Cyanoacetylation of 5-Aminopyrazole: Synthesis of 2-(1-Aryl-4-substituted pyrazolo[3,4-*d*]pyrimidin-6-yl)acetonitrile Derivatives

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Z. Naturforsch. **2009**, *64b,* 840 – 846; received March 19, 2009

*N*1-Substituted-5-amino-4-cyanopyrazoles were cyanoacetylated with a mixture of cyanoacetic acid and acetic anhydride. Cyclization with $POCl_3$ gave 4-chloro-pyrazolo[3,4-*d*]pyrimidine derivatives. From the reaction with hydrazine and arylhydrazines, the hydrazinyls and their oxidized forms, the azo products, were obtained. The structure of the compounds obtained has been confirmed by ^{1}H and ^{13}C NMR spectroscopy.

Key words: Cyanoacetylations, Cyanopyrazoles, Pyrazolo[3,4-*d*]pyrimidines, Acetonitrile Derivatives

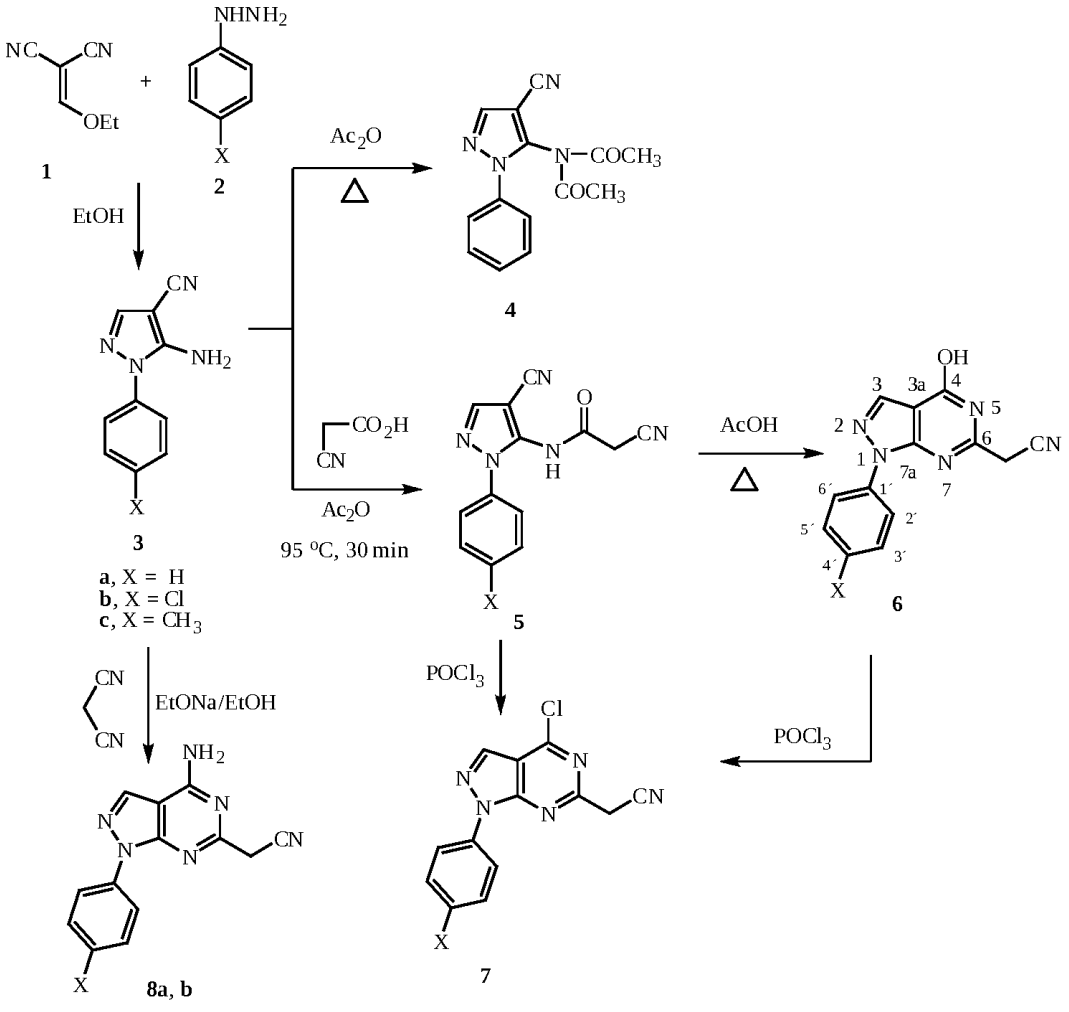
Introduction

Pyrazole and pyrimidine derivatives received considerable attention from organic chemists due to their biological and chemotherapeutic importance. Pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. They are known to function as CNS (Central Nervous System) depressants [1], neuroleptic agents [2], and tuberculostatic agents [3]. Pyrazolo[3,4-*d*]pyrimidines were identified as a general class of adenosine receptors [4, 5]. Moreover, a series of [1-aryl-1*H*-pyrazolo [3,4-*d*]pyrimidin-4-yl]arylhydrazones were discovered as novel inhibitors of glycogen synthase kinase-3 (GSK-3) [6].

