

# An Aminoimidazole and Its Utility in Heterocyclic Synthesis

Yehya M. Elkholy<sup>1</sup> and Ayman W. Erian<sup>2</sup>

<sup>1</sup>Department of Chemistry, Faculty of Science, Helwan University, Cairo, Ain-Helwan, Egypt

<sup>2</sup>Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Received 14 February 2003

**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  $\beta$ -crotononitrile to yield pyridine derivative **20**. Imidazo[1,2-*a*]pyridine derivative **23** could be obtained via the reaction of **20** with DMFDMA.  
© 2003 Wiley Periodicals, Inc. *Heteroatom Chem* 14:503–508, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10178

## 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<sub>1</sub>- and H<sub>2</sub>-receptor agonist and antagonist activity [8–12]. Other unrelated aminoimidazole derivatives are selective 5-HT<sub>3</sub> receptor antagonists, which are potentially useful in the treatment of chemotherapy-induced emesis [12].

Novel cephalosporins with incorporated aminoimidazole rings display both Gram-positive and Gram-negative antibacterial activity as well as good  $\beta$ -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].

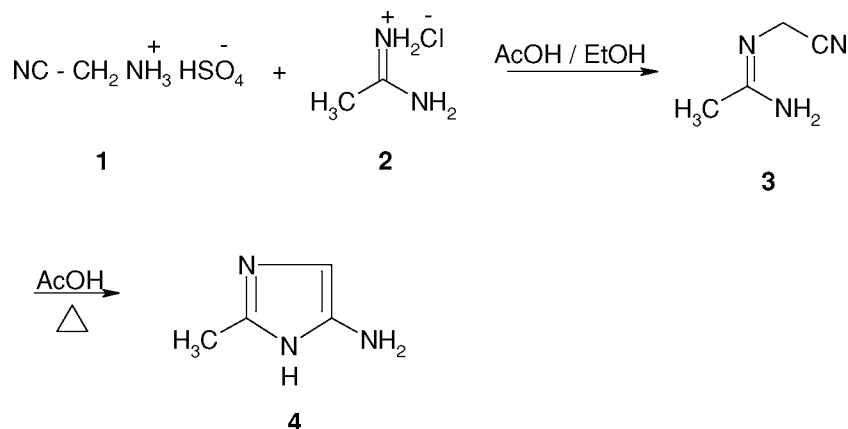
## RESULTS AND DISCUSSION

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 benzylidene-malononitrile (**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

Correspondence to: Yehya M. Elkholy; e-mail: y.elkholy@yahoo.com.  
© 2003 Wiley Periodicals, Inc.

