Heterocyclic synthesis with nitriles: Synthesis of pyrazolopyrimidine and pyrazolopyridine derivatives

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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, pyrazolo[3,4-*d*]pyrimidines, pyrazolo[3,4-*b*]pyridines, diethylmalonate, malononitrile.

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] due to 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] 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 has been carried out of a substituted aminopyrazole, which contains a cyano group in the *ortho* position, with malononitrile and diethylmalonate.

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

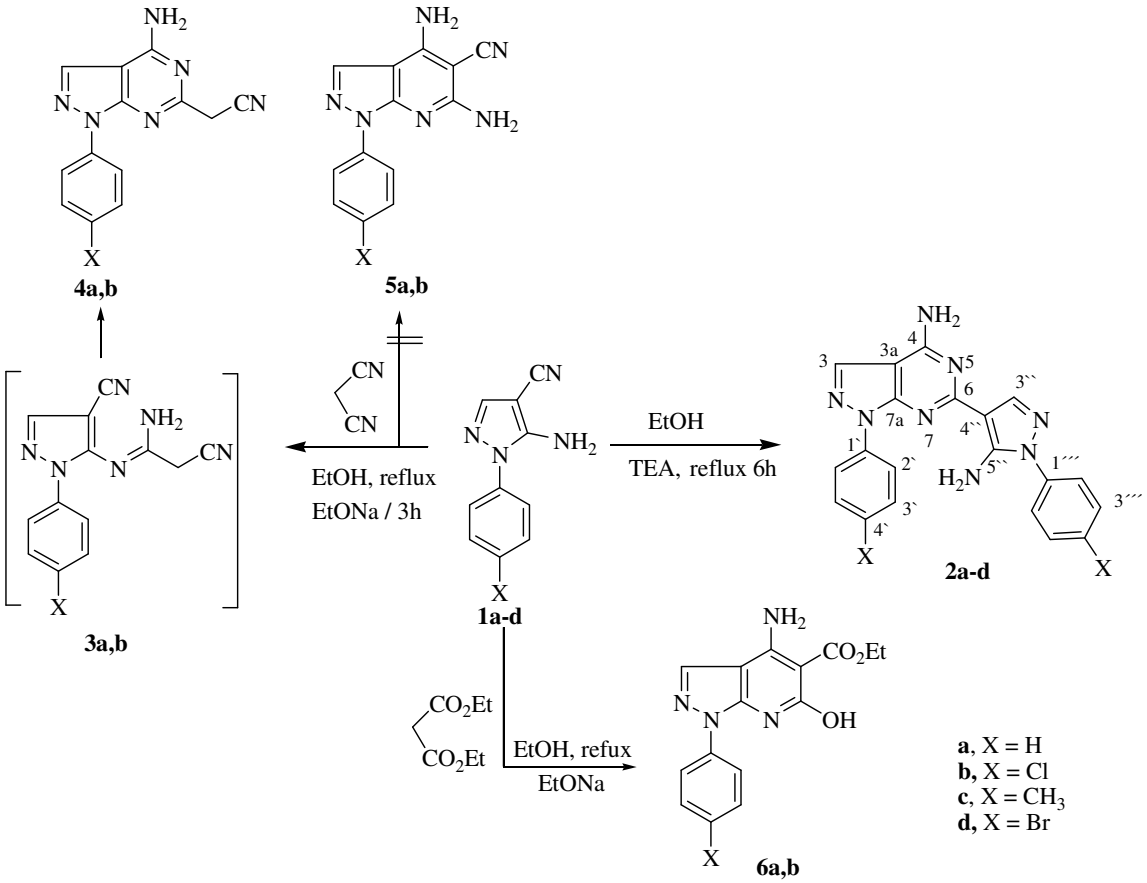
It has been found that reaction of compound **1a** with malononitrile in refluxing ethanol in the presence of triethylamine afforded a yellow crystalline solid of mp 254-256^{o}C. It was expected that this reaction would give the pyrazolopyrimidine **4a** or pyrazolopyridine **5a** via the intermediate **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 displays an absorption at 3463 cm^{-1}, corresponding to NH_2 stretching, and no CN absorption. The ^{1}H NMR spectrum reveals 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**.

