SHORT PAPER

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Selective synthesis of novel biimidazole derivatives, bis-biimidazole and tri-biimidazole

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The 2,2'-biimidazole derivatives containing imidazole or benzimidazole moieties, bis-biimidazole and tri-biimidazole have been obtained by selective N-alkylation.

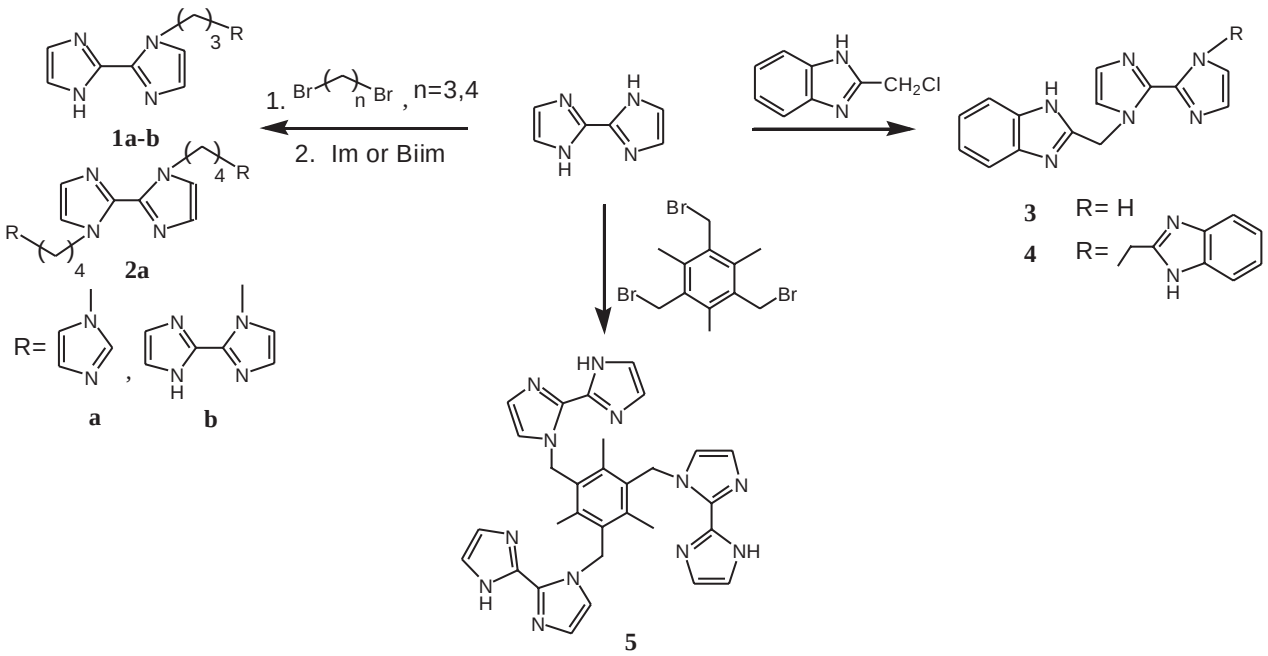
Keywords: *N*-alkylation reaction, selective synthesis, 2,2'-biimidazole derivative, bis-biimidazole, tri-biimidazole

2,2'-Biimidazole (Biim) and its derivatives have been widely studied on the basis of crystal structure, metal binding ability[1] and biological activity[2,3] Biim derivatives developed rapidly in recent years as monomers for polymers[4,5] and intermediates for macrocyclic complexes.[6] Biim itself has been used as a biomimetic ligand in models for metalloezymes incorporating the histidine functionality.[3] However, inspecting the impressive list, examples dealing with artificial enzymes are quite rare and their activity and selectivity are not represented.

Imidazole is of biochemical importance due to its being a catalytic group in the active sites of some enzymes and proteins. It can serve as proton donor–acceptor, general acid–base, nucleophile and binding group. The search for multi-imidazole complexes that could mimic the active sites of metalloproteins such as carbonic anhydrase, hemerythrin, hemocyanic, urease and others[7] has led to an extensive synthetic effort to obtain novel imidazole-containing ligands. We have published our work[8-13] on imidazole derivatives. These compounds have served as multi-imidazole hosts in molecular recognition and also as ligands to build binuclear or heteronuclear metal enzyme models for biomimetic catalysis.

