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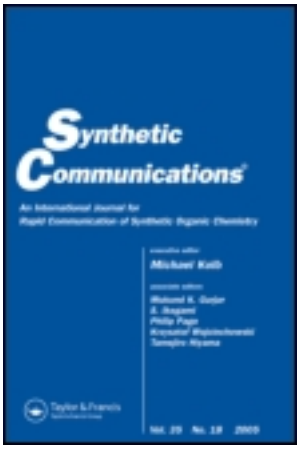

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Improved Synthesis of 2-Chlorinated Imidazo[1,2-α]-pyridines and the Application of this Procedure for the Synthesis of Several New Polychlorinated Imidazo[1,2-α]Pyridnes.

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Published online: 22 Aug 2006.

To cite this article: Kristjan S. Gudmundsson , John C. Drach & Leroy B. Townsend (1997): An Improved Synthesis of 2-Chlorinated Imidazo[1,2-α]-pyridines and the Application of this Procedure for the Synthesis of Several New Polychlorinated Imidazo[1,2-α]Pyridnes., Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:10, 1763-1775

To link to this article: http://dx.doi.org/10.1080/00397919708004089

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SYNTHETIC COMMUNICATIONS, 27(10), 1763-1775 (1997)

AN IMPROVED SYNTHESIS OF 2-CHLORINATED IMIDAZO[1,2-*a*]-PYRIDINES AND THE APPLICATION OF THIS PROCEDURE FOR THE SYNTHESIS OF SEVERAL NEW POLYCHLORINATED IMIDAZO[1,2-*a*]PYRIDINES.

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ABSTRACT: Polychlorinated imidazo[1,2-*a*]pyridines were synthesized as analogs of certain chlorinated benzimidazoles. The imidazo[1,2-*a*]pyridines were obtained by a condensation of ethyl bromoacetate and chlorinated 2-aminopyridines. These condensation products were treated with an ion exchange resin to effect an exchange of hydrobromide salts with hydrochloride salts. These compounds were subsequently treated with $POCl_3$ to convert the imidazo[1,2-*a*]pyridin-2-ones into 2-chloroimidazo[1,2-*a*]pyridines.

Diazaindanes, such as imidazo[1,2-*a*]pyridines,[1] have long been of interest to both the organic chemist and biochemist because of their structural relationship

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to purines. The imidazo[1,2-*a*]pyridine heterocycle was first synthesized in 1925 by a condensation of 2-aminopyridine with bromoacetaldehyde. While several alternative methods for the synthesis of imidazo[1,2-*a*]pyridines have been developed, the condensation of 2-aminopyridines with halocarbonyl derivatives is still the most frequently used approach for their synthesis.[2] We became interested in the synthesis of chlorinated imidazo[1,2-*a*]pyridines as analogs of chlorinated benzimidazoles, such as 2,5,6-trichlorobenzimidazole, which have shown antiviral activity.[3]

Synthesis of 2,7-dichloro-, 2,7,8-trichloro and 2,6,7,8-tetrachloroimidazo[1,2-*a*]pyridines has not been reported while low yielding preparations of the 2,6-dichloro- and 2,6,7-trichloroimidazo[1,2-*a*]pyridines were reported in two patents.[4] We now want to report an improved method for the synthesis of the 2,6-dichloro- and the 2,6,7-trichloroimidazo[1,2-*a*]pyridines and the synthesis of the previously unknown 2,7-dichloro-, 2,7,8-trichloro and 2,6,7,8-tetrachloroimidazo[1,2-*a*]pyridines.

Results and Discussion. We decided initially to investigate the synthesis of 2,6-dichloroimidazo[1,2-*a*]pyridine (**4**) from the commercially available 2-amino-5-chloropyridine (**1**). Attempts to condense chloroacetic acid with **1** in CH_3CN in the presence of Et_3N, as described in the literature,[4] gave only a 10-15 % yield of the hydrochloride salt of 6-chloroimidazo[1,2-*a*]pyridin-2-one (**2**). The condensation of **1** with chloroacetic acid in basic aqueous solution as well as attempts to condense **1** with ethyl chloroacetate at reflux in ethanol gave low

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yields (10 - 20 %) of **2**. These approaches had been used previously, by Reindel[5] and Tschitschibabin,[1e] respectively, to synthesize imidazo[1,2-*a*]pyridin-2-one from 2-aminopyridine in high yields. The initial step in a condensation of the aminopyridine with the chlorocarbonyl derivatives is a displacement of the α-chlorine by the pyridine nitrogen. We postulated that the low yield might be the result of reduced nucleophilicity of the pyridine nitrogen caused by the electron withdrawing effect of the chloro substituent.

