# A Novel Synthetic Route to 1,2-Dimethyl-5-phenyl-1*H*-imidazo[4,5-*b*]pyridin-7-ol



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Heating a mixture of 4-amino-1,2-dimethyl-1*H*-imidazole-5-carboxylic acid ethyl ester with ethyl benzoyl acetate resulted in the formation of 8-ethoxycarbonyl-6,7-dimethyl-4-oxo-2-phenylimidazo[1,5-*a*]pyrimidin-5-ium, hydroxide, inner salt. This compound was then transformed into 1,2-dimethyl-5-phenyl-1*H*-imidazo-[4,5-*b*]pyridin-7-ol *via* several intermediates. A number of structurally interesting compounds were also isolated during the course of this work. Thus, the target ring system was formed by a circuitous series of ring-chain tautomerizations/rearrangements.

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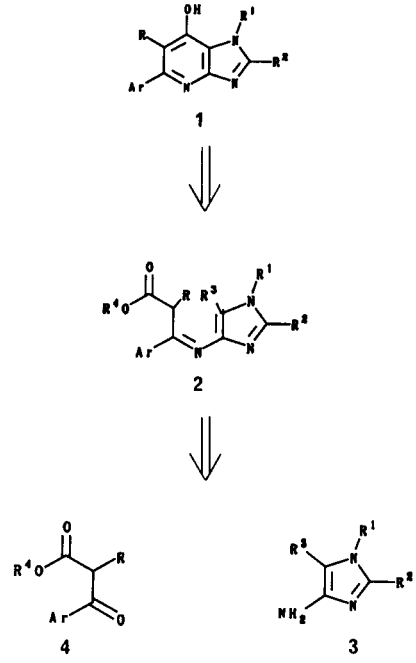
During the course of our studies on preparing novel cardiovascular agents we were in need of synthesizing various substituted 5-aryl-1*H*-imidazo[4,5-*b*]pyridin-7-ols **1** (R = H, $R^1$, $R^2$ = lower alkyl) (Scheme 1). One way, in theory, of preparing this ring system would be from the cyclization of imine **2**, [*cf.* 1] which in turn would result from the availability of various amino imidazoles **3** ($R^3$ = H) and aryloxyacetates **4**. A survey of the literature reveals that amino imidazoles **3** ($R^3$ = H) are unstable [2] but can exist if they

Scheme 1



are stabilized by an electron withdrawing group (*i.e.* $R^3$ = $CONH_2$, $COOCH_2CH_3$, CN, $COCH_3$, Br, Cl) [3-6]. This does not create a problem if the electron withdrawing group could become part of the target ring system (*i.e.* enol carbon of **1**). Thus, our initial approach was a Dieckmann cyclization of **2** (R = H, $R^3$ = $COOCH_2CH_3$) to **1** (R = $COOCH_2CH_3$) [*cf.* 7]. Decarboethoxylation of **1** (R = $COOCH_2CH_3$) would then give rise to the desired ring system **1** (R = H).

With this in mind, 4-amino-1,2-dimethyl-1*H*-imidazole-5-carboxylic acid ethyl ester **5** [4] was heated with an excess of ethyl benzoyl acetate in refluxing diphenyl ether for 2.5 hours. Much to our surprise desired ester **6** was not formed but instead an unknown compound was isolated in 38% yield (Scheme 2). The $^{13}C$-nmr spectrum of the product of this reaction displayed seven quaternary carbon signals which is inconsistent with structure **6**. Structure **7** is consistent with this nmr spectrum and unambiguous proof of this ring system was established by a single-crystal X-ray analysis of a derivative of **7** (*vide infra*).

