GLC analysis of the residue obtained on workup showed a single product. Samples of piperidine **5** for analysis were collected by preparative GLC: picrate, mp 224–225 °C; 100-MHz ^{1}H NMR δ 0.88 (s, 2 CH_3), 2.12 (dd, 2 CH), ca. 0.98–1.94 (m, $CH_2CH_2CH_2$); 200-MHz ^{13}C NMR 26.3 (C_4), 27.0 (6 CH_3), 27.2 (C_3), 34.1 (2 quaternary C), 67.0 (2 CH). Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 78.94; H, 13.92; N, 6.98.

Chemical Shift Reagent Studies. Studies were attempted by using *trans*-2,6-di-*tert*-butylpiperidine (**2**) and the tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato) derivatives of ytterbium(III), praseodynium(III), and europium-(III):[Yb(FOD)$_3$, Pr(FOD)$_3$, and Eu(FOD)$_3$ respectively] obtained from Alfa-Ventron and tris(diisobutyrylmethanato)ytterbium(III) [Yb(DIMB)$_3$], which was prepared from a known[11] procedure.

In the shift reagent study of 2,6-di-*tert*-1,2,5,6-tetrahydropyridine (**1**) progressively larger amounts of Yb(FOD)$_3$ were added to 0.30 M solutions of tetrahydropiperidine **1** in $CDCl_3$. The data from these studies are summarized in Figure 1.

Computer Analysis of NMR Parameters. NMR parameters of 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine (**1**) were obtained by using NMRIT IV and NMREN I: chemical shifts ($\delta \pm 0.001$) 1.854 (H_{5a}), 1.950 (H_{5e}), 2.635 (H_6), 3.035 (H_2), 5.819 (H_3), 5.917 (H_4); coupling constants (Hz ● 0.2) $J_{2,3} = 3.4$, $J_{2,4} = -1.9$, $J_{2,5a} = 2.9$, $J_{2,5e} = 0$, $J_{2,6} = 0$, $J_{3,4} = 10.8$, $J_{3,5a} = -2.5$, $J_{3,5e} = 0$, $J_{3,6} = 0$, $J_{4,5a} = 4.3$, $J_{4,5e} = 0$, $J_{4,6} = 0$, $J_{5a,5e} = -10.0$, $J_{5a,6} = 10$, $J_{5e,6} = 4.3$.

Acknowledgment. We express appreciation for support of this research to the Robert A. Welch Foundation and the Organized Research Fund of The University of Texas at Arlington.

Registry No. **1**, 101166-51-2; **2**, 101166-52-3; **5**, 66922-18-7; 2,6-di-*tert*-butylpyridine, 585-48-8; pyridine, 110-86-1; *tert*-butyllithium, 594-19-4.

[2-(Trimethylsilyl)ethoxy]methyl (SEM) as a Novel and Effective Imidazole and Fused Aromatic Imidazole Protecting Group

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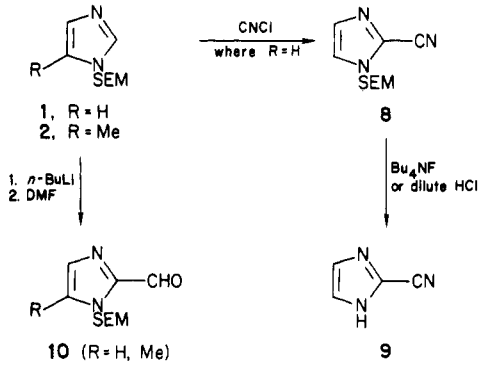
The abundance of imidazole-containing pharmaceutical, agricultural, and natural products has led to an extensive synthetic effort to obtain novel imidazoles. Synthesis often requires protection and subsequent deprotection of the imidazole 1H nitrogen. Many of the imidazole nitrogen protecting groups that have been commonly used often are not removable under reaction conditions compatible with other functional groups in the molecule.[1] There have been several recent advances in imidazole protection, notably the diethoxymethyl[1] and trityl groups.[2] However, the diethoxymethyl group is extremely moisture-sensitive, while trityl-protected imidazoles are often obtained in poor yields.[3] We required a novel imidazole protecting group which was easily introduced, stable, selectively removed, and which assisted purification.[4,5]

The [2-(trimethylsilyl)ethoxy]methyl group (SEM) fulfills the above criteria based on the following observations: *N*-Alkoxymethyl groups are easily introduced into imidazole and increase the selectivity of certain reactions, e.g., metalations.[6] The silyl-modified alkoxymethyl group, the SEM group, has recently been used as an alcohol protecting group which is easily introduced and stable to a wide range of conditions but is also easily removed.[7] Finally, the SEM group has recently been used as a pyrrole protecting group.[8]

