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AN IMPROVED LARGE SCALE SYNTHESIS OF 2-AMINO-4-CHLOROPYRIDINE AND ITS USE FOR THE CONVENIENT PREPARATION OF VARIOUS POLYCHLORINATED 2-AMINOPYRIDINES.

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ABSTRACT: An efficient large scale synthesis of 2-amino-4-chloropyridine (**3**) has been achieved through a modification of existing literature procedures. Compound **3** was used to prepare the previously unreported 2-amino-4,5-dichloropyridine (**4**). The known 2-amino-3,4-dichloropyridine (**5**) and 2-amino-3,4,5-trichloropyridine (**6**) were prepared from **3** by new routes and in higher yields than previously reported.

As part of our studies toward the synthesis of structurally related analogues of the nucleoside 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole,[1] a potent inhibitor of human cytomegalovirus, we required large quantities of the polychlorinated 2-aminopyridines, 2-amino-4,5-dichloropyridine (**4**), 2-amino-3,4-

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dichloropyridine (**5**) and 2-amino-3,4,5-trichloropyridine (**6**). These compounds were crucial intermediates for the preparation of our target heterocycles. A literature search revealed that **4** was unknown, that **5** had been prepared from 2,3,4-trichloropyridine,[2] and that **6** had been prepared from 6-amino-3,4,5-trichloropicolinic acid.[3] Neither 2,3,4-trichloropyridine nor 2-amino-3,4,5-trichloro-6-picolinic acid are commercially available and reported methods for the synthesis of these compounds were low yielding, multistep approaches.

A retrosynthetic analysis revealed that **4**, **5** and **6** could be obtained from a common precursor, 2-amino-4-chloropyridine (**3**).[4] Compound **3**, however, was not commercially available and the reported methods[4-6] for the preparation of **3** from picolinic acid hydrochloride (**1**)[7] gave only low to moderate yields.

Graf[4] reported that chlorination of **1** with thionyl chloride at reflux for several days gave 4-chloropicolinic acid in 50-55 % yield after aqueous workup. In our hands, repeated attempts to chlorinate **1** using the Graf procedure met with limited success. The yield of 4-chloropicolinic acid was less than 20 %. Bubbling SO_2 into the reaction mixture and quenching the reaction with MeOH should give the methyl ester **2**, as described by Mosher and Look.[6] However, these reaction conditions did not significantly improve the isolated yields. An alternative route from 4-nitropyridine N-oxide was reported to give 4-chloropicolinic acid in an overall yield of 55 % in five steps.[8] However this lengthy preparation appeared unsuitable for a large scale preparation.

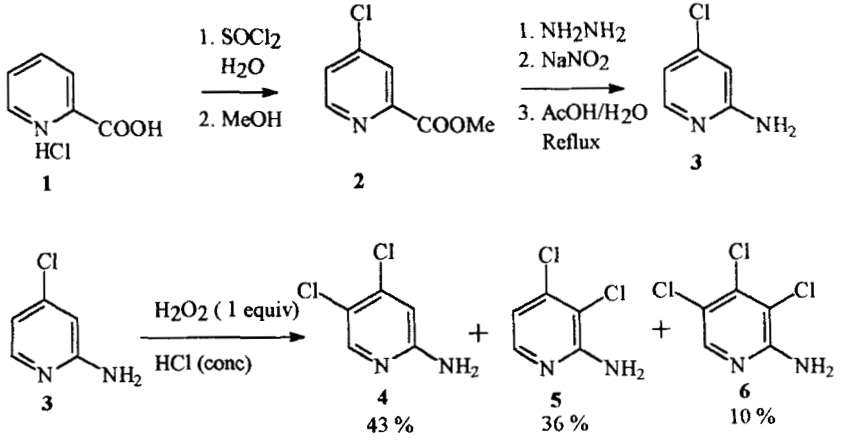
As it was necessary to prepare a considerable quantity of **3**, the one step chlorination reaction was reinvestigated with the intent of developing an improved

and reproducible method for the synthesis of methyl 4-chloropicolinate (**2**). The addition of concentrated aqueous mineral acids such as HCl, H_2SO_4, or H_2SO_3 to the mixture of thionyl chloride and **1** was found to improve the yield significantly. The addition of H_2SO_3 increased the yield of **2** to 70-80 % after workup with MeOH. Since H_2SO_3 contains a considerable amount of H_2O, the addition of H_2O alone to the reaction mixture of **1** in thionyl chloride was also tried. The addition of H_2O (1 equiv) to the reaction mixture was followed by heating the reaction mixture under reflux for 4 days. This was found to give consistently 80-90 % yields of **2** after workup with methanol. This reaction has been accomplished on a 2 mole scale with similar results. The reaction of **2** with hydrazine, followed by reaction with sodium nitrite and a subsequent Curtius rearrangement gave **3** in 60 % yield.