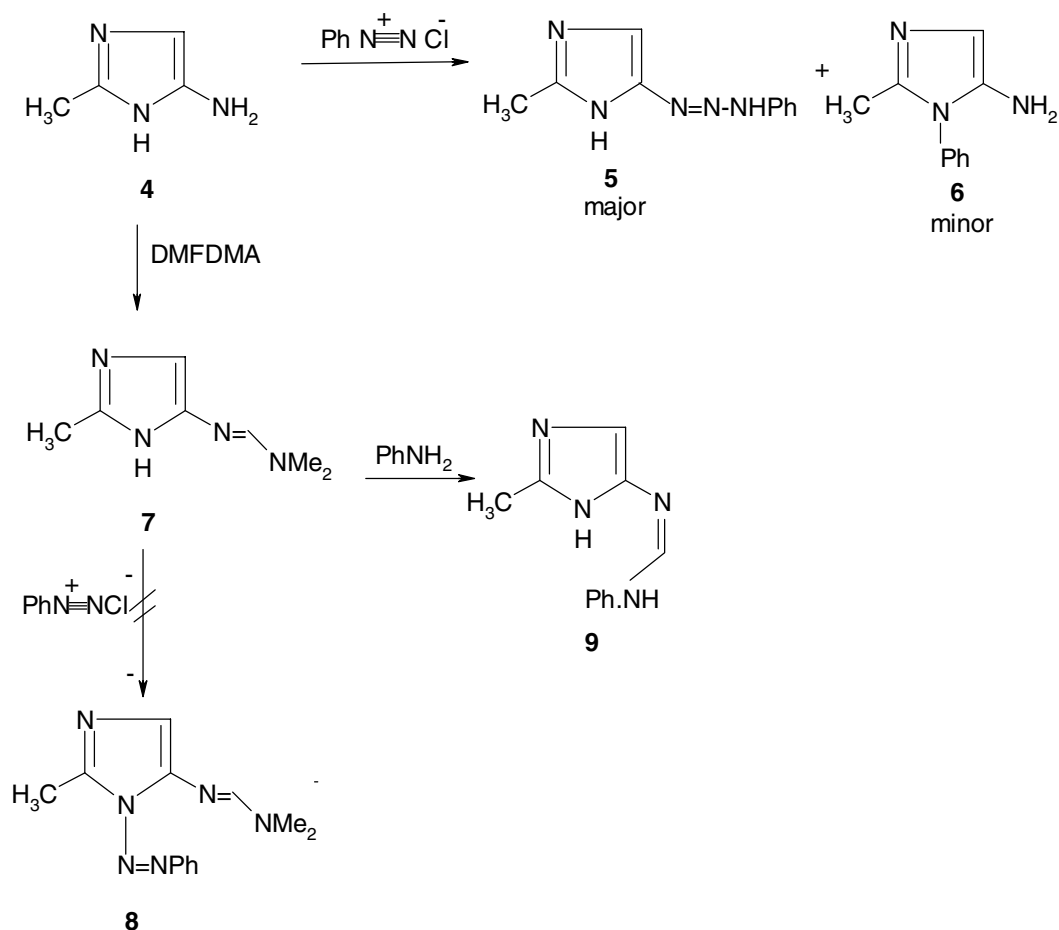


SCHEME 1

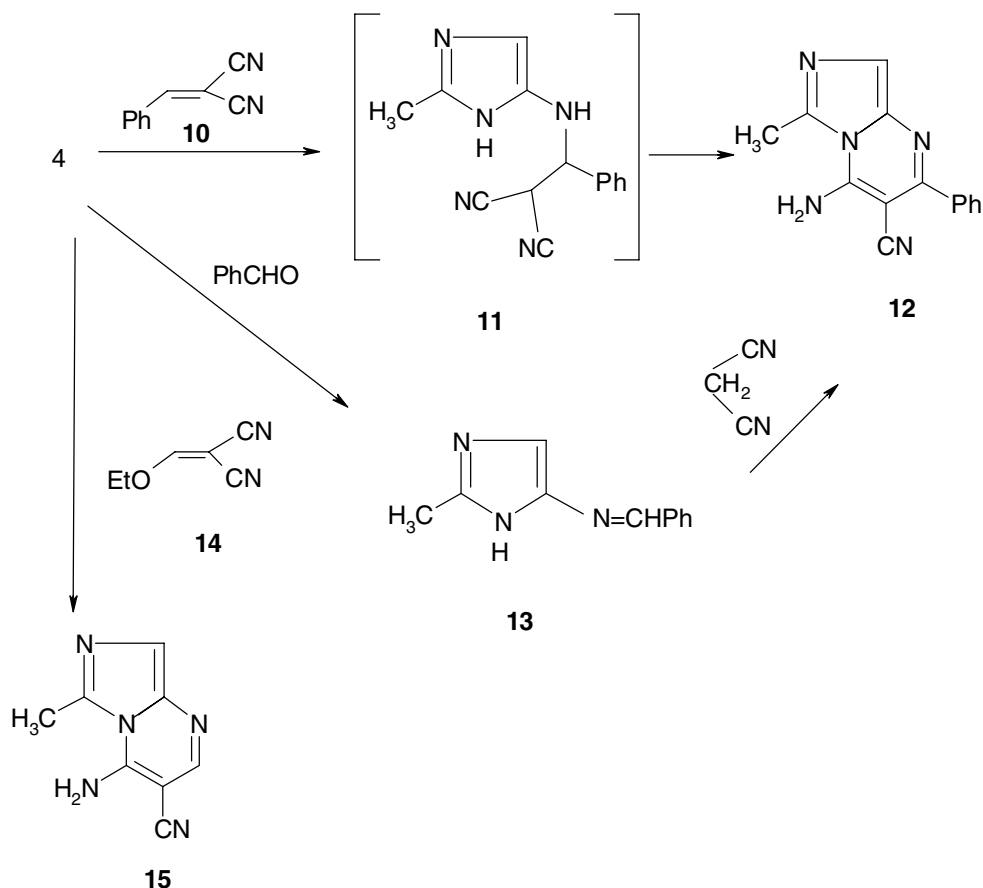
**12** could also be obtained via reaction of **4** with benzaldehyde and subsequent addition of malononitrile to the so-formed Schiff's base derivative **13**. Similarly, compound **15** could be obtained on treat-

ment of **4** with ethoxymethylene malononitrile **14** (Scheme 3).

