ATTEMPT TOWARDS SYN-BENZOTHIAZOLOPHANE: SYNTHESIS AND CONFORMATIONAL STUDY OF SYN-DITHIA-[3.3](2,6) BENZOTHIAZOLOPHANE

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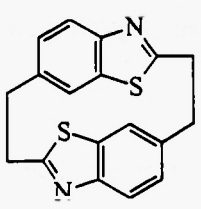
Abstract: Synthesis of syn-[2.2](2,6) benzothiazolophane 2 was targeted via oxidative C-C coupling of the key intermediate 7. Compound 7 was synthesized as shown in the Scheme 1. However, several attempts to effect the conversion of 7 to syn-benzothiazolophane 2 failed under the metallation/oxidation protocols, perhaps on account of high ring strain involved during the ring closure step. However, synthesis of syn-dithia-[3.3](2,6) benzothiazolophane 3, a potential precursor en route to 2 could be successfully accomplished via stepwise construction of two thia-bridges using bromo-ester 15 and monothia-bromide 18 for the first and subsequent thia bridge formations, respectively as outlined in the Scheme 2. On the basis of variable temperature ^{1}H NMR analysis, heterophane 3 has been found to be conformationally rigid upto 150 ^{0}C on the NMR time scale.

Introduction

Availability of diverse heterocycles provides continuing opportunity to place them into the cyclophane framework to study the effects of ring proximity on structure and reactivity. Not surprisingly, a plethora of [2.2]heterophanes composed of 6-π donor and 6-π acceptor heteronuclei have been synthesized and their structures and conformational behaviors are well documented (1). While, [2.2]heterophanes derived from smaller oxygen and nitrogen heteroatoms, for instance, furanophane (2), oxazolophane (3,4), pyridinophane (5) and isoxazolophane (6) are found to exhibit free ring rotations, in contrast those containing the bulkier sulfur atom, namely, thiophenophane (7) and thiazolophanes (4) exist as conformationally non-interconvertible systems owing to longer C-S bond and the larger size requirement of sulfur atom, which severely hinder the inversion process (8).



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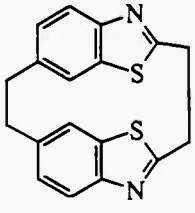

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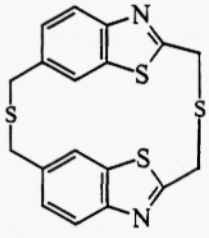

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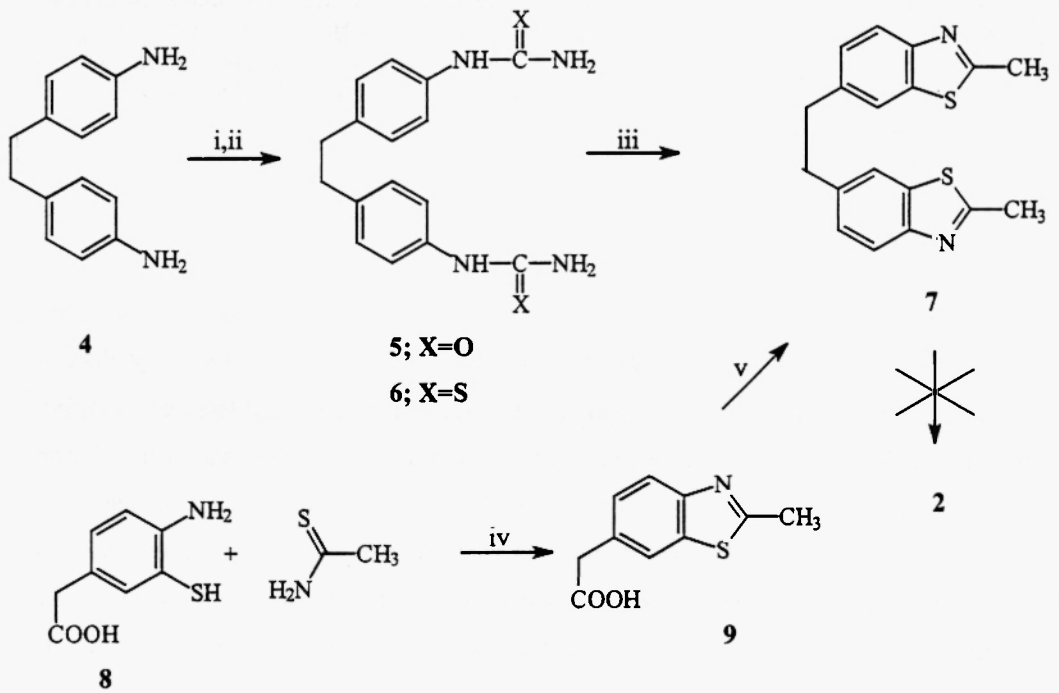
In context to our ongoing interest in the conformational dynamics of heterophanes, we recently described the synthesis of anti-[2.2](2,6) benzothiazolophane 1, being the first example of a fused 10–π heterophane (9). Conformational analysis by VT-NMR revealed 1 to be an immobile phane with an estimated barrier to ring flipping in upward of 20 kcal/mol. Herein, we report the synthesis and conformational property of heterophane 3, which is a potential precursor en route to syn-[2.2](2,6) benzothiazolophane 2.

