Generation and Trapping of 4-Methylene-5-(bromomethylene)-4,5-dihydrothiazole with Dienophiles

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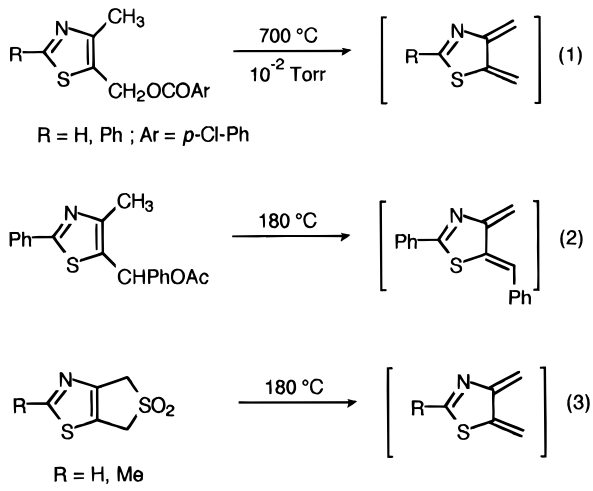
4-(Bromomethyl)-5-(dibromomethyl)thiazole (**1**) was prepared in good yields by bromination of 4,5-dimethylthiazole with 3.3 equiv of NBS in the presence of AIBN. Treatment of **1** with sodium iodide led to a thiazole *o*-quinodimethane **2** which was trapped *in situ* with dienophiles such as *N*-phenylmaleimide, DMAD, or acrylate derivatives. From the latter, 6-substituted-4,5-dihydrobenzothiazoles **7** are selectively formed. Anthra[2,3-*b*]thiazole-4,5-diones **13**−**15** were obtained from naphthoquinones. With 2- or 3-bromonaphthoquinones (**11** or **12**), the cycloadditions were found highly regioselective. Structural assignment of the regioisomers was made by a 2D $^{1}H-^{13}C$ HMBC technique performed on the aromatized cycloadduct **15b**. Calculations of HOMO and LUMO frontier orbital coefficients by the semiempirical PM3 method show that the regiochemistry observed in the cycloadditions of **2** toward acrylate dienophiles or naphthoquinones **11** and **12** did not agree with the corresponding values.

Because of the many proven applications of synthetic heteroaromatic compounds, the Diels−Alder trapping of heterocyclic analogues of *o*-quinodimethane (*o*-QDM) has recently received attention.[1] In this context, the preparation and cycloadditions of *o*-dimethylene thiazoles have remained largely unexplored. The few known examples of this type of reaction require very harsh conditions for generation of the *o*-QDM. Thus, 4,5-dimethylene-4,5-dihydrothiazole and its 2-phenyl derivative were obtained by flash pyrolysis of the corresponding *p*-chlorobenzoate esters[2] (Scheme 1, eq 1). But only the latter was reported to be trapped, although not with a dienophile. A heated dichlorobenzene solution of α-(2-phenyl-4-methylthiazol-5-yl)-α-phenylmethyl acetate gave, after acetic acid elimination, an *o*-QDM (eq 2).[3] The latter was successfully trapped with symmetrical dienophiles. On the other hand, thiazole-fused 3-sulfolenes were described as high temperature precursors of thiazole *o*-quinodimethanes (eq 3).[4]

Scheme 1



In order to get readily available precursors which would give *o*-QDM under milder conditions, we turned our attention to the preparation and use of the unknown 4-(bromomethyl)-5-(dibromomethyl)thiazole (**1**) since polybrominated compounds of thiophene,[5] pyrazole,[6] and furan[7] give the corresponding *o*-QDM by treatment with sodium iodide. This tribrominated thiazole derivative was selected in order to obtain a well polarized "diene", expected to undergo highly regioselective Diels−Alder reactions.

Treatment of the commercially available 4,5-dimethylthiazole with 3.3 equiv of *N*-bromosuccinimide (NBS) and 10% of 2,2′-azobis(isobutyronitrile) (AIBN) in refluxing carbon tetrachloride yielded compound **1** selectively in 65% yield (Scheme 2). The structure of **1** was assigned unambiguously by chemical correlation. Thus, 5-formyl-4-methylthiazole (**3**)[8] was reacted with bromine in the presence of triphenyl phosphite[9] to give the dibromo derivative **4**. Bromination of the latter with NBS (1.1 equiv) in the presence of AIBN (10%) led to the tribromo derivative **1** identical with the compound prepared by the above procedure.

