A Remarkably Efficient and Direct Route for the Synthesis of Binucleating 1,4,7-Triazacyclononane Ligands

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Received 14 August 2001

Abstract: An extremely efficient and direct route towards a range of binucleating analogues of 1,4,7-triazacyclononane **5a–f**, has been developed. In all cases the reactions of benzylic and aliphatic diamines with ditosylate ester **3** proceed to give the target binucleating ligands almost exclusively and in excellent yield.

Key words: macrocycles, azamacrocycles, binucleating ligands, polyazacycloalkanes, 1,4,7-triazacyclononane

The synthesis and application of triazamacrocyclic ligands such as 1, has been an area of enormous interest and diversity in recent years.² Included in this generic class of ligands is a series of binucleating analogues, for example 2, that have been of particular utility in bioinorganic chemistry³ and catalysis.⁴ Metal complexes of these triazacyclononane ligands have found application e.g. as oxidation catalysts⁵ and as hydrolase enzyme mimics, e.g. capable of the non-oxidative cleavage of RNA and DNA.⁶ In both of these cases, dramatic increases in the effectiveness of the catalysts were observed when a binucleating variant of the triazacyclononane ligand, like 2, was used rather than its mononucleating analogue, like 1.4,8a There is particularly strong spectroscopic evidence, for manganese oxidation catalysts based on triazacyclononane ligands, that a binuclear metal complex is formed during the catalytic cycle.⁷ It is therefore not surprising that, by forcing two metal centres into close proximity by using such binucleating ligands, the catalytic properties in the resultant complexes are enhanced. Unfortunately, in spite of the remarkable properties and catalytic activity that these ligands incur on their metal complexes, there are considerable difficulties associated with their syntheses; two general procedures have been reported,⁸ both of which involve the synthesis and subsequent derivatisation of the preformed 1,4,7-triazacyclononane system (Figure).

We are currently interested in developing efficient routes to both unsymmetrically and symmetrically substituted triazamacrocyclic ligands and recently reported an efficient route for their syntheses (Scheme).⁹ We observed that formation of the desired nine-membered ring of **4** was highly favoured when benzylamine was reacted with **3** using potassium carbonate as the base in acetonitrile. We wondered whether this could also provide a considerably more direct and efficient synthesis of binucleating analogues like 5a and 5b. We therefore decided to investigate the reaction of the commercially available *m*- and *p*-xylenediamines with 3 under identical reaction conditions (Scheme). Intuitively one might expect a complex mixture of products to be formed under such reaction conditions viz. larger marcocycles, higher order macrocycles e.g. 2+2, oligomers and polymeric species. However, ¹H NMR analysis of the crude reaction mixtures indicated that the formation of single compounds had almost exclusively occurred and their spectra were consistent with the target binucleating ligands 5a and 5b. This was corroborated by infrared spectroscopy, which revealed that the highly characteristic bands of the tosylamide protected 1,4,7-triazacyclononane ring were present at 1599, 1495, 1450, 1090, 996, 815, 712 and 692 cm⁻¹. The structural integrity of the products was further supported by ¹³C NMR and mass spectral analysis. Analytically pure materials could be readily prepared by simple recrystallisation from acetonitrile to give 5a and 5b in 76% and 66% isolated yield respectively. This is a remarkable result and reflects that the formation of the nine-membered triaza-ring is highly favoured under the reaction conditions we have developed. That this combined intermolecular and intramolecular reaction involving four nucleophilic displacements should occur in such high yield is impressive in itself; that it should occur exclusively to form the binucleating ligands 5a and 5b, when many other reactions are possible is, in our view, quite remarkable.





As a result of the efficiency of the reactions with benzylic diamines, we extended our study to a series of other aliphatic diamines. These were similarly found to be high yielding and extremely clean reactions with the desired binucleating ligands **5c–5f** being almost exclusively formed. Purification by column chromatography was required in these cases to provide analytically pure materi-

Synthesis 2001, No. 16, 30 11 2001. Article Identifier: 1437-210X,E;2001,0,16,2381,2383,ftx,en;E15501SS.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0039-7881



Scheme Reagents and conditions: (i) $BnNH_2$, CH_3CN , K_2CO_3 , 5 days, 70% (ii) $NH_2(R)NH_2$, CH_3CN , K_2CO_3

als, however, the crude products of the reactions were sufficiently pure for use in subsequent reactions.

