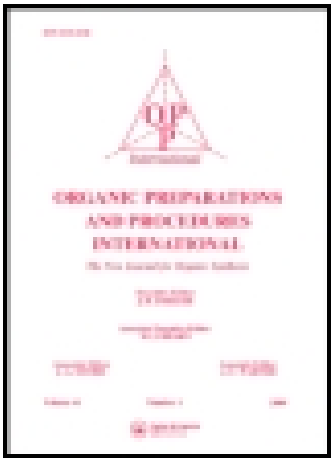

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A FACILE SYNTHESIS OF 3-AMINO-1(2)H-PYRAZOLO[3,4-c]PYRIDINE

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A FACILE SYNTHESIS OF 3-AMINO-1(2)H-PYRAZOLO[3,4-c]PYRIDINE

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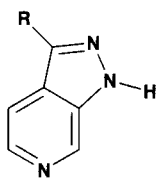
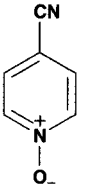
Recently[1] the hydrochloride of 1(2)H-pyrazolo[3,4-c]pyridine **1** (R = H), which may be regarded as a deaza analogue of the base found in the C-nucleoside Formycin A, has been studied by X-ray diffraction.

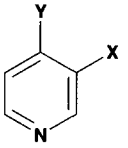
Unfortunately, this ring system is not readily accessible and all current methods of synthesis are rather time consuming.[2-4] Our interest in ring systems fused to pyridines has led us to develop a simple procedure to prepare the 3-amino derivative of this system, *e. g.* **1** (R = NH_2)



1
R = NH_2



2



3) X = Cl, Y = CN
4) X = N_3, Y = CN
5) X = Br, Y = CO_2H
6) X = Br, Y = $CONH_2$
7) X = Br, Y = CN

starting from either commercially available isonicotinonitrile N-oxide **2** or from readily accessible 3-bromoisonicotinic acid **5**.

In the first variation, reaction of **2** with $PCl_5/POCl_3$[5] gave the chloro compound **3**, which was easily converted into the azido derivative **4**,[6] in yields comparable to the literature yields. Suschitzky[7] has reported that reaction of 2-azidobenzonitrile with hydrazines leads to the formation of 3-aminoindazole, and this suggested to us that a similar transformation should be possible starting from **4**. Thus, when **4** was heated with a small excess of hydrazine hydrate in ethanol solution, the title compound **1** (R = NH_2) resulted in 78-82% yield. The same product was also obtained when **4** was treated with methylhydrazine (cf. ref.[7]) under identical conditions, although in this case the reaction appeared to be slower and the yield was only 60-65%. In order to obtain **1** (R = NH_2) is larger quantities, it was found more convenient to proceed from the corresponding bromo derivative **7**, since all attempts to prepare large quantities of **3** by the literature procedure gave a product consistently contaminated with 2-chloronicotinonitrile and purification (by fractional recrystallization) was not easy. The starting point in this approach was the acid **5** (obtained in two steps from 4-picoline),[8] which was converted into **7** by modification of the literature methods. These improved procedures gave consistently good quality products in higher yields. Thus treatment of **5** with ethyl chloroformate followed by treatment with gaseous ammonia afforded the amide **6** in good yield; dehydration of the latter with neat $POCl_3$ gave **7** in nearly quantitative yield. (Alternatively, **7** may be obtained directly from 3-bromo-4-picoline in 41% yield by treatment with potassium amide followed by the addition of *n*-propyl nitrate.)[9] Reaction

of **7** with sodium azide gave **4** and subsequent cyclization with hydrazine hydrate produced **1** (R = NH_2) in 87% yield.

EXPERIMENTAL SECTION

Melting points were taken with an Electrothermal Melting Point Apparatus and are uncorrected. Infrared spectra were recorded as KBr discs using a Perkin Elmer 137 instrument. ^{1}H-NMR spectra were recorded at either 60 or 90 MHz with a Jeol PMX 60SI or a Jeol FX 90Q spectrometer using tetramethylsilane as internal standard. Mass spectra were measured at 70 eV with an AEI MS 920S spectrometer. Compounds **3, 4** (from **3**) and **5** were prepared as described in the literature [5-6,8] and their physical constants were in accord with the published data.

Note: Whilst no problems were encountered in reactions involving sodium azide and 3-azidoisonicotinonitrile, it is recommended that these be carried out behind a safety screen.

