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An Aminoimidazole and Its Utility in Heterocyclic Synthesis

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ABSTRACT: *Aminoacetonitrile (**1**) reacted with acetamidinium chloride to give 4-aminoimidazole (**4**), which reacted with DMFDMA to yield imidazole derivative **7** and with benzylidinemalononitrile and ethoxymethylene malononitrile to give imidazo[1,5-a]pyrimidine derivatives **12** and **15**. Compound **1** reacted with β-crotononitrile to yield pyridine derivative **20**. Imidazo[1,2-a]pyridine derivative **23** could be obtained via the reaction of **20** with DMFDMA.*
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INTRODUCTION

The aminoimidazole ring structure is of particular interest especially within the realms of medicinal chemistry. Several classes of marine natural products possessing this structure were recently discovered and identified [1–7]. Many of these compounds display biological activities including antibacterial, anti-inflammatory, anticancer, and antiviral activity. Synthetic aminoimidazole derivatives, including aminohistamine, have been shown to have H_1- and H_2-receptor agonist and antagonist activity [8–12]. Other unrelated aminoimidazole derivatives are selective 5-HT_3 receptor antagonists, which are potentially useful in the treatment of chemotherapy-induced emesis [12].

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Novel cephalosporins with incorporated aminoimidazole rings display both Gram-positive and Gram-negative antibacterial activity as well as good β-lactamase stability [13]. In addition, aminoimidazole can serve as an important starting material in the preparation of azomycin, a naturally occurring antibiotic [14–17].

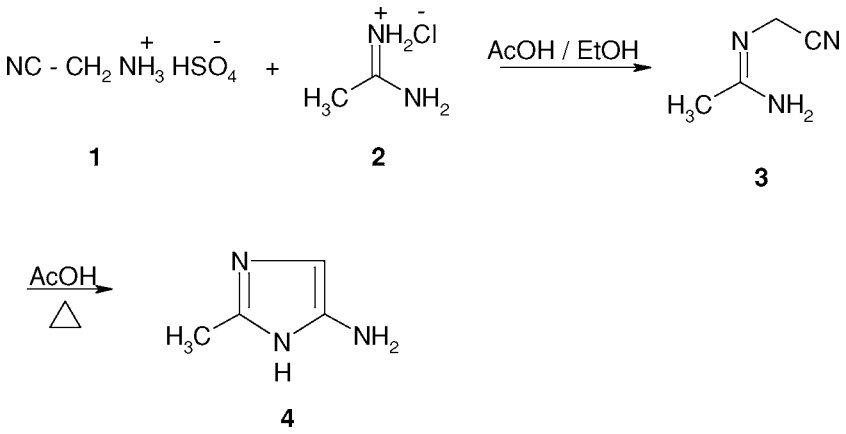
We try to develop convenient syntheses of biologically active heterocycles [18–20].

RESULTS AND DISCUSSION

Treatment of aminoacetonitrile (**1**) with acetamidinium chloride (**2**) in an ethanol/AcOH mixture afforded *N*-cyanomethyl-acetamidine (**3**). Compound **3** could be cyclized on refluxing AcOH to give the target 4-aminoimidazole (**4**) (Scheme 1).

It reacted readily with a variety of electrophiles to give unique heterocyclic compounds. Thus, it coupled with phenyldiazonium salt to give the diazo amino compound **5** as a major and the *N*-phenylimidazole (**6**) as a minor product [21], which prove that the amino group is the most nucleophilic center in the molecule. After reacting the amino group with dimethylformamide dimethylacetal (DMFDMA) to give **7**, all the coupling trials failed. Treatment with aniline **7** gave **9** (Scheme 2).