Heterocycles containing a cyanoacetyl group are relatively unexplored. Most of the reported preparations involved nucleophilic displacement of halide in haloacetyl derivatives by cyanide [7], or of an alkyl carboxylates using acetonitrile in the presence of a strong base, like sodium amide [8]. The cyanoacetylating reagent (acetic anhydride and cyanoacetic acid under heating) has been used in the synthesis of 6-aminouracils *via* urea [9] and N-acetylation and C-acetylation of enamines [10]. Other activation procedures, such as conversion to cyanoacetyl chloride, have also been described, although this reagent has the tendency to self-polymerize (particularly when heated) [11]. We have concentrated our attention on *ortho*-aminocyanopyrazoles and their pyrazolo[3,4-*d*]pyrimidine derivatives as antioxidants [12]. With the objective of synthesizing members of this class of compounds we started from the key intermediates **5a – c** (2-cyano-*N*-(1-aryl-4-cyano-1*H*-pyrazol-5-yl)acetamides). These compounds are readily prepared from **3** using a synthetic strategy depicted in Scheme 1.

Result and Discussions

The *N*1-substituted 5-amino-4-cyanopyrazoles **3** [13] were used as starting materials as they contain an amino and a cyano group in adjacent positions, which is required for the synthesis of the condensed systems including pyrimidine [14 – 16]. When compound **3a** was heated in refluxing acetic anhydride, the diacetyl derivative **4** was obtained. In order to get cyanoacetylation, the pyrazoles **3a – c** were poured onto a solution of the cyanoacetylating reagent (cyanoacetic acid and acetic anhydride) and heated to 95 °C for 30 min. *N*-Substituted 2-cyanoacetamide derivatives **5a – c** were isolated as solid products by simple filtration, and no C-acetylation products were isolated. The structures of **5a – c** were confirmed by elemental analyses and spectral (MS, IR and ^{1}H NMR) data (see Experimental Section). For example, their ^{1}H NMR spectra in [D_6]DMSO revealed, in each case, a characteristic signal in the region $\delta = 4.0 – 4.2$ assignable to the $–CH_2–$ protons, at $\delta = 8.1 – 8.3$ for the pyrazole 3-H and at $\delta = 10.9 – 11.1$ for the NH proton. The IR spectra showed the characteristic band for the N–H stretch of the NH



Scheme 1.

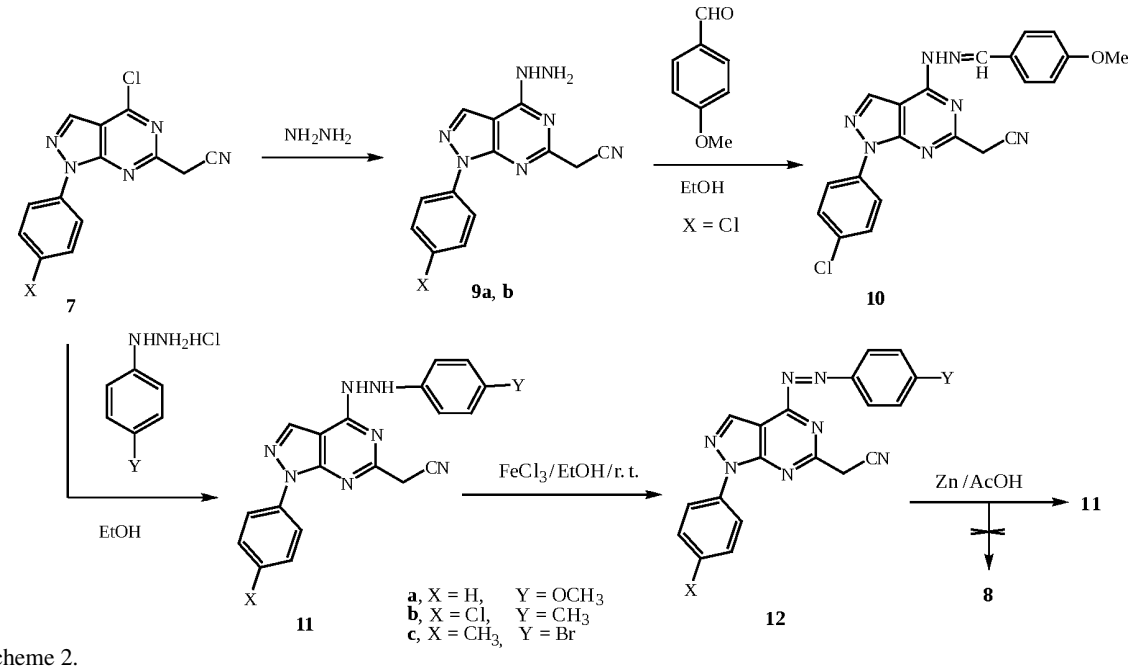
group in the region 3350 – 3180 cm^{-1} and characteristic bands for the C=O stretch in the region 1700 – 1730 cm^{-1}.

