Synthesis of Imidazo[4,5-*b*]pyridines from Aminoimidazolecarbaldehydes

Francisco Perandones and José L. Soto*

Departamento de Química Orgánica, Facultad de Química,
Universidad Complutense,
28040-Madrid, Spain

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4-Amino-1,2-dimethylimidazole-5-carbaldehyde (**1**) and 5-amino-1-methylimidazole-4-carbaldehydes **3** were prepared by reduction of the corresponding aminoimidazolecarbonitriles **2** and **4**. Condensation of **1** and **3** with carbonitriles, ketones and polyfunctional carbonyl compounds bearing the -CH_2CO- moiety afforded to the imidazo[4,5-*b*]pyridine derivatives.

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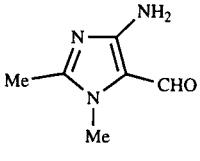
The synthesis of imidazo[4,5-*b*]pyridines has attracted attention in recent years due to their variety of biological and pharmacological properties [1,2]. Compounds containing the imidazo[4,5-*b*]pyridine system have been usually prepared by reaction of 2,3-diaminopyridines with β-dicarbonyl compounds [3]. However, the synthesis of imidazo[4,5-*b*]pyridines by the Friedländer [4,5] reaction has been almost neglected in the literature. In this paper, we report the preparation of the aminoimidazolecarbaldehydes **1** and **3**, and the formation of further condensed imidazole ring systems.

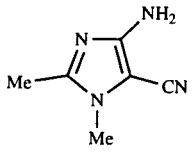
The 4-aminoimidazole-5-carbaldehydes **1** and **3** were prepared by catalytic reduction of the corresponding 4-aminoimidazole-5-carbonitriles [4,6] **2** and **4**.

The reduction of heterocyclic nitriles to aldehydes has been accomplished under a variety of different conditions [7-9]. Extensive experimentation by different methods of chemical and catalytic reduction of the nitrile group in compounds **2** and **4** revealed that hydrogenation using 10% Pd/C in dilute sulfuric acid was the best method. Although aldehydes are readily hydrogenated to the corresponding alcohols at room temperature and moderate pressures, under properly controlled conditions no similar reduction appears to occur, and good yields (55-80%) of the aldehydes **1** and **3** were obtained, uncontaminated with either **2** or **4**, respectively (Figure 1).

Figure 1



1



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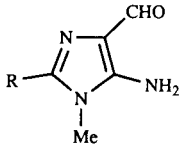
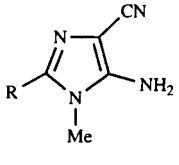


3

3,4a: R = Me
b: R = Ph



4

Analytical and spectroscopic data fully support the structural assignments for compounds **1** and **3**. The ^1H nmr spectra showed the presence of broad singlets corresponding to the protons of the primary amino groups and a singlet in the region δ 9.3-9.5 due to the proton of the formyl group. The ir spectrum of the aminoimidazolecarbaldehydes prepared in this work showed an absorption band at 1650 cm^{-1} due to CO stretching vibrations and, significantly, the peaks due to the cyano group were absent.

When a mixture of **1** or **3** and malononitrile or ethyl cyanoacetate is heated under reflux in ethanol in the presence of sodium ethoxide as the catalyst for 2-4 hours, good yields of the corresponding 5-aminoimidazo[4,5-*b*]-pyridine derivatives **5**, **8** and **12** were obtained.

The 5-aminoimidazo[4,5-*b*]pyridine-6-carbonitriles are versatile synthetic intermediates and their preparation in good overall yield from aminoimidazolecarbaldehydes **1** and **3** provides the opportunity for preparing a variety of novel 1-deazapurine analoges [10,11].

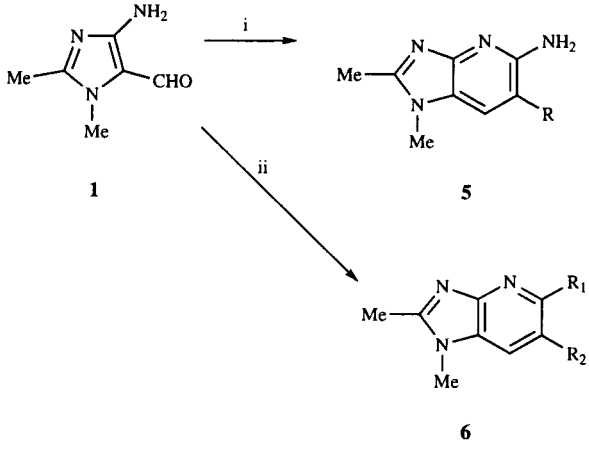
The novel compounds **5**, **8** and **12** were fully identified by their analytical and spectroscopic properties. The infrared spectrum of **5a**, **8a** and **12a** indicated the presence of a conjugated nitrile group at 2200 cm^{-1}; on the other hand, compounds **5b**, **8b** and **12b** show a band at 1680-1700 cm^{-1} due to the carbonyl group, in addition to the strong N-H bands in the 3100-3400 cm^{-1} region, revealing a primary amino group.

