; H, 5.23; N, 24.20. Found: C, 53.84; H, 5.31; N, 24.27.

3-Amino-*N*′-(*p*-methoxybenzylidene)-5-methylthio-1*H*-pyrazole-4-carbohydrazide (**10c**)

Yield 71 %, m.p. 236–237 °C. IR (KBr, cm^{-1}): 3,320, 3,276, 3,192 (NH_2 and NH), 1,650 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.50 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 7.00 (d, 2H, Ar–H), 7.60 (d, 2H, Ar–H), 8.05 (s, 2H, NH_2), 8.20 (s, 1H, CH=N), 10.15 (s, 1H, NH), 12.60 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 18.22, 55.95, 88.74, 126.70 (2C), 130.04 (2C), 132.18, 134.48, 151.35, 154.45, 158.14, 163.65. MS (*m/z*, relative intensity): 305 (M^+, 100 %). Anal. Calcd. for $C_{13}H_{15}N_5O_2S$ (305.36): C, 51.13; H, 4.95; N, 22.94. Found: C, 51.29; H, 4.98; N, 23.03.

General synthesis of 3-amino-*N*′-arylidene-5-methylthio-1-phenylsulfonyl-1*H*-pyrazole-4-carbohydrazides **11a–c**

To the solution of **9** (3 mmol) in DMF (20 mL), benezenesulfonyl hydrazide (3 mmol) and anhydrous potassium carbonate (0.42 g) were added. The reaction mixture was heated under reflux for 4 h and then left to cool. The reaction mixture was poured onto ice-cold water (100 mL) and the resulting solid was filtered off, dried well, and re-crystallized from ethanol to yield compounds **11a–c** as yellow crystals.

3-Amino-*N*′-benzylidene-5-methylthio-1-phenylsulfonyl-1*H*-pyrazole-4-carbohydrazide (**11a**)

Yield 48 %, m.p. 211–212 °C. IR (KBr, cm^{-1}): ,3344, 3,282, 3,191 (NH_2 and NH), 1,642 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 2.50 (s, 3H, SCH_3), 7.40–7.80 (m, 10H, Ar–H), 8.25 (s, 1H, CH=N), 9.05 (s, 2H, NH_2), 11.15 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{17}N_5O_3S_2$ (415.49): C, 52.03; H, 4.12; N, 16.86. Found: C, 52.16; H, 4.08; N, 16.91.

3-Amino-*N*′-(*p*-methylbenzylidene)-5-methylthio-1-phenylsulfonyl-1*H*-pyrazole-4-carbohydrazide (**11b**)

Yield 61 %, m.p. 224–225 °C. IR (KBr, cm^{-1}): 3,367, 3,275, 3,182 (NH_2 and NH), 1,650 (C=O). ^{1}H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 7.20–7.80 (m, 9H, Ar–H), 8.30 (s, 1H, CH=N), 9.20 (s, 2H, NH_2), 12.05 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{19}N_5O_3S_2$ (429.52): C, 53.13; H, 4.46; N, 16.31. Found: C, 53.04; H, 4.48; N, 16.36.

3-Amino-*N*′-(*p*-methoxybenzylidene)-5-methylthio-1-phenylsulfonyl-1*H*-pyrazole-4-carbohydrazide (**11c**)

Yield 56 %, m.p. 218–219 °C. IR (KBr, cm^{-1}): 3,411, 3,356, 3,282 (NH_2 and NH), 1,648 (C=O). ^{1}H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 2.55 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3), 7.00 (d, 2H, Ar–H), 7.40–7.80 (m, 7H, Ar–H), 8.30 (s, 1H, CH = N), 9.30 (s, 2H, NH_2), 12.15 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 18.08, 55.95, 88.46, 123.04, 126.28 (2C), 128.62 (2C), 129.40 (2C), 130.12 (2C), 133.22, 134.82, 138.36, 152.34, 154.50, 158.04, 163.54. MS (*m/z*, relative intensity): 446 (M^++1, 67 %). Anal. Calcd. for $C_{19}H_{19}N_5O_4S_2$ (445.52): C, 51.22; H, 4.30; N, 15.72. Found: C, 51.13; H, 4.34; N, 15.66.

