SYNTHESIS OF NOVEL DERIVATIVES OF A VERSATILE SYNTON: 4-AMINO-3-CYANOPYRAZOLE

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Abstract: Diazotisation of substituted arylamines followed by reaction with malononitride gave substituted arylazomalononitriles. Cyclisation of these intermediates with two carbon sources and base gave the corresponding new 4-amino-3-cyanopyrazoles, in moderate yields. In one case the corresponding oxo-pyrazolopyrimidine was prepared.

Keywords: pyrazole, cyanopyrazole, oxo-pyrazolopyrimidine

Introduction

Pyrazole derivatives constitute an important family of compounds due to their applications as pharmaceuticals (analgesics, anti-inflammatory, anti-bacterial, and antidepressant), agrochemicals (insecticides) and dye stuffs.[1-3] Recently aminopyrazoles were found potentially useful to prevent protein aggregation which is the first phase of Alzheimer or Creutzfeldt-Jakob diseases.[4] Pyrazoles are also important synthons for the preparation of biologically active derivatives.[5-7]

The synthesis of this type of heterocyclic rings and related structures was reviewed.[8-10] Various methods of synthesis of pyrazoles are known and the most important involves the reaction between hydrazine derivatives with 1,3-difunctional compounds, [11] such as malononitrile.[12] To obtain the compounds described in this paper we followed Gewald’s method and used arylazomalononitriles as intermediates. It is noteworthy that these compounds may be biologically active on their own namely, against mollusca and their eggs. [7] The arylazomalononitriles may originate arylpyrazoles through reaction with a two carbon source, such as chloroacetonitrile in basic medium.

Results and discussion

The work described in this paper starts by diazotization of substituted anilines and reaction of the corresponding diazonium salts with malononitrile to give arylazomalononitriles (1) as before.[13] The intermediate 1a was described before, [14], 1b and 1c were isolated as yellow solids in yields 10-36%.

It was decided to obtain 4-amino-3-cyanopyrazoles containing a CN or CO\textsubscript{2}Et in position 5. When the preparation of 2a was attempted using DMF, K\textsubscript{2}CO\textsubscript{3} and bromo ethylacetate the pure product was obtained in 27%. A similar reaction with DMF, NE\textsubscript{t}3, and chloroacetonitrile gave only 2% yield of 2b, possibly due to decomposition during the longer heating period. However, when we used triethylamine as the base and chloroacetonitrile both
in excess the cyclization occurred and after purification by column chromatography the 4-amino-3,5-dicyano-3’nitrophenyl-pyrazole 2c was obtained as solid material in 36%. This product is not fluorescent on the tlc plate and this was misleading, since all the previous products gave fluorescent spots. Then the mixture was heated for 12 hours and possibly this lead to some decomposition. When this method was applied to prepare derivatives with different groups higher yields were obtained. [14]

The formation of pyrazoles 2 was confirmed by their 1H NMR spectra where the signals at highest chemical shift (δ≈ 12 ppm), corresponding to the N-H in the intermediates 1, were replaced by signals at δ≈ 6 ppm, assigned to the NH2 group of the pyrazoles. The expected pattern for the substituted phenyl ring was observed.

The presence of cyano groups was confirmed by one band in their IR spectra, e.g. υ 2238 and 2222 cm⁻¹ for compound 2a and 2b, respectively.

Compound 2a was used to prepare the pyrazolopyrimidine 3 in 15% overall yield. Reaction of pyrazole 2a with triethyl orthoformate and acetic anhydride yielded the imidate 4 which in aqueous ammonia solution generated the final product 3. [15]

The structure of 3 was confirmed by HRMS and spectroscopic data, namely, IR absorption bands at 1715 and 2241 cm⁻¹; and the singlet at 11.8 ppm due to NH. 13C signals were assigned based on DEPT and HMBC techniques.

**Experimental**

All melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were determined on a Perkin Elmer FTIR-1600 using Nujol emulsions between NaCl plates. UV spectra were determined on a Hitachi U-2000. NMR spectra were run at 25 ºC. 1H NMR spectra were recorded at 300 MHz and 13C NMR spectra were determined at 75.4 MHz.
both on a Varian Unity Plus Spectrometer. In the NMR spectra Me₄Si or the solvent peak were used as internal reference. In ¹H NMR spectra all signals mentioned as d, t, are in fact pseudo doublets and triplets.

