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New methods for the preparation of 3,4-diaminopyridine (**5**) and imidazo[4,5-*c*]pyridines **7a,7b** based on direct nitration of 4-acylaminopyridines **3a, 3b** have been explored.

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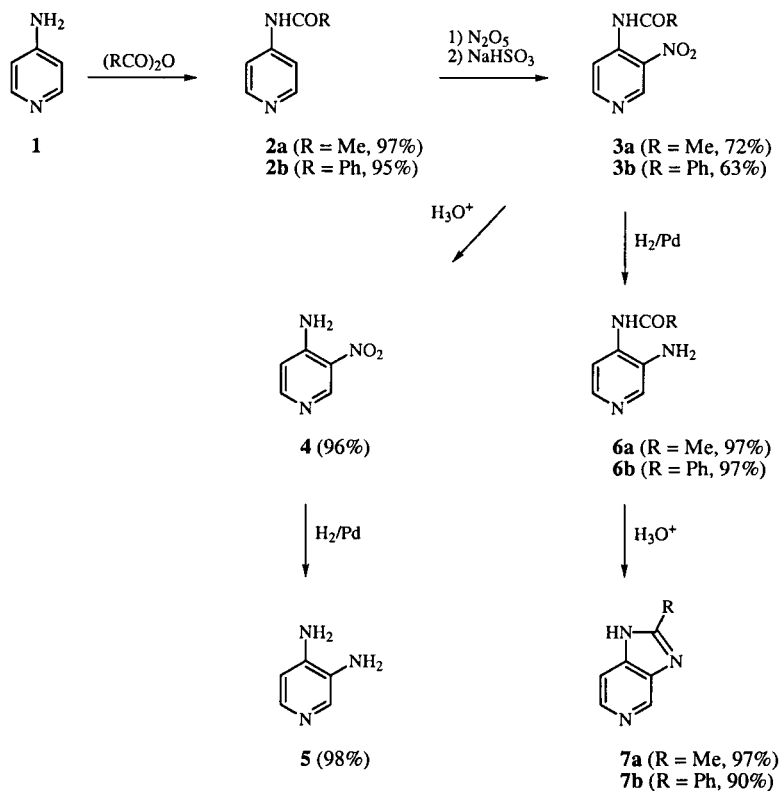
Due to the electron-deficient nature of the pyridine ring, electrophilic aromatic substitution of inactivated pyridines takes place with a great difficulty. Typically, nitration of pyridine at 300° gave a 5% yield of 3-nitropyridine [1]. Even pyridines activated by electron-donating substituents cannot be nitrated by nitric acid/sulfuric acid mixture in all cases due to *e.g.* oxidation of picolines, formation of nitramines from aminopyridines [2] or hydrolysis of acylaminopyridines.

Some time ago we found it was possible to nitrate pyridine compounds in the β -position with dinitrogen pentoxide in liquid sulfur dioxide or aqueous sodium bisulfite. As the conditions and mechanism [3] of this nitration differ considerably from classical electrophilic aromatic substitution, we were able to obtain 3-nitropyridines that

have been difficult to prepare earlier [4]. We now report the direct nitration of 4-acylaminopyridines in the 3-position and further exploitation of the products of the nitration for the synthesis of 3,4-diaminopyridine (**5**) and imidazo[4,5-*c*]pyridines **7a,7b**.

3,4-Diaminopyridine is a drug approved for clinical use in the treatment of Lambert-Eaton myasthenic syndrome [5] and a precursor of many biologically active heterocycles. In spite of the fact that 3,4-diaminopyridine is so widely used, there is still no simple way for its preparation. The previous five-step synthesis [6] gave 3,4-diaminopyridine in the total yield 52% starting from 4-hydroxypyridine. We have developed a new, four-step synthesis for preparing 3,4-diaminopyridine (**5**, Scheme 1) in a total yield of 66%, starting from commercially available

Scheme 1



4-aminopyridine (**1**). This was first converted to 4-acetamidopyridine (**2a**) to prevent formation of 4-nitraminopyridine in the subsequent nitration step. It has been reported [2] that reaction of **1** with nitric acid/sulfuric acid mixture led to 4-nitraminopyridine that gave 4-amino-3-nitropyridine (**4**) in 63% yield on heating, but this method can hardly be used for multigram preparations due to the conditions required. Reaction of **2a** with dinitrogen pentoxide, followed by addition to a buffered sodium bisulfite solution gave a 72% yield of 4-acetamido-3-nitropyridine (**3a**). This was then hydrolyzed under acidic conditions and the resulting 4-amino-3-nitropyridine (**4**) was finally reduced to **5**.

