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Heterocycles LXXVIII. Electrophilic Substitution of 2′-Phenyl-4*R*-2,4′-bisthiazoles

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Summary. The behaviour of some 2′-phenyl-4*R*-2,4′-bisthiazoles with respect to electrophilic substitution reactions (halogenation and nitration) has been studied in order to establish relationships between structure and reactivity of the two thiazole rings. The entry of the electrophilic reactants in position 5 or 5′ of the 2,4′-bisthiazole system depends on the nature of the residue in position 4.

Keywords. Atropisomerism; 2,4′-Bisthiazoles; Halogenation; Nitration.

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Zusammenfassung. Zur Ermittlung von Zusammenhängen zwischen Struktur und Reaktivität der beiden Thiazolringe wurde das Verhalten einiger 2′-Phenyl-4*R*-2,4′-bisthiazole bezüglich elektrophiler Substitution (Halogenierung und Nitrierung) untersucht. Der Eintritt der Substituenten in die Positionen 5 bzw. 5′ des Bisthiazolsystems hängt von der Natur des Substituenten in Position 4 ab.

Introduction

The presence of the 2,4′-bisthiazole system in bleomicine, an anticancerous antibiotic, prompted us to synthetize a series of 2′-aryl-4R_1-5R_2-2,4′-bisthiazoles with different substituents in position 4 and 5 [1] in order to establish qualitative relationships between chemical structure and biological activity [2].

In a previous paper, the applicability of the *Sommelet* and *Krohnke* reactions in a series of 2′-aryl-4-halomethyl-2,4′ bisthiazoles was presented [3]. Herein, our studies of halogenation and nitration in the series of 2′-phenyl-4*R*-2,4′-bisthiazoles, with two electrophilic centres in position 5 and 5′ are continued, taking into account our earlier observations that the phenyl substituent shows a $+E$ effect with respect to the thiazole ring, thus increasing the electronic density in position 5 [4–6].

Results and Discussion

The reactions of 2′-phenyl-4*R*-2,4′-bisthiazoles **1a**,**b** with equimolar amounts of bromine in acetic acid lead to a mixture or 5- and 5′- monobromo derivatives **2a**,**b**

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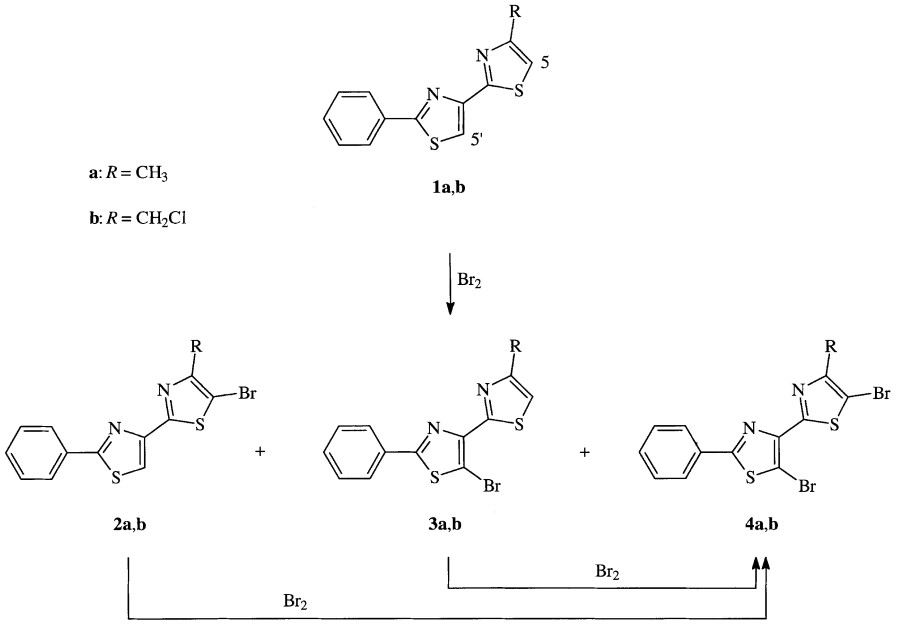


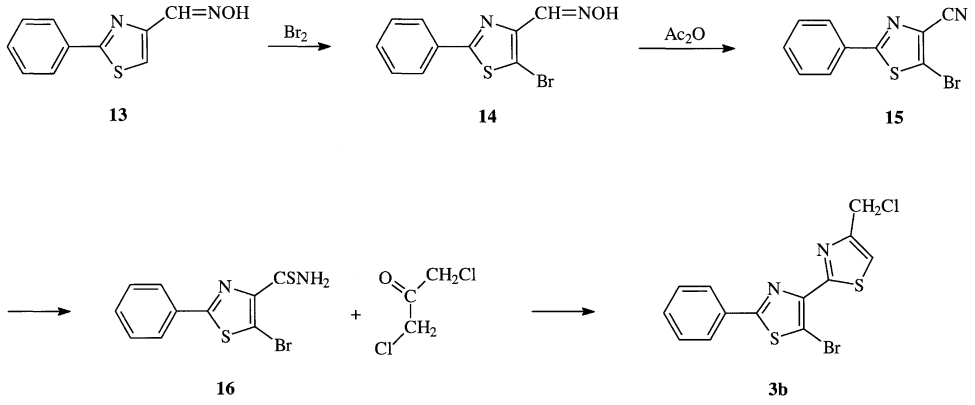
Scheme 1

and **3a**,**b** as well as to 5,5′-dibromo derivatives **4a**,**b**, respectively (Scheme 1). Further bromination of **2a**,**b** and **3a**,**b** results in **4a**,**b**.

