– Br). Anal. Calcd for $C_{10}H_{11}BrN_4S_2$: C, 36.26; H, 3.35; Br, 24.12. Found: C, 36.32; H, 3.39; Br, 24.19.

The ^1H NMR NOE difference spectrum was taken for a solution of **4a** in $CDCl_3$ dried with freshly activated 3A molecular sieves. Irradiation of NH (δ 6.80) resulted in a strong NOE at H-4 (δ 5.32) of the same ring and a strong NOE at H-4′ and H-6′ (δ 8.52) of the adjacent ring.

5-Bromo-2,2′-bis(methylthio)-4,5′-bipyrimidine (6a). To a solution of **4a** (0.4 g, 1.2 mmol) in toluene (20 mL) was added a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (0.36 g, 1.6 mmol) in toluene (20 mL). The reaction mixture was stirred at room temperature for 3 h, then a solution of NaOH (10%, 50 mL) was added, and stirring was continued for an additional 30 min. The organic layer was separated, washed with water, dried, and evaporated to give a solid that was recrystallized from methanol: yield, 0.37 g (93%); mp 136–137 °C; ^1H NMR δ 9.00 (s, 2 H), 8.58 (s, 1 H), 2.61 (s, 3 H), 2.55 (s, 3 H); MS, *m/e* 328/330 (bromine isotopes, M^+). Anal. Calcd for $C_{10}H_9BrN_4S_2$: C, 36.48; H, 2.76; Br, 24.27. Found: C, 36.58; H, 2.79; Br, 24.19.

2,2′-Bis(methylthio)-4,5′-bipyrimidine (7a). (a) To a solution of **4a** (0.4 g, 1.2 mmol) in benzene (20 mL) was added triethylamine (3 mL). The mixture was left overnight at room temperature and then filtered from crystals of triethylamine hydrobromide. The filtrate was washed with water, dried, and evaporated to give a solid that was recrystallized from methanol: yield, 0.3 g (100%); mp 158–159 °C; ^1H NMR δ 9.11 (s, 2 H), 8.52 (d, J = 5 Hz, 1 H), 7.28 (d, J = 5 Hz, 1 H), 2.60 (s, 6 H); MS, *m/e* (relative intensity) 250 (100, M^+), 249 (6), 235 (31, $M^+ - CH_3$). Anal. Calcd for $C_{10}H_{10}N_4S_2$: C, 47.98; H, 4.03. Found: C, 47.92; H, 4.04.

(b) To a solution of sodium methoxide prepared from methanol (75 mL) and sodium (15 mg, 0.65 mmol) was added **4a** (0.2 g, 0.6 mmol). The reaction mixture was stirred for 12 h, then treated with a small piece of solid CO_2, and evaporated. The residue was extracted with benzene and worked up as described above; yield, 0.15 g (100%).

2,2′-Bis(methylthio)-4,5′-bipyrimidine-5-*d*$_1$. (a) A mixture of **4a** (0.2 g, 0.6 mmol), benzene (20 mL), and D_2O (1 mL) was stirred for 10 min and then evaporated. The residue was dissolved in benzene (20 mL) and treated with D_2O (0.5 mL) and triethylamine (3 mL). Workup as described above gave the title compound: ^1H NMR δ 7.28 (d, J = 5 Hz, 0.05 H); MS, *m/e* (relative intensity) 251 (100, M^+), 250 (14).

(b) To a solution of sodium methoxide prepared from MeOD (10 mL) and sodium (15 mg, 0.65 mmol) was added a solution of **4a** (0.2 g, 0.6 mmol) in benzene (10 mL). Workup (see above) gave deuterated **7a**: ^1H NMR δ 7.28 (0.07 H).