The applications of imidazole are amplified when they are incorporated in the dimeric analogue Biim. Biim is characterised by its great chemical stability and it has a near planar structure, which provides the optimum environment for enzyme mimic and selective catalysis. More importantly Biim possesses bidentate chelating sites and might function as a bridging ligand. The incorporation of pendant groups provides suitable shapes and binding sites in addition. These ligands can mimic the biological unit concerning composition, ligand type, structure and oxidation state. Biim lends itself particularly well to providing a new family of multidentate ligands to bind transition metal ions or guest molecules. They also provide key synthetic intermediates for macromolecule species and cyclophanes.

Our interest has been focused on the fact that Biim and its derivatives are implicated in a number of enzymatic active-site models.[3,6] We herein report selective synthesis of novel Biim derivatives, bis- and tri-Biim. These new compounds have not been recorded previously. To our knowledge, bis- and tri-Biim are the first example of two or three Biims bridged by a hydrocarbon skeleton. They are synthesised by selective alkylation of the Biim 1N-position. Their structures are confirmed by MS, ^{1}H NMR and element analyses. The synthetic pathway is outlined in Scheme 1.



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

The N-alkylation of Biim is usually convenient[14]. However competing reactions such as elimination of halides, reactions of multi-position selectivity, steric hindrance to multi-substitution, quaternisation and product decomposition by moisture may lead to poor yields. The reaction conditions have a significant influence on the selectivity. The reaction of Biim with α,ω-dihaloalkanes or xylylene dihalides usually leads to N,N′-bridged derivatives or bis-annelated biimidasolium salts.[15] Cyclised products are more stable than open-chain alternatives when chains are short. By controlling low temperature and basicity, these competitive reactions can be minimised. Open-chain 1,1'-disubstitution of Biim is far slower than 1-substitution. In a strongly basic medium, we could not form 1,1'-bis(3-bromopropyl)-2,2'-biimidazole because of cyclisation.[16] The yields of compounds **1a**, **3** and **4** are typically 50–90%; the low isolated yield of **1b**, **2a** and **5** can be attributed to decomposition by moisture and steric hindrance to substitution. Multi-substitution products are prepared by adding material slowly. In fact, monosubstitution of 1,3,5-tri(bromomethyl)-2,4,6-trimethylbenzene can be monitored more easily than bi- or tri-substitution.

Biomimetic studies of metal complexes and the catalytic behaviour of target compounds are in progress.

Experimental

Melting points were determined on a XSP-I micro-melting point apparatus and are uncorrected. Mass spectra were measured on an EI-MS Finnigan Mat 4510 instrument. ^{1}H NMR spectra were recorded on Varian INOVA-400 (400 MHz) spectrometers. Elemental analyses were carried out on a Carlo Erba 1106 analyzer.

Biim,[15] 2-(chloromethyl)benzimidazole[17] and 1,3,5-tri(bromomethyl)-2,4,6-trimethylbenzene[18] were prepared according to the literature. Dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF) and tetrahydrofuran (THF) were dried over $MgSO_4$ for 1 day. Other chemicals or regents were obtained commercially and used without further purification.

1-[3-(1-Imidazolyl)propyl]-2,2'-biimidazole **1a:** A mixture of Biim (0.70 g, 5.20 mmol), NaH (0.12 g, 5.20 mmol) in DMF (10 ml) was stirred at room temperature for 3 h. To this dark green solution, 1,3-dibromopropane (1.05 g, 5.20 mmol) in THF (5 ml) was added and stirred overnight. The precipitate gave 0.33 g of recovered starting material (47.0%). 1-(3-Bromopropyl)-2,2'-biimidazole (BPB) was present in the filtrate. After concentration, this was purified on a silica gel column (THF/C_2H_5OH=4/1). Yellowish crystals were obtained in 28.0% yield. m.p.243–245°C. EI-MS (*m/z*, RA%): 174 (M^+-Br, 100). ^{1}H NMR (D_2O, ppm) δ: 2.53 (s, 2H, CH_2), 4.28 (bs, 4H, CH_2N, CH_2Br), 7.08 (s, 2H, Biim5-H), 7.14 (s, 2H, Biim4-H).