Reaction of imidazole, 4-methylimidazole, and 4-(trifluoromethyl)imidazole and even the highly unstable 4-methoxyimidazole[9] with 50% sodium hydride in DMF followed by treatment with SEMCl gave the corresponding [[2-(trimethylsilyl)ethoxy]methyl]imidazole derivatives as mixtures of the 4(5) isomers (**1–4**) as distillable, stable



liquids in 64–85% yield (see Table I). Using similar procedures, the SEM group was also introduced as a N protecting group on the fused aromatic imidazole derivatives benzimidazole, 4-azabenzimidazole, and even on the highly insoluble 2,2′-bi-1*H*-imidazole[4,10] to give distillable, stable liquids (**5–7**) in good yields.

Removal of the SEM group from alcohols and pyrroles has been reported to proceed with concentrated anhydrous tetrabutylammonium fluoride solutions.[7,8] We have found that reaction of SEM-imidazoles with 1 M tetrabutylammonium fluoride solutions at reflux resulted in good yields of the deprotected imidazoles. More conveniently, the SEM-imidazole derivatives can be deprotected in excellent yield by warming with dilute acid.

SEM-protected imidazoles were shown to be amenable to a number of synthetic operations. SEM-imidazole (**1**) was converted to 2-cyano-SEM-imidazole (**8**) in 66% yield by treatment with cyanogen chloride and a suitable base.[5] Subsequent treatment with 1 M tetrabutylammonium fluoride in THF at reflux for 45 min provided 2-cyanoimidazole (**9**) in 70% yield. Alternatively, deprotection with 0.5 M aqueous ethanolic HCl gave **9** in quantitative yield.

1-SEM-imidazole (**1**) and 1-SEM-4(5)methylimidazole (**2**) were readily metalated with *n*-butyllithium in the 2-position, and subsequent treatment with DMF provided almost quantitative yields of imidazole-2-carboxaldehydes **10**. 1-SEM-7-azabenzimidazole (**6**) on similar treatment

(1) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038.
(2) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381.
(3) Kelley, J. L.; Miller, C. A.; McLean E. W. *J. Med. Chem.* **1977**, *20*, 721.
(4) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *Synthesis*, in press.
(5) McCarthy, J. R.; Matthews, D. P.; Whitten, J. P. *Tetrahedron Lett.* **1985**, *26*, 6273.
(6) Tang, C. G.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.
(7) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343. Lipshutz's group has also informed us that they are currently investigating the use of the SEM group as an imidazolo protecting group.
(8) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203. Edwards, M. P.; Ley, S. V.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630.
(9) Hosmane, R. S. *Tetrahedron Lett.* **1984**, *25*, 363.
(10) 2,2′-Bi-1*H*-imidazole has a water solubility of 1.2 mg/L at 25 °C and approximately 1 g/L in boiling DMF.

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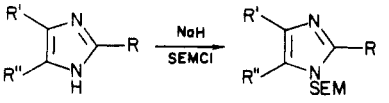
Table I. Yields and Characterization of SEM-Protected Imidazole and Fused Aromatic Imidazole Derivatives



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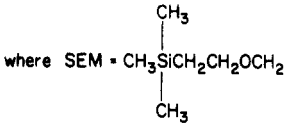
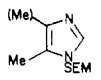
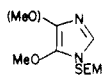
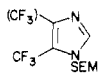
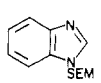
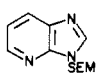
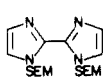
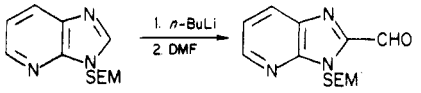