It was found that aminoimidazolecarbaldehyde **1** does not react [12,13] with ketones and dicarbonyl compounds under base-catalyzed conditions. This difficulty in the cyclocondensation reactions of **1** with ketones and similarly

activated methylene containing compounds may be attributed to the conjugative effect on the electrophylic formyl group and the nucleophylic amino group. The presence of intramolecular hydrogen bonds may also contribute to the decrease in reactivity of both the carbonyl and the amino groups.

According to the usual procedure for the Friedländer reaction, **1** was treated in boiling acetic acid for an appropriate period of time with compounds such as acetophenone, ethyl acetoacetate, acetylacetone, cyclohexanone and cyclopentanone to give the corresponding imidazo-[4,5-*b*]pyridine derivatives **6a-f**, although in low yields. With methyl ethyl ketone only one direction of ring closure was observed, although formation of small amounts of isomeric products undetected in the reaction mixture can not be ruled out (Scheme 1).

Scheme 1



Reagents and conditions: i, R-CH_2-CN, EtOH-EtONa, reflux; ii, $R_1COCH_2R_2$, AcOH, boil.

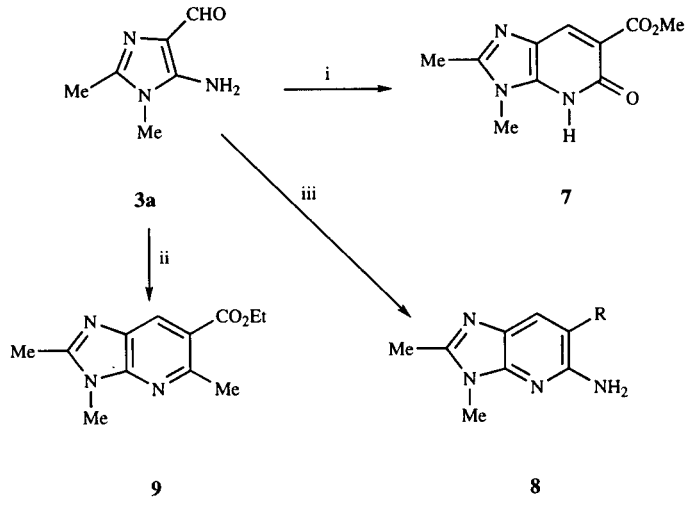
5a: R = CN
b: R = CO_2Et
6a: R_1 = Ph, R_2 = H
b: R_1 = Me, R_2 = Me
c: R_1 = Me, R_2 = CO_2Et
d: R_1 = Me, R_2 = COMe
e: R_1 = R_2 = -$(CH_2)_3$-
f: R_1 = R_2 = -$(CH_2)_4$-

The structures of these compounds were confirmed by their elemental analysis, nmr and infrared spectra. The elemental analysis of 6-ethoxycarbonyl derivative **6c** shows the presence of 1.5 molecules of water, confirmed by strong infrared absorptions in the 3550-3100 cm^{-1} region.

Some of the compounds **6** have a strong tendency to retain water of crystallization and need to be dried at high temperatures, under reduced pressure, in order to get correct elemental analyses.

The reaction of **3a** with diethyl malonate in the presence of sodium methoxide as a catalyst afforded to the imidazo[4,5-*b*]pyridine derivative **7** in good yield. However, the reaction of **3a** with ethyl acetoacetate, had to be carried out in acidic medium to afford compound **9** (Scheme 2).

Scheme 2



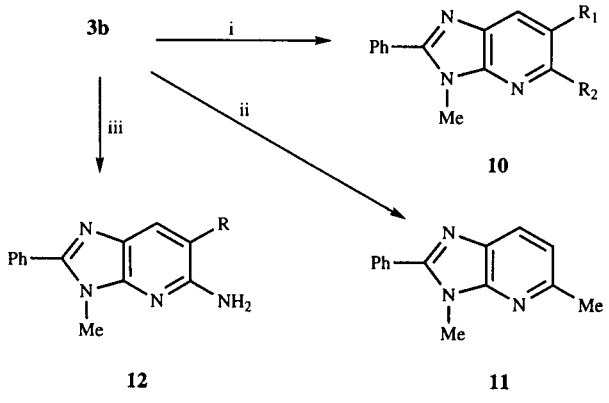
Reagents and conditions: i, $CO_2EtCH_2CO_2Et$, MeOH-MeONa, reflux; ii, CH_3COCH_2Et, AcOH, reflux; iii, RCH_2CN, MeOH-MeONa, reflux.

