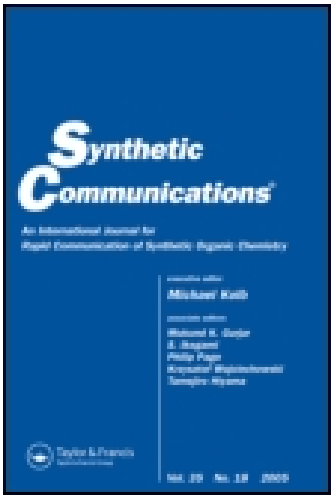

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 4-Amino-3,5-dicyano-arylpyrazoles, Part 2: Isolation and Characterization of By-Products

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Accepted author version posted online: 17 Nov 2011.Published online: 03 Feb 2012.

To cite this article: M. S. T. Gonçalves, A. M. F. Oliveira-Campos, L. M. Rodrigues & M. F. R. P. Proença (2012) Synthesis of 4-Amino-3,5-dicyano-arylpyrazoles, Part 2: Isolation and Characterization of By-Products, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:11, 1695-1703, DOI: 10.1080/00397911.2010.543304

To link to this article: http://dx.doi.org/10.1080/00397911.2010.543304

Synthetic Communications®, 42: 1695–1703, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.543304

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SYNTHESIS OF 4-AMINO-3,5-DICYANO-ARYLPYRAZOLES, PART 2: ISOLATION AND CHARACTERIZATION OF BY-PRODUCTS

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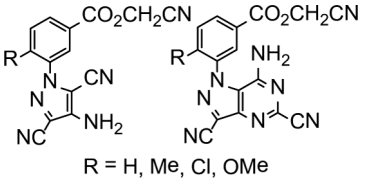
GRAPHICAL ABSTRACT



Abstract *Reaction of (dicyanomethylidene-hydrazino)benzoic acids with chloroacetonitrile, under basic conditions, gave cyanomethyl-3-(7-amino-3,5-dicyano-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl-benzoates and* para*-substituted cyanomethyl benzoates, in addition to the expected cyanomethyl 3-(4-amino-3,5-dicyano-1*H*-pyrazol-1-yl)-benzoates.*

Keywords Aminocyanopyrazoles; aminopyrazoles; malononitrile; pyrazolo[4,3-*d*]-pyrimidines

INTRODUCTION

Pyrazole derivatives are well recognized for their biological activities as potential HIV-1 inhibitors, antiviral, anticancer agents, insecticides, and fungicides.[1–4]

Pyrazole fused-heterocycles, namely pyrazolo[4,3-*d*]pyrimidine derivatives, are also of great interest as potential biologically active molecules. Several members of this class exhibit recognized pharmacological activities for treatment of thromboembolic disorders, with affinity at adenosine receptors for the treatment of bronchoconstriction and cardiac insufficiency, as well as Hsp90 inhibitory activity.[5–7]

A classical method of pyrazole synthesis involves the reaction between hydrazines and β-difunctional compounds, and it was applied to the preparation of 4-amino-1-phenyl-1*H*-pyrazole-3,5-dicarbonitrile **1** (Fig. 1).[8] This methodology was initially used by our research group to synthesize aminocyanopyrazoles containing a carboxylic ester group, such as compounds **2** (Fig. 1).[9] Following this successful

Received October 27, 2010.

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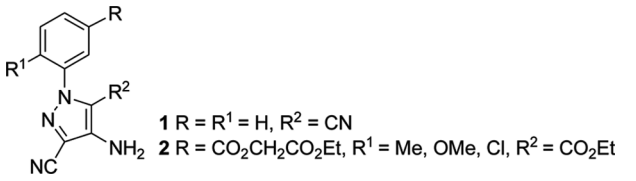
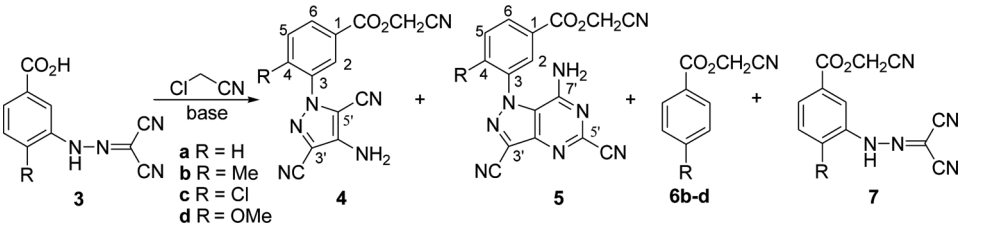


Figure 1. Structure of pyrazoles **1** and **2**.



