SHORT PAPER

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Synthesis of anti-[2.2](2-phenylthiazolophane): a new heterocyclic biphenylophane†

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Synthesis of a heterocyclic variant of the biphenylophanes, namely anti-[2.2](2-phenylthiazolophane) (**1**), is described via a sequence involving the pyrolysis of an intermediate bis-lactone (**8**). Dynamic ^{1}H NMR analysis revealed both the bis-lactone **8** and the target heterophane **1** to be conformationally mobile on the NMR time scale at temperatures down to -55 °C.

Keywords: cyclophanes, thiazoles, lactones, decarboxylation, flash vacuum pyrolysis

The study of conformational properties of constrained cyclophanes continues to provide impetus for creating new cyclophane structures. The dynamics of conformational flipping processes in cyclophanes vary widely, depending mainly upon (i) the length of the *ansa* bridges, (ii) the size of the cavity, and (iii) the size of the substituent or ring component that needs to pass through the cavity during the ring inversion. [2.2]Biphenylophanes, made up of the biphenyl structural motif, constitute a small group within the 'phane' family that exhibit novel stereochemical properties, being conformationally more flexible than the corresponding single ring analogs, for example [2.2]paracyclophane and [2.2]metaparacyclophane.[1,2] Literature search showed that only one example of a heterocyclic variant of the biphenylophanes has been reported to date.[3] Consequently, little information is currently available concerning the structural or conformational aspects of such systems. This, coupled with our continuing interest in the chemistry of heterophanes,[4] prompted us to explore the synthesis and conformational properties of a new addition to the heterocyclic analog of biphenylophanes, namely anti-[2.2](2-phenylthiazolophane)[5] **1**.

The synthesis of **1** (Scheme 1) starts with conversion of the known 4-methoxymethylbenzonitrile **2**[6] into the thioamide **3** by reacting with dry H_2S in dry pyridine. The Hantzsch condensation of **3** with bromo-ester **4** in dry THF followed by work-up and SiO_2 column purification of the crude product afforded phenylthiazole **5** in 68 % yield as an oil. Base catalysed hydrolysis of **5** followed by acidification under cold condition gave acid **6**. The treatment of **6** with 49% HBr at reflux led to the formation of bromo-acid **7** in high yield. After several abortive attempts, the lactonization of **7** was finally successfully achieved under Regen's protocol[7] to afford the key precursor, bis-lactone **8**, a colourless solid, m.p. 270–275 °C in 42% yield. Though, there are precedents in the literature of the photo-decarboxylation of bis-lactones[8] as a route to generate cyclophanes, including our own recent example of the synthesis of anti-[2.2]benzothiazolophane[4a], but unfortunately all attempts to effect photo-decarboxylation of **8** to form heterophane **1** failed under a variety of experimental conditions. However, pyrolysis of **8** under flash vacuum conditions (600 °C at 0.1 mm Hg) proved successful giving the target **1** in 43% yield, m.p. 232–235 °C, *m/e* 375 (M^++1) and *m/z* 187. To the best of our knowledge, the conversion of **8** into **1** is the first example of the thermal CO_2 extrusion in the synthesis of a cyclophane system.

From dynamic ^{1}H NMR analysis ($CDCl_3$, 500 MHz), we found the bis-lactone **8** to be a freely inverting molecule since the singlets associated with the bridge methylene protons at δ 3.8 (CH_2CO_2) and δ 5.23 ($COOCH_2$) remained essentially unchanged down to –55 °C. This behavior is consistent with other known four atom bridged phanes which are also reported to be conformationally mobile systems.[4a,9]

The ^{1}H NMR spectra (500 MHz) of **1**, which was found to be temperature independent from +135 to –55 °C revealed the presence of triplet each at δ 2.88 and δ 3.05 due to the $–CH_2$- groups attached to phenyl and thiazole rings, respectively. Two sets of doublets were noticed for the phenyl protons (δ 6.65 and 7.17, J = 8Hz each) whereas the thiazole ring proton is seen as a sharp signal at δ 7.25. The observation of A_2B_2 multiplicity for the bridged CH_2 protons (and not AA'BB' type) seems to indicate free bridge inversions in heterophane **1**. Further, the equivalence of the phenyl protons Ha with Ha' and Hb with Hb? in an otherwise nonsymmetrical environment caused by the cofacial thiazole ring can be interpreted as being due to the occurrence of unhindered ring inversion in **1** on the NMR time scale. The equivalence of the phenyl protons could be caused either by inversion of both phenyl and the thiazole ring or just from the inversion of one of these rings. However, the flipping of the phenyl ring with two hydrogen atoms passing through the "phane cavity" would be expected to impose a much higher energy barrier than would the inversion of the thiazole ring via the sterically less demanding nitrogen lone pair.[10]