3-Bromoisonicotinamide (6).- A mixture of the acid **5** (80g, 0.39 mol), dry THF (1000 mL) and dry triethylamine (60 mL) was stirred at 0° and then treated dropwise over a 2 hour period with ethyl chloroformate (46.6g, 0.43 mol). The mixture was stirred for a further hour and dry ammonia gas passed through the solution at the same temperature for 1.5 h. The solids were removed by filtration, washed twice with hot acetone and discarded. The solvents were evaporated *in vacuo* and residual white solid recrystallized from hot ethanol to afford the pure amide in two crops 29.7g and 26.2g (yield 71%), mp. 166-168°, lit.[8] mp. 165°. ^{1}H NMR (60 MHz, DMSO-d_6): δ 7.31 (d, $J_{5,6}$ = 4.8 Hz, H-5), 7.80 (broad d, exchangeable, NH_2), 8.46 (d, $J_{5,6}$ = 4.8 Hz, H-6), 8.64 (s, H-2). IR: 3315 and 3045 (both NH_2), 1675 (CO) cm^{-1}. MS (m/z, %): 201.9593 (98) and 199.9579 (100).

Anal. Calcd. for $C_6H_5BrN_2O$: C, 35.85; H, 2.51; Br, 39.75; N, 13.93
Found: C, 35.67; H, 2.64; Br, 39,90; N, 13.76

3-Bromonicotinonitrile (7).- The amide **6** (36g, 0.18 mol) was added portionwise to ice cold phosphoryl chloride (150 mL) and the mixture heated under gentle reflux for 2.5 h. The mixture was cooled, poured onto ice (ca 4 kg) with stirring and, when the excess phosphoryl chloride was completely hydrolyzed, cautiously neutralized by the addition of sodium hydroxide solution (40%). The precipitated solids were collected, the filtrates extracted with ether (2 x 250 mL) and the solids dissolved in the combined ethereal extracts. The solution was washed with saturated sodium bicarbonate solution, treated with a little charcoal, filtered, dried and then concentrated under reduced pressure. Recrystallization of the residue from light petroleum gave the nitrile (26.8g) whilst concentration of the recrystallization liquors afforded a further crop (4.8g) to give a total yield of 96%. Both crops had mp. 93-94°, lit.[8] mp. 93°. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.57 (d, $J_{5,6}$ = 4.8 Hz, H-5), 8.71 (d, $J_{5,6}$ = 4.8 Hz, H-6), 8.92 (s, H-2). IR: 2240 (CN) cm^{-1}. MS (m/z, %): 183.9408 (100) and 181.9443 (100).

Anal. Calcd. for $C_6H_3BrN_2$: C, 39.38; H, 1.65; Br, 43.66; N, 15.31
Found: C, 39.45; H, 1.60; Br, 43.45; N, 15.44

3-Azidoisonicotinonitrile (4).- A mixture of the bromo derivative **7** (27.26g, 0.15 mol), sodium azide (12.5g) and dry DMF (200 mL) was heated at 90-100° for 6.5 h. The solvents were removed *in vacuo*, water (140 mL) added and the solids produced were removed and washed with water. The combined

aqueous residues were extracted with dichloromethane (2 X 300 mL) and the combined organic extracts washed once with cold water (100 mL). The solids were added to the extracts, dried and concentrated at reduced pressure. Recrystallization of the residue from cyclohexane gave pure **4** (17.4g, 80%) as colorless crystals which turned green on prolonged exposure to light, mp. 84-85.5°, lit.[6] mp. 82-83°. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.48 (d, $J_{5,6}$ = 4.8 Hz, H-5), 8.52 (d, $J_{5,6}$ = 4.8 Hz, H-6), 8.77 (s, H-2). IR: 2240 (CN), 2120 (N_3) cm^{-1}.

Anal. Calcd. for $C_6H_3N_5$: C, 49.66; H, 2.08; N, 48.26. Found: C, 49.41; H, 2.00; N, 48.44

3-Aminopyrazolo[3,4-c]pyridine (1) (R = NH_2).- A solution of the azido compound **4** (36g, 0.25 mol) in ethanol (400 mL) was treated with hydrazine hydrate (14 mL, 0.29 mol) and the mixture heated under reflux for 4 h. The solvents were reduced to approximately 100 mL at reduced pressure, the resulting solids removed by filtration and recrystallized from ethanol to yield the pure title compound as colorless crystals (27.1g). Further concentration of the mother liquors gave more product (1.75g, total yield 87%). Both crops had mp. 214-215° (with decomp.), lit.[4] mp. 213-214°. ^{1}H NMR (90 MHz, DMSO-d_6): δ 5.61 (broad s, exchangeable, NH_2), 7.68 (dd, $J_{4,5}$ = 5.7 Hz and $J_{4,7}$ = 1.3 Hz, H-6), 8.06 (d, $J_{4,5}$ = 5.7 Hz, H-5), 8.75 (d, $J_{4,7}$ = 1.3 Hz, H-7), 10.82 (broad s, exchangeable H-1(2)). IR: 3405, 3300-2700 (complex) and 1620 (all NH_2) cm^{-1}. MS (m/z, %): 134.0620 (100).

Anal. Calcd. for $C_6H_6N_4$: C, 53.73; H, 4.51; N, 41.77. Found: C, 53.85; H, 4.59; N, 41.64

Both the conversion of **4** (produced from **3**) to **1** (R = NH_2) and reactions using methylhydrazine in place of hydrazine hydrate were carried out as described above.

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