Regioselective Symmetrical Bromination of Protected 2,2'-Biimidazole

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Treatment of the benzyl and (trimethylsilylethoxymethyl) SEM protected 2,2'-biimidazoles, **2a** and **2b**, with 2 equivalents of *N*-bromosuccinimide (NBS) allows obtaining the 5,5'-dibromo and 4,4'-dibromo substituted biimidazoles, **3a** and **5b** respectively. The use of 4 equivalents of NBS, followed by treatment of the corresponding tetrabromoderivatives **4a** and **5b** with butyl lithium (BuLi), yields the 4,4'-dibromoderivatives **5a** (G=Bn) and **5b** (G=SEM).

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The chemistry of 2,2'-biimidazole (**1**), first obtained by Debus in 1858 by reaction of glyoxal and ammonia (Figure 1) [1], has received little attention despite its potential uses in research areas such as material science [2] or pharmacology [3,4]. The reasons for such lack of interest lie in the fact that the synthesis of the bicyclic structure is extremely laborious, not easily allowing the synthesis of substituted 2,2'-biimidazole rings. Furthermore, the great insolubility of **1** in organic solvents has limited the direct functionalization of the ring.

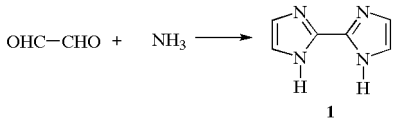

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Figure 1. 2,2'-Biimidazole synthesis.

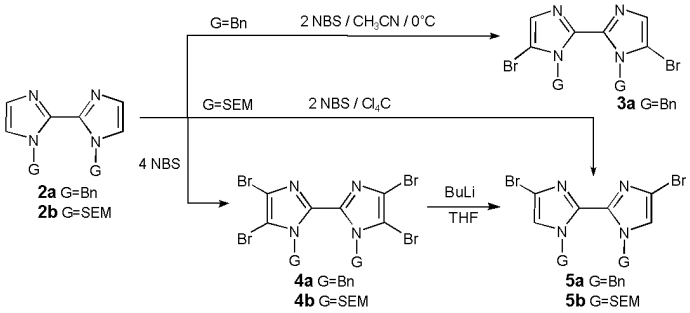
As a part of our ongoing research in the area of biimidazole chemistry, we decided to use **1** as a building block in macrocyclic chemistry [5]. In this context, we were interested in a general method for the synthesis of symmetrically halogenated protected biimidazoles. A literature search revealed that only the tetrabromo and 4,4'-dibromo-substituted 2,2'-biimidazoles were described in 1943 by treatment of **1** with Br_2 in acidic medium [6]. More recently, the monobromo substituted biimidazole was described by treatment of the SEM-protected biimidazole (**2b**) (SEM = trimethylsilylethoxymethyl) with *N*-bromosuccinimide (NBS) [7].

Consequently, in order to selectively functionalize 2,2'-bimidazole (**1**), we decided to investigate the direct halogenation of protected biimidazoles (**2**) (Scheme 1). The present paper presents the results obtained in such study.

Results and Discussion.

Among the different methods assayed for the synthesis of 2,2'-biimidazole (**1**) [8-12], we have finally selected the procedure of Kirchner *et al* due to its simplicity [11]. Thus, from inexpensive starting materials such us Glyoxal and Ammonia we obtained (**1**) in 15% yield.

Two protecting groups were used to block the NH groups of **1**: the benzyl group, cheap and easily removable by hydrogenolysis [13], and the SEM group that can be easily removed by mild acid hydrolysis or treatment with fluoride anion [14]. Thus, treatment of the disodium salt of 2,2'-biimidazole (**1**), obtained by treatment of **1** with NaOH in DMSO/H_2O, with benzyl chloride at reflux afforded the benzyl protected biimidazole (**2a**). On the other hand, **1** was converted to the SEM protected biimidazole **2b** by using (trimethylsilylethoxymethyl chloride) SEMCl in (dimethylformamide) DMF in the presence of NaH as reported previously [7].



Scheme 1. Synthetic Pathway

We used NBS as the halogenating agent for our study (Scheme 1). The first part of such study was carried out using 2 equivalents of NBS and, surprisingly, **2a** and **2b** afforded two different dibromo regioisomers. Thus, when **2a** was treated with 2 equivalents of NBS in CH_3CN at 0 °C, the 5,5'-dibromo substituted 2,2'-biimidazole **3a** was obtained in 53% yield. On the contrary, the use of the SEM protected biimidazole **2b** in CCl_4 at reflux yielded the 4,4'-dibromo regioisomer **5b** in 64% yield. The different behavior of **2a** and **2b** seems to be attributable to the greater steric hindrance caused by the SEM group that precludes the substitution at C5 and C5'.