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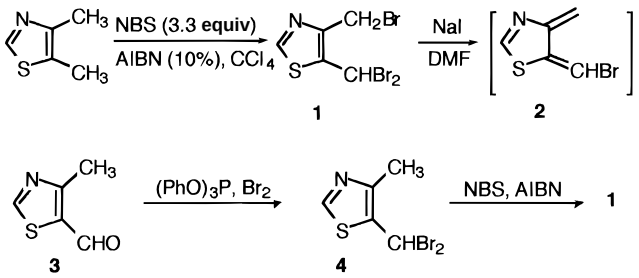
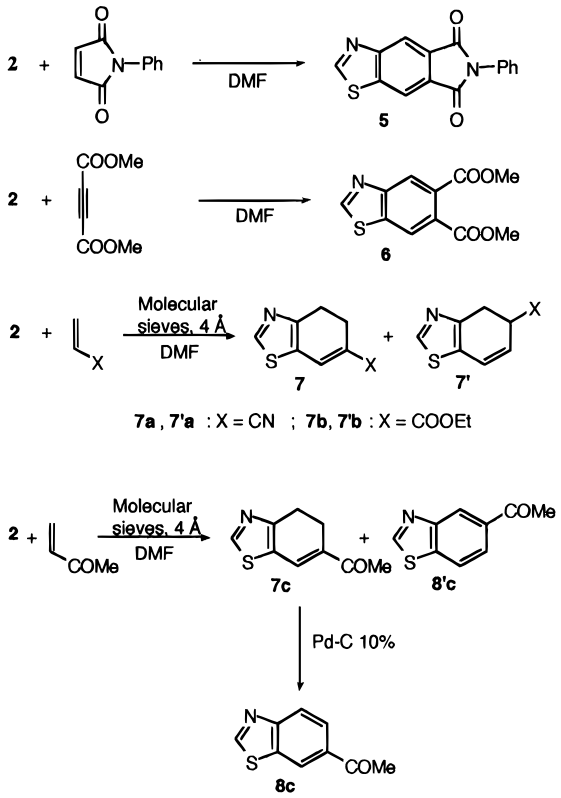
Scheme 2



Scheme 3



Subsequent generation of 4-methylene-5-(bromomethylene)-4,5-dihydrothiazole **2** was performed with sodium iodide in DMF. The *o*-QDM **2** formed was trapped *in situ* with a set of dienophiles (Scheme 3). The corresponding aromatized cycloadducts **5** and **6** or the dihydro derivatives **7** were obtained in good yields. The cycloadditions of *o*-QDM **2** with unsymmetrical dienophiles are highly regioselective. The ^{1}H-NMR spectra of the crude products indicate that the dihydro adducts **7** are the major regioisomers (**7a**/**7′a**: 95/5, **7b**/**7′b**: 87/13). Trapping **2** with methyl vinyl ketone yielded a mixture of 4,5-dihydro-6-acetylbenzothiazole (**7c**) and the spontaneously aromatized 5-acetyl derivative **8′c** in a respective ratio (**7c**/**8′c**: 81/19). The structure of **8′c** was assigned by comparison of its spectroscopic data with those of **8c**. The latter was obtained by treatment of **7c** with Pd−C (10%) in refluxing diphenyl ether.

On the other hand, some naturally occurring alkaloids like the cytotoxic derivative kuanoniamine A (**I**)[10,11] contain a thiazole ring fused to a quinone−imine system while the recently synthesized naphthothiazoledione **II**[12] exhibits pharmacological properties. A straightforward access to thiazolo anthraquinone derivatives **13**−**15** of biological interest makes use of condensations between *o*-QDM **2** and naphthoquinones **9**−**12** (Scheme 4).

The results of these cycloadditions are summarized in Table 1. First, **2** was generated under the sodium iodide protocol (method A) and trapped with naphthoquinone (**9a**) and naphthazarine (**9b**) to give the corresponding aromatized tetracyclic compounds **13a** and **13b** in good yields. With 5-substituted naphthoquinones **10**, the condensations of **2** afford a mixture of the regioisomers **14**+**15**. Opposite regioisomers were obtained from juglone (**10a**) and acetyljuglone (**10b**) (entries 3 and 5, respectively).[13] Using tetrabutylammonium iodide (method B) to prepare **2**, a poorer regioselectivity was observed (entries 4 and 6) than in method A (entries 3 and 5). Highly regioselective Diels−Alder reactions were performed by the use of 2- or 3-bromonaphthoquinones (**11** or **12**) (entries 7−10). The 1,6-regioisomers **14** obtained as the major products from quinones **11** (entries 7 and 8) and the 1,9-regioisomers **15** formed in higher amounts from **12** (entries 9 and 10) indicate that the regiochemistry is under control of the bromine atom position.

The 1,6- and 1,9-regioisomers are differentiated by the ^{1}H-NMR chemical shifts of H-4 and H-11 (Table 2). In compound **14a**, the H-4 signal is shifted to lower field by 0.11 ppm relative to that of **14b** while for **15a** a similar shift of 0.14 ppm was observed for H-11.