product	yield,[a] %	bp, °C (mm)	mol form[b]	NMR[c]
 1	65	94 (0.2 mm)	$C_9H_{18}N_2OSi$	0.07 (s, 9 H), 0.96 (t, 2 H), 3.51 (t, 2 H), 5.25 (s, 2 H), 7.04 (s br, 1 H), 7.59 (s, 1 H)
 2[d]	85	112–115 (0.5 mm)	$C_{10}H_{20}N_2OSi$	0.10 (s, 9 H), 0.87–1.13 (t, 2 H), 2.33 (s, 3 H), 3.42–3.70 (t, 2 H), 5.27 (s, 2 H), 6.80 (s br, 1 H), 7.53 (s, 1 H)
 3[d]	64	180 (0.3 mm)	$C_{10}H_{20}N_2O_2Si$	0.07 (s, 9 H), 0.82–1.08 (t, 2 H), 3.35–3.76 (t, 2 H), 3.84 (s, 3 H), 5.08 (s, 2 H), 6.34 (m, 1 H), 7.22 (m, 1 H)
 4[d]	75	180 (1.0 mm)	$C_{10}H_{17}F_3N_2OSi$	0.04 (s, 9 H), 0.86–1.12 (t, 2 H), 3.44–3.71 (t, 2 H), 5.20 (s, 2 H), 7.32–7.78 (m, 2 H)
 5	50	220 (0.2 mm)	$C_{13}H_{20}N_2OSi$	0.08 (s, 9 H), 1.00 (t, 2 H), 3.58 (t, 2 H), 5.51 (s, 2 H), 7.20–7.95 (m, 4 H), 8.03 (s, 1 H)
 6[e]	53	230–235 (0.3 mm)	$C_{12}H_{19}N_3OSi$	0.05 (s, 9 H), 0.95 (t, 2 H), 3.6 (t, 2 H), 5.62 (s, 2 H), 7.3 (dd, 1 H, J = 4.9, J = 7.8), 8.1 (dd, 1 H, J = 7.8, J = 1.4), 8.4 (dd, 1 H, J = 5.9, J = 1.4)
 7[f]	79	260 (0.2 mm)	$C_{18}H_{34}N_4O_2Si_2$	0.06 (s, 18 H), 0.99 (t, 4 H), 3.66 (t, 4 H), 6.04 (s, 4 H), 7.28 (m, 4 H)

[a] Yield after distillation. [b] Compounds 1, 2, 4–7 gave satisfactory analytical data (±0.4%; C, H, N). Compound 3 Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 52.59; H, 8.83; N, 12.27. Found: C, 52.08; H, 8.73; N, 12.46. All compounds gave CI mass spectra (70 eV; CH_4) for M + 1. [c] $CDCl_3$ (δ). [d] Mixture of 4 and 5 isomers. [e] Purified by flash chromatography (silica gel, EtOAc) followed by distillation to yield the single isomer 5.[13] [f] Purified by flash chromatography (silica gel, EtOAc) followed by distillation.

with n-butyllithium followed by addition of DMF gave a 93% yield of the 2-aldehyde (11).



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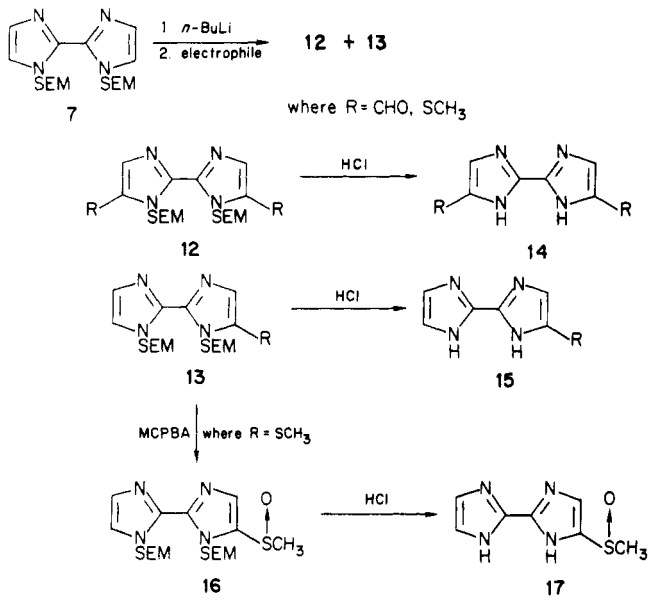
2,2′-Bi-1H-imidazole has found wide utility,[11] yet few derivatives are known, thus making metalation reactions of 7 of greater interest. Optimum conditions for metalation of 1,1′-di-SEM-2,2′-bi-1H-imidazole (7) were found to require 2.5 equiv of n-butyllithium in the presence of 1 equiv of tetramethylethylenediamine (TMEDA). One equivalent of n-butyllithium resulted in modest yields and 3 equiv gave high yields of disubstituted 2,2-bi-1H-imidazoles 12. Treatment of the anion of 7 with DMF or methyl disulfide resulted in 21% to 23% yield of monosubstituted biimidazoles 13 and 12–17% of disubstituted biimidazoles 12. The mono- (13) and disubstituted (12) compounds were separable be flash chromatography. These results parallel those found on metalation of SEM-pyrrole.[8]

Deprotection of the SEM-biimidazoles 12 and 13 with dilute acid gave 14 and 15 (R = CHO, SMe) in excellent yields.

