Generation and Diels-Alder Trapping of 4,5-Bis(bromomethylene)-4,5-dihydrothiazole

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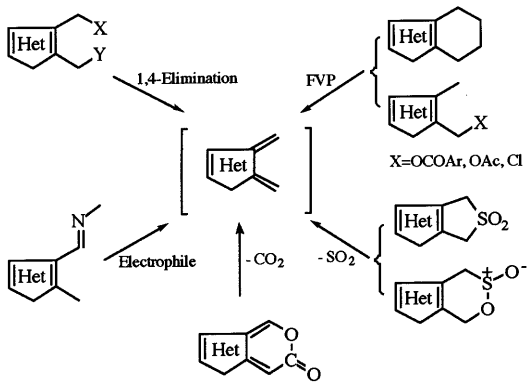
Treatment of 4,5-bis(dibromomethyl)thiazole (**1a**) with sodium iodide in DMF led to 4,5-bis(bromomethylene)-4,5-dihydrothiazole (**2a**). Trapping the latter in situ with dienophiles afforded directly the aromatized cycloadducts. Starting with 5-hydroxynaphthoquinone or its 2- and 3-bromo derivatives **6** gave a mixture of the tetracyclic quinones **10** + **11** from which the 1,6-regioisomer **10** predominates. Using acrylate dienophiles gave 6-substituted benzothiazoles **13** as the major products. The regiochemistry of the cycloadditions between **2a** and naphthoquinones **6** agrees with the predictions of the frontier molecular orbital theory. In contrast, the regioselectivity observed from **2a** and acrylate dienophiles **12**, similar to that previously obtained with 5-bromomethylene-4-methylene-4,5-dihydrothiazole (**2b**), is opposite to that predicted and could be better accomodated by a competitive Michael addition followed by a cyclization-elimination step.

ortho-Quinodimethanes (*o*-QDMs) are highly reactive dienes in [4+2] cycloaddition reactions and their applications in this field have proved very useful for the building of polycyclic aromatic compounds.[1] Their five-membered heterocyclic analogues have received recent attention due to the wide variety of the pentagonal heteroaromatic rings.[2] However, their synthetic potential through Diels-Alder reactions has been little explored. Among the methods employed for their generation (Scheme 1), flash vacuum pyrolysis (FVP) of furanocyclohexene, suitable esters or chloromethyl derivatives needs usually very harsh conditions[3] (temperatures may vary from 600 to 900°C) while chelotropic extrusion of sulfur dioxide from five-membered heteroaromatic fused 3-sulfolenes[4][5] has been shown to be a versatile alternative using temperatures between 170 and 220°C. Moreover, furano-, thieno- and pyrrolo-fused sultines are described as precursors for non-classical *o*-QDMs[6] while pyrrolopyranones are considered as stable cyclic analogues of pyrrole-2,3-quinodimethane. The latter undergo Diels-Alder reactions with alkynes to give indoles after loss of carbon dioxide.[7] Tautomerism of imino derivatives bearing a methyl group in an *ortho* position offers another method for the generation of five-membered heterocyclic *o*-QDMs.[8] Trapping such intermediates with dienophiles by an intramolecular [4+2] cycloaddition has constituted an efficient strategy towards the total synthesis of indole alkaloids. 1,4-Exocyclic eliminations are also largely employed to generate *o*-QDMs since they are carried out under very mild conditions. Thus, *o*-QDMs are prepared from various precursors and reagents. Indeed, eliminations may be induced by a nucleophilic attack of fluoride ion on the silicon atom of substrates bearing a silyl group and a good leaving group (X = SiR_3, Y = OAc or R_3N^+),[9] by treatment of a tributylstannylfuryl derivatives (X = Bu_3Sn, Y = OAc) with boron trifluoride–diethyl ether[10] or by the well-known reductive debromination of vicinal bromomethyl derivatives.[11] This last method, although older, is still valuable due to the easy availability of the *o*-QDM precursors.