In order to investigate the reactivity of this novel ring system, ester **7** was treated with 3 equivalents of sodium hydroxide in aqueous ethanol followed by acidification. This afforded mainly imine acid **8** (88%) and only a small amount of the corresponding acid **9** (5%) (Scheme 2). A way to circumvent ring opening was to prepare the sodium salt of **9** (*i.e.* **10**) followed by protonation with a stoichiometric amount of methanesulfonic acid. This afforded acid **9** in 57% yield. Both imine acid **8** and **9** were employed in synthesizing the desired imidazo[4,5-*b*]pyridinol **11**. Heating imine acid **8** to about 350° or refluxing in diphenyl ether afforded **11** in 88 and 84% yields, respec-

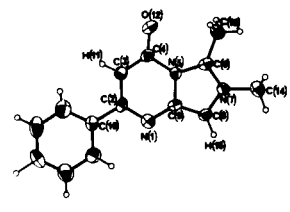
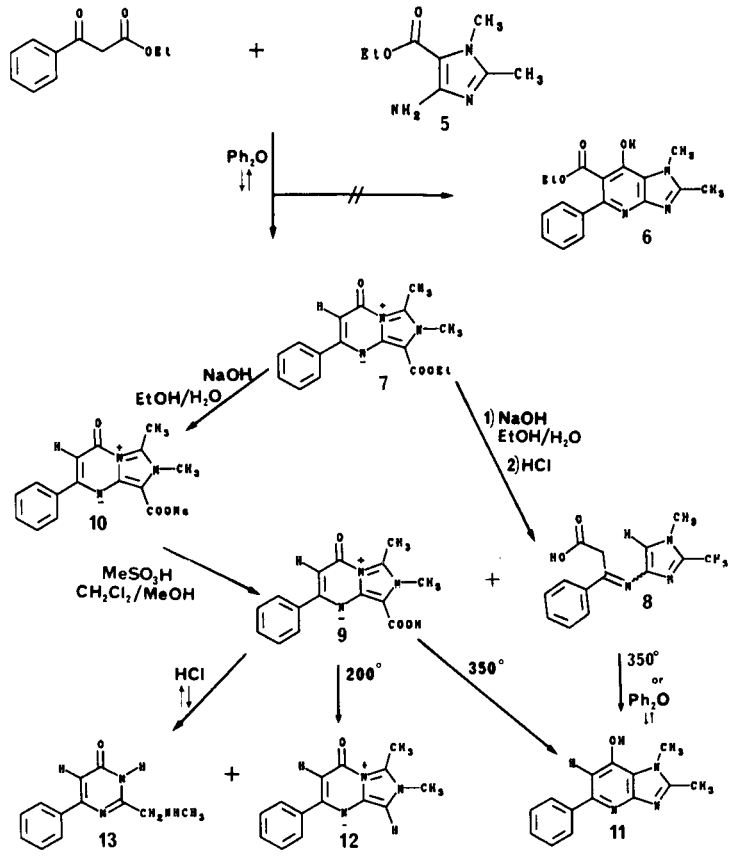


Figure 1. ORTEP drawing of 12

SCHEME 2




tively, When acid **9** was heated to its melting point it lost carbon dioxide and then resolidified. The product of this reaction was determined by single-crystal X-ray analysis and shown to be **12**, which is drawn in only one of a number of tautomeric forms. An ORTEP drawing of **12** is shown in Figure 1. Selected bond lengths and angles for **12** are listed in Tables 1 and 2, respectively [8].

**Table 1**

Selected Bond Lengths (Å) in 6,7-Dimethyl-4-Oxo-2-Phenyl-imidazo[1,5-a]pyrimidin-5-ium, hydroxide, inner salt, **12**

| Atoms | Distance | Atoms | Distance |
|---|---|---|---|
| O(12)-C(4) | 1.247(8) | N(1)-C(9) | 1.359(9) |
| N(5)-C(4) | 1.429(9) | C(10)-C(2) | 1.504(11) |
| N(5)-C(6) | 1.360(10) | C(2)-C(3) | 1.411(11) |
| N(5)-C(9) | 1.394(9) | C(3)-C(4) | 1.382(11) |
| N(7)-C(6) | 1.326(9) | C(6)-C(13) | 1.486(11) |
| N(7)-C(8) | 1.379(9) | C(8)-C(9) | 1.366(11) |
| N(7)-C(14) | 1.466(11) | C(3)-H(11) | 0.93(8) |
| N(1)-C(2) | 1.337(9) | C(8)-H(15) | 0.93(6) |