General synthesis of *N*′-arylidene-2-cyano-3-methylthio-3-phenylamino-acrylohydrazides **13a**–**c**

To a stirred suspension of finely powdered potassium hydroxide (10 mmol) in dry dimethyl formamide (20 mL), first *N*′-arylidene-2-cyanoacetohydrazides **7** (10 mmol) and then phenyl isothiocyanate (10 mmol) were added gradually. The reaction mixture was stirred at room temperature for 3 h, treated with methyl iodide (10 mmol), and stirred at room temperature for an additional 6 h. Then, it was poured into ice-water; the resulting precipitate was filtered off, dried, and recrystallized from ethanol to give **13**.

N′-benzylidene-2-cyano-3-methylthio-3-phenylamino-acrylohydrazide (**13a**)

Yield 58 %, m.p. 162–163 °C. IR (KBr, cm^{-1}): 32,13, 3,144 (2NH), 2,120 (C≡N), 1,655 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 2.50 (s, 3H, SCH_3), 6.70–7.60 (m, 10H, Ar–H), 8.30 (s, 1H, CH=N), 9.20 (s, 1H, NH), 10.25 (s, 1H, NH). Anal. Calcd. for

$C_{18}H_{16}N_4OS$ (336.41): C, 64.26; H, 4.79; N, 16.65. Found: C, 64.36; H, 4.86; N, 16.74.

2-Cyano-*N*′-(*p*-methylbenzylidene)-3-methylthio-3-phenylamino-acrylohydrazide (**13b**)

Yield 65 %, m.p. 155–156 °C. IR (KBr, cm^{-1}): 3,189, 3,152 (2NH), 2,125 (C≡N), 1,648 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 2.40 (s, 3H, Ar–CH_3), 2.50 (s, 3H, SCH_3), 6.80–7.60 (m, 9H, Ar–H), 8.30 (s, 1H, CH=N), 9.30 (s, 1H, NH), 10.45 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 18.78, 21.29, 98.28, 114.92, 126.18 (2C), 128.39 (3C), 129.30 (2C), 130.08 (2C), 132.62, 135.53, 140.59, 155.28, 162.86, 179.74. MS (*m/z*, relative intensity): 351 (M^++1, 77 %). Anal. Calcd. for $C_{19}H_{18}N_4OS$ (350.44): C, 65.12; H, 5.18; N, 15.99. Found: C, 65.28; H, 5.23; N, 15.91.

2-Cyano-*N*′-(*p*-methoxybenzylidene)-3-methylthio-3-phenylamino-acrylohydrazide (**13c**)

Yield 54 %, m.p. 180–182 °C. IR (KBr, cm^{-1}): 3,231, 3,177 (2NH), 2,124 (C≡N), 1,651 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 2.50 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 6.80–7.80 (m, 9H, Ar–H), 8.35 (s, 1H, CH=N), 9.35 (s, 1H, NH), 10.30 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (366.44): C, 62.28; H, 4.95; N, 15.29. Found: C, 62.19; H, 4.90; N, 15.37.

General synthesis of 3-amino-*N*′-arylidene-5-phenylamino-1*H*-pyrazole-4-carbohydrazides **14a–c**

A mixture of ketene-*N*,S-acetal **13** (3 mmol) and hydrazine hydrate 80 % (9 mmol) was heated on a steam bath for 1 h and left to cool. The reaction mixture was triturated with ethanol and the resulting solid was filtered off and recrystallized from ethanol to give compounds **14a–c** as white crystals.

3-Amino-*N*′-benzylidene-5-phenylamino-1*H*-pyrazole-4-carbohydrazide (**14a**)

Yield 76 %, m.p. 272–273 °C. IR (KBr, cm^{-1}): 3,372, 3,311, 3,263, 3,177 (NH_2 and NH), 1,655 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 6.90–7.80 (m, 10H, Ar–H), 8.25 (s, 1H, CH=N), 8.90 (s, 2H, NH_2), 10.20 (s, 1H, NH), 11.05 (s, 1H, NH), 12.50 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{16}N_6O$ (320.35): C, 63.74; H, 5.03; N, 26.23. Found: C, 63.82; H, 5.08; N, 26.18.