Scheme 1. Synthesis of pyrazoles **4** and their secondary products.

work, similar heterocyclic compounds **4** containing a cyano group in the pyrazole ring replacing the ethyl ester were obtained by the same route[10] (Scheme 1). The synthesis started by diazotisation of *m*-aminobenzoic acids and further reaction of the resulting diazonium salts with malononitrile giving (dicyanomethylidene-hydrazino)benzoic acids **3**, which cyclized by treatment with chloroacetonitrile in dimethylformamide (DMF), triethylamine being used as the base.[8] When the results obtained by heating the reaction mixtures at reflux for short periods (5–15 min) were compared to those of heating at 80–90 °C for longer times (1–4 h), it was found that in some cases, the last procedure led to lower yields, and this was attributed to possible decomposition (as monitored by thin-layer chromatography TLC) and/or formation of by-products, which was not investigated at that point.

As part of our research interest in the synthesis and study of pyrazoles and their related fused heterocycles,[9–14] it was decided to reconsider the previously reported synthesis and use other bases, namely 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and sodium hydride. The products were identified as the pyrazolo[4,3-*d*]pyrimidines **5**, the *para*-substituted cyanomethyl benzoates **6**, and the expected pyrazoles **4**.[10]

RESULTS AND DISCUSSION

3-[2-(Dicyanomethylene)hydrazinyl]-(5-(un)substituted)-benzoic acids **3**, obtained by diazotization of the corresponding aminobenzoic acids followed by reaction with malononitrile,[10] were reacted with chloroacetonitrile in DMF using a non-nucleophilic organic base or an inorganic base, namely DBU or sodium hydride, respectively (Scheme 1). After purification by column chromatography in silica gel, pyrazolo[4,3-*d*]pyrimidines **5** and *para*-substituted cyanomethyl benzoates **6** were isolated simultaneously with the expected pyrazoles **4**, in variable yields, as

shown in Table 1. The open chain ester, such as compound **7**, was observed in all the experiments on TLC, but only **7a** was quantitatively determined for the reaction from 3-[2-(dicyanomethylene)hydrazinyl]benzoic acid **3a**.

Cyclization of 3-[2-(dicyanomethylene)hydrazinyl]benzoic acid **3a** using sodium hydride added stepwise gave the best yields for the pyrazoles **4a** and pyrazolo[4,3-*d*]pyrimidine **5a**, and the cyanomethylester **7a** was also isolated (Table 1, entry 1). Starting from precursor **3b** and using the same base, pyrazolo[4,3-*d*]pyrimidine **5b** was obtained in addition to the pyrazole **4b** and the cyanomethyl ester **6b** (Table 1, entry 3).

When these reactions were repeated under the same conditions, they were not reproducible. Thus, it was decided to use DBU as the base when the yields of pyrazoles **4a** and **4b** were 17% and 21%, respectively (Table 1, entries 2 and 4).

The cyclization of **3c** with DBU gave a poor yield of the pyrazole **4c**, and this preparation was repeated for a shorter period with a minute improvement (Table 1, entries 5 and 6). Reaction under the same conditions with the methoxylated compound **3d** gave the lowest yield and it was decided to repeat the reaction using a larger excess of base and no solvent. However, this gave a slight improvement only (Table 1, entries 7 and 8).

Compounds **5** and **6** were fully characterized by high-resolution mass spectrometry (HRMS) or elemental analysis, IR, and NMR (^{1}H and ^{13}C) spectroscopy. Compounds **4** [10] and **7a**[9] were described previously.

