SHORT PAPER

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Synthesis and conformational analysis of syn-dithia[3.3][2,4]thiazolophane and syn-dithia[3.3]([1,4]phenyl[2,4]thiazolophane)†

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Synthesis of syn-dithia[3.3][2,4]thiazolophane **1** and syn-dithia[3.3]([1,4]phenyl[2,4]thiazolophane) **2** was accomplished via the stepwise construction of two thiapropylene (CH_2SCH_2) bridges. Dynamic ^{1}H NMR analysis reveals the heterophanes **1** and **2** to be conformationally mobile on the NMR time scale down to –55 °C.

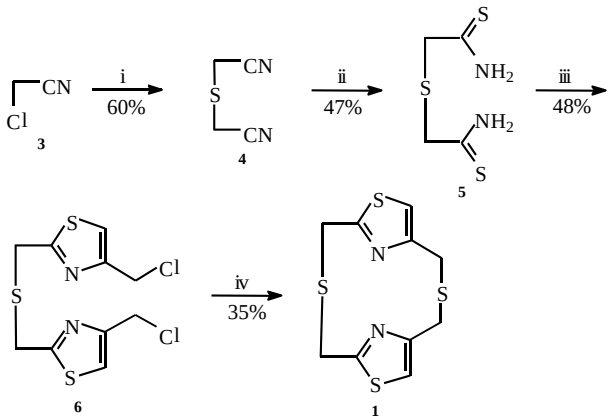
Keywords: cyclophanes, thiazoles, DNMR, conformational mobility

There is an on-going interest in the synthesis and conformational dynamics of constrained heterophane systems.[1] It is well documented that [2.2]heterophanes derived from rings containing the smaller oxygen and nitrogen heteroatoms, for instance furanophane, oxazolophane, pyridinophane and isoxazolophane, exhibit free conformational ring rotations.[2,3a] In contrast, heterophanes containing the bulkier sulfur atom, namely thiophenophane and thiazolophanes, exist as conformationally non-interconvertible systems owing to the longer C–S bond and greater bulk of the sulfur atom which hinders the inversion process.[3] Among the thia-bridged [3.3]cyclophanes, both conformationally rigid[4] (*e.g.*, [3.3]dithia-naphthalenophane) and conformationally mobile[5] (*e.g.*, dithia[3.3]pyridinophane, 9,8-dimethyl-2,11–dithia[3.3]metacyclophane and dithia[3.3]benzene-azulenophane) have been described in the literature. Recently, we have reported[6] the syntheses of anti-[2.2]benzothiazolophane and syn-dithia-[3.3](2,6)benzothiazolophane and found them to be conformationally immobile on the NMR time scale up to 150 °C.

Literature search indicated that very few examples of dithia[3.3]heterophanes are known; consequently only little information is currently available concerning their structural and dynamic properties. In continuation of our interest in the chemistry of thiazole-derived heterophanes, we now report on the synthesis and conformational behaviour of syn-dithia[3.3]thiazolophane **1** and syn-dithia[3.3](phenylthiazolophane) **2**.[7] A further point of interest in the synthesis of the thiazolophanes **1** and **2** stems from the possibility of the existence of chirality in these molecules on account of the presence of the unsymmetrical thiazole moiety (due to the 1,3-disposition of the N and S heteroatoms), and subject to their conformational rigidity.

Synthesis of heterophanes 1 and 2

For the synthesis of both heterophanes **1** and **2**, we designed a common strategy that entailed stepwise construction of two thia bridges. Towards the synthesis of **1**, we started with the known[8] bis-thioamide **5** which was prepared in two steps by adapting the literature procedure by first reacting chloroacetonitrile **3** with Na_2S (2:1 ratio) under phase transfer conditions, followed by treatment of the resulting thia-bis-nitrile **4**[8] with dry H_2S in pyridine solvent containing a catalytic amount of Et_3N. For the preparation of the bis-chloromethyl thiazole **6**, we applied the well known Hantzsch protocol.[9] Accordingly, condensation of thioamide **5** with 1,3-dichloropropanone (1 : 2 ratio) was carried out in dry THF under ambient conditions. Usual work-up of the reaction followed by SiO_2 column chromatographic purification afforded the expected thia-bis chloromethyl thiazole **6** as an unstable oil in 48% yield. For the subsequent thia-bridge construction, a freshly prepared sample of **6** was immediately reacted with Na_2S in a dry THF-benzene solvent system under high dilution conditions in the presence of a catalytic amount of cetyltrimethylammonium bromide (CTAB). Purification of the crude product afforded the target syn-dithia[3.3]thiazolophane (**1**) in 35% yield.