5-Bromo-2,2′,4′,6-tetrakis(methylthio)-4,5′-bipyrimidine (6b). To a solution of **1b** (1 g, 3.98 mmol) in THF (30 mL) at −80 °C was added dropwise a solution of *n*-BuLi in hexane (2.6 M, 0.84 mL, 2.18 mmol). The resultant mixture was kept at −45 °C for 1 h and then quenched at −45 °C with a solution of AcOH (0.13 g, 2.18 mmol) and water (0.05 mL) in THF (1 mL). A solution of DDQ (0.7 g, 3 mmol) in toluene (30 mL) was added slowly at −45 °C, and the resultant mixture was stirred and allowed to warm up to room temperature over 10 h. A solution of NaOH (10%, 50 mL) was added, and stirring was continued for an additional 30 min. The organic layer was separated, washed with water, and concentrated. Preparative TLC using CH_2Cl_2 as eluent gave 2,2′,4′,6-tetrakis(methylthio)-4,5′-bipyrimidine (**7b**, 0.47 g, 70%) identified by the ^1H NMR spectrum[1a] and 5-bromo-2,2′,4′,6-tetrakis(methylthio)-4,5′-bipyrimidine (**6b**): yield, 42 mg (5%); mp 164–165 °C; ^1H NMR δ 8.15 (s, 1 H), 2.58 (m, 12 H); MS, *m/e* 405/407 (bromine isotopes, $M^+ - CH_3$), 341 ($M^+ - Br$); CI-MS, *m/e* 421/423 (bromine isotopes, $M^+ + 1$), 327 ($M^+ + 1 - CH_3 - Br$). Anal. Calcd for $C_{12}H_{13}BrN_4S_4$: C, 34.20; H, 3.11; Br, 18.96. Found: C, 34.27; H, 3.14; Br, 18.99.

2,4-Bis(methylthio)-6-(2-thienyl)pyrimidine (9c). 2-Thienyllithium was prepared by adding *n*-BuLi in hexane (2.6 M, 4.6 mL, 12 mmol) to thiophene (1 mL, 12.5 mmol) in ether (30 mL) at 0 °C.[11] This solution was maintained at −30 °C while a solution of **1b** (3 g, 12 mmol) in ether (90 mL) was added slowly with stirring during 10 min. The reaction mixture was stirred at −20 °C for 10 min and then quenched at −20 °C with stirring with a mixture of AcOH (0.72 g, 12 mmol), water (1 mL), and THF (5 mL). After addition of toluene (125 mL) and stirring for 5 min the solution was decanted and stored below −10 °C.

Half (125 mL) of this solution was stirred with aqueous $NaHCO_3$ (10%, 50 mL) at room temperature for 30 min. The organic layer was separated and evaporated to give crude **9c**, which was purified by flash chromatography using a mixture of CH_2Cl_2 and hexanes (1:1) as eluent and recrystallized from ethanol: yield, 1.37 g (90%); mp 101–101.5 °C; ^1H NMR δ 7.69 (2 d, J_1 = 1.2 Hz, J_2 = 3.8 Hz, 1 H), 7.47 (2 d, J_1 = 1.2 Hz, J_3 = 5.0 Hz, 1 H), 7.11 (2 d, J_2 = 3.8 Hz, J_3 = 5.0 Hz, 1 H), 7.08 (s, 1 H), 2.62 (s, 3 H), 2.60 (s, 3 H); MS *m/e* 254 (M^+), 293 ($M^+ - CH_3$). Anal. Calcd for $C_{10}H_{10}N_2S_3$: C, 47.21; H, 3.96. Found: C, 47.16; H, 3.97.

