

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

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

Received November 13, 1986

2,2'-Bi-1*H*-imidazole, when protected with the [2-(trimethylsilyl)ethoxy]methyl (SEM) blocking group, on treatment with *N*-bromosuccinimide or *N*-chlorosuccinimide yields predominantly the monohalogenated derivatives **4a** and **4b**. The [2-(trimethylsilyl)ethoxy]methyl group is subsequently removed to yield pure mono-halo-2,2'-bi-1*H*-imidazoles **2**.

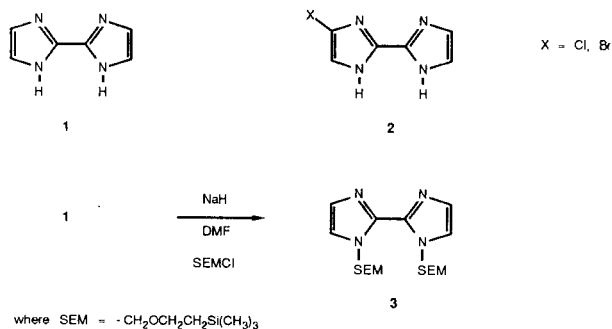
J. Heterocyclic Chem., **24**, 689 (1987).

The importance of developing methodology for the selective halogenation of nitrogen heterocycles has recently been noted [1]. These compounds not only provide key synthetic intermediates for biologically important molecules but also possess biological activity [2]. Monohalogenated 2,2'-bi-1*H*-imidazoles, **2**, (X = Cl, Br) have not been reported, and since these compounds are potentially useful intermediates, a simple and selective route was desired. 2,2'-Bi-1*H*-imidazole (**1**) was first synthesized in 1858 [3] and we have recently reported a convenient synthesis [4]. This compound has found extensive application to many branches of chemistry [5] including pharmaceuticals [6].

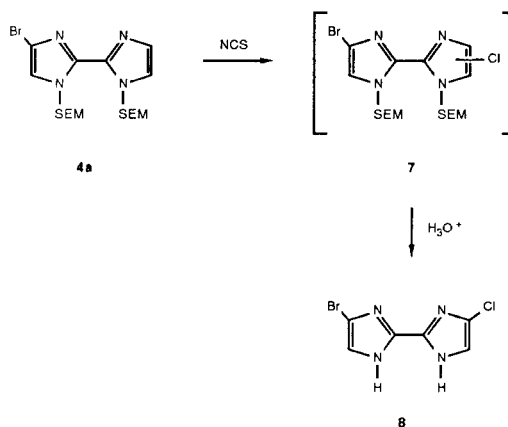
Direct halogenation of 2,2'-bi-1*H*-imidazole (**1**) with bromine has been reported to yield mainly perbromo-2,2'-bi-1*H*-imidazole with no monobromo-2,2'-bi-1*H*-imidazole, **2**, (X = Br) isolated [7]. This lack of selectivity also occurs on bromination of imidazole. However, *N*-methylimidazole is selectively brominated with 2,4,4,6-tetrabromocyclohexa-2,5-dienone, to provide 4-bromo-*N*-methylimidazole in good yield [8]. Thus we felt that *N*-protected 2,2'-bi-1*H*-imidazole could be converted to monohalogenated products by similar methods.

The trityl, methoxymethyl (MOM), benzyl and diethoxymethyl imidazole *N*-protecting groups were considered for use on 2,2'-bi-1*H*-imidazole (**1**), but these groups are often difficult to introduce, deactivate the ring to electrophilic substitution or are difficult to remove [9]. The [2-(trimethylsilyl)ethoxy]methyl group (SEM) which is easily introduced, stable to most conditions and easily removed appeared to be an ideal *N*-protecting group for 2,2'-bi-1*H*-imidazole [10,11,12] to obtain selective halogenation. Treatment of 2,2'-bi-1*H*-imidazole with 50% sodium hydride in DMF followed by [2-(trimethylsilyl)ethoxy]methyl chloride (SEMCl) gave 1,1'-bis[[2-(trimethylsilyl)ethoxy]methyl]-2,2'-bi-1*H*-imidazole (**3**) in 79% yield as a distillable liquid, soluble in most organic solvents. This is in sharp contrast to the very insoluble parent heterocycle **1** [13].

