Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Heterocyclic Synthesis with Nitriles: Synthesis of Pyrazolopyrimidine and Pyrazolopyridine Derivatives

Abdellatif M. Salaheldin [a], Ana M. F. Oliveira-Campos [a] & Lígia M. Rodrigues [a]
[a] Chemistry Center, IBQF, University of Minho, Campus de Gualtar , Braga, Portugal
Published online: 04 Mar 2009.

To cite this article: Abdellatif M. Salaheldin , Ana M. F. Oliveira-Campos & Lígia M. Rodrigues (2009) Heterocyclic Synthesis with Nitriles: Synthesis of Pyrazolopyrimidine and Pyrazolopyridine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:7, 1186-1195

To link to this article: http://dx.doi.org/10.1080/00397910802517814

*Synthetic Communications*®, 39: 1186–1195, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802517814

Taylor & Francis
Taylor & Francis Group



# Heterocyclic Synthesis with Nitriles: Synthesis of Pyrazolopyrimidine and Pyrazolopyridine Derivatives

**Abdellatif M. Salaheldin, Ana M. F. Oliveira-Campos, and Lígia M. Rodrigues**
Chemistry Center, IBQF, University of Minho, Campus de Gualtar, Braga, Portugal

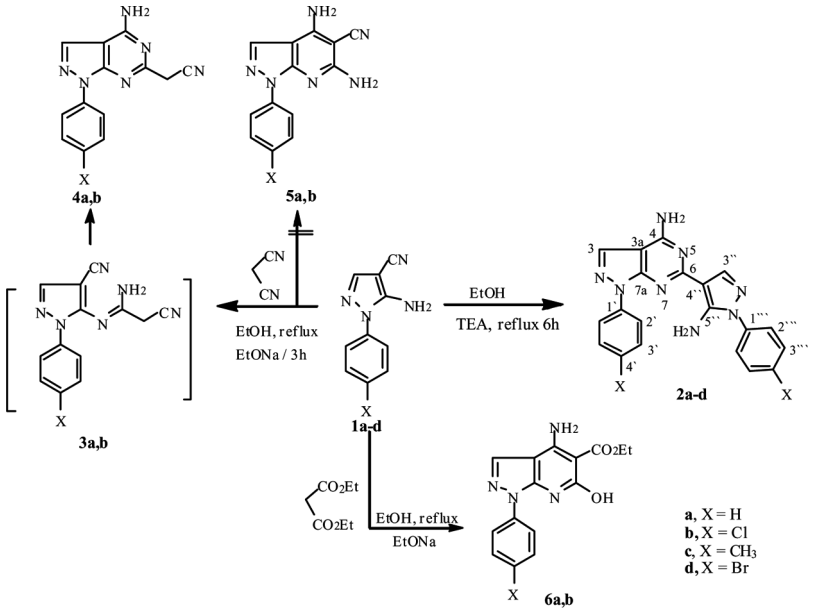
**Abstract:** The reaction of $N_1$-substituted-5-amino-4-cyanopyrazoles with malononitrile and diethylmalonate occurs with formation of 6-substituted pyrazolo[3,4-*d*]pyrimidines, and pyrazolo[3,4-*b*]pyridines respectively. The structures of the products and conceivable mechanisms are discussed.

**Keywords:** Aminopyrazole, diethylmalonate, malononitrile, pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*d*]pyrimidines

## INTRODUCTION

Pyrazolopyridines, pyrazolopyrimidines, and related fused heterocycles are of interest as potential bioactive molecules. Pyrazolo[3,4-*d*]pyrimidines were identified as a general class of adenosine receptors[1–3] because of the similarity between their structures and purines. Pyrazolo[3,4-*b*] pyridines are also important compounds as a result of their biological activity and structural relationship to azaindoles. A number of pyrazolo-[3,4-*b*]pyridines are potentially biologically active compounds as new inhibitors of xantine oxidase.[4,5]

Received April 4, 2008.
Address correspondence to Abdellatif M. Salaheldin, Centro de Química, IBQF, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal. E-mail: salaheldin@quimica.uminho.pt




***Scheme 1.*** Reaction of compound **1** with active methylene reagents.

Because of this wide range of activities, we have been interested on *ortho*-aminocyanopyrazoles[5,6] or their derivatives as inhibitors of xanthine oxidase.[7] For this purpose, we started from the key intermediates **1a**–**d** ($N_1$-substituted-5-amino-4-cyanopyrazoles) **1** (Scheme 1) and reacted them with malononitrile and diethylmalonate to obtain pyrazolo[3,4-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines respectively.