The remarkable efficiency of this reaction route towards the direct synthesis of a range of binucleating triazacyclononane ligands **5a–f**, has been clearly demonstrated. It is hoped that this procedure will allow such ligands to be readily prepared so that a thorough investigation of the catalytic properties of their complexes can be undertaken. Investigations along these lines are currently underway in our laboratories.

TableBinucleating ligands prepared by the Direct Reaction of Di-amines with 3.

Entry	R	Time (d)	Compound	Yield (mol%)
1	m-CH ₂ C ₆ H ₄ CH ₂₋	5	5a	76
2	p-CH ₂ C ₆ H ₄ CH ₂	5	5b	66
3	(CH ₂) ₂	10	5c	81
4	(CH ₂) ₃	10	5d	89
5	(CH ₂) ₄	10	5e	82
6	CH ₂ CH(OH)CH ₂	10	5f	51

Reagents and solvents were standard grade commercial products and were used without further purification unless otherwise stated. Diamines were purified by distillation from KOH prior to use. CH₃CN was refluxed overnight with CaH₂ in an atmosphere of nitrogen and then distilled from CaH₂. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were obtained using a Carlo Erba 1106 elemental analyser. ¹H NMR and ¹³C NMR spectra were recorded as CDCl₃ solutions on a JEOL JNM-EX spectrometer at 270 MHz and at 67.9 MHz respectively and were referenced to residual CHCl₃ as the internal standard. J values are given in Hertz. IR spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrometer with a solid state ATR attachment. UV-Spectra were recorded on a Hewlett-Packard 8453 diode array UV-vis spectrophotometer. Mass spectra were recorded on a VG Instruments ZAB-SE using xenon gas at 8 kV in a matrix of 3-nitrobenzyl alcohol (MNBA) and sodium iodide (FAB).

All binucleating macrocyclic ligands were prepared in an identical manner, which is typified by the synthesis of **5c**. The only variations

in procedure were in the reaction times, which were 5 days for 5a and **5b** and 10 days for **5c–5f**.

1,3-Bis[*N*,*N*'-bis(*p*-toluenesulfonyl)-1,4,7-triaza-1-cyclonon-1-ylmethyl]benzene (5a)

The off white solid produced from the crude reaction mixture was recrystallised from hot CH_3CN to yield **5a** as a white crystalline solid (0.93 g, 76%); mp 192–194 °C.

IR: 1597, 1494, 1446, 1317 $(SO_2)_{NTs}$, 1148 $(SO_2)_{NTs}$, 1090, 950, 816, 710, 689 cm⁻¹.

¹H NMR: δ = 2.42 (s, 12 H, ArCH₃), 3.00 (b s, 8 H, TsNCH₂CH₂N), 3.17 (bs, 8 H, TsNCH₂CH₂N), 3.50 (s, 8 H, TsNCH₂CH₂NTs), 3.76 (s, 4 H, NCH₂Ar), 7.30 (m, 12 H, *J* = 8.3, CH₂C₆H₄CH₂ and CH₃CCH), 7.66 (d, 8 H, *J* = 8.3, SO₂CCH).

¹³C NMR: δ = 21.48, 51.50, 52.51, 54.69, 61.00, 127.20, 127.88, 128.23, 129.75, 135.53, 139.03, 143.37.

 $\begin{array}{l} MS \ \textit{m/z:} \ 977 \ (100\%) \ (M+H), \ 822 \ (60) \ (M+H-Ts), \ 665 \ (19) \ (M-H-2Ts), \ 539 \ (17) \ (C_{28}H_{33}N_3O_4S_2^{+}), \ 450 \ (8) \ (C_{21}H_{28}N_3O_4S_2^{+}), \ 385 \ (6) \ (C_{21}H_{27}N_3O_2S^{+}). \end{array}$

HRMS (*m/z*): calcd for C₄₈H₆₁N₆O₈S₄, 977.3434; found, 977.3391.

Anal. Calcd for $\textbf{5a}{\cdot}\text{H}_2$ O, $\text{C}_{48}\text{H}_{62}\text{N}_6\text{O}_9\text{S}_4\text{:}$ C, 57.9; H, 6.3; N, 8.4. Found: C, 58.2; H, 6.0; N, 8.4.