High resolution mass spectra were obtained on a AutoSpec E spectrometer. Elemental analyses were obtained on a Leco CHNS-932. TLC was carried out on plates coated with 0.25 mm thick silica gel 60 F₂₅₄. Column chromatography was performed on silica gel (<230 mesh) under conditions that are described below. Light petroleum refers to the fraction boiling in the range 40-60 °C.

**General method for synthesizing intermediates 1**

To a cooled (0 °C) solution of the 3-substituted phenylamine (27 mmol) in 2M HCl (40 mL), a solution of NaNO₂ (1.86 g, 27 mmol) in water (7.4 mL) was added with stirring. The mixture was kept stirring at RT for 10 minutes and excessive nitrite (the reaction was followed with starch-iodide paper) was destroyed with urea. The resulting diazonium solution was slowly added, with stirring, at low temperature (0 °C) to a solution of malononitrile (1.78 g, 27 mmol) and 2M sodium acetate (20 mL) in methanol (20 mL). The mixture was kept stirring for 30 minutes and then left standing for 3h at RT. The solid precipitate was filtered, washed with ice water and dried. The yields obtained varied from 10 to 36% for the first crop only.

(3-Bromophenyl)hydrazono]malononitrile (Ia): 3-bromo-phenylamine was used as starting material. Compound 2a was obtained as a bright yellow solid, m.p. 188.4-190.6 °C [14]. ¹H (CDCl₃) δ 7.35-7.47 (3H, m, H-4, H-5 and H-6), 7.61 (1H, d J 1.5 Hz, H-2), 12.8 (1H, very br s, NH). Found: C43.36; H, 2.14; N, 22.30. Expected for C₉H₅N₄Br: C, 43.38; H, 2.01; N, 22.49 %.

(3-Acetylphenyl)hydrazono]malononitrile (Ib): 3-acetyl-phenylamine was used as starting material. Compound 1b was obtained as a light yellow solid, m.p. 177.2-177.8 °C. ¹H (acetone-d₆) δ 7.46 (1H, t J 8.1 Hz, H-5), 7.80 (1H, m, H-6), 7.90 (1H, m, H-4), 8.13 (1H, t J 8.0 Hz, H-2), 11.90 (1H, br s, NH).

(3-Nitrophenyl)hydrazono]malononitrile (Ic): 3-nitrophenylamine was used as starting material. Compound 1c was obtained as a light yellow solid, m.p. 169.2-170.2 °C. ¹H (acetone-d₆) δ 7.80 (1H, t J 8.1, H-5), 7.99 (1H, m, H-4), 8.13 (1H, m, H-6), 8.39 (1H, t J 2.1 Hz, H-2), 12.10 (1H, br s, NH).

Ethyl 4-amino-1-(3’-bromophenyl)-3-cyano-1H-pyrazole-5-carboxylate (2a): To a solution of the intermediate 1a (1 mequiv.) in dry DMF (1.2 mL), K₂CO₃ (2.6 mequiv.), and bromo ethylacetate (2.1 mequiv.) were added and the mixture was kept stirring at 120 °C for three hours. The mixture was cooled to 70 °C and triethylamine (1.2 mequiv.) added. The temperature was then taken up to 90 °C and the reaction mixture kept at this temperature for one hour. After cooling the dark oily mixture obtained was poured over a mixture of water and crushed ice and left overnight, the precipitate formed was filtered. The product was obtained as a light brown solid (27%), m.p. 121-123.7 °C; λ_max (EtOH, ε) 211 (10290), 323 (7368); ν_max (Nujol) 3488, 3358, 3227, 2238, 1721, 1628, 1587, 1566, 1505, 1466, 1349, 1302, 1281, 1216, 1139, 1029, 875, 780, 766 cm⁻¹; ¹H (acetone-d₆) δ 1.19 (3H, t J 7.2 Hz, OCH₂CH₃) ,
4.25 (2H, q J 7.2 Hz, OCH₂CH₃), 5.75 (2H, br s, NH₂), 7.51 (1H, t J 8 Hz, H-5), 7.58 (1H, dq J 1.5, 2.1 and 8.1 Hz, H-6), 7.74 (1H, dq J 1.2, 1.8 and 7.7 Hz, H-4), 7.90 (1H, t J 1.9 Hz, H-2).