Furthermore, **4** reacted with benzylidenemalononitrile (**10**) to yield imidazo[1,5-*a*]pyrimidine derivative **12**. This product is assumed to be formed via addition of the amino group in **4** to the double bond in **10** to yield a Michael adduct **11**, which then cyclizes and autoxidizes to **12**. Similar autoxidation has been previously reported [22,23]. Compound

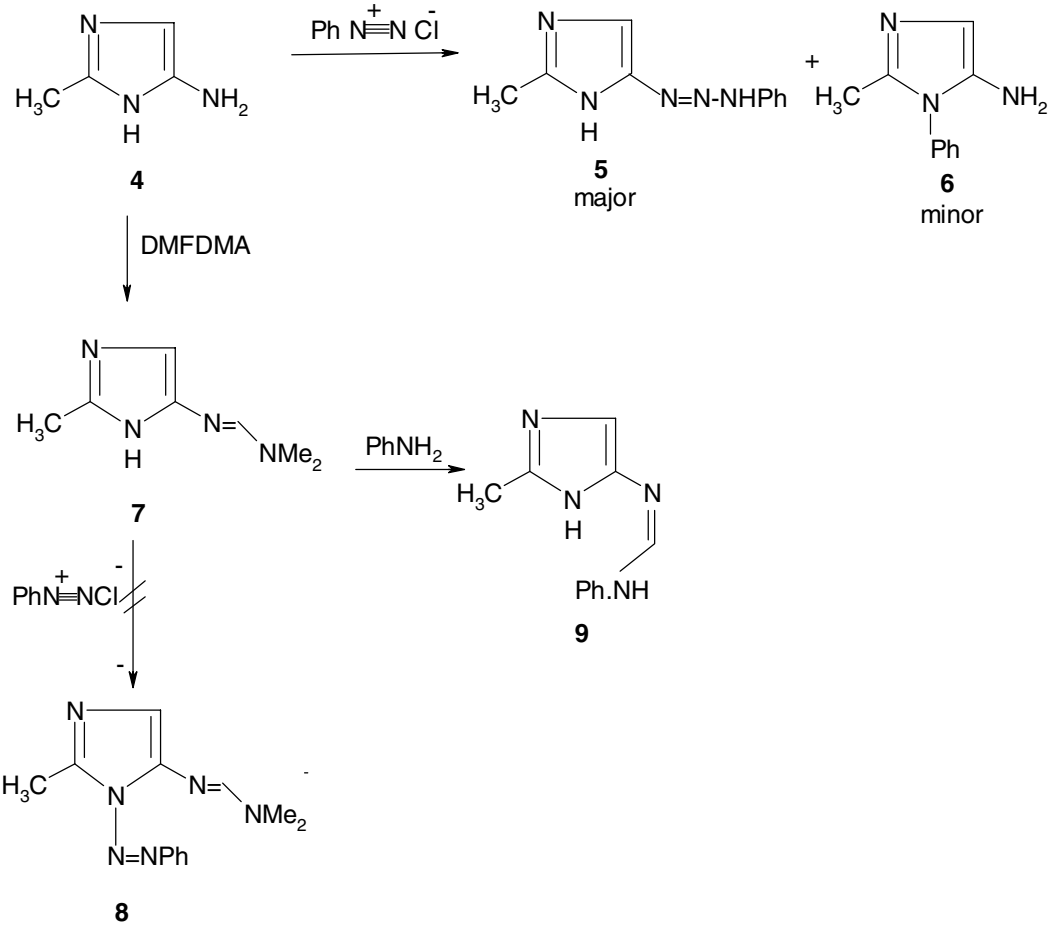


1 **2** **3** **4**

SCHEME 1

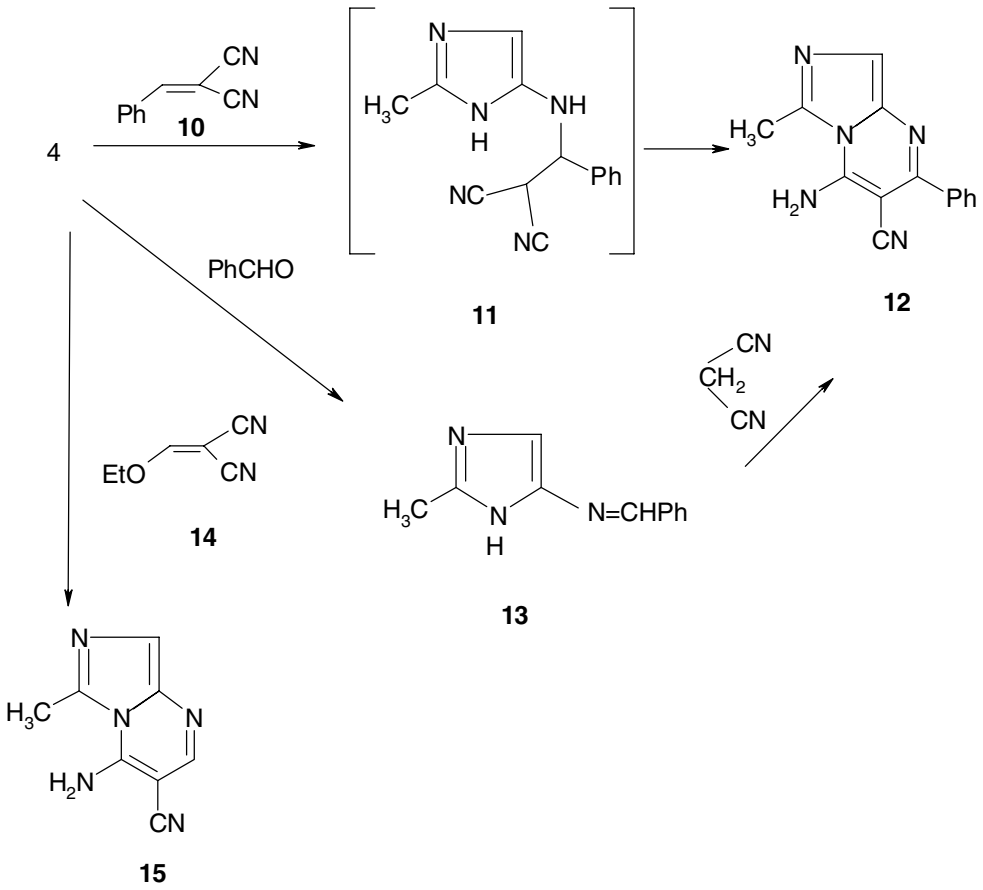
12 could also be obtained via reaction of **4** with benzaldehyde and subsequent addition of malononitrile to the so-formed Schiff's base derivative **13**. Similarly, compound **15** could be obtained on treatment of **4** with ethoxymethylene malononitrile **14** (Scheme 3).

Attempts to prepare the 1:1 condensation 4-aminopyrrole derivative **18** via the reaction of



4 **5** major **6** minor **7** **8** **9**

SCHEME 2



SCHEME 3

