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Direct conversion of macrocyclic furans into macrocyclic isothiazoles

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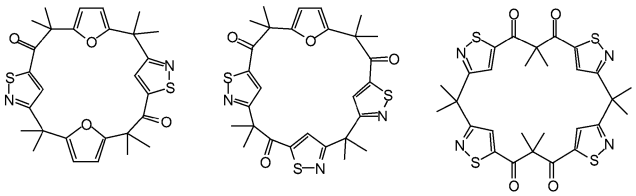
Received (in Cambridge, UK) 12th November 2001, Accepted 3rd December 2001
First published as an Advance Article on the web 17th January 2002

The first calixhetarenes with more than one heteroatom in the constituent rings are prepared in one step by treatment of calix[4]furan 1a and calix[6]furan 1b with ethyl carbamate, thionyl chloride and pyridine to give 2, 3, 4 and 5, 6, 7 respectively; these products have been characterised by X-ray crystallography which reveals that in 2 all eight heteroatoms lie on one face of the macrocycle.

Compared to the vast attention devoted to calixarenes,[1] their heterocyclic analogues have been much less developed, and are limited almost entirely to calix-furans, thiophenes, pyrroles and their hybrid systems.[2] As far as we are aware, heterocyclic rings with more than one heteroatom have not previously been incorporated into these macrocycles. We now report the synthesis of the isothiazole analogues by a new approach, the direct one-pot conversion of preformed calixfurans.

Recently[3] we demonstrated the ready and simple conversion of 2,5-disubstituted furans into 5-acyl-3-substituted isothiazoles by treatment with ethyl carbamate, thionyl chloride and pyridine (Scheme 1). The active reagent in this reaction is thiazyl chloride (N≡S–Cl), optimally generated from 4.3 equivalents each of urethane and thionyl chloride and an excess of pyridine[4] for each equivalent of the furan. We have now applied this reaction to a number of macrocyclic furans, the calix[n]furans **1**, particularly **1a** and **1b**, and have isolated and characterised a series of novel macrocyclic isothiazoles.

Calix[n]furans are well-known systems,[5] synthesised by reaction of furans with acetone and an acid catalyst or *via* a more rational synthesis of their linear precursors.[6] Calix[4]furan **1a**, which has a roughly square and fairly rigid structure,[7] reacts with the above thiazyl chloride reagent to give bis- **2**, tris- **3** or tetrakis-isothiazole **4** macrocycles depending upon conditions. No *mono*-isothiazole product was detectable; presumably it is more reactive towards thiazyl chloride than the more compact starting material. Optimal yields (17%) of the symmetrical *anti*-bisisothiazole **2** were obtained utilising 4.3 : 8.6 : 1 molar ratios of urethane : thionyl chloride : calixfuran in refluxing benzene for 30 minutes in the presence of molecular sieves (4 Å). When the reagent amounts were doubled the tris-isothiazole **3** was almost the sole product (27%), with minor amounts (~1%) of the tetrakis-isothiazole **4** being isolable also. The reactive mono-isothiazole first formed (*cf.* Scheme 1) is presumably converted into the observed calixarene **2** with alternating furan and isothiazole rings. Since this product cannot be converted into the tris-isothiazole **3** without a profound molecular rearrangement, it is likely that the mono-isothiazole is also converted into an isomer of **2** with the isothiazole rings adjacent, and thence into the observed product **3**. Similarly, the bis-isothiazole **2** could be converted into a tris-isothiazole which can finally yield the observed calix[4]isothiazole **4**.



2 **3** **4**

A single crystal X-ray analysis† of the bis-isothiazole **2** shows that in the solid state the molecule has a square box-like geometry (Fig. 1) with the planes of the furan and isothiazole rings inclined by 76 and 66° respectively to the mean plane of the four isopropylidene carbon atoms. The molecule has crystallographic C_2 symmetry with, surprisingly, all eight heteroatoms lying on the same face of the macrocycle. This geometry is in striking contrast to the 'up–down–up–down' D_{2d} arrangement observed in the solid state for the parent calix[4]furan **1a**.[7] The molecules pack to form cone-in-cone polar stacks.