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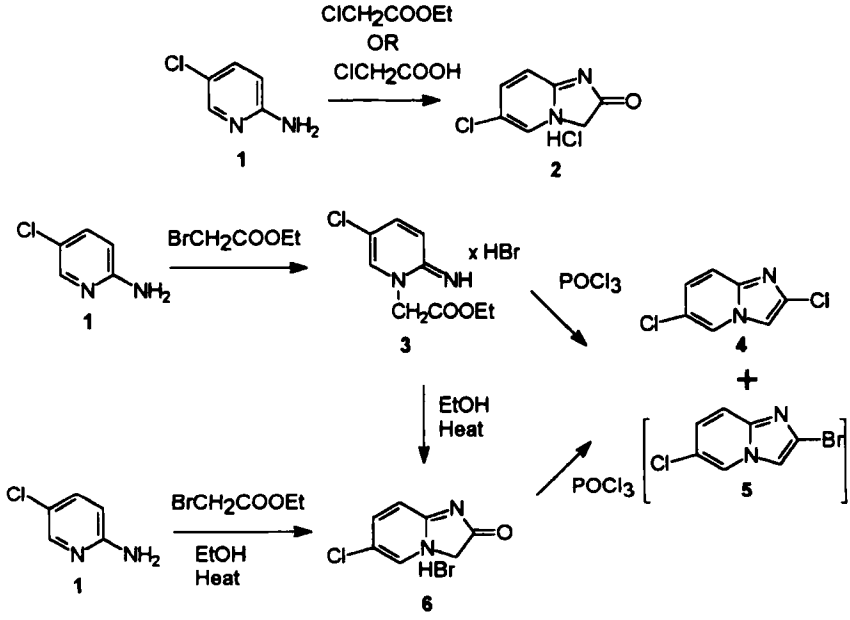
SCHEME 1



Attempts to facilitate the alkylation by adding a catalytic amount of sodium iodide, stochiometric amounts of trimethylamine, or the use of other solvents, such

as DMF and CH_3CN, failed to improve the yields. We then used the more reactive ethyl bromoacetate as a replacement for the α-chloro carbonyl compounds.

The coupling of ethyl bromoacetate with **1** in ethanol at reflux gave a 50 % yield of the hydrobromide salt of 6-chloroimidazo[1,2-*a*]pyridin-2-one (**6**). By treating **1** at room temperature with ethyl bromoacetate (neat), the iminium derivative **3** was obtained in a 95 % yield. This iminium intermediate **3** was recrystallized and purified to homogeneity. 6-Chloroimidazo[1,2-*a*]pyridin-2-one (**6**) was obtained (85 % yield, 80 % overall yield from **1**) as a hydrobromide salt by heating a solution of **3** in ethanol at reflux for 2 hours. Treatment of the hydrobromide salts of either **3** or **6** with $POCl_3$ at reflux gave a 50 % yield of 2,6-dichloroimidazo[1,2-*a*]pyridine (**4**), contaminated with 5 % of a byproduct. This byproduct was shown to be 2-bromo-6-chloroimidazo[1,2-*a*]pyridine (**5**) by ^{13}C-NMR and mass spectral data. Compounds **4** and **5** could not be easily separated by chromatographic methods (flash chromatography and HPLC) or by recrystallization. Therefore, the hydrobromide salts of **3** or **6** could not be used directly without obtaining a mixture of products. This prompted us to use the ion exchange resin Amberlyst IRA-47 (Cl^--form) to exchange the hydrobromide salts of **3** and **6** for the corresponding hydrochloride salts. These hydrochloride salts of **3** or **6** gave **4** upon treatment with $POCl_3$ in a 50 - 60 % yield, while no **5** was detected.