Imidazole (0.20 g, 3.00 mmol) and NaH (0.14 g, 6.00 mmol) in dry THF (10 ml) were stirred at room temperature for 3 h and then warmed to boiling. The BPB (0.51 g, 2.00 mmol) in THF (10 ml) was added dropwise over 12 h. The resulting mixture was concentrated under reduced pressure. The crude product was subjected to column chromatography (SiO_2, THF/C_2H_5OH=1/1) to give colourless rhomboid pellets, yield 66.5%. m.p.165–167°C. EI-MS (*m/z*, RA%): 213 (M^+-HCN, 5), 197 (10), 174 (M^+-Im, 100), 146 (30), 134 (15), 68 (23). ^{1}H NMR (D_2O, ppm) δ: 2.77 (bs, 2H, CH_2), 4.41 (bs, 4H, CH_2N), 6.63 (s, 2H, Im4,5-H), 7.50 (bs, 4H, Biim-H), 8.55 (s, 1H, Im2-H). Anal. Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.60; H, 5.98; N, 34.84.

1,3-Bis[1-(2,2'-biimidazolyl)]propane **1b:** Biim (0.27 g, 2.00 mmol), NaH (0.06 g, 2.50 mmol) and dry DMSO (10 ml) were stirred for 0.5 h until the suspension disappeared. Then 1.3-dibromopropane (0.20 g, 1.00 mmol) in THF (2 ml) was added and stirred for a day at room temperature. The clear top layer containing BPB was separated. NaH was added to the residue of Biim until the precipitate redissolved. Then the solution of BiimNa was heated to 85°C and the above mentioned layer containing BPB was dropped into it over 1 day. The procedures of separation, basification and dropwise addition were repeated once. The little non-reacted Biim was removed by filtration. The filtrate was concentrated and purified over a silica gel column (THF/C_2H_5OH=1/1). Yellowish crystals were collected in 32.1% yield. m.p. >300°C. EI-MS (*m/z*, RA%): 309 (M^++1, 10). ^{1}H NMR (D_2O, ppm) δ: 1.97 (s, 2H, CH_2), 3.99 (s, 4H, CH_2N), 7.22 (s, 4H, Biim5-H), 7.38 (s, 4H, Biim4-H). Anal. Calcd. for $C_{15}H_{16}N_8$: C, 58.43; H, 5.23; N, 36.34. Found: C, 58.30; H, 5.08; N, 36.40.

1,1'-Bis[4-(1-imidazolyl)butyl]-2,2'-biimidazole **2a**: Biim (0.67 g, 5.00 mmol) and NaH (0.36 g, 15.00 mmol) and dry DMSO (10 ml) were stirred for 0.5 h until the suspension disappeared. This solution was added dropwise to 1,4-dibromobutane (3.24 g, 15.00 mmol) in DMSO (5 ml) at 60°C over 1 day. The precipitate gave 0.38 g of recovered Biim (56.7%). The filtrate of 1,1'-bis(4-bromobutyl)-2,2'-biimidazole was directly transferred to next step, or was evaporated to dryness when pure yellowish crystals could be obtained by recrystallisation (THF/C_2H_5OH=1/2) in 30.2% yield m.p. 285–286°C. EI-MS (*m/z*, RA%): 324 (M-Br, 5), 243 (M-2Br, 15). ^{1}HNMR(D_2O, ppm) δ: 2.08 (t t, 4H, J_2=5Hz, J_3=9Hz, CH_2-CH_2Br), 2.41 (t t, 4H, J_1=13Hz, J_2=5Hz, CH_2-CH_2N), 2.81 (t, 4H, J_3=9Hz, CH_2Br), 4.23 (t, 4H, J_1=13Hz, CH_2N), 8.03 (d, 2H, Biim5-H), 8.14 (d, 2H, Biim4-H).