The UV-visible spectrum of **1** displayed an absorption band at 294 nm in $CHCl_3$ whereas for the open-chain model compound, 2-(4-methylphenyl)-5-methylthiazole, λ_{max} appears at 299 nm. In analogy to [2.2]cyclophanes, a small blue shift observed in the heterophane **1** compared to the model system suggests the presence of a weak transannular π–π interaction in **1**. In $CHCl_3$ containing 1% CF_3CO_2H, heterophane **1** and the model compound displayed bathochromic shifts of their absorption bands by 10 and 8 nm, respectively. The red shifts could be attributed to through-bond charge transfer interaction from the donor phenyl ring to the acceptor thiazolium ring in the acidic conditions.[11,12]

In conclusion, we have synthesised a new heterocyclic variant of biphenylophane, namely anti-[2.2](2-phenylthiazolophane) **1**. From the dynamic ^{1}H NMR analysis, we find that the precursor bis-lactone **8** as well as the target heterophane **1** are conformationally mobile down to –55 °C. This observation is in accord with the conformational behavior of other known [2.2]biphenylophanes.[1]

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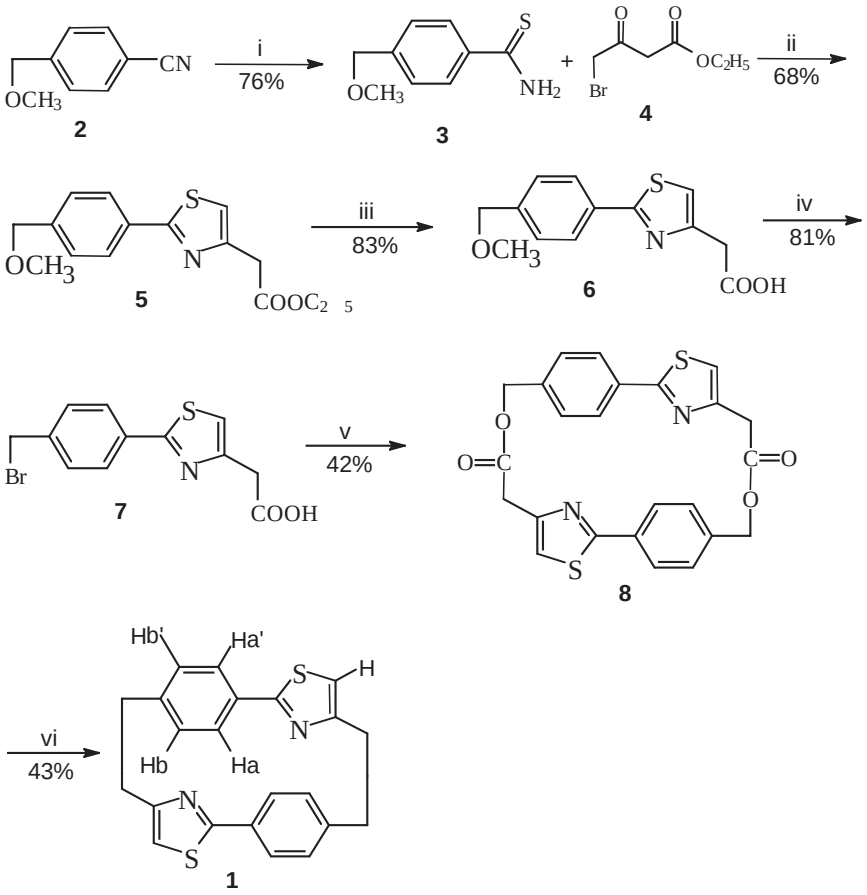

Scheme 1[9] *Reagents and conditions:* (i) Dry H_2S/dry pyridine/Et_3N, 10h. (ii) Dry THF, Δ, 12 h. (iii) KOH/MeOH, RT, 8h, followed by acidification at 0 °C. (iv) 49% aq HBr, Δ, 6h. (v) Anhyd K_2CO_3, dry THF, cat. CTAB, N_2 atm., Δ, 25h. (vi) Flash vacuum pyrolysis, 600 °C, 0.1mm Hg, 0.5h.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-4200 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian- VR (60 and 500 MHz) instrument using TMS as an internal standard.