In the solid state† the tetramer **4** adopts a different conformation from that of **2**, having crystallographic C_i symmetry with an 'up–up–down–down' sequence for the isothiazole rings and alternating *cis*- and *trans*-relationships for the adjacent C–S and C=O linkages (Fig. 2). The planes of the isothiazole rings are inclined by 75 and 82° to the plane of the four isopropylidene carbon atoms. Crystals of **4**, however, are not isomerically pure and are seen to contain *ca*. 10% of an isomer having the same 'up–up–down–down' and *cis*- and *trans* sequences for the 5-acylisothiazole units but with a head-to-tail reversal of a diametrically opposite pair of these units.[8] Preliminary investigations of crystals of **3** indicate the presence

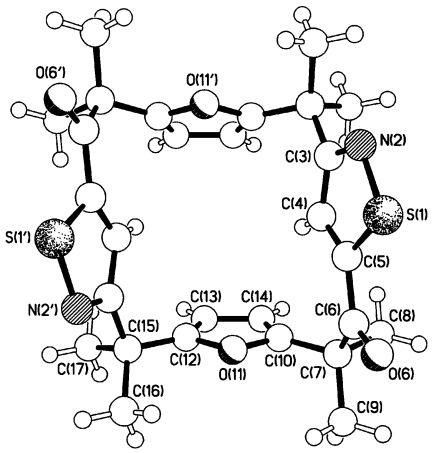
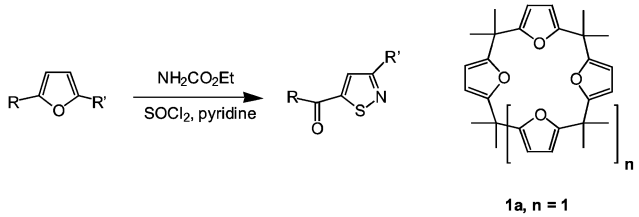


Fig. 1 The molecular structure of **2**. Selected bond lengths (Å); S(1)–N(2) 1.653(3), N(2)–C(3) 1.313(4), C(3)–C(4) 1.420(4), C(4)–C(5) 1.354(4), C(5)–S(1) 1.714(3).



Scheme 1

DOI: 10.1039/b110287g

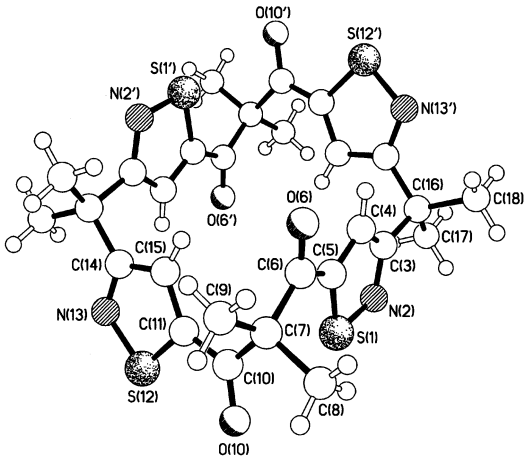
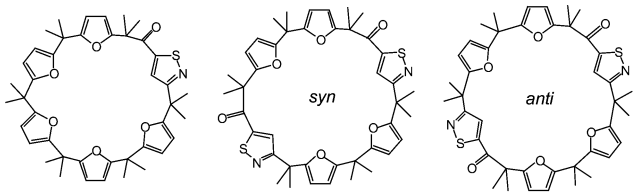


Fig. 2 The molecular structure of the major isomer present in the crystals of **4**. Selected bond lengths (Å); S(1)–N(2) 1.644(8), N(2)–C(3) 1.329(11), C(3)–C(4) 1.397(13), C(4)–C(5) 1.342(12), C(5)–S(1) 1.707(9), S(12)–N(13) 1.652(8), N(13)–C(14) 1.312(10), C(14)–C(15) 1.443(11), C(15)–C(11) 1.373(11), C(11)–S(12) 1.710(8).

of a mixture of conformational isomers with just one 5-acylisothiazole unit (that diametrically opposite to the furan ring) exhibiting an analogous head-to-tail reversal, but with a more equal ratio of isomers.

Similar studies with the more flexible calix[6]furan **1b** allowed synthesis of the mono-, bis- and tris-isothiazole derivatives. Optimum yields (15%) of the mono-isothiazole **5** were formed after 2 hours heating at 80 °C with urethane : thionyl chloride in the ratio 4.3 : 8.6 moles per mole **5**, whilst doubling the reagent amounts with added 4 Å molecular sieves and 1 hour heating at the same temperature yielded an inseparable mixture of the bis-isothiazoles **6** and **7**, with the



5 **6** **7**

second isothiazole remote from the first, and with the two 5-acylisothiazoles *syn* and *anti* respectively. In all of these reactions, small amounts (up to 4%) of the tris-isothiazole were also isolated (confirmed by mass spectrometry), probably as an inseparable mixture of isomers.