5-Bromo-2,4-bis(methylthio)-6-(2-thienyl)pyrimidine (9d). A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.27 g, 10 mmol) in the THF (20 mL) was added at −10 °C to the remaining solution (125 mL) from the experiment above. The mixture was stirred at −10 °C for 10 h and then was allowed to reach room temperature within 5 h. A solution of NaOH (10%, 50 mL) was added, and stirring was continued for an additional 30 min. The organic layer was separated, washed with water, dried, and evaporated to give a mixture of **9c** and **9d** (1:3), which was separated by flash chromatography using a mixture of CH_2Cl_2 and hexanes (1:1) as an eluent. Final recrystallization from hexanes gave 1.2 g (61%) of **9d**: mp 119–120 °C; ^1H NMR δ 8.27 (2 d, J_1 = 1.2 Hz, J_2 = 3.8 Hz, 1 H), 7.51 (2 d, J_1 = 1.2 Hz, J_3 = 5.0 Hz, 1 H), 7.12 (2 d, J_2 = 3.8 Hz, J_3 = 5.0 Hz), 2.58 (s, 3 H), 2.53 (s, 3 H); MS, *m/e* 332/334 (bromine isotopes, M^+), 253 ($M^+ - Br$). Anal. Calcd for $C_{10}H_9BrN_2S_3$: C, 36.04; H, 2.72; Br, 23.98. Found: C, 35.97; H, 2.75; Br, 23.94.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. **1a**, 14001-67-3; **1a** (5–Li), 103191-83-9; **1b**, 60186-81-4; **3b**, 103191-82-8; **4a**, 103191-85-1; **5b**, 103191-84-0; **6a**, 103191-86-2; **6b**, 103191-89-5; **7a**, 103191-87-3; **7a** (5-*d*), 103191-88-4; **7b**, 60186-83-6; **9c**, 103191-90-8; **9d**, 103191-91-9; 2-thienyllithium, 2786-07-4; thiophene, 110-02-1.

(11) Brown, D. J.; Cowden, W. B.; Strekowski, L. *Aust. J. Chem.* **1982**, *35*, 1209.

A Convenient Procedure for the Preparation of 4(5)-Cyanoimidazoles

Donald P. Matthews,* Jeffrey P. Whitten, and James R. McCarthy

Merrell Dow Research Institute, Indianapolis Center, Indianapolis, Indiana 46268-0470

Received January 6, 1986

During a recent synthetic program we required 4(5)-cyanoimidazoles **3** and 4(5)-cyano-2,2′-bi-1*H*-imidazoles (**3**, R = 2-imidazolyl).[1] It was surprising to us to find no general and/or facile method for the preparation of these compounds.[2-4] In this note we wish to report a facile, high yield method for the preparation of 4(5)-cyanoimidazoles **3** and the corresponding biimidazoles.

The conversion of 2-(trifluoromethyl)imidazoles to 2-cyanoimidazoles has been reported.[6,7] However, the

(1) These compounds proved to be of biological interest: Matthews, D. P.; Whitten, J. P.; McCarthy, J. R.; Marshall, F.; Wenger, M. A.; Burkhard, T., manuscript in preparation.

(2) 4(5)-Cyano-2,2′-bi-1*H*-imidazoles are unreported in the literature. For two methods to **3a**, see ref 3 and 4.

(3) Mitsuhashi, K.; Itho, E.; Kawahara, T.; Tanaka, K. *J. Heterocycl. Chem.* **1983**, *20*, 1103.

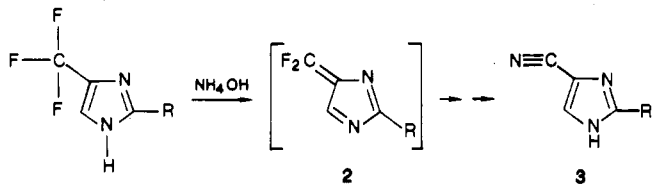
(4) Ferris, J. P.; Trimmer, R. W. *J. Org. Chem.* **1976**, *41*, 19.

(5) For a convenient preparation of 2,2′-1*H*-biimidazole, see: Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *Synthesis* **1986**, 336.

0022-3263/86/1951-3228$01.50/0

transformation required 5% ammonium hydroxide under high dilution conditions (1.2 g/L), a 50–100 h reaction time, and in many cases the evaporation of large quantities of aqueous solution to isolate the product. In addition, the yields reported for the preparation of the 2-(trifluoromethyl)imidazoles were less than 5% for many examples.[8]

Kimoto and Cohen[6] proposed the intermediacy of a difluorodiazafulvene in their preparation of 2-cyanoimidazoles. We reasoned that a 4(5)-(trifluoromethyl)imidazole **1** would also form a transient difluorodiazafulvene **2** on treatment with dilute ammonium hydroxide. Indeed, we found that **1** was converted to the



