A Novel Route to 4-Aminopyrazoles and Aminopyrazolo[4,3-*b*]pyridines

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3-Oxo-2-arylhydrazononitriles **6** are readily converted into 4-aminopyrazoles **1** *via* reaction with α-haloketones, chloroacetonitrile and ethyl chloroacetate. The aminopyrazoles are readily converted into aminopyrazolo[4,3-*b*]pyridines upon treatment with malononitrile. Compounds are readily diazotized to yield unstable diazonium salts that readily cyclized into pyrazolo[4,3-*c*]pyridazines.

Key words: 2-Arylhydrazononitriles, Aminopyrazoles, α-Haloketones, Aminopyrazolo[4,3-*b*]pyridines, Pyrazolo[4,3-c]pyridazine

Introduction

The synthesis of 4-aminopyrazole-5-carboxylates **1** is now receiving considerable interest [1 – 4] as these compounds are important precursors to important pharmaceuticals among which Viagra (**2**) and allopurinal (**3**) are two well-known compounds [5 – 8]. Moreover, 4-aminopyrazoles can also be considered as interesting precursors to dyes. 4-Derivatives of **1** are generally prepared *via* nitration of pyrazole **4** and reduction of formed nitro derivatives **5** [9]. This approach is both multistageous and environmentally non-friendly.

Results and Discussion

In conjunction to our interest in synthesis and reactivity of aminopyrazoles we report a simple and efficient route to **1**. Moreover, results of our investigation on the reactivity of **1** is reported. The work enabled developing a novel efficient route to pyrazolo[4,3-*b*]pyridines (Scheme 1).

We have found that **6** reacts readily with chloroacetonitrile in dioxane in the presence of triethylamine (10 equivalents) to yield products of a molecular formula corresponding to **7** or isomeric **1a** with excellent yield. Structure **1a** was readily established based on ^{1}H NMR data that revealed the absence of a signal for a methylene function and the appearance of a two-protons D_2O-exchangeable signal at $\delta = 5.24$ ppm for the amino function. It is assumed that **1a** has resulted from *in situ* cyclization of initially formed **7**. Recently, a similar result has been reported with poor to moderate yield [10].

Similar to its behavior toward chloroacetonitrile, compound **6** also reacted with ethyl chloroacetate and with chloroacetone to yield **1b, c**, respectively, in good yields.

We have investigated the possible utility of compound **1** as precursors to pyrazoloazines. It was found that compound **1a** reacted with malononitrile in refluxing ethanol and in the presence of piperidine to yield the pyrazolo[4,3-*b*]pyridine derivative **9** (Scheme 2). Initial formation of **8** seems most likely; however, attempted isolation of **8** failed. Clearly, the aromaticity of the cyclization product is a driving force for the immediate formation of **9**.

Diazotization of **1** afforded unstable diazonium salts **10** that readily cyclized into pyrazolo[4,3-*c*]pyridazine **11**. Acetylation of compound **1** in acetic anhydride afforded **13** in excellent yield. The IR spectrum of compound **15** shows absorptions of two carbonyl group at 1710 and 1673, a cyano group at 2230 and a NH group at 3337 cm^{-1}. The ^{1}H NMR spectrum reveals two CH_3 groups at $\delta = 2.10$ and 2.58 ppm which indicates that no further cyclization has occurred.

Experimental Section

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye Unicam SP 3-300 Spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide [D_6]-DMSO or deutrated chloroform ($CDCl_3$) at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS)