When any of the 2-cyanoacetamide derivatives **5a** – **c** was refluxed in acetic acid, it cyclized into the corresponding 4-hydroxypyrazolopyrimidine derivative (**6a** – **c**). The structures of **6a** – **c** were confirmed by spectral and elemental analysis. Heating of compounds **6a** – **c** in $POCl_3$ afforded the 4-chloro derivatives **7a** – **c**. Compounds **7** can be prepared *via* the one-pot reaction of compounds **5** with $POCl_3$. The products isolated were the 4-chloropyrazolo[3,4-*d*]pyrimidine derivatives **7a** – **c**, whose spectral characteristics were completely coincident with the samples obtained before (Scheme 1).

Moreover, recently we described the reaction of compounds **3a**, **b** with malononitrile form which the 4-aminopyrazolo[3,4-*d*]pyrimidine derivatives **8a**, **b** were obtained [14].

When compounds **7a**, **b** were treated with hydrazine hydrate in ethanol at reflux temperature, they afforded the corresponding hydrazinyl derivatives **9a**, **b**, respectively. The ^1H NMR spectrum of compound **9a** showed a signal at δ = 4.94 ppm (s, 2H, NH_2, exchangeable with D_2O), and a signal at δ = 9.32 ppm (s, 1H, NH, exchangeable with D_2O). Compound **10** was prepared by condensation of the hydrazinyl derivative **9b** with the *p*-methoxybenzaldehyde [6] (Scheme 2). The structure of hydrazone **10** was confirmed based on spectroscopic and elemental analysis data. The ^1H NMR spectrum of compound **10** revealed a signal at δ = 8.34 ppm for the N=CH proton and a signal at δ = 12.15 ppm (s, 1H, NH, exchangeable with D_2O).

Similarly, when **7a** – **c** were reacted with phenylhy-



Scheme 2.

drazine derivatives under reflux condition, the arylhydrazinyl derivatives **11a – c** were obtained. All these hydrazinyls have not been reported hitherto. Their structures were confirmed by their elemental and spectral analyses (MS, IR and ^{1}H, ^{13}C NMR) data (see Experimental Section). For example, the ^{1}H NMR spectra of compound **11b** revealed two singlet signals at δ = 8.30 and 10.0 ppm for the two NH groups.

Treatment of the hydrazinyl derivatives **11a – c** with 2 equivalents of iron(III) chloride in ethanol for 2 h at r. t. gave, in each case, the corresponding azo product, as evidenced by TLC analysis. Elemental analyses and mass spectra revealed that each of the isolated products has two hydrogens less than the respective hydrazinyl derivative. This finding was confirmed by the ^{1}H NMR spectra, which indicated the absence of the two NH protons. On the basis of this finding, the isolated products were assigned the diazenyl structures **12a – c** (Scheme 2). Moreover, compound **12** could be converted into compound **11** by reduction using zinc in acetic acid. Compound **8** was not obtained. These results also prove the correct structures of compounds **11** and **12**, as suggested in Scheme 2.

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were registered on a Perkin Elmer FTIR-1600 instrument using Nujol emulsions between NaCl plates. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded in [D_6]DMSO or $CDCl_3$ on a Varian Unity Plus spectrometer using tetramethylsilane (TMS) as an internal reference, and results are expressed as δ values. Double resonance HMQC and HMBC experiments were carried out for complete assignment of proton and carbon signals in the NMR spectra, whenever possible. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were obtained on a Leco CHNS-932 instrument. Compounds **3a – c** were prepared as previously reported by us [14, 15].