Preparation of 4-methoxymethylbenzothioamide (**3**): 4-methoxymethylbenzonitrile **2**[6] (15 g, 102 mmol) was dissolved in dry pyridine (40 ml) containing a catalytic amount of triethylamine (1 ml) and dry H_2S was bubbled into the solution at room temperature over 10h. The reaction mixture was then decomposed by ice to give a yellow solid, which was filtered and crystallised from ethanol to give yellow crystals of **3** in 76% yield (14 g, m.p. 112–115 °C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.4 (s, 4H, $PhCH_2OC\underline{H}_3$), 4.4 (s, $PhC\underline{H}_2OCH_3$),7.1–8.2 (m, 4H, Ar-H), 9.6 (s, 2H, NH_2); IR (KBr): ν/cm^{-1} 3300, 3100, 1623, 1444, 1315, 1120, 906, 827; Found: C, 59.36; H, 6.27; N, 7.89; S, 17.44 %. $C_9H_{11}NOS$ requires C, 59.66; H, 6.07; N, 7.73; S, 17.68 %.

Preparation of phenylthiazole **5**: 4-methoxymethylbenzothioamide **3** (4.525 g, 25 mmol) was added to solution of dry THF (75ml) containing ethyl bromoacetoacetate (6.265 g, 30 mmol) and the reaction was stirred at R.T. for 10h and then refluxed for 2h. The crude product obtained upon work-up was purified by SiO_2 column chromatography (1 : 1 chloroform- pet. ether) to give **5** as a brown oil in 68% yield (4.95 g). ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 3H, $COOCH_2C\underline{H}_3$), 4.20 (q, 2H, $COOC\underline{H}_2CH_3$), 3.85 (s, 2H, thiazole-$C\underline{H}_2COOC_2H_5$), 4.45 (s, 2H, $CH_3OC\underline{H}_2Ph$), 3.30 (s, 3H, $C\underline{H}_3OCH_2Ph$), 7.35 (s, 1H, thiazole-H), 7.20 (d, 2H, Ar-H, *J* = 7 Hz), 7.85 (d, 2H, Ar-H, *J* = 7 Hz). IR (film): ν (cm^{-1}) 3100, 3000, 2900, 2800, 1740, 1520, 1460, 1410, 1370, 1340, 1250, 1200, 1160, 1100, 1040, 1000, 920, 850, 820, 760, 660, 600. Anal: found C, 61.52; H, 6.14; N, 4.50; S, 11.27. $C_{15}H_{17}NO_3S$ requires C, 61.86; H, 5.84; N, 4.81; S, 10.99.

Preparation of methoxy-acid **6:** Phenylthiazole ester **5** (6.0 g, 20.62 mmol) was stirred with 10 % methanolic KOH (50ml) at R.T for 8h. The reaction was diluted with water and methanol boiled off on a steam-bath. The aqueous solution after cooling in ice was acidified with dil HCl (1 : 1) to precipitate the methoxy-acid **6** in 83% yield, m.p. 91–95 °C. ^{1}H NMR (60MHz, $CDCl_3$-DMSO-d_6): δ 3.85 (s, 2H,-$C\underline{H}_2COOH$), 4.5 (s, 2H, $PhC\underline{H}_2OCH_3$), 3.40 (s, 3H, $PhCH_2OC\underline{H}_3$), 7.40 (s, 1H, thiazole-H), 7.20 (d, 2H, Ar-H, *J* = 8Hz), 7.80 (d, 2H, Ar-H, *J* = 8Hz), 10.40 (bs, 1H,-COOH). IR (KBr): ν (cm^{-1}) 3414, 3100, 3021, 1730, 1525, 1410, 1354, 1329, 1206, 1003, 816. Anal: found C, 58.96; H, 4.78; N, 5.62; S, 11.88. $C_{13}H_{13}NO_3S$ requires C, 59.32; H, 4.94; N, 5.32; S, 12.17.

Preparation of bromo-acid **7:** Methoxy-acid **6** (4.0 g, 15.25 mmol) was dissolved in 49% aqueous HBr (50 ml) and the reaction mixture was heated on steam bath for about 6h. The reaction mixture was then poured over crushed ice and the precipitated solid collected by filtration. The crude solid was air dried and then purified by SiO_2 column chromatography (9 : 1 pet. ether- ethyl acetate) to give **7** as a white crystalline solid in 81% yield (3.85 g, m.p. 155–158 °C). ^{1}H NMR (60MHz, $CDCl_3$-DMSO-d_6): δ 4.20 (s, 2H, $C\underline{H}_2COOH$), 4.60 (s, 2H, $PhC\underline{H}_2Br$), 7.75 (s, 1H, thiazole-H), 7.60 (d, 2H, Ar-H, *J* = 8Hz), 8.10 (d, 2H, Ar-H, *J* = 8Hz), 13.40 (bs, 1H, COOH). IR (KBr): ν (cm^{-1}) 3400, 3100, 3013, 1715, 1513, 1425, 1220, 1012, 840. Anal: found C, 45.65; H, 3.14; N, 4.64; S, 10.02; Br, 25.29. $C_{12}H_{10}BrNO_2S$ requires C, 46.15; H, 3.21; N, 4.49; S, 10.26; Br, 25.64.