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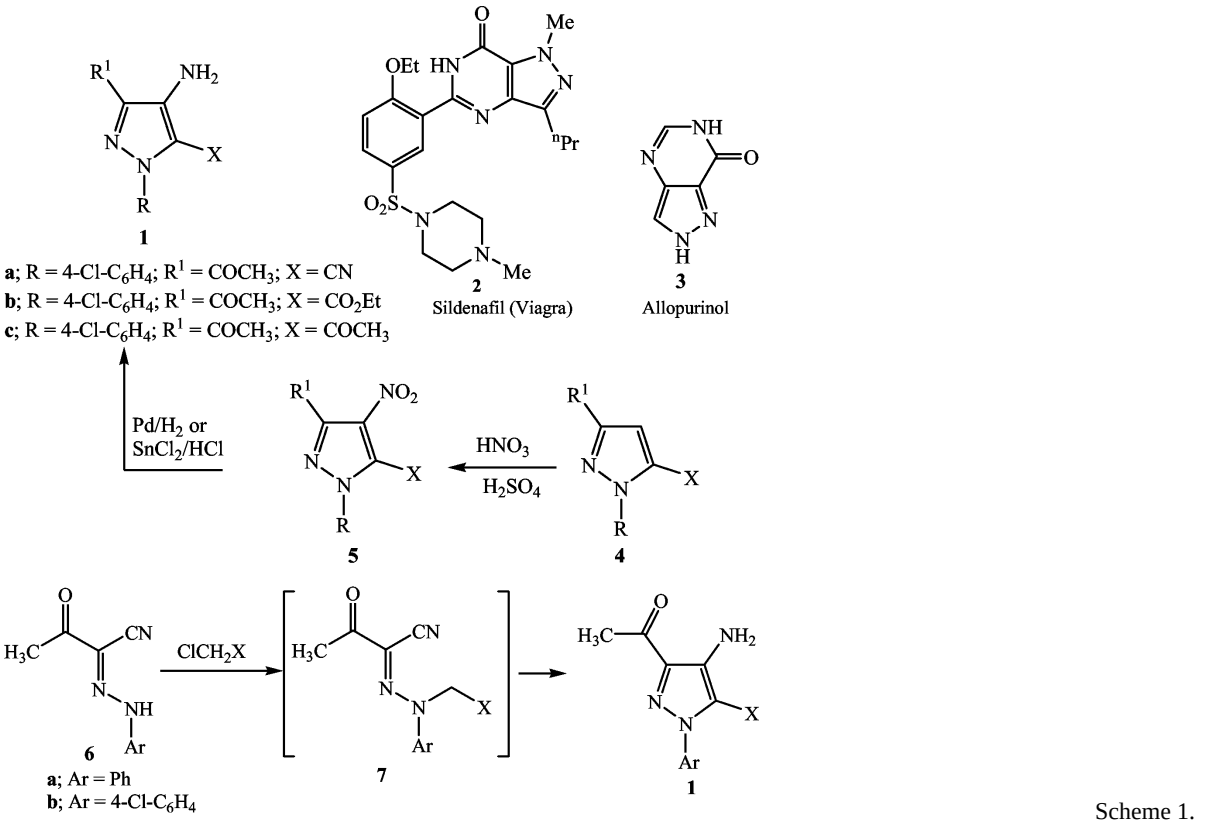


Scheme 1.

as an internal reference and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The azo derivatives **6a, b** were prepared as previously reported in the literature [11].

General procedure for the preparation of compounds **1a** – **c**

To a solution of **6b** (2.21 g, 0.01 mol) in dioxane (25 ml) and triethylamine (10.1 g, 0.1 mol) chloroacetonitrile, ethyl chloroacetate or chloroacetone (1 ml, 0.016 mol) was added. The reaction mixture was refluxed for 3 h, then evaporated *in vacuo*, and the solid product was filtered off and crystallized from ethanol.