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



SCHEME 2



SCHEME 3

aminoacetonitrile (**1**) with  $\beta$ -aminocrotonitrile (**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.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Varian EM-390 spectrometer in  $[\text{D}_6]\text{H}_2\text{O}$  as solvent and TMS as internal reference; chemical shifts  $\delta$  are reported in ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Microanalytical

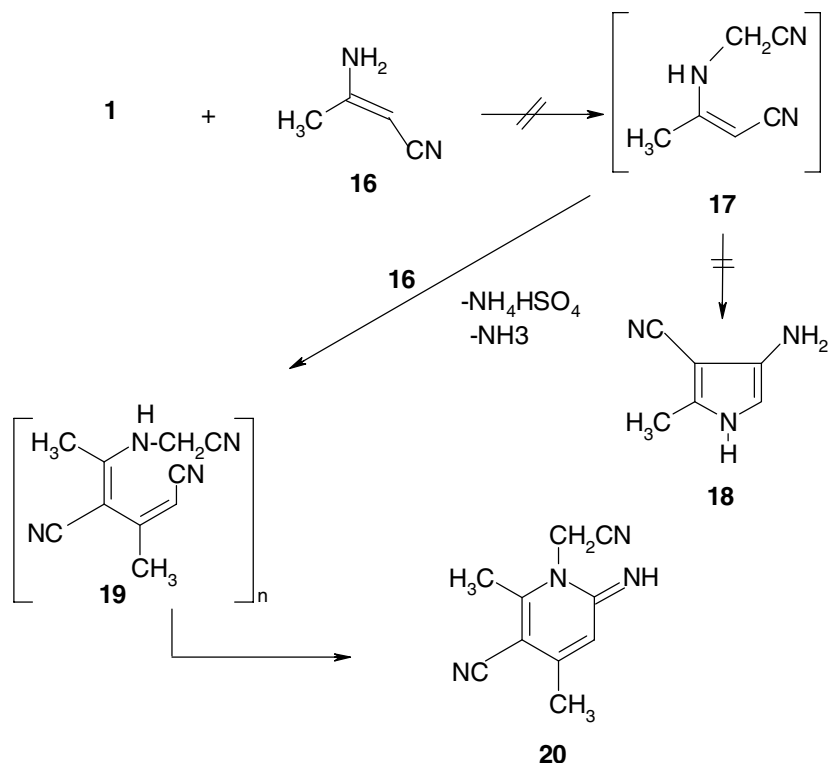
data were obtained from the microanalytical data unit at Cairo University.

### 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):  $\nu = 3350$  ( $\text{NH}_2$ ); 2210 (CN).  $^1\text{H}$  NMR:  $\delta = 2.40$  (s, 3H,  $\text{CH}_3$ ); 3.81 (s, 2H,  $\text{CH}_2$ ), 5.61 (s, 2H,  $\text{NH}_2$ ).  $\text{C}_4\text{H}_7\text{N}_3$  (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,  $\text{NH}_2$ ).  $^1\text{H}$  NMR:  $\delta = 2.04$  (s, 3H,  $\text{CH}_3$ ); 6.36