The main feature on the ^{1}H NMR spectra for pyrazolo[4,3-*d*]pyrimidines **5a–d** is the position of the NH_2 that moves to 7.41–7.45 (acetone-d_6) or to 8.16–8.20 (DMSO-d_6) ppm, as compared with 6.50–6.68 (DMSO-d_6) (for **4a–d**),[10] while the remaining signals do not change significantly. Their EI mass spectra showed always a molecular ion that was 52 units higher than that of the corresponding aminopyrazoles **4a–d**.[10] In their EI mass spectra, losses due to the ester side chain were observed together with ions due to loss of 52 (C_2N_2) or 53 (C_2N_2+H), which might result from cleavage on the pyrazole or pyrimidine moieties.

Table 1. Experimental conditions, and yields for the synthesis of pyrazoles **4** (chloroacetonitrile 2.2 mequiv., was used in all reactions)

Entry	Starting material	Time (h)/ temp. (°C)[a]	Base (mequiv.)	Product yield (%)			
				4	**5**	**6**	**7**
1	**3a**	5/80 + 10/100	NaH (4.2)[c]	54	21	—	3
2	**3a**[b]	10	DBU (2.2)	17	—	—	3
3	**3b**	5/80 + 10/100	NaH (4.2)[c]	16	32	6	—
4	**3b**	10	DBU (2.2)	21	—	—	—
5	**3c**	10	DBU (2.2)	6	10	18	—
6	**3c**	2	DBU (2.2)	11	4	—	—
7	**3d**	2	DBU (2.2)	2	10	—	—
8	**3d**[d]	5	DBU (6.0)	14	2	3	—

[a]The reaction temperature was 100–120 °C except when otherwise stated.
[b]Similar result was obtained when the reaction was carried out under N_2.
[c]Stepwise addition of base.
[d]Reaction carried out without solvent.

A detailed analysis of the ^{13}C NMR data showed a set of signals that was very similar in both the corresponding aminopyrazole **4a–d**[10] and the new compound **5a–d**, and this was assigned to the benzene nucleus. Three signals for cyano groups could be observed for all the compounds; for example, for compound **5d** they appear at 116.2, 115.1, and 116.0 ppm.

The full assignment of ^{13}C signals for compound **5d** was carried out by bidimensional heteronuclear multiple bond correlation (HMBC) and heteronuclear multiple quantum correlation (HMQC) techniques, and this allowed us to conclude that they would fit the proposed structure.

The infrared (IR) spectra of these fused heterocycles **5a–d**, as in the case of pyrazoles **4a–d**,[10] showed the expected bands, due to stretching vibrations of the cyano groups (2220–2250 cm^{-1}), the amine (3225–3500 cm^{-1}) and ester functions (1707–1735 cm^{-1}), as well as a strong band of the C=N bond (1588–1643 cm^{-1}) as result of the heterocyclic ring.

In most preparations, a by-product identified as the *para*-substituted cyanomethyl benzoate **6** was also isolated, and its ^1H NMR spectrum conclusively showed signals due to an aromatic ring containing two substituents in *para* position and a methylenic signal at about 5 ppm. Although the cyano absorption band was not present in the IR spectrum, it is known that the intensity of such a band may be very low.[15] Therefore, because the amounts obtained were minute, it was decided to prepare the esters **6c** and **6d** by an independent method, from the corresponding benzoic acids and chloroacetonitrile. The ^1H NMR showed two doublets in the aromatic region and the methylenic group at δ 4.89 (**6c**) or 4.93 (**6d**) ppm, but no cyano group was detected on their IR spectra. When EI mass spectra were obtained, however, they showed the expected M^+ ion and also the base peak corresponding to loss of the fragment OCH_2CN. For both compounds, ^{13}C NMR spectra also showed a signal at δ 115.9 (**6c**) or 116.2 (**6d**) ppm, which was attributed to the cyano carbon. It is thought that these compounds are very prone to hydrolysis and this might explain why, to the knowledge of the authors, they were not reported in the literature before.