aminoacetonitrile (**1**) with β-aminocrotononitrile (**16**) failed; the reaction gave the 1:2 condensate product **20** instead. The reaction is believed to proceed via the acyclic 1:2 condensation intermediate **19** (Scheme 4).

Compound **20** could be further cyclized to 2-aminoimidazo[1,2-*a*]pyridine derivative **21** by boiling in basic medium.

Imidazo[1,2-*a*]pyridine derivative **23** could be obtained via reaction of **20** with DMFDMA. The reaction proceeds via the intermediate enamine derivative **22** (Scheme 5).

EXPERIMENTAL

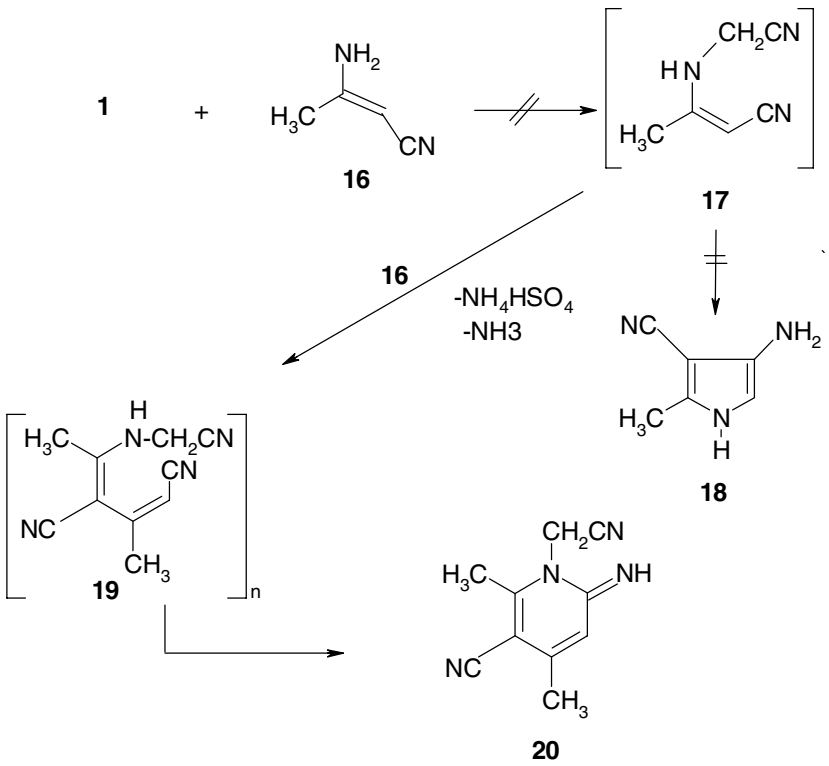
All melting points are uncorrected. IR spectra were recorded (KBr disc) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian EM-390 spectrometer in [$^2H_6$] DMSO as solvent and TMS as internal reference; chemical shifts δ are reported in ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Microanalytical data were obtained from the microanalytical data unit at Cairo University.

