

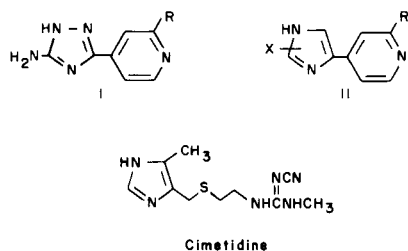
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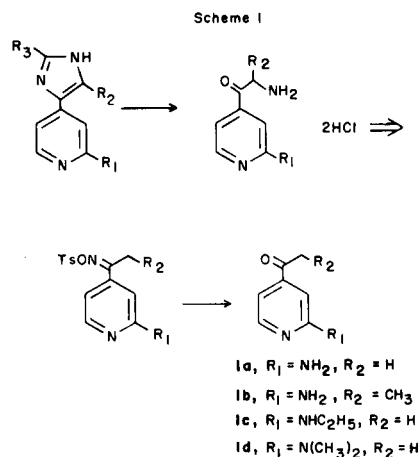
A general synthetic scheme for the preparation of 2-amino-4-(4-imidazolyl)pyridines, potential histamine H_2 antagonists, is described. The synthesis is based on the Neber rearrangement of 1-(4-pyridyl)-1-alkanone oxime *O*-tosylates to the appropriate α -aminoketones or α -aminoketals, which are then converted to the corresponding imidazoles. The reaction of Grignard reagents with 2-chloroisonicotinonitrile, as well as nucleophilic displacement of chloride by amines on 2-chloroisonicotinonitrile and derivatives, are discussed in relation to the preparation of the ketone intermediates.

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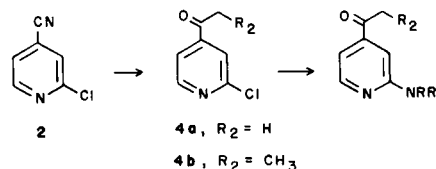
Recent work from these laboratories has led to a series of novel histamine H_2 receptor antagonists, compounds of interest in the treatment of gastrointestinal disorders (1). These compounds, represented by structure I, differ from current commercially available histamine H_2 antagonists, such as cimetidine, in that they contain two heterocyclic rings linked directly to each other. The activity of these 5-aminotriazoles prompted interest in derivatives in which the triazole was replaced by a variety of 4-imidazoles such as II. The rationale for such a modification was three-fold: first histamine is itself a substituted imidazole; second, cimetidine is also an imidazole derivative; third, imidazoles are generally well-tolerated physiologically. This paper describes the synthesis of a variety of 2-amino-4-(4-imidazolyl)pyridines which involved a number of reactions in the chemistry of pyridines which were not straightforward despite expectations to the contrary. Specifically, the reaction of Grignard reagents with 2-chloroisonicotinonitrile, the reaction of amines with 2-chloro-4-substituted-pyridines, and the use of α -aminoacetals for the synthesis of imidazoles are highlighted in this paper.



Analysis of the target structures suggested that the most direct general synthesis would involve building the imidazole onto a preformed pyridine (Scheme I). Of the varied methods of preparing imidazoles, that involving α -aminoketones seemed most appealing in that such an approach allowed for flexibility in the choice of imidazole substituents. A simple entry into α -aminoketones containing electron-deficient aromatic rings is the Neber rearrangement of ketooxime tosylates (2). Thus, the key synthetic intermediates necessary for the preparation of the target molecules can be reduced to ketones **1a-d**.



2-Chloroisonicotinonitrile, **2**, was selected as our primary starting material for this series of reactions, since the formation of 4-pyridyl ketones *via* the reaction of ethyl magnesium bromide with isonicotinonitrile has been reported (3). Furthermore, it was believed that subsequent displacement of the halide with amines would afford the necessary ketones. However, despite literature precedent, reaction of **2** with Grignard reagents did not prove to be straightforward. Our results are summarized in Table I.



Reaction of isonicotinonitrile with a slight excess of ethyl magnesium bromide affords, after an aqueous work-up, 73% of the expected 1-(4-pyridyl)-1-propanone, **3**, after four hours. However, when this same reagent is reacted with **2**, only 12% of ketone **4b** is obtained after the same amount of time. In this case it was found that a longer reaction time is necessary, and moderate yields can be obtained after 20 hours. Neither longer reaction times (60 hours), nor another equivalent of reagent significantly alters the yield of **4b**. This is *not* true in the reaction of **2**

Table 1

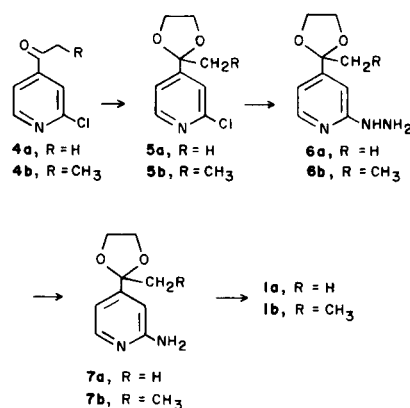
Grignard Reactions of Isonicotinonitriles