The imidazo[4,5-*c*]pyridine structure is incorporated in a number of biologically active compounds [7,8]. Synthesis of 2-methyl-1*H*-imidazo[4,5-*c*]pyridine (**7a**) was based on reduction of **3a** to 4-acetamido-3-aminopyridine (**6a**) and subsequent cyclization under acidic conditions. The synthesis of 2-phenyl-1*H*-imidazo[4,5-*c*]pyridine (**7b**) was analogous and it is worth mentioning that nitration of **2b** took place in the 3-position of the pyridine ring and not on the phenyl ring. We also attempted to nitrate 4-formamidopyridine by dinitrogen pentoxide/sodium bisulfite without success due to instability of the formyl group towards oxidation and hydrolysis. Previous syntheses of 1*H*-imidazo[4,5-*c*]pyridines were usually based on reaction of 3,4-diaminopyridine (**5**) with an acid or an anhydride [9,10] in some cases only in moderate yields. Our method avoids the use of **5** and utilizes the very smooth cyclization of 3-amino-4-acylaminopyridines **6a** or **6b** to 1*H*-imidazo[4,5-*c*]pyridines **7a**, **7b**.

EXPERIMENTAL

The nmr spectra were recorded on Bruker DPX 300 and 400 MHz spectrometers with tetramethylsilane as the internal standard. Mass spectra were recorded on an AEI MS 902 double-focusing high-resolution instrument. Melting points were determined in a Büchi oil bath apparatus and are uncorrected. Elemental analyses were determined by the Laboratory of Organic Elemental Analysis, Prague Institute of Chemical Technology, Czech Republic. Dinitrogen pentoxide was prepared from dinitrogen tetroxide and ozone [11].

4-Acetamidopyridine (**2a**).

To a solution of 4-aminopyridine (1.88 g, 20 mmoles) and triethylamine (4.04 g, 40 mmoles) in acetonitrile (20 ml) was added acetic anhydride (4.08 g, 40 mmoles) at 0°. The reaction mixture was stirred for 1 hour at room temperature, saturated sodium bicarbonate solution (30 ml) added and the mixture continuously extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated to give light beige 4-acetamidopyridine, yield 2.65 g (97%), mp 150-151°, lit [12] mp 146-148°; ¹H nmr (400 MHz, dimethyl-*d*₆ sulfoxide): δ 2.09 (3H, s, CH₃), 7.54 (2H, dd, *J* = 4.80, 1.66, H-3,5), 8.40 (2H, dd, *J* = 4.77, 1.56, H-2,6), 10.31 (1H, broad s, NH); ms: 136.0 (M⁺).

Anal. Calcd. for C₇H₈N₂O: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.78; H, 5.87; N, 20.54.

4-Benzamidopyridine (**2b**).

To a solution of 4-aminopyridine (4.71 g, 50 mmoles) and triethylamine (7.6 g, 75 mmoles) in acetonitrile (70 ml) was added benzoic anhydride (17.0 g, 75 mmoles) at 0°. The reaction mixture was stirred for 2 hours at room temperature, ethyl acetate (300 ml) was added, the mixture was heated to 50° and saturated sodium carbonate (75 ml) was added. The organic phase was separated, dried over sodium sulfate and evaporated. The product was crystallized from acetone to give colorless 4-benzamidopyridine, yield 9.43 g (95%), mp 212-214°, lit [13] mp 205-206°; ¹H nmr (400 MHz, dimethyl-*d*₆ sulfoxide): δ 7.56 (2H, m, H-3', 5'), 7.63 (1H, tt, *J* = 7.21, 1.33, H-4'), 7.79 (2H, dd, *J* = 4.70, 1.69, H-3,5), 7.97 (2H, m, H-2',6'), 8.48 (2H, dd, *J* = 4.90, 1.54, H-2,6), 10.60 (1H, broad s, NH); ms: 198.0 (M⁺).

Anal. Calcd. for C₁₂H₁₀N₂O: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.62; H, 5.08; N, 14.13.

4-Acetamido-3-nitropyridine (**3a**).