8a: R = CN
b: R = CO_2Et

Condensation reactions of **3b** with carbonyl compounds in acidic medium gave the expected products **10a-g** in moderate yields. However, the cyclocondensation of **3b** with ethyl acetoacetate in methanol-sodium methoxide gave a crystalline product which was identified by ^1H nmr spectroscopy as the 2-phenyl-3,5-dimethylimidazo[4,5-*b*]pyridine (**11**) and the same was observed with acetylacetone. In particular, the strongly coupled (J = 8.1 Hz) pyridine protons are clearly observed at δ = 7.12 and 7.95 ppm. The ^1H nmr spectrum of **10b** revealed a singlet at δ = 8.64 ppm corresponding to the pyridine proton. As expected, compound **10b** showed a carbonyl absorption band at 1730 cm^{-1} in its ir spectrum. However, **11** did not show absorption in the carbonyl region. This finding confirms that cyclization from imidazole **3b** with ethyl acetoacetate or acetylacetone in basic medium take place with loss of the carbonyl group (see Experimental).

On the other hand, when acetophenone was used in the cyclization reaction with **3b**, in acidic medium, compound **10c** was obtained in low yield (10%). A better result was obtained in basic medium although **10c** was obtained only in moderate yield (30%) (Scheme 3).

Scheme 3



Reagents and conditions: i, $R_1CH_2COR_2$, AcOH or MeOH-MeONa, reflux; ii, $CH_3COCH_2CO_2Et$ or $CH_3COCH_2COCH_3$, MeOH/MeONa, reflux; iii, RCH_2CN, MeOH-MeONa, reflux.

10a: R_1 = COMe; R_2 = Me
b: R_1 = CO_2Et; R_2 = Me
c: R_1 = H, R_2 = Ph
d: R_1 = Me; R_2 = Me
e: R_1 = OH; R_2 = CO_2Me
f: R_1 = R_2 = -$(CH_2)_3$-
g: R_1 = R_2 = -$(CH_2)_4$-
12a: R = CN
b: R = CO_2Me

EXPERIMENTAL

Melting points were determined on a Büchi 530 or on a Gallenkamp open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer 781 instrument in potassium bromide pellets, and nmr spectra were recorded at 300 MHz on a Varian VXR 300S spectrometer. Chemical shifts are recorded in parts per million (δ) relative to TMS as internal standard. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by tlc performed on silica gel plates (Merck 60-F) and using chloroform-ethanol or toluene-ethyl acetate as the eluant.

General Procedure for the Reduction of the Aminoimidazolecarbonitriles **2** and **4**.

A mixture of the corresponding aminoimidazolecarbonitrile (18.1 mmoles), sulfuric acid (1.77 g, 18.1 mmoles) and 10% Pd/C (0.20 g) in water (30 ml) was hydrogenated in a Parr apparatus at room temperature and an initial pressure of 25 psi until the calculated amount of hydrogen was absorbed (1 hour). After removal of the catalyst, the *p*H of the filtrate was adjusted to 8 with concentrated ammonium hydroxide, and the solution was evaporated to dryness. Chromatography on silica gel with chloroform:ethanol (10:1, v/v) as the eluent yielded the corresponding aminoimidazolecarbaldehyde.

4-Amino-1,2-dimethylimidazole-5-carbaldehyde (**1**).

This compound was obtained from 4-amino-1,2-dimethylimidazole-5-carbonitrile (**2**) in a yield of 80%, yellow crystals, mp >220° (from ethanol); ir (potassium bromide): 3420, 3290, 3120 (NH_2), 2800, 1650 (aldehyde CO) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.32 (1H, s, CHO), 6.17 (2H, br s, NH_2), 3.60 (3H, s, 1-Me), 2.18 (3H, s, 2-Me).

Anal. Calcd. for $C_6H_9N_3O$ (139.07): C, 51.77; H, 6.53; N, 30.20. Found: C, 51.83; H, 6.50; N, 30.19.

5-Amino-1,2-dimethylimidazole-4-carbaldehyde (**3a**).

This compound was obtained from 5-amino-1,2-dimethylimidazole-4-carbonitrile (**4a**) in a yield of 55%, as a yellow solid, mp 222-224° dec (from ethanol); ir (potassium bromide): 3400, 3300, 3200 (NH_2), 2810, 1640 (aldehyde CO), 1590, 1540 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.35 (1H, s, CHO), 6.63 (2H, br s, NH_2), 3.38 (3H, s, 1-Me), 2.17 (3H, s, 2-Me).

Anal. Calcd. for $C_6H_9N_3O$ (139.07): C, 51.77; H, 6.53; N, 30.20. Found: C, 51.99; H, 6.42; N, 30.08.

5-Amino-1-methyl-2-phenylimidazole-4-carbaldehyde (**3b**).