Substrate	Reagent (Equivalents)	Reaction Time	Products (Yield)
Isonicotinonitrile	C ₂ H ₅ MgBr (1.1)	4 hours	3 (73%)
2-Chloroisonicotinonitrile (2)	C ₂ H ₅ MgBr (1.0)	4 hours	4b (12%)
(2)	C ₂ H ₅ MgBr (1.0)	20 hours	4b (48%)
(2)	C ₂ H ₅ MgBr (1.0)	60 hours	4b (52%)
(2)	C ₂ H ₅ MgBr (2.0)	60 hours	4b (45%)
(2)	CH ₃ MgBr (1.0)	20 hours	4b (8%)
(2)	CH ₃ MgBr (2.0)	20 hours	4a (55%)

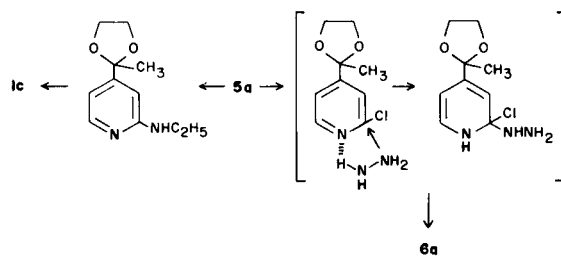
with methyl magnesium bromide, in which two equivalents of this reagent are necessary for obtaining reasonable yields of **4a**. Thus, the addition of a halogen at the 2-position of isonicotinonitrile changes both the stoichiometry and the time course for the Grignard reaction. Yet, the reaction *does* remain chemoselective since no other products, which may be envisioned to arise by either exchange or coupling, are isolated. The exact reason for the difference between the reactivity of **2** and isonicotinonitrile is not certain. It may, however, be simply due to complexation between the reagent and the pyridine nitrogen. In the reaction of ethyl magnesium bromide with isonicotinonitrile, this complex may readily dissociate, thus allowing reaction of the reagent with the nitrile. In the reaction of ethyl magnesium bromide with **2**, dissociation occurs less readily, and the reaction is slower. In the case of methyl magnesium bromide and **2**, dissociation is so slow that a second equivalent of reagent is required to obtain the desired reaction. It should be stressed that despite the addition of this extra equivalent of reagent, no products resulting from halogen displacement are detected. Clearly, further work is warranted to obtain a better understanding of this reaction. For our purposes, however, it was convenient to perform Grignard reactions of 2-hetero-substituted isonicotinonitriles with two equivalents of reagent over a 20 hour period.

Attention was next turned to the incorporation of the appropriate amino functions at the 2-pyridyl position. Not unexpectedly, attempts to convert **4a** directly to 1-(2-amino-4-pyridyl)ethanone, **1a**, using aqueous ammonia failed under a variety of standard conditions, presumably due to concomitant complications involving the carbonyl. The ketone was then begrudgingly protected as ketal **5a**, thereby removing the carbonyl's inductive electron-withdrawing effect, which would be expected to enhance the desired conversion. Despite protection, direct displacement of the chloride in **5a** with ammonia failed, and it appeared that a better nucleophile was needed. Thus, a two-step process was adopted in which **5a** was first reacted with hydrazine to give **6a**. Catalytic hydrogenation of **6a** cleanly afforded amine **7a**, which gave the desired **1a**

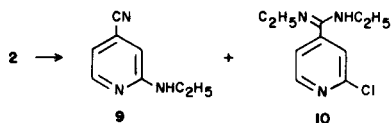
upon hydrolysis. Despite the number of steps involved, the overall yield of **1a** from **4a** was 65%. Similarly, 1-(2-chloro-4-pyridyl)propanone, **4b**, was converted to **1b** in an overall yield of 67%.



The relative ease with which hydrazine reacts with **5a** (110°, 10 hours) contrasts with similar displacements designed to prepare the *N*-ethylamino derivative, **8**, from **5a**. It was eventually found that, by using *N*-methyl-2-pyrrolidinone as solvent in a closed vessel at 170° for 16 hours, **8** could be prepared in excellent yield. Hydrolysis of the ketal then gave the desired 1-(2-*N*-ethylamino-4-pyridyl)ethanone, **1c**, in 75% yield from **5a**. The greater reactivity of hydrazine with **5a** may be attributed not only to the greater nucleophilicity of hydrazine, but also to the hydrogen bonding capability of the protons on its α -amino function, thus facilitating intermolecular reaction. This potential for hydrogen bonding is obviously not possible for *N*-ethylamine.

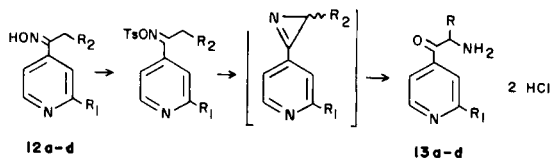


As was mentioned above, the nature of the 4-substituent on the pyridine ring has a dramatic inductive effect on the displacement potential of the 2-chloro moiety. Treatment of 2-chloroisonicotinonitrile, **2**, with *N*-ethylamine (closed vessel, 150°) resulted in complete consumption of **2** after only four hours. In this case, however, not only was displacement observed to give 48% of 2-*N*-ethylaminoisonicotinonitrile, **9**, but attack by the amine on the nitrile to give amidine, **10** (12%), also occurred. Thus, although the reaction of *N*-ethylamine is much more rapid with **2** than with ketal **5a**, the latter method is preferred for the synthesis of **1c**.



