SHORT PAPER

J. Chem. Research (S),
2002, 267–269

A direct synthetic approach to tripodal imidazole compounds†

Yi Yuan, Rong Xiao, Ge Gao, Xiao-Yu Su, Hua Yu, Jinsong You and Ru-Gang Xie*

Department of Chemistry, Sichuan University, Chengdu 610 064, P. R. China

Convenient syntheses of tripodal histidine, 2-benzimidazolylthio, imidazole and benzimidazole compounds (**1–4**) is reported.

Keywords: Imidazoles, benzimidazoles, histidine, tripodal compounds

Imidazole plays important roles in various biochemical processes, serving as proton donor–acceptor, general acid–base, nucleophile and coordination groups in the active centres of enzymes.[1] In recent years heterocycle-based ligands and macrocycles have been receiving increasing attention in coordination chemistry, host–guest chemistry and biomimetic chemistry,[2] but the study of imidazole-based compounds in these areas is relatively little explored.[3] The molecules with an aromatic skeleton connecting tripodal functional arms make an important contribution to the special requirements of host–guest interactions, because they have the preorganisation of the coordination sites for cooperative binding of the guests, especially for the trigonal planar or tetrahedral anions and molecules.[4] However, to our knowledge, only few works deal with multiple bridged imidazole compounds and their coordination and molecular recognition abilities.[5] We report herein convenient and efficient syntheses of new tripodal compounds containing three imidazole or benzimidazole groups connected to an aromatic skeleton (Scheme 1). These compounds have C_3-symmetry with multiple coordination sites and can be used as multidentate ligands to bind transition metal ions or other guest molecules. They are also versatile intermediates for the synthesis of dendrimers and other types of three-dimensional macromolecules.

Compound **1** was synthesised directly from L-histidine by selective acylation with 1,3,5-tris(chlorocarbonyl)benzene. Multiply-bridged histidines are generally considered to be difficult to prepare because histidine has several reactive sites and it is difficult to control the selective reaction.[6] After repeated experiments we found an efficient way to prepare triply bridged histidine without any protection technique.[7] In an ice-salt bath the amino group of histidine was first released from its ammonium form by using an equivalent amount of base in water. Then tetrahydrofuran (THF) was added and the reaction system was vigorously stirred to well mixed. While the THF solution of 1,3,5-tris(chlorocarbonyl)benzene was added dropwise, one equivalent of aqueous potassium hydroxide (KOH) solution was added at the same time to neutralise hydrochloric acid formed during the acylation of the amine. The temperature control and the simultaneous addition of acyl chloride and base is the crucial technique for a successful synthesis of compound **1**. Although 1,3,5-tris(chlorocarbonyl) benzene has high reactivity, its hydrolysis was moderated efficiently when the reaction was carried out in an ice-salt bath. The simultaneous addition of acyl chloride and one equivalent of aqueous KOH also avoided side reactions such as the racemization of histidine in strong basic media and *N*-acylation of the imidazole ring. The oily crude product solidified gradually when the acidified mixture in acetone-water co-solvent was shaked vigorously. Then the target compound **1** was easily purified by recrystallisation.

1,3,5-Tris(2-benzimidazolylthiomethyl)-2,4,6-trimethylbenzene (**2**) has three benzimidazole subunits connected to a benzene ring by thiomethylene groups. It was synthesised by the selective *S*-alkylation of potassium 2-benzimidazolylthiolate with the requisite tribromide in THF without protection technique.[8] The reaction condition was controlled to be nearly neutral to avoid the *N*-alkylation side reaction because the sulfur anion is more nucleophilic than the nitrogen atoms in the benzimidazole ring. The target compound was obtained in a satisfactory yield.