This compound was obtained from 5-amino-1-methyl-2-phenylimidazole-4-carbonitrile (**4b**) in a yield of 70% as a yellow solid, mp 156-157° (from ethanol); ir (potassium bromide): 3390, 3300, 3180 (NH_2), 1640 (aldehyde CO), 1610, 1550, 1510 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.50 (1H, s, CHO), 7.60-7.63 (2H, m, 2', 6'-H), 7.42-7.45 (3H, m, 3', 4', 5'-H), 6.86 (2H, br s, NH_2), 3.43 (3H, s, 1-Me).

Anal. Calcd. for $C_{11}H_{11}N_3O$ (201.09): C, 65.64; H, 5.52; N, 20.88. Found: C, 65.60; H, 5.27; N, 20.76.

General Procedures for the Preparation of 5-Aminoimidazo-[4,5-*b*]pyridines.

A mixture of aminoimidazolecarbaldehyde (1.5 mmoles) and malononitrile or ethyl cyanoacetate (1.5 mmoles) in sodium methoxide solution (20 mg of sodium dissolved in 15 ml of methanol) was refluxed for 2 hours. The solvent was then evaporated under reduced pressure and the resulting residue was crushed with ice-water (30 ml). The solid obtained was collected by filtration, washed with water followed by ethanol and dried. The 5-aminoimidazo[4,5-*b*]pyridines were usually recrystallized from ethanol.

5-Amino-1,2-dimethyl-1*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (**5a**).

This compound was obtained from aminoimidazolcarbaldehyde **1** (208 mg, 1.5 mmoles) and malononitrile (99 mg, 1.5 mmoles) by following the above general procedure in a yield of 80%, mp >300°; ir (potassium bromide): 3460, 3360 (NH_2), 2200 (CN), 1620 (C=N), 920 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.0 (1H, s, 7-H), 6.2 (2H, br s, NH_2), 3.6 (3H, s, 1-Me), 2.5 (3H, s, 2-Me).

Anal. Calcd. for $C_9H_9N_5$ (187.08): C, 57.73; H, 4.85; N, 37.41. Found: C, 57.85; H, 5.04; N, 37.10.

5-Amino-2,3-dimethyl-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (**8a**).

This compound was obtained from aminoimidazolecarbaldehyde **3a** (208 mg, 1.5 mmoles) and malononitrile (99 mg, 1.5 mmoles) by following the above general procedure in a yield 55%, white crystals, mp >300° (from ethanol:water 2:1, v/v) [lit [11] 320°].

Methyl 5-Amino-2,3-dimethyl-3*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**8b**).

This compound was obtained from compound **3a** (208 mg,

1.5 mmoles) and ethyl cyanoacetate (169 mg, 1.5 mmoles) by following the above general procedure in a yield 55% as white crystals, mp 202-203°; ir (potassium bromide): 3400, 3290, 3190 (NH_2), 1680 (CO), 1620 (C=N), 1580 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.13 (1H, s, 7-H), 7.15 (2H, br s, NH_2), 3.77 (3H, s, Me), 3.52 (3H, s, Me), 2.42 (3H, s, 2-Me).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$ (220.10): C, 54.52; H, 5.50; N, 25.44. Found: C, 54.51; H, 5.46; N, 25.18.

5-Amino-3-methyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (**12a**).

This compound was similarly prepared from aminoimidazolecarbaldehyde **3b** (301 mg, 1.5 mmoles) by cyclocondensation reaction with malononitrile (99 mg, 1.5 mmoles) in 73% yield as white crystals, mp 251°; ir (potassium bromide): 3410, 3280, 3130 (NH_2), 2190 (CN), 1600, 1550 (C=N), 1400 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.22 (1H, s, 7-H), 7.79-7.85 (2H, m, 2', 6'-H), 7.50-7.56 (3H, m, 3', 4', 5'-H), 6.80 (2H, s, NH_2), 3.71 (3H, s, 3-Me).

Anal. Calcd. for $C_{14}H_{11}N_5$ (248.09): C, 67.72; H, 4.07; N, 28.21. Found: C, 67.74; H, 4.50; N, 28.27.

Methyl 5-Amino-3-methyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6-carboxilate (**12b**).

This compound was similarly prepared from aminoimidazolecarbaldehyde **3b** (301 mg, 1.5 mmoles) by cyclocondensation reaction with ethyl cyanoacetate (169 mg, 1.5 mmoles) in 64% yield as a white solid, mp 202-204° (from ethyl acetate); ir (potassium bromide): 3410, 3290, 3190 (NH_2), 1680 (CO), 1630, 1610, 1580 (C=N), 1410 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.54 (1H, s, 7-H), 7.75-7.82 (2H, m, 2', 6'-H), 7.50-7.57 (3H, m, 3', 4', 5'-H), 6.55 (2H, br s, NH_2), 3.92 (3H, s, Me), 3.81 (3H, s, Me).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$ (282.11): C, 63.81; H, 5.01; N, 19.85. Found: C, 64.03; H, 5.04; N, 19.89.

Ethyl 5-Amino-1,2-dimethyl-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**5b**).