Synthesis of bis-lactone **8:** Bromo-acid **7** (3.0gm, 9.62 mmol) was dissolved in dry THF (150ml) and added dropwise to a solution of dry THF (250 ml) containing anhydrous K_2CO_3 (3.5gm, 25.36 mmol) and catalytic amount of cetyltrimethylammonium bromide (CTAB) (50mg) at 50–56 °C under N_2 during 8h. The reaction was further heated for 25h. The hot reaction mixture was filtered through a pad of celite and the crude product obtained after solvent removal was purified by SiO_2 column chromatography (1:1, chloroform-pet. ether) to obtain **8** as a colourless crystalline solid in 42% yield (1.08 g, m.p. 270–275 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 4H, $C\underline{H}_2COO$), 5.23 (s, 4H, $PhC\underline{H}_2OCO$), 7.11 (s, 2H, thiazole-H), 7.34 (d, 4H, Ar-H, *J* = 7Hz), 7.68 (d, 4H, Ar-H, *J* = 7Hz). IR (KBr): ν (cm^{-1}), 3020, 1724, 1525, 1370, 1308, 1234, 1121, 1000, 983, 820. MS: m/e 462 (M^+, 50%), 434 (15), 417 (10), 373 (20), 347 (10), 303 (10), 187 (100), 116 (40), 89 (10), 71 (30), 44 (25). Found: C, 61.94; H, 3.48; N, 6.50; S, 14.26. $C_{24}H_{18}N_2O_4S_2$ requires C, 62.34; H, 3.89; N, 6.06; S, 13.85.

Synthesis of anti-[2.2](2-phenylthiazolophane) **1:** Flash vacuum pyrolysis of bis-lactone **8** (100 mg, 0.22mmol) was carried out at 600 °C at 0.1Hg-mm and the solid product collected in the cold receiver was purified by SiO_2 column chromatography (1 : 1, chloroform–pet. ether) to afford the target molecule **1** as a colorless solid in 43% yield (35 mg), m.p. 234–236 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (t, 4H, thiazole-$CH_2C\underline{H}_2$Ph), 3.05 (t, 4H, thiazole-$C\underline{H}_2CH_2$Ph), 7.25 (s, 2H, Tz-H), 6.65 (d, 4H, Ar-H, *J* = 8Hz), 7.17 (d, 4H, Ar-H, *J* = 8Hz). IR (KBr): ν (cm^{-1}), 3054, 1600, 1504, 1483, 1465, 1242, 1189, 1100, 1004, 826. MS: m/e 374 (M^+, 40%), 303 (15), 229 (100), 190 (20), 133 (15). Found: C, 70.19; H, 5.16; N, 7.02; S, 17.61. $C_{22}H_{18}N_2S_2$ requires C, 70.58; H, 4.81; N, 7.49; S, 17.11.

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5 This name, while sufficient for present purposes, does not, of course, describe the molecule completely. Using the Baeyer system, **1** would be 3,13-dithia-23,26-diazapentacyclo [16.2.2.$2^{8,11}$.$1^{2,5}$.$1^{12,15}$] hexaconta-1(20),2(23),4,8,10,12(26),14,18,21,-24-decaene.

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11 The thiazole nucleus is sufficiently basic (pK_a is 2.52) to be able to undergo protonation in the presence of CF_3CO_2H. See J.V. Metzger, in *Comprensive Heterocyclic Chemistry*, 1984, Pergamon Press, New York, USA, Vol 6 (K. T. Potts, ed.), p. 252.

12 When ^{1}H NMR of **1** was recorded in $CDCl_3$ containing a drop of CF_3CO_2H, there was observed downfield shifts of the protons associated with both the phenyl (δ 7. 1 and 7. 43) as well as the thiazole ring (δ 7. 54) as a consequence of the presence of the positive charge on the thiazole rings. Furthermore, a single set of absorptions for these protons strongly indicated bis-protonation of heterophane **1** in the presence of CF_3CO_2H.