Recently Sun and his colleagues reported the coordination chemistry of the 1,3,5-tris(imidazolylmethyl)benzene (**3**).[9] Ligand **3** was prepared in only 30% yield, and no synthetic details were provided. We have reported the efficient synthesis of the tripodal compound 1,3,5-tris(imidazolylmethyl)-2,4,6-trimethylbenzene by *N*-alkylation of imidazole with 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene in the presence of strong base in dry DMF in up to 90% yield.[10] This high yield is probably due to the electron effect of the methyl groups on the *m*-position of benzene ring of 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene. Using our method, we also synthesised the tripodal imidazole and benzimidazole compounds (**3** and **4**) without the methyl groups on the benzene ring in moderate to good yields. The yields were 50% and 71% for compounds **3** and **4**, respectively.

The structures of compounds **1–4** were identified by ^{1}H NMR, MS, IR and elemental analysis. The ^{1}H NMR spectra of all compounds are beautifully simple. In D_2O, the active protons of the bridged histidine **1** were deuterated, and only the signals of the protons of aromatic rings and methene groups can be seen. The structures of these compounds are consistent with the data from the ^{1}H NMR spectra, which showed the correct ratios of the signals of protons of the spacer to those of the heterocycles.

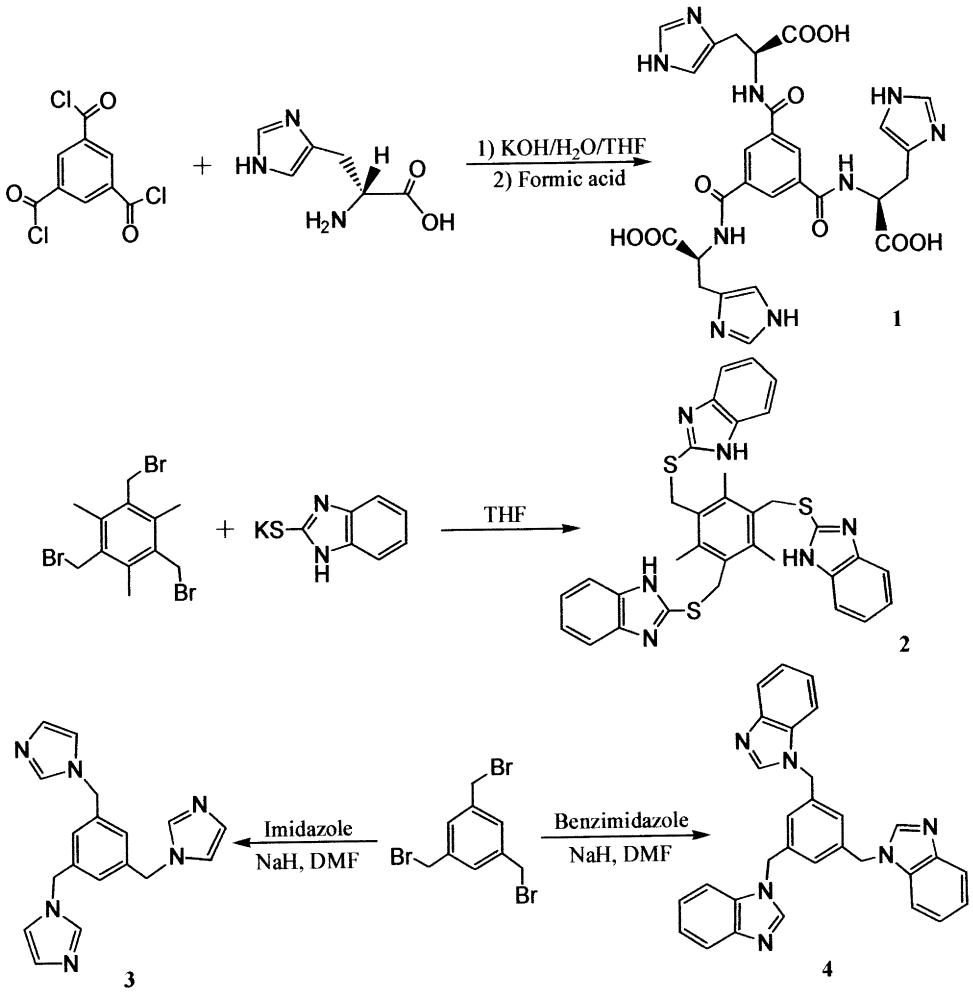
In summary, we have developed a facile and efficient synthetic route for the preparation of tripodal imidazole and benzimidazole compounds. The applications of these compounds in coordination chemistry and molecular recognition are currently under investigation.