Treatment of **3** with *N*-bromosuccinimide provided the readily separable isomers **4a** and **4b** (X = Br) in a com-

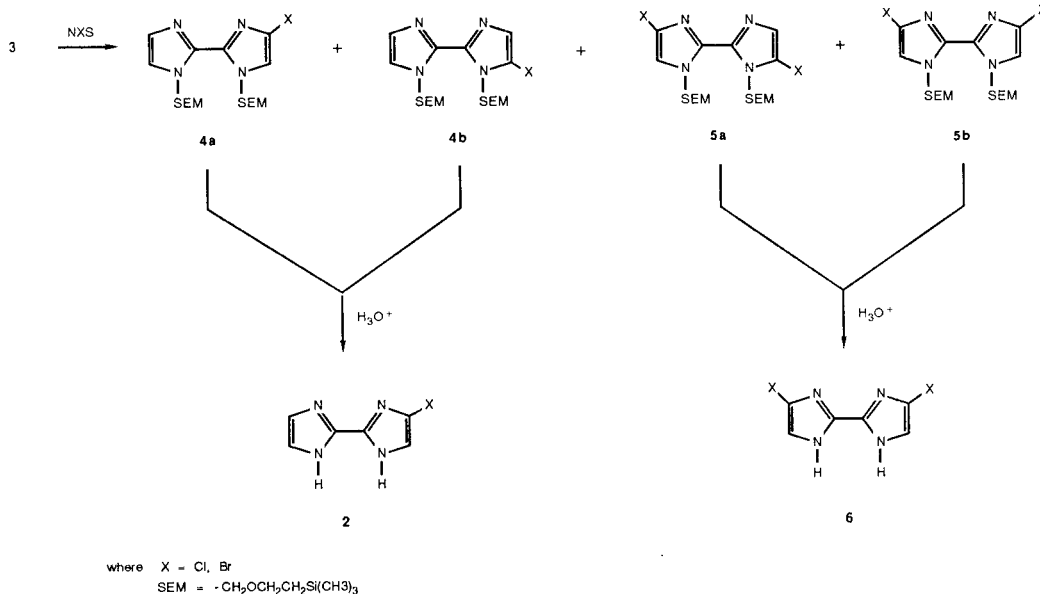


bined yield of 67%. In addition, dibromoimidazole **5a** (X = Br) was isolated in 17%. *N*-Chlorosuccinimide also gave monochloro-2,2'-biimidazole isomers **4a** and **4b**, X = Cl, (36%) and dichloro compound **5b**, (X = Cl) (26%). It should be noted that the only product isolated after treatment of **3** with *N*-iodosuccinimide was 2,2'-bi-1*H*-imidazole (**1**). Reaction of **4a** (X = Br) with *N*-chlorosuccinimide gave a 22% yield of the monobromo-chloro-2,2'-bi-1*H*-imidazole **7**.



Structural assignments of the isomers **4a**, **4b**, **5a** and **5b** (X = Cl, Br) were based on pmr spectra (see Table 1). A halogen atom in the 4-position of 1,1'-bis[[2-(trimethylsilyl)ethoxy]methyl]-2,2'-bi-1*H*-imidazole (**3**) would be expected to have little effect on the methylene in the 2-[trimethylsilyl]ethoxy]methyl group. In contrast, halogen sub-

Scheme 1



stitution in the 5-position would be expected to deshield the methylene group. As shown in Table 1, compounds with a halogen assigned to the 5-position, **4b**, (X = Cl and Br) displayed a downfield shift of the methylene as well as an upfield shift of the methylene on the adjacent ring. Consistent with these assignments, compounds with a halogen in the 4-position, **4a** and **5b**, displayed no shift in the methylene groups (δ 5.80 and δ 5.84, respectively). It is interesting to note that dibromination of **3** led to the 4,5'-dibromo compound **5a** (X = Br), whereas dichlorination of **3** provided the symmetrical 4,4'-dichloro derivative **5a** (X = Cl).