To a solution of dinitrogen pentoxide (2.16 g, 20 mmoles) in nitromethane (20 ml) at 0° was slowly added 4-acetamidopyridine (1.36 g, 10 mmoles) dissolved in hot nitromethane (20 ml). The mixture stirred for 10 minutes under nitrogen. A solution of sodium bisulfite (3.12 g, 30 mmoles) and ammonium dihydrogenphosphate (5.75 g, 50 mmoles) in water (25 ml), acidified to pH 2.9 with concentrated acetic acid was then added to the reaction mixture. The resulting two-phase mixture was stirred for 2 hours at 0° and then overnight (14 hours) at room temperature. Ethyl acetate (30 ml) was added and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic phase was washed with hydrochloric acid solution (pH 1) (10 ml), then neutralized with a sodium hydroxide solution to pH 8.5 and finally washed with saturated sodium chloride solution (20 ml). The organic phase was dried over sodium sulfate and evaporated to give light yellow 4-acetamido-3-nitropyridine, yield 1.30 g (72%), mp 111.5-113°; ¹H nmr (400 MHz, deuteriochloroform): δ 2.34 (3H, s, CH₃), 8.67 (1H, d, *J* = 5.90, H-5), 8.77 (1H, d, *J* = 5.94, H-6), 9.37 (1H, s, H-2), 10.48 (1H, broad s, NH); ms: 181.1 (M⁺).

Anal. Calcd. for C₇H₇N₃O₃: C, 46.40; H, 3.90; N, 23.20. Found: C, 46.29; H, 4.14; N, 22.99.

4-Benzamido-3-nitropyridine (**3b**).

To a suspension of 4-benzamidopyridine (3.97 g, 20 mmoles) in nitromethane (80 ml) at 0° was added dinitrogen pentoxide (4.32 g, 40 mmoles) and the reaction mixture was stirred for 30 minutes under nitrogen. A solution of sodium bisulfite (4.16 g, 40 mmoles) and sodium dihydrogenphosphate dihydrate (15.6 g, 100 mmoles) in water (100 ml), acidified to pH 2.8 with concentrated acetic acid, was added to the reaction mixture and the resulting two-phase mixture stirred for 2 hours at 0° and then overnight (14 hours) at room temperature. Ethyl ether (150 ml) was added and the phases separated. The organic phase was washed with saturated sodium bicarbonate solution (3 x 100 ml) and saturated sodium chloride solution (50 ml), dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel (eluent: acetone/dichloromethane 1:9) to give light yellow 4-benzamido-3-nitropyridine, yield 3.07 g (63%), mp 115-116.5°; tlc (acetone/dichloromethane 1:9), R_f = 0.41; ¹H nmr (400 MHz, dimethyl-*d*₆ sulfoxide): δ 7.61 (2H, m, H-3', 5'), 7.70 (1H, tt, *J* = 7.33, 1.37, H-4'), 7.98 (2H, m, H-2',6'),

8.04 (1H, d, $J = 5.58$, H-5), 8.79 (1H, d, $J = 5.54$, H-6), 9.15 (1H, s, H-2), 11.11 (1H, broad s, NH); ms: 243.0 (M^+).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.17; H, 4.02; N, 17.30.

4-Amino-3-nitropyridine (4).

4-Acetamido-3-nitropyridine (1.81 g, 10 mmoles) was added to 2 *M* hydrochloric acid (7 ml) and stirred for 5 hours at 70°. The mixture was then neutralized with 30% ammonium hydroxide to pH 8, the formed precipitation filtered and washed with cold water on a fritted glass funnel to give yellow 4-amino-3-nitropyridine, yield 1.33 g (96%), mp 202-204°, lit [6] mp 197-201°; 1H nmr (400 MHz, dimethyl- d_6 sulfoxide): δ 6.89 (1H, d, $J = 6.03$, H-5), 7.88 (2H, broad s, NH_2), 8.13 (1H, d, $J = 6.01$, H-6), 8.96 (1H, s, H-2); ms: 139.0 (M^+).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.32; H, 3.83; N, 30.06.

3,4-Diaminopyridine (5).

4-Amino-3-nitropyridine (696 mg, 5 mmoles) was hydrogenated for 20 hours at room temperature in methanol (8 ml) in the presence of 5% Pd/C (120 mg) at a constant hydrogen pressure of 7 bars. The catalyst was removed by filtration and the filtrate evaporated to give white 3,4-diaminopyridine, yield 535 mg (98%), mp 215-217°, lit [6] mp 218-219°; 1H nmr (400 MHz, dimethyl- d_6 sulfoxide): δ 4.46 (2H, broad s, NH_2), 5.29 (2H, broad s, NH_2), 6.38 (1H, d, $J = 5.20$, H-5), 7.46 (1H, d, $J = 5.13$, H-6), 7.62 (1H, s, H-2); ms: 109.0 (M^+).