Scheme 1



In continuation of our investigations directed towards the ability of thiazole derivatives to generate *o*-quinodimethanes by heating with sodium iodide,[12] we decided to evaluate the suitability of 4,5-bis(dibromomethyl)thiazole (**1a**)[13] as a precursor for 4,5-bis(bromomethylene)-4,5-dihydrothiazole (**2a**). Trapping the latter with acrylate dienophiles

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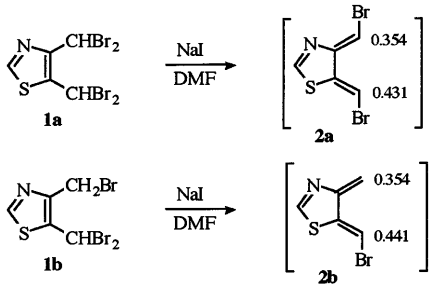
Scheme 2

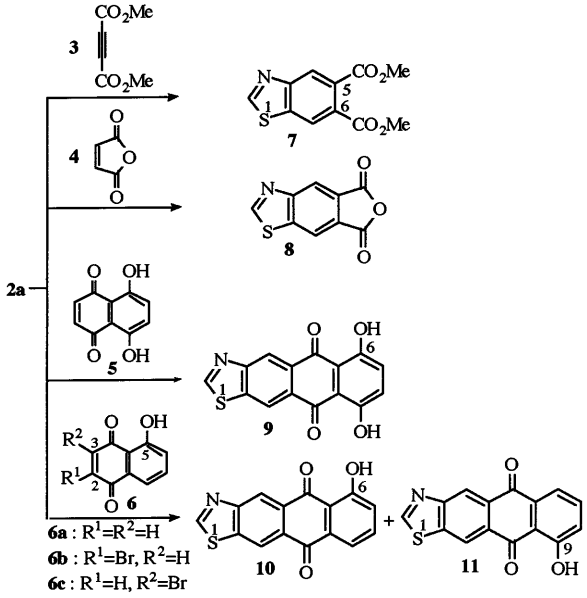


would be of interest due to the directly aromatized adducts that it may afford. Moreover, a comparison of the regiochemistry of its [4+2] cycloadditions with that of 5-bromomethylene-4-methylene-4,5-dihydrothiazole (**2b**) previously prepared and trapped with unsymmetrical dienophiles[12] would be helpful to elucidate the regiocontrol of such reactions.

Results and Discussion

Subsequent generation of *o*-QDM **2a** was performed according to the procedure described for **2b** by treating the tetrabrominated precursor **1a** with sodium iodide in DMF (Scheme 2). Then, **2a** was trapped in situ with a set of dienophiles. Starting with the symmetrical dienophiles **3**, **4** and **5** and following method A, we obtained the aromatized cycloadducts **7** and **9** in higher amounts than from **2b**. In contrast, compound **8** was isolated in a very poor yield (Scheme 3 and Table 1). Trapping **2a** with juglone (**6a**) and its 2- or 3-bromo derivatives **6b** and **6c** afforded a mixture of the regioisomeric tetracyclic quinones **10** and **11**. Comparison of these results with those obtained from **2b** (Table 1) indicates that compounds **10** and **11** are isolated in a similar range of yield (66−75% on one hand and 60−73% on the other hand) but using **2a** the regioselectivity observed is lower than that obtained from **2b**. In contrast with our precedent results,[12] no inversion of the regiochemistry

Scheme 3



was observed in the cycloaddition of **2a** and 3-bromojuglone (**6c**) comparatively to **6a** and **6b**.