3-Amino-*N*′-(*p*-methylbenzylidene)-5-phenylamino-1*H*-pyrazole-4-carbohydrazide (**14b**)

Yield 80 %, m.p. 250–251 °C. IR (KBr, cm^{-1}): 3,358, 3,272, 3,194 (NH_2 and NH), 1,654 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3), 6.90–7.70 (m, 9H, Ar–H), 8.25 (s, 1H, CH=N), 8.85 (s, 2H, NH_2), 9.75 (s, 1H, NH), 10.75 (s, 1H, NH), 12.60 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 21.54, 97.23, 127.08 (2C), 128.63

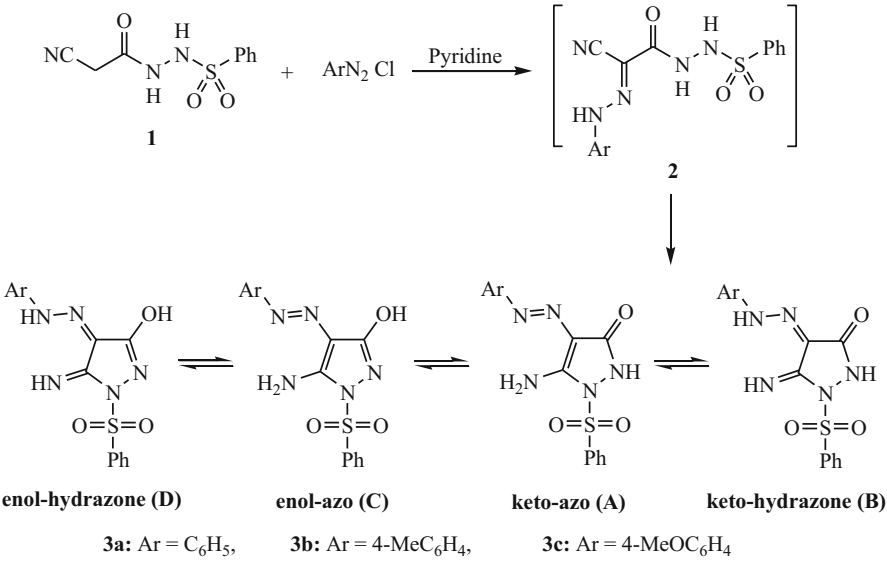
(3C), 129.15 (2C), 130.26 (2C), 132.74, 135.96, 141.37, 146.41, 153.40, 156.24, 163.11. MS (*m/z*, relative intensity): 335 (M^++1, 100 %). Anal. Calcd. for $C_{18}H_{18}N_6O$ (334.38): C, 64.66; H, 5.43; N, 25.13. Found: C, 64.47; H, 5.37; N, 25.21.

3-Amino-*N*′-(*p*-methoxybenzylidene)-5-phenylamino-1*H*-pyrazole-4-carbohydrazide (**14c**)

Yield 74 %, m.p. 285–286 °C. IR (KBr, cm^{-1}): 3,412, 3,283, 3,247, 3,165 (NH_2 and NH), 1,657 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 3.85 (s, 3H, OCH_3), 6.90–7.80 (m, 9H, Ar–H), 8.20 (s, 1H, CH=N), 9.10 (s, 2H, NH_2), 9.85 (s, 1H, NH), 10.80 (s, 1H, NH), 12.45 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{18}N_6O_2$ (350.37): C, 61.70; H, 5.18; N, 23.99. Found: C, 61.82; H, 5.22; N, 23.91.