**Table 2**

Selected Bond Angles (degrees) in 6,7-Dimethyl-4-Oxo-2-Phenyl-imidazo[1,5-a]pyrimidin-5-ium, hydroxide, inner salt **12**

| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(4)-N(5)-C(6) | 128.9(6) | N(1)-C(2)-C(3) | 123.6(8) |
| C(4)-N(5)-C(9) | 121.9(6) | C(10)-C(2)-C(3) | 120.7(7) |
| C(6)-N(5)-C(9) | 109.2(6) | C(2)-C(3)-C(4) | 122.9(8) |
| C(6)-N(7)-C(8) | 111.3(7) | O(12)-C(4)-N(5) | 118.8(7) |
| C(6)-N(7)-C(14) | 124.8(7) | O(12)-C(4)-C(3) | 128.6(8) |
| C(8)-N(7)-C(14) | 123.6(7) | N(5)-C(4)-C(3) | 112.6(8) |
| C(2)-N(1)-C(9) | 115.3(7) | N(5)-C(6)-N(7) | 106.5(7) |
| N(1)-C(2)-C(10) | 115.7(7) | N(5)-C(6)-C(13) | 127.6(7) |
| N(7)-C(8)-C(9) | 106.3(7) | N(7)-C(6)-C(13) | 125.9(8) |
| N(5)-C(9)-N(1) | 123.6(7) | C(2)-C(3)-H(11) | 121.(5) |
| N(5)-C(9)-C(8) | 106.7(7) | C(4)-C(3)-H(11) | 115.(5) |
| N(1)-C(9)-C(8) | 129.7(7) | N(7)-C(8)-H(15) | 123.(4) |
| | | C(9)-C(8)-H(15) | 131.(4) |

Based on the work of Kato [9] it was expected that compound **12** could be rearranged to **11**. This was indeed what happened when **12** was heated to 350°. The complete

transformation (*i.e.* **9** → **12** → **11**) takes place in 89% yield without the use of solvent. This product (*i.e.* **11**) was identical to that prepared from **8**. The structure of **11** was assigned on the basis of the elemental analysis and spectroscopic evidence [10] (see Experimental).

Compound **12** was also formed by heating acid **9** in 18% aqueous hydrochloric acid. A significant amount of pyrimidinone **13** also formed under these conditions. The stability of **12** can be demonstrated by the following reaction. Heating **12** with 18% aqueous hydrochloric acid overnight afforded only a trace of **13** (tlc analysis) with the remaining **12** being recovered unchanged. Under the same conditions imine acid **8** gave exclusively **13** (tlc analysis). This indicates that acid **9** undergoes ring opening followed by decarboxylation yielding imine acid **9**, an intermediate in the synthesis of **13**.

## EXPERIMENTAL

Proton nuclear magnetic resonance ($^1$H-nmr) spectra (300 MHz) and ($^{13}$C-nmr) spectra (75 MHz) were taken on a Varian XL-300 instrument. Proton spectra were obtained in DMSO-$d_6$ or deuteriochloroform and referenced to tetramethylsilane at 0.00 ppm. Carbon spectra were obtained in DMSO-$d_6$ and referenced to the solvent septet at 39.5 ppm. Infrared (ir) spectra were taken on a Perkin-Elmer 1720 Fourier Transform spectrometer as a potassium bromide pellet. Elemental analyses were performed by the analytical department of Belex Laboratories, Inc., or Microlit Laboratories, Inc., Caldwell, NJ. Melting points were obtained on an Electrothermal digital capillary melting point apparatus and are uncorrected. Low resolution fast atom bombardment (FAB) mass spectra (ms) were obtained on a Kratos MS 25 spectrometer at 1.33 kV (900 $\mu$ range). A saddle field gun (FAB11NF, Ion Tech) was used with xenon gas at 8 kV and 1.2 mA. Glycerol or "magic bullet" (dithiothreitol:dithioerythritol, 3:1) was used as the matrix. Woelm silica gel (63-200 mesh) was used for column chromatography. Ultraviolet (uv) spectra were taken on a Hewlett Packard 8450A Diode Array Spectrophotometer in methanol.