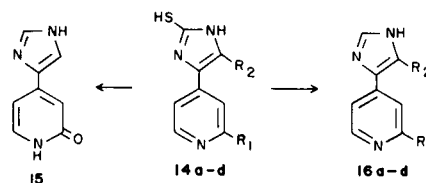
Amidine formation is precluded when **2** is reacted with a secondary amine such as *N,N*-dimethylamine. Treatment of **2** with *N,N*-dimethylamine afforded 69% of 2-*N,N*-dimethylaminoisonicotinonitrile, **11** (4), which, on reaction with methyl magnesium bromide, gave 1-(2-*N,N*-dimethylamino-4-pyridyl)ethanone, **1d**, in 61% yield. Thus, the synthesis of the target ketone precursors was complete.

Oximation of these ketones proceeded without incident. Tosylation of oxime **12a**, however, using *p*-toluenesulfonyl chloride in pyridine resulted not only in tosylation of the oxime oxygen as desired, but also in tosylation of the 2-aminopyridine moiety. Clean oxime tosylation was realized by first preparing the sodium salt of the oxime (sodium ethoxide, ethanol) in order to enhance the nucleophilicity of the oxygen. Treatment with *p*-toluenesulfonyl chloride then gave the *O*-tosyloximes, which were directly subjected to the Neber rearrangement, thereby affording the α -aminoketone dihydrochlorides in good overall yield.

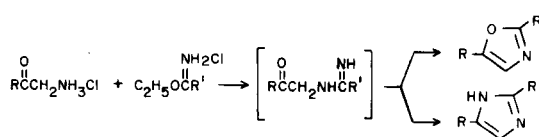


It now simply remained to convert these intermediates to the imidazoles. Compounds **13a-d** all reacted smoothly with potassium thiocyanate to give the corresponding 2-thiolimidazoles, **14a-d**. Attempted desulfurization of **14a** using the classical nitric acid oxidation (5) resulted in desulfurization along with concomitant conversion of the 2-aminopyridine to its 2-pyridone, **15**. This was somewhat surprising since **14a** is stable to 6*N* hydrochloric acid solution at 90°. Apparently, the nitric acid oxidation process involves formation of nitrous acid, which subsequently converts the amino function into the hydroxyl group *via*

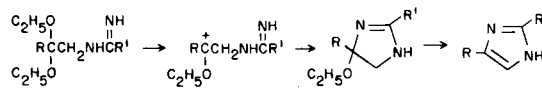
diazotization/hydrolysis. The desired desulfurization was accomplished using Raney nickel/dimethylformamide, thereby affording targets **16a-d**.



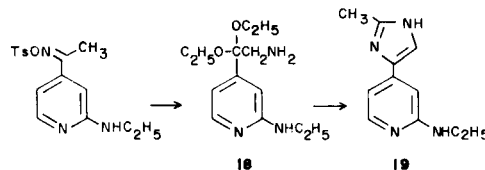
Other ring closures also proved successful. For example, reaction of **13d** with cyanamide gave 58% of 2-*N,N*-dimethylamino-4-(2-amino-4-imidazolyl)pyridine, **17**. Alkyl groups can also be inserted at the 2-position of the imidazole but a modified approach is required. α -Aminoketones are reported to react with imino ethers to give mixtures of oxazoles and imidazoles, although the latter compounds predominate (6).



One way of preventing oxazole formation is to have the ketone protected as a ketal (7). Then, after adduct formation with the imino ether, treatment with acid results in intramolecular capture by the amidine, thereby giving solely the imidazole.



α -Aminoketals can also be prepared using the Neber rearrangement if absolute ethanol is used as the nucleophilic solvent in place of water (8). In this manner, the oxime tosylate of 1-(2-*N*-ethylamino-4-pyridyl)ethanone, **1c**, was converted to ketal **18**. Reaction of **18** with ethyl acetimidate hydrochloride, followed by treatment with concentrated hydrochloric acid, gave imidazole **19**. No oxazole was isolated from this reaction.



In summary, the synthetic route described above allows for the synthesis of 4-imidazolylpyridines, which contain a variety of substituents on the imidazole ring as well as amino groups at the 2-pyridyl position. The biological activity of these compounds will be described elsewhere (9).

This study has also demonstrated that, despite unusual stoichiometric effects that are observed in the reaction of Grignard reagents with 2-chloroisonicotinonitrile, reasonable yields of the desired ketones can be obtained. In addition, conditions have been found to effect nucleophilic displacement of the chloride by amines, regardless of the electronic nature of the 4-substituents. Finally, α -aminoacetals have been shown to be very useful in the synthesis of imidazoles.