2-Amino-4-chloropyridine (**7**), 2-amino-4,5-dichloropyridine (**8**), 2-amino-3,4-dichloropyridine (**9**) and 2-amino-3,4,5-trichloropyridine (**10**)[6] were

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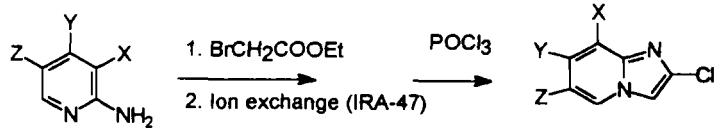
SCHEME 2



1 X=H; Y=H; Z=Cl
7 X=H; Y=Cl; Z=H
8 X=H; Y=Cl; Z=Cl
9 X=Cl; Y=Cl; Z=H
10 X=Cl; Y=Cl; Z=Cl

4 X=H; Y=H; Z=Cl
11 X=H; Y=Cl; Z=H
12 X=H; Y=Cl; Z=Cl
13 X=Cl; Y=Cl; Z=H
14 X=Cl; Y=Cl; Z=C

subsequently treated with ethyl bromoacetate, ion exchange resin and chlorinated to give the corresponding imidazo[1,2-*a*]pyridines **11** - **14**. Yields decreased with increased chlorination of the aminopyridines, presumably due to decreased nucleophilicity of the pyridine nitrogen.

In conclusion, we have developed an improved method for the synthesis of 2-chlorinated imidazo[1,2-*a*]pyridines which give compounds such as **4** in five fold higher yield than the previously reported synthesis. This method has been applied for the synthesis of several new polychlorinated imidazo[1,2-*a*]pyridines and would appear to be a general route for the synthesis of various polysubstituted imidazo[1,2-*a*]pyridines.

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

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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.

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Ethyl 2-imino-5-chloro-1,2-dihydropyridin-1-yl-acetate hydrobromide (3). To 2-amino-5-chloropyridine (**1**, 10 g, 0.078 mol) was added ethyl bromoacetate (30 mL, 0.269 mol) and the reaction mixture stirred at room temperature for 8 hours. The heavy white precipitate was removed by filtration and recrystallized from EtOH to yield 21.9 g (95 %) yield of **3** as white crystals: mp > 300 °C (decomposes); R_f 0.23 (EtOAc/EtOH/Acetone/H_2O 20:2:2:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 9.0 (s, 2H, D_2O exchangeable), 8.44 (d, 1H, J = 2.2 Hz), 8.04 (dd, 1H, J = 2.2 Hz, J= 9.6 Hz), 7.25 (d, 1H, J = 9.6 Hz), 5.17 (s, 2H), 4.19 (q, 2H), 1.24 (t, 3H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 165.54, 153.76, 143.00, 138.00, 117.67, 116.45, 62.11, 53.96, 13.96. Anal. Calcd. for $C_9H_{12}BrClN_2O_2$: C, 36.57; H, 4.08; N, 9.48. Found: C, 36.49; H, 4.05; N, 9.36.

2,6-Dichloroimidazo[1,2-*a*]pyridine (4). The imino derivative **3** (10 g, 0.03 mol) was dissolved in water (100 mL) and treated with IRA-47 (Cl^--form) ion exchange resin (60 g) with stirring at room temperature for 30 min. The resin was