8-Ethoxycarbonyl-6,7-dimethyl-4-oxo-2-phenylimidazo[1,5-*a*]-pyrimidin-5-ium, Hydroxide, Inner Salt (**7**).

A mixture of 4-amino-1,2-dimethyl-1*H*-imidazole-5-carboxylic acid ethyl ester [4] (14.9 g, 81 mmoles) and ethyl benzoyl acetate (28 ml, 162 mmoles) in diphenyl ether (100 ml) was heated under argon at reflux for 2.5 hours. After cooling to room temperature the crystals that formed were collected and washed with hexane then triturated with ethyl acetate and filtered to give **7** (9.6 g, 38%) mp 284-286° (ethanol); ir (potassium bromide): 1670 (C=O) cm$^{-1}$; $^1$H-nmr (deuteriochloroform): $\delta$ = 1.54 (t, 3H), 3.25 (s, 3H), 4.12 (s, 3H), 4.76 (q, 2H), 6.28 (s, 1H), 7.45 (m, 3H) and 8.10 (m, 2H); $^{13}$C-nmr (deuteriochloroform): $\delta$ 163.22, 160.42, 158.80, 145.65, 138.17, 135.09, 130.23, 128.37, 127.34, 105.87, 91.80, 60.96, 33.66, 14.43 and 12.33; ms: m/z 312 (M+H)$^+$; uv (methanol): 272 nm ($\epsilon$ = 32,121 L mol$^{-1}$ cm$^{-1}$).

*Anal.* Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.33; H, 5.51; N, 13.51.

3-[(1,2-Dimethyl-1*H*-imidazol-4-yl)imino]-3-phenylpropanoic Acid 1/3 Hydrate (**8**).

A mixture of **7** (620 mg, 2.0 mmoles), 1*N* sodium hydroxide (6 ml, 6.0 mmoles), ethanol (35 ml) and water (20 ml) was heated at 80° for 30 minutes. After concentrating *in vacuo*, water was added and the *p*H adjusted to 3.0 with 18% hydrochloric acid. The precipitate that formed was collected to give **8** (320 mg, 61%). The filtrate was extracted with dichloromethane (2 x 100 ml) and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) using 5% methanol in dichloromethane as eluent. This provided additional **8** (150 mg, 27% (88% total)) and **9** (30 mg, 5%).

Compound **8** had mp 211-212°; ir (potassium bromide): 1667 (C=O) cm$^{-1}$; $^1$H-nmr (dimethyl sulfoxide-$d_6$, 125°): $\delta$ = 2.10 (s, 3H), 3.08 (br s, 3H), 4.48 (s, 2H), 7.46 (m, 3H) and 8.00 (m, 2H); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$, 85°): $\delta$ = 170.37, 162.43, 160.10, 158.40, 135.93; 129.87, 128.17, 126.30, 106.77, 49.25, 36.84 and 20.72; ms: m/z 258 (M+H)$^+$.

*Anal.* Calcd. for $C_{14}H_{15}N_3O_2 \cdot \frac{1}{3}\ H_2O$: C, 63.88; H, 6.00; N, 15.96. Found: C, 64.28; H, 5.76; N, 15.63.

8-Carboxyl-6,7-dimethyl-4-oxo-2-phenylimidazo[1,5-*a*]pyrimidin-5-ium, Hydroxide, Inner Salt, Sodium Salt 1¾ Hydrate (**10**).