Further corroboration for the structure assignments of regioisomers **14** and **15** was made by 2D ^{1}H−^{13}C NMR HMBC correlations performed on **15b** and then by chemical transformations. The HMBC technique correlates the protons with the carbon atoms through ^1J, ^2J, and ^3J couplings. For aromatic compounds, it is known that long range ^3J couplings are larger than ^2J. The spectral data of **15b** are reported in Table 3. Thus, C-3a and C-11a were first determined. Indeed, C-3a and C-11a gave ^3J couplings with the same proton H-2. But, the former appeared as a doublet characteristic of a cross peak through the nitrogen atom of a thiazole nucleus ($^3J_{C3a-H2}$ = 15.3 Hz) while the second one was an unresolved singlet (indicating a coupling of <5 Hz for the $^3J_{C11a-H2}$).[15] Then, the three ^{3}J couplings, C-11a with H-4, C-5 with H-4, and C-5 with H-6, permit assignment of the 1,9-regioisomeric structure to **15b**. Only two ^3J couplings should be observed from the hypothetical opposite 1,6-regioisomer since no proton would be available for coupling on C-6: C-11a with H-4 on one hand, and C-5 with H-4 on the other hand (Table 3).

Treatment of the acetate **15b** with 10% KOH in ethanol afforded the corresponding hydroxyl derivative. The ^{1}H-NMR spectrum of this compound is identical with that of **15a** obtained by cycloaddition from **12a**. Then, the 1,6-structure was attributed to **14a** and **14b**.

The results given in Scheme 3 and Table 1 indicate that the regiochemistry of the cycloadditions between **2** and **11** or **12** is governed both by the position of the bromine atom on the dienophile and on the "diene".

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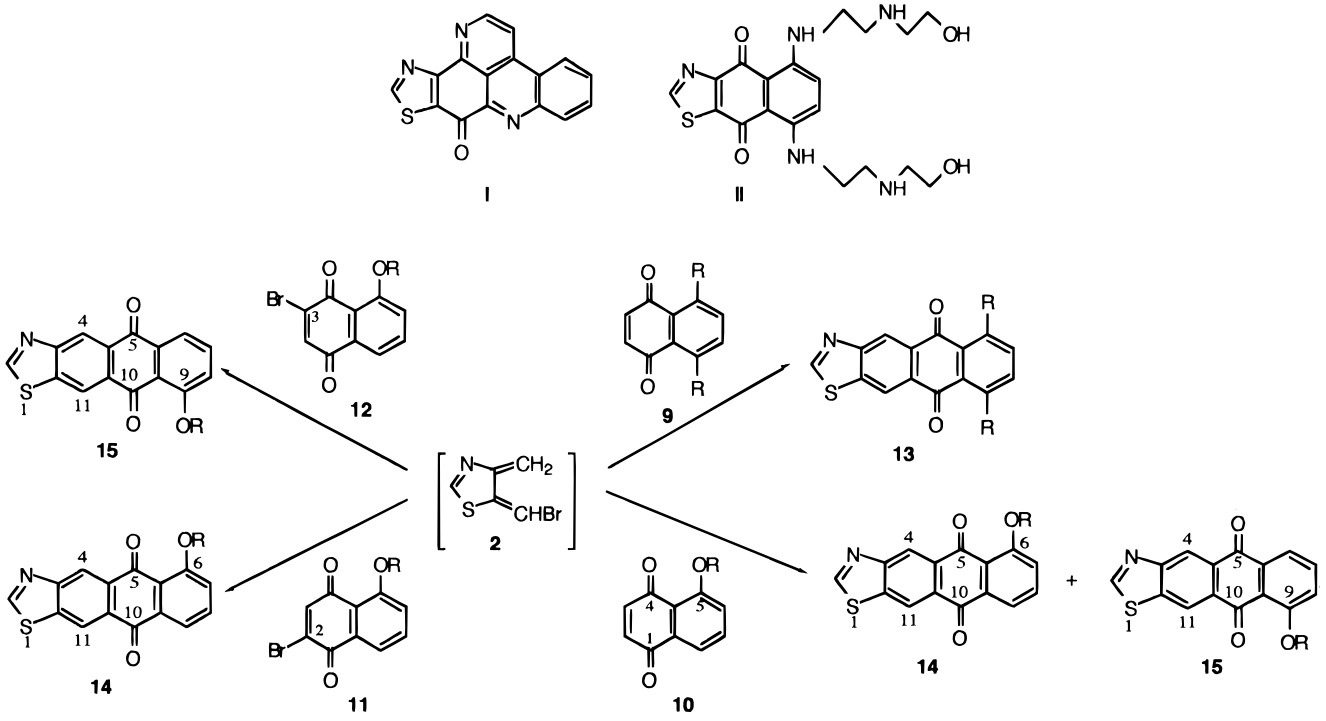
(13) The regiochemistry observed agrees with the known directing effect of the 5-peri OH group in juglone **5a** and the opposite one in acetyljuglone **5b**.[14]

(14) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5513−5514 and references cited therein.