EXPERIMENTAL

The ^1H nmr spectra were obtained on a Varian T-60 spectrometer. Chemical shifts from tetramethylsilane are reported on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus. Solvents and reagents were commercially available unless otherwise noted and were used directly.

1-(2-Chloro-4-pyridyl)ethanone (4a).

A solution of 34.6 g (0.25 mole) of 2-chloroisonicotinonitrile (10) in 500 ml of absolute ether was stirred at room temperature under a nitrogen atmosphere and 166 ml (0.50 mole) of a 3.0 M solution of methyl magnesium bromide in ether (Aldrich) was added dropwise over 15 minutes. After stirring at room temperature for 20 hours, the precipitate was collected and added immediately to a mixture of 600 g of ice, 300 ml of water, and 150 ml of 6N hydrochloric acid. The aqueous solution was extracted (4×100 ml) with ether, and the combined ether extracts were dried (sodium sulfate), filtered, and concentrated leaving an oil. This was extracted with warm petroleum ether (4×50 ml), and the extracts were combined and cooled in a dry-ice/acetone bath. The resulting precipitate was collected and dried to give 21.3 g (55%) of **4a** as a white crystalline solid, mp 36-38° (lit 36-39°) (9).

1-(2-Chloro-4-pyridyl)propanone (4b).

Using the same procedure described for the synthesis of **4a**, **4b** was prepared in 52% yield as a white solid, mp 34-35°.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{ClNO}$: C, 56.65; H, 4.76; N, 8.26. Found: C, 56.55; H, 4.75; N, 8.57.

1-(2-Chloro-4-pyridyl)-1-ethylenedioxyethane (5a).

A mixture of 21.3 g (0.137 moles) of **4a**, 0.5 g of *p*-toluenesulfonic acid, 40 ml of ethylene glycol, and 300 ml of toluene was placed in a flask, fitted with a Dean-Stark trap and condenser, and was heated at reflux for 16 hours. The mixture was cooled, then concentrated leaving an oil. Distillation under reduced pressure afforded 23.6 g (86%) of **5a** as a colorless oil, bp 65° (0.05 torr).

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{ClNO}_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.06; H, 4.98; N, 7.16.

1-(2-Chloro-4-pyridyl)-1-ethylenedioxypropane (5b).

Using the same procedure described for the synthesis of **5a**, **5b** was prepared in 80% yield, bp 69° (0.05 torr).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{ClNO}_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.08; H, 5.58; N, 6.66.

1-(2-(Hydrazino-4-pyridyl)-1-ethylenedioxyethane (6a).

A mixture of 11.4 g (57 mmoles) of **5a** and 50 ml of 98% hydrazine hydrate was heated at 110° for 10 hours. The mixture was cooled at 0° and, after 2 hours, the resulting precipitate was collected, then dried *in vacuo* to afford 10.3 g (92%) of **6a** as a white crystalline solid, mp 111-113°; nmr (DMSO- d_6): 7.67 (d, 1H), 7.2 (b, 1H), 6.47 (s, 1H), 6.18 (d, 1H), 4.0-3.2 (b + m, 6H), 1.18 (s, 3H). An analytical sample (mp 112-113°) was prepared by recrystallization from 50/50 toluene-cyclohexane.

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.14; H, 6.64; N, 21.03.

1-(2-Hydrazino-4-pyridyl)-1-ethylenedioxypropane (6b).

Using the same procedure described for the synthesis of **6a**, **6b** was prepared in 92% yield, mp 92-93° (cyclohexane); nmr (DMSO- d_6 /deuterium oxide): 7.70 (d, 1H), 6.53 (s, 1H), 6.39 (d, 1H), 3.9-3.3 (m, 4H), 1.82 (q, 2H), 0.83 (t, 3H).

Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.54; H, 7.05; N, 20.05.

1-(2-Amino-4-pyridyl)-1-ethanone (1a).

A mixture of 9.56 g (49 mmoles) of **6a**, 35 g of Raney nickel, and 150 ml of absolute ethanol was hydrogenated on a Parr apparatus at room temperature and 3 atmospheres for 4 hours. The catalyst was removed by filtration through Celite, and the filtrate concentrated to give 1-(2-amino-4-pyridyl)-1-ethylenedioxyethane, **7a**, as a white solid, mp 123-126°. This was dissolved in 60 ml of 2N hydrochloric acid and heated at 75° for 3 hours. The mixture was cooled, neutralized with solid sodium bicarbonate, and extracted with chloroform (6×30 ml). The combined extracts were dried (sodium sulfate), filtered, and evaporated leaving a solid. Recrystallization from toluene afforded 5.0 g (75%) of **1a**, mp 133-133.5°; nmr (DMSO- d_6): 7.87 (d, 1H), 6.68 (s + d, 2H), 6.0 (b, 2H), 2.28 (s, 3H); ir (potassium bromide): 1700 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{N}_2\text{O}$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.87; H, 5.95; N, 20.64.

1-(2-Amino-4-pyridyl)-1-propanone (1b).