These halogenated biimidazoles **4a**, **4b**, **5a**, **5b** (X = Cl, Br) and **7** were subsequently deprotected by acid treatment to give excellent yields of the previously unreported monochloro-, monobromo- and 4-chloro-4'-bromo-2,2'-bi-1*H*-imidazoles.

In summary we have found that *N*-bromosuccinimide and *N*-chlorosuccinimide halogenate 2,2'-biimidazole when protected with the [2-(trimethylsilyl)ethoxy]methyl (SEM) blocking group to the predominately monohalogenated derivatives. This protecting group is easily removed to yield pure monohalo-2,2'-bi-1*H*-imidazoles.

EXPERIMENTAL

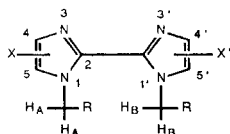
Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance (¹H-nmr) spectra were recorded on Varian EM-360 (60 MHz) and Varian XL-300 (300 MHz) spectrometers. All chemical shifts were reported in ppm (δ units) from tetramethylsilane 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, Ohio. No attempt was made to optimize yields.

1,1'-Bis(SEM)-2,2'-bi-1*H*-imidazole (**3**).

Under a blanket of nitrogen, 8.2 g (0.172 mole) of 50% sodium hydride was washed with hexane. The flask was charged with 250 ml of dry *N,N*-dimethylformamide and 11.5 g (0.086 mole) of 2,2'-bi-1*H*-imidazole [**5**] was added in small portions. After stirring at room temperature for 1.5 hours, 30.8 g (0.185 mole) of SEM-Cl was added dropwise. The reaction warmed to 40° and stirred for 1 hour, quenched with water and extracted with ethyl acetate (3 × 200 ml). The combined organic layers were shaken with water (2 × 300 ml), dried (anhydrous sodium sulfate) and concentrated to give 33.4 g of a tan oil. The product was purified by preparative hplc (ethyl acetate) to give 26.9 g (79%) of product as a tan oil. A small portion was distilled, bp 260° at 0.2 mm; nmr (deuterio-

Table 1

¹H NMR Assignments of Structural Isomers



where R = $\text{OCH}_2\text{CH}_2\text{SiMe}_3$

Compound	X	X'	H _A (δ ppm)	H _B
3	H	H	5.84	5.84
4a (X = Br)	4-Br	H	5.80	5.80
4b (X = Br)	5-Br	H	5.95	5.70
4b (X = Cl)	5-Cl	H	5.90	5.65
5a (X = Br)	4-Br	5'-Br	5.71	5.94
5b (X = Cl)	4-Cl	4'-Cl	5.84	5.84

chloroform): δ -0.14 (s, 18H), 0.79 (t, 4H, $J = 7$ Hz), 3.39 (t, 4H, $J = 7$ Hz), 5.84 (s, 4H), 7.09 (m, 4H); ms: (70 eV chemical ionization, methane) m/e 395 ($M^+ + 1$), 423 ($M^+ + 29$), 435 ($M^+ + 41$).

Anal. Calcd. for $C_{18}H_{34}N_4O_2Si_2$: C, 54.78; H, 8.68; N, 14.20. Found: C, 54.75; H, 8.72; N, 14.29.

Reaction of 1,1'-Bis(SEM)-2,2'-bi-1*H*-imidazole (**3**) with *N*-bromosuccinimide.

A mixture of 4.1 g (0.0140 mole) of 1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (**3**), 2.3 g (0.013 moles) of *N*-bromosuccinimide and 200 ml of carbon tetrachloride was heated to reflux. After 1-1/2 hours, the reaction was cooled, filtered and the filtrate concentrated to give 5.8 g of crude product. The components were separated by flash chromatography (ethyl acetate/hexane; 1:9).