The regiochemistry of the substituents in 12 and 13 would be predicted to be in the 5-position from a SEM-assisted metalation.[6] The regiochemistry of 13 (R = SMe) was demonstrated by oxidation to the sulfoxide 16. A strong geminal coupling for one of the SEM N-methylenes was observed in the ^{1}H NMR spectrum. This coupling is explained by a SEM methylene interaction with the sulfoxide, which is only possible when the sulfoxide is in the 5-position. By analogy, the structures of compounds 12 and 13 were assigned as shown. It should be noted that the structural assignments of the products resulting from the removal of the SEM protecting groups are unequivocal.

Thus, the SEM group, a novel imidazole protecting group, is introduced in high yield onto imidazole, benzimidazole, azabenzimidazole and 2,2′-bi-1H-imidazole. These N-protected imidazoles are easily purified as distillable oils. They are stable to a wide variety of common

(11) Bernhard, P.; Lehmann, H.; Ludi, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1216. Rasmussen, P. G.; Hough, R. L.; Anderson, J. E.; Bailey, O. H.; Bayon, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6155. Williams, J. F.; Heugebaert, F. C.; Pollet, R. J. *Res. Discl.* **1975**, *136*, 39; *Chem. Abstr.* **1975**, *83*, 186250y. Schoof, S.; Gusten, H.; Heinze, J.; Baumgaertel, H.; Ger. Offen DE 2 232 260, 1974; *Chem. Abstr.* **1974**, *81*, 14722w. Chromecek, R. C.; Friends, G. D.; Wissman, L. Y.; Atchison, R., Eur. Pat. Appl. Ep 79721 A2, 1983; *Chem. Abstr.* **1983**, *99*, 93790q. Klose, W.; Boettcher, I., Ger. Offen. DE3141063A1, 1983; *Chem. Abstr.* **1983**, *99*, 88196w. Melloni, P.; Dradi, E.; Logemann, W.; DeCarneri, I.; Trane, F. *J. Med. Chem.* **1972**, *15*, 926.



organic reactions and can be deprotected in excellent yield.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM-360 (60 MHz) and Varian XL-300 (300 MHz) spectrometers. All chemical shifts were reported in ppm (δ units) 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. Microanalyses were performed by the Analytical Laboratories of Merrell Dow Pharmaceuticals, Cincinnati, OH.

General Procedure for SEM Protection of Imidazole and Imidazole Derivatives. Under a blanket of nitrogen, 8.2 g (0.17 mol) 50% sodium hydride was washed with hexane. The flask was charged with 250 mL of dry DMF and the imidazole derivative (0.175 mol) was added in small portions. After stirring at room temperature for 1.5 h, 30.8 g (0.185 mol) of [2-(trimethylsilyl)-ethoxy]methyl chloride (SEMCl) was added dropwise. The reaction became slightly warm and was stirred for 1 h and then quenched with water and extracted into ethyl acetate (3 × 200 mL). The combined organic layers were shaken with water (3 × 200 mL), dried, (Na_2SO_4), and concentrated to give a tan oil. The products were purified by distillation as shown in Table I.

1*H*-Imidazole-2-carbonitrile (9). Cyanogen chloride (3.1 g, 50 mmol) was bubbled into a 50-mL four-necked flask equipped with a stirring bar, nitrogen bubbler, gas inlet tube, thermometer, and septum and CH_3CN (20 mL) (ice bath was used to avoid mild heat of solution). The reaction was cooled in an ice bath, and a solution of 1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazole (1) (1.0 g, 5 mmol) in CH_3CN (ca. 5 mL) was added via syringe. The colorless solution turned yellow-orange and within a few minutes a yellow-orange crystalline solid started to form. After 2 h, the thick slurry was cooled to −20 °C and triethylamine (7 mL, 50 mmol) was added at such a rate as to prevent the temperature from rising above 0 °C. The mixture was stirred for 1 h while being warming to room temperature, poured into saturated aqueous $NaHCO_3$ (100 mL), and extracted with ether (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and purified by Kugelrohr distillation. After a forerun of diethyl cyanamide, 8 was collected at 110–120 °C (0.4 mm) (0.74 g, 66%): IR (thin film) 2230 cm^{-1}; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 0.0 (s, 9 H), 0.91 (t, 2 H, J = 8.2 Hz), 3.55 (t, 2 H, J = 8.2 Hz), 5.57 (s, 2 H), 7.3 (d, 1 H, J = 1.5 Hz), 7.84 (d, 1 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.56, 17.52, 67.34, 75.92, 110.63, 121.06, 132.08; MS (CI/CH_4), m/z 224 (MH^+). Anal. Calcd for $C_{10}H_{17}N_3OSi$: C, 53.77; H, 7.67; N, 18.81. Found: C, 53.77; H, 7.66; N, 18.43.