Treatment of **3** with 1 equiv of 32 % aqueous H_2O_2 in concentrated HCl gave a 43:36:10 mixture of 2-amino-4,5-dichloropyridine (**4**), 2-amino-3,4-dichloropyridine (**5**) and 2-amino-3,4,5-trichloropyridine (**6**), respectively. The formation of nitropyridines or pyridine N-oxides was not observed. The yield of **6** was increased to 80 % upon treatment of **3** with 2 equiv of 32 % aqueous H_2O_2 in concentrated HCl. This was a significant improvement in yield over previously reported routes. Although the yield of **5** was only 36 % from **3**, this is the best method to prepare **5**.

To obtain **4** selectively, the amino group was protected as the trimethyl acetamide which simultaneously deactivated and sterically blocked the 3-position toward chlorination. Thus, treatment of **3** with trimethylacetyl chloride gave the

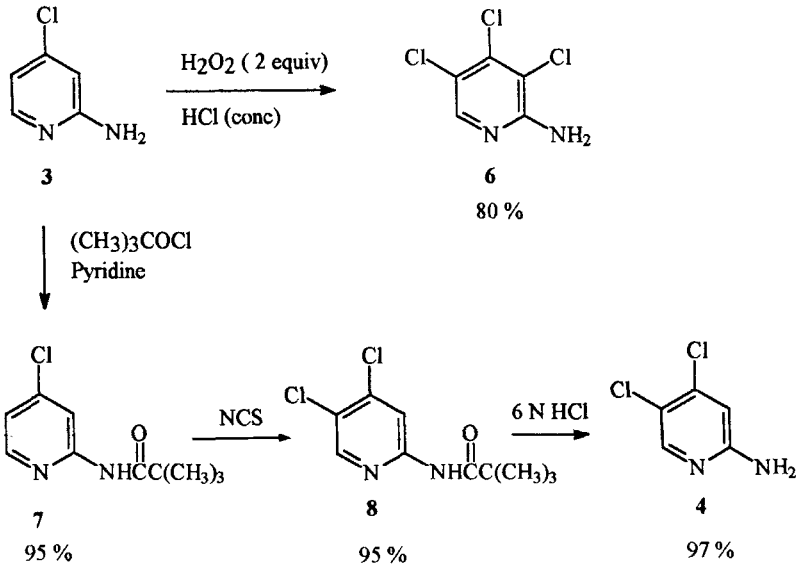
SCHEME I.



amide **7** which was in turn chlorinated using excess NCS in CH_3CN at reflux for 2 hours to give exclusively **8**. Deprotection of **8** with 6N HCl gave **4** in 88 % yield from **3**.

In conclusion, we have found that the yield of **2** by chlorination of **1** with thionyl chloride is improved from 50 % to 90 % by the addition of H_2O (1 equiv) to the reaction mixture. This chlorination is very reproducible and has been accomplished on a 2 mole scale. The reaction of **2** with hydrazine and subsequent treatment of the product with sodium nitrite gave an azide which upon a Curtius rearrangement gave **3**. The reaction of **3** with H_2O_2 (2 equiv) in concentrated HCl gave **6** in high yield. The reaction of **3** with H_2O_2 (1 equiv) in concentrated HCl gave a mixture of **4**, **5** and **6**, from which **5** was obtained in 36 % yield. The conversion of **3** to the trimethylacetylamide 7 followed by the chlorination of 7 with NCS gave **8**. Hydrolysis of **8** gave **4** in excellent overall yield.

SCHEME 2.