The first fraction **5a** (dibromo) ($X = Br$) was obtained in a yield of 17% (1.0 g) as an orange oil; ms: (70 eV, chemical ionization, methane) m/e 55 ($M^+ + 1$), 581 ($M^+ + 29$); nmr (deuteriochloroform): δ -0.14 (s, 18H), 0.69-1.89 (m, 4H), 3.39-3.54 (m, 4H), 5.71 (s, 2H), 5.94 (s, 2H), 7.08 (s, 1H), 7.25 (s, 1H).

The second fraction **4a** (4-bromo) ($X = Br$) was obtained in a yield of 43% (2.1 g) as a tan oil; ms: (70 eV, chemical ionization, methane) m/e 475 ($M^+ + 1$); nmr (deuteriochloroform): δ -0.14 (s, 18H), 0.79 (t, 4H, $J = 8$ Hz), 3.39 (t, 4H, $J = 8$ Hz), 5.80 (s, 4H), 7.09 (m, 3H).

Anal. Calcd. for $C_{18}H_{33}BrN_4O_2Si_2$: C, 45.65; H, 7.02; N, 11.83; Br, 16.87. Found: C, 45.74; H, 7.32; N, 11.67; Br, 17.02.

The third fraction **4b** (5-bromo) ($X = Br$) was obtained in a yield of 24% (1.2 g) as a tan oil; ms (70 eV, chemical ionization, methane) m/e 475 ($M^+ + 1$); nmr (deuteriochloroform): δ 0.14 (s, 18H), 0.79 (m, 4H), 3.27-3.51 (m, 4H), 5.70 (s, 2H), 5.95 (s, 2H), 6.91-7.20 (m, 3H).

4(5)-Bromo-2,2'-bi-1*H*-imidazole **2** ($X = Br$).

4-Bromo-1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (**4a**, $X = Br$) (4.06 g, 8.57 mmoles) was mixed with 30 ml of ethanol and 60 ml of 25% hydrobromic acid. The mixture was refluxed for 3 hours, cooled to room temperature and ethanol removed under reduced pressure. The aqueous solution was carefully basified with saturated potassium carbonate and the gray solid collected, washed with water and dried to give 1.55 g (85%) product (2-propanol), mp > 260°C; nmr (dimethylsulfoxide- d_6): δ 7.23 (s, 2H), 7.32 (s, 1H); ms: (70 eV, electron impact) m/e 212 (M^+), 133 ($M^+ - Br$), 106 ($M^+ - HCN$).

Anal. Calcd. for $C_6H_5BrN_4$: C, 33.85; H, 2.37; N, 26.32. Found: C, 34.18; H, 2.46; N, 25.91.

4,4'(5,5')-Dibromo-2,2'-bi-1*H*-imidazole (**6**, $X = Br$).

4,5'-Dibromo-1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (1.0 g, 1.8 mmoles) was mixed with 30 ml of 30% hydrobromic acid and heated at 50°C for five hours. The cooled reaction was diluted with water and filtered to remove insolubles and the filtrate was basified with aqueous potassium carbonate. The white solid was collected and washed with water. After drying, 0.36 g (69%) of **6** was obtained as a white solid mp > 260°C; nmr (dimethyl sulfoxide- d_6): δ 7.00 (s, 2H), 7.17 (s, 1H); ms: (70 eV, chemical ionization, methane) m/e 293 ($M^+ + 1$), 321 ($M^+ + 29$), 333 ($M^+ + 41$).

Anal. Calcd. for $C_6H_4Br_2N_4$: C, 24.69; H, 1.38; N, 19.19. Found: C, 24.41; H, 1.35; N, 19.02.

Reaction of *N*-Chlorosuccinimide with 1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (**3**).

A mixture of 1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (1.0 g, 2.5 mmoles), *N*-chlorosuccinimide (0.4 g, 2.8 mmoles) and 30 ml of carbon tetrachloride was refluxed for two hours. After filtration and concentration, 1.4 g of crude product was obtained as a tan oil. The mono- and di-chlorinated products were separated by flash chromatography (15% ethyl acetate/hexane) to give 0.475 g (44.3%) of monochloro and 0.39 g (34%) of dichloro products.