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removed by filtration and the filtrate treated again with resin (60 g) for 30 min, resin removed by filtration and the aqueous filtrate evaporated to dryness. The resulting solid was dissolved in ethanol (100 mL) and evaporated to dryness to give the HCl salt as a reddish brown foam. The HCl salt was treated with $POCl_3$ (30 mL) and the mixture heated at reflux, under a $CaSO_4$ drying tube, for 2 h. The reaction mixture was cooled to room temperature and excess $POCl_3$ removed under reduced pressure to give a dark syrup. Ice water was added to this syrup and NH_4OH was added to the resulting solution until it remained basic to litmus (pH 8). The solution was extracted with $CHCl_3$ (80 mL x 3), the organic phase dried over magnesium sulfate, filtered and the filtrate evaporated to dryness to give a solid. This solid was purified by flash chromatography (EtOAc/hexane 1:2, 15 cm x 5 cm), the fractions containing product were pooled, solvent removed under reduced pressure and the resulting white solid was crystallized from MeOH to give 3.4 g (60 %) of **4**: mp 155-156 °C (Ref.[4] 155-156 °C); R_f 0.45 (EtOAc/hexane); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.19 (d, 2H), 7.48 (d, 1H), 7.50 (d, 1H); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.78 (d, 1H, J = 2.0 Hz), 8.00 (s, 1H), 7.57 (d, 1H, J = 9.6 Hz), 7.37 (dd, 1H, J = 9.6 Hz, J = 2.0 Hz); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 141.47 (C8a), 134.54 (C2), 126.53 (C7), 124.60 (C5), 119.78 (C6), 116.87 (C8), 109.77 (C3)[1]; UV λ_{max} (EtOH) 288 (4351), 230 (7965);

[1] The assignment of the ^{13}C-NMR signals for **4** and **12** were made on the basis of fully coupled and partially decoupled spectral data, as well as on chemical shift trends. Assignments of ^{13}C-NMR signals for **11**, **13** and **14** were made by analogy with the assignments for **4** and **12**.

(pH11) 275 (14016), 230 (33863); (pH 1) 281 (9265), 221 (26718).

2,7-Dichloroimidazo[1,2-*a*]pyridine (11). 2-Amino-4-chloropyridine (7, 3.9 g, 0.03 mol) was added to ethyl bromoacetate (20 mL, 0.18 mol) and the solution was stirred at room temperature for 8 hours. The resulting precipitate was removed from the reaction mixture by filtration and dissolved in water (80 mL). The solution was treated with IRA-47 (Cl^--form) ion exchange resin (40 g) with stirring at room temperature for 30 min. The resin was removed by filtration and the filtrate treated again with resin (40 g) for 30 min, resin removed by filtration and the aqueous filtrate evaporated to dryness. The resulting solid was dissolved in ethanol (50 mL) and evaporated to dryness to give the HCl salt as a reddish brown foam. The HCl salt was treated with $POCl_3$ (30 mL) and the resulting mixture heated at reflux, under a $CaSO_4$ drying tube, for 2 h. The reaction mixture was cooled to room temperature and the excess $POCl_3$ removed under reduced pressure to give a dark syrup. This syrup was treated with ice water and NH_4OH was added until the solution remained basic to litmus (pH 8). The solution was extracted with $CHCl_3$ (80 mL x 3), the organic phase dried over magnesium sulfate, filtered and the filtrate evaporated to dryness to give a white solid. This solid was purified by flash chromatography (EtOAc/hexane 1:2, 15 cm x 5 cm). The fractions containing product were pooled, the solvent was removed under reduced pressure and the obtained solid was crystallized from MeOH to give 2.8 g (50 %) of **11**: mp 153-154 °C; R_f 0.45 (EtOAc/hexane); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 0.8 Hz, J = 7.2 Hz), 7.52 (dd, 1H, J = 0.8 Hz, J = 2.1

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Hz), 7.49 (s, 1H), 6.83 (dd, 1H, J= 7.2 Hz, J = 2.1 Hz); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.781 (C8a), 134.54 (C2), 130.84 (C7), 127.65 (C5), 114.89 and 114.08 (C8 and C6), 109.58 (C3); UV λ_{max} (EtOH) 306 (4421), 284 (5080), 231 (13182); (pH 11) 283 (5702), 229 (22170); (pH 1) 281 (10914) 221 (22532). Anal. Calcd. for $C_7H_4Cl_2N_2$: C, 44.95; H, 2.16; N, 14.98. Found: C, 44.74; H, 2.36; N, 14.95.