Using the same procedure described for the synthesis of **1a**, **1b** was prepared from **6b** in an overall yield of 78%, mp 135-137° (toluene); nmr (DMSO- d_6 /deuterium oxide): 7.90 (d, 1H), 6.83 (s + d, 2H), 2.80 (q, 2H), 0.90 (t, 3H); ir (potassium bromide): 1705 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.50; H, 6.67; N, 18.42.

1-(2-N-Ethylamino-4-pyridyl)-1-ethanone (1c).

A mixture of 18.8 g (94 mmoles) of 1-(2-chloro-4-pyridyl)-1-ethylenedioxyethane, **5a**, 50 ml of *N*-ethylamine, and 80 ml of *N*-methyl-2-pyrrolidone was sealed in a steel bomb and heated at 170° for 15 hours. The bomb was cooled, and the contents distilled under reduced pressure to remove excess solvent. The residue was dissolved in 100 ml of methylene chloride, and this organic solution was extracted (3×25 ml) with 2N hydrochloric acid. The combined acid extracts were heated at 80° for 3 hours, cooled, then made basic with sodium carbonate. The aqueous mixture was extracted with methylene chloride (4×25 ml), and the combined organic extracts were dried (sodium sulfate), filtered, and evaporated leaving 11.5 g (75%) of an oil, which solidified on standing, mp 55-57°; nmr (deuteriochloroform): 8.26 (d, 1H), 6.96 (d, 1H), 6.87 (s, 1H), 5.0 (b, 1H), 3.30 (m, 2H), 2.58 (s, 3H), 1.23 (t, 3H). An analytical sample was prepared by recrystallization from cyclohexane to give a pale yellow crystalline solid, mp 62-63°.

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.48; H, 7.34; N, 17.12.

Reaction of 2-Chloroisonicotinonitrile (2) with *N*-Ethylamine.

A mixture of 10.0 g (72 mmoles) of 2-chloroisonicotinonitrile (10), 24 ml of *N*-ethylamine (360 mmole), 80 ml of toluene, and 20 ml of tetrahydrofuran was sealed in a steel bomb and heated at 150° for 4 hours. The mixture was cooled, then concentrated leaving an oil which was partitioned between 100 ml each of ether and water. The ether solution was separated, dried (sodium sulfate), filtered, and evaporated leaving 9.0 g of a crude solid, consisting of two materials as shown by tlc. This material was chromatographed over 180 g of silica gel using 19:1 chloroform/methanol as eluent. The major product eluted first in fractions 10-17 (25 ml portions). This amounted to 5.0 g (48%) of 2-*N*-ethylaminoisonicotinonitrile, **9**, mp 78-80° (cyclohexane); nmr (deuteriochloroform): 8.06 (d, 1H), 6.58 (d, 1H), 6.50 (s, 1H), 5.4 (b, 1H), 3.27 (m,

2H), 1.26 (t, 3H); ir (potassium bromide): 2250 cm^{-1} (CN).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.10; H, 6.14; N, 28.69.

The column was next eluted with ethanol and the minor product eluted in fractions 66-98 (25 ml portions) to give 1.84 g (12%) of amidine **10**, mp 117-118° (cyclohexane); nmr (deuteriochloroform): 8.42 (d, 1H), 7.30 (s, 1H), 7.22 (d, 1H), 3.15 (q, 4H), 1.20 (t, 6H).

Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{ClN}_3$: C, 56.74; H, 6.67; N, 19.85; Cl, 16.74. Found: C, 56.52; H, 6.60; N, 20.24; Cl, 16.20.

1-(2-Dimethylamino-4-pyridyl)-1-ethanone (**1d**).

A solution of 7.4 g (50 mmoles) of 2-*N,N*-dimethylaminoisonicotinonitrile **11** (**4**), in 150 ml of absolute ether was stirred at room temperature under a nitrogen atmosphere and 33 ml (100 mmoles) of a 3*M* solution of methyl magnesium bromide in ether (Aldrich) was added dropwise over 15 minutes. The mixture was stirred at room temperature for 16 hours, then quenched by the careful addition of 50 ml of 2*N* hydrochloric acid. The aqueous solution was separated, and the organic solution was extracted further with 2*N* hydrochloric acid (2 \times 10 ml). The combined acid extracts were neutralized with sodium carbonate, and extracted with chloroform (5 \times 50 ml). The combined chloroform extracts were dried (sodium sulfate), filtered, and concentrated leaving an oil. Distillation of this oil under reduced pressure gave 5.0 g (61%) of **1d** as a colorless oil, bp 110° (1.0 torr). On standing the oil solidified to white crystals, mp 37-42°; nmr (deuteriochloroform): 8.24 (d, 1H), 6.86 (s + d, 2H), 3.08 (s, 6H), 2.52 (s, 3H).

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}$: C, 65.83; H, 7.37; N, 17.06; O, 9.74. Found: C, 65.48; H, 7.22; N, 16.99.

1-(2-Amino-4-pyridyl)-1-ethanone Oxime (**12a**).