To understand the pathway leading to compounds **4**, **5**, and **6**, an NMR study was carried out on the evolution of compound **3** in dimethylformamide and in the presence of 1,8-diazabicyclo[5.4.]undec-7-ene and chloroacetonitrile. The starting material **3** (15 mg) was dissolved in DMF-d_6 (0.5 mL) in an NMR tube, 2 equivalents of both chloroacetonitrile and DBU were added, and the NMR spectra were registered after 30, 60, 90, and 120 min. The signals at δ 8.0–8.20, 7.53, 6.97, 6.70, and 6.53 ppm from compounds **6**, **3**, **5**, hydrocyanic acid, and **4**, respectively, were followed to quantify the relative ratio of these materials in solution. The results obtained from this study are shown in Fig. 2 and Table 2. They indicate that the disappearance of the starting material originated mainly at compound **4** and that compounds **5** and **6** were always present in a 1:1 molar ratio. After 30 min at room temperature, 9.6% of **4**, 2.4% of hydrocyanic acid, and 0.6% of both **5** and **6** were identified in solution. After a period of 2 h the reaction mixture still contained approximately 50% of the starting material **3**, together with 22% of **4**, 4.6% of hydrocyanic acid, 10% of **6**, and 10% of **5**. This suggests that the major pathway leads to the formation of compound **4** from the reaction of **3** with chloroacetonitrile. The formation of **5** possibly results from the reaction between two molecules of **4**, eliminating hydrocyanic acid and the aromatic moiety **6**. The compound mixture generated in the NMR study was

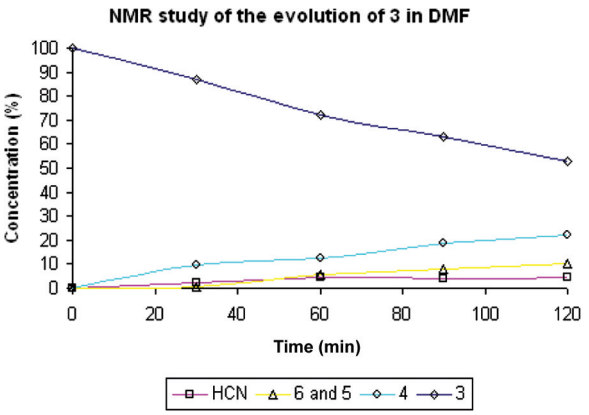


Figure 2. NMR study of the evolution of **3d** in DMF with DBU and chloroacetonitrile. (Figure is provided in color online.)

Table 2. Data obtained by NMR study of the reaction of compound **3d**

	Concentration (%) of compounds				
Time (min)	**3d**	**HCN**	**6d**	**5d**	**4d**
0	100	0	0	0	0
30	87	2.4	0.6	0.6	9.6
60	72	4.3	5.6	5.6	12.5
90	63	4.1	8.2	8.2	18.5
120	53	4.6	10	10	22

separated by preparative layer chromatography (PLC), confirming the structure assignment to all the heterocyclic/aromatic products.

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting-point apparatus and are uncorrected. IR spectra were registered on a Perkin-Elmer FTIR-1600. Ultraviolet (UV) spectra were determined on a Hitachi U-2000. NMR spectra were obtained on a Varian Unity Plus spectrometer at an operating frequency of 300 MHz for ^{1}H NMR and 75.4 MHz for ^{13}C NMR or a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR using the solvent peak as internal reference at 25 °C. All chemical shifts are given in parts per million (ppm) using δ_H $Me_4Si = 0$ ppm as reference and J values are given in hertz (Hz). Assignments were made by comparison of chemical shifts, peak multiplicities, and J values and were supported by spin decoupling–double resonance and bidimensional heteronuclear HMBC and HMQC correlation techniques.

Low-resolution EI mass spectra were determined on a Unicam GC-MS 120. High-resolution mass spectra were obtained on a VG Ultima or AutoSpec E spectrometers. Elemental analyses were obtained on a Leco CHNS-932. TLC and PLC were carried out on plates coated with silica gel 60 F_{254}. Column chromatography was

performed on silica gel (<230 mesh) with mixtures of light petroleum and diethyl ether of increasing polarity, unless other conditions are described. Light petroleum refers to the fraction boiling in the range 40–60 °C.

General Procedures for the Cyclization of Compounds 3a–d

Method 1. To a solution of the intermediate (**3**, 1 mequiv.) in dry DMF (1.6 mL), DBU (2.2 mequiv., except for **3d**, Table 1), and chloroacetonitrile (2.2 mequiv.) were added, and the mixture was kept stirring at the temperature and time indicated in Table 1. After cooling, the solvent was removed under reduced pressure and the dark oily mixture obtained was purified by column chromatography or PLC.