*Acetamidinoacetonitrile (**3**)*

A solution of aminoacetonitrile (**1**) (0.01 mol) and acetamidinium chloride (**2**) (0.01 mol) was stirred overnight in ethanol/AcOH for 2 h. The solvent was removed and the solid product, so formed, was collected by filtration and crystallized from ethanol. Yield: 68%; m.p. 116°C. IR (KBr): $\nu = 3350$ (NH_2); 2210 (CN). ^{1}H NMR: $\delta = 2.40$ (s, 3H, CH_3); 3.81 (s, 2H, CH_2), 5.61 (s, 2H, NH_2). $C_4H_7N_3$ (97.14): calcd C 49.45, H 7.28, N 43.27; found C 49.72, H 7.51, N 43.50.

*5-Amino-2-methyl-1H-imidazole (**4**)*

A solution of **3** (0.01 mol) in acetic acid was refluxed for 2 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from ethanol. Yield: 70%; m.p. 165°C. IR (KBr): $\nu = 3400$–3350 (NH, NH_2). ^{1}H NMR: $\delta = 2.04$ (s, 3H, CH_3); 6.36

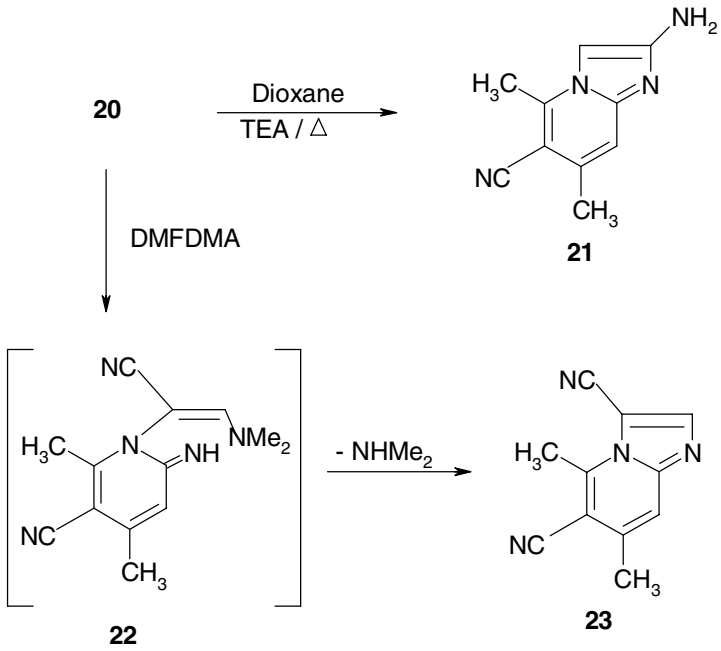


SCHEME 4

(s, 1H, imidazole-H), 7.29 (br s, 2H, NH_2), 10.91 (br s, 1H, NH). ^{13}C NMR: (300 MHz, DMSO): $\delta = 154.92$ (C-2), 129.24 (C-4), 119.37 (C-5), 29.14 (CH_3). $C_4H_7N_3$ (97.14): calcd C 49.45, H 7.28, N 43.27; found C 49.61, H 7.43, N 43.51.

Diazotization of **4**

Phenyldiazonium chloride (0.01 mol) was added to a cold mixture of **4** (0.01 mol) and sodium acetate trihydrate (5 g) in EtOH (30 ml). The mixture was



SCHEME 5

stirred for 30 min, water was then added, and the precipitate formed was filtered off and recrystallized from ethanol.