Results and discussion

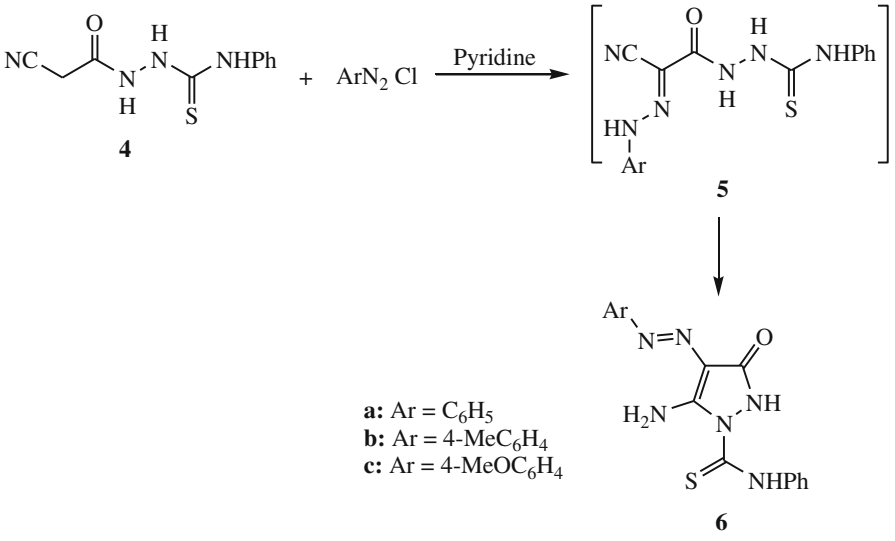
The *N*′-phenylsulfonyl-2-cyanoacetohydrazide (**1**) was prepared by the reaction of 2-cyanoacetohydrazide with benzenesulfonyl chloride according to the literature procedure [31]. Coupling of compound **1** with a variety of aryl diazonium chlorides afforded the corresponding cyanoaceto-*N*-phenylsulfonyl hydrazide intermediates **2** which underwent intramolecular cyclization to give the 5-amino-4-arylazo-1-phenylsulfonyl-4-pyrazolin-3-ones **3a–c** (Scheme 1).



Scheme 1 Synthetic route to 5-amino-4-arylazo-1-phenylsulfonyl-4-pyrazolin-3-ones **3a–c** and their possible tautomeric structures

Pyrazoles **3a–c** can be formulated in four different possible tautomeric structures, namely keto-azo (**A**), keto-hydrazone (**B**), enol-azo (**C**), and enol-hydrazone tautomer (**D**) (Scheme 1). The tautomeric structures (**B**) and (**D**) were excluded from the ^{1}H NMR spectra of the studied compounds as they lacked signals in the region of $\delta = 13.83–13.92$ ppm assignable to the hydrazone proton (–CH = N–NH–) [32]. The enol-azo form (**C**) was also ruled out due to the presence of the pyrazole-NH signal at 11.27 ppm [33] in ^{1}H NMR spectra and the absence of an OH group at 3,445 cm^{-1} in their IR spectra. The ^{13}C NMR spectra of **3b** revealed a characteristic peak in the region $\delta = 161.62$ ppm due to a carbonyl carbon and validated tautomeric structure (**A**). It is worth mentioning that the predominant formation of the keto-azo form (A) is also in the line with similar structures reported earlier by Morkovnik and coworkers [34].

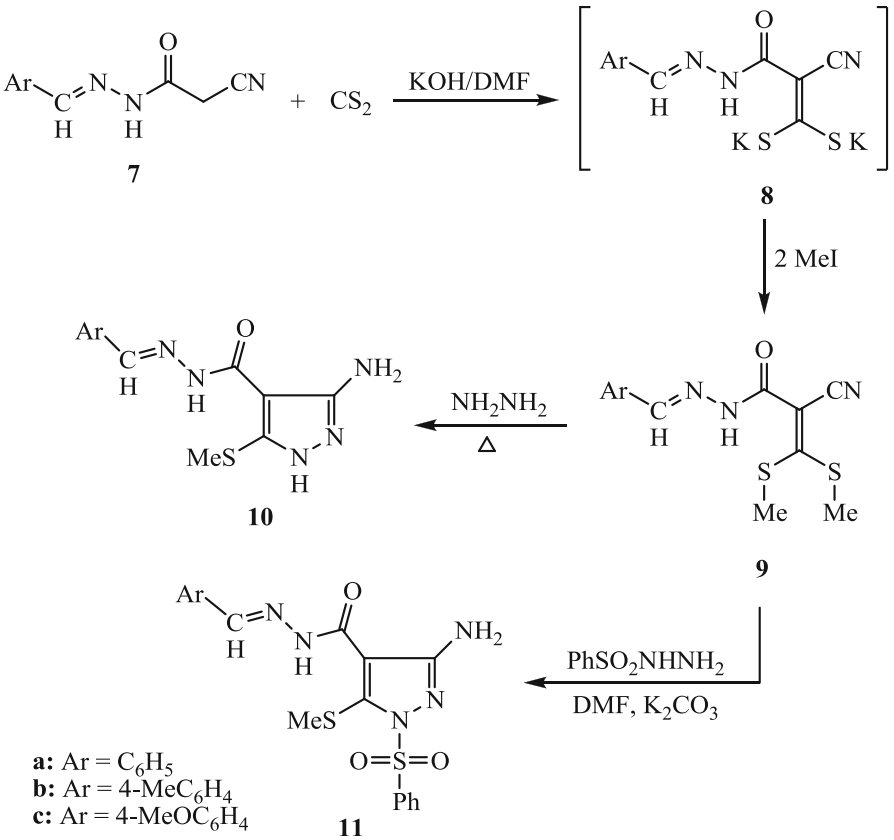
Coupling of 1-cyanoacetyl-4-phenyl-thiosemicarbazide **(4)** [35] with a variety of aryl diazonium chlorides afforded the corresponding 5-amino-4-arylazo-1-phenylthiocarbamoyl-4-pyrazolin-3-ones **6a–c** via intramolecular cyclization of cyanoaceto-*N*-phenylthiocarbamoyl hydrazide intermediates **5** (Scheme 2). Spectral studies indicated the superiority of the keto-azo structure **6** rather than other tautomeric structures. The IR spectrum of the representative example **6b** exhibited absorption bands at 3,417, 3,366, 3,305, and 3,186 cm^{-1} attributed to NH_2 and NH vibrations, respectively, while the C=O vibration was observed at 1,631 cm^{-1}. Its ^{1}H NMR spectrum showed the methyl protons as a singlet signal at δ 2.35 ppm. The aromatic protons resonated at δ 6.75–7.40 ppm. The NH_2 protons appeared as a singlet signal at δ 9.05, and the protons of the NH groups appeared as two singlet signals at δ 11.10 and 13.15 ppm. Moreover, the mass spectrum of **6b** clearly showed the molecular ion peak at *m/z* 353 corresponding to the molecular weight of the molecular formula $(C_{17}H_{16}N_6OS)+1$.