Hydroxylamine hydrochloride (3.1 g, 45 mmoles) was dissolved in 10 ml of water and this was added to 22.5 ml of 2*N* sodium hydroxide solution. To this solution was added 3.6 g (26 mmoles) of **1a** and the mixture was boiled for 5 minutes. Methanol was added occasionally to maintain homogeneity. Heating was continued until a precipitate began to form. The mixture was then cooled to 0°, and the resulting precipitate was collected, washed with water, then dried *in vacuo*. Recrystallization from ethyl acetate afforded 3.6 g (92%) of **12a**, mp 215-217°.

Anal. Calcd. for $\text{C}_7\text{H}_7\text{N}_3\text{O}$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.61; H, 6.09; N, 27.57.

Oximes **12b-d** were all prepared using this same procedure.

1-(2-Amino-4-pyridyl)-1-propanone Oxime (**12b**).

This was obtained in 83% yield from **1b** as white needles, mp 167.5-168° (ethyl acetate).

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.50; H, 6.64; N, 25.70.

1-(2-*N*-Ethylamino-4-pyridyl)-1-ethanone Oxime (**12c**).

This was obtained in 93% yield from **1c** as a crystalline solid, mp 154-155° (toluene).

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}$: C, 60.32; H, 7.31; N, 23.45. Found: C, 59.93; H, 7.25; N, 23.58.

1-(2-*N,N*-Dimethylamino-4-pyridyl)-1-ethanone Oxime (**12d**).

This was obtained in 86% yield from **1d** as a pale yellow solid, mp 145-148° (toluene).

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.32; H, 7.36; N, 23.56.

4-(2-Amino-4-pyridyl)imidazole-2-thiol (**14a**).

Sodium (0.72 g, 31 mmoles) was dissolved in 60 ml of absolute ethanol at room temperature, and to this was added 4.59 g (30.4 mmoles) of **12a**. After stirring at room temperature for 5 minutes (to generate the oxime amine), *p*-toluenesulfonyl chloride (6.10 g, 32 mmoles) was added directly to the ethanol mixture. This mixture was stirred at room temperature under nitrogen for one hour, thereby generating the oxime tosylate *in situ*. This mixture was then added directly to an ethanolic potassium

ethoxide solution (prepared by dissolving 1.41 g of potassium in 30 ml of ethanol) in order to effect the Neber rearrangement. This mixture was stirred at room temperature under a nitrogen atmosphere for 0.5 hour, during which time a gelatinous suspension formed. The mixture was diluted with 800 ml of absolute ether, stirred vigorously for 0.5 hour, then filtered through Celite. The filtrate, which contained the azirine intermediate, was concentrated and the residue taken up in 100 ml of ether, then extracted with 2*N* hydrochloric acid (4 \times 25 ml). The combined acid extracts were concentrated to give α -aminoketone, **13a**, as a yellow solid, mp >270°. This was dissolved in 60 ml of water containing 5.83 g (60 mmoles) of potassium thiocyanate. The resulting solution was heated on a steam bath for 2 hours, then cooled. The resulting precipitate was collected, and stirred in 40 ml of a saturated aqueous sodium bicarbonate solution. The insoluble solid was collected, washed well with water, and dried *in vacuo* to give 3.21 g (55%) of **14a** as a yellow solid, mp 262-264° dec; nmr (DMSO- d_6 /deuterium oxide): 7.66 (d, 1H), 7.31 (s, 1H), 6.62 (s + d, 2H). An analytical sample was prepared by recrystallization from water.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{S}\cdot\text{H}_2\text{O}$: C, 45.69; H, 4.79; N, 26.64. Found: C, 45.49; H, 4.89; N, 26.24.

4-(2-Amino-4-pyridyl)-5-methylimidazole-2-thiol (**14b**).

Using the same procedure described for the preparation of **14a**, 1-(2-amino-4-pyridyl)-1-propanone oxime (**12b**) gave a 56% yield of **14b** as a pale yellow amorphous solid, mp >300°; nmr (DMSO- d_6): 7.96 (d, 2H), 6.73 (s + d, 2H), 6.0 (b, 2H), 2.32 (s, 3H).

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_4\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 50.21; H, 5.15; N, 26.02. Found: C, 49.90; H, 4.76; N, 25.41.

4-[2-(*N*-Ethylamino)-4-pyridyl]imidazole-2-thiol (**14c**).

Using the same procedure described for the preparation of **14a**, 1-[2-(*N*-ethylamino)-4-pyridyl]-1-ethanone oxime, **12c**, afforded 64% of **14c** as an amorphous yellow solid (11), mp >260°; nmr (DMSO- d_6): 7.82 (d, 1H), 7.48 (s, 1H), 6.9-6.2 (m, 4H), 3.18 (m, 2H), 1.06 (t, 3H).

4-(2-*N,N*-Dimethylamino-4-pyridyl)imidazole-2-thiol (**14d**).