Aminoimidazolecarbaldehyde **1** (160 mg, 1.1 mmoles) and ethyl cyanoacetate (125 mg, 1.1 mmoles) were added to a solution of sodium (20 mg) in ethanol (15 ml). The reaction mixture was heated at reflux for 2 hours. The solvent was then evaporated under reduced pressure, the resulting residue was added into ice-water (30 ml). The solid obtained was collected by filtration and recrystallized from ethanol to yield 121 mg (47%) of **5b**, mp 244-246°; ir (potassium bromide): 3440, 3300, 3180 (NH_2), 1700 (CO), 1650, 1620 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.1 (1H, s, 7-H), 6.8 (2H, br s, NH_2), 4.3 (2H, c, OCH_2CH_3), 3.7 (3H, s, 1-Me), 2.5 (3H, s, 2-Me), 1.3 (3H, t, OCH_2CH_3).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$ (234.11): C, 56.39; H, 6.03; N, 23.94. Found: C, 56.05; H, 6.29; N, 24.01.

General Procedure for the Cyclization Reactions of Compound **1** with Active Methylene Compounds.

A mixture of compound **1** (1.5 mmoles) and the corresponding methylene compound (1.5 mmoles) in glacial acetic acid (10 ml) was refluxed for 10 hours. After cooling, the reaction mixture was concentrated under reduced pressure, neutralized with dilute ammonium hydroxide and evaporated to dryness. The resulting residue was submitted to silica gel column chromatography. Elution with chloroform:ethanol (10:1, v/v) gave a crystalline substance identified as the corresponding imidazopyridine.

1,2-Dimethyl-5-phenyl-1*H*-imidazo[4,5-*b*]pyridine (**6a**).

This compound was obtained from compound **1** (208 mg, 1.5 mmoles) and acetophenone (180 mg, 1.5 mmoles) by following the above general procedure in 26% yield, mp >220°; ^1H nmr (deuteriochloroform): δ 8.14 (1H, dd, J = 8 Hz, 6, 7-H); 7.65 (2H, c, 2', 6'-H); 7.35-7.45 (3H, m, 3', 4', 5'-H); 3.76 (3H, s, 1-Me), 2.67 (3H, s, 2-Me).

Anal. Calcd. for $C_{14}H_{13}N_3$ (223.11): C, 75.30; H, 5.88; N, 18.82. Found: C, 75.38; H, 5.86; N, 18.95.

1,2,5,6-Tetramethyl-1*H*-imidazo[4,5-*b*]pyridine (**6b**).

This compound was prepared by condensation of compound **1** (208 mg, 1.5 mmoles) with methyl ethyl ketone (108 mg, 1.5 mmoles) in 32% yield; ir (potassium bromide): 1600, 1560, 1510, 1470, 1280, 1000 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.29 (1H, s, 7-H), 3.68 (3H, s, 1-Me), 2.59 (3H, s, Me), 2.57 (3H, s, Me), 2.38 (3H, s, Me).

Anal. Calcd. for $C_{10}H_{13}N_3$ (175.11): C, 68.53; H, 7.49; N, 23.98. Found: C, 68.19; H, 7.51; N, 23.80.

1,2-Dimethylcyclopenta[*e*]-1*H*-imidazo[4,5-*b*]pyridine (**6e**).

This compound was similarly prepared from aminoimidazolecarbaldehyde **1** (208 mg, 1.5 mmoles) by cyclocondensation reaction with cyclopentanone (126 mg, 1.5 mmoles) in 21% yield, mp 221° dec (from toluene-ethanol); ir (potassium bromide): 1600, 1570, 1520, 1400, 1320, 1260 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.37 (1H, s, 8-H), 3.68 (3H, s, 1-Me), 3.08 (2H, t, 5-H), 3.00 (2H, t, 7-H), 2.60 (3H, s, 2-Me), 2.17 (2H, q, 6-H).

Anal. Calcd. for $C_{11}H_{13}N_3$ (187.11): C, 70.56; H, 7.00; N, 22.44. Found: C, 70.18; H, 7.11; N, 22.80.

Ethyl 1,2,5-Trimethyl-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**6c**).

A solution of compound **1** (208 mg, 1.5 mmoles) and ethyl acetoacetate (195 mg, 1.5 mmoles) in glacial acetic acid (15 ml) was refluxed for 10 hours. After cooling, the solution was concentrated under reduced pressure and neutralized with ammonium hydroxide. The resulting suspension was kept in the refrigerator overnight. The deposited white crystals were filtered off and washed with water, to give 220 mg of **6c**, mp 168° (from ethanol); ir (potassium bromide): 3600-3000 (OH), 1710 (CO), 1620, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.18 (1H, s, 7-H), 4.41 (2H, c, J = 7 Hz, OCH_2CH_3), 3.78 (3H, s, 1-CH_3), 2.93 (3H, s, CH_3), 2.67 (3H, s, CH_3), 1.44 (3H, t, J = 7 Hz, OCH_2CH_3).