Scheme 2 Synthetic route to 5-amino-4-arylazo-1-phenylthiocarbamoyl-4-pyrazolin-3-ones **6a–c**

Furthermore, the reaction of *N′*-arylidene-2-cyanoacetohydrazides **7** [36] with carbon disulfide in dimethyl formamide, in the presence of potassium hydroxide, gave the non-isolable intermediate **8**. The latter was converted into the corresponding ketene dithioacetal **9** by treatment with methyl iodide at room temperature in a moderate yield (Scheme 3). The structure of **9** was confirmed by analytical and spectroscopic data. The IR spectrum of **9c** showed absorption bands at 3,183 (NH), 2,108 (C≡N), and 1,641 (C=O). Its ^{1}H NMR spectrum in DMSO-d_6 revealed the presence of singlet signals at δ 2.45, 2.55, and 3.85 ppm, characteristic for three methyl groups. The two doublet signals at δ 6.90 and 7.40 ppm were attributed to aromatic protons. Two singlet signals at δ 8.20 and 11.35 ppm were assigned to N=CH and NH protons, respectively. Also, the structure **9c** is supported by its mass spectrum which showed a molecular ion peak at $m/z = 322$ (52.4 %) corresponding to the formula $(C_{14}H_{15}N_3O_2S_2)+1$.

Polarized α-cyanoketene dithioacetals are versatile starting materials for the synthesis of a wide variety of heterocycles. Thus, heating of ketene dithioacetals **9**