Experimental

Physical measurements: Melting points were taken on a micro-melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker DPX-300 instrument and chemical shifts in ppm are reported with TMS or DSS as the internal standard. MS were measured on a Finnigan MAT-4510 instrument. Elemental analyses were performed on a Carlo Erba 1106 instrument. IR spectra were obtained with a

* To receive any correspondence.
E-mail: schemorg@mail.sc.cninfo. net

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



Scheme 1

Nicolet FT-IR 170SX spectrophotometer. Optical rotation was taken on a WZZ-1 polarimeter.

Reagents and general techniques: Anhydrous THF was purified according to the standard method. 1,3,5-Trimethylbenzene, imidazole and benzimidazole were distilled or recrystallised before use. The following compounds were prepared according to literature procedures: 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene[11], 1,3,5-tris(bromomethyl)benzene[12] and potassium 2-benzimidazolethiolate[8]. 1,3,5-Benzenetricarboxylic (trimesic) acid was prepared by oxidation of 1,3,5-trimethylbenzene with $KMnO_4$ in 84% yield. 1,3,5-Tris(chlorocarbonyl)benzene was obtained by treatment of the tricarboxylic acid with $SOCl_2$ in 96% yield. Other chemicals and reagents used were of reagent grade and were employed as purchased without further purification.

2-[4,6-Bis[(1-carboxy-2-imidazolyl)ethylcarbamoyl]benzenecarbonyl]amino-3-imidazolylpropionic acid (**1**): To a suspension of L-histidine (15 mmol, 2.34 g) in 5 ml water the solid KOH (14 mmol, 0.96 g in 82 % content) was added in an ice-salt bath. After the solid was dissolved 25 ml THF was added. To the vigorously stirred solution were added simultaneously a solution of 1,3,5-tris(chlorocarbonyl)benzene (5 mmol, 1.33 g) in 20 ml THF and a solution of 5 ml of 3.2 mol/dm^3 aqueous KOH over 6 h at the same temperature. The reaction mixture was stirred for 3 h, then the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h followed by evaporation of THF *in vacuo*. A solution of formic acid was added until the pH of the solution reached 4. Acetone was added with shaking to result in a white precipitate. The bridged histidine (**1**) was obtained as a white powder after recrystallisation from aqueous ethanol in 67% yield, m.p. 252 ºC (dec.). $[\alpha]_D^{20} = -7.0$ (*c* 1.0, H_2O). ^{1}H NMR (D_2O): 3.30–3.44 (m, 3H, $ImCH_{2a}$), 3.46–3.55 (m, 3H, $ImCH_{2b}$), 7.42 (s, 3H, ArH), 8.31 (s, 3H, ImH-5), 8.69 (s, 3H, ImH-2). MS (*m*/*z*, %): 621 (M$^+$, 15). IR (KBr, cm^{-1}): 3404(s), 3148(s), 3039(m), 2881(m), 2632(m), 1653(s), 1631(s), 1593(s), 1539(s), 1434(m), 1367(s), 1267(s), 1104(m), 800(s), 740(s), 661(s), 626(s). Anal. calcd. for $C_{27}H_{27}N_9O_9$: C, 52.16; H, 4.38; N, 20.27; found: C, 51.91; H, 4.31; N, 20.24 %.