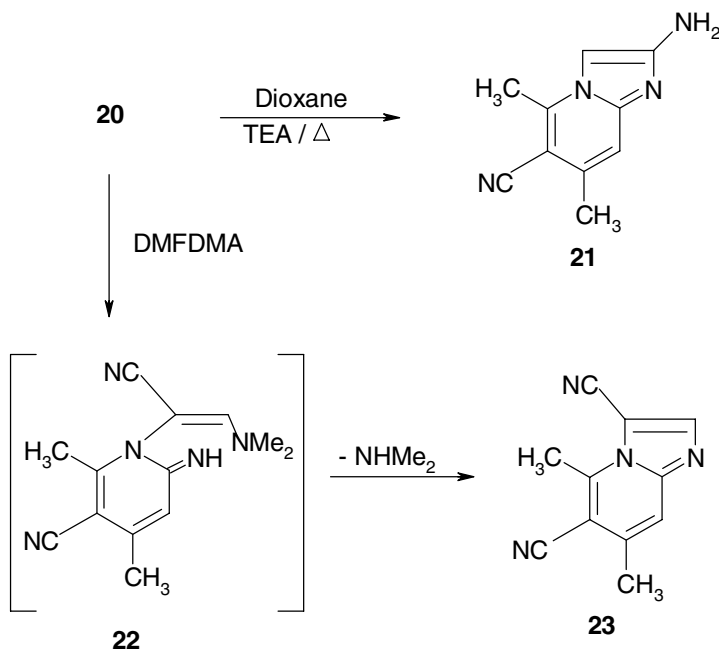


SCHEME 4

(s, 1H, imidazole-H), 7.29 (br s, 2H,  $\text{NH}_2$ ), 10.91 (br s, 1H, NH).  $^{13}\text{C}$  NMR: (300 MHz, DMSO):  $\delta$  = 154.92 (C-2), 129.24 (C-4), 119.37 (C-5), 29.14 ( $\text{CH}_3$ ).  $\text{C}_4\text{H}_7\text{N}_3$  (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).  $^1\text{H}$  NMR:  $\delta = 2.04$  (s, 3H,  $\text{CH}_3$ ), 6.36 (s, 1H, imidazole-H), 7.81–7.93 (m, 5H, phenyl-H); 10.91 (s, 1H, NH), 11.95 (s, 1H, NH).  $\text{C}_{10}\text{H}_{11}\text{N}_5$  (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):  $\nu = 3440, 3350$  ( $\text{NH}_2$ ).  $^1\text{H}$  NMR:  $\delta = 2.03$  (s, 3H,  $\text{CH}_3$ ); 6.36 (s, 1H, imidazole-H), 7.29 (br s, 2H,  $\text{NH}_2$ ), 7.34–7.65 (m, 5H, phenyl-H).  $\text{C}_{10}\text{H}_{11}\text{N}_3$  (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*-Dimethylaminomethylideneamino-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).  $^1\text{H}$  NMR:  $\delta = 2.03$  (s, 3H,  $\text{CH}_3$ ); 2.51 (s, 6H,  $\text{NMe}_2$ ); 3.5 (s, 1H,  $-\text{N}=\text{CH}-$ ); 6.58 (s, 1H, imidazole-H); 10.92 (s, 1H, NH).  $\text{C}_7\text{H}_{12}\text{N}_4$  (152.23): calcd C 55.23, H 7.96, N 36.81; found C 55.51, H 8.10, N 36.94.

**5-Anilinomethylideneamino-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).  $^1\text{H}$  NMR:  $\delta = 2.05$  (s, 3H,  $\text{CH}_3$ ); 3.40 (s, 1H,  $-\text{N}=\text{CH}-$ ); 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).  $\text{C}_{11}\text{H}_{12}\text{N}_4$  (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 recrystallized from ethanol. Yield: 66%; m.p. 243°C. IR (KBr):  $\nu = 3350, 3220$  ( $\text{NH}_2$ ), 2210 (CN).  $^1\text{H}$  NMR:  $\delta = 2.04$  (s, 3H,  $\text{CH}_3$ ); 6.24 (s, 1H, imidazole-H), 6.24 (br s, 2H,  $\text{NH}_2$ ); 7.63–7.81 (m, 5H, phenyl-H).  $\text{C}_{14}\text{H}_{11}\text{N}_5$  (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 recrystallized from ethanol. Yield: 61%; m.p. 198°C. IR (KBr):  $\nu = 3350$  (NH).  $^1\text{H}$  NMR:  $\delta = 2.10$  (s, 3H,  $\text{CH}_3$ ), 6.24 (s, 1H, imidazole-H), 6.5 (s, 1H,  $-\text{N}=\text{CH}$ ) 7.4–7.6 (m, 5H, phenyl-H), 10.91 (s, 1H, NH).  $\text{C}_{11}\text{H}_{11}\text{N}_3$  (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 ethoxymethylene-malononitrile (**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):  $\nu = 3350$  ( $\text{NH}_2$ ), 2210 (CN).  $^1\text{H}$  NMR:  $\delta = 2.04$  (s, 3H,  $\text{CH}_3$ ), 6.52 (s, 1H, imidazole-H), 6.81 (s, 1H, pyrimidine-H); 7.29 (br s, 2H,  $\text{NH}_2$ ).  $\text{C}_8\text{H}_7\text{N}_5$  (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  $\beta$ -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).  $^1\text{H}$  NMR:  $\delta = 2.10$  (s, 3H, 4-methyl), 2.41 (s, 3H, 2-methyl), 4.20 (s, 2H,  $-\text{CH}_2\text{CN}$ ), 6.8 (s, 1H, pyridine-H), 10.81 (s, 1H, NH).  $^{13}\text{C}$  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 ( $\text{CH}_2$ ), 21.01 ( $\text{CH}_3$ ), 20.52 ( $\text{CH}_3$ ). MS (EI, 70 eV):  $m/z = 186$  [ $\text{M}^+$ ].