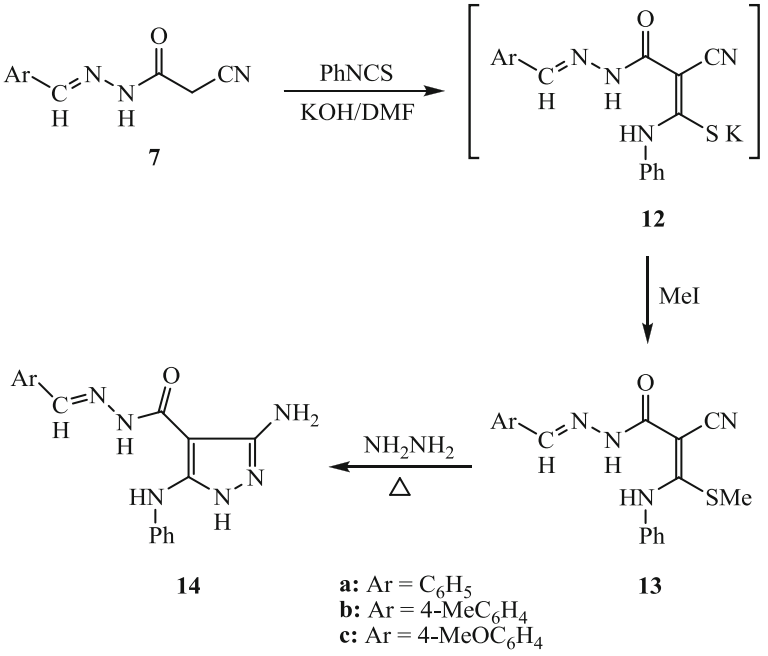


Scheme 3 Synthetic route to 3-amino-*N′*-arylidene-5-methylthio-1*H*-pyrazole-4-carbohydrazides **10a–c** and **11a–c**

with hydrazine hydrate afforded the corresponding 3-Aminopyrazole derivatives **10**. The chemical structure of compounds **10** was secured by their correct spectral data (IR, ^{1}H NMR, and MS) and elemental analyses.

Cyclocondensation of compound **9** with benzenesulfonyl hydrazide in refluxing DMF containing potassium carbonate furnished the novel aminopyrazole derivative **11**. The formation of **11** is assumed to proceed through Michael′s addition of the amino group to the ethylenic bond in **9** with elimination of methanethiol followed by intramolecular cyclization at the cyano group to form **11**. The chemical structure of product **11** was established by analytical and spectral data. The infrared spectrum of compound **11b** was characterized by the appearance of absorption bands at 3,367, 3,275, 3,182 cm^{-1} corresponding to NH_2 and NH functions, in addition to the carbonyl absorption at 1,650 cm^{-1}. Also, the ^{1}H NMR spectrum displayed two singlet signals at δ 2.40 and 2.55 ppm for two methyl groups, a multiplet signal in the range δ 7.20–7.80 ppm for aromatic protons, a singlet signal at 8.30 ppm due to the CH=N proton and two singlet signals at δ 9.20 and 12.05 ppm due to NH_2 and NH protons, respectively.

Our investigation was extended to examine the base-promoted nucleophilic addition of compound **7** into phenyl isothiocyanate in DMF containing potassium hydroxide. Subsequent treatment of the non-isolable sulfide salt **12** with an equimolar amount of methyl iodide afforded the corresponding ketene-N,S-acetal **13**. The aminopyrazole derivatives of the type **14** were synthesized in high yields by refluxing a mixture of ketene-*N*,S-acetal **13** with hydrazine hydrate in ethanol for



Scheme 4 Synthetic route to 3-amino-*N*′-arylidene-5-phenylamino-1*H*-pyrazole-4-carbohydrazides **14a–c**

4 h as shown in Scheme 4. The structure of the obtained products was confirmed from their agreeable elemental and spectral data. Bands at 3,358, 3,272, 3,194 cm^{-1} (NH_2 and NH), and 1,654 cm^{-1} (C=O) in the IR spectrum and molecular ion peak *m*/*z* at 335 (100 %) in the mass spectrum confirmed the structure of compound **14b**. The ^1H NMR spectrum of compound **14b** showed a singlet signal at δ 2.48 ppm due to methyl protons, a multiplet signal in the range δ 6.90–7.70 ppm for the aromatic protons, a singlet signal at δ 8.25 ppm for CH=N proton, and a singlet signal at δ 8.85 ppm assignable to NH_2 protons, in addition to three singlet signals at δ 9.75, 10.75, and 12.60 for three NH groups.

Conclusion

In summary, 15 different functionalized 3-amino- and 5-aminopyrazole derivatives were efficiently synthesized under mild reaction conditions. 5-Amino-1-substituted-4-pyrazolin-3-one derivatives **3** and **6** were obtained by coupling of *N*′-substituted-2-cyanoacetohydrazide with different aryl diazonium chlorides, while 3-amino-5-1*H*-pyrazole-4-carbohydrazide derivatives **10**, **11**, and **14** were obtained by cyclocondensation of ketene dithioacetal **9** and ketene-*N*,S-acetal **13** with hydrazine and/or benzenesulfonyl hydrazide. The synthesized aminopyrazole derivatives were characterized by IR, NMR, mass spectroscopy, and elemental analyses.

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