Monochloro (**4b**, $X = Cl$).

This compounds had ¹H nmr (deuteriochloroform): δ -0.14 (m, 18H), 0.79 (overlapping triplets, 4H), 3.39 (t, 4H, $J = 7$ Hz), 5.65 (s, 2H), 5.90 (s,

2H), 6.90 (s, 1H), 7.05 (s br, 2H); ms: (70 eV, chemical ionization, methane) m/e 429 ($M^+ + 1$), 457 ($M^+ + 29$), 469 ($M^+ + 41$); bp 250° at 2.0 mm.

Anal. Calcd. for $C_{18}H_{33}ClN_4O_2Si_2$: C, 50.38; H, 7.75; N, 13.06; Cl, 8.26. Found: C, 50.56; H, 8.12; N, 12.58; Cl, 8.03.

Dichloro **5b** ($X = Cl$).

This compound had ¹H nmr (deuteriochloroform): δ -0.14 (s, 18H), 0.79 (t, 4H, $J = 7$ Hz), 3.39 (t, 4H, $J = 7$ Hz), 5.84 (s, 4H), 6.9 (s, 2H); ms: (70 eV, chemical ionization, methane) 463 ($M^+ + 1$), 491 ($M^+ + 29$), 503 ($M^+ + 41$).

4(5)-Chloro-2,2'-bi-1*H*-imidazole (**2**, $X = Cl$).

4-Chloro-1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (**4a**, $X = Cl$) (1.1 g, 2.57 mmoles) was warmed in 100 ml of 5*N* hydrochloric acid for 1.5 hours. The cooled reaction was carefully basified with aqueous potassium carbonate. The white solid was collected, washed with water and dried to yield 260 mg (60%) of desired 5-chloro-2,2'-bi-1*H*-imidazole (2-propanol), mp > 270°C; nmr (dimethyl sulfoxide- d_6): δ 7.33 (s, 2H), 7.50 (s, 1H); ms: (70 eV, electron impact) 168 (M^+), 132 ($M^+ - Cl$).

Anal. Calcd. for $C_6H_5ClN_4$: C, 42.78; H, 2.99; N, 33.26. Found: C, 42.98; H, 3.19; N, 33.36.

4,4'(5,5')-Dichloro-2,2'-bi-1*H*-imidazole (**6**, $X = Cl$).

4,4'-Dichloro-1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (**5b**, $X = Cl$) (12.2 g, 0.0264 mole) was mixed with 100 ml ethanol and 200 ml of 6*N* hydrochloric acid. The mixture was refluxed for five hours, cooled to room temperature and carefully neutralized with saturated potassium carbonate. The buff solid was collected, washed with water and dried to give 3.83 g (71%) product (2-propanol), mp > 255°C; nmr (dimethyl sulfoxide- d_6): δ 7.28 (s, 2H); ms (70 eV, chemical ionization, methane) m/e 203 ($M^+ + 1$), 231 ($M^+ + 29$), 243 ($M^+ + 41$).

Anal. Calcd. for $C_6H_4Cl_2N_4$: C, 35.50; H, 1.98; Cl, 34.93; N, 27.60. Found: C, 35.61; H, 2.25; Cl, 34.63; N, 27.90.

4(5)-Bromo-4(5)-chloro-2,2'-bi-1*H*-imidazole (**8**).

4-Bromo-1,1'-bis(SEM)-2,2'-bi-1*H*-imidazole (**4a**, $X = Br$) (6.6 g, 0.0139 moles), *N*-chlorosuccinimide (2.0 g, 0.0149 mole) and 200 ml of carbon tetrachloride was refluxed for two hours. The cooled reaction was filtered and the filtrate concentrated to give 6.7 g of a dark oil. Purification by flash chromatography (10% ethyl acetate/90% hexane) gave 2.4 g (36%) recovered starting material and 1.0 g (22% based on reacted material) of **7** as a tan oil; ms: (70 eV, chemical ionization, methane) 507 ($M^+ + 1$), 536 ($M^+ + 29$).