Results and Discussion

For the synthesis of heterophane 2 , (10), we chose the oxidative intramolecular C-C coupling of bis-benzothiazole intermediate 7 as the key step. Towards the preparation of 7 (Scheme 1), the known 4,4'-diaminobibenzyl 4 (11) was acetylated under standard conditions to provide diacetamide 5. Thionation of 5 with the Lawesson's reagent in refluxing toluene, followed by work up and crystallization afforded dithioamide 6 in 45%yield. The Jacobson oxidative cyclization (12) of 6 with $K_3Fe(CN)_6$ under alkaline condition led to the formation of 7 in 42% yield.



Scheme-1. *Reagents & Conditions*: i) $(CH_3CO)_2O$/ pyridine. ii) Lawesson's reagent/ Toluene, Δ iii) $K_3Fe(CN)_6$ in 10% NaOH iv) $(CH_2OH)_2$, conc. HCl, 100°C, 8 h. v) $Na_2S_2O_8$ and 100mg $AgNO_3$ in 50% Aq CH_3CN, 80°C/4h.

Alternatively, compound 7 was also prepared in two steps by first condensing 2-aminothiophenol 8 with thioacetamide as the carboxylic acid equivalent by adopting our recently reported methodology (13). The

resulting 2-methybenzothiazole carboxylic acid 9 (68% yield) upon treatment with $Na_2S_2O_8/Ag^+$ reagents (14) in aqueous acetonitrile underwent decarboxylative dimerization to furnish 7 in 37% yield after SiO_2 column chromatographic purification. Although, overall yield in this method was comparable to the Jacobson method, the procedure was not amenable to large-scale (>10 g) manipulations.

Metallation of heteroaryl methyl groups followed by oxidative dimerizations are widely documented in the literature, including successful precedence in the synthesis of [2.2] pyridinophane (15). We attempted this methodology on the intermediate 7 for its crucial conversion into the desired syn-benzothiazolophane 2. However, all efforts directed towards achieving the intramolecular ring closure on 7 under a variety of conditions and reagents i.e., n-BuLi followed by $CuCl_2/O_2$, LDA then $CuCl_2/O_2$, LDA/I_2, and EtMgBr/$AgNO_2$ unfortunately failed to deliver 2 (16); only intractable material being produced in these reactions. The fact that metallation was not the problem was proved by D_2O quenching of the reactions prior to introducing the oxidants, which showed ca. 65-80% deuterium incorporation at methyl carbons (vide ^1H NMR). The failure of dimetallated 7 to cyclize to form 2 could well be due to the high molecular strain associated with the folded transition state required during the cyclization.

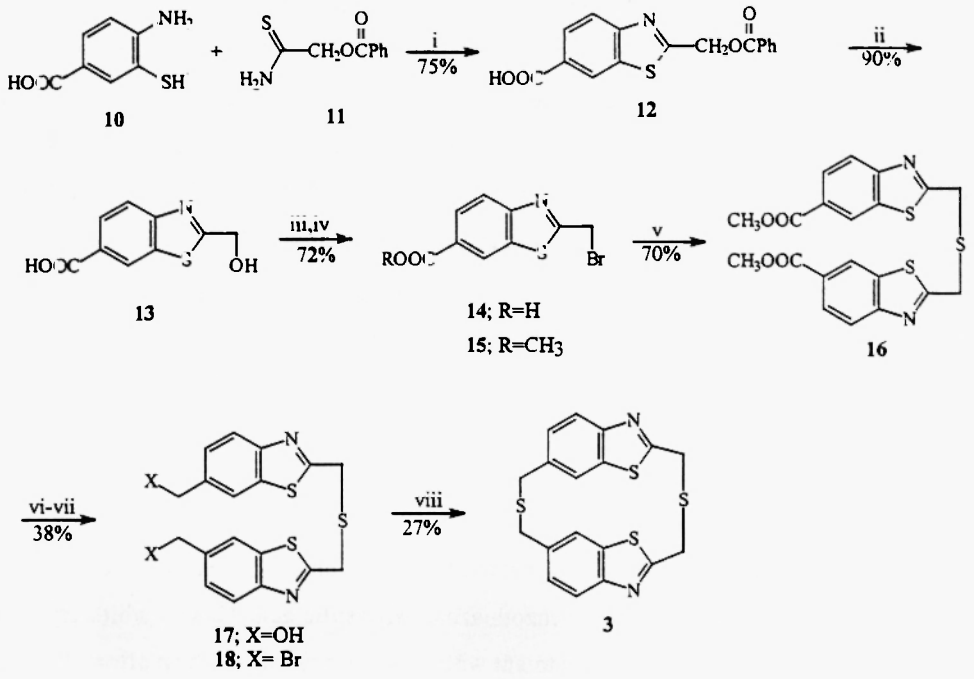
We then settled for a relatively less strained system, namely, dithia-bridged syn–benzothiazolophane 3 (Scheme 2) which could be elaborated to 2 by applying the known sulfur ring contraction methods. Thus, in pursuit of the Scheme-2, benzyloxy thiomides 11 (17) was condensed with 4-amino-3-mercapto benzoic acid 10 (9) in ethylene glycol under acidic condition to give benzothiazole carboxylic acid 12 as a white crystalline solid in 75% yield. Hydrolysis of 12 was achieved by treatment with aqueous ammonia, which afforded on acidification hydroxymethyl benzothiazole 13 in good yield. The treatment of 13 with 33% HBr in glacial acetic acid provided bromomethyl derivative 14 in 65% yield. Esterification of 14 with $SOCl_2$ in dry methanol gave after SiO_2 column chromatographic purification the ester 15 in 80% yield. The conversion of 15 to the mono-thia bridge diester 16 was affected with $Na_2S.9H_2O$ in CH_2Cl_2 containing a catalytic amount of cetyltrimethylammonium bromide as the phase transfer catalyst. The crude solid, after purification through a pad of celite and crystallisation gave 16 in 70% yield.