*N-Acetyl-N-(4-cyano-1-phenyl-1H-pyrazol-5-yl)acetamide (**4**)*

A mixture of 5-amino-4-cyano-1-phenylpyrazole (**3a**) (0.01 mol) and 20 mL of acetic anhydride was heated under reflux for 7 h and then evaporated under reduced pressure. The residue was treated with ethanol, and the solid product so formed was collected by filtration, washed with ethanol and crystallized from EtOH. M. p. 132 – 134 °C. Yield: 72 %. – IR (Nujol): ν = 2210 (CN), 1688 (C=O), cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.28 (s, 6H, 2CH_3), 7.35 – 7.38 (m, 2H, Ar-H), 7.50 – 7.52 (m, 3H, Ar-H), 8.07 (s, 1H, 3-H). – MS (EI, 70 eV): *m/z* (%) = 268 (74) [M]$^+$. – $C_{14}H_{12}N_4O_2$ (268.27): calcd. C 62.68, H 4.51, N 20.88; found C 62.78, H 4.55, N 20.64.

General procedure for the preparation of 2-cyano-N-(4-cyano-1-substituted-1H-pyrazol-5-yl)acetamides ***5a – c***

Pyrazole derivatives **3a – c** (0.02 mol) were added to a mixture of cyanoacetic acid (0.03 mol) and Ac_2O (30 mL) and heated at 95 °C for 30 min. The mixture was allowed to cool and poured on ice. The precipitate formed was collected, washed with EtOH and dried.

*2-Cyano-N-(4-cyano-1-phenyl-1H-pyrazol-5-yl)acetamide (**5a**)*

M. p. 160 – 161 °C (EtOH). Yield: 75 %. – IR (Nujol): ν = 3202 (NH), 2227, 2215 (CN), 1737 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.99 (s, 2H, CH_2), 7.52 – 7.54 (m, 5H, Ar-H), 8.29 (s, 1H, 3-H), 11.04 (s, 1H, NH). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 25.94 (CH_2), 89.45 (C-4), 112.50 (CN), 115.16 (CN), 124.05 (C-2′,6′), 128.99 (C-4′), 129.59 (C-3′,5′), 137.08 (C-1′), 139.58 (C-5), 142.61 (C-3), 162.27 (CO). – MS (EI, 70 eV): *m/z* (%) = 251 (77) $[M]^+$. – $C_{13}H_9N_5O$ (251.24): calcd. C 62.15, H 3.61, N 27.87; found C 61.97, H 3.69, N 27.79.

*N-[1-(4-Chlorophenyl)-4-cyano-1H-pyrazol-5-yl]-2-cyano-acetamide (**5b**)*

M. p. 216 – 217 °C (EtOH). Yield: 70 %. – IR (Nujol): ν = 3220 (NH), 2228, 2211 (CN), 1724 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.0 (s, 2H, CH_2), 7.43 – 7.59 (m, 4H, Ar-H), 8.31 (s, 1H, 3-H), 11.05 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 285 (90) [M, $^{35}Cl]^+$, 287 (26) [M, $^{37}Cl]^+$. – $C_{13}H_8ClN_5O$ (285.69): calcd. C 54.65, H 2.82, N 24.51; found C 54.72, H 3.09, N 24.70.

*2-Cyano-N-(4-cyano-1-p-tolyl-1H-pyrazol-5-yl)acetamide (**5c**)*

M. p. 212 – 214 °C (EtOH). Yield: 79 %. – IR (Nujol): ν = 3198 (NH), 2237, 2219 (CN), 1723 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.36 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 7.32 – 7.42 (m, 4H, Ar-H), 8.27 (s, 1H, 3-H), 10.97 (s, 1H, NH). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 20.62 (CH_3), 25.88 (CH_2), 89.27 (C-4), 112.51 (CN), 115.13 (CN), 122.93 (C-2′,6′), 129.92 (C-3′,5′), 134.63 (C-4′), 138.68 (C-1′), 139.44 (C-5), 142.40 (C-3), 162.22 (CO). – MS (EI, 70 eV): *m/z* (%) = 265 (80) $[M]^+$. – $C_{14}H_{11}N_5O$ (265.27): calcd. C 63.39, H 4.18, N 26.40; found C 63.47, H 3.99, N 26.29.

General procedure for the preparation of 2-(1-aryl-4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetonitriles ***6a – c***

A mixture of **5a – c** (0.01 mol) and acetic acid (20 mL) was heated under reflux for 6 h and then evaporated under reduced pressure. The residue was treated with water, and the solid product so formed was collected by filtration, washed with ethanol and crystallized from EtOH-DMF (2 : 1).