## RESULTS AND DISCUSSION

With the aim of obtaining condensed pyrazolo[3,4-*d*]pyrimidine and pyrazolo[3,4-*b*]pyridine systems, the condensation was carried out with a substituted aminopyrazole, which contains a cyano group in the *ortho* position, with malononitrile and diethylmalonate.

The $N_1$-substituted-5-amino-4-cyanopyrazoles **1**, were used as starting materials as they contain an amino and a cyano group in adjacent positions, which are required for the synthesis of the condensed systems including pyridine and pyrimidine.

Reaction of compound **1a** with malononitrile in refluxing ethanol in the presence of triethylamine afforded a yellow crystalline solid of

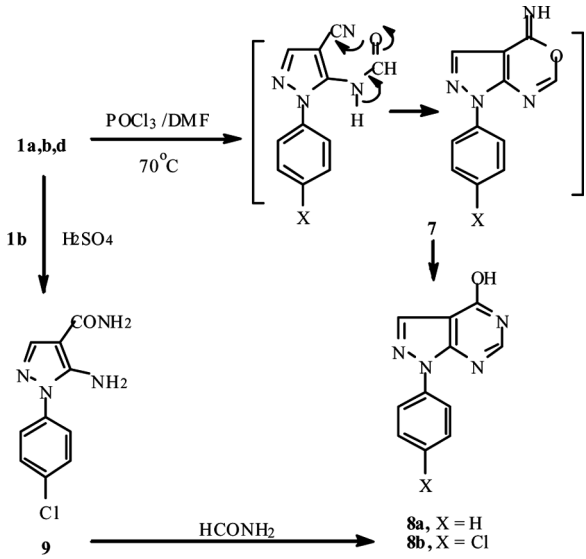
mp 254–256 °C. It was expected that this reaction would give the pyrazolopyrimidine **4a** or pyrazolopyridine **5a** via the intermediate **3a**. However, the micro-analytical data showed that this product has the molecular formula $C_{20}H_{16}N_8$. Furthermore, the mass spectrum (EI) of this product showed a molecular ion at $m/z = 368$, and the IR spectrum displayed an absorption at 3463 $cm^{-1}$, corresponding to $NH_2$ stretching, and no CN absorption. The $^1H$ NMR spectrum revealed two singlets for the amino groups at 5.44 and 5.88 ppm and two singlets for the pyrazole H-3 protons. Structure **2a** was thus suggested for this product. The formation of compound **2a** may be envisaged via initial condensation of the amino group of one molecule of the *o*-aminonitrile with the cyano group of a second molecule to give an intermediate amidine, which then undergoes a second, but intramolecular, amine–nitrile condensation to give the isolated product. To confirm this hypothesis, reflux of compound **1a** in ethanol and triethylamine afforded a product completely identical to **2a**. A similar result had been established by Taylor and Borror in the formation of **2a** (Scheme 1).[8]

Compounds **1b–d** were refluxed under the same reaction conditions to afford **2b–d**.

In ethanolic sodium ethoxide solution, compounds **1a** and **1b** reacted with malononitrile to afford white powders of mp 242–244 °C for **4a** and 296–298 °C for **4b**, respectively. The $^1H$ NMR spectrum of compound **4a** revealed a methylene singlet at $\delta$ 4.17 ppm and pyrazole H-3 as a singlet at 8.34 ppm besides other signals attributable to an aromatic compound and only one $NH_2$ group at 8.0 ppm as expected. Based on these data, it seemed that a $-CH_2CN$ side chain was present and that the cyclization took place by addition of the $NH_2$ in the pyrazole **1** to the CN of the malononitrile to form the amidine intermediate **3**, followed by an attack of the newly formed amino group to the CN of **1** to afford the pyrazolopyrimidine **4** and not the pyrazolopyridine **5**, as shown in Scheme 1. Similar cyclizations with other nitriles have been reported.[9]