(15) A similar cross peak through nitrogen was reported to appear as a doublet in the HMBC spectrum of benzothiazole or kuanoniamine A.[10]

Scheme 4



9a, **13a** : R = H ; **9b**, **13b** : R = OH

10a, **11a**, **12a**, **14a**, **15a** : R = H ; **10b**, **11b**, **12b**, **14b**, **15b** : R = $COCH_3$

Table 1. Formation and Trapping of *o*-QDM 2 with Naphthoquinones 9−12

entry	starting quinone	method[a]	compounds	ratio of **14**/**15**[b]	yield [%][c]
1	**9a**	A	**13a**	−	52
2	**9b**	A	**13b**	−	70
3	**10a**	A	**14a** + **15a**	70/30	70
4	**10a**	B	**14a** + **15a**	57/43	63
5	**10b**	A	**14b** + **15b**	40/60	37
6	**10b**	B	**14b** + **15b**	46/54	46
7	**11a**	A	**14a** + **15a**	92/8	60
8	**11b**	A	**14b** + **15b**	95/5	56
9	**12a**	A	**14a** + **15a**	8/92	73
10	**12b**	A	**14b** + **15b**	5/95	58

[a] Method A: NaI/DMF; method B: $Bu_4N^+I^-$/toluene. [b] Determined by ^{1}H-NMR at 300 MHz. [c] From isolated pure products.

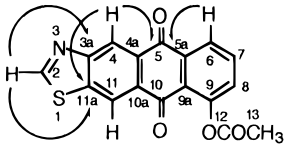
Table 2. Chemical Shifts (300 MHz, DMSO-d_6, δ) of H-4 and H-11 for Compounds 14 and 15

regioisomer (1,6-)	H-11	H-4	regioisomer (1,9-)	H-11	H-4
14a	9.12	8.80	**15a**	9.19	8.76
14b	9.10	8.69	**15b**	9.05	8.73

Thus, the unsubstituted carbon atom of bromonaphthoquinones is attacked by the unbrominated methylene end of *o*-QDM **2**. These observations are in contradiction with some [4 + 2] cycloadditions in which juglone **10a** and its 3-bromo derivative **12a** gave the same orientation while an opposite one was observed between **10a** and 2-bromojuglone **11a**.[16] An analogous kind of orientational control occurred in the Diels−Alder trapping of the brominated *o*-xylylene **16** with 2-bromobenzoquinones **17** or **18**[17] (Scheme 5).

In search for a better understanding of *o*-QDM **2** behavior in cycloaddition reactions, we calculated, by the semiempirical PM3 method,[18] the energies of HOMO and

Table 3. 2D ^{1}H−^{13}C NMR HMBC Correlations for Compound 15b (DMSO-d_6, δ)



15b

position	1H (300 MHz)	^{13}C (75 MHz)	HMBC (J_{C-H}) ^1J	^2J	^3J
2	9.74	162.2	H-2	-	-
3a	-	156.1	-	-	H-2, H-11
4	8.73	121.0	H-4	-	-
4a	-	131.7	-	-	H-11
5	-	181.6	-	-	H-4, H-6
5a	-	135.2	-	-	H-7
6	7.67	125.3	H-6	-	H-8
7	7.99	135.4	H-7	-	-
8	8.25	130.3	H-8	H-7	H-6
9	-	150.0	-	H-8	H-7
9a	-	124.8	-	-	H-6, H-8
10	-	180.9	-	-	H-11
10a	-	130.3	-	-	H-4
11	9.05	122.9	H-11	-	-
11a	-	140.2	-	-	H-2, H-4
12		168.7			
13	2.45	20.9			

LUMO for the most stable (*Z*) configuration. Comparison of these values (HOMO = −9.051 and LUMO = 0.983) with those of buta-1,3-diene (HOMO = −9.502 and LUMO = 0.282) and 1-methoxybuta-1,3-diene (HOMO = −8.854 and LUMO = 0.351) suggests that the reactivity of **2** is intermediate between that of a neutral and an electron rich diene. Then, calculations of HOMO orbital coefficients at the ends of (*Z*)- or (*E*)-**2** and **16** indicate that their Diels−Alder reactions with unsymmetrical and

Scheme 5

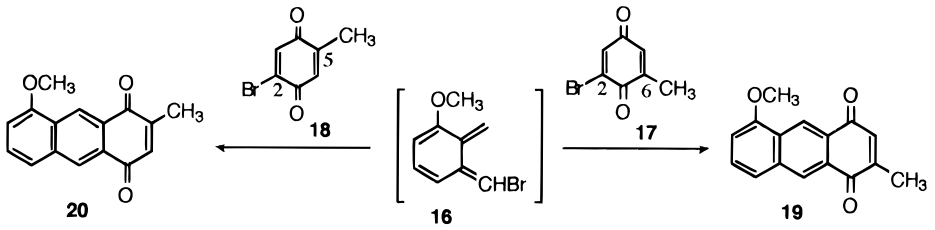
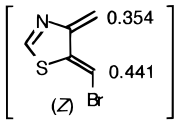
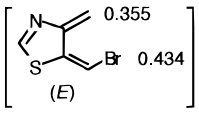
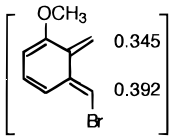