Method 2. NaH (2.2 or 4.2 mequiv.) was suspended in DMF (2 mL), and a solution of the intermediate (1 mequiv.) in DMF (3 mL) was added slowly with stirring. Chloroacetonitrile (2.2 mequiv.) was added, and the mixture was heated at the temperature and time mentioned in Table 1.

After cooling, water and then 6 N HCl were added until a dark solid precipitated. This was filtered, dried in the oven (45 °C), and purified by chromatography. In some of the attempts, only water was added and a brown oil separated, which was extracted with acetone. The solvent was removed and the resulting oil was purified by column chromatography or PLC.

Cyanomethyl 3-(7-Amino-3,5-dicyano-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl)benzoate 5a

After column chromatography, the pyrazolopyrimidine **5a** was obtained as a yellow solid (21%), mp 225.9–228.6°C, IR (KBr, cm^{-1}): 3500, 3317, 3225, 2960, 2920, 2232, 2220, 1732, 1633, 1571; UV (EtOH): 230 nm (log ε 4.48), 260 nm (log ε 4.27), 375 nm (log ε 3.91); ^{1}H NMR (300 MHz, DMSO-d_6): 5.29 (2H, s, CH_2), 7.84 (1H, t *J* 8.0 Hz, 5-H), 8.08 (1H, dt *J* 8.0 and 1.0 Hz, 4-H), 8.25 (2H, br s, NH_2), 8.42–8.48 (1H, m, 6-H), 8.61 (1H, t *J* 1.0 Hz, 2-H); ^{13}C NMR (75.4 MHz, DMSO-d_6): 50.12 (CH_2), 111.5, 115.0 (CN), 115.8 (CN), 116.3 ($CH_2\underline{C}N$), 119.9, 122.2, 126.8, 128.9, 129.3, 130.4, 130.6, 137.7, 143.8, 155.6 (C-7′), 163.9 (CO); *m*/*z* (%) (EI) 345 ($M^+ + 1$, 24), 344 (M^+, 100), 292 ($M^+ - C_2N_2$, 12), 288 ($M^+ - OCH_2CN$, 87), 287 (21), 261 (11), 260 ($M^+ - CO_2CH_2CN$, 27), 208 (41), 207 (21), 206 (32), 181 (34), 144 (54), 129 (23), 119 (18), 116 (21), 103 (23), 102 (52), 92 (30), 90 (22), 83 (16), 77 (22), 76 (31), 66 (24), 65 (33), 64 (99), 63 (49), 61 (52). Anal. calcd. for $C_{16}H_8N_8O_2$: C, 55.82; H, 2.33; N, 32.56%. Found: C, 55.62; H, 2.5; N, 32.30%.

Cyanomethyl-3 (7-Amino-3,5-dicyano-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl)-4-methylbenzoate 5b

After column chromatography followed by washing with diethyl ether, the pyrazolopyrimidine **5b** was obtained as a yellow solid (32%), mp 253.8–255.2 °C; IR (KBr, cm^{-1}): 3340, 3332, 3236, 2250, 2240, 1735, 1645, 1630, 1571; UV (EtOH): 230 nm (log ε 4.32), 315 nm (log ε 3.70), 375 nm (log ε 4.04); ^{1}H MNR (300 MHz, acetone-d_6): 2.34 (3H, s, Me), 5.26 (2H, s, CH_2), 7.45 (2H, br s, NH_2), 7.76 (1H, d *J* 7.6 Hz, 5-H), 8.18–8.20 (1H, br s, 2-H), 8.22 (1H, dd *J* 7.6 and 1.9 Hz, 6-H);

^{13}C NMR (75.4 MHz, DMSO-d_6): 17.7 (CH_3), 49.9 (CH_2), 115.0 (CN), 115.8 (CN), 115.9 ($CH_2\underline{C}N$), 116.6, 119.6, 125.8, 126.7, 128.9, 130.9, 132.1, 142.2, 144.4, 155.8 (C-7′), 163.5 (CO); m/z (EI) (%) 359 ($M^+ + 1$, 22), 358 (M^+, 91), 357 (24), 318 ($M^+ - CH_2CN$, 47), 306 ($M^+ - C_2N_2$, 48), 305 (79), 302 ($M^+ - OCH_2CN$, 17), 274 ($M^+ - CO_2CH_2CN$, 16), 273 (14), 239 (18), 222 (40), 221 (19), 214 (38), 104 (21), 103 (53), 102 (24), 92 (35), 91 (33), 90 (45), 89 (100), 78 (45), 77 (78), 76 (46). HRMS (EI): calcd. for $C_{17}H_{10}N_8O_2$ [M^+]: 358.0929; found: 358.0916.