1 **2** **3**

corresponding 4(5)-cyanoimidazoles **3** in good to excellent yields on treatment with 5% ammonium hydroxide (See Table I). This reaction was found to be synthetically useful by significant modification of the original conditions used to prepare 2-cyanoimidazoles.[6] These modifications included increasing the concentration of reactants and the temperature of the reaction. The reactants could be increased from 1.2 up to 100 g/L. However, the concentration of ammonium hydroxide was found to be as important for the conversion of **1** to **3** as it was in the formation of 2-cyanoimidazoles.[6] At high concentrations of **1**, additional ammonium hydroxide was added to the reaction medium to keep the concentration near 5%. A small volume of methanol could be added to the reaction to increase the solubility of the starting material, even though this had a somewhat detrimental effect on the rate of reaction. Finally, the reaction time could be shortened from 50–100 h to 1–16 h by warming to 60 °C.

The number of examples of this transformation listed in Table I illustrate the generality of the reaction. As anticipated, *N*-substituted 4(5)-(trifluoromethyl)imidazoles (see **1k**) failed to afford the desired cyanoimidazoles **3**.

In conclusion, we have developed a general synthesis of 4(5)-cyanoimidazoles **3** (Table 1) starting with 4(5)-(trifluoromethyl)imidazole **1**, which are easily prepared by reported procedures.[9-11] These transformations were conveniently run in an Erlenmeyer flask on multigram scales. Furthermore, this route complements our recently reported one-pot method for the preparation of 2-cyanoimidazoles via *N*-cyanoimidazolium ylides,[12] thus providing convenient syntheses of a wide variety of substituted cyanoimidazoles.[13]

Experimental Section

Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM-360 (60 MHz) spectrometer. All chemical shifts were reported in ppm (δ) from tetramethylsilane as an internal standard. Coupling constants were reported in Hertz (Hz). Low-resolution mass spectra were recorded on a Finnigan 4023 GC/MS/DS instrument.

General Procedure for the Preparation of 4(5)-Cyanoimidazoles. 4(5)-Cyano-2,2′-bi-1*H*-imidazole (3d). A mixture of 4(5)-(trifluoromethyl)-2,2′-bi-1*H*-imidazole (**1d**, 2.5 g, 1.4 mmol) and 5% aqueous NH_4OH 200 mL was warmed to 60 °C. The progress of the reaction was followed by TLC (EtOAc) and HPLC (particle 10 ODS C18 column) (1:2.5:2.5 acetonitrile–0.04 M sodium dihydrogen phosphate–0.04 M sodium hydrogen phosphate, 1.5 mL/min). After 1 h the cooled reaction was carefully neutralized with glacial acetic acid to give 1.71 g (87%) of **3d** as a light tan solid. (In a few examples, the product did not precipitate on neutralization. In these cases the neutralized solution was extracted with ethyl acetate and the product obtained from the evaporated ethyl acetate extracts.) Recrystallization (2-methoxyethanol) gave analytically pure material: mp >260 °C; UV max (CH_3OH) 273 mm (ϵ 38 160); IR (Nujol) 2200 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.13 (s, 2), 8.08 (s, 1); MS (EI at 70 eV), *m/z* 159 ($M^{\cdot+}$, base peak), 132 ($M^{\cdot+}$ – HCN).

Anal. Calcd for $C_7H_5N_5$: C, 52.83; H, 3.17; N, 44.00. Found: C, 52.64; H, 3.29; H, 44.21.

In a similar experiment, **1d** (10 g, 0.05 mol) was mixed with 5% ammonium hydroxide (100 mL) at 60 °C. After 5 h, TLC (ethyl acetate) showed that some starting material still remained. An additional 3 mL of concentrated ammonium hydroxide was added and heating continued for 10 hours. The product was isolated as above to provide 7.4 g (93%) of **3d** as a light tan solid, mp >260 °C, identical with the product prepared above.