Scheme 1 Reagents and conditions:
(i) Na2S/CH2Cl2, CTAB, R.T, 24h; (ii) dry H2S, dry pyridine, Et3N, 4h; (iii) $ClCH_2COCH_2Cl$, Dry THF, 8h iv) Na2S/benzene-THF, CTAB, R.T, 60h.

For the synthesis of the next target, the syn-dithia[3.3](phenylthiazolophane) (**2**) (Scheme 2), a strategy similar to that used for **1** was followed. Thus, the thia-bisnitrile **8** was prepared in good yield by reacting 4-bromomethyl benzonitrile (**7**)[10] with Na_2S in dry CH_2Cl_2 containing CTAB as the PTC. Compound **8** was then converted into the thia-bis thioamide **9** (H_2S/pyridine) and the latter upon condensation with 1,3-dichloropropanone provided thia-bis(chloromethyl-thiazole) **10** as a stable solid in 52% yield. The reaction of **10** with Na_2S as described above for **6** led to the formation of **2** as a colourless crystalline solid in 42% yield.

Conformational analysis of heterophanes 1 and 2

The ^{1}H NMR spectrum of dithia-syn **1** displayed sharp singlets at δ 4.26 and 3.95 which can be assigned to the protons of the bridge methylene groups attached to the C2 and C4 positions of the thiazole ring, respectively. This assignment is based on the analogy that C2 methyl group resonates to lower

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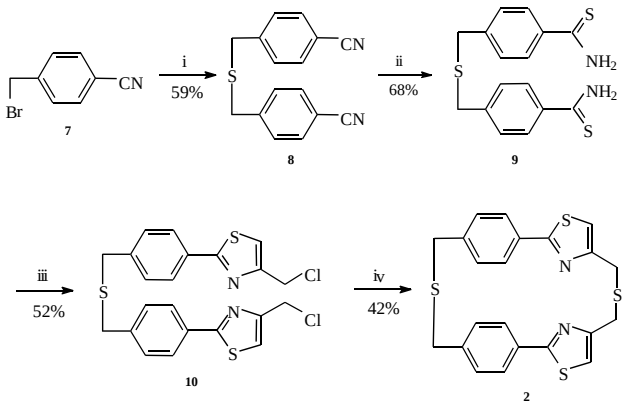

Scheme 2 *Reagents and conditions:* (i)Na_2S/CH_2Cl_2, CTAB, R.T, 25h; (ii) Dry H_2S, Pyridine, Et_3N, 12h; (iii) $ClCH_2COCH_2Cl$, Dry THF, 8h; (iv) Na_2S/benzene-THF, CTAB, R.T, 60h.

field (δ 2.61) of the C4 methyl group (δ 2.33) in 2,4-dimethylthiazole.[11] The appearance of sharp singlets for the bridge CH_2 protons suggests free conformational inversion that results in the fast equilibrium exchange between these protons. In order to study the dynamic processes in **1,** we carried out variable temperature NMR analysis (500 MHz, $CDCl_3$) down to –55 °C. However, the sharp singlets associated with the CH_2 protons as well as the singlet for the thiazole ring proton (δ 6.89) remained practically unchanged. This observation suggests that syn-**1** exists as a freely inverting molecule even at –55 °C on the NMR time scale.

The ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of dithia syn **2** was also found to be temperature-independent from RT to –55 °C. The bridge $–CH_2–$ groups attached to the thiazole and phenyl rings appeared as sharp singlets at δ 3.99 and 3.85, respectively. The phenyl ring protons showed a pair of doublets (δ 6.96 and 7.35, A_2B_2 system, J = 8 Hz) and the thiazole proton is found as a singlet at δ 7.26. The appearance of sharp singlets for the bridge $–CH_2–$ groups implies free rotation in dithia-syn **2** as observed in the case of **1**. Although, the conformational energy barrier is not measurable due to free conformational inversion in **2**, nevertheless, the flipping of the phenyl ring with two hydrogen substituents passing through the phane cavity would be expected to be more energy-demanding compared to the flipping of the thiazole ring via the sterically small nitrogen lone pair.[1c] On account of the speed of the conformational inversions, the thiazolophanes **1** and **2** are expected to exist as non-resolvable molecules.[3a]