A mixture of 4.0 g (22 mmoles) of 1-(2-*N,N*-dimethylamino-4-pyridyl)-1-ethanone oxime, **12d**, 4.8 g (25 mmoles) of *p*-toluenesulfonyl chloride, and 25 ml of pyridine was stirred at room temperature for 24 hours. The mixture was poured into 250 ml of water, and the resulting precipitate was collected, washed with water, and dried *in vacuo*. Recrystallization from toluene/cyclohexane gave 3.8 g (52%) of 1-(2-*N,N*-dimethylamino-4-pyridyl)-1-ethanone oxime *O*-tosylate, mp 136° dec. A solution of 3.0 g (9 mmoles) of this tosylate in 35 ml of ethanol was added to an ethanolic potassium ethoxide solution (0.40 g of potassium in 10 ml of ethanol), and this mixture was stirred at room temperature for one hour. The mixture was diluted with 250 ml of ether, and the insoluble material was removed by filtration. The filtrate was concentrated, and the residue was taken up into 100 ml of ether. This organic solution was extracted with 2*N* hydrochloric acid (3 \times 20 ml), and the combined acid extracts were concentrated leaving the α -aminoketone dihydrochloride, **13d**, as a yellow solid. This was dissolved in 10 ml of water, and 1.75 g (18 mmoles) of potassium thiocyanate was added. The aqueous solution was heated on a steam bath for 2 hours, cooled, and the resulting precipitate collected. This solid was added to 40 ml of saturated sodium bicarbonate solution, and stirred at room temperature for 15 minutes. This solid was collected, washed well with water, and dried *in vacuo*, to afford 1.4 g (71%) of **14d**, as a pale yellow solid (11), mp >270°; nmr (DMSO- d_6): 7.9 (s + d, 2H), 7.25 (s, 1H), 7.10 (d, 1H), 3.2 (d, 6H).

2-Amino-4-(4-imidazolyl)pyridine (**16a**).

A mixture of 2.3 g (12 mmoles) of **14a**, 8 g of Raney nickel, and 60 ml of dimethylformamide was heated at 115° for 3 hours. The mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated leaving a brown solid. After trituration with boiling chloroform, the solid was taken up into 50 ml of ethanol, treated with charcoal, and the filtered solution was concentrated to a small volume. The precipitate was filtered and dried, leaving 1.12 g (60%) of **16a** as a white

solid, mp 193-196°. An analytical sample was prepared by chromatography over florisil using 9:1 chloroform/methanol as eluent to give **16a**, mp 196-198°; exact mass: Calcd. for $C_8H_8N_4$, m/e 160.0749; Found: m/e 160.0743; nmr (DMSO- d_6 , deuterium oxide): 8.0-7.6 (s + s + d, 3H), 7.1-6.9 (s + d, 2H).

Anal. Calcd. for $C_8H_8N_4 \cdot \frac{1}{4}H_2O$: C, 58.34; H, 5.20; N, 34.02. Found: C, 58.46; H, 4.98; N, 33.97.

2-Amino-4-(5-methyl-4-imidazolyl)pyridine (16b)

Using the same procedure described for the synthesis of **16a**, 61% of **16b** was isolated as a white solid, mp 258° dec; exact mass: Calcd. for $C_9H_{10}N_4$, m/e 174.0906; Found: C, m/e 174.0898; nmr (DMSO- d_6 /deuterium oxide): 7.90 (d, 1H), 7.63 (s, 1H), 6.0-6.8 (s + d, 2H), 2.37 (t, 3H).

Anal. Calcd. for $C_9H_{10}N_4 \cdot \frac{1}{2}H_2O$: C, 59.00; H, 6.05; N, 30.58. Found: C, 58.60; H, 5.73; N, 30.86.

2-Hydroxy-4-(4-imidazolyl)pyridine (15)

A solution of 7 ml of concentrated nitric acid, and 50 ml of water was heated on a steam bath, and to this was slowly added 961 mg (5.0 mmoles) of 4-(2-amino-4-pyridyl)imidazole-2-thiol, **14a**. The mixture was heated on a steam bath for 1 hour, then cooled to 5°. The resulting precipitate was collected, briefly dried, then added to 25 ml of saturated sodium bicarbonate solution. After stirring for 15 minutes, the solid was collected, washed with water, and dried *in vacuo* to give 510 mg (64%) of **15** as a white solid. Recrystallization from water afforded **15** as a crystalline solid, mp 282-284° dec; exact mass: Calcd. for $C_8H_7N_3O$, m/e 161.0589; Found: m/e 161.0586; nmr (DMSO- d_6): 7.70 (s, 2H), 7.32 (d, 2H), 6.57 (s + d, 2H).

Anal. Calcd. for $C_8H_7N_3O \cdot H_2O$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.82; H, 4.79; N, 24.00.

2-N-Ethylamino-4-(4-imidazolyl)pyridine (16c)

A mixture of 1.1 g (5.0 mmoles) of **14c**, 4.0 g of Raney nickel, and 30 ml of dimethylformamide was heated at 120° for 4 hours. The catalyst was removed by filtration through Celite, and the filtrate concentrated leaving an oil, which solidified upon trituration with ether. Purification by chromatography over 35 g of silica gel using 19:1 chloroform/methanol as eluent gave 384 mg (41%) of **16c**, as a white solid, mp 135-137°.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.76. Found: C, 63.40; H, 6.39; N, 29.40.