In contrast, reaction of compounds **1a,b** with diethylmalonate in ethanolic sodium ethoxide solution gave pyrazolopyrimidines **6a,b**. The structure of compounds **6** was confirmed by mass and NMR spectroscopic data. The $^1H$ NMR spectrum of compound **6a** revealed the ester group as a triplet for the $CH_3$ protons at 1.33 ppm and a quartet for the $CH_2$ protons at 4.40 ppm, besides other signals assigned to aromatics, pyrazole H-3, one $NH_2$ group, and an OH signal at 12.31 ppm (Scheme 1).[10]

In an attempt to introduce a formyl group at position 3 in pyrazole **1**, aminopyrazole **1** was reacted with Vilsmeier reagent ($DMF–POCl_3$) at 70 °C for 3 h. For the product which was obtained, structure **8** was proposed based on the NMR data, which indicated the presence of an OH group and the pyrazole H-3. The reaction proceeded via the intermediacy




*Scheme 2.* Preparation of 4-hydropyrazolopyrimidine **8**.

of **7** (Scheme 2). The structure of compound **8b** could be confirmed by an alternative synthesis, as described previously, converting **1b** to the amide **9**, by treatment with cold concentrated sulfuric acid, followed by boiling compound **9** [mp 202–204 °C (lit. mp 204–205 °C)[11]], in formamide. The product isolated was the 4-hydroxypyrazolo[3,4-*d*]pyrimidine **8b**, whose spectral characteristics were completely coincident with the sample obtained before (Scheme 2).

Compound **8b**, 4-hydroxypyrazolopyrimidine, was easily converted to the corresponding 4-chloropyrazolopyrimidine, the precursor to the 4-substituted aminopyrazolopyrimidine, as we described recently.[6]

## EXPERIMENTAL

### General Procedures

Melting points were determined on a Gallenkamp melting-point apparatus and are uncorrected. IR spectra were registered on a Perkin-Elmer FTIR-1600. $^{1}$H NMR (300 MHz) and $^{13}$C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus spectrometer. Double resonance, heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) experiments were carried out for

complete assignment of proton and carbon signals in the NMR spectra whenever possible. High-resolution mass spectra (HRMS) were determined on a AutoSpec E spectrometer. Elemental analyses were obtained on a Leco CHNS-932 instrument. Compound **9** was prepared by a known method.[11]

## General Procedure for Preparation of 2a–d

A solution of $N_1$-substituted-5-amino-4-cyanopyrazoles **1a–d** (0.2 mol) in ethanol (20 mL) and triethylamine (2 mL) was heated under reflux for 7 h and then concentrated under reduced pressure. The solid product so formed was collected by filtration, washed with ethanol, and crystallized from EtOH–$H_2O$.

## Data

6-(5-Amino-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazolo[3,4-d]-pyrimidin-4-amine (**2a**)

Pale yellow solid (84%), mp 254–256 °C (EtOH) (lit.[8] mp 255–257 °C); $\upsilon_{max}$ (Nujol mull): 3462 and 3302 ($NH_2$) $cm^{-1}$; $\delta$H ($CDCl_3$): 5.57 (s, 2H, C-5″-$NH_2$), 5.89 (s, 2H, C-4-$NH_2$), 7.30–7.42 (m, 2H, Ar-H), 7.52 (d, 2H, 8.1 Hz, Ar-H), 7.60–7.67 (m, 2H, Ar-H), 8.02 (s, 1H, H-3″), 8.11 (d, 2H, $J = 8.1$ Hz, Ar-H), 8.23 (s, 1H, H-3); $\delta_C$ ($CDCl_3$): 99.04 (C-4″), 103.34 (C-3a), 121.72 (C-2′, C-6′ or C-2‴, C-6‴), 123.78 (C-2′, C-6′ or C-2‴, C-6‴), 126.45 (C-4′ or C-4‴), 127.68 (C-4‴ or C-4′), 129.06 (C-3′, C-5′ or C-3‴, C-5‴), 129.64 (C-3′, C-5′ or C-3‴, C-5‴), 132.30 (C-3″), 138.23 (C-1′ or C-1‴), 139.12 (C-1‴ or C-1′), 141.03 (C-3), 146.89 (C-7a), 154.19 (C-5″), 157.14 (C-4), 160.42 (C-6). $m/z$ (%) 368 [$M^+$] (100). Anal. calcd. for $C_{20}H_{16}N_8$ (368.39): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.10; H, 4.46; N, 29.99.