1-[[2-(Trimethylsilyl)ethoxy]methyl]-1*H*-imidazole-2-carbonitrile (8) (0.225 g, 1 mmol) was mixed with 1 M tetrabutylammonium fluoride in THF (5 mL) and heated to reflux under a nitrogen atmosphere. After 45 min the reaction was cooled and diluted with pH 7.00 buffer (20 mL). The resulting mixture was extracted ether (5 × 50 mL), and the organic layers combined and washed with pH 7.00 buffer (5 mL). The solution was then dried ($MgSO_4$) and evaporated to dryness. Recrystallization from benzene yielded 65 mg of white crystalline 1*H*-imidazole-2-carbonitrile (9); mp 173–176 °C (lit.[12] mp 176–178 °C): IR, NMR, and MS were identical with that of an authentic sample.

1-[[2(Trimethylsilyl)ethoxy]methyl]-1*H*-imidazole-2-carbonitrile (8) (0.225 g, 1 mmol) was mixed with ethanol (10 mL) and 1 M aqueous HCl (10 mL) and heated under a nitrogen atmosphere at 50 °C. After 5 h the reaction was cooled and neutralized with 1 M NaOH. The resulting mixture was extracted with ether (5 × 50 mL), and the organic extracts were combined, dried ($MgSO_4$), and evaporated to a white crystalline solid. Recrystallization from benzene yielded 90 mg of white crystalline 9; mp 174–175 °C: IR, NMR, and MS were identical with that of an authentic sample.

1-[[2-(Trimethylsilyl)ethoxy]methyl]-4(5)-methyl-1*H*-imidazole-2-carboxaldehyde (10, R = Me). Under nitrogen, a mixture of 2 g (9.4 mmol) of 2 and 50 mL of THF was cooled to −40 °C. Then 6.5 mL (9.4 mmol) of 1.45 M *n*-butyllithium in hexane was added. After 15 min 0.9 mL of DMF was added, the reaction was stirred for 12 h and hydrolyzed with 20 mL of saturated NH_4Cl, and the product was extracted into ethyl acetate. Drying (Na_2SO_4) and concentration gave 2.0 g (89%) of a clear oil, bp 160 °C (1 mm): ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 1.1 (m, 2 H), 2.2 (s, 3 H), 3.72 (t, 2 H, J = 7 Hz), 6.05 (s, 2 H), 7.12 (s, 1 H), 10.1 (s, 1 H); MS (CI/CH_4), m/z 241 (MH^+), 213 (MH^+ − CO), 197 (213 − H − CH_3), 183 (213 − 2CH_3). Anal. Calcd for $C_{11}H_{20}N_2O_2Si$: C, 54.96; H, 8.39; N, 11.65. Found: C, 54.82; H, 8.38; N, 11.67.

1-[[2-(Trimethylsilyl)ethoxy]methyl]-1*H*-imidazole-2-carboxaldehyde (10, R = H). Using a procedure identical with that used for the preparation of **10** (R = Me), **10** (R = H) was prepared starting with 1 in 96%, bp 156 °C (0.1 mm): ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 1.1 (m, 2 H), 3.72 (t, 2 H, J = 3 Hz), 6.05 (s, 2 H), 7.12 (s, 1 H), 8.05 (s, 1 H), 10.1 (s, 1 H); MS (CI/CH_4), m/z 213 (MH^+). Anal. Calcd for $C_{10}H_{18}N_2O_2Si$; C, 53.07; H 8.01; N, 12.38. Found: C, 53.19; H, 7.86; N, 12.30.

1-[[2-(Trimethylsilyl)ethoxy]methyl]-1*H*-imidazo[4,5-*b*]pyridine-2-carboxaldehyde (11). Using a similar procedure to that used for the preparation of **10** (R = Me), **11** was prepared in 93% as a clear oil after flash chromatography (MeOH/$CHCl_3$, 97:3): ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.84–1.17 (t, 2 H), 3.60–3.90 (t, 2 H), 6.17 (s, 2 H), 7.34–7.58 (m, 1 H), 8.23–8.77 (m, 2 H), 10.23 (s, 1 H); MS (CI/CH_4), m/z 278 (MH^+). Anal. Calcd for $C_{13}H_{19}N_3O_2Si$; C, 56.29; H, 6.90; N, 15.15. Found: C, 56.50; H, 7.17; N, 15.10.