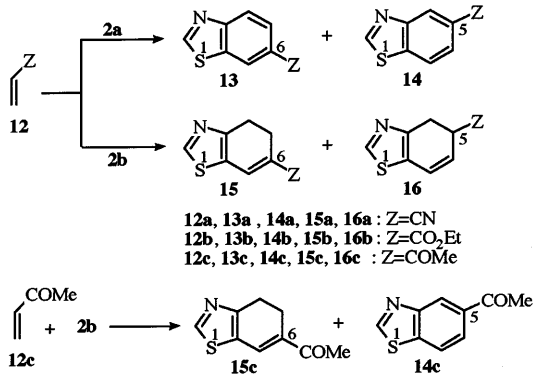
Trapping *o*-QDM **2a** with acrylate dienophiles **12** (method B, molecular sieves 4 Å) afforded a mixture of the aromatized adducts **13** and **14** (Scheme 4, Table 1). In the absence of molecular sieves (method A), the reaction between **2a** and **12b** afforded the mixture of **13b** and **14b** in the same ratio (70:30) but with a lower yield (30%). The structural assignment for the regioisomers **13** and **14** was made by comparison of their ^{1}H-NMR spectral data with those of samples obtained by aromatization of **15** and **16**. Indeed, for the 6-substituted benzothiazoles **13**, the protons 2-H and 7-H are deshielded while the signals of 4-H are shifted to higher fields (Table 2). Thus, with these unsymmetrical dienophiles the orientation of the cycloadditions is

Table 1. Trapping of *o*-QDMs **2** with dienophiles

o-QDM	Dienophile	Method	Adducts	Yield (%)[a]	Ratio of regioisomers
2a	**3**	A	**7**	73	–
2b	**3**		**7**	56[12]	–
2a	**4**	A	**8**	8	–
2b	**4**		**8**	30	–
2a	**5**	A	**9**	95	–
2b	**5**		**9**	70[12]	–
2a	**6a**	A	**10+11**	75	**10/11** = 75:25
2b	**6a**		**10+11**	70[12]	**10/11** = 70:30
2a	**6b**	A	**10+11**	66	**10/11** = 79:21
2b	**6b**		**10+11**	60[12]	**10/11** = 92:8
2a	**6c**	A	**10+11**	71	**10/11** = 70:30
2b	**6c**		**10+11**	73[12]	**10/11** = 08:92
2a	**12a**	B	**13a+14a**	57	**13a/14a** = 67:33
2b	**12a**		**15a+16a**	57[12]	**15a/16a** = 95:5
2a	**12b**	B	**13b+14b**	50	**13b/14b** = 71:29
2b	**12b**		**15b+16b**	75[12]	**15b/16b** = 87:13
2a	**12c**	B	**13c+14c**	51	**13c/14c** = 68:32
2b	**12c**		**15c+14c**	64[12]	**15c/14c** = 81:19

[a] Yields are calculated from isolated pure products.

Scheme 4



Scheme 5

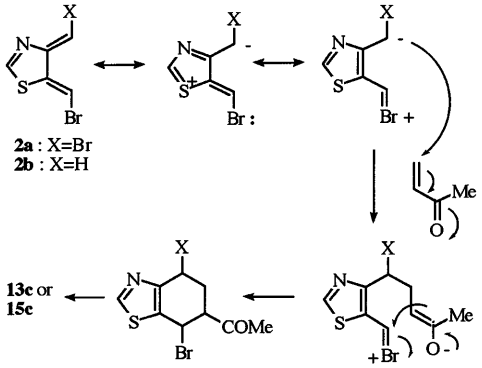


Table 2. ^{1}H-NMR data (δ ppm, $CDCl_3$, 200 Mhz) of 2-H, 4-H and 7-H for benzothiazoles **13** and **14**

Compound	2-H	4-H	7-H
13a	9.15	8.15	8.26
14a	9.08	8.38	8.01
13b	9.09	8.15	8.64
14b	9.01	8.76	8.15
13c	9.17	8.18	8.62
14c	9.10	8.71	8.08

similar to that observed from **2b** although with a lower regioselectivity.

To understand the regiochemistry observed, we calculated by the semiempirical PM3 method,[14] the energies of HOMO and LUMO for the most stable (*Z*,*Z*) configuration of **2a**. Comparison of these values (HOMO = −9.151 eV and LUMO = −1.235 eV) with those of buta-1,3-diene (HOMO = −9.502 eV and LUMO = 0.282 eV) and 1-methoxybuta-1,3-diene (HOMO = −8.854 eV and LUMO = 0.351 eV) indicates that the behaviour of **2a** towards dienophiles would be intermediate between that of a neutral and an electron-rich diene. Then, calculations of HOMO orbital coefficients at the ends of (*Z*,*Z*)-**2a** show that it is a polarized diene as well as **2b** (Scheme 2).