A mixture of **7** (4.1 g, 13.2 mmoles), 1*N* sodium hydroxide (26.4 ml, 26.4 mmoles), and ethanol (50 ml) was heated to 80° for 40 minutes then concentrated *in vacuo*. The yellow crystals obtained were triturated with etanol/water (4:1), filtered, washed with ethanol and dried yielding **10** (3.5 g, 79%) mp 248-254° dec; ir (potassium bromide): 1662 (C=O) cm$^{-1}$; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ = 3.10 (s, 3H), 4.12 (s, 3H), 5.67 (s, 1H), 7.29 (m, 3H) and 7.78 (m, 2H).

*Anal.* Calcd. for $C_{15}H_{12}N_3O_3Na \cdot 1\frac{3}{4}\ H_2O$: C, 53.49; H, 4.64; N, 12.48; Na, 6.83. Found: C, 53.24; H, 4.35; N, 12.36; Na, 7.11.

8-Carboxy-6,7-dimethyl-4-oxo-2-phenylimidazo[1,5-*a*]pyrimidin-5-ium, Hydroxide, Inner Salt (**9**).

Compound **10** (61 mg, 0.18 mmole) was added to a stirred solution of methanesulfonic acid (16.5 mg, 0.17 mmole) in dichloromethane (10 ml) and methanol (2 ml). Once the mixture became homogeneous it was concentrated *in vacuo*. The yellow crystals obtained were triturated with water, filtered, and dried to give **9** (35 mg, 72%) mp 192-194° (gas evolution); ir (potassium bromide): 1728, 1681 (C=O) cm$^{-1}$; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ = 3.11 (s, 3H), 4.07 (s, 3H), 6.18 (s, 1H), 7.51 (m, 3H), and 8.03 (m, 2H); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): $\delta$ = 160.30, 159.11, 157.33, 145.46, 137.76, 136.65, 130.34, 128.62, 126.75, 103.93, 91.04, 32.84 and 11.59; ms: m/z 284 (M+H)$^+$.

*Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.62; N, 14.83. Found: C, 63.47; H, 4.55; N, 14.88.

1,2-Dimethyl-5-phenyl-1*H*-imidazo[4,5-*b*]pyridin-7-ol (**11**).

Compound **8** (20 mg, 0.07 mmole) was heated to *ca.* 360° for 5 minutes then cooled to room temperature. The resulting light brown solid was triturated with methanol, filtered, and air dried giving **11** (15 mg, 89%) mp 347-353°; ir (potassium bromide): 3435, 1597 cm$^{-1}$; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ = 2.45 (s, 3H), 3.97 (s, 3H), 6.23 (br s, 1H), 7.48 (m, 3H), and 7.75 (m, 2H); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$/deuteriotrifluoroacetic acid): $\delta$ = 155.78, 154.55, 152.37, 147.12, 135.50, 130.24, 129.13, 127.33, 115.93, 104.73, 33.17, and 12.29; ms: m/z 240 (M+H)$^+$; uv (methanol): 242 nm ($\delta$ = 25,906 L mol$^{-1}$ cm$^{-1}$), 282 nm ($\delta$ = 22,076 L mol$^{-1}$ cm$^{-1}$).

*Anal.* Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.47; N, 17.56. Found:

C, 70.05; H, 5.48; N, 17.42.

Compound **11** was also prepared by heating **8** (100 mg, 0.38 mmole) in refluxing diphenyl ether for 96 hours. The crystals obtained were collected and washed with hexanes and gave **11** (76 mg, 84%).

6,7-Dimethyl-4-oxo-2-phenylimidazo[1,5-*a*]pyridin-5-ium, Hydroxide, Inner Salt (**12**).