1,3,5-Tris(2-benzimidazolylthiomethyl)-2,4,6-trimethylbenzene (**2**): To a well-stirred solution of potassium 2-benzimidazolethiolate (3.3 mmol, 0.62 g) in 30 ml THF, a solution of 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene (1.0 mmol, 0.40 g) in 15 ml THF was added dropwise and the mixture was heated to reflux. The resulting mixture was refluxed for 7 h. After the mixture was cooled, the mixture was filtered and washed with THF and water. A white powder was obtained after recrystallised from ethanol and water in 83% yield. m.p. 246–248ºC. ^{1}H NMR (DMSO-d_6): 2.67 (s, 9H, CH_3), 4.91 (s, 6H, CH_2), 7.24 (s, 3H, N-H), 7.46–7.49 (m, 6H, BIH-5,6), 7.74–7.77 (m, 6H, BIH-4,7). MS (*m*/*z*, %): 606 (M$^+$, 19), IR (KBr, cm^{-1}): 3030(m), 2964(m), 2820(m), 2696(m), 1623(m), 1517(s), 1457(s), 1431(s), 1399(s), 1373(m), 1266(m), 1201(s), 1013(s), 970(m), 808(m), 747(vs), 613(s). Anal. calcd. for $C_{33}H_{30}N_6S_3$: C, 65.32; H, 4.98; N, 13.85; Found: C, 65.17; H, 4.91; N, 13.99 %.

Tris-imidazole and -benzimidazole compounds: NaH (18 mmol, 0.43 g) was added to a solution of imidazole (15 mmol, 1.02 g) or benzimidazole (15 mmol, 1.83 g) in 30 ml dry DMF under nitrogen. After stirred at room temperature for 0.5 h, 1,3,5-tris(bromomethyl)benzene (5 mmol, 1.78 g) in 30 mL DMF was added dropwise over 5 h. The mixture was stirred for 48 h, the solvent was removed *in vacuo* and the residue was extracted by EtOH (15ml×3). The solution was evaporated to dryness *in vacuo* and the crude product was purified by column chromatography on silica gel (EtOAc – EtOH, 2 : 1 v/ v) followed by recrystallisation from acetone-petroleum ether to give compounds **3**[9] or **4**.

1,3,5-Tris(1-imidazolylmethyl)benzene (**3**) was obtained as white needles, m.p. 184–185 ºC, in 50% yield after recrystallisation from

acetone – petroleum ether. ^{1}H NMR (DMSO-d_6): 5.27 (s, 6H, CH_2), 7.01 (s, 3H, ArH), 7.20–7.23 (d, 6H, ImH-4,5), 7.82 (s, 3H, ImH-2). MS (*m*/*z*, %): 319 (M^++1, 37). IR (KBr, cm^{-1}): 3073(s), 2995(w), 1609(m), 1500(vs), 1436(s), 1240(s), 1074(s), 906(s), 824(s), 742(s), 664(s). Anal. calcd. for $C_{18}H_{18}N_6$: C, 67.90; H, 5.70; N, 26.40; Found: C, 68.03; H, 5.59; N, 26.56 %.

1,3,5-Tris(1-benzimidazolylmethyl)benzene (**4**) formed white needles, m.p. 229–231 ºC, in 72% yield after recrystallisation from acetone–petroleum ether. ^{1}H NMR (DMSO-d_6): 5.67 (s, 6H, CH_2), 7.18–7.37 (m, 12H, BIH-4,5,6,7), 7.77-7.80 (d, 3H, ArH), 8.40 (s, 3H, BIH-2). MS (*m*/*z*, %): 468 (M^+, 15). IR (KBr, cm^{-1}): 3051(w), 2920(w), 1733(w), 1616(m), 1588(m), 1490(vs), 1459(m), 1435(m), 1368(s), 1266(s), 1162(s), 1023(m), 857(m), 766(m), 743(vs), 621(m). Anal. calcd. for $C_{30}H_{24}N_6$: C, 76.90; H, 5.16; N, 17.94; Found: C, 76.69; H, 5.07; N, 18.10 %.

The project was supported by the National Natural Science Foundation of China.

Received: 5 June 2001; accepted 29 January 2002
Paper 01/965

References

1 A.D. Hamilton, *Bioorganic Chemistry Frontiers;* Vol. *2*, H. Dugas, Ed.; Springer-Verlag: New York, 1992; S. Mallik, R.D. Johnson and F.H. Arnold, *J. Am. Chem. Soc.,* 1994, **116**, 8902; K.J. Oberhausen, J.F. Richardson, R.M. Buchanan, J.K. McCusker, D.N. Hendrickson and J.-M. Latour, *Inorg. Chem.,* 1991, **30**,1357.