A mixture of **7** (1.0 g, 1.96 mmoles), 50 ml of ethanol and 50 ml of 5*N* hydrochloric acid. The reaction was refluxed for four hours then cooled and diluted with 100 ml of water. The mixture was filtered, and the filtrate neutralized with aqueous potassium carbonate. The white solid was collected, washed with water and dried to give 0.36 g (64%) of **8** as a white solid (2-propanol), mp > 265°C, nmr (dimethyl sulfoxide- d_6): δ 7.30 (s, 1H), 7.35 (s, 1H); ms (70 eV, chemical ionization, methane) m/e 247 ($M^+ + 1$), 275 ($M^+ + 29$), 287 ($M^+ + 41$), 213 ($M^+ + 1 - Cl + H^+$), 169 ($M^+ + 1 - Br + H^+$).

Anal. Calcd. for $C_6H_4BrClN_4 \cdot 1/2H_2O$: C, 28.09; H, 1.96; N, 21.84. Found: C, 28.35; H, 1.68; N, 21.42.

REFERENCES AND NOTES

- [1] A. G. Mistry, K. Smith and M. R. Bye, *Tetrahedron Letters*, **27**, 1051 (1986).
- [2] C. Christophersen, *Acta Chem. Scand.*, **39B**, 517 (1985).
- [3] H. Debus, *Liebigs. Ann. Chem.*, **107**, 199 (1858).
- [4] D. P. Matthews, J. P. Whitten, and J. R. McCarthy, *Synthesis*, 336 (1986).
- [5] P. Bernhard, H. Lehmann, and A. Ludi, *J. Chem. Soc., Chem. Commun.*, 1216 (1981); P. G. Rasmussen, R. L. Hough, J. E. Anderson, O. H. Bailey, and J. C. Bayon, *J. Am. Chem. Soc.*, **104**, 6155 (1982); J. F. Williams, F. C. Heugebaert, and R. J. Pollet, *Res. Dis.*, **136**, 39 (1975);

Chem. Abstr., **83**, 186250 (1975); S. Schoof, H. Gusten, J. Heinze, and H. Baumgaertel, German Offen. DE 2232260 17 Jan 1976; *Chem. Abstr.*, **81**, 14722w (1981); R. C. Chromecek, G. D. Friends, L. Y. Wissman, and R. A. Atchison, European Patent Application EP 79721 A2 25 May 1983; *Chem. Abstr.*, **99**, 93790q (1983); W. Klose and I. Boettcher, German Offen. DE 3141063 A1, 28 Apr 1983; *Chem. Abstr.*, **99**, 88196w (1983); P. Melloni, E. Dradi, W. Logemann, I. DeCarneri, and F. Trane, *J. Med. Chem.*, **15**, 926 (1972).

[6] P. Melloni, R. Metelli, B. D. Fusar, C. Confalonieri, W. Logemann, and I. DeCarneri, *Arzneim.-Forsch.*, **25**, 9 (1975).

[7] K. Lehmsstedt and H. Rolker, *Ber.*, **76**, 879 (1943).

[8] V. Calo, F. Ciminale, L. Lopez, F. Naso, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. I*, 2567 (1972).

[9] N. J. Curtis and R. S. Brown, *J. Org. Chem.*, **45**, 4038 (1980).

[10] J. R. McCarthy, D. P. Matthews, and J. P. Whitten, *Tetrahedron Letters*, **26**, 6273 (1985).

[11] J. P. Whitten, D. P. Matthews, and J. R. McCarthy, *J. Org. Chem.*, **51**, 1891 (1986).

[12] B. H. Lipshutz, W. Vaccaro, and B. Hoff, *Tetrahedron Letters*, 4095 (1986).

[13] 2,2'-Bi-1*H*-imidazole has a solubility of 1.2 mg/l in water and approximately 1.0 g/l in boiling DMF.