Table 4. Orbital Coefficients of HOMO for *o*-QDMs and LUMO for Acrylate Dienophiles and Unsymmetrical Quinones

	o-QDM		
2			
16			
	Acrylate Dienophile	**C-1**	**C-2**
	CH_2=CH-CN	0.244	0.566
	CH_2=CH-COOEt	0.495	0.656
	CH_2=CH-COMe	0.438	0.620
	Quinone (NQ or BQ)[a]	**C-2**	**C-3**
10a	5-Hydroxy NQ (*syn*)[b]	0.357	0.335
11a	2-Bromo-5-hydroxy NQ (*syn*)[b]	0.374	0.363
12a	3-Bromo-5-hydroxy NQ (*syn*)[b]	0.386	0.351
10b	5-Acetoxy NQ	0.284	0.295
11b	2-Bromo-5-acetoxy NQ	0.315	0.336
12b	3-Bromo-5-acetoxy NQ	0.326	0.327
17	2-Bromo-6-methyl BQ	0.364	0.379
18	2-Bromo-5-methyl BQ	0.375	0.382

[a]NQ = Naphthoquinone; BQ = Benzoquinone

[b]*Syn* = structure in which the 5-hydroxy group is chelated with the 4-CO

polarized dienophiles should be highly regioselective. On the other hand, the larger coefficients are located at the brominated carbon atom (Table 4). The LUMO orbital coefficients for the unsymmetrical acrylate dienophiles and naphthoquinones **10a**, **11a**, and **12a** show that the larger values are situated at C-2. Concerning 5-acetoxynaphthoquinones, the larger values of LUMO orbital coefficients are at C-3 for **10b** and **11b**, but they are similar for **12b**. For 2-bromobenzoquinones **17** and **18**, the larger coefficients are situated at the unbrominated carbon C-3. So, calculations of frontier orbital coefficients agree with the regiochemistry observed in the cycloadditions between **2** and quinones **10a** (*syn*), **10b**, and bromoquinone **11a**, but they remain unsufficient to explain it in the cases of bromoquinones **11b**, **12a**, **12b**, **17**, **18**, and acrylate dienophiles as well.

This work describes the ability of 4-(bromomethyl)-5-(dibromomethyl)-4,5-dihydrothiazole (**1**) to afford an *o*-quinodimethane analogue **2** under mild conditions. Trapping of **2** with *N*-phenylmaleimide, DMAD, or acrylate derivatives provides an efficient route to 5,6-disubstituted or 4,5-dihydro-6-substituted benzothiazoles, the latter not readily available by other methods. Anthrathiazole-5,10-dione derivatives **14** or **15** were regioselectively obtained from 2- and 3-bromo-5-substituted naphthoquinones. Indeed, strategic placement of bromine atoms on the *o*-QDM and naphthoquinones provides highly regiocontrolled cycloadditions to give the 1,6- (or 1,9-) regioisomers. The regiochemistry observed on one hand with acrylate dienophiles and on the other hand with bromoquinones **11b**, **12a**, and **12b** is opposite to that predicted by calculations of the frontier orbital coefficients by the semiempirical PM3 method. In the case of quinones, the blocking effect of bromine seems a more significant factor for the regiochemical control. Further investigations will be developed to generate other brominated thiazole *o*-quinodimethanes by this method in order to elucidate the regiocontrol of their Diels−Alder trapping.

Experimental Section

Melting points were measured in a capillary tube. Column chromatography was carried out with silica gel (60 Å, 35−70 μm). ^{1}H- and ^{13}C-NMR spectra were recorded with tetramethylsilane as an internal standard. For recording out 2D ^{1}H−^{13}C HMBC spectra, 5 mg of compound **15b** were dissolved at room temperature in 0.5 mL of DMSO-d_6. The HMBC technique was performed with gradients selection[19] which gave a very clean 2D matrix with very small T_1 noise. The *J* filter and transfer time for long range coupling were fixed, respectively, to 3.22 and 80 ms. The acquisition parameters were AQ = 0.18 ms, SW2 = 2793 Hz, SW1 = 3586 Hz, NE = 512, NS = 48, and relaxation delay D_1 = 1.5 s. Prior to the FFT, the signal was weighted by a nonshifted sine bell in the two dimensions. The size of the final matrix was 1K × 1K.

The energies and coefficients of the molecular frontier orbitals were calculated from MOPAC of SYBYL program.