Cyanomethyl 3-(7-Amino-3,5-dicyano-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl)-4-chlorobenzoate 5c

After colunm chromatography followed by PLC, the pyrazolopyrimidine **5c** was obtained as a yellow solid (4 or 10%), mp 233.7–235.7 °C; IR (KBr, cm^{-1}): 3454, 3343, 3250, 2241, 1733, 1622, 1585, 1571, 1541; UV (EtOH): 230 nm (log ε 3.48), 300 nm (log ε 3.45) nm, 375 (log ε 3.78); ^{1}H NMR (300 MHz, DMSO-d_6): 5.22 (2H, s, CH_2), 7.98 (1H, d *J* 8 Hz, 5-H), 8.16 (2H, br s, NH_2), 8.20 (1H, dd *J* 8 and 2 Hz, 6-H), 8.31 (1H, d *J* 2 Hz, 2-H); ^{13}C NMR (75.4 MHz, DMSO-d_6): 49.9 (CH_2), 115.0 (CN), 115.5, 115.8 (CN), 116.5 ($CH_2\underline{C}N$), 120.3, 125.5, 131.3, 131.6, 133.0, 134.0, 128.3, 137.1, 144.9, 156.0 (C-7′), 163.0 (CO); HRMS (EI): calcd. for $C_{16}H_7N_8O_2{}^{35}Cl$ [M^+]: 378.0383; found: 378.0366.

Cyanomethyl 3-(7-Amino-3,5-dicyano-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl)-4-methoxybenzoate 5d

After column chromatography followed by PLC, the pyrazolopyrimidine **5d** was obtained as a yellow solid (2 or 10%), that decomposes at 200 °C without melting; IR (KBr, cm^{-1}): 3473, 3366, 2242, 2228, 1707; UV (EtOH): 234 nm (log ε 4.41), 308 nm (log ε 3.70) nm, 374 nm (log ε 3.98); ^{1}H NMR (400 MHz, DMSO-d_6): 3.87 (3H, s, OCH_3), 5.21 (2H, s, CH_2), 7.49 (1H, d *J* 8.8 Hz, 5-H), 8.06 (2H, br s, NH_2), 8.13 (1H, d *J* 2 Hz, 2-H), 8.23 (1H, dd *J* 8.8 and 2.4 Hz, 6-H); ^{13}C NMR (100.6 MHz, DMSO-d_6): 49.9 (CH_2), 56.8 (OCH_3), 113.5 (C-5), 115.1 (CN), 116.0 (CN), 116.2 ($CH_2\underline{C}N$), 119.6 (C-3′ or C-7′a), 120.3 (C-1), 124.7 (C-3), 125.5 (C-3′ or C-7′a), 130.8 (C-2), 133.9 (C-6), 144.8 (C-5′), 155.9 (C-7′), 159.3 (C-4), 163.4 (CO); HRMS (EI): calcd. for $C_{17}H_{10}N_8O_3$ [M^+]: 374.087586; found: 374.086754.

Esters 6 Obtained During the Preparation of Pyrazoles 4

Cyanomethyl 4-methylbenzoate 6b. After PLC the ester **6b** was obtained as an oil (6%); IR (neat) (cm^{-1}): 2921, 2838, 1729, 1612; ^{1}H NMR (300 MHz, $CDCl_3$): 2.45 (3H, s, CH_3), 4.97 (2H, s, CH_2), 7.30 (2H, d *J* 8.2 Hz, 3-H and 5-H), 7.96 (2H, d *J* 8.2 Hz, 2-H and 6-H); *m/z* (%) (EI) 175 (M^+, 14), 120 (9), 119 ($M^+ - OCH_2CN$, 100), 91 (39), 89 (10), 65 (4).