Anal. Calcd. for $C_{12}H_{15}N_3O_2 \cdot 3/2H_2O$ (260.12): C, 55.36; H, 6.98; N, 16.16. Found: C, 55.26; H, 6.97; N, 16.16.

6-Acetyl-1,2,5-trimethyl- 1*H*-imidazo[4,5-*b*]pyridine (**6d**).

This compound was prepared in 35% yield from the compound **1** (208 mg, 1.5 mmoles) and acetylacetone (150 mg, 1.5 mmoles) by a procedure analogous to that described above for the preparation of **6c**. The product was recrystallized from ethanol-ethyl acetate, as light yellow needles, mp 193-195° dec; ir (potassium bromide): 1680 (CO), 1620, 1550, 1500 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.41 (1H, s, 7-H), 3.80 (3H, s, 1-Me), 2.67 (3H, s, Me), 2.64 (3H, s, Me), 2.58 (3H, s, Me).

Anal. Calcd. for $C_{11}H_{13}N_3O$ (203.10): C, 64.99; H, 6.46; N, 20.68. Found: C, 64.49; H, 6.41; N, 20.43.

1,2-Dimethyl-5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*b*]quinoline (**6f**).

A solution of compound **1** (208 mg, 1.5 mmoles) and cyclohexanone (196 mg, 2.0 mmoles) in glacial acetic acid (15 ml) was refluxed for 10 hours. After removal of most of the acetic acid under reduced pressure, the resulting residue was dissolved in dilute ammonium hydroxide (20 ml) and the aqueous solution was extracted with ethyl acetate (20 x 20 ml). The extracts were combined, dried (potassium carbonate), and evaporated under reduced pressure to give an oil which set to a solid mass on cooling. The resulting solid was collected and recrystallization from toluene to give the product **6f** in 71% yield, mp 157-160°; ir (potassium bromide): 1610, 1590, 1560, 1430, 1370, 1280, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.28 (1H, s, 9-H), 3.67 (3H, s, 1-Me), 3.04 (2H, t, 5-H), 2.90 (2H, t, 8-H), 2.59 (3H, s, 2-Me), 1.80-1.96 (4H, m, 6,7-H).

Anal. Calcd. for $C_{12}H_{15}N_3$ (201.13): C, 71.59; H, 7.53; N, 20.88. Found: C, 71.31; H, 7.88; N, 20.43.

Ethyl 2,3,5-Trimethyl-3*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**9**).

Compound **3a** (208 mg, 1.5 mmoles) and ethyl acetoacetate (169 mg, 1.5 mmoles) were added in glacial acetic acid (15 ml). The mixture was refluxed for 3 hours. After cooling, the reaction mixture was concentrated under reduced pressure to give a residue, which was dissolved in dilute ammonium hydroxide (30 ml), and then extracted with ethyl acetate. The extracts were concentrated under reduced pressure to give a residue, which was subject to silica gel column chromatography. Elution with chloroform-ethanol (15:1, v/v) gave ethyl 2,3,5-trimethylimidazo[4,5-*b*]pyridine-6-carboxylate (**9**) (168 mg, 48%); ir (potassium bromide): 1720 (CO), 1610, 1520 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.48 (1H, s, 7-H), 4.40 (2H, c, OCH_2CH_3), 3.81 (3H, s, 3-Me), 2.92 (3H, s, Me), 2.64 (3H, s, Me), 1.42 (3H, t, OCH_2CH_3).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$ (233.11): C, 61.77; H, 6.49; N, 18.02. Found: C, 61.79; H, 6.48; N, 17.68.

2,3-Dimethyl-6-methoxycarbonyl-3*H*-imidazo[4,5-*b*]pyridin-5(4*H*)-one (**7**).

Compound **3a** (208 mg, 1.5 mmoles) and diethyl malonate (240 mg, 1.5 mmoles) were dissolved in a solution of sodium methoxide/methanol, prepared from sodium (20 mg) and dry methanol (20 ml). The solution was refluxed for 10 hours. After cooling, the reaction mixture was neutralized with 10% acetic acid, and concentrated under reduced pressure to give a residue, which was extracted with chloroform. The chloroform extract was concentrated under reduced pressure to give a crystalline substance, which was recrystallized from ethyl acetate to furnish the 2,3-dimethyl-6-methoxycarbonyl-3*H*-imidazo[4,5-*b*]-pyridin-5(4*H*)-one (**7**) (222 mg, 67%), mp 150-153°; ir (potassium bromide): 1710 (CO), 1680 (CO), 1620, 1590, 1530 cm^{-1}; ^1H nmr (deuteriochloroform): δ 11.80 (1H, br s, NH), 8.44 (1H, s, 7-H), 4.01 (3H, s, Me), 3.75 (3H, s, Me), 2.61 (3H, s, 2-Me).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$ (221.08): C, 54.28; H, 5.02; N, 18.99. Found: C, 53.97; H, 5.00; N, 18.59.