Having in mind that the larger LUMO orbital coefficients for naphthoquinones **6** are located at C-2 independently of the presence or the position of the bromine atom,[12] we observed that the regiochemistry of the [4+2] cycloadditions between **2a** and **6** is in good agreement with the molecular frontier orbital theory since the major regioisomer is, in each case, compound **10**.

In the trapping of *o*-QDMs **2** with acrylate dienophiles, the observed regiochemistry is opposite to that predicted by the calculations. Indeed, the larger LUMO orbital coefficients, previously calculated for dienophiles **12**,[12] are located at the unsubstituted carbon atom. A similar failure is reported for the Diels-Alder reaction between acrylic acid and vinylacrylic acid.[15] To explain this opposite orientation, we can envisage the possibility for a portion of the major regioisomers **13** or **15** to result from a competitive initial Michael addition followed by a cyclization-elimination step (Scheme 5). An analogous mechanism has been proposed for the trapping of benzofuran-2,3-quinodimethane with methyl vinyl ketone.[16]

In summary this work describes the generation of 4,5-bis(bromomethylene)-4,5-dihydrothiazole (**2a**) by a reductive debromination of 4,5-bis(dibromomethyl)thiazole (**1a**) with sodium iodide. Diels-Alder trapping of **2a** with unsymmetrical dienophiles is found regioselective although the regioselectivity is lower than that observed with 5-bromomethylene-4-methylene-4,5-dihydrothiazole (**2b**). Starting with juglone (**6a**) or its 2- and 3-bromo derivatives **6b** and **6c**, respectively, the reactions afford a mixture of the tetracyclic quinones **10** and **11** from which the 1,6-regioisomer **10** predominates. The regiochemistry of the [4+2] cycloadditions agree with the predictions of the frontier molecular orbital theory. Trapping **2a** with the acrylate derivatives **12** gives the directly aromatized 6-substituted benzothiazoles **13** as the major regioisomers. This orientation, similar to that observed with **2b**, is in contradiction with the calculations of the frontier orbital coefficients. It could be better explained by a competition between a Michael addition and the Diels-Alder reaction.

Experimental Section

General: Melting points were determined in open capillary tubes with a Büchi 510 apparatus. − ^{1}H-NMR spectra were recorded at 200 and 300 MHz with Bruker AM 200 or AM 300 spectrometers. Chemical shifts are given as δ values (int. standard: TMS). Elemental analyses were performed at the Centre de Microanalyses du CNRS at Solaize. The energies and coefficients of the frontier molecular orbitals were calculated using MOPAC of the SYBYL program. − 2-Bromo-5-hydroxynaphthoquinone (**6b**)[17] and 3-bromo-5-hydroxynaphthoquinone (**6c**)[18] were prepared according to procedures described in the respective references.

General Procedure for the Generation and Trapping of 4,5-Bis(bromomethylene)-4,5-dihydrothiazole (**2a**). − *Method A:* A solution of the tetrabromo derivative **1a** (0.25 g, 0.6 mmol) in DMF (2 ml) was added over 10 min to a stirred and heated (70°C) mixture of NaI (0.36 g, 2.4 mmol) and the appropriate dienophile (3 mmol) in DMF (4 ml). Then, the reaction mixture was heated for 30 min. After cooling, 50 ml of water was added to the brown solution and the latter was decolorated with a 10% aqueous solution of $NaHSO_3$. The solution was extracted with 2 × 30 ml of EtOAc and the organic phase dried with $MgSO_4$. Evaporation of the solvent left a residue which was purified by column chromatography on silica gel using EtOAc/hexane (5:5) as the eluent or by

recrystallization from an appropriate solvent. − *Method B:* A mixture of the tetrabromo derivative **1a** (0. 25 g, 0.6 mmol) in DMF (2 ml) and the corresponding acrylate derivative **12** (20 mmol) in 3 ml of DMF was added over 10 min to a stirred, heated (70°C) solution of NaI (0.6 g, 4 mmol) and highly activated molecular sieves 4 Å (0.6 g) in DMF (3 ml). Stirring and heating were continued for 30 min. After elimination of molecular sieves and the same work-up as above, the residue was purified by column chromatography on silica gel using EtOAc/petroleum ether (4:6) as the eluent.