6-(5-Amino-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-1-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2b**)

Pale yellow solid (72%), mp 277–278 °C (EtOH–DMF); $\upsilon_{max}$ (Nujol mull): 3463 and 3304 ($NH_2$) $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 6.89 (s, 2H, $NH_2$), 7.56–7.70 (m, 6H, Ar-H), 7.92 (br s, 2H, $NH_2$), 8.08 (s, 1H, H-3 or H-3″), 8.28 (s, 1H, H-3 or H-3″), 8.30 (d, 2H, $J = 9.0$, Ar-H). Anal. calcd. for $C_{20}H_{14}Cl_2N_8$ (437.28): C, 54.93; H, 3.23; N, 25.62. Found: C, 55.00; H, 3.23; N, 25.47.

6-(5-Amino-1-p-tolyl-1H-pyrazol-4-yl)-1-p-tolyl-1H-pyrazolo[3,4-d]-pyrimidin-4-amine (**2c**)

Pale yellow solid (78%), mp 262–264 °C (EtOH); $\upsilon_{max}$ (Nujol mull): 3395, 3336, and 3318 ($NH_2$) $cm^{-1}$; $\delta$H (DMSO-$d_6$): 2.35 (3H, s, $CH_3$), 2.36 (3H, s, $CH_3$), 6.74 (2H, s, C-4-$NH_2$), 7.33 (2H, d, $J = 8.1$ Hz, H-3′, H-5′ or H-3‴, H-5‴), 7.34 (2H, d, $J = 8.1$ Hz, H-3′, H-5′ or H-3‴, H-5‴), 7.50 (2H, d, $J = 8.4$ Hz, H-2′, H-6′ or H-2‴, H-6‴), 7.81 (2H, br s, C-5″-$NH_2$), 7.98 (1H, s, H-3), 8.04 (2H, d, $J = 8.4$ Hz, H-2′, H-6′ or H-2‴, H-6‴), 8.24 (1H, s, H-3″); $\delta_C$ (DMSO-$d_6$): 20.66 ($CH_3$), 20.61 ($CH_3$), 98.58 (C-4″), 102.40 (C-3a), 120.58 (C-2′, C-6′ or C-2‴, C-6‴), 123.24 (C-2′, C-6′ or C-2‴, C-6‴), 129.65 (C-3′, C-5′ or C-3‴, C-5‴), 129.81 (C-3′, C-5′ or C-3‴, C-5‴), 134.05 (C-3″), 135.12 (C-4′ or C-4‴), 136.21 (C-4‴ or C-4′), 136.41 (C-1′ or C-1‴), 136.90 (C-1‴ or C-1′), 140.05 (C-3), 147.71 (C-7a), 153.82 (C-5″), 157.98 (C-4), 160.14 (C-6). Anal. calcd. for $C_{22}H_{20}N_8$ $2\frac{1}{2}$ $H_2O$ (441.45): C, 59.80; H, 4.53; N, 25.37. Found: C, 59.82; H, 4.83; H, 25.06.

6-(5-Amino-1-(4-bromophenyl)-1H-pyrazol-4-yl)-1-(4-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2d**)

Pale yellow solid (74%), mp 284–285 °C (EtOH–DMF); $\upsilon_{max}$ (Nujol mull): 3449, 3391, and 3301 ($NH_2$) $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 6.90 (2H, s, $NH_2$), 7.33 (2H, d, $J = 9.0$ Hz, Ar-H), 7.69–7.78 (4H, m, Ar-H), 7.92 (2H, br s, $NH_2$), 8.09 (1H, s, H-3 or H-3″), 8.26 (2H, d, $J = 9.0$ Hz, Ar-H), 8.28 (1H, s, H-3″ or H-3′). $m/z$ (%) ($FAB^+$) 525 [$M^+ + 1$, $^{79}Br$, $^{79}Br$] (18), 527 [$M^+ + 1$, $^{79}Br$, $^{81}Br$] (32), 529 [$M^+ + 1$, $^{81}Br$, $^{81}Br$] (19). Anal. calcd. for $C_{20}H_{14}Br_2N_8$ (526.19): C, 45.65; H, 2.68; N, 21.30. Found: C, 45.70; H, 2.75; N, 21.05.