A suspension of imidazole (1.36 g, 2.00 mmol) and NaH (0.72 g, 30.00 mmol) in THF (50 ml) was stirred overnight at room temperature and then was warmed to 60°C. The above filtrate of 1,1′-bis(4-bromobutyl)- 2,2′-biimidazole was added in small portions over 1 day. The reaction mixture was evaporated to dryness and then was purified over a silica gel column (THF/C_2H_5OH=1/2). Light yellow flakes were obtained in 46.3% yield. m.p. 264–266°C. EI-MS (*m/z*, RA%): 377 (M^+-1, 50). ^{1}H NMR (D_2O, ppm) δ: 1.61 (t, 4H, J_2=2.8Hz, J_3=11.6Hz, CH_2-CH_2Im), 2.23 (t, 4H, J_1=9.8Hz, J_2=2.8Hz, CH_2-CH_2Biim), 3.79 (t, 4H, J_3=11.6Hz, CH_2Im), 4.12 (t, 4H, J_1=9.8Hz, CH_2Biim), 6.63 (s, 4H, Im4,5-H), 7.64 (s, 4H, Biim-H), 8.55 (s, 2H, Im2-H). Anal. Calcd. for $C_{20}H_{26}N_8$: C, 63.47; H, 6.92; N, 29.61. Found: C, 63.60; H, 6.98; N, 29.84.

1-(2-Benzimidazolylmethyl)-2,2'-biimidazole **3**: To a well-stirred suspension of NaH (0.12 g, 5.00 mmol) in dry THF (50 ml), Biim (0.67 g, 5.00 mmol) was added. The mixture was stirred for 3 h and then heated to 50°C. A solution of 2-(chloromethyl)benzimidazole (0.83 g, 5.00 mmol) in THF (50 ml) was added in small portions over 8–10 h. A little insoluble impurity was removed by filtration. The filtrate was concentrated and subjected to column chromatography (SiO_2, petroleum ether/THF=3/1) affording a pale yellow solid, yield 70.2%. m.p. 143-145°C. EI-MS (*m/z*, RA%): 264 (M, 100). ^{1}H NMR ($CDCl_3$, ppm) δ: 3.00 (s, 2H, CH_2), 7.19–7.21 (AA′BB′, 4H, Bim-H), 7.27–7.30 (m, 4H, Biim-H). Anal. Calcd. for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.60; H, 3.98; N, 31.84.

1,1'-Bis(2-benzimidazolylmethyl)-2,2′-biimidazole **4**: **3** (1.32 g, 5.00 mmol), NaH (0.12 g, 5.00 mmol) and THF (50 ml) were warmed to 60°C. While stirring, 2-(chloromethyl)benzimidazole (0.83 g, 5.00 mmol) in THF (10 ml) was added slowly over 1 day. THF was removed and the crude product was purified over a silica column (petroleum ether/THF=4/1). Tan crystals were obtained in 80.6% yield. m.p. 190–194°C. EI-MS (*m/z*, RA%): 395 (M^++1, 10). ^{1}H NMR ($CDCl_3$, ppm) δ: 3.75 (s, 4H, CH_2), 7.00–7.09 (AA′BB′, 8H, Bim-H), 7.19(d, 2H, *J*=7.6Hz Biim5-H), 7.28 (d, 2H, *J*=8.8Hz, Biim4-H). Anal. Calcd. for $C_{22}H_{18}N_8$: C, 66.99; H, 4.60; N, 28.41. Found: C, 67.10; H, 4.78; N, 28.64.

1,3,5-Trimethyl-2,4,6-tri[1-(2,2'-biimidazol)yl]benzene **5**: NaH (0.12 g, 5.00 mmol) and Biim (0.67 g, 5.00 mmol) in dry DMF (10 ml) were heated to approximately 60°C. While stirring, 1,3,5-tri(bromomethyl)-2,4,6-trimethylbenzene (0.60 g, 1.50 mmol) in THF (5 ml) was added over 1 day. At half reaction, NaH (0.12 g, 5.00 mmol) was added to keep Biim from precipitation. The reaction mixture was evaporated to dryness and then was purified over a silica gel column (THF/C_2H_5OH=1/2). A pink sample was obtained in 31.0% yield. m.p. >300°C. EI-MS (*m/z*, RA%): 559 (M^++1, 9). ^{1}H NMR (DMSO-d_6, ppm) δ: 2.38 (s, 9H, CH_3), 5.90 (s, 6H, CH_2), 7.21 (s, 6H, Biim5-H), 7.26 (s, 6H, Biim4-H). Anal. Calcd. for $C_{30}H_{30}N_{12}$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.60; H, 5.58; N, 29.84.

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