General Procedure for the Dehydrogenation of Compounds **15** *and* **16**: To a solution of the corresponding dihydro adduct (0.6 mmol) in diphenyl ether (2 ml) was added 0.15 equiv. of 10% Pd/C. The suspension was stirred and heated at 220°C until the dihydro adduct disappeared (monitored by TLC). After cooling, the reaction mixture was filtered through Celite 545 (Merck). The filtrate was concentrated under vacuum and chromatographed on silica gel using EtOAc/petroleum ether (4:6) as the eluent. The benzothiazole derivatives **13** and **14** obtained were recrystallized from hexane.

Thiazolo[4,5-e]benzofuran-5,7-dione (**8**): Compound **8** was prepared from *o*-QDM **2a** or **2b** and dienophile **4** according to method A. It was obtained as a white solid. M.p. 267−268°C (acetone). − IR (KBr): $\tilde{\nu}$ = 1840 cm^{-1}, 1770 (CO). − ^1H NMR (300 MHz, [D_6]DMSO): δ = 9.81 (s, 1 H, 2-H), 9.04 (s, 1 H, 8-H), 8.74 (s, 1 H, 4-H). − $C_9H_3NO_3S$ (205.2): calcd. C 52.68, H 1.47, N 6.83, S 15.63; found C 52.44, H 1.69, N 6.69, S 15.38.

5- and 6-Cyanobenzothiazole (**13a** and **14a**): Compounds **13a** and **14a** were obtained from *o*-QDM **2a** and dienophile **12a** (method B) as a mixture while dehydrogenation of **15a** gave 51% of **13a** as a white solid. − **13a**: M.p. 139°C (hexane). − IR (KBr): $\tilde{\nu}$ = 2220 cm^{-1} (CN). − ^1H NMR (200 MHz, $CDCl_3$): δ = 9.15 (s, 1 H, 2-H), 8.26 (d, 1 H, *J* = 1.5 Hz, 7-H), 8.15 (d, 1 H, *J* = 8 Hz, 4-H), 7.70 (dd, 1 H, *J* = 8 and 1.5 Hz, 5-H). − **14a**: ^1H NMR (200 MHz, $CDCl_3$): 9.08 (s, 1 H, 2-H), 8.38 (d, 1 H, *J* = 1.5 Hz, 4-H), 8.01 (d, 1 H, *J* = 8 Hz, 7-H), 7.60 (dd, 1 H, *J* = 8 and 1.5 Hz, 6-H). − $C_8H_4N_2S$, 0.33 H_2O (166.1): calcd. C 57.84, H 2.83, N 16.86 S 19.30; found C 57.63, 2.45, 16.79, 19.66.

5- and 6-Ethoxycarbonylbenzothiazole (**13b** and **14b**): Compounds **13b** and **14b** were both obtained as a white solid mixture from *o*-QDM **2a** and dienophile **12b** (method B) or by dehydrogenation of **15b** and **16b** in 51% yield. − IR (KBr): $\tilde{\nu}$ = 1700 cm^{-1} (CO). − ^1H NMR (200 MHz, $CDCl_3$): **13b**: δ = 9.09 (s, 1 H, 2-H), 8.64 (s, 1 H, 7-H), 8.15 (m, 2 H, 4-H and 5-H), 4.38 (q, 2 H, *J* = 6.2 Hz, CH_2), 1.37 (t, 3 H, *J* = 6.2 Hz, CH_3); **14b**: δ = 9.01 (s, 1 H, 2H), 8.76 (d, 1 H, *J* = 1.3 Hz, 4-H), 8.15 (m, 2 H, 7-H and 6-H), 4.38 (q, 2 H, *J* = 6.2 Hz, CH_2), 1.37 (t, 3 H, *J* = 6.2 Hz, CH_3). − $C_8H_4N_2S$, 0.33 H_2O (213.2): calcd. C 57.84, H 2.83, N 16.86 S 19.30; found C 57.63, 2.45, 16.79, 19.66.

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