Compound **9** (28 mg, 0.10 mmole) was heated to *ca.* 200° until gas evolution ceased and resolidification took place. The light orange crystals obtained were collected yielding **12** (22.4 mg, 95%) mp 341-345° (2-propanol); ir (potassium bromide): 3392, 1662 $cm^{-1}$; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ = 3.09 (s, 3H), 3.86 (s, 3H), 5.82 (s, 1H), 7.43 (m, 3H), 7.46 (s, 1H) and 7.98 (m, 2H); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): $\delta$ = 159.52, 157.62, 141.73, 138.81, 129.19, 128.86, 128.24, 126.58, 106.36, 86.12, 34.22 and 11.35; ms: m/z 240 $(M+H)^+$; uv (methanol): 264 nm ($\delta$ = 26,119 L $mol^{-1}$ $cm^{-1}$).

*Anal.* Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.47; N, 17.56. Found: C, 70.30; H, 5.39; N, 17.75.

2-[(Methylamino)methyl]-6-phenyl-4(3*H*)-pyrimidinone ⅓ Hydrate (**13**).

A mixture of **9** (65 mg, 0.23 mmole), 18% hydrochloric acid (2 ml), and ethanol (5 ml) was heated at reflux for 17 hours. The reaction mixture was then concentrated *in vacuo* and the *p*H adjusted to 8.0 with 1*N* sodium hydroxide and extracted with dichloromethane (2 x 50 ml) and concentrated *in vacuo*. The residue was chromatographed on silica gel (25 g) using 2% methanol in dichloromethane and gradually increasing the eluent strength to 20% methanol in dichloromethane. This afforded **12** (25 mg, 46%) followed by **13** (26 mg, 52%).

Compound **13** had mp 150-153°; ir (potassium bromide): 3359, 1668 $cm^{-1}$; $^1$H-nmr (deuteriochloroform): $\delta$ = 2.52 (s, 3H), 3.87 (s, 2H), *ca.* 5.0 (br s, 1H), 6.74 (s, 1H), 7.46 (m, 3H) and 7.95 (m, 2H); $^{13}$C-nmr (deuteriochloroform): $\delta$ = 163.39, 162.83, 159.96, 136.44, 130.61, 128.76, 108.18, 53.14 and 36.40; ms: m/z 216 $(M+H)^+$.

*Anal.* Calcd. for $C_{12}H_{13}N_3O \cdot \frac{1}{3}H_2O$: C, 65.14; H, 6.22; N, 18.99. Found: C, 65.29; H, 5.99; N, 18.88.

X-Ray Crystallography.

A colorless thin plate crystal of **12** recrystallized from isopropanol with dimensions 0.05 x 0.25 x 0.45 mm was mounted on a Picker four-cycle goniostat equipped with a Furnas Monochrometer (HOG crystal) and Picker X-ray generator is interfaced to a TI980 minicomputer with Slo-Syn stepping motors to drive angles. The minicomputer is interfaced by low speed data lines to a CYBER170-855 (NOS operating system) where all computations are performed. A systematic search of a limited hemisphere of reciprocal space located a set of diffraction maxima with symmetry and systemic absences corresponding to the unique orthorombic space group Pbca with cell dimensions (at −155°) $a$ = 7.719(1) Å, $b$ = 23.760(5) Å, $c$ = 12.892(2) Å, $V$ = 2364.35 Å$^3$ and $D_c$ = 1.344414 g $cm^{-3}$ (for Z = 8).

Data were collected in the usual manner using a continuous $\theta$-$2\theta$ scan with fixed backgrounds and reduced to a unique set of intensities and associated sigmas in the usual manner. The structure was solved by a combination of direct methods (MULTAN78) and Fourier techniques. All hydrogen atoms were clearly visible in a difference Fourier synthesis phased on the non-hydrogen parameters. All hydrogen atoms were refined isotropically and non-hydrogen atoms anisotropically in the final cycle. All atoms were located and refined to a final residuals R(F) = 0.0821 and $R_w$(F) = 0.0719. Selected bond lengths and angles, along with their standard deviations, are presented in Tables 1 and 2, respectively.

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[10] Compound **11** is in its enol form as evident from its ir spectrum; see A. Albert and E. Spinner, *J. Chem. Soc.*, 1221 (1960).