*2-[4-Hydroxy-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl] acetonitrile (**6a**)*

M. p. 299 – 301 °C. Yield: 86 %. – IR (KBr): ν = 3327 (OH), 2227 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.25 (s, 2H, CH_2), 7.40 (t, 1H, *J* = 7.9 Hz, 4′-H), 7.56 (t, 2H, *J* = 7.9 Hz, 3′, 5′-H), 8.03 (d, 2H, *J* = 7.6 Hz, 2′, 6′-H), 8.32 (s, 1H, 3-H), 12.62 (s, 1H, OH). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 24.42 (CH_2), 106.21 (C-3a), 115.34 (CN), 121.34 (C-2′,6′), 127.15 (C-4′), 129.25 (C-3′,5′), 136.06 (C-3), 138.23 (C-1′), 151.46 (C-7a), 152.58 (C-6), 157.37 (C-4). – MS (EI, 70 eV): *m/z* (%) = 251 (68) $[M]^+$. – $C_{13}H_9N_5O$ (251.24): calcd. C 62.15, H 3.61, N 27.87; found C 62.24, H 3.57, N 27.74.

*2-[1-(4-Chlorophenyl)-4-hydroxy-1H-pyrazolo[3,4-d]-pyrimidin-6-yl]acetonitrile (**6b**)*

M. p. 308 – 310 °C. Yield: 81 %. – IR (KBr): ν = 3330 (OH), 2225 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.27 (s, 2H, CH_2), 7.61 (d, 2H, *J* = 9.3 Hz, 3′, 5′-H), 8.26 (d, 2H, *J* = 9.3 Hz, 2′, 6′-H), 8.38 (s, 1H, 3-H), 12.70 (s, 1H, OH). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 27.18 (CH_2), 100.32 (C-3a), 117.36 (CN), 121.18 (C-2′,6′), 129.82 (C-3′,5′), 130.23 (C-4′), 135.63 (C-3), 137.78 (C-1′), 153.90 (C-7a), 158.69 (C-6), 159.93 (C-4). – MS (EI, 70 eV): *m/z* (%) = 285 (81) [M, $^{35}Cl]^+$, 287 (19) [M, $^{37}Cl]^+$. – $C_{13}H_8ClN_5O$ (285.69): calcd. C 54.65, H 2.82, N 24.51; found C 54.79, H 2.98, N 24.64.

*2-[4-Hydroxy-1-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl] acetonitrile (**6c**)*

M. p. 312 – 314 °C. Yield: 80 %. – IR (KBr): ν = 3320 (OH), 2216 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.30 (s, 3H, CH_3), 4.21 (s, 2H, CH_2), 7.53 (d, 2H, *J* = 8.8 Hz, 3′, 5′-H), 8.08 (d, 2H, *J* = 8.8 Hz, 2′, 6′-H), 8.35 (s, 1H, 3-H), 12.58 (s, 1H, OH). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 27.77 (CH_2), 100.13 (C-3a), 117.61 (CN), 124.66 (C-2′,6′), 129.54 (C-3′,5′), 134.14 (C-3), 136.45 (C-4′), 138.86 (C-1′), 153.75 (C-7a), 158.34 (C-6), 159.76 (C-4). – MS (EI, 70 eV): *m/z* (%) = 265 (76) $[M]^+$. – $C_{14}H_{11}N_5O$ (265.27): calcd. C 63.39, H 4.18, N 26.40; found C 63.54, H 4.30, N 26.54.

General procedure for the preparation of 2-(1-aryl-4-chloro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetonitriles ***7a – c***

A mixture of 4-hydroxypyrazolopyrimidines **6a – c** or cyanoacetamide derivatives **5a – c** (0.01 mol) and phosphorus oxychloride (25 mL) was refluxed for 7 h. After completion

of the reaction, the excess of phosphorus oxychloride was removed under vacuum. The cooled reaction mixture was then added to crushed ice (25 g). The resulting solid was filtered, washed with sodium bicarbonate (5 % w/v) followed by cold water, dried, and crystallized from ethanol and chloroform (8 : 2 v/v).

*2-[4-Chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl]-acetonitrile (**7a**)*

M. p. 138 – 139 °C. Yield: 72 %. – IR (KBr): ν = 2221 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.61 (s, 2H, CH_2), 7.42 – 7.47 (m, 1H, 4′-H), 7.58 – 7.65 (m, 2H, 3′, 5′-H), 8.15 – 8.18 (m, 2H, 2′, 6′-H), 8.78 (s, 1H, 3-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 25.24 (CH_2), 107.14 (C-3a), 116.62 (CN), 121.04 (C-2′,6′), 126.80 (C-4′), 129.44 (C-3′,5′), 137.14 (C-3), 138.89 (C-1′), 152.19 (C-7a), 153.10 (C-4), 158.98 (C-6). – MS (EI, 70 eV): *m/z* (%) = 269 (77) [M, $^{35}Cl]^+$, 271 (20) [M, $^{37}Cl]^+$. – $C_{13}H_8ClN_5$ (269.69): calcd. C 57.90, H 2.99, N 25.97; found C 57.81, H 2.85, N 26.15.