2-Bromo-5-hydroxynaphthoquinone (**11a**) and 2-bromo-5-acetoxynaphthoquinone (**11b**) were prepared according to Grunwell et al.[16] 3-Bromo-5-hydroxynaphthoquinone (**12a**) was obtained by treating juglone with bromine in glacial acetic acid.[20] By this method 13% of the 2-bromo derivative **11a** was

(16) It was demonstrated that the electron rich end of carbodienes[16a] or azadienes[16b,c] attacks exclusively the unbrominated carbon of naphthoquinones **6** and **7**. (a) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91−95. (b) Bouammali, B. Pautet, F.; Fillion, H. *Tetrahedron* **1993**, *49*, 3125−3130. (c) Chaker, L.; Pautet, F.; Fillion, H. *Heterocycles* **1995**, *41*, 1169−1179.

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(20) Thomson, R. H. *J. Org. Chem.* **1948**, *13*, 377−383.

also formed which was removed by recrystallization from acetone. Acetylation of **12a** was performed as described for **10b**.[21] The melting points of **11** and **12** are identical with the values reported in the literature.[22,23]

4-(Bromomethyl)-5-(dibromomethyl)thiazole (1). To a stirred solution of 4,5-dimethylthiazole (0.560 g, 5 mmol) in CCl_4 (100 mL) were added NBS (2.94 g, 16.5 mmol) and AIBN (0.1 g, 10%). Then, the reaction mixture was heated to reflux for 1 h. After cooling, the succinimide was removed by filtration. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel using a mixture of ether/CH_2Cl_2/petroleum ether 3/3/4 as the eluent. The corresponding tribromo derivative **1** was obtained in 65% yield. It was not stable at room temperature but may be stored at −18 °C for several days. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.80 (s, 1H, H-2), 7.0 (s, 1H, 5-$CHBr_2$), 4.60 (s, 2H, 4-CH_2Br). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 153.3 (C-2), 147.0 (C-5), 140.2 (C-4), 26.3 (5-*C*HBr_2), 23.4 (4-*C*H_2Br). MS: *m*/*z* (%): 349.6 (M^+, 0.6), 269.8 (100), 190.9 (42), 188.9 (41). HRMS cannot be measured due to the very low percentage of the molecular peak.

5-Formyl-4-methylthiazole (3). Aldehyde **3** was prepared according to the procedure described in reference.[8] Mp 74 °C (lit.[8] 66−70 °C). IR (KBr): ν 2890, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 10.12 (s, 1H, CHO), 8.96 (s, 1H, H-2), 2.77 (s, 3H, 4-CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 182.3 (5-CHO), 161.7 (C-5), 158.7 (C-2), 132.8 (C-4), 16.1 (4-*C*H_3).

4-Methyl-5-(dibromomethyl)thiazole (4). The procedure used to obtain the dibromo derivative **4** from aldehyde **3** was that described in reference 9. Compound **4** is unstable. Yield: 40%. It may be stored in CH_2Cl_2 at −18 °C for few days. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.77 (s, 1H, H-2), 6.91 (s, 1H, 5-$CHBr_2$), 2.46 (s, 3H, 4-CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 151.6 (C-2), 147.6 (C-5), 135.0 (C-4), 27.2 (5-*C*HBr_2), 14.4 (4-*C*H_3).

6-Phenylthiazolo[2,3-*f*]isoindol-5,7(6*H*)-dione (5). A solution of the tribromo derivative **1** (0.21 g, 0.6 mmol) in DMF (2 mL) was added over 10 min to a stirred, heated (70 °C) mixture of NaI (0.36 g, 2.4 mmol) and *N*-phenylmaleimide (0.519 g, 3 mmol) in DMF (4 mL). The reaction mixture was heated at 70 °C for 20 min. After cooling, the brown solution was poured into 50 mL of water and treated with a 10% aqueous solution of $NaHSO_3$ until its decoloration. The solution was extracted with EtOAc (2 × 30 mL) and the organic phase dried over anhydrous $MgSO_4$. After elimination of the solvent, the residue was purified by column chromatography on silica gel using EtOAc/hexane (5:5) as the eluent. Compound **5** was obtained as a white solid in 88% yield. Mp 246 °C (methanol). IR (KBr): ν 1715, 1610, 1500, 1460 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 9.73 (s, 1H, H-2), 8.91 (s, 1H, H-8), 8.57 (s, 1H, H-4), 7.51 (m, 5H, C_6H_5). Anal. Calcd for $C_{15}H_8NO_2S$, 0.66 H_2O: C, 61.66; H, 2.85; N, 9.44; S, 10.64. Found: C, 61.59; H, 3.21; N, 9.58; S, 10.97.

5,6-Bis(methoxycarbonyl)benzothiazole (6). Compound **6** was prepared from the tribromo derivative **1** and DMAD (0.43 g, 3 mmol) as above. Stirring and heating were maintained for 2.5 h. After the same workup and purification described above, the white solid was recrystallized from EtOAc/hexane, affording **6** in 56% yield. Mp 120 °C. IR (KBr): ν 3120, 2960, 1740, 1715, 1600, 1445, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.19 (s, 1H, H-2), 8.48 (s, 1H, H-7), 8.38 (s, 1H, H-4), 3.97 (s, 3H, $COOCH_3$), 3.95 (s, 3H, $COOCH_3$). Anal. Calcd for $C_{11}H_9NO_4S$: C, 52.58; H, 3.61; N, 5.57; S, 12.76. Found: C, 52.49; H, 3.60; N, 5.57; S, 12.60.