In conclusion, we have synthesised two new thia-bridged [3.3]heterophanes **1** and **2** and find them to be freely inverting molecules on the ^{1}H NMR time scale. This behaviour is analogous to that observed for several other [3.3] phane systems.[5]

Experimental

Melting points were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian- EM-360L (60 MHz) and Bruker-AMX-500 (500 MHz) using TMS as internal standard. Microanalyses were performed by the microanalytical section of the Department. Mass spectra were recorded on GCMS-QP 5050A Shimadzu spectrophotometer.

Preparation of bis-thioamide **5***:* Thia-bis-nitrile **8**[8] (8.4 gm, mmol) was dissolved in dry pyridine (50 ml), a catalytic amount of triethylamine was added, and dry H_2S was bubbled in over a period of 4h. The reaction mixture was then poured onto ice, and the yellow solid obtained was filtered and crystallised from water to give yellow crystals of **8** (6.35 g, 47%), m.p. 125 °C (lit.[9] m.p. 124–125°C).

Preparation of dichloro compound **6**: Bis-thioamide **5** (1.80 g, 10mmol) was dissolved in dry THF (75ml) and 1,3-dichloropropanone (2.54 g, 20 mmol) was added. The reaction mixture was stirred at RT for about 6h. It was then heated to reflux followed by the addition of conc HCl (1ml) for 2h. The solvent was removed under reduced pressure, the residual oil dissolved in chloroform and washed with a saturated solution of $NaHCO_3$. The crude product obtained upon concentration was purified on a silica gel column (1 : 1 chloroform - pet. ether) to isolate thia-bis(chloromethylthiazole) **6** as an oil in 48% yield (1.56 gm). ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.42 (s, 4H, CH_2Cl), 3.85 (s, 4H, thiazole–C<u>H</u>$_2$–S), 6.89 (s, 2H, thiazole-H); IR (KBr): ν cm^{-1}, 3000, 2900, 1600, 1510, 1504, 1408, 1403, 1242, 1193, 1157, 1145, 1100, 905, 764, 700. Found: C, 36.50; H, 3.58; N, 8.95; S, 29.21; Cl, 21.52%. $C_{10}H_{10}Cl_2N_2S_3$ requires C, 36.92; H, 3.08; N, 8.62; S, 29.54; Cl, 21.85%.

Synthesis of syn-dithia[3.3][2,4]thiazolophane (3,6,10,14-dithia-15,16-diazatricyclo[10.2.1.1^{5,8}]hexadeca-1(15),5(16),7,12-tetraene) **1**: Thia-bis(chloromethylthiazole) **6** (975 mg, 3 mmol) in dry THF – benzene (100ml, 1 : 1) was added dropwise to a stirred solution of Na_2S (700 mg, 9mmol) in dry THF-benzene (80 ml, 1 : 1) containing a catalytic amount of CTAB (50 mg) over 12 h. After addition was complete the reaction was stirred at room temperature for 48 h. The reaction mixture was filtered through celite and concentrated and the semisolid residue was purified by SiO_2 column chromatography (1 : 4 ethyl acetate – pet. ether) to obtain the desired syn-dithia **1** in 35% yield (300mg), m.p. 168–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 4H, C4–thiazole–C<u>H</u>$_2$S) , 4.26 (s, 4H, C2-thiazole–C<u>H</u>$_2$S–), 6.89 (s, 2H, thiazole–H); IR (KBr): ν cm^{-1}, 3084, 2966, 2908, 1652, 1558, 1508, 1450, 1409, 1315, 1224, 1205, 1145, 1110, 1105, 975, 925, 773, 744; MS: m/z 287 (M^++1), 114, 93; Found: C, 42.35; H, 3.85; N, 10.21; S, 45.26%. $C_{10}H_{10}N_2S_4$ requires C, 41.96; H, 3.50; N, 9.79; S, 44.76%.