2-N,N-Dimethylamino-4-(4-imidazolyl)pyridine (16d)

Using the same procedure described for the preparation of **16c**, 4-(2-N,N-dimethylamino-4-pyridyl)imidazole-2-thiol, **14d**, was converted in 53% yield to **16d**, mp 173-173.5°; nmr (DMSO- d_6): 8.0 (d, 1H), 7.87 (bs, 2H), 6.93 (s + d, 2H), 3.07 (s, 6H).

Anal. Calcd. for $C_{10}H_{14}N_4$: C, 63.81; H, 6.43; N, 29.76. Found: C, 63.63; H, 6.54; N, 29.64.

2-(N,N-Dimethylamino)-4-(2-amino-4-imidazolyl)pyridine (17)

Potassium (500 mg, 12.5 mmoles) was dissolved in 10 ml of absolute ethanol at room temperature under a nitrogen atmosphere, and to the resulting solution was added a slurry of 3.8 g (11 mmoles) of 1-(dimethylamino-4-pyridyl)-1-ethanone oxime *O*-tosylate in 10 ml of ethanol. The mixture was allowed to stir at room temperature for one hour during which time a thick precipitate formed. The mixture was diluted with 400 ml of ether and extracted (4 × 25 ml) with 2N hydrochloric acid. The combined acid extracts were concentrated to dryness and the residue dissolved in 30 ml of water containing 1.35 g (32 mmoles) of cyanamide. The pH was brought to 4.5 by the addition of 2N sodium hydroxide solution and solution heated on a steam bath for 1 hour. The cooled reaction mixture was made basic with concentrated ammonium hydroxide, and the resulting precipitate filtered, washed with water and dried *in vacuo*, to give 1.34 g (58%) of **17**, mp >270°; nmr (DMSO- d_6): 7.70 (d, 1H), 6.93 (s, 1H), 6.54 (s + d, 2H), 5.3 (b, 2H), 2.87 (s, 6H). An analytical sample was

prepared by recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{13}N_5$: C, 59.09; H, 6.45; N, 34.45. Found: C, 58.64; H, 6.50; N, 33.99.

2-[2-(N-Ethylamino)-4-pyridyl]-2,2-diethoxyethylamine (18)

To a solution of sodium ethoxide, formed by dissolving 740 mg (32 mmoles) of sodium in 30 ml of ethanol at room temperature under a nitrogen atmosphere, was added 5.38 g (30 mmoles) of 1-[2-(N-ethylamino)-4-pyridyl]-1-ethanone oxime, **12c**, and the resulting mixture stirred until homogenous. *p*-Toluenesulfonyl chloride (6.1 g, 33 mmoles) was added and the mixture was stirred for 1 hour at room temperature. The mixture was added directly to a solution of potassium ethoxide, prepared by dissolving 1.35 g (35 mmoles) of potassium in 30 ml of ethanol, and the mixture allowed to stir for 30 minutes at room temperature under a nitrogen atmosphere. The resulting gelatinous mass was diluted with 300 ml of ether and the solids filtered. Hydrogen chloride gas was bubbled into the filtrate for 15 minutes, then the mixture was concentrated. The residue was dissolved in 250 ml of water and made basic by the addition of solid sodium carbonate. The product was extracted with chloroform (3 × 40 ml) and the combined extracts were dried over sodium sulfate and concentrated to give 7.6 g (100%) of **18** as an oil; nmr (deuteriochloroform): 8.08 (d, 1H), 6.66 (s + d, 2H), 5.0 (b, 1H), 3.42 (q, 6H), 2.98 (s, 2H), 1.19 (t, 9H). This material was used without further purification since either distillation or chromatography resulted in decomposition.

2-(N-Ethylamino)-4-(2-methyl-4-imidazolyl)pyridine (19)

A mixture of 2.0 g (8 mmoles) of **18**, 1.0 g (8.3 mmoles) of ethyl acetimidate hydrochloride, and 30 ml of absolute ethanol was heated at reflux for 1.3 hours. The mixture was concentrated, and the residue taken up into a 10 ml of concentrated hydrochloric acid. The acid solution was heated on a steam bath for 1 hour, cooled, then made basic with potassium carbonate. The mixture was extracted with chloroform (4 × 15 ml), and the combined extracts were dried, then concentrated leaving a crude solid. This was chromatographed over 35 g of silica gel using 19:1 chloroform/methanol as eluent to give 0.51 g (30%) of **19**, as a white solid, mp 214-216°; nmr (DMSO- d_6): 7.94 (d, 2H), 7.53 (s, 1H), 6.92 (s + d, 2H), 6.30 (t, 1H), 3.36 (m, 2H), 2.36 (s, 3H), 1.20 (t, 3H).

Anal. Calcd. for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 64.98; H, 7.29; N, 27.22.

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