4(5)-Cyanoimidazole (3a). The water solubility of **3a** and extensive hydrolysis to amide that we observed on removal of water in vacuo, on completion of the reaction, led to an alternate isolation procedure for **3a**. A mixture of 2.0 g (0.015 mol) 4(5)-(trifluoromethyl)imidazole (**1a**)[9] and 5% NH_4OH (100 mL) was heated at 60 °C for 8 h. The cooled reaction was neutralized to pH 7 with glacial acetic acid, saturated with NaCl, and continuously extracted with CH_2Cl_2 for 24 h. After removal of the CH_2Cl_2 and drying under vacuum, 1.19 g (87%) of **3a** was obtained as a light yellow powder: mp 141–144 °C (lit.[3] mp 143.5–144.5 °C); mp 142–144 °C ($CHCl_3$/CH_3CN); IR (Nujol) 2230 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.95 (m, 1), 8.08 (m, 1); MS (EI at 70 eV), *m/z* 93 ($M^{\cdot+}$), 66 ($M^{\cdot+}$ – HCN).

Anal. Calcd for $C_4H_3N_3$: C, 51.61; H, 3.24; N, 45.14. Found: C, 51.54; H, 3.21; N, 44.93.

2-[4-(1*H*-Imidazol-1-yl)phenyl]-1*H*-imidazole-4-carbonitrile (3b) (Table I): IR (Nujol) 2220 cm^{-1}; ^{1}H NMR (1:1 (Me_2SO-d_6–$CDCl_3$) δ 7.4 (s, 1), 7.8–8.5 (m, 7); MS (EI at 70 eV), *m/z* 235 ($M^{\cdot+}$).

Anal. Calcd for $C_{13}H_9N_5 \cdot {}^1/_2H_2O$: C, 63.82; H, 4.12; N, 28.67. Found: C, 63.45; H, 3.95; N, 28.33.

2,2′-(1,4-Phenylene)bis(1*H*-imidazole-4-carbonitrile) (3c) (Table I): IR (Nujol) 2250 cm^{-1}; ^{1}H NMR (1:1 Me_2SO-d_6–$CDCl_3$) δ 7.98 (s, 2), 8.0 (m, 4); MS (EI at 70 eV), m/z 260 ($M^{\cdot+}$).

Anal. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29. Found: C, 64.59; H, 3.06; N, 32.70.

[2,2′-Bi-1*H*-imidazole]-4,4′-dicarbonitrile (3e) (Table I): IR (Nujol) 2220 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.35 (s); MS (EI at 70 eV), *m/z* 184 ($M^{\cdot+}$, base peak).

Anal. Calcd for $C_8H_4N_6$: C, 52.18; H, 2.19; N, 45.63. Found: C, 51.90; H, 2.35; N, 45.79.

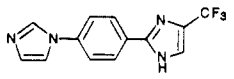
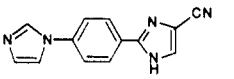
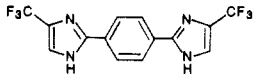
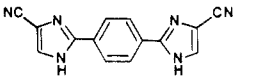
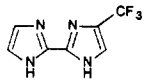
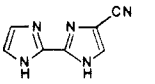
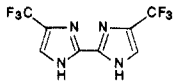
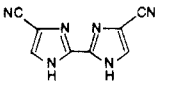
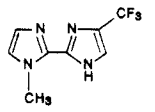
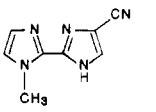
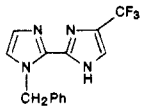
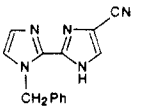
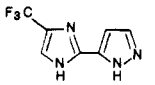
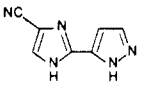
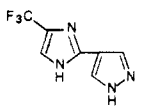
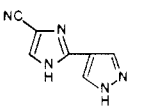
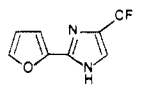
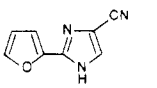
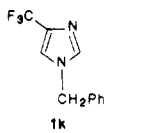
1′-Methyl-[2,2′-bi-1*H*-imidazole]-4-carbonitrile (3f) (Table I): IR (Nujol) 2220 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.0 (s, 3), 7.05 (d, 1, J = 1.5 Hz), 7.35 (d, 1, J = 1.5 Hz), 8.2 (s, 1); MS (EI at 70 eV), *m/z* 173 ($M^{\cdot+}$, base peak).

Anal. Calcd for $C_8H_7N_5$: C, 55.49; H, 4.08; N, 40.44. Found: C, 55.27; H, 4.18; N, 40.29.