General Procedure for the Synthesis of 4,5-Dihydro-6-substituted Benzothiazole (7). A mixture of the tribromo derivative **1** (0.35 g, 1 mmol) and the corresponding dienophile (20 mmol) in DMF (3 mL) was added over 10 min to a stirred solution of NaI (0.6 g, 4 mmol) heated at 70 °C and highly activated molecular sieves (4 Å, 1 g) in DMF (3 mL). Stirring and heating were maintained for 30 min. After the same workup described as above, the residue was purified by column chromatography on silica gel using EtOAc/petroleum ether (8:2) as the eluent.

6-Cyano-4,5-dihydrobenzothiazole (7a). Starting with cyanoethylene as the dienophile, the cycloaddition gave a mixture of regioisomers **7a**+**7′a** (**7a**/**7′a**: 95/5) from which compound **7a** was isolated as a white solid in 55% yield after recrystallization from hexane. Mp 99 °C. IR (KBr): ν 3060, 2900, 2200, 1590, 1500, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.78 (s, 1H, H-2), 7.25 (t, 1H, J = 1.6 Hz with allylic coupling, H-7), 3.14 (m, 2H, H-4), 2.76 (m, 2H, H-5). Anal. Calcd for $C_8H_6N_2S$: C, 59.24; H, 3.73; N, 17.27; S, 19.76. Found: C, 58.99; H, 3.78; N, 17.39; S, 19.24.

4,5-Dihydro-6-(ethoxycarbonyl)benzothiazole (7b). Starting with ethyl acrylate as the dienophile, the cycloaddition gave a mixture of regioisomers **7b**+**7′b** (**7b**/**7′b**: 87/13) from which compound **7b** was isolated as an oil by column chromatography on silica gel using EtOAc/hexane 30/70 as the eluent. Yield: 67%. IR (KBr): ν 3080, 2900, 1700, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.61 (s, 1H, H-2), 7.50 (s, 1H, H-7), 4.24 (q, 2H, CH_2CH$_3$), 3.05 (t, 2H, H-4), 2.71 (t, 2H, H-5), 1.22 (t, 3H, CH$_2$CH_3). Anal. Calcd for $C_{10}H_{11}NO_2S$, 0.2 H_2O: C, 56.42; H, 5.39; N, 6.58; S, 15.06. Found: C, 56.59; H, 5.42; N, 6.44; S, 15.09.

6-Acetyl-4,5-dihydrobenzothiazole (7c) and 5-Acetylbenzothiazole (8′c). Starting with methyl vinyl ketone as the dienophile, the dihydro derivative **7c** was obtained as a white solid admixed with the aromatized **8′c** (12%). These compounds were separated by column chromatography as described in the general procedure. **7c**: Yield 52%. Mp 106 °C (hexane). IR (KBr): ν 2900, 1640, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.75 (s, 1H, H-2), 7.45 (s, 1H, H-7), 3.02 (t, 2H, H-4), 2.79 (t, 2H, H-5), 2.39 (s, 3H, $COCH_3$). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81; S, 17.89. Found: C, 60.45; H, 5.13; N, 7.77; S, 17.96. **8′c** : Yield 12%. Mp 102 °C (hexane). IR (KBr): ν 3080, 1680, 1360, 1300 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.10 (s, 1H, H-2), 8.71 (s, 1H, H-4), 8.08 (m, 2H, H-6 and H-7), 2.72 (s, 3H, $COCH_3$). Anal. Calcd for C_9H_7NOS, 0.2 H_2O: C, 59.78; H, 4.12; N, 7.74. Found: C, 59.63; H, 4.04; N, 7.43.

6-Acetylbenzothiazole (8c). A stirred suspension of compound **7c** (0.13 g, 0.73 mmol) and Pd−C 10% (0.077 g, 0.1 equiv) in diphenyl ether (2mL) was heated at 220 °C for 27 h. After cooling, the reaction mixture was filtered through Celite and the latter washed with CH_2Cl_2. The filtrate and dichloromethane fractions were combined, concentrated under vacuum, and chromatographed on silica gel using EtOAc/petroleum ether 40/60 as the eluent. Compound **8c** was obtained as a white solid in 44% yield. Mp 94 °C (hexane). IR (KBr): ν 3100, 1675, 1435, 1300, 1280, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.17 (s, 1H, H-2), 8.62 (s, 1H, H-7), 8.18 (m, 2H, H-4 and H-5), 2.72 (s 3 H, $COCH_3$). Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 61.06; H, 3.84; N, 7.65; S, 17.77.