2,6,7-Trichloroimidazo[1,2-*a*]pyridine (12). 2-Amino-4,5-dichloropyridine (**8**, 3.3 g, 0.02 mol) was treated with neat ethyl bromoacetate (20 mL, 0.18 mol) at 60 °C for 24 hours. The precipitate that formed was isolated by filtration, dissolved in water (100 mL) and treated with IRA-47 (Cl^--form) ion exchange resin (2 x 100 g). After the resin had been removed by filtration, the aqueous filtrate was evaporated to dryness to give a HCl salt as a reddish foam. The HCl salt was treated with $POCl_3$ (30 mL) as described above to give after flash chromatography (EtOAc/hexane 1:2, 15 cm x 5 cm) and recrystallization from EtOH 1.8 g (40 %) of **12** as white crystals: mp 180-181 °C; R_f 0.47 (EtOAc/hexane 1:2); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.68 (s, 1H), 7.49 (s, 1H); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.02 (s, 1H), 8.00 (s, 1H) ;^{13}C-NMR (90 MHz, $CDCl_3$) δ 142.51 (C8a), 137.72 (C2), 131.22 (C7), 124.03 (C5), 121.07 (C6), 117.08 (C8), 108.75 (C3); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 141.60 (C8a), 135.27 (C2), 129.33 (C7), 126.13 (C5), 118.52 (C6), 116.14 (C8), 109.86 (C3) ; UV λ_{max} (EtOH) 315 (4237), 294 (4118), 234 (13496); (pH11) 292 (4542), 233 (23989); (pH 1) 293 (7576), 226 (24237); HRMS m/z

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calcd for $C_7H_3Cl_3N_2$ 219.9362, found 219.9360. Anal. Calcd for $C_7H_3Cl_3N_2$: C, 37.96; H, 1.37; N, 12.65. Found: C, 37.81; H, 1.39; N, 12.55.

2,7,8-Trichloroimidazo[1,2-*a*]pyridine (13). 2-Amino-3,4-dichloropyridine (**9**, 1.0 g, 6.1 mmol) was treated with ethyl bromoacetate (5.0 mL, 45.0 mmol) at 60 °C for 24 hours to give a white solid. This solid was removed by filtration, dissolved in water, treated with ion exchange resin and chlorinated with $POCl_3$ as described above to give after purification by flash chromatography (EtOAc/hexane 1:2, 15 cm x 4 cm) and recrystallization from MeOH, 700 mg (52 %) of **13** as white crystals: mp 220-221 °C; R_f 0.29 (EtOAc/hexane 1:2); ^{1}H-NMR (360 MHz, $CDCl_3$) δ 7.93 (d, 1H, J=7.15 Hz), 7.56 (s, 1H), 6.94 (d, 1H, J=7.15 Hz); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 141.77 (C8a), 137.20 (C2), 129.87 (C7), 123.52 (C5), 121.30 (C8), 115.08 (C6), 110.39 (C3); UV λ_{max} (EtOH) 304 (5250), 288 (5825), 233 (10434); (pH 11) 287 (6566), 232 (24612); (pH 1) 287 (8865), 231 (26610); HRMS m/z calcd for $C_7H_3Cl_3N_2$ 219.9362, found 219.9355. Anal. Calcd for $C_7H_3Cl_3N_2 \bullet 1/4\ H_2O$: C, 37.21; H, 1.56; N, 12.40. Found: C, 37.40; H, 1.46; N, 12.22.

2,6,7,8-Tetrachloroimidazo[1,2-*a*]pyridine (14). 2-Amino-3,4,5-trichloropyridine (**10**, 1.0 g, 5.1 mmol) was treated with neat ethyl bromoacetate (5.0 mL, 45.0 mmol) at 80 °C for 24 hours. The resulting black solution was applied to a silica gel pad (50 g) and washed with EtOAc/hexane 1:2 (500 mL) to remove the excess ethyl bromoacetate. Subsequent washing of the silica gel with MeOH (200 mL) eluted a highly fluorescent compound. Removal of the MeOH