1′-(Phenylmethyl)-[2,2′-bi-1*H*-imidazole]-4-carbonitrile (3g) (Table I): IR (Nujol) 2210 cm^{-1}; ^{1}H NMr δ 5.8 (s, 2), 7.1 (d, 1, J = 1 Hz), 7.3 (s, s), 7.45 (d, 1, J = 1 Hz), 8.2 (s, 1); MS (EI at 70 eV), *m/z* 249 ($M^{\cdot+}$).

(6) Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1979**, *44*, 2902.
(7) Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1980**, *45*, 3831.
(8) Kimoto, H.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3403.
(9) Baldwin, J. J.; Kasinger, P. A., Novello, F. C.; Sprague, J. M.: Duggan, D. E. *J. Med. Chem.* **1975**, *18*,, 895.
(10) Lombardino, J. G. *J. Heterocycl. Chem.* **1973**, *10*, 697.
(11) Kimoto, H.; Fujii, S. *J. Org. Chem.* **1982**, *47*, 2867.
(12) McCarthy, J. R.; Matthews, D. P.; Whitten, J. P. *Tetrahedron Lett.* **1985**, *26*, 6273.
(13) At the editors suggestion, we would like to report the conversion of 2-(trifluoromethyl)imidazole to 2-cyanoimidazole is 99.3% in 1 h under the conditions reported in the Experimental Section (60 °C).

Table I. Preparation of 4(5)-Cyanoimidazoles 3[a]

substrate[b]	product[c]	% yield[d]	mp, °C	recryst solvent
 1a[e]	 3a	87	142–144[f]	$CHCl_3/CH_3CN$
 1b	 3b	65	>250	H_2O
 1c	 3c	48	>250	DMF
 1d	 3d	93	>260	HOAc or $MeOCH_2CH_2OH$
 1e	 3e	70	>250	$EtOH/H_2O$
 1f	 3f	94	>270	$MeOCH_2CH_2OH$
 1g	 3g	69	239–241	$MeOCH_2CH_2OH/H_2O$
 1h	 3h	80	259–261	*i*-$PrOH/H_2O$
 1i	 3i	94	258–259	*i*-$PrOH/H_2O$
 1j	 3j	77	229–232	$MeOH/H_2O$
 1k		*g*		

[a] See Experimental Section for reaction conditions. [b] Experimental procedures for unreported substrates are available in the supplementary material and utilized the method of Baldwin and co-workers (ref 9). [c] All products exhibited ^1H NMR, IR, and MS characteristics consistent with the assigned structure. [d] Satisfactory C, H, N analysis was obtained on all new compounds. [e] See ref 9. [f] Literature[3] mp 143.5–144.5 °C. [g] No reaction.

Anal. Calcd for $C_{14}H_{11}N_5$: C, 67.46; H, 4.45; N, 28.09. Found: C, 67.21; H, 4.61; N, 27.81.

2-(1*H*-Pyrazol-3-yl)-1*H*-imidazole-4-carbonitrile (3h) (Table I): IR (Nujol) 2245 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.82 (d, 1, J = 2 Hz) 7.92 (d, 1, J = 2 Hz), 8.25 (s, 1). MS (EI at 70 eV), m/z 159 ($M^{\bullet+}$).

Anal. Calcd for $C_7H_5N_5$: C, 52.83; H, 3.17; N, 44.00. Found: C, 52.66; H, 3.16; N, 43.62.

2-(1*H*-Pyrazol-4-yl)-1*H*-imidazole-4(5)-carbonitrile (3i) (Table I): IR (Nujol) 2230 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.00 (s, 2), 8.03 (s, 1); MS (EI at 70 eV), m/z 159 ($M^{\bullet+}$).

Anal. Calcd for $C_7H_5N_5$: C, 52.83; H, 3.17; N, 44.00. Found: C, 52.95; H, 3.21; N, 43.69.

2-(2-Furanyl)-1*H*-imidazole-4(5)-carbonitrile (3j) (Table I): IR (Nujol) 2220 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.6 (dd, 1, J = 2 Hz, J = 4 Hz), 6.96 (d, 1, J = 4 Hz), 7.8 (d, 1, J = 2 Hz), 8.1 (s, 1); MS (CI/CH_4), m/z 160 (MH^+).