1,1′-Bis[[2-(trimethylsilyl)ethoxy]methyl]bi-1*H*-imidazole-4-carboxaldehyde (13, R = CHO) and 1,1′-Bis-[[2-(trimethylsilyl)ethoxy]methyl]bi-1*H*-imidazole-4,4′-dicarboxaldehyde (12, R = CHO). Under nitrogen, a mixture of 940 mg (2.4 mmol) of 1,1′-bis[[2-(trimethylsilyl)ethoxy]methyl-2,2′-bi-1*H*-imidazole (7), 280 mg (2.4 mmol) of TMEDA, and 30 mL of THF was cooled to −40 °C; 2.67 M *n*-butyllithium in hexane (2.5 mL, 6.6 mmol) was added, and after 15 min, 0.23 mL (3.0 mmol) of DMF in THF was added. The reaction was allowed to proceed for 1 h at room temperature, diluted with 1 N HCl, and extracted with ethyl acetate. After drying (Na_2SO_4) and concentrating, 1.07 g of yellow oil was obtained. Flash chromatography (hexane/EtOAc; 1:1) gave 80 mg of recovered starting material (7) (7%), 230 mg of **13** (22.7%), 80 mg of **12** (7%), and 60 mg of a 1:1 mixture of **12** and **13** (8.5%).

13 (R = CHO): ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 0.18 (s, 9 H), 1.1 (m, 4 H), 3.72 (t, 4 H, J = 7 Hz), 6.05 (s, 2 H), 6.55 (s, 2 H), 7.42 (s br, 2 H), 8.00 (s, 1 H), 10.08 (s, 1 H).

12 (R = CHO): ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 18 H), 1.05 (m, 4 H), 3.70 (t, 4 H, J = 7 Hz), 6.51 (s, 4 H), 8.03 (s, 2 H), 10.01 (s, 2 H).

2,2′-Bi-1*H*-imidazole-4-carboxaldehyde (15, R = CHO). The protected aldehyde **13** (R = CHO) (0.6 g, 1.42 mmol) was warmed

(12) Barltrop, J. A.; Day, A. C.; Mack, A. G.; Shahrisa, A.; Wakamatsu, S. *J. Chem. Soc., Chem. Commun.* **1981**, 604.
(13) Elguero, J.; Fruchier, A.; Mignonac-Mondon, S. *Bull. Soc. Chim. Fr.* **1972**, 2916.

at 50 °C with 30 mL of 5 M HCl for 3 h. The cooled reaction was neutralized with saturated K_2CO_3 solution and extracted with EtOAc (5 × 25 mL). After drying (Na_2SO_4) and concentrating, 0.22 g (96%) of yellow solid 2,2′-bi-1*H*-imidazole-4-carboxaldehyde (**15**, R = CHO) was obtained. TLC (30% MeOH/CH_2Cl_2) showed one spot. The solid was warmed with ethanolic HCl to prepare the dihydrochloride salt (EtOH), mp 229–231 °C: ^{1}H NMR (D_2O/DSS) δ 7.62 (s, 2 H), 8.30 (s, 1 H), 9.81 (s, 1 H); MS (CI/CH_4), *m/z* 163 (M^+ + 1), 191 (M^+ + 29), 203 (M^+ + 41). Anal. Calcd for $C_7H_6N_4O$·2HCl·EtOH: C, 40.16; H, 4.87; N, 20.82. Found: C, 39.97; H, 4.90; N, 20.50.

2,2′-Bi-1*H*-imidazole-4,4′-dicarboxaldehyde (14, R = CHO). Aldehyde **12** (R = CHO) (0.7 g, 1.56 mmol) was refluxed with 30 mL of 5 N HCl for 1.5 h. The cooled reaction was neutralized with aqueous K_2CO_3 and then concentrated to dryness. The solid residue was slurried with 25 mL of H_2O, collected by vacuum filtration, and washed with 50 mL of cold H_2O. After drying, 0.2 g (67.5%) of 2,2′-bi-1*H*-imidazole-4,4′-dicarboxaldehyde (**14**, R = CHO) was obtained as a tan solid, mp >255 °C: NMR (Me_2SO-d_6) δ 7.90 (s, 2 H), 9.66 (s, 2 H); MS (CI/CH_4), *m/z* 191 (M^+ + 1, base peak), 219 (M^+ + 41), 163 (M^+ + 1 − CHO); HRMS calcd for $C_8H_6N_4O_2$ 190.0492, found 190.0502.

1,1′-Bis[[2-(trimethylsilyl)ethoxy]methyl]-4,4′-bis(methylthio)-2,2′-bi-1*H*-imidazole (12, R = SCH_3) and 1,1′-Bis-[[2-(trimethylsilyl)ethoxy]methyl]-4-(methylthio)-2,2′-bi-1*H*-imidazole (13, R = SCH_3). Under nitrogen, a mechanically stirred solution of 18.3 g (0.046 mmol) of **7**, 7.0 mL (0.046 mmol) of TMEDA, and 150 mL of THF was cooled to −40 °C, and 37.6 mL (0.116 mmol) of 3.1 M *n*-butyllithium in hexane was added. The thick slurry was stirred for 15 min and 10.2 mL (0.113 mmol) of methyl disulfide was added. The solid immediately dissolved. The reaction was allowed to warm to room temperature overnight. The reaction was diluted with H_2O and extracted into EtOAc (3 × 125 mL). The EtOAc layers washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated to give 17.9 g of crude product. Flash chromatography (800 g of silica gel, 30% EtOAc/hexane) gave 4.2 g (20.8%) of **13** and 3.8 g (17%) of **12**.