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under reduced pressure gave a black tarry residue, which was dissolved in water and treated with IRA-47 (Cl^--form) ion exchange resin (40 g) with stirring at room temperature for 30 min. The resin was removed by filtration and the filtrate treated again with resin (40 g) for 30 min, resin removed and the aqueous filtrate evaporated to dryness. The resulting solid was dissolved in ethanol (100 mL) and evaporated to dryness to give the HCl salt as a black residue. This residue was treated with $POCl_3$ (20 mL) and the resulting mixture heated at reflux, under a $CaSO_4$ drying tube, for 2 h. The reaction mixture was cooled to room temperature and the excess $POCl_3$ removed under reduced pressure to give a dark syrup. This syrup was treated with ice water and NH_4OH was added until the solution remained basic to litmus (pH 8). The solution was extracted with $CHCl_3$ (50 mL x 3), the organic phase dried over magnesium sulfate, filtered and the filtrate evaporated to dryness to give a dark solid. This solid was purified by flash chromatography (EtOAc/hexane 1:2, 15 cm x 2 cm), the fractions containing product were pooled, solvent removed under reduced pressure and the solid was crystallized successively from EtOH and MeOH to give 200 mg (16 %) of **14** as a white solid: mp 232-233 °C; R_f 0.58 (EtOAc/hexane 1:2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.55 (s, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 139.45 (C8a), 135.32 (C2), 127.97 (C7), 124.85 (C5), 124.34 (C8), 118.46 (C6), 111.74 (C3); UV λ_{max} (EtOH) 298 (5592), 235 (15388); (pH11) 297 (6100), 232 (27300); (pH 1) 296 (6560), 228 (29120); HRMS m/z calcd for $C_7H_2Cl_4N_2$ 253.8972, found 253.8967. Anal. Calcd for $C_7H_2Cl_4N_2$ •3/4 H_2O: C, 31.2; H, 1.20; N,10.40. Found: C, 31.0; H, 0.89; N, 10.0.

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Acknowledgment. These studies were supported by research grant U19-AI31718 from the National Institute of Allergy and Infectious Diseases of the National Institute of Health.

References:

1. For reviews: (a) Blewitt, H. L. In Special Topics in Heterocyclic Chemistry, Vol. 30; Weissberger, A.; Taylor, E. C., Eds.; John Wiley: New York, **1979**; pp 117-170. (b) Montgomery, J. A.; Secrist III, J. A. In: Comprehensive Heterocyclic Chemistry, Vol. 5; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, **1984**; pp 608-635.

2. (a) Mosby, W. L. In: Heterocyclic Systems with Bridgehead Nitrogen Atoms; Weisberg, A., Eds.; Interscience Publishers Inc.: New York, **1961**; pp 460-505. (b) Katsura, Y.; Nishino, S.; Takasugi, H. *Chem. Pharm. Bull.* **1991**, *39*, 2937-2943. (c) Almirante, L.; Mugnaini, A.; Toma, N.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1970**, *13*, 1048-1051. (d) Lombardino, J. G. *J. Chem. Soc.* **1965**, *30*, 2403-2407. (e) Tschitschibabin, A. E. *Ber.* **1924**, *57*, 2092-2101.

3. Townsend, L. B.; Devivar, R. V.; Turk, S. R.; Nassiri, R. M.; Drach, J. C. *J. Med. Chem.* **1995**, *38*, 4098-4106.

4. (a) Ishida, Y.; Ohta, K.; Nakahama, T.; Yoshikawa, H. European Patent no 0 238 070 A2, **1987**. (b) Kazunari, O.; Ishida, Y.; Hurutoshi, Y. European Patent no 0 383 319 A2, **1990**.

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5. Reindel, F. *Ber.* **1924**, *57*, 1381-1386.

6. For the preparation of aminopyridines: (a) Gudmundsson, K. S.; Hinkley, J. M.; Brieger, M. S.; Drach, J. C.; Townsend, L. B. *Syn. Comm.* in press. (b) Graf, R. *Ber.* **1931**, *64*, 21-26. (c) Den Hertog, H. J.; Schogt, J. C. M.; De Bruyn, J.; De Klerk, A. *Rec. Trav. Chim.* **1950**, *69*, 673-699. (d) Giacobbe, T. J.; McGregor, S. D.; Beman, F. L. *J. Heterocycl. Chem.* **1974**, *11*, 889-897.

(Received in the USA 03 December 1996)

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