Anal. Calcd for $C_8H_5N_3O$: C, 60.38; H, 3.17; N, 26.41. Found: C, 60.38; H, 3.29; N, 26.33.

Acknowledgment. We thank Dr. Roger Sargent for developing assays for monitoring conversions by HPLC.

Registry No. **1a**, 33468-69-8; **1b**, 102807-84-1; **1c**, 63874-92-0; **1d**, 102807-85-2; **1e**, 102807-86-3; **1f**, 102807-87-4; **1g**, 102807-88-5; **1h**, 102807-89-6; **1i**, 102807-90-9; **1j**, 33468-88-1; **3a**, 57090-88-7; **3b**, 102807-91-0; **3c**, 102807-92-1; **3d**, 102807-93-2; **3e**, 102807-94-3; **3f**, 102807-95-4; **3g**, 102807-96-5; **3h**, 102807-97-6; **3i**, 102807-98-7; **3j**, 102807-99-8; **4**, 10199-67-4; **5**, 63874-95-3; **6**, 63874-96-4; **7**, 102808-00-4; **8**, 102808-01-5; **9**, 102781-70-4; **10**, 102808-02-6; DMF, 68-12-2; $Br_2CHCOCF_3$, 431-67-4; $CH(OEt)_3$, 122-51-0; 4-(imidazol-1-yl)benzaldehyde, 10040-98-9; terephthaldehyde, 623-27-8;

2-formylimidazole, 10111-08-7; 1-methyl-2-formylimidazole, 13750-81-7; 1-benzyl-2-formylimidazole, 10045-65-5; 2-furaldehyde, 98-01-1.

Supplementary Material Available: An example of the procedure for the synthesis of 1 is provided. Additional procedures needed to obtain **1e**, **1h**, **1i**, and **1k** are provided and outlined in Schemes I and II. Table II with % yield, mp, and recrystallization solvent for **1b–k** is included as well (6 pages). Ordering information is given on any current masthead page.

An Unusual Bisulfite Addition Compound from 3,5-Dipyrrolidinophenol

Robert J. Highet

Laboratory of Chemistry, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892

Received March 13, 1986

Earlier investigations have shown that 3,5-dipyrrolidinophenol (1) exhibits a facile tautomerism in solution between phenolic and dienone forms depending on the nature of the solvent. In solvents capable of accepting a hydrogen bond, such as dimethyl sulfoxide, the molecule exists as the phenolic form,[1] while in solvents that donate a hydrogen bond, such as water or trichloroethanol, it exists in a dienone form.[2] This note describes the formation of a zwitterionic bisulfite addition derivative of the carbonyl form.

In the course of exploratory studies of a series of solvents, a solution of 1 in sulfur dioxide was examined. ^1H and ^{13}C NMR spectra of the solution showed only the phenolic form, but addition of water led to an unexpected product. Although no carbonyl peak appeared in the ^{13}C spectrum, in view of the facile tautomerism of 1, it seemed reasonable to view the material as a derivative of the ketonic form. The presence of a fully saturated carbon atom with a chemical shift of 83.2 ppm suggested that the sulfurous acid generated by addition of water produced a bisulfite addition product, with the balancing positive charge borne by the vinamidinium system, i.e., 4, (Scheme I).

The spectra of 4 and other NMR data in Table I support this structure. All of the spectra of 4 show the presence of an element of symmetry. The AB quartet of the methylene protons of the alicyclic ring is approximately four times the area of the olefinic singlet. Peaks in ^{13}C spectrum show heights approximately proportional to the number of atoms represented of protonated (C-2 plus C-6 vs. C-4) and nonprotonated carbon atoms (C-3 plus C-5 vs. C-1). A single peak appears in the ^{15}N spectrum, with a midfield resonance appropriate to an vinamidinium nitrogen.[3] The observed chemical shifts and multiplicities in off-resonance spectra are appropriate to the nature of the assigned carbon atoms. The difference in chemical shifts of the methylene protons evidently arises from the adjacent C-1 substituents. In the rigidly planar vinamidinium system, the two α (or β) carbon atoms of a pyrrolidine ring differ, being cis to the alicyclic methylene group or to the olefinic carbon. As a consequence, they show different chemical shifts.