On the other hand, treatment of **2a** and **2b** with 4 equivalents of NBS at reflux in CH_3CN and CCl_4, respectively, yielded the corresponding tetrabromo substituted biimidazoles **4a** and **4b** in 46% and 51% yield. Due to the ALP (Adjacent Lone Pair) effect [15] that presents the C4 position of each imidazole ring, the 4,4'-dibromo substituted biimidazole **5a** was obtained in 78% yield when **4a** was treated with BuLi at -78 °C followed by quenching with isopropanol [15]. Similarly, the SEM protected 4,4'-dibromobiimidazole **5b** (98%) was obtained upon treatment of **4b** in the same reaction conditions. The structural assignments of **3a**, **5a**, and **5b** were carried out on the basis of NOE and NOESY experiments. Thus, irradiating the N-CH_2 protons of **5a** and **5b** there was an enhancement in the intensity of H5-H5' signals of 7.5% and 6.1% respectively.

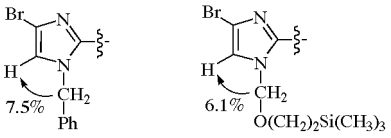


Figure 2. NOE Irradiations.

The results obtained, which are in agreement with those described in the literature for imidazoles, open the door to the symmetrical functionalization of the biimidazole ring either in positions C4-C4' or C5-C5'[16]. Moreover, the fact of having two different protecting groups in the case of structure **5** should allow the use of a wide range of reaction conditions for such functionalization.

In conclusion, we have developed a synthetic method that allows obtaining all the possible symmetrically substituted dibromo 2,2'-biimidazoles in a straightforward manner from a common precursor. The uses of these symmetrically halogenated protected 2,2'-biimidazoles as starting materials for the synthesis of macrocyclic compounds will be object of a series of forthcoming papers.

EXPERIMENTAL

2,2'-Biimidazole (**1**).

Ammonia was bubbled into 300mL of 20% aqueous glyoxal. The temperature was maintained at 30-40 °C. After 10 hours, the dark suspension is filtered and the solid was dissolved in 10% hydrochloric acid, the solution was refluxed for 15 minutes with Darco. The yellow solution is carefully neutralised with saturated potassium carbonate to yield 8.7g (64.9 mmol, 15%) of **1** as a white solid, ir (potassium bromide): 3174, 3074, 3002, 2897, 2806, 1545, 1480, 1405, 1104, 939, 884, 747, 689 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.06 (s, Ar-H).

1,1'-Dibenzyl-2,2'-biimidazole (**2a**).

Benzyl chloride (3.8 g, 30.0 mmol) were added to a solution of 2 g (14.9 mmol) of 2,2'-biimidazole in 6 mL of 12.5 *M* NaOH and 5 mL of DMSO. The mixture is refluxed for 30 minutes, cooled, and diluted with water. The resulting solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was digested in hexane/acetone to yield 3.8g (12.1 mmol, 81%) of **2a** as a white solid: mp 147-148 °C (EtOH); ir (film): 3109, 3029, 2992, 1605, 1495, 1438, 1283, 726 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.24 (m, 3H, ArH), 7.13-7.12 (m, 1H, H4), 7.05-7.01 (m, 2H, ArH), 6.93-6.92 (m, 1H, H5), 5.70 (s, 2H, CH_2); ^{13}C nmr (deuteriochloroform) δ:138.3, 137.3, 128.6 128.4, 127.6, 127.5, 121.4, 50.8; ms: (70eV, electron impact) *m/z* 314(100), 237(22), 223(64), 91(33).

Anal. Calcd for $C_{20}H_{18}N_4$: C, 76.41; H, 5.77; N, 17.82. Found: C, 76.39; H, 5.75; N, 17.82.

1,1'-Dibenzyl-5,5'-dibromo-2,2'-biimidazole (**3a**).

NBS (1.4 g, 7.9 mmol) were added portionwise to a solution of 1 g (3.2 mmol) of the benzyl protected biimidazole **2a** in 200 mL of CH_3CN cooled to 0 °C. The mixture was stirred for 30 minutes at 0 °C, concentrated *in vacuo* and the residue obtained was dissolved in CH_2Cl_2. The resulting solution was washed with water (4 x 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford 0.8 g (1.7 mmol, 53%) of **3a** as a white solid: mp 171-172 °C (EtOH); ir (potassium bromide): 3031, 1487, 1454, 1389, 1262, 913, 727 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.17-7.16 (m, 3H, ArH), 7.12 (s, 1H, H4), 6.88-6.85 (m, 2H, ArH), 5.80 (s, 1H, CH_2); ^{13}C nmr (deuteriochloroform): δ 138.7, 136.3, 129.1, 128.6, 127.4, 126.8, 106.4, 48.9; ms: (70eV, electron impact) *m/z* 472 (85), 391(17), 381(55), 91(100).

Anal. Calcd for $C_{20}H_{16}N_4Br_2$: C, 50.87; H, 3.41; N, 11.86. Found: C, 50.83; H, 3.05; N, 11.60.

1,1'-Dibenzyl-4,4',5,5'-tetrabromo-2,2'-biimidazole (**4a**).