¹³C (acetone- d₆) δ 159.4; 143.7; 142.3; 132.7; 131.0; 129.8; 125.9; 121.7; 117.8; 115.0; 113.2; 61.5; 14.2. Found: M⁺ 336.0053. Expected for C₁₃H₁₁O₂N₄: 336.0045.

4-Amino-1-(3´-acetylphenyl)-1H-pyrazole-3,5-dicarbonitrile (2b): To a solution of the intermediate (1 mequiv.) in dry DMF (1.2 mL), NEt₃ (2.6 mequiv.), and bromoacetonitrile (2.1 mequiv.) were added and the mixture was kept stirring at 120-140 °C for six hours. The reaction mixture was poured over a mixture of water and crushed ice and stirred for two hours. A gum was obtained which was purified by column chromatography. The product was obtained as a light brown solid (2%), m.p. 115-117.0 °C; νmax (Nujol) 3420, 3348, 2222, 1686, 1660, 1583, 1356, 1302, 1252, 794, 722, 695 cm⁻¹; ¹H (acetone- d₆) δ 6.10 (2H, br s, NH₂), 7.82 (1H, t J 7.8 Hz, H-5), 8.05 (1H, H-6), 8.19 (1H, m, H-4), 8.36 (1H, t J 1.5 Hz, H-2).

4-Amino-1-(3´-nitrophenyl)-1H-pyrazole-3,5-dicarbonitrile (2c): To the intermediate (1 mmol), chloroacetonitrile (1 mL) and NEt₃ (5 mmol) were added with external cooling and the mixture was refluxed for 12 hours. After cooling it was poured into water (50 mL) and this was extracted with ethyl acetate (4 x 25 mL). The organic extracts were dried (MgSO₄) and evaporated to dryness giving a yellow oily solid 38%. ¹H (acetone- d₆) δ 6.20 (2H, br s, NH₂), 8.02 (1H, t J 8.1 Hz, H-5), 8.29 (1H, m, H-6), 8.47 (1H, H-4), 8.70 (1H, t J 2.1 Hz, H-2).

1-(3´-Bromophenyl)-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-3-carbonitrile (3) Acetic anhydride (1.02 g, 10 mmol) and triethyl orthoformate (2.8 g, 20.6 mmol) were added to pyrazole (2a) (0.56 g, 1.67 mmol) and the mixture was heated under reflux for 24 hours. Removal of the volatiles on a rotary evaporator followed by addition of hexane to the residue gave compound 4 as a brown solid (40%). ¹H (acetone- d₆) δ 1.18 (3H, t J 7.2 Hz, OCH₂CH₃), 1.43 (3H, t J 7.2 Hz, OCH₂CH₃), 4.25 (3H, q J 7.2 Hz, OCH₂CH₃), 4.45 (3H, q J 7.2 Hz, OCH₂CH₃), 7.51 (1H, t J 7.8 Hz, H-5), 7.67-7.81 (2H, m, H-4 and H-6), 7.86-7.92 (1H, m, H-2), 8.27 (1H, s, H-C=N). Aqueous ammonia solution (0.5 mL) was added to a solution of crude compound 4 (0.42 g, 1.22 mmol) in methanol (10 mL) and the mixture was stirred for 2h, when the title compound precipitated out as a white yellow solid (overall yield 15%), m.p. 238.1-239.4 °C. λmax (EtOH, ε) 206 (19642), 300 (9974) nm; νmax (Nujol) 2241 (CN), 1715 (C=O), 1580, 1460, 1376, 1366, 1304, 1233, 1157, 1027, 960, 867, 793, 711, 691 cm⁻¹. ¹H (acetone- d₆) δ 7.59 (1H, t J 8.1 Hz, H-5´), 7.76-7.92 (2H, m, H-4´ and H-6´), 8.11 (1H, t J 8.1 Hz, H-2´), 8.26 (1H, s, H-C=N), 11.80 (1H, br s, NH). ¹³C (acetone- d₆) 152.6 (C 7), 147.4 (C 5´), 144.9 (C 3a), 140.6 (C 3´), 133.0, 131.3, 128.8, 124.8, 122.2 (C 1´), 121.7 (C-CN), 112.3 (CN). The signal due to C 7a is not observed. Found: (M⁺ +1) 314.9755. Expected for C₁₂H₆N₅O₇Br: 314.9756.

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