Cyanomethyl 4-chlorobenzoate 6c. After column chromatography followed by PLC, ester **6c** was obtained as a white oil that later solidified (18%); the experimental data confirmed its structure and were in accordance with those obtained in an independent synthesis.

Cyanomethyl 4-methoxybenzoate 6d. After column chromatography and PLC, the ester **6d** was obtained as a colorless oil that later solidified (3%), mp 58.9–59.7°C; the experimental data confirmed its structure and were in accordance with those obtained in an independent synthesis.

Synthesis of the Esters 6c and 6d

Cyanomethyl 4-chlorobenzoate 6c. Potassium carbonate (0.44 g, 3.2 mequiv.) and chloroacetonitrile (0.2 mL, 3.2 mequiv.) were added to a solution of *p*-chlorobenzoic acid (0.5 g, 3.2 mequiv.) in dry DMF (3 mL), and the mixture was kept stirring overnight. Water was added, and the mixture was extracted with ether. The organic extracts were dried ($MgSO_4$), and the solvent removed to give ester **6c** as an oil, which later solidified (0.41 g, 65%), mp 48.5–50.3°C; IR (neat, cm^{-1}): 3455, 2943, 1736, 1670, 1589; ^1H NMR (300 MHz, $CDCl_3$): 4.89 (2H, s, CH_2), 7.27 (2H, d *J* 9 Hz, 3 and 5-H) 7.80 (2H, d *J* 9 Hz, 2 and 6-H). ^{13}C NMR (75.4 MHz, DMSO-d_6): 50.0 (CH_2), 115.9 (CN), 126.8 (C-1), 129.2 (C-3 and C-5), 131.3 (C-2 and C-6), 139.2 (C-4), 163.9 (C=O); *m/z* (%) (EI) 197 ($M^{+,\ 37}Cl$, 30), 195 ($M^{+,\ 35}Cl$, 84), 141 (34), 139 (100), 113 (24), 111 (72), 76 (19), 75 (57), 74 (26). Anal. calcd. for $C_9H_6NO_2Cl$: C, 55.26; H, 3.09; N, 7.16%. Found: C, 55.50; H, 3.05; N, 7.15.

Cyanomethyl 4-methoxybenzoate 6d. Following the method just described for **6c** and using *p*-methoxybenzoic acid, the ester **6d** was obtained as a reddish brown solid (79%), mp 60.2–62.0°C; IR (KBr, cm^{-1}): 3426, 3014, 2972, 2939, 2844, 1916, 1724, 1608, 1580, 1513; ^1H NMR (300 MHz, DMSO-d_6): 3.84 (3H, s, OCH_3), 5.17 (2H, s, CH_2), 7.09 (2H, dd *J* 6.1 and 2.1 Hz, 3-H and 5-H), 7.95 (2H, dd *J* 6.9 and 2.1 Hz, 2-H and 6-H); ^{13}C NMR (75.4 MHz, DMSO-d_6): 49.5 (CH_2), 55.7 (OCH_3), 114.4 (C-3 and C-5), 116.2 (CN), 120.0 (C-1), 131.8 (C-2 and C-6), 163.9 (C-4), 164.3 (CO); *m/z* (EI) (%) 192 ($M^+ + 1$, 8), 191 (M^+, 57), 136 (10), 135 ($M^+ - OCH_2CN$, 100), 107 (14), 92 (29), 77 (13), 64 (6). HRMS (EI): calcd for $C_{10}H_{19}NO_3$ [M^+]: 191.058243; found: 191.058294.

ACKNOWLEDGMENTS

We thank *Junta Nacional de Investigação Científica e Tecnológica* (Portugal) for financial support through (IBQF-UM) and PRAXIS XXI for support under project PRAXIS/2/2.1/QUI/44/94 and for a scholarship to M. S. T. Gonçalves (BD-2566-93-RM). The NMR spectrometer Bruker Avance III 400 is part of the National NMR Network and was purchased in the framework of the National Program for Scientific Re-equipment, Contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and FCT. We thank Miss Elisa Pinto for obtaining the NMR, low-resolution mass, and elemental analyses data.