*2-[4-Chloro-1-(4-chlorophenyl)-1H-pyrazolo[3,4-d]-pyrimidin-6-yl]acetonitrile (**7b**)*

M. p. 123 – 125 °C. Yield: 61 %. – IR (KBr): ν = 2227 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.71 (s, 2H, CH_2), 7.54 (d, 2H, *J* = 8.7 Hz, 3′, 5′-H), 8.20 (d, 2H, *J* = 8.7 Hz, 2′, 6′-H), 8.88 (s, 1H, 3-H). – $C_{13}H_7Cl_2N_5$ (304.13): calcd. C 51.34, H 2.32, N 23.03; found C 51.50, H 2.58, N 23.19.

*2-[4-Chloro-1-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl]-acetonitrile (**7c**)*

M. p. 145 – 146 °C. Yield: 70 %. – IR (KBr): ν = 2224 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.29 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 7.37 (d, 2H, *J* = 9.0 Hz, 3′, 5′-H), 7.90 (d, 2H, *J* = 9.0 Hz, 2′, 6′-H), 8.62 (s, 1H, 3-H). – MS (EI, 70 eV): *m/z* (%) = 283 (85) [M, $^{35}Cl]^+$, 285 (22) [M, $^{37}Cl]^+$. – $C_{14}H_{10}ClN_5$ (283.72): calcd. C 59.27, H 3.55, N 24.68; found C 59.39, H 3.41, N 24.85.

*General procedure for the preparation of 4-hydrazino derivatives **9a – c***

Compound **7a**,**b** (3 mmol) was dissolved in 20 mL of absolute ethanol, then 2 mL of hydrazine hydrate (99 %) was added, and the reaction mixture was heated at reflux temperature for 3 h, evaporated under reduced pressure, and the residue was recrystallized from dioxane.

*2-[4-Hydrazinyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile (**9a**)*

M. p. 246 – 248 °C. Yield: 80 %. – IR (KBr): ν = 3420 – 3307 (NH, NH_2), 2215 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.14 (s, 2H, CH_2), 4.94 (s, 2H, NH_2), 7.29 – 7.35 (m, 1H, 4′-H), 7.50 – 7.56 (m, 2H, 3′, 5′-H), 8.19 – 8.22 (m, 2H, 2′, 6′-H), 8.57 (s, 1H, 3-H), 9.32 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 265 (76) $[M]^+$. – $C_{13}H_{11}N_7$ (265.27): calcd. C 58.86, H 4.18, N 36.96; found C 58.80, H 4.25, N 37.20.

*2-[1-(4-Chlorophenyl)-4-hydrazinyl-1H-pyrazolo[3,4-d]-pyrimidin-6-yl]acetonitrile (**9b**)*

M. p. 256 – 258 °C. Yield: 73 %. – IR (KBr): ν = 3420 – 3325 (NH, NH_2), 2215 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.18 (s, 2H, CH_2), 4.96 (s, 2H, NH_2), 7.59 (d, 2H, *J* = 9.0 Hz, Ar-H), 8.30 (d, 2H, *J* = 9.0 Hz, Ar-H), 8.58 (s, 1H, 3-H), 9.38 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 299 (68) [M, $^{35}Cl]^+$, 301 (14) [M, $^{37}Cl]^+$. – $C_{13}H_{10}ClN_7$ (299.72): calcd. C 52.10, H 3.36, N 32.71; found C 52.22, H 3.49, N 32.89.

*2-[1-(4-Chlorophenyl)-4-(2-(4-methoxybenzylidene)hydrazinyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile (**10**)*

To a mixture of 4-hydrazinopyrazolo[3,4-*d*]pyrimidine **9b** (2 mmol) and *p*-methoxy benzaldehyde (3 mmol) in ethanol (30 mL), a few drops of acetic acid were added and the reaction mixture refluxed for 2 h and then cooled. The precipitate, formed upon cooling, was filtered off, washed with water and then with ethanol and finally crystallized from dioxane to give the hydrazone derivative **10**. M. p. 268 – 288 °C. Yield: 81 %. – IR (KBr): ν = 3265 (NH), 2229 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.81 (s, 3H, OCH_3), 4.15 (s, 2H, CH_2), 7.04 (d, 2H, *J* = 8.8 Hz, 3″,5″-H), 7.62 (d, 2H, *J* = 9.0 Hz, 3′,5′-H), 7.77 (d, 2H, *J* = 9.0 Hz, 2′,6′-H), 8.27 (d, 2H, *J* = 8.8 Hz, 2″,6″-H), 8.34 (s, 1H, N=CH), 8.61 (s, 1H, 3-H), 12.15 (s, 1H, NH). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 25.94 (CH_2), 55.31 (OCH_3), 100.69 (C-3a), 114.54 (C-3″,5″), 115.89 (CN), 122.14 (C-2′,6′), 146.58 (C-1″), 128.69 (C-3′,5′), 129.17 (C-2″,6″), 130.21 (C-4′), 136.98 (C-3), 137.68 (C-1′), 146.18 (N=CH), 153.97 (C-7a), 156.04 (C-6), 156.96 (C-4), 160.83 (C-4″). – MS (EI, 70 eV): *m/z* (%) = 417 (71) [M, $^{35}Cl]^+$, 419 (21) [M, $^{37}Cl]^+$. – $C_{21}H_{16}ClN_7O$ (417.85): calcd. C 60.36, H 3.86, N 23.46; found C 60.21, H 3.69, N 23.54.