1,4-Bis[*N*,*N*'-bis(*p*-toluenesulfonyl)-1,4,7-triaza-1-cyclonon-1-ylmethyl]benzene (5b)

The off white solid produced from the crude reaction mixture was recrystallised from hot CH_3CN to yield **5b** as a white crystalline solid (0.81 g, 66%); mp 217–218 °C.

IR: 1597, 1451, 1324 (SO₂)_{NTs}, 1150 (SO₂)_{NTs}, 1088, 950, 812, 710, 689 cm⁻¹.

¹H NMR: δ = 2.40 (s, 12 H, ArCH₃), 2.94 (bs, 8 H, TsNCH₂CH₂N), 3.11 (bs, 8 H, TsNCH₂CH₂N), 3.48 (s, 8 H, TsNCH₂CH₂TsN), 3.70 (s, 4 H, NCH₂Ar), 7.28 (m, 12 H, *J* = 8.3, CH₂C₆H₄CH₂ and CH₃CCH), 7.64 (d, 8 H, *J* = 8.3, SO₂CCH).

¹³C NMR: δ = 21.48, 51.43, 52.40, 54.75, 60.68, 127.19, 129.06, 129.75, 135.54, 138.11, 143.38.

 $\begin{array}{l} MS \ m/z: 977 \ (100\%) \ (M+H), 822 \ (40) \ (M+H-Ts), \ 665 \ (15) \ (M+H-2Ts), \ 540 \ (22) \ (C_{28}H_{34}N_3O_4S_2^{\ +}), \ 450 \ (20) \ (C_{21}H_{28}N_3O_4S_2^{\ +}), \ 385 \ (72) \ (C_{21}H_{27}N_3O_2S^{\ +}) \ . \end{array}$

HRMS (*m/z*): calcd for C₄₈H₆₁N₆O₈S₄, 977.3434.; found, 977.3391.

Anal. Calcd for $C_{48}H_{60}N_6O_8S_4$: C, 59.0; H, 6.2; N, 8.6. Found: C, 58.6; H, 6.2; N, 8.4.

1,2-Bis[*N*,*N*'- bis(*p*-toluenesulfonyl)-1,4,7-triaza-1-cyclonon-yl]ethane (5c)

To a stirred suspension of **3** (2.00 g, 2.60 mmol), potassium carbonate (1.08 g, 7.80 mmol) in anhyd CH₃CN (20 mL) was added ethylenediamine (87 μ L, 1.30 mmol) dropwise under a N₂ atmosphere. The resultant mixture was heated at 85 °C under reflux for 10 d. The inorganic salts were removed by filtration and the filtrate concentrated in vacuo to yield the crude product as an off-white solid which was purified by column chromatography (ethyl acetate–petroleum spirits b.p.40–60 °C, 2:1) to yield **5c** (0.95 g, 81%);¹⁰ mp 250–252 °C.

IR: 1597, 1492, 1449, 1321 (SO₂)_{NTs}, 1149 (SO₂)_{NTs}, 1088, 961, 811, 709, 694 cm⁻¹.

¹H NMR: δ = 2.40 (s, 12 H, ArCH₃), 2.71 (s, 4 H, NCH₂CH₂N), 2.92 (bs, 8 H, TsNCH₂CH₂N), 3.17 (bs, 8 H, TsNCH₂CH₂N), 3.47 (bs, 8 H, TsNCH₂CH₂TsN), 7.30 (d, 8 H, *J* = 8.3, CH₃CCH), 7.64 (d, 8 H, *J* = 8.3, SO₂CCH).

 ^{13}C NMR: $\delta = 21.49,\,51.39,\,52.61,\,55.31,\,55.69,\,127.36,\,129.79,\,135.44,\,143.41.$

HRMS (*m/z*): calcd for C₄₂H₅₇N₆O₈S₄, 901.3121; found, 901.3126.

Anal. Calcd for: C, 56.0; H, 6.3; N, 9.3. Found: C, 56.2; H, 6.5; N, 9.0.

1,3-Bis [N, N'- bis(p-toluenesulfonyl)-1,4,7-triaza-1-cyclonon-yl]propane (5d)

The crude reaction mixture was purified by column chromatography (Et₂O–CH₂Cl₂, 2:1) to yield **5d** (1.01 g, 89%) as a white crystalline solid;¹⁰ mp 144–146 °C.