The task of forming the second bridge at the C-6 position of benzothiazole nuclei required the conversion of 16 into dihalo derivative 18. This was readily accomplished by reducing diester 16 with $LiAlH_4$ (dry THF, 0-5°C, 1h) to form diol 17 which was smoothly converted into the corresponding dibromide 18, m.p.167-68 °C (38% yield in 2 steps) by heating with 33% HBr in glacial acetic acid. Next, for the construction of the second crucial thia-bridge, dibromide 18 was allowed to react with $Na_2S.9H_2O$ in 1:1 ethanol-benzene solvent system at room temperature using high dilution conditions to afford the key dithia-syn benzothiazolophane 3, m.p. 231-32 ^0C in 27% yield.

Structure and conformation of syn-dithiabenzothiazoiphane

As expected for the molecular formula $C_{18}H_{14}N_2S_4$, heterophane 3 revealed in its FAB mass spectrum, MH^+ peak at m/z 387. Its ^1H NMR (200 MHz, DMSO-d_6) showed a complex multiplet between 3.83 to 4.4 δ (8H,

AB and A'B' systems) arising from C-2 and C-6 bridge methylene protons. The internal aromatic C-7 proton appeared upfield at 6.65 δ as a singlet, whereas, C-4 and C-5 aryl protons are observed as a doublet each at 7.55 δ (8Hz) and 7.22 δ (8Hz), respectively. In the open chain 2,6-dimethylbenzothiazole, the C-7 proton is reported



Scheme-2. *Reagents and Conditions:* i) $(CH_2OH)_2$, conc. HCl, 100°C,8h ii) NH_4OH, Δ, followed by acidification. iii) 33% HBr in AcOH, Δ, 4h. iv) Dry CH_3OH and 1.5 equiv. $SOCl_2$. v) $Na_2S.9H_2O$ in CH_2Cl_2 containing cetyltrimethylammonium bromide (50mg), R.T. 24 h. v) $LiAlH_4$-Dry THF,R.T, 4h. vii) 33% HBr in AcOH, Δ, 2h. viii) $Na_2S.9H_2O$, EtOH-Benzene (1:1), 48h.

to absorb at 7.77 δ (18). Thus, in comparison to this model compound, the C-7 aromatic proton in 3 experiences upfield shift by about 1.1 δ. Such upfield shifts for the internal aromatic protons caused by ring anisotropy are characteristic features of the π-stacked cyclophane frameworks.

The appearance of a complex multiplet for the bridge protons between 3.83 to 4.4 δ indicates nonequivalence (diasteriotropic nature) of these protons. This observation strongly implies that the dithia syn-3 is conformationally non-interconvertible or nearly so on the NMR time scale. In order to study dynamic process in 3 , variable temperature NMR scans (in DMSO-d_6 solvent) were recorded from room temperature up to 150 ^{0}C with temperature increments of 25 ^{0}C. Since, no coalescing of the multiplet due to the bridge methylene protons was observed even up to 150 ^{0}C, it can be reasonably concluded that syn- 3 exists as a conformationally rigid system with an estimated energy barrier to ring rotation of greater than 20 kcal/mol (9). Among [3.3]

cyclophanes, both conformationally rigid (e.g., [3.3]dithia-naphthalenophane) (19) and conformationally mobile phanes (i.e., dithia [3.3]pyridinophane (20), 9,8-dimethy-2,11-dithia[3.3]metacyclophane (21), and dithia[3.3]benzene-azulenophane (22)) have been reported in the literature. The observed conformational immobility of 3 may be attributed to a large steric barrier imposed together by C-7 internal hydrogen and the bulky 'S' atom of the benzothiazole nuclei to the ring flipping process. Space filling CPK model also indicated the presence of a constricted cavity in 3 which appears too small to accommodate the orthogonal transition state during the ring rotation (23). It is of interest to note that because of the restricted rotation and the unsymmetrical nature of the benzothiazole nucleus, the potential exists for the presence of chirality in heterophane 3. Presently, work is in progress to carry out the ring contraction of compound 3 to complete the synthesis of the heterophane, syn[2.2]benzothiazolophane 2.

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