*2-Methyl-5-phenyldiazoamino-1H-imidazole (**5**)*

Yield: 80%; m.p. 181°C. IR (KBr): $\nu = 3350$ (NH). ^{1}H NMR: $\delta = 2.04$ (s, 3H, CH_3), 6.36 (s, 1H, imidazole-H), 7.81–7.93 (m, 5H, phenyl-H); 10.91 (s, 1H, NH), 11.95 (s, 1H, NH). $C_{10}H_{11}N_5$ (201.26): calcd C 59.67, H 5.52, N 34.8; found C 59.72, H 5.74, N 34.62.

*5-Amino-2-methyl-1-phenylimidazole (**6**)*

Yield: 20%; m.p. 201°C. IR (KBr): $\nu = 3440$, 3350 (NH_2). ^{1}H NMR: $\delta = 2.03$ (s, 3H, CH_3); 6.36 (s, 1H, imidazole-H), 7.29 (br s, 2H, NH_2), 7.34–7.65 (m, 5H, phenyl-H). $C_{10}H_{11}N_3$ (173.34): calcd C 69.33, H 6.41, N 24.26; found C 69.51, H 6.52, N 24.53.

*5-(N,N-Dimethylaminomethylidineamino-2-methyl-1H-imidazole (**7**)*

A mixture of compound **4** (0.01 mol) and DMFDMA (0.01 mol) was refluxed in dioxane (20 ml) for 3 h. The reaction mixture was partially concentrated. The solid obtained was collected by filtration and recrystallized from ethanol. Yield: 68%; m.p. 213°C. IR (KBr): $\nu = 3210$ (NH). ^{1}H NMR: $\delta = 2.03$ (s, 3H, CH_3); 2.51 (s, 6H, NMe_2); 3.5 (s, 1H, —N=CH—); 6.58 (s, 1H, imidazole-H); 10.92 (s, 1H, NH). $C_7H_{12}N_4$ (152.23): calcd C 55.23, H 7.96, N 36.81; found C 55.51, H 8.10, N 36.94.

*5-Anilinomethylidineamino-2-methyl-1H-imidazole (**9**)*

A mixture of **7** (0.01 mol) and aniline (0.01 mol) was refluxed in ethanol (20 ml) for 3 h, and then left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from ethanol. Yield: 66%; m.p. 193°C. IR (KBr): $\nu = 3250$ (NH). ^{1}H NMR: $\delta = 2.05$ (s, 3H, CH_3); 3.40 (s, 1H, —N=CH—); 6.82 (s, 1H, imidazole-H), 7.63–7.82 (m, 5H, phenyl-H); 9.05 (br s, 1H, NH); 10.91 (s, 1H, NH). $C_{11}H_{12}N_4$ (200.27): calcd C 65.97, H 6.05, N 27.98; found C 66.10, H 6.31, N 28.23.

*4-Amino-6-methyl-2-phenylimidazo[1,5-a]pyrimidine-3-carbonitrile (**12**)*

Method A. A mixture of **4** (0.01 mol) and benzylidenemalononitrile (**10**) (0.01 mol) was refluxed in ethanol in the presence of triethylamine (3 ml) for 3 h. The solvent was removed and the solid product, so formed, was collected by filtration and recystallized from ethanol. Yield: 66%; m.p. 243°C. IR (KBr): $\nu = 3350$, 3220 (NH_2), 2210 (CN). ^{1}H NMR: $\delta = 2.04$ (s, 3H, CH_3); 6.24 (s, 1H, imidazole-H), 6.24 (br s, 2H, NH_2); 7.63–7.81 (m, 5H, phenyl-H). $C_{14}H_{11}N_5$ (249.31): calcd C 67.37, H 4.41, N 28.07; found C 67.51, H 4.42, N 28.31.

*Method B (Via 5-Benzylideneamino-2-methylimidazole (**13**)).* A mixture of **4** (0.01 mol) and benzaldehyde (0.02 ml) was refluxed in ethanol and in the presence of triethylamine (3 ml) for 3 h. The solid product, so formed, was collected by filtration and recrystallizd from ethanol Yield: 61%; m.p. 198°C. IR (KBr): $\nu = 3350$ (NH). ^{1}H NMR: $\delta = 2.10$ (s, 3H, CH_3), 6.24 (s, 1H, imidazole-H), 6.5 (s, 1H, —N=CH) 7.4–7.6 (m, 5H, phenyl-H), 10.91 (s, 1H, NH). $C_{11}H_{11}N_3$ (185.25): calcd C 71.3, H 5.9, N 22.68; found C 71.50, H 6.11, N 22.75.