13 (R = SMe): ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 18 H), 0.81–1.14 (m, 4 H), 2.48 (s, 3 H), 3.46–3.79 (m, 4 H), 5.98 (s, 2 H), 6.17 (s, 2 H), 7.27 (s, br, 2 H), 7.36 (s, 1 H); MS (CI/CH_4), *m/z* 441 (M^+ + 1).

12 (R = SMe): ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 18 H), 0.95 (t, 4 H, *J* = 7 Hz), 2.49 (s, 6 H), 3.63 (t, 4 H, *J* = 7 Hz), 6.15 (s, 4 H), 7.35 (s, 2 H); MS (CI/CH_4), *m/z* 487 (M^+ + 1), 515 (M^+ + 29), 527 (M^+ + 41).

4-(Methylthio)-2,2′-bi-1*H*-imidazole (15, R = SCH_3). A mixture of 1.5 g (3.4 mmol) of **13** (R = SCH_3), 50 mL of EtOH, and 100 mL of 5 N HCl was refluxed for 3 h. The EtOH was removed in vacuo and the remaining aqueous solution neutralized with K_2CO_3 solution. The white solid which formed was collected and dried to give 0.77 g of crude product. Recrystallization (isopropyl alcohol) gave 0.3 g (49%) of 4-(methylthio)-2,2′-bi-1*H*-imidazole (**15**, R = SMe), mp >250 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.68 (s, 3 H), 7.08 (s, 2 H), 7.11 (s, 1 H); MS (CI/CH_4), *m/z* 181 (MH^+), 209 (M^+ + 29), 221 (M^+ + 41); HRMS calcd for $C_7H_8N_4S$ 180.0471, found 180.0457.

4,4′-Bis(methylthio)-2,2′-bi-1*H*-imidazole (14, R = SCH_3). Using a procedure identical with that for the preparation of **15** (R = SMe), 4,4′-bis(methylthio)-2,2′-bi-1*H*-imidazole (**14**, R = SMe) was prepared in 86.3% (IPA) yield; mp >260 °C: NMR (Me_2SO-d_6) δ 2.39 (s, 6 H), 7.18 (s, 2 H); MS (EI), *m/z* 226 (M^+), 221 (M^+ − CH_3), 193 (M^+ − SH). HRMS calcd for $C_8H_{10}N_4S_2$ 226.0349, found 226.0348. Anal. Calcd for $C_8H_{10}N_4S_2$: C, 42.48; H, 4.47; N, 24.77. Found: C, 42.83; H, 4.32; N, 22.52.

4(5)-(Methylsulfinyl)-2,2′-bi-1*H*-imidazole (17). A mixture of 2.1 g of **13** (R = SMe) (0.0048 mmol) in 100 mL of CH_2Cl_2 was cooled to 0 °C. Solid 80% *m*-chloroperbenzoic acid (1.08 g, 0.0050 mmol) was added in small portions. The progress of the reaction was followed by TLC (10% hexane/EtOAc) and after 1 h the reaction was quenched with aqueous K_2CO_3 and extracted with EtOAc (2 × 100 mL). The organic layer was shaken with aqueous K_2CO_3 a second time. Drying (Na_2SO_4) and concentration gave 1.95 g (89%) of crude product. Flash chromatography (500 g of silica gel, 10% hexane/EtOAc) gave 1.3 g (59%) of 5-(methylsulfinyl)-1,1′-bis[[2-(trimethylsilyl)ethoxy]methyl]-2,2′-bi-1*H*-imidazole (**16**) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 18 H), 0.98 (t, 4 H, *J* = 7 Hz), 3.14 (s, 3 H), 3.48–3.85 (m, 4 H), 5.93 (s, 2 H), 6.26 (q, 2 H, J_{gem} = 12 Hz), 7.26 (m, 2 H), 7.63 (s, 1 H); MS (CI/CH_4), *m/z* 457 (MH^+). A mixture of 1.25 g (2.74 mmol) of **16**, 50 mL of EtOH, and 100 mL of 5 N HCl was refluxed for 2.5 h. The EtOH was removed in vacuo and the aqueous solution carefully neutralized with K_2CO_3 solution. The resultng solid (**9**) was collected and the filtrate concentrated to dryness. Flash chromatography (2:18:80 concentrated NH_4OH/MeOH/$CHCl_3$) of the EtOH-soluble material gave 0.15 g (28%) of **17**, mp 87–90 °C: ^{1}H NMR (Me_2SO-d_6) δ 2.90 (s, 3 H), 7.31 (s, 2 H), 7.87 (s, 1 H); MS (EI), *m/z* 196 (M^+), 181 (M^+ − CH_3, base peak); HRMS calcd for $C_7H_8N_4OS$ 196.042, found 196.0411.