IR: 1597, 1492, 1448, 1327 $(SO_2)_{NTs}$, 1152 $(SO_2)_{NTs}$, 1088, 976, 814, 711, 690 cm⁻¹.

¹H NMR: δ =1.65 (br, 2 H, NCH₂CH₂CH₂N), 2.40 (s, 12 H, ArCH₃), 2.58 (t, 4 H, *J* = 7.0, NCH₂CH₂CH₂N), 2.85 (s, 8 H, TsNCH₂CH₂N), 3.16 (s, 8 H, TsNCH₂CH₂N), 3.46 (s, 8H, TsNCH₂CH₂TsN), 7.28 (d, 8 H, *J* = 8.3, CH₃CCH), 7.64 (d, 8 H, *J* = 8.3, SO₂CCH).

 ^{13}C NMR: δ = 21.46, 26.23, 51.54, 52.69, 55.46, 55.83, 127.22, 129.77, 135.47, 143.34.

 $\begin{array}{l} \text{MS } m/z: \ 937 \ (16\%) \ (M+\text{Na}), \ 915 \ (54), \ (M+\text{H}), \ 760 \ (23) \ (M-\text{Ts}), \\ 478 \ (17) \ (C_{23}\text{H}_{32}\text{N}_3\text{O}_4\text{S}_2^+), \ 464 \ (7) \ (C_{22}\text{H}_{30}\text{N}_3\text{O}_4\text{S}_2^+), \ 450 \ (100) \\ (C_{21}\text{H}_{28}\text{N}_3\text{O}_4\text{S}_2^-), \ 296 \ (28), \ (C_{14}\text{H}_{22}\text{N}_3\text{O}_2\text{S}^+). \end{array}$

HRMS (m/z): calcd for C₄₃H₅₉N₆O₈S₄, 915.3277; found, 915.3301.

Anal. Calcd for $\textbf{5d} \cdot H_2O,~C_{43}H_{60}N_6O_9S_4{:}$ C, 55.3; H, 6.4; N, 9.0. Found: C, 55.4; H, 6.2; N, 8.7.

1,4-Bis [*N*, *N*'- bis(*p*-toluenesulfonyl)-1,4,7-triaza-1-cyclonon-yl]butane (5e)

The crude reaction mixture was recrystallised from hot EtOH to yield 5e (0.61 g, 82%).

IR: 1597, 1492, 1448, 1328 $(\mathrm{SO}_2)_{\mathrm{NTs}},$ 1151 $(\mathrm{SO}_2)_{\mathrm{NTs}},$ 1088, 979, 814, 711, 691 cm^{-1}.

Mp, ¹H NMR and $^{13}\mathrm{C}$ NMR spectra were consistent with the reported data. $^{8\mathrm{b}}$

HRMS (m/z): calcd for C₄₄H₆₁N₆O₈S₄, 929.3434; found, 929.3475.

1,3-Bis [N, N'- bis(p-toluenesulfonyl)-1,4,7-triaza-1-cyclononyl]propan-2-ol (5f)

The crude reaction mixture was purified by column chromatography (EtOAc– petroleum spirits, b.p. 40–60 °C, 2:1) to yield **5f** (0.58 g, 51%); mp 105 °C.

IR: 1597, 1492, 1450, 1350 $(SO_2)_{NTs}$, 1149 $(SO_2)_{NTs}$, 1088, 982, 813, 710, 689 cm⁻¹.

¹H NMR: $\delta = 2.39$ (s, 12 H, ArCH₃), 2.59 (dd, 2 H, J = 12.9 and 8.2, NHCHCHOH), 2.73 (dd, 2 H, J = 12.9 and 2.5, NHCHCHOH), 3.00 (bs, 8 H, NCH₂CH₂NTs), 3.23 (bs, 8 H, NCH₂CH₂NTs), 3.45 (bs, 8 H, TsNCH₂CH₂NTs), 3.75 (bm, 1 H, CH₂CHOHCH2), 7.28 (d, 4 H, J = 8.3, CH₃CH), 7.64 (d, 4 H, J = 8.3, SO₂CCH).

¹³C NMR were consistent with the reported data.¹¹

MS m/z: 1063 (47%) (M+Cs), 953 (54), (M+Na), 931 (59) (M+H), 775 (14) (M–Ts), 450 (100) (C₂₁H₂₈N₃O₄S₂⁺).