REFERENCES

1. Larsen, J. S.; Zahran, M. A.; Pedersen, E. B.; Nielsen, C. Synthesis of triazenopyrazole derivatives as potential inhibitors of HIV-1. *Monatsh. Chem.* **1999**, *130*, 1167–1173.

2. Dai, H.; Li, Y. Q.; Du, D.; Qin, X.; Zhang, X.; Yu, H. B.; Fang, J. X. Synthesis and biological activities of novel pyrazole oxime derivatives containing a 2-chloro-5-thiazolyl moiety. *J. Agric. Food Chem.* **2008**, *56*, 10805–10810.
3. Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Micky, J. A.; Abdel-Megeid, F. M. E. Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 7102–7106.
4. Bouabdallah, I.; M'barek, L. A.; Zyad, A.; Ramadan, A.; Zidane, I.; Melhaoui, A. Anticancer effect of three pyrazole derivatives. *Nat. Prod. Res.* **2006**, *20*, 1024–1030.
5. Pinto, D. J. P.; Quan, M. L.; Woerner, F. J.; Li, R. Int. Patent WO 02000655 A1, 2002.
6. Brady, T.; Vu, K.; Barber, J. R.; Ng, S. C.; Zhou, Y. Synthesis of novel 2,3-substituted-2, 4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones. *Tetrahedron Lett.* **2009**, *50*, 6223–6227.
7. Semeraro, T.; Mugnaini, C.; Manetti, F.; Pasquini, S.; Corelli, F. Practical synthesis of novel purine analogues as Hsp90 inhibitors. *Tetrahedron* **2008**, *64*, 11249–11255.
8. Gewald, K.; Jaensch H. J.; Calderon, O. E. Ger. Patent 113 359, 1975.
9. Moura, J. C. V. P.; Oliveira-Campos, A. M. F.; Griffiths, J.; Maia, H. L. S.; Gomes, J. I. N. R. Synthesis of carboxylic acid derivatives of aminocyanopyrazoles: Useful precursors for a new class of fiber-reactive azo dyes. *J. Chem. Res., Synop.* **1995**, 128–129; *Miniprint* 924–937 (part I).
10. Gonçalves, M. S. T.; Oliveira-Campos, A. M. F.; Rodrigues, L. M.; Proença, M. F. R. P. Griffiths, J.; Maia, H. L. S.; Kaja, M.; Hrdina, R. Synthesis of novel derivatives of 4-amino-3,5-dicyanopyrazole. *J. Chem. Res.* **2004**, 115–117.
11. Oliveira-Campos, A. M. F.; Salaheldin, A. M.; Rodrigues, L. M. Synthesis of some novel pyrazolo[3,4-*d*]pyrimidine derivatives. *Arkivoc* **2007**, *16*, 92–100.
12. Gupta, S.; Rodrigues, L. M.; Esteves, A. P.; Oliveira-Campos, A. M. F.; Nascimento, M. S. J.; Nazareth, N.; Cidade, H.; Neves, M. P.; Fernandes, E.; Pinto, M.; Cerqueira, N. M. F. S. A.; Brás, N. Synthesis of *N*-aryl-5-amino-4-cyanopyrazole derivatives as potent xanthine oxidase inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 771–780.
13. Salaheldin, A. M.; Oliveira-Campos, A. M. F.; Rodrigues, L. M. Heterocyclic synthesis with nitriles: Synthesis of pyrazolopyrimidine and pyrazolopyridine derivatives. *Synth. Commun.* **2009**, *39*, 1186–1195.
14. Salaheldin, A. M.; Oliveira-Campos, A. M. F.; Rodrigues, L. M. 3-Aminopyrroles and their application in the synthesis of pyrrolo[3,2-*d*]pyrimidine (9-deazapurine) derivatives. *Arkivoc* **2008**, *14*, 180–190.
15. Hosni, H. M.; Basyouni, W. M.; El-Nahas, H. A. Thienopyrimidines, part III: Synthesis of novel substituted thieno[2,3-*d*]pyrimidinone derivatives and their condensed products with molluscicidal and larvicidal activities. *J. Chem. Res. Synop.* **1999**, 646–647; *Miniprint*, 2775–2794.