4-Acetamido-3-aminopyridine (6a).

4-Acetamido-3-nitropyridine (1.81 g, 10 mmoles) was hydrogenated for 23 hours at room temperature in methanol (20 ml) in the presence of 5% Pd/C (300 mg) at a constant hydrogen pressure of 7 bars. The catalyst was removed by filtration and the filtrate evaporated to give white 4-acetamido-3-aminopyridine, yield 1.46 g (97%), mp 187-193° dec, mp 201-204° dec (from ethanol/petroleum ether); 1H nmr (300 MHz, dimethyl- d_6 sulfoxide): δ 2.09 (3H, s, CH_3), 5.11 (2H, broad s, NH_2), 7.52 (1H, d, $J = 5.23$, H-5), 7.71 (1H, d, $J = 5.26$, H-6), 8.00 (1H, s, H-2), 9.25 (1H, broad s, $NHCO$); ms: 151.0 (M^+).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.60; H, 6.00; N, 27.81. Found: C, 55.66; H, 6.10; N, 27.73.

3-Amino-4-benzamidopyridine (6b).

4-Benzamido-3-nitropyridine (730 mg, 3 mmoles) was hydrogenated for 21 hours at room temperature in methanol/dichloromethane 1:1 (15 ml) in the presence of 5% Pd/C (150 mg) at a constant hydrogen pressure of 7 bars. Methanol/dichloromethane 1:1 (100 ml) was then added and the mixture was refluxed for 30 minutes. The catalyst was removed by filtration and the filtrate evaporated to give light yellow 3-amino-4-benzamidopyridine, yield 620 mg (97%), mp 183-186° dec, mp 206-209° dec (from methanol); 1H nmr (400 MHz, dimethyl- d_6 sulfoxide): δ 5.20 (2H, broad s, NH_2), 7.43 (1H, d, $J = 5.22$, H-5), 7.54 (2H, m, H-3',5'), 7.62 (1H, tt, $J = 7.21$, 1.32, H-4'), 7.81 (1H, d, $J = 5.15$, H-6), 7.97 (2H, m, H-2',6'), 8.11 (1H, s, H-2), 9.77 (1H, broad s, $NHCO$); ms: 213.1 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.55; H, 5.44; N, 19.83.

2-Methyl-1*H*-imidazo[4,5-*c*]pyridine (7a).

A solution of 4-acetamido-3-aminopyridine (302 mg, 2 mmoles) in acetic acid (5 ml) was refluxed for 90 minutes, then

cooled and evaporated. The residue was neutralized with saturated sodium bicarbonate solution to pH 9, the salts removed by flash chromatography on short column of silica gel (eluent: methanol/dichloromethane 3:7) to give white 2-methyl-1*H*-imidazo[4,5-*c*]pyridine, yield 260 mg (97%), mp 178-179°, lit [10] mp 164-166°; 1H nmr (400 MHz, dimethyl- d_6 sulfoxide): δ 2.53 (3H, s, CH_3), 7.45 (1H, d, $J = 5.13$, H-7), 8.22 (1H, d, $J = 5.48$, H-6), 8.77 (1H, s, H-4), 12.62 (1H, broad s, H-1); ms: 133.0 (M^+).

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 62.70; H, 5.40; N, 31.25.

2-Phenyl-1*H*-imidazo[4,5-*c*]pyridine (7b).

A solution of 3-amino-4-benzamidopyridine (1.07 g, 5 mmoles) and 37% hydrochloric acid (2 ml) in 1-butanol (30 ml) was refluxed for 60 minutes, then cooled. Saturated sodium bicarbonate solution (35 ml) was added and the product extracted with ethyl acetate (50 ml). The organic phase was separated, washed with saturated sodium chloride solution (30 ml), dried over sodium sulfate and evaporated. The residue was crystallized from water/ethanol to give white 2-phenyl-1*H*-imidazo[4,5-*c*]pyridine, yield 0.88 g (90%), mp 229-230°, lit [9] 230-231°; 1H nmr (400 MHz, dimethyl- d_6 sulfoxide): δ 7.55-7.61 (4H, m, H-3',4',5',7'), 8.22 (2H, m, H-2',6'), 8.31 (1H, d, $J = 5.51$, H-6), 8.94 (1H, s, H-4), 13.34 (1H, broad s, H-1); ms: 195.0 (M^+).

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