*3-Acetyl-4-amino-1-(4-chlorophenyl)-1H-pyrazole-5-carbonitrile (***1a***)*

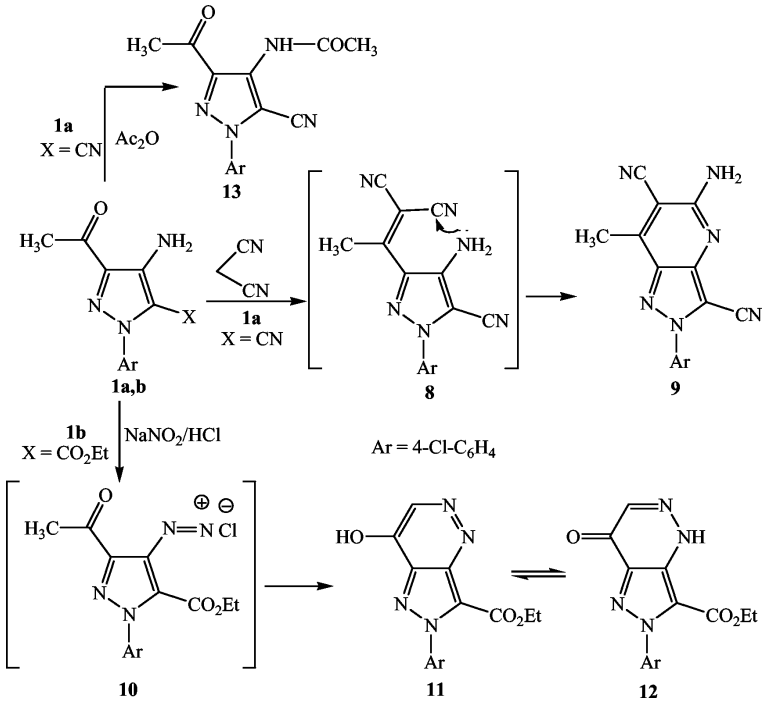
M. p. 156 °C. Yield: 85%. – IR: $\nu = 3451, 3348$ (NH_2); 2217 (CN), 1671 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): $\delta = 2.61$ (s, 3H, CH_3), 5.24 (s, 2H, NH_2), 7.50 (d, 2H, $J = 12$ Hz, 2H Ar), 7.69 (d, 2H, $J = 12$ Hz, 2H Ar). – ^{13}C NMR (75 MHz, [D_6]-DMSO): $\delta = 197.91$ (CO), 139.03 (C-3), 137.62, 135.94 (C-4), 134.62, 128.81, 122.23, 119.75 (C-5), 115.91 (CN), 24.80 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 260 (20) [M^+]. – $C_{12}H_9ON_4Cl$ (260.6): calcd. C 55.29, H 3.48, N 21.49, Cl 13.60; found C 55.10, H 3.60, N 21.30, Cl 13.50.

*Ethyl 3-acetyl-4-amino-1-(4-chlorophenyl)-1H-pyrazole-5-carboxylate (***1b***)*

M. p. 143 °C. Yield: 75 %. – IR: $\nu = 3492, 3380$ (NH_2), 1711, 1672 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): $\delta = 1.23$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.60 (s, 3H, CH_3), 4.21 (q, 2H, $J = 7.2$ Hz, CH_2), 5.78 (s, 2H, NH_2), 7.29 (d, 2H, $J = 12$ Hz, 2H Ar), 7.35 (d, 2H, $J = 12$ Hz, 2H Ar). – MS (EI, 70 eV): *m/z* (%) = 307 (27) [M^+]. – $C_{14}H_{14}O_3N_3Cl$ (307.7): calcd. C 54.64, H 4.59, N 13.65, Cl 11.52; found C 54.60, H 4.40, N 13.70, Cl 11.60.

*1-[5-Acetyl-4-amino-2-(4-chlorophenyl)-2H-pyrazol-3-yl]-ethanone (***1c***)*

M. p. 138 °C. Yield: 72%. – IR: $\nu = 3445, 3350$ (NH_2), 1678, 1669 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): $\delta = 2.55$ (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.31 (s, 2H, NH_2), 7.39 (d, 2H, $J = 12$ Hz, 2H Ar), 7.52 (d, 2H, $J = 12$ Hz, 2H Ar). – MS (EI, 70 eV): *m/z* (%) = 277 (18)



Scheme 2.

[M^+]. – $C_{13}H_{12}O_2N_3Cl$ (277.7): calcd. C 56.22, H 4.36, N 15.13, Cl 12.77; found C 56.10, H 4.35, N 15.20, Cl 12.80.

*5-Amino-2-(4-chlorophenyl)-7-methyl-2H-pyrazolo[4,3-b] pyridine-3,6-dicarbonitrile (***9***)*

A mixture of **1a** (2.6 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in ethanol (25 ml) was refluxed for 4 h. The solvent was evaporated under vacuo, and the crude product was collected and crystallized from ethanol. – M. p. 202 °C. Yield: 77%. – IR: ν = 3460, 3350 (NH_2), 2220, 2215 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 2.48 (s, 3H, CH_3), 5.68 (s, 2H, NH_2), 7.29 (d, 2H, J = 12 Hz, 2H Ar), 7.45 (d, 2H, J = 12 Hz, 2H Ar). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 157.05, 148.73, 143.58, 137.91, 134.67, 129.84, 125.30, 124.35, 114.83 (CN), 111.14 (CN), 110.88, 97.95, 15.16 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 308 (22) [M^+]. – $C_{15}H_9N_6Cl$ (308.7): calcd. C 58.36, H 2.94, N 27.22, Cl 11.48; found C 58.50, H 3.11, N 27.35, Cl 11.50.