6-Acetyl-3,5-dimethyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (**10a**).

A solution of compound **3b** (302 mg, 1.5 mmoles) and acetylacetone (150 mg, 1.5 mmoles) in glacial acetic acid (15 ml) was heated under reflux (10 hours). The cooled reaction was neutralized with dilute ammonium hydroxide, and the mixture was extracted with chloroform (4 x 20 ml). The combined extracts were washed with water (2 x 20 ml), dried (magnesium sulfate) and evaporated under reduced pressure. Column chromatography of the residue using silica gel (15 g) and elution with ethyl acetate:toluene (3:1, v/v) gave a solid product, which was recrystallized from ethanol, and identified as **10a** (171 mg, 45%); ir (potassium bromide): 1670 (CO), 1610, 1570, 1490 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.44 (1H, s, 7-H), 7.83-7.85 (2H, m, 2', 6'-H), 7.56-7.59 (3H, m, 3', 4', 5'-H), 4.00 (3H, s, 3-Me), 2.90 (3H, s, CH_3CO), 2.69 (3H, s, 5-Me).

Anal. Calcd. for $C_{15}H_{15}N_3O$ (253.12): C, 71.12; H, 5.58; N, 16.59. Found: C, 71.00; H, 5.76; N, 16.36.

Ethyl 3,5-Dimethyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**10b**).

Similarly, the cyclization of the compound **3b** (302 mg, 1.5 mmoles) with ethyl acetoacetate (195 mg, 1.5 mmoles) gave ethyl 3,5-dimethyl-2-phenylimidazo[4,5-*b*]pyridine-6-carboxylate (**10b**) (133 mg, 30%), mp 109-110° (from ethanol); ir (potassium bromide): 1730 (CO), 1610, 1580, 1490, 1380, 1260, 1220, 1070 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.64 (1H, s, 7-H), 7.82-7.86 (2H, m, 2', 6'-H), 7.55-7.57 (3H, m, 3', 4', 5'-H), 4.41 (2H, c, OCH_2CH_3), 3.99 (3H, s, 3-Me), 2.97 (3H, s, 5-Me), 1.43 (3H, t, OCH_2CH_3).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$ (295.13): C, 69.12; H, 5.81; N, 14.23. Found: C, 68.89; H, 5.76; N, 14.06.

General Procedure for the Cyclization Reactions of Compound **3b** with Active Methylene Compounds.

A mixture of compound **3b** (1.5 mmoles) and the corresponding methylene compound (1.5 mmoles) were dissolved in a solution of sodium methoxide-methanol, prepared from sodium (20 mg) and dry methanol (15 ml). The mixture was refluxed for 10 hours. After cooling, the reaction mixture was poured into water (30 ml), stirred, and extracted with chloroform (4 x 20 ml). The chloroform extract was concentrated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with toluene:ethyl acetate (2:1, v/v) yielded the corresponding imidazopyridine.

2,5-Diphenyl-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**10c**).

This compound was obtained from compound **3b** (302 mg, 1.5 mmoles) and acetophenone (180 mg, 1.5 mmoles) by following the above general procedure in 34% yield, as white needles, mp 190-191° (from ethyl acetate-hexane); ^1H nmr (deuteriochloroform): δ 8.12 (1H, d, J = 8 Hz, 7-H), 8.10-7.85 (4H, m, phenyl protons), 7.75 (1H, d, J = 8 Hz, 6-H), 7.40-7.60 (6H, m, phenyl protons), 4.06 (3H, s, 3-Me).

Anal. Calcd. for $C_{19}H_{15}N_3$ (285.13): C, 79.96; H, 5.31; N, 14.73. Found: C, 79.40; H, 5.50; N, 14.31.

2-Phenyl-3,5,6-trimethyl-3*H*-imidazo[4,5-*b*]pyridine (**10d**).

This compound was obtained from compound **3b** (302 mg, 1.5 mmoles) and ethyl methyl ketone (108 mg, 1.5 mmoles) by following the above general procedure in 32% yield, mp 123-125° (from ethyl acetate-hexane); ir (potassium bromide): 1610, 1580, 1490, 1470, 1400, 1390, 1290, 1030, 780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.79-7.83 (3H, m, 7-H, 2', 6'-H),

7.51-7.54 (3H, m, 3', 4', 5'-H), 3.96 (3H, s, 3-Me), 2.62 (3H, s, Me), 2.42 (3H, s, Me).

Anal. Calcd. for $C_{15}H_{15}N_3$ (237.13): C, 75.91; H, 6.38; N, 17.71. Found: C, 75.55; H, 6.32; N, 17.66.

2-Phenyl-3-methyl-5,6,7,8-tetrahydro-3*H*-imidazo[4,5-*b*]quinoline (**10g**).