A solution of **13** (0.01 mol) in ethanol (20 ml) and in the presence of triethylamine (5 ml) was refluxed with malononitrile (0.01 mol) for 3 h. The solid product, so formed, was collected by filtration and recrystallized from ethanol.

*4-Amino-6-methylimidazo[1,5-a]pyrimidine-3-carbonitrile (**15**)*

A mixture of **4** (0.01 mol) and ethoxymethylenemalononitrile (**14**) (0.01 mol) in ethanol (20 ml) in the presence of triethylamine (3 ml) was refluxed for 3 h. The solid product, so formed, was collected by filtration and recrystallized from ethanol. Yield: 68%; m.p. 234°C. IR (KBr): $\nu = 3350$ (NH_2), 2210 (CN). ^{1}H NMR: $\delta = 2.04$ (s, 3H, CH_3), 6.52 (s, 1H, imidazole-H), 6.81 (s, 1H, pyrimidine-H); 7.29 (br s, 2H, NH_2). $C_8H_7N_5$ (173.2): calcd C 55.47, H 4.08, N 40.4; found C 55.61, H 4.20, N 40.63.

*1-Cyanomethyl-2,4-dimethyl-1,6-dihydro-6-iminopyridine-3-carbonitrile (**20**)*

A mixture of **1** (0.01 mol) and β-aminocrotononitrile (**16**) (0.02 mol) in ethanol (20 ml) was refluxed in the presence of sodium hydroxide (5 g) for 3 h. The solid product, so formed, was collected by filtration and recrystallized from ethanol. Yield: 63%; m.p. 135°C. IR (KBr): $\nu = 3350$ (NH), 2210, 2218 (2CN). ^{1}H NMR: $\delta = 2.10$ (s, 3H, 4-methyl), 2.41 (s, 3H, 2-methyl), 4.20 (s, 2H, —CH_2CN), 6.8 (s, 1H, pyridine-H), 10.81 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO): $\delta = 165.95$ (C-6), 144.31 (C-5), 139.25 (C-3), 125.98 (C-2), 124.28 (C-4), 121.73 (CN), 116.64 (CN), 33.48 (CH_2), 21.01 (CH_3), 20.52 (CH_3). MS (EI, 70 eV): $m/z = 186$ [M^+].

$C_{10}H_{10}N_4$ (186.23): calcd C 64.51, H 5.37, N 30.10; found C 64.82, H 5.2, N 30.15.

*2-Amino-5,7-dimethylimidazo[1,2-a]pyridine-6-carbonitrile (**21**)*

A solution of **20** (0.01 mol) in dioxane (20 ml) in the presence of triethylamine (3 ml) was refluxed for 3 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from ethanol. Yield: 71%; m.p. 228°C. IR (KBr): $\nu = 3400$, 3220 (NH_2), 2210 (CN). ^{1}H NMR: $\delta = 2.10$ (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.52 (s, 1H, imidazole-H), 6.80 (s, 1H, pyridine-H), 7.29 (br s, 2H, NH2). $C_{10}H_{10}N_4$ (186.25): calcd C 64.5, H 5.3, N 30.10; found C 64.63, H 5.5, N 30.34.

*5,7-Dimethylimidazo[1,2-a]pyridine-3,6-dicarbonitrile (**23**)*

A mixture of **20** (0.01 mol) and DMFDMA (0.01 mol) was refluxed in dioxan (20 ml) for 3 h. The solid product, so formed, was collected by filtration and recystallized from ethanol. Yield: 63%; m.p. 210°C. IR (KBr): $\nu = 2210$, 2218 (2 CN). ^{1}H NMR: $\delta = 2.10$ (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.54 (s, 1H, imidazole-H), 6.84 (s, 1H, pyridine-H). $C_{11}H_8N_4$ (196.23): calcd C 67.32, H 4.12, N 28.56; found C 67.51, H 4.5, N 28.71.

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