*Ethyl 2-(4-chlorophenyl)-7-hydroxy-2H-pyrazolo[4,3-c]pyridazine-3-carboxylate (***11***)*

A mixture of **1b** (3.07 g, 0.01 mol), sodium nitrite (0.69 g, 0.01 mol) and concentrated hydrochloric acid (2 ml) in acetic acid (15 ml) was stirred at r. t. for 2 h. The reaction mixture was poured into ice-water, the product so formed was collected by filtration and crystallized from ethanol to give **11**. – M. p. 210 °C. Yield: 72%. – IR: ν = 3421 (OH), 1728 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 1.15 (t, 3H, J = 7.5 Hz, CH_3), 4.32 (q, 2H, CH_2), 7.40 (d, 2H, J = 12 Hz, 2H Ar), 7.66 (d, 2H, J = 12 Hz, 2H Ar), 7.76 (s, 1H), 13.30 (s, 1H, OH). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 173.40 (CO), 166.52 (C-7), 140.12, 138.38, 136.22 (C-3), 128.21, 127.24, 120.23, 116.41, 112.60, 108.83, 61.63 (CH_2), 12.55 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 318 (31) [M^+]. – $C_{14}H_{11}O_3N_4Cl$ (318.7): calcd. C 52.76, H 3.48, N 17.58, Cl 11.12; found C 52.70, H 3.55, N 17.60, Cl 11.10.

*N-[3-Acetyl-1-(4-chlorophenyl)-5-cyano-1H-pyrazol-4-yl]-acetamide (***13***)*

A solution of **1a** (2.6 g, 0.01 mol) in acetic anhydride (25 ml) was refluxed for 3 h. The reaction mixture was cooled and the solid that separated was collected and crystallized from ethanol to give **13**. – M. p. 195 °C; yield: 75%. – IR: ν = 3337 (NH), 2230 (CN), 1707, 1673 (CO) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 2.10 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.45 (s, 1H, NH), 7.22 (d, 2H, J = 10 Hz, 2H Ar), 7.45 (d, 2H, J = 10 Hz, 2H Ar). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 193.60 (CO), 168.23 (CO), 140.84, 136.59, 134.62, 129.79, 128.22, 127.18, 126.03, 110.94 (CN), 27.21 (CH_3), 22.84 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 302 (24) [M^+]. – $C_{14}H_{11}O_2N_4Cl$ (302.7): calcd C 55.55, H 3.66, N 18.51, Cl 11.71; found C 55.50, H 3.55, N 18.40, Cl 11.80.

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[1] J. Quiroga, B. Insusty, S. Gruz, P. Hernandez, A. Bolanos, R. Moreno, A. Hormaza, J. Heterocyclic Chem. **35**, 333 (1998).
[2] S. M. AL-Mousawi, M. A. Mohammad, M. H. Elnagdi, J. Heterocyclic Chem. **41**, 989 (2001).
[3] M. H. Elnagdi, N. Al-Awadi, A. W. Erian, in A. R. Katritizky, C. W. Rees, E. F. Scriven, C. A. Ramsden (eds): Comprehensive Heterocyclic Chemistry II, Vol. 7, pp. 431 – 488, Elevier, Amsterdam (1996).
[4] T. M. Elmaati, F. M. El-Taweel, J. Heterocyclic Chem. **41**, 109 (2004)
[5] B. E. Blass, A. Sirvastava, K. R. Coburn, A. L. Faulkner, W. L. Seibel, Tetrahedron Lett. **44**, 3009 (2003).
[6] K. Unverferth, J. Engel, N. Hoefen, A. Rostock, R. Guenther, J. Med. Chem. **41**, 63 (1988).
[7] K. Harada, S. Nishino, T. Harada, M. Ogami, Jpn. Tokkyo Koho, JP. 294576, (2001); Chem. Abstr. 135:303884p (2001).
[8] H. Braum, U. S. Pat. Appl. Pupl. US 9044 (2001); Chem. Abstr. 135:126915b (2001).
[9] H. M. E. Hassaneen, H. M. Hassaneen, M. H. Elnagdi, Z. Naturforsch. **59b**, 1132 (2004).
[10] M. S. T. Goncalves, A. M. F. Oliveira-Campos, L. M. Rodrigues, M. F. R. P. Proenca, J. Griffiths, H. S. Maia, M. Kaja, R. Hrdina, J. Chem. Res. 115 (2004).
[11] M. H. Elnagdi, M. M. M. Sallam, H. M. Fahmy, S. A. M. Ilias, M. A. M. Ibraheim, Helv. Chim. Acta **59**, 550 (1976).