*General procedure for the preparation of **11a – c***

To a solution of 4-chloropyrazolo[3,4-*d*]pyrimidines **7a – c** (0.01 mol) in ethanol (20 mL) was added the phenylhydrazine derivative (0.01 mol) and a catalytic amount of triethylamine. The reaction mixture was heated under reflux for 3 h, left to cool to r. t. and then poured onto ice. The solid formed was filtered off and crystallized from EtOH to produce the product as a white powder.

*2-[4-(2-(4-Methoxyphenyl)hydrazinyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile (**11a**)*

M. p. 224 – 225 °C. Yield: 76 %. – IR (KBr): ν = 3240 (NH), 2204 (CN) cm^{-1}. – ^1H NMR (300 MHz, $[D_6]$DMSO, 25 °C, TMS): δ = 3.85 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2), 6.01 (brs, 1H, NH), 7.25 (d, 2H, J = 9.0 Hz, Ar-H), 7.31 – 7.75 (m, 1H, Ar-H), 7.51 – 7.65 (m, 5H, Ar-H, NH), 8.20 – 8.25 (m, 2H, Ar-H), 8.28 (s, 1H, 3-H). – MS (EI, 70 eV): *m/z* (%) = 371 (68) $[M]^+$. – $C_{20}H_{17}N_7O$ (371.40): calcd. C 64.68, H 4.61, N 26.40; found C 64.54, H 4.70, N 26.32.

*2-[1-(4-Chlorophenyl)-4-(2-p-tolylhydrazinyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile (**11b**)*

M. p. 238 – 240 °C. Yield: 77 %. – IR (KBr): ν = 3310, 3230 (NH), 2218 (CN) cm^{-1}. – ^1H NMR (300 MHz, $[D_6]$DMSO, 25 °C, TMS): δ = 2.29 (s, 3H, CH_3), 4.0 (s, 2H, CH_2), 6.08 (s,1H, NH), 6.34 (d, 2H, J = 8.8 Hz, 2″,6″-H), 7.11 (d, 2H, J = 8.8 Hz, 3″,5″-H), 7.48 (d, 2H, J = 8.7 Hz, 3′,5′-H), 8.17 (d, 2H, J = 8.7 Hz, 2′,6′-H), 8.28 (s, 1H, NH), 8.39 (s, 1H, 3-H). – ^{13}C NMR (75.4 MHz, $[D_6]$DMSO): δ = 20.55 (CH_3), 27.64 (CH_2), 99.71 (C-3a), 112.40 (C-2″,6″), 116.70 (CN), 122.20 (C-2′,6′), 128.71 (C-4″), 129.15 (C-3′,5′), 129.69 (C-3″,5″), 130.73 (C-4′), 136.43 (C-3), 137.26 (C-1′), 139.90 (C-1″), 154.55 (C-7a), 157.33 (C-6), 161.21 (C-4). – MS (EI, 70 eV): *m/z* (%) = 389 (84) [M, $^{35}Cl]^+$, 391 (24) [M, $^{37}Cl]^+$. – $C_{20}H_{16}ClN_7$ (389.84): calcd. C 61.62, H 4.14, N 25.15; found C 61.48, H 4.25, N 25.04.

*2-[4-(2-(4-Bromophenyl)hydrazinyl)-1-p-tolyl-1H-pyrazolo-[3,4-d]pyrimidin-6-yl]acetonitrile (**11c**)*

M. p. 198 – 200 °C. Yield: 74 %. – IR (KBr): ν = 3320 – 3240 (NH), 2219 (CN) cm^{-1}. – ^1H NMR (300 MHz, $[D_6]$DMSO, 25 °C, TMS): δ = 2.14 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 6.20 (s, 1H, NH), 6.83 (d, 2H, J = 9.0 Hz, Ar-H), 7.38 (d, 2H, J = 9.0 Hz, Ar-H), 7.49 (d, 2H, J = 8.9 Hz, Ar-H), 8.16 (d, 2H, J = 8.9 Hz, Ar-H), 8.20 (s, 1H, NH), 8.40 (s, 1H, 3-H). – $C_{20}H_{16}BrN_7$ (434.29): calcd. C 55.31, H 3.71, N 22.58; found C 55.45, H 3.94, N 22.37.