Preparation of thia bis-nitrile **8**: 4-Bromomethylbenzonitrile10 (10 g, 51 mmol) was dissolved in dry methylene chloride (100 ml) and a catalytic amount of CTAB (100mg) was added. While stirring at room temperature, a solution of Na_2S (3.5 g, 45 mmol) was added in portions over 1h. After 24 h of further stirring the reaction mixture was filtered through celite. Solvent removal gave a solid material which was crystallised from pet ether – chloroform to obtain white crystals of **8** (8.0 g, 59%), m.p. 96 – 98 °C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.6 (s, 4H, PhC<u>H</u>$_2$S), 7.4 (d, 4H, Ar–H), 6.8 (d, 4H, Ar–H); IR (KBr): ν/cm^{-1} 3100, 2900, 2235, 1615, 1500, 1424, 1302, 1084, 1025, 844. Found: C, 72.51; H, 4.72; N, 11.04; S, 12.42 %. $C_{16}H_{12}N_2S$ requires C, 72.72; H, 4.55; N, 10.61; S, 12.12 %.

Preparation of thia bis-thioamide **9**: Thia bis-thioamide **9** was prepared under the same conditions as described for **5**, using thia bis-nitrile **8** (6g, 22.73 mmol) in dry pyridine (50 ml); a catalytic amount of triethylamine was also added and dry H_2S was bubbled for 10 h. The reaction mixture was then poured onto ice, the yellow solid obtained was filtered, washed with water and air-dried. Yield 5.12 g (68%), m.p. 174–76 °C. ^{1}H NMR (60MHz, DMSO-d_6): δ 3.2 (s, 4H, CH_2S), 7.2 (d, 4H, Ar–H), 7.8 (d, 4H, Ar–H), 9.6 (s, 4H, NH_2); IR (KBr): ν/cm^{-1} 3300, 3100, 2900, 1623, 1595, 1414, 1315, 906, 857. Found: C, 57.38; H, 5.12; N, 8.89; S, 29.24 %. $C_{16}H_{16}N_2S_3$ requires C, 57.83; H, 4.82; N, 8.43; S, 28.92 %.

Preparation of thia-bis(chloromethylthiazole) **10**: Bis-thioamide **9** (2 g, 6 mmol) was reacted with 1,3-dichloropropanone (1.524 g, 12 mmol) following the same procedure as described for **6**. The crude product obtained upon work-up was purified by SiO_2 column chromatography (1 : 1 chloroform – pet. ether) to give **10** as a yellow solid, (1.50 g, 52%), m.p. 120–22 °C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.4 (s, 4H, CH_2Cl), 3.3 (s, 4H, CH_2S), 6.70–7.80 (m, 10H, Ar-H and thiazole–H); IR (KBr): ν/cm^{-1} 3100, 2900, 1510, 1466, 1405, 1262, 1165, 1114, 1000, 845; Found: C, 54.92; H, 3.65; N, 5.42; S, 20.55; Cl, 15.36%. $C_{22}H_{18}Cl_2N_2S_3$ requires C, 55.35; H, 3.77; N, 5.87; S, 20.13; Cl, 14.88%.

Synthesis of syn-dithia[3.3]([1,4]phenyl[2,4]thiazolophane) (3,7,11,18-tetrathia-27,28-diazapentacyclo[21.2.2.2^{13,16}.1^{2,5}.1^{9,12}]octaconta-2,4,9,12(27),13,15,20,22,23,25-decaene) **2**: Thia-bis (chloromethylthiazole) **10** (954 mg, 2 mmol) was reacted with Na_2S (468 mg, 6 mmol) using the procedure described for **1**. The crude product upon puification on SiO_2 column (1 : 4 ethyl acetate – pet. ether) gave a yellow solid, m.p. 185–186 °C (370 mg, 42 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (s, 4H, PhC<u>H</u>$_2$S), 3.99(s, 4H, thiazole–C<u>H</u>$_2$S), 7.26 (s, 2H, thiazole-H) , 7.35 (d, 4H, J = 7 Hz, Ar-H), 6.96 (d, 4H, J = 7 Hz, Ar–H); MS: *m/z* 438 (M^+), 437, 410, 405, 392, 219, 188, 116, 104, 89, 83, 71; IR (KBr): ν/cm^{-1} 3100, 2900, 1504, 1455, 1402, 1314, 1245, 1100, 1010, 940, 838, 799, 728. Found C, 59.79; H, 4.56; N, 5.95; S, 29.62%. $C_{22}H_{18}N_2S_4$ requires C, 60.27; H, 4.11; N, 6.39; S, 29.22%.

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References and notes

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