Experimental:

General. Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 360 or 300 MHz with a Bruker WP 360 SY or Bruker 300 SY. The chemical shift values are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. Elemental analysis were performed by the Analytical Laboratory of the Chemistry Department, University of Michigan. Flash column chromatography was performed using silica gel 60 230-400 mesh (ICN). Thin layer chromatography (TLC) was performed on prescored Silica gel GHLF plates (Analtech, Newark, DE, USA). Compounds were visualized by illumination under UV light (254 nm). Solutions were concentrated under reduced

pressure (water aspirator) with water bath temperatures below 40 °C unless otherwise specified.

Methyl 4-chloropicolinate hydrochloride (2).

Note: This reaction generates copious amounts of SO_2 and HCl.

H_2O (18 mL) was added dropwise to a stirred suspension of picolinic acid hydrochloride[7] (**1**, 157.9 g, 1.0 mol) in thionyl chloride (400 mL). The resulting mixture was heated at reflux for 4 days giving a clear orange solution. After cooling to ambient temperature, the solution was concentrated to a syrup and the residue coevaporated with toluene (2 x 500 mL). The residue was dissolved in toluene (1 L) and cooled to 0-5 °C. Methanol (44.0 g, 1.3 mol) was then added dropwise to the cold reaction mixture giving a white precipitate. This precipitate was collected by filtration, washed with toluene (3 x 100 mL), and dried at 40 °C for 24 h to give 176.5 g (85 %) of **2** as a white crystalline solid: mp 131-132 °C (dec); ^{1}H-NMR (360 MHz, $CDCl_3$): δ 8.67 (q, 1H), 8.04 (q, 1H), 7.81 (q, 1H), 3.86 (s, 3H). Anal. Calcd for $C_6H_7ClNO_2 \bullet HCl \bullet 1/4\ H_2O$: C, 39.56; H, 3.56; N, 6.59. Found: C, 39.73; H, 3.36; N, 6.54.

2-Amino-4-chloropyridine (3). Compound **2** (100 g, 0.48 mol) in MeOH (0.5 L) was treated with hydrazine hydrate (210 mL) giving a precipitate. The suspension was stirred for 2 hours and the precipitated hydrazide was collected by filtration. The hydrazide was dissolved in 1N HCl (450 mL) and the solution was cooled to 0-5 °C. A solution of sodium nitrite (37.2 g, 0.54 mol) in water (150 mL) was added dropwise giving a precipitate. After stirring for 15 min the precipitate was collected by filtration and washed with water. The moist precipitate was added to

a 1:1 mixture of acetic acid and water (800 mL) and the solution was heated on a steam bath until gas evolution ceased. The reaction mixture was cooled to ambient temperature, the pH was adjusted to 7 and the resulting precipitate collected by filtration. Recrystallization from EtOH gave 37 g (60 %) of **3** as a white crystalline solid: mp 129-131 °C , (Lit[4]: 130-131 °C); ^{1}H-NMR (360 MHz , DMSO-d_6):δ 7.85 (d, 1H, J=5.5 Hz), 6.53 (q, 1H, J=5.5 Hz and J=1.9 Hz), 6.48 (d, 1H, J=1.9 Hz), 6.26 (broad s, 2H, D_2O exchangeable); ^{13}C-NMR (90 MHz, DMSO-d_6): δ 160.86, 149.28, 142.79, 111.69, 106.84.

2-Amino-4,5-dichloropyridine (4), 2-amino-3,4-dichloropyridine (5), 2-amino-3,4,5-trichloropyridine (6). 2-Amino-4-chloropyridine (**3**) (15.0 g, 0.117 mol) was dissolved in conc HCl (60 mL). The solution was cooled to 0^0C in an ice bath and H_2O_2 (0.117 mol, 11.9 mL of 32 % H_2O_2 in water) was then added. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 2 h. The reaction mixture was poured into 200 mL of water, made basic to litmus (pH 8) by the addition of solid Na_2CO_3, then extracted with EtOAc (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to afford a yellow solid, which was shown by TLC to contain three major compounds. These compounds were separated by chromatography (EtOAc/hexane 1:2, 10 cm x 20 cm). The first compound that eluted from the column was **6**. Fractions containing **6** were combined and evaporated to dryness to give after recrystallization from toluene 2.3 g (10 %) of **6:** mp 160-161 °C (Lit[3]: 160-161 °C); R_f 0.48 (EtOAc/hexane 1:2); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.08 (s, 1H), 6.85 (broad s, 2H, D_2O exchangeable). The second compound