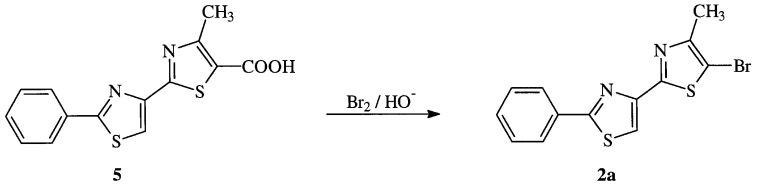
In the case of 2′-phenyl-4-chloromethyl-2,4′-bisthiazole (**1b**), the 5′-monobromoderivative **3b** exceeds the 5-monobromoderivative **2b** as a result of the preferential attack of the bromine in the thiazole ring A. The ^{1}H NMR spectrum of **3b** (*DMSO*-d_6) lacks the signal of the thiazole proton H5′ (at $\delta = 7.91$ ppm), whereas in that of the dibromoderivative **4b** the signals of both H5′ and H5 ($\delta = 7.15$ ppm) disappear.

Bromination of 2′-phenyl-4-methyl-2,4′-bisthiazole (**1a**) leads to an attack at position 5 of thiazole ring B and affords preferentially the 5-monobromoderivative **2a**. The ^{1}H NMR spectrum confirms the disappearance of the signal at $\delta = 6.97$ ppm belonging to the proton of the B thiazole ring, whereas the signal of the proton of the thiazole ring ($\delta = 7.9$ ppm) remains visible in the spectrum. In the IR spectra of dibromoderivatives **4a**,**b**, the corresponding νC5-H and νC5′-H absorption bands in the region of 3080–3100 cm^{-1} could not be detected. The preferential location of bromine attack in the case of 2′-phenyl-4-chloromethyl-2,4′-bisthiazole was also confirmed by the direct synthesis of 2′-phenyl-5′-bromo-4-chloromethyl-2,4′-bisthiazole (**3b**) starting from the oxime of 2-phenyl-4-formyl-thiazole (**13**) (Scheme 2).

3b obtained in this way is identical with the major compound resulting from bromination of 2′-phenyl-4-chloromethyl-2,4′-bisthiazole (**1b**). The preferential bromination of the thiazole ring B in the case of 2′-phenyl-4-methyl-2,4′-bisthiazole (**1a**) was confirmed by decarboxylative bromination of 2′-phenyl-5-carboxy-4-methyl-2,4′-bisthiazole (**5**) in alkaline medium with an equimolar quantity of bromine (Scheme 3) [7].



Scheme 2



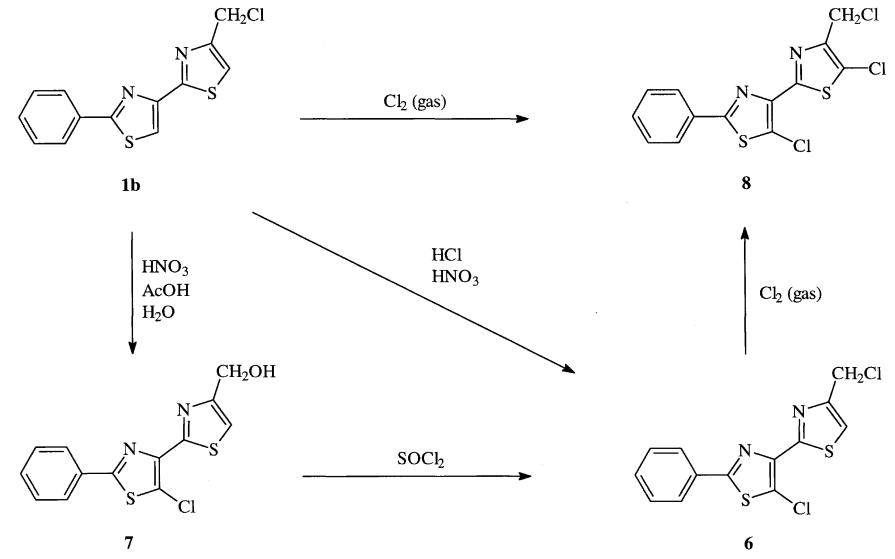
Scheme 3