The crystal structure† of **5** shows the molecule to have a distinctly folded, self-filling geometry with no significant free pathway through the macroring centre and an absence of a distinctive 'up–down' pattern for the furan and isothiazole ring systems; the 5-acylisothiazole unit has a *cis*-C–S···C=O relationship (Fig. 3). The conformation of **5** is very different to that of the parent calix[6]furan which has a planar discoid shape with crystallographic C_2 symmetry.[2a,5j] Preliminary studies of crystals of the calix[4]furan[2]isothiazole revealed them to contain a mixture of the *syn* and *anti* isomers **6** and **7**.

These novel calixfuranisothiazoles and calixisothiazoles are thus available in two steps from furan and acetone followed by ethyl carbamate and thionyl chloride. Their host–guest chemistry, which should be enriched by the extra heteroatoms, is under investigation.

We thank Professor F. H. Kohnke of the University of Messina, for providing samples of the calix[4]- and calix[6]furans and for helpful discussions, and MDL Information Systems (UK), Parke-Davis, Pfizer, SmithKline Beecham, the University of Sunderland and Zeneca for financial support.

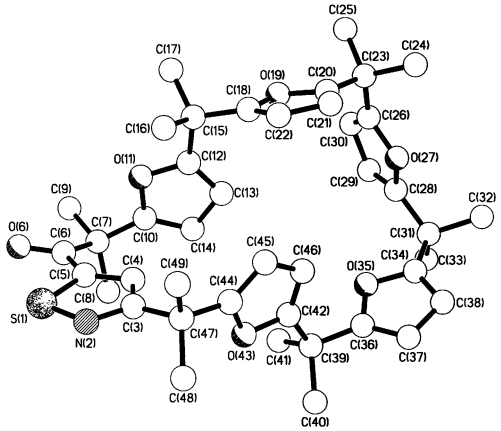


Fig. 3 The molecular structure of **5**. Selected bond lengths (Å); S(1)–N(2) 1.647(4), N(2)–C(3) 1.325(5), C(3)–C(4) 1.421(5), C(4)–C(5) 1.374(5), C(5)–S(1) 1.707(3).

Notes and references

† *Crystal data* for **2**: $C_{28}H_{30}N_2O_4S_2$, M = 522.7, monoclinic, space group $C2/c$ (no. 15), a = 21.001(2), b = 6.808(1), c = 19.521(1) Å, β = 101.90(1)°, V = 2731.2(3) Å^3, Z = 4 (C_2 symmetry), D_c = 1.271 g cm^{-3}, μ(Cu-Kα) = 20.6 cm^{-1}, T = 293 K; 2148 independent reflections, F^2 refinement, R_1 = 0.049, wR_2 = 0.111, 1687 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 124°$], 164 parameters. For **4**: $C_{28}H_{28}N_4O_4S_4$, M = 612.8, triclinic, space group $P\bar{1}$ (no. 2), a = 7.120(2), b = 10.052(2), c = 10.710(3) Å, α = 83.54(2), β = 74.42(2), γ = 82.83(2)°, V = 730.0(3) Å^3, Z = 1 (C_i symmetry), D_c = 1.394 g cm^{-3}, μ(Cu-Kα) = 33.3 cm^{-1}, T = 293 K; 2154 independent reflections, F^2 refinement, R_1 = 0.084, wR_2 = 0.151, 1187 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 120°$], 261 parameters. There are two different ring systems present in the crystals in a 90 : 10 ratio. For **5**: $C_{42}H_{47}NO_6S$, M = 693.9, triclinic, space group $P\bar{1}$ (no. 2), a = 12.234(2), b = 13.685(2), c = 14.102(3) Å, α = 85.07(2), β = 69.15(2), γ = 64.01(1)°, V = 1976.4(6) Å^3, Z = 2, D_c = 1.166 g cm^{-3}, μ(Cu-Kα) = 10.9 cm^{-1}, T = 293 K; 5868 independent reflections, F^2 refinement, R_1 = 0.060, wR_2 = 0.145, 3835 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 120°$], 452 parameters. CCDC 174287–174289. See http://www.rsc.org/suppdata/cc/b1/b110287g/ for crystallographic files.

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8 The major isomer can be visualised (Fig. 2) as having cyclically an ···N–S···S–N···N–S···S–N··· sequence, whereas in the minor isomer the sequence is ···S–N···S–N···S–N···S–N···.