## General Procedure for Preparation of 4a,b and 6a,b

A mixture of 1 (20 mmol) and malononitrile or diethylmalonate (20 mmol) was added to 20 mL freshly prepared sodium ethoxide solution [prepared by adding 1.0 g sodium metal into absolute ethanol (20 mL)], and the mixture was refluxed for 7 h and left to cool overnight. The solid product so formed was collected by filtration, washed with ethanol, and crystallized from ethanol, unless otherwise stated.

## Data

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

Pale yellow crystals (77%), mp 242–244 °C (EtOH); $\upsilon_{max}$ (Nujol mull): 3463 and 3296 ($NH_2$), 2213 (CN) $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 4.17 (s, 2H, $CH_2$), 7.33 (t, 1H, $J = 7.5$ Hz, H-4′), 7.54 (t, 2H, $J = 7.2$ Hz, H-3′, H-5′), 8.00 (br s, 1H, $NH_2$), 8.07 (br s, 2H, $NH_2$), 8.10–8.25 (br s, 1H, $NH_2$), 8.20 (d, 2H, $J = 7.5$ Hz, H-2′, H-6′), 8.34 (s, 1H, H-3); $\delta_C$ (DMSO-$d_6$): 27.77 ($CH_2$), 100.13 (C-3a), 117.61 (CN), 120.45 (C-2′, C-6′), 124.12 (C-4′), 129.12 (C-3′, C-5′), 134.13 (C-3), 138.86 (C-1′), 153.75 (C-7a), 158.34 (C-4), 159.67 (C-6). Anal. calcd. for $C_{13}H_{10}N_6$ (250.26): C, 62.39; H, 4.03; N, 33.58. Found: C, 62.27; H, 4.22; N, 33.63.

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

Yellow powder (81%), mp 296–298 °C (EtOH–DMF); $\upsilon_{max}$ (Nujol mull): 3469 and 3306, ($NH_2$), 2218 (CN) $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 4.17 (s, 2H, $CH_2$), 7.61 (d, 2H, $J = 9.3$ Hz, H-3′, H-5′), 8.04 (br s, 2H, $NH_2$), 8.25 (d, 2H, $J = 9.0$ Hz, H-2′, H-6′), 8.37 (s, 1H, H-3); $\delta_C$ (DMSO-$d_6$): 27.81 ($CH_2$), 100.23 (C-3a), 117.63 (CN), 121.82 (C-2′, C-6′), 129.18 (C-3′, C-5′), 130.22 (C-4′), 134.63 (C-3), 137.75 (C-1′), 153.89 (C-7a), 158.37 (C-4), 159.90 (C-6). *m/z* (%) (TOF) 284 [$M^+$, $^{35}Cl$] (100), 286 [$M^+$, $^{37}Cl$] (18). $C_{13}H_9ClN_6$ (284.70): C, 54.84; H, 3.19; N, 29.52. Found: C, 54.78; H, 3.08; N, 29.42.

Ethyl 4-Amino-1-(phenyl)-6-hydroxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (**6a**)

White powder (89%), mp 197–199 °C (EtOH); $\upsilon_{max}$ (Nujol mull): 3505 and 3395 ($NH_2$), 3245 (br, OH), 1660 (C=O) $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 1.34 (t, 3H, $J = 7.5$ Hz, $CH_3$), 4.38 (q, 2H, $J = 7.5$ Hz, $CH_2$), 7.31 (t, 1H, $J = 7.5$ Hz, H-4′), 7.51 (t, 2H, $J = 7.5$ Hz, H-3′), 8.06 (d, 4H, $J = 7.8$ Hz, H-2′, H-6′, $NH_2$), 8.44 (s, 1H, H-3), 12.32 (br s, 1H, OH); $\delta_C$ (DMSO-$d_6$): 14.30 ($CH_3$), 61.24 ($CH_2$), 86.57 (C-5), 102.09 (C-3a), 121.01 (C-2′, C-6′), 126.05 (C-4′), 129.05 (C-3′, C-5′), 135.12 (C-3), 138.87 (C-1′), 148.95 (C-7a), 152.76 (C-4), 165.99 (C-6), 170.33 (C=O). Anal. calcd. for $C_{15}H_{14}N_4O_3$ (298.30): C, 60.40; H, 4.73; N, 18.78. Found: C, 59.99; H, 4.93; N, 18.58.