Scheme I. Conversion of 1 to Dienone Tautomers 2 and 3 and to the Bisulfite Addition Compound 4

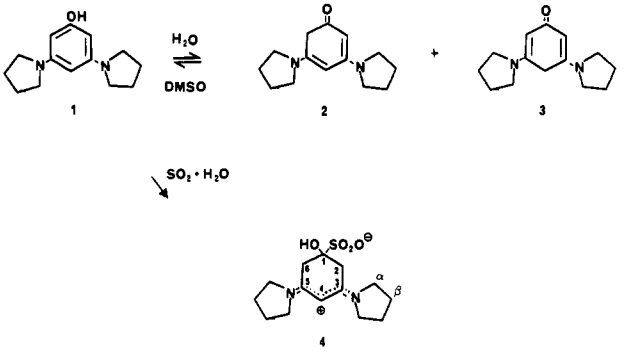


Table I. NMR Characteristics of Compounds 1–4

C	^{13}C NMR, ppm 1	2	3	4	^1H NMR, ppm (J, Hz) 4
1	158.6	179.6	185.0	83.2	
2	88.4	89.2[a]	92.0	33.8	3.01, 3.05 (−17.3)
3	149.4	161.6[b]	154.7	162.0	
4	87.8	82.8[a]	30.60	87.8	5.10
5	149.4	155.6[b]	154.7	162.0	3.01, 3.05 (−17.3)
6	88.4	36.2	92.0	33.8	
α	47.3	46.1, 46.7	[c]	48.8, 48.6	3.2–3.0
β	24.9	23.0	[c]	23.6, 23.1	2.0–2.15

^{15}N NMR, ppm 1	2	3	4
74.3	121.4, 115.6	109.3	143.8

[a,b] Assignments can be interchanged. [c] Obscured.

^{15}N spectra offered a further characterization of the series. The parent phenol in dimethyl sulfoxide showed a chemical shift somewhat downfield from that of *N,N*-dimethylaniline (71.9 vs. 44.6 ppm; cf., *N*-methylpyrrolidine, 43.6 ppm, vs. trimethylamine, 17.1 ppm).[4] The trichloroethanol solution showed the three peaks listed in Table I, although earlier studies had shown only the existence of the 2,4-dienone 2. However, ^{13}C spectra of the solution at the higher field and sensitivity now available showed the presence of a second dienone in approximately 10% of the concentration of the major material, with the peaks listed in Table I, attributable to the symmetrical 2,5-dienone 3. The ^{15}N frequencies observed are comparable to that of 3-(*N*-pyrrolidinyl)cyclohexenone, 105.8 ppm.[4]

The formation of sodium bisulfite addition compounds from ketones and aldehydes is known to proceed via the sulfite dianion.[5] In this case, the reaction is assisted by the increased stability of the resonating vinamidinium system of 4.

Evaporation of the sulfur dioxide from the solution of 4 left a white powder, which was insoluble in organic solvents and reverted to the phenol 1 in water. Preparation of 4 in a solution of sulfur dioxide and ca. 30% dioxane produced colorless prisms, which also reverted to the phenol on standing.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian XL-200 NMR spectrometer. Solutions for ^1H and ^{13}C spectra of 1 were approximately 0.5 M and included tetramethylsilane as an internal reference (=0 ppm). Solutions for ^{15}N spectra included nitromethane as an internal reference (=379 ppm, NH_3 = 0 ppm);[4]

(1) Effenberger, F.; Niess, R. *Chem. Ber.* **1966**, *101*, 3787.
(2) Highet, R. J.; Chou, F. E. *J. Am. Chem. Soc.* **1977**, *99*, 3538.
(3) Rabiller, C.; Ricolleau, G.; Martin, M. L.; Martin, G. J. *Nouv. J. Chim.* **1980**, *4*, 35.
(4) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Resonance Spectroscopy*; Wiley: New York, 1979.
(5) Green, L. R.; Hine, J. *J. Org. Chem.* **1974**, *39*, 3896.