This compound was obtained from **3b** (302 mg, 1.5 mmoles) and cyclohexanone (139 mg, 1.5 mmoles) by following the above general procedure, by refluxing for 7 hours in 41% yield), mp 134-135° (from ethyl acetate); ir (potassium bromide): 1600, 1580, 1490, 1390, 1280, 920, 780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.80-7.83 (2H, m, 2', 6'-H), 7.73 (1H, s, 9-H), 7.50-7.56 (3H, m, 3', 4', 5'-H), 3.94 (3H, s, 3-Me), 3.07 (2H, t, 5-H), 2.95 (2H, t, 8-H), 1.82-2.00 (4H, m, 6, 7-H).

Anal. Calcd. for $C_{17}H_{17}N_3$ (263.14): C, 77.52; H, 6.52; N, 15.96. Found: C, 77.16; H, 6.55; N, 15.94.

2-Phenyl-3-methylcyclopenta[*e*]-3*H*-imidazo[4,5-*b*]pyridine (**10f**).

This compound was obtained from **3b** (302 mg, 1.5 mmoles) and cyclopentanone (126 mg, 1.5 mmoles) by following the above general procedure, by refluxing for 5 hours in 27% yield, as white needles, mp 182° (from ethanol); ir (potassium bromide): 1600, 1570, 1460, 1400, 1270, 920 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.86 (1H, s, 8-H), 7.85-7.78 (2H, m, 2', 6'-H), 7.58-7.50 (3H, m, 3', 4', 5'-H), 3.97 (3H, s, 3-Me), 3.13 (2H, t, 5-H), 3.06 (2H, t, 7-H), 2.23 (2H, q, 6-H).

Anal. Calcd. for $C_{16}H_{15}N_3$ (249.13): C, 77.07; H, 6.08; N, 16.86. Found: C, 76.86; H, 6.16; N, 16.77.

Methyl 5-Hydroxy-2-phenyl-3-methyl-3*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**10e**).

Compound **3b** (250 mg, 1.2 mmoles) and diethyl malonate (192 mg, 1.2 mmoles) were dissolved in a solution of sodium methoxide-methanol, prepared from sodium (20 mg) and dry methanol (15 ml). The solution was refluxed for 5 hours. The reaction mixture was concentrated under reduced pressure to give a crystalline solid, which was filtered, and dissolved in a small amount of water. The aqueous solution was neutralized with dilute acetic acid. The solid which formed upon cooling was collected, recrystallized from ethanol and identified as compound **10e** (248 mg, 73%), mp 158-160°; ir (potassium bromide): 2800-3200 (OH), 1670 (CO), 1630, 1600 (C=N), 1450, 1400, 1350, 1250 cm^{-1}; ^1H nmr (deuteriochloroform): δ 11.86 (1H, s, OH), 8.57 (1H, s, 7-H), 7.75-7.82 (2H, m, 2', 6'-H), 7.55-7.65 (3H, m, 3', 4', 5'-H), 4.03 (3H, s, Me), 3.91 (3H, s, Me).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$ (283.09): C, 63.59; H, 4.63; N, 14.83. Found: C, 63.59; H, 4.72; N, 14.97.

3,5-Dimethyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (**11**).

(1) By Cyclization with Ethyl Acetoacetate.

To a solution of sodium (20 mg) in dry methanol (15 ml), 4-amino-3-methyl-2-phenylimidazole-5-carbaldehyde (302 mg, 1.5 mmoles) and ethyl acetoacetate (195 mg, 1.5 mmoles) were added. The reaction mixture was stirred at room temperature for 24 hours. Water (30 ml) was then added to the mixture, and this aqueous mixture was extracted with chloroform (4 x 25 ml). The chloroform extracts were combined, dried (magnesium sulfate), and evaporated under reduced pressure to give a residue. Column chromatography of this residue using silica gel (15 g) and elution with toluene:ethyl acetate (2:1, v/v) yielded compound **11** (201 mg, 60%), mp 144° (from ethyl acetate-hexane); ir (potassium bromide): 1590, 1480, 1390, 1270, 830, 800 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.95 (1H, d, J = 8 Hz, 7-H), 7.81-7.84 (2H, m, 2', 6'-H), 7.52-7.55 (3H, m, 3', 4', 5'-H), 7.12 (1H, d, J = 8 Hz, 6-H), 3.97 (3H, s, 3-Me), 2.70 (3H, s, 5-Me).

Anal. Calcd. for $C_{14}H_{13}N_3$ (223.11): C, 75.30; H, 5.88; N, 18.82. Found: C, 75.23; H, 6.04; N, 18.79.

(2) By Cyclization with Acetylacetone.

In a similar procedure the cyclocondensation reaction of **3b** (302 mg, 1.5 mmoles) with acetylacetone (150 mg, 1.5 mmoles) gave compound **11** (161 mg, 48%), which was identified by comparison with an authentic sample.

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