Ethyl 4-Amino-1-(4-chlorophenyl)-6-hydroxy-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate (**6b**)

White powder (82%), mp 314–315 °C (EtOH–DMF); $\upsilon_{max}$ (Nujol mull): 3486 and 3363 ($NH_2$), 3179 (br, OH), 1687 (C=O) $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 1.32 (t, 3H, $J = 7.5$ Hz, $CH_3$), 4.36 (q, 2H, $J = 7.5$ Hz, $CH_2$), 7.55 (d, 2H, $J = 7.0$ Hz, Ar-H), 7.95 (s, 2H, $NH_2$), 8.20 (d, 2H, $J = 7.0$ Hz, Ar-H), 8.40 (s, 1H, H-3), 11.80–12.90 (br s, 1H, OH). $m/z$(%) (TOF) 332 [$M^+$, $^{35}Cl$] (16), 334 [$M^+$, $^{37}Cl$] (5). Anal. calcd. for $C_{15}H_{13}ClN_4O_3$ (332.74): C, 54.14; H, 3.94; N, 16.84. Found: C, 54.25; H, 4.09; N, 16.66.



## General Procedure for Preparation of 8a,b

A mixture of **1** (20 mmol) and phosphoryl chloride (3.83 g, 25 mmol) in anhydrous DMF (5 mL) was heated under stirring at 70 °C for 3 h. Then, the reaction mixture was poured onto ice and treated with aqueous ammonia (pH 8). A white solid separated, and it was filtered off, washed with water, dried, and recrystallized from an appropriate solvent to afford the products in 60–82% yields.

## Data

1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**8a**)

White powder (70%), mp 294–296 °C (EtOH–DMF) (lit. mp 299 °C[11]); $\delta_H$ (DMSO-$d_6$): 7.38 (t, 1H, $J = 7.8$ Hz, H-4′), 7.54 (t, 2H, $J = 7.8$ Hz, H-3′ and H-5′), 8.03 (d, 2H, $J = 7.5$ Hz, H-2′, H-6′), 8.19 (s, 1H, H-6), 8.32 (s, 1H, H-3), 12.46 (br s, 1H, OH); $\delta_C$ (DMSO-$d_6$): 107.62 (C-3a), 121.75 (C-2′, C-6′), 127.13 (C-4′), 129.22 (C-3′, C-5′), 136.00 (C-3), 132.22 (C-1′), 148.81 (C-6), 151.85 (C-7a), 157.23 (C-4). Anal. calcd. for $C_{11}H_8N_4O$ (212.21): C, 62.26; H, 3.80; N, 26.40. Found: C, 61.89; H, 3.87; N, 26.75.

1-(4-Chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**8b**)

White powder (74%), mp 314–316 °C (EtOH–DMF) (lit. mp > 300 °C[11]); $\delta_H$ (DMSO-$d_6$): 7.63 (d, 2H, $J = 9.3$ Hz, Ar-H), 8.10 (d, 2H, $J = 9.0$ Hz, Ar-H), 8.22 (s, 1H, H-6), 8.35 (s, 1H, H-3), 12.30–12.70 (br s, 1H, OH). Anal. calcd. for $C_{11}H_7ClN_4O$ (246.65): C, 53.56; H, 2.86; N, 22.71. Found: C, 53.16; H, 3.04; N, 22.55.