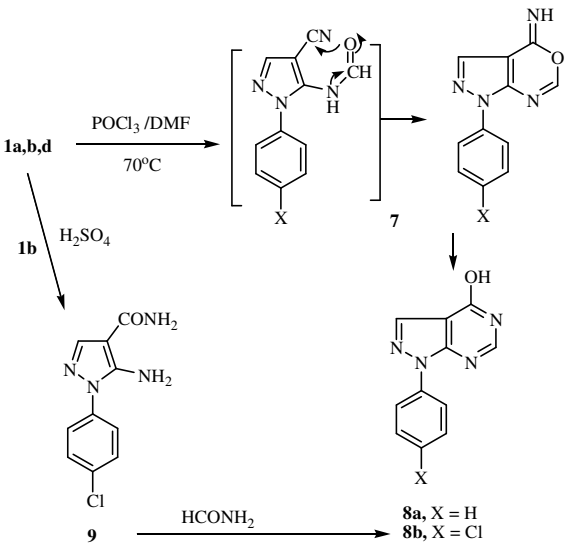
In ethanolic sodium ethoxide solution, compounds **1a** and **1b** reacted with malononitrile to afford white powders of mp 242-244^{o}C for **4a** and 296-298^{o}C for **4b**, respectively. The ^{1}H NMR spectrum of compound **4a** revealed a methylene singlet at δ 4.17 ppm and pyrazole H-3 as a singlet at 8.34 ppm besides other signals attributable to an aromatic compound and only one NH_2 group at 8.0 ppm as expected (cf. Experimental). Based on these data it seemed that a $–CH_2CN$ side chain is 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]

On the contrary, 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 ^{1}H 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 70ºC for 3h. To the product which was obtained structure **8** was proposed based on the NMR data which indicate the presence of OH group and the pyrazole H-3, the reaction proceeding via the intermediacy of **7** (Scheme 2). The structure of compound **8b** could be confirmed by an alternative synthesis, as described before, converting **1b** to the amide **9**, by treatment with cold concentrated sulfuric acid, followed by boiling compound **9**, mp 202-204 ºC (Lit. mp 204-205ºC)[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).



Scheme 1



Scheme 2

The 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, HMQC and HMBC experiments were carried out for complete assignment of proton and carbon signals in the NMR spectra, whenever possible. High resolution mass spectra 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

To a solution of 5-amino-4-cyano-1-substituted pyrazole **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^{o}C (EtOH) (Lit. [8] mp 255-257^{o}C); (max (Nujol mull): 3462 and 3302 (NH2) cm-1; δH (CDCl3): 5.57 (s, 2H, NH2-C-5”), 5.89 (s, 2H, NH_2-C-4), 7.30-7.42 (m, 2H, Ar-H), 7.52 (appt, 4H, 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); υ_{max} (Nujol mull): 3463 and 3304 (NH_2) cm^{-1}; δ_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); υ_{max}(Nujol mull): 3395, 3336, and 33187 (NH_2) cm-1; δH (DMSO-d6): 2.35 (3H, s, CH_3), 2.36 (3H, s, CH_3), 6.74 (2H, s, NH_2-C-4), 7.33 (2H, d, J=8.1 Hz, H-3´, H5´or H-3´´´, H-5´´´), 7.34 (2H, d, J=8.1 Hz, H-3´, H5´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, NH_2-C-5"), 7.98 (1H, s, H-3), 8.04 (2H, d, *J*= 8.4 Hz, H-2´, H-6´or H2´´´, H-6´´´), 8.24 (1H, s, H-3"); δ_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 $C_{22}H_{20}N_8$ 2½ 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); υ_{max} (Nujol mull): 3449, 3391 and 3301 (NH_2) cm^{-1}; δ_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); υ_{max} (Nujol mull): 3463 and 3296 (NH_2), 2213 (CN) cm^{-1}; δ_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); δ_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); υ_{max} (Nujol mull): 3469 and 3306, (NH_2), 2218 (CN) cm^{-1}; δ_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); δ_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); υ_{max} (Nujol mull): 3505 and 3395 (NH_2), 3245 (br, OH), 1660 (C=O) cm^{-1}; δ_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); δ_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); υ_{max} (Nujol mull): 3486 and 3363 (NH_2), 3179 (br, OH), 1687 (C=O) cm^{-1}; δ_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.

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]) δ_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); δ_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]) δ_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]), υ_{max} (Nujol mull): 3471, 3337, (NH_2), 1662 (C=O) cm-1; δ_H ($CDCl_3$): 6.42 (s, 2H, NH_2), 6.857 (br s, 1H, NH), 7.41 (br s, 1H, NH), 7.54-7.57 (m, 4H, Ar-H), 7.90 (s, 1H, H-3); δ_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.

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