Registry No. **1**, 101226-33-9; **2** (5-isomer), 101226-34-0; **2** (4-isomer), 101226-54-4; **3** (5-isomer), 101226-35-1; **3** (4-isomer), 101226-55-5; **4** (5-isomer), 101226-36-2; **4** (4-isomer), 101226-56-6; **5**, 101226-37-3; **6**, 101226-38-4; **7**, 101226-39-5; **8**, 101226-40-8; **9**, 31722-49-3; **10** (R = Me), 101226-41-9; **10** (R = H), 101226-42-0; **11**, 101226-43-1; **12** (R = CHO), 101226-45-3; **12** (R = SMe), 101226-48-6; **13** (R = CHO), 101226-44-2; **13** (R = SMe), 101226-49-7; **14** (R = CHO), 101226-47-5; **14** (R = SMe), 101226-51-1; **15** (R = CHO), 101226-46-4; **15** (R = SMe), 101226-50-0; **16**, 101226-53-3; **17**, 101226-52-2; $Me_3Si(CH_2)_2OCH_2Cl$, 76513-69-4; imidazole, 288-32-4; 5-methylimidazole, 822-36-6; 5-methoxyimidazole, 88945-43-1; 5-(trifluoromethyl)imidazole, 33468-69-8; 1*H*-benzimidazole, 51-17-2; 1*H*-imidazo[4,5-*b*]pyridine, 273-21-2; 2,2′-bi-1*H*-imidazole, 492-98-8.

Synthesis of 1,4-Oxathiins and 5,6-Dihydro-1,4-oxathiins

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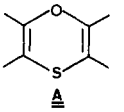
Various 1,4-oxathiin derivatives possess significant systemic fungicidal properties.[1] Whereas considerable interest has focused on the syntheses of 5,6-dihydro-1,4-oxathiins B,[2,3] only occasional reports have been published concerning 1,4-oxathiins A themselves.[3a,4-6] Most of these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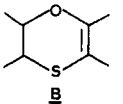
B

examples have dealt with benzoannelated 1,4-oxathiins A. Only two monocyclic derivatives or A have been syn-

(1) (a) Grewe, F. *Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel*; Wegler, R., Ed.; Springer: Berlin, 1970; Vol. 2, pp 104–105. (b) Melnikow, N. N. *Chemistry of Pesticides*; Springer: New York, 1971; pp 423–424. (c) Krämer, W. *Pflanzenschutz und Schädlingsbekämpfung*; Büchel, K.-H., Ed.; Thieme: Stuttgart, 1977; p 147.

(2) For reviews, see: (a) Asinger, F.; Saus, A. "Oxathiine, Dithiine und Thiomorpholine auf Basis billiger Rohstoffe; *Forschungsberichte des Landes Nordrhein-Westfalen*; Westdeutscher Verlag: Oplanden, 1978; No. 2757. (b) Ejmocki, Z.; Eckstein, Z. *Przem. Chem.* **1981**, *60*, 82; *Chem. Abstr.* **1981**, *95*, 24861.

(3) (a) Verheijen, J. H.; Klosterziel, H. *Synthesis* **1975**, 451. (b) Mühlstädt, M.; Kuhl, P. *J. Prakt. Chem.* **1978**, *320*, 873. (c) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548. (d) Rooney, R. P.; Dyer, J. C.; Evans, S. A. *Org. Magn. Reson.* **1981**, *16*, 266. (e) Tegeler, J. J.; Ong, H. H.; Profitt, J. A. *J. Heterocycl. Chem.* **1983**, *20*, 867.

(4) Schoufs, M.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pay-Bas* **1980**, *99*, 12.

(5) Puig-Torres, S.; Womack, C. H.; Martin, G. E.; Smith, K. *J. Heterocycl. Chem.* **1982**, *19*, 1561 and earlier reports.

(6) For a sulfone derivative of 1, see: Baliah, V.; Ganapathy, K.; Ananthapadmanabhan, S. *Indian J. Chem., Sect. B* **1981**, *20B*, 334.

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