General Procedures for the Synthesis of Anthra[2,3-*b*]thiazole-5,10-diones (13, 14, and 15). Method A: A solution of the tribromo derivative **1** (0.316 g, 0.6 mmol) in DMF (2 mL) was slowly added to a stirred hot (60 °C) solution of the corresponding quinone (0.5 mmol) and NaI (5 equiv) in 3 mL of DMF. Stirring and heating were maintained for 1 h, and then the reaction mixture was cooled to room temperature. The precipitated product was filtered off and washed with water and then with EtOAc. Evaporation of the filtrate gave an additional fraction of the corresponding tetracyclic quinones. The anthra[2,3-*b*]thiazole-5,10-diones were purified by column chromatography using a mixture of EtOAc/hexane 40/60 or 70/30 as the eluent. In each case, the major regioisomer was isolated from the mixture by recristallization from an appropriate solvent.

Method B: A solution of the tribromo derivative **1** (0.316 g, 0.6 mmol) in toluene (3 mL) was added in 10 min to a stirred hot (80 °C) mixture of quinone **10a** or **10b** (0.5 mmol) and $Bu_4N^+I^-$ (0.93 g, 3 mmol) in 15 mL of toluene. Stirring and heating were maintained for 15 min. By cooling the reaction mixture, a precipitate of the corresponding tetracyclic quinones was formed. It was collected by filtration and washed with EtOAc. An additionnal fraction of the aromatized cycloadducts

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was isolated after evaporation of the filtrate and then, a column chromatography of the residue was performed as above.

Anthra[2,3-*b*]thiazole-5,10-dione (13a). Mp 294 °C dec. IR (KBr) ν 1675 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.76 (s, 1H, H-2), 9.14 (s, 1H, H-11), 8.78 (s, 1H, H-4), 8.29 (m, 2H, H-7 and H-8), 7.98 (m, 2H, H-6 and H-9). Anal. Calcd for $C_{15}H_7NO_2S$: C, 67.91; H, 2.66; N, 5.28; S, 12.08. Found: C, 67.79; H, 2.92; N, 5.30; S, 11.90.

6,9-Dihydroxyanthra[2,3-*b*]thiazole-5,10-dione (13b). Mp > 300 °C. IR (KBr) ν 1640 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.81 (s, 2H, OH), 9.80 (s, 1H, H-2), 9.24 (s, 1H, H-11), 8.85 (s, 1H, H-4), 7.49 (s, 2H, H-7 and H-8). Anal. Calcd for $C_{15}H_7NO_4S$: C, 60.59; H, 2.37; N, 4.71; S, 10.78. Found: C, 60.48; H, 2.49; N, 4.45; S, 10.69.

6 (and 9)-Hydroxyanthra[2,3-*b*]thiazole-5,10-diones (14a and 15a). 14a (1,6-regioisomer): Mp > 300 °C (DMF). IR (KBr) ν 1670, 1640 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.54 (s, 1H, OH); 9.76 (s, 1H, H-2), 9.12 (s, 1H, H-11); 8.80 (s, 1H, H-4), 7.84 (m, 2H, H-8 and H-9); 7.43 (d, 1H, J = 12 Hz, H-7). **15a** (1,9-regioisomer): Mp > 300 °C (DMF); IR (KBr) ν 1670, 1640 (CO) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.54 (s, 1H, OH); 9.76 (s, 1H, H-2), 9.19 (s, 1H, H-11); 8.76 (s, 1H, H-4), 7.84 (m, 2H, H-8 and H-9); 7.43 (d, 1H, J = 12 Hz, H-7). **14a**+**15a**: Anal. Calcd for $C_{15}H_7NO_3S$: C, 64.05; H, 2.50; N, 4.98; S, 11.39. Found: C, 64.03; H, 2.46; N, 5.03; S, 11.58.

6 (and 9)-Acetoxyanthra[2,3-*b*]thiazole-5,10-diones (14b and 15b). 14b (1,6-regioisomer): Mp 257 °C (DME). IR (KBr) ν 1770, 1670 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H, H-2), 9.10 (s, 1H, H-11), 8.69 (s, 1H, H-4), 8.24 (d, 1H, J = 8 Hz, H-7); 7.99 (t, 1H, J = 8 Hz, H-8), 7.67 (d, 1H, J = 8 Hz, H-9), 2.44 (s, 3H, $OCOCH_3$). **15b** (1,9-regioisomer): Mp 253 °C (acetone). IR (KBr) ν 1770, 1670 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H, H-2), 9.05 (s, 1H, H-11), 8.73 (s, 1H, H-4), 8.25 (d, 1H, J = 8 Hz, H-8), 7.99 (t, 1H, J = 8 Hz, H-7); 7.67 (d, 1H, J = 8 Hz, H-6), 2.45 (s, 3H, $OCOCH_3$). **14b**+**15b**: Anal. Calcd for $C_{17}H_9NO_4S$: C, 62.80; H, 2.85; N, 4.31; S, 9.86. Found: C, 62.53; H, 2.80; N, 4.55; S, 9.90.

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