The procedure was the same as stated above for **3a** but using 6.1 g (19.4 mmol) of **2a** and 16.9 g (94 mmol) of NBS in 800 mL of CH_3CN cooled at 0 °C. The mixture was stirred for 30 minutes at 0 °C and then was heated at reflux until complete conversion (tlc analysis, circa 2 hours). The yield was 5.6 g (8.9 mmol, 46%) of **4a** as a slightly yellow solid**:** mp 204-205 °C (EtOH); ir (film): 2985, 1484, 1435, 1370, 1240, 979, 721 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.21-6.87 (m, 5H, Ph), 5.79 (s, 2H, CH_2); ^{13}C nmr (deuteriochloroform): δ 137.3, 135.5, 128.7, 127.6, 126.9, 116.9, 107.6, 50.5; ms: (70eV, electron impact) *m/z* 630(10), 539(4), 91(100).

Anal. Calcd for $C_{20}H_{14}N_4Br_4$: C, 38.13; H, 2.24; N, 8.89. Found: C, 38.27; H, 1.82; N, 8.63.

1,1'-Bis(trimethylsilylethoxymethyl)-4,4',5,5'-tetrabromo-2,2'-biimidazole (**4b**).

The procedure was the same as stated above for **4a** but using 1 g (2.5 mmol) of **2b** in 30 mL of CCl_4. The yield was 0.91 g (1.3 mmol, 51%) of **4b** as colourless oil which crystallizes on standing: ir (potassium bromide) 2953, 2925, 1486, 1375, 1249, 1103, 836 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.93 (s, 2H, NCH_2), 3.60-3.54 (t, *J*=9 Hz, 2H,CH_2), 0.93-0.87 (t, *J*=9 Hz, 2H, CH_2), -0.04 (s, 9H, CH_3); ^{13}C nmr (deuteriochloroform): δ 137.5, 117.4, 107.8, 75.0, 66.7, 17.8, -1.5; ms: (70eV, electron impact) *m/z* 710(17), 609(28), 579(100), 577(70).

Anal. Calcd for $C_{18}H_{30}N_4O_2Br_4Si_2$: C, 30.44; H, 4.26; N, 7.89. Found: C, 30.53; H, 4.52; N, 7.57.

1,1'-Dibenzyl-4,4'-dibromo-2,2'-biimidazole (**5a**).

A 1.6 *M* solution of BuLi (13 mL, 20 mmol) in hexane were added dropwise to a solution of 5.6 g (8.9 mmol) of the tetra-

bromo substituted biimidazole **4a** in 300 mL of anhydrous THF cooled to –78 °C. After being stirred for 30 minutes at –78 °C, the resulting solution was quenched with 20 mL of isopropanol and further stirred for 15 minutes. The mixture was allowed to warm to room temp, and then was poured into a saturated solution of NH_4Cl (200 mL). The mixture was extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo* to yield 3.28 g (6.9 mmol, 78%) of **5a** as a white solid: mp 214-215 °C(EtOH); ir (potassium bromide): 3135, 2922, 1497,1455, 1394, 1240, 957, 759, 728, 709 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 7.28-7.26 (m, 3H, ArH), 7.15-7.09 (m, 2H, ArH), 6.88 (s, 1H, H5), 5.64 (s, 2H, H); ^{13}C nmr (deuteriochloroform): δ 136.9, 136.2, 128.8, 128.1, 127.9, 120.9, 114.7, 51.4; ms: (70eV, electron impact) *m/z* 472(28), 393(11), 381(17), 91(100).

Anal. Calcd for $C_{20}H_{16}N_4Br_2$: C, 50.87; H, 3.41; N, 11.86. Found: C, 50.99; H, 3.13; N, 11.61.

1,1'-Bis(trimethylsilylethoxymethyl)-4,4'-dibromo-2,2'-biimidazole (**5b**).

(a) Starting from **2b**: The procedure was the same as stated above for **3a** but using 500 mg (1.3 mmol) of the SEM protected biimidazole **2b** in 20 mL of CCl_4 at reflux. The crude material was filtered and column chromatographed (silica gel 70-230 mesh ASTM) using hexane as eluent to give 452 mg (0.82 mmol, 64%) of **5b** as a colourless oil which crystallises on standing: ir (film): 3134, 2953, 2895, 1499, 1370, 1249, 1092, 836 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.14 (s, 1H, H5), 5.87 (s, 2H,CH_2), 3.60-3.54 (t, 2H, *J*= 9 Hz, CH_2), 0.96-090 (t, 2H, *J*= 9 Hz, CH_2), -0.03 (s, 9H, CH_3); ^{13}C nmr (deuteriochloroform): δ 136.7, 120.4, 115.1, 76.3, 66.8, 17.8, -1.5, ms: (70eV, electron impact) *m/z* 552(27), 451,(26), 421(100), 348(12), 181(22), 131(40).

Anal. Calcd for $C_{18}H_{32}N_4O_2Br_2Si_2$: C, 39.13; H, 5.84; N, 10.14. Found: C, 39.43; H, 5.88; N, 10.13.

(b) Starting from **4b**: The procedure was the same as stated above for **5a** but using 800 mg (1.1 mmol) of the tetrabromo substituted biimidazole **4b**. The yield was 612 mg (1.1 mmol, 98%) of **5b**.

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