$C_{10}H_{10}N_4$  (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).  $^1H$  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,  $NH_2$ ).  $C_{10}H_{10}N_4$  (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 recrystallized from ethanol. Yield: 63%; m.p. 210°C. IR (KBr):  $\nu = 2210, 2218$  (2 CN).  $^1H$  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.

## REFERENCES

- [1] Alvi, K. A.; Peters, B. M.; Hunter, L. M.; Crews, P. *Tetrahedron* 1993, 49, 329.
- [2] Tsuda, M.; Shigemori, H.; Ishibashi, M.; Kobayashi, J. *Tetrahedron Lett* 1992, 33, 2597.
- [3] Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G.; Rittschof, D.; Rinehart, K. L. *J Org Chem* 1991, 56, 2965.
- [4] Morales, J. J.; Rodriguez, A. D. *J Nat Prod* 1991, 54, 629.
- [5] Alvi, K. A.; Crews, P.; Laughhead, D. G. *J Nat Prod* 1991, 54, 1684.
- [6] Bedoya Zurita, M.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* 1989, 45, 6713.
- [7] Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J Am Chem Soc* 1981, 103, 6772.
- [8] Nagai, W.; Kirk, K. L.; Cohen, L. A. *J Org Chem* 1973, 38, 1971.
- [9] Dismukes, K.; Rogers, M.; Daily, J. W. *J Neurochem* 1976, 26, 785.
- [10] Lipinski, C. A.; La Mattina, J. L.; Hohnke, L. A. *J Med Chem* 1985, 28, 1628.
- [11] Impicciatore, M.; Morini, G.; Chiavarini, M.; Plazzi, P. V.; Bordini, F.; Vitali, F. *Agents Actions* 1986, 18, 134.
- [12] Haaksma, E. E. J.; Donne-Op den Kelder, G. M.; Timmerman, H.; Weinstein, H. *Agents Actions Suppl* 1991, 313; *Ann Drug Data Rep* 1993, 15, 513.
- [13] Jung, F.; Boucherot, D.; Delvare, C.; Olivier, A.; Davies, G. M.; Betts, M. J.; Brown, R.; Stevenson, R.; Joseph, M.; Kingston, J. F.; Pittam, J. D. *J Antibiot* 1993, 46, 992.
- [14] Gomez, E.; Avendano, C.; Mckillopa, A. *Tetrahedron* 1986, 42, 2625.
- [15] James, P. C.; Minzohong; Simona, C. *J Chem Research (S)* 2001, 195.
- [16] Jenkins, T. C.; Naylor, M. A.; O'Neill, P.; Threadgill, M. D.; Cole, S.; Stratford, I. J.; Adams, G. E.; Fielden, E.; Suto, M. J.; Stier, M. A. *J Med Chem* 1990, 33, 2603.
- [17] Adams, G. E.; Stratford, I. J. *Biochem Pharm* 1986, 35, 71.
- [18] Elkholy, Y. M.; Abu-Shanab, F. A.; Erian, A. W. *Phosphorus Sulfur Silicon* 2000, 167, 151.
- [19] Abu-Shanab, F. A.; Elkholy, Y. M.; Elnagdi, M. H. *Synthetic Commun* 2002, 32, 22.
- [20] Elassar, A. A.; Elkholy, Y. M.; Elnagdi, M. H. *Pharmazie* 1996, 51, 10.
- [21] Elnagdi, M. H.; Erian, A. W. *Arch Pharm (Weinheim)* 1991, 324, 853.
- [22] Elnagdi, M. H.; Abdelrazek, F. M.; Ibrahim, N. S.; Erian, A. W. *Tetrahedron* 1989, 45, 3597.
- [23] Elgemeie, G. E. H.; Sherif, S. M.; Abdelall, F. A. E. M.; Elnagdi, M. H. *Z Naturforsch* 1986, 41b, 781.