eluted from the column was **5**. Fractions containing **5** were combined, concentrated to dryness and crystallized from ethanol to give 6.8 g (38 %) of **5**: mp 99-100 °C (Lit[2]: 99-100 °C); R_f 0.33 (EtOAc/hexane 1:2); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 7.84 (d, 1H, J=5.3 Hz), 6.77 (d, 1H, J=5.3 Hz), 6.65 (broad s, 2H, D_2O exchangeable). Finally, compound **4** was eluted from the column and recrystallized from ethanol to give 8.17 g (43 %) of **4**: mp 140-141 °C; R_f 0.28 (EtOAc/hexane 1:2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.61 (s, 1H), 4.58 (broad s, 2H, D_2O exchangeable); ^{1}H-NMR (360 MHz, DMSO-d_6): δ 8.03 (s, 1H), 6.65 (s, 1H), 6.43 (broad s, 2H, D_2O exchangeable). Anal. Calcd for $C_5H_4Cl_2N_2$: C, 36.83; H, 2.47; N, 17.19. Found: C, 37.20; H, 2.54; N, 17.16.

2-Amino-3,4,5-trichloropyridine (6). 2-Amino-4-chloropyridine (**3**) (5.0 g, 0.04 mol) was dissolved in conc HCl (20 mL) and the solution cooled to 0°C in an ice bath. H_2O_2 (0.08 mol, 8.1 mL of 32 % H_2O_2 in water) was added to the solution and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was then poured into 100 mL of water, made basic to litmus (pH 8) by the addition of solid Na_2CO_3 and then extracted with EtOAc (3 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated to provide a yellow solid which was recrystallized from toluene to give 6.3 g (80 %) of **6**: mp 160-162 °C (^{1}H-NMR and R_f also identical to that of **6** described above).

4-Chloro-2-(trimethylacetamido)pyridine (**7**). Trimethylacetyl chloride (39.2 mL, 0.32 mol) was added dropwise to a solution of **3** (27.3 g, 0.21 mol) in pyridine (100 mL). The resulting mixture was stirred for 12 hours at ambient

temperature. Water (200 mL) was added and the aqueous mixture was extracted with EtOAc (3 x 100 mL). The combined EtOAc extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a solid which was crystallized from EtOH to give 43.2 g (95 %) of 7 as a white solid: mp 86-87 °C; R_f 0.70 (EtOAc/hexane 2:1); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 8.36 (q, 1H), 8.15 (q, 1H), 8.06 (broad s, 1H, D_2O exchangeable), 7.04 (q, 1H), 1.32 (s, 9H). Anal. Calcd for $C_{10}H_{13}ClN_2O \bullet 1/8\ H_2O$: C, 55.88; H, 6.20; N, 13.03. Found: C, 55.88; H, 5.84; N, 13.05.

4,5-Dichloro-2-(trimetylacetamido)pyridine (8). NCS (79.45 g, 0.6 mol) was added to a solution of 7 (25.8 g, 0.12 mol) in dry CH_3CN (300 mL). The resulting suspension was heated at reflux for 2 hours and then cooled to room temperature. After washing with 10 % aqueous NaOH (2 x 150 mL), then water (2 x 200 mL) the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a solid. This solid was recrystallized from EtOH to give 28.7 g (95 %) of **8** as white crystals: mp 105-106 °C; R_f 0.75 (EtOAc/hexane 2:1); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.26 (s, 1H), 8.02 (broad s, 1H, D_2O exchangeable), 1.33 (s, 9H). Anal. Calcd for $C_{10}H_{12}Cl_2N_2O$: C, 48.60; H, 4.89; N, 11.34. Found: C, 48.48; H, 4.72; N, 10.96.

2-Amino-4,5-dichloropyridine (4). Compound **8** (10 g, 0.04 mol) in 6 N HCl (50 mL) was heated at reflux for 10 h. This solution was neutralized with Na_2CO_3 (to pH 7 by litmus) and then extracted with EtOAc (3 x 150 mL). The combined EtOAc extracts were dried ($MgSO_4$) and concentrated to give a solid residue,

which after recrystallization from EtOH gave 6.3 g (97 %) of **4**: mp 140-141 °C; (^{1}H-NMR and R_f also identical to that of **4** described above).

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