5-Amino-1-(4-chlorophenyl)-1H-pyrazole-4-carboxamide (**9**)

White powder (81%), mp 202–204 °C (EtOH) (lit. mp 204–205 °C[11]); $\upsilon_{max}$ (Nujol mull): 3471, 3337, ($NH_2$), 1662 (C = O) $cm^{-1}$; $\delta_H$ ($CDCl_3$): 6.42 (s, 2H, $NH_2$), 6.86 (br s, 1H, NH), 7.41 (br s, 1H, NH), 7.54–7.57 (m, 4H, Ar-H), 7.90 (s, 1H, H-3); $\delta_C$ ($CDCl_3$): 97.65 (C-4), 124.75 (C-2′, C-6′), 129.30 (C-3′, C-5′), 131.21 (C-4′), 137.13 (C-1′), 139.30 (C-3), 149.48 (C-5), 166.03 (C=O). *m/z* (%) (TOF) 236 [$M^+$, $^{35}Cl$] (30), 238 [$M^+$, $^{37}Cl$] (6). Anal. calcd. for $C_{10}H_9ClN_4O$ (236.66): C, 50.75; H, 3.83; N, 23.67. Found: C, 51.21; H, 3.91; N, 23.71.



## ACKNOWLEDGMENTS

We thank Fundação para a Ciência e Tecnologia and FEDER (POCTI-SFA-3-686) and are grateful for a postdoctoral grant for A. Salaheldin (SFRH/BPD/31490/2006). We thank Elisa Pinto for obtaining the NMR and elemental analysis data.

## REFERENCES

1. Hamilton, H. W.; Ortwine, D. F.; Worth, D. F.; Bristol, J. A. Synthesis and structure–activity relationships of pyrazolo[4,3-*d*]pyrimidin-7-ones as adenosine receptor antagonists. *J. Med. Chem.* **1987**, *30*, 91–96.
2. Poulsen, S. A.; Quinn, R. J. Synthesis and structure–activity relationship of pyrazolo[3,4-*d*]pyrimidines: Potent and selective adenosine $A_1$ receptor antagonists. *J. Med. Chem.* **1996**, *39*, 4156–4161.
3. Harden, F. A.; Quinn, R. J.; Scammells, P. J. Synthesis and adenosine receptor affinity of a series of pyrazolo[3,4-*d*]pyrimidine analogs of 1-methylisoguanosine. *J. Med. Chem.* **1991**, *34*, 2892–2898.
4. Lynck, B. M.; Khan, M. A.; Teo, H. C.; Pedrotti, F. Pyrazolo[3,4-*b*]pyridines: Syntheses, reactions, and nuclear magnetic resonance spectra. *Can. J. Chem.* **1988**, *66*, 420–428.
5. Salaheldin, A. M.; Campos, A. M.; Rodrigues, L. M. N-Bromosuccinimide assisted oxidation of 5-aminopyrazoles: Formation of bis diazenylderivatives. *Tetrahedron Lett.* **2007**, *48*, 8819–8822.
6. Campos, A. M.; Salaheldin, A. M.; Rodrigues, L. M. Synthesis of some novel pyrazolo[3,4-*d*]pyrimidine derivatives. *Arkivoc* **2007**, *14*, 92–100.
7. Gupta, S.; Rodrigues, L. M.; Esteves, A. P.; Oliveira-Campos, A. M. F.; Nascimento, M. S. J.; Nazareth, N.; Cidade, H.; Neves, M. P.; Pinto, E. F. M.; Cerqueira, N. M. F.; Brás, N. Synthesis of *N*-aryl-5-amino-4-cyanopyrazole derivatives as potent xanthine oxidase inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 771.

8. Taylor, E. D.; Borror, A. L. The reaction of nitriles with o-aminonitriles: A convenient synthesis of fused 4-aminopyrimidine. *J. Org. Chem.* **1961**, *26*, 4967–4974.
9. Smyrl, N. R.; Smithwick, R. W. Hydroxide-catalyzed synthesis of heterocyclic aromatic amine derivative from nitriles. *J. Heterocycl. Chem.* **1982**, *19*, 493–496.
10. Veronese, A. C.; Callegari, R.; Salah, S. A. Tin(VI) chloride-promoted reaction of $\beta$-dicarbonyl compounds with nitrile: Synthesis of aminopyridines and aminoquinolines. *Tetrahedron. Lett.* **1990**, *31*, 3485–3488.
11. Cheng, C. C.; Robins, R. K. Potential purine antagonists, VI: Synthesis of 1-alkyl-and 1-aryl-4-substituted pyrazolo[3,4-*d*]pyrimidines. *J. Org. Chem.* **1956**, *21*, 1240–1256.