2 J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995; (b) J.L. Atwood, J.E.D. Davies, D.D. MacNicol and F. Vögtle, Eds. *Comprehensive Supramolecular Chemistry,* Vols. *1-11*, Elsevier: New York, 1996; (e) J.W. Steed and J.L. Atwood, *Supramolecular Chemistry: a Concise Introduction;* John Wiley & Sons: Chichester, 2000.

3 K.S. Oh, C.-W. Lee, J.S. Choi, S.J. Lee and K.S. Kim, *Org. Lett.,* 2000, **2**, 2679; C.M. Hartshorn and P.J. Steel, *Aust. J. Chem.,* 1995, **48**, 1587.

4 S. Hiraoka, Y. Kubota and M. Fujita, *Chem. Commun*., 2000, 1509; M.C.T. Tyfe, J. N. Lowe, J.F. Stoddart and O.J. Williams, *Org. Lett*., 2000, **2**, 1221; J. Chin, C. Walsdorff, K.S. Oh, J.B. Stranix, H.J. Chung, S.-M. Park and K. Kim, *Angew. Chem. Int. Ed.,* 1999, **38**, 2756; A. Metzger and E.V. Anslyn, *Angew. Chem. Int. Ed. Engl.,* 1998, **37**, 649; P.J. Garratt, A.J. Ibbett, J.E. Ladbury, R. O'Brien, M.B. Hursthouse and K.M. Abdul Malik, *Tetrahedron*, 1998, **54**, 949; A. Metzger, V.M. Lynch and E.V. Anslyn, *Angew. Chem. Int. Ed. Engl.,* 1997, **36**, 862; C.M. Hartshorn and P.J. Steel, *J. Chem. Soc. Chem. Commun.,* 1997, 541; C.M. Hartshorn and P.J. Steel, *Angew. Chem. Int. Ed. Engl.,* 1996, **35**, 2655.

5 J.-L. Thomas, J. Howarth, K. Hanlon and D. McGuirk, *Tetrahedron Lett.,* 2000, **41**, 413; K. Sato, S. Arai and T. Yamagishi, *Tetrahedron Lett.,* 1999, **40**, 5219; H.V.R. Dias and W. Jin, *Tetrahedron Lett.,* 1994, **35,** 1365; I. Lazar and A.D. Sherry, *J. Chem. Soc. Chem. Commun.,* 1991, **18**, 1251.

6 S. Sun, M.A. Fazal, B.C. Roy and S. Mallik, *Org. Lett.,* 2000, **2**, 911.

7 J.S. You, X.Q. Yu, C.L. Liu and R.G. Xie, *Synth. Commun.,* 1999, **29**, 2447; J.S. You, X.Q. Yu, G.L. Zhang, Q.X. Xiang, J.B. Lan and R.G. Xie, *Chem. Commun*., 2001, 1816.

8 C.-L. Liu, Y. Yuan, L. Zhang, X.-Y. Su and R.-G. Xie, *Huaxue Yanjiu Yu Yingyong* (*Chem. Res. Appl*.), 1999, **11**, 684.

9 H.-K. Liu, W.-Y. Sun, D.-J. Ma, K.-B. Yu and W.-X. Tang, *Chem. Commun*., 2000, 591.

10 Y. Yuan, Z.L. Jiang, J.M. Yan, G. Gao, A.S. C. Chan and R.G. Xie, *Synth. Commun*., 2000, **30**, 4555; M.V. Baker, M.J. Bosnich, C.C. Williams, B.W. Skelton and A.H. White, *Aust. J. Chem*., 1999, **52**, 823.

11 J. Závada, M. Pánkova, P. Holý and M. Tichy, *Synthesis*, 1994, 1132; A.W. wan der Made and R.H. wan der Made, *J. Org. Chem.* 1993, **58**, 1262.

12 F. Vögtle, M. Zuber and R.G. Lichenthaler, *Chem. Ber.,* 1973, **106**, 717; W. Offermann, and F. Vögtle, *Synthesis*, 1977, 272.