HRMS (m/z): calcd for C₄₃H₅₉N₆O₉S₄,931.3226; found, 931.3250.

Anal. Calcd for $\rm C_{43}H_{58}N_6O_9S_4:$ C, 55.5; H, 6.3; N, 9.0. Found: C, 55.2; H, 6.4; N, 8.7.

Acknowledgement

We are grateful to the following bodies for financial support: EPS-RC (CASE awards for New Academics, Award 00800316, KS), Queen Mary, University of London for the provision of a studentship (SP), The Royal Society, The Nuffield Foundation, The University of London Central Research Fund and Warwick International Limited.

References

- (1) Present address: Associated Octel, Oil Sites Road, Ellesmere Port, Merseyside, U.K.
- (2) Wainwright, K. P. Coord. Chem. Rev. 1997, 166, 35.
- (3) (a) Sessler, J. L.; Sibert, J. W.; Lynch, L.; Markert, J. T.; Wooten, C. L. *Inorg. Chem.* **1993**, *32*, 621. (b) Brudenell, S. J.; Spiccia, L.; Bond, A. M.; Fallon, G. D.; Hockless, D. C. R.; Lazarev, G.; Mahon, P. J.; Tiekink, E. R. T. *Inorg. Chem.* **2000**, *39*, 881.
- (4) Hage, R.; Iburg, J. E.; Kerschner, J.; Koek, J. H.; Lempers, E. L. M.; Martens, R. J.; Racherla, U. S.; Russell, S. W.; Swarthoff, T.; van Vliet, M. R. P.; Warnaar, J. B.; van der Wolf, L.; Krijnen, B. *Nature* **1994**, *369*, 637.
- (5) See for example (a) De Vos, D.; Bein, T. Chem. Commun. 1996, 917. (b) Zondervan, C.; Hage, R.; Feringa, B. L. Chem. Commun. 1997, 419. (c) De Vos, D. E.; Sels, B. F.; Reynaers, M.; Subba Rao, Y. V.; Jacobs, P. A. Tetrahedron Lett. 1998, 3221. (d) Barton, D. H. R.; Li, W.; Smith, J. A. Tetrahedron Lett. 1998, 39, 7055. (e) Shul'pin, G. B.; Süss-Fink, G.; Lindsay Smith, J. R. Tetrahedron 1999, 55, 5345.
- (6) (a) Young, M. J.; Chin, J. J. Am. Chem. Soc. 1995, 117, 10577. (b) Hegg, E. L.; Burstyn, J. N. Inorg. Chem. 1996, 35, 7474. (c) McCue, K. P.; Voss, D. A.; Marks, C.; Morrow, J. R. J. Chem. Soc., Dalton Trans. 1998, 2961.
- (7) (a) De Vos, D. E.; Meinershagen, J. L.; Bein, T. Angew. Chem. Int. Ed. Engl. 1996, 35, 2211. (b) Gilbert, B. C.; Kamp, N. W. J.; Lindsay Smith, J. R.; Oakes, J. J. Chem. Soc., Perkin Trans 2. 1997, 2161. (c) De Vos, D. E.; de Wilderman, S.; Sels, B. F.; Grobert, P. J.; Jacobs, P. A. Angew. Chem. Int. Ed. 1999, 38, 980.
- (8) (a) Weisman, G. R.; Vachon, D. J.; Johnson, V. B.;
 Gronbeck, D. A. J. Chem. Soc., Chem. Commun. 1987, 887.
 (b) Sessler, J. L.; Sibert, J. W.; Lynch, V. Inorg. Chem. 1990, 29, 4143. (c) Blake, A. J.; Danks, J. P.; Li, W.-S.; Lippolis, V.; Schröder, M. J. Chem. Soc., Dalton Trans. 2000, 3034.
- (9) Pulacchini, S.; Watkinson, M. *Eur. J. Org. Chem.* accepted for publication.
- (10) Wieghardt K., Tolksdorf I., Herrmann W.; *Inorg. Chem.*; 1985, 24: 1230-1235; the original report of these compounds provides no experimental data and indicates that the compounds contain impurities as judged by ¹³C NMR.
- (11) Sessler, J. L.; Sibert, J. W.; Burrell, A. K.; Lynch, V.; Markert, J. T.; Wooten, C. L. *Inorg. Chem.* **1993**, *32*, 4277.