*General procedure for the preparation of **12a – c***

To a solution of the appropriate hydrazinyl derivatives **11a – c** (1 mmol) in ethanol (25 mL) was added a solution of ferric chloride (2 M, 2 mL), and the mixture was stirred at r. t. for 2 h. The precipitated solid was filtered off, washed with water and then with ethanol and finally crystallized from DMF-EtOH to give **12a – c** as an orange powder.

*2-[4-((4-Methoxyphenyl)diazenyl)-1-phenyl-1H-pyrazolo-[3,4-d]pyrimidin-6-yl]acetonitrile (**12a**)*

M. p. 168 – 170 °C. Yield: 70 %. – IR (KBr): ν = 2210 (CN) cm^{-1}. – ^1H NMR (300 MHz, $[D_6]$DMSO, 25 °C, TMS): δ = 3.88 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 7.28 (d, 2H, J = 9.0 Hz, Ar-H), 7.44 (m, 1H, Ar-H), 7.52 – 7.57 (m, 2H, Ar-H), 7.65 (d, 2H, J = 9.0 Hz, Ar-H), 8.21 – 8.26 (m, 2H, Ar-H), 8.30 (s, 1H, 3-H). – MS (EI, 70 eV): *m/z* (%) = 369 (76) $[M]^+$. – $C_{20}H_{15}N_7O$ (369.38): calcd. C 65.03, H 4.09, N 26.54; found C 64.95, H 4.15, N 26.61.

*2-[1-(4-Chlorophenyl)-4-(p-tolyldiazenyl)-1H-pyrazolo-[3,4-d]pyrimidin-6-yl]acetonitrile (**12b**)*

M. p. 202 – 204 °C. Yield: 68 %. – IR (KBr): ν = 2223 (CN) cm^{-1}. – ^1H NMR (300 MHz, $[D_6]$DMSO, 25 °C, TMS): δ = 2.30 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.43 (d, 2H, J = 8.7 Hz, Ar-H), 7.55 (d, 2H, J = 8.7 Hz, Ar-H), 8.10 (d, 2H, J = 8.8 Hz, Ar-H), 8.29 (d, 2H, J = 8.8 Hz, Ar-H), 8.66 (s, 1H, 3-H). – MS (EI, 70 eV): *m/z* (%) = 387 (91) [M, $^{35}Cl]^+$, 389 (27) [M, $^{37}Cl]^+$. – $C_{20}H_{14}ClN_7$ (387.83): calcd. C 61.94, H 3.64, N 25.28; found C 62.11, H 3.55, N 25.34.

*2-[4-((4-Bromophenyl)diazenyl)-1-p-tolyl-1H-pyrazolo-[3,4-d]pyrimidin-6-yl]acetonitrile (**12c**)*

M. p. 230 – 231 °C. Yield: 69 %. – IR (KBr): ν = 2220 (CN) cm^{-1}. – ^1H NMR (300 MHz, $[D_6]$DMSO, 25 °C, TMS): δ = 2.28 (s, 3H, CH_3), 4.18 (s, 2H, CH_2), 7.37 (d, 2H, J = 9.0 Hz, Ar-H), 7.90 (d, 2H, J = 9.0 Hz, Ar-H), 8.09 (d, 2H, J = 8.9 Hz, Ar-H), 8.32 (d, 2H, J = 8.9 Hz, Ar-H), 8.63 (s, 1H, 3-H). – $C_{20}H_{14}BrN_7$ (432.28): calcd. C 55.57, H 3.26, N 22.68; found C 55.66, H 3.19, N 22.57.

*Conversion of compounds **12** to **11***

To a solution of diazenyl derivatives **12** (0.01 mol) in glacial acetic acid (15 mL), Zn dust (1 g) was added. The reaction mixture was refluxed for 2 h during which time the color turned to pale yellow. The reaction mixture was filtered while hot, left to cool to r. t. and then poured onto crushed ice (25 g). The precipitated solid was collected by filtration and recrystalized from EtOH-$CHCl_3$ to afford the corresponding hydrazinyl derivative which was found identical in all respects with that obtained from the above reaction (TLC, m. p., NMR). (**11a**, 70 % yield, **11b**, 52 % yield, **11c**, 65 % yield).

Acknowledgements

We thank Fundação para a Ciência e Tecnologia (FCT-Portugal) for a fellowship grant, Prof. A. M. Campos for hospitality and continuous help, and Miss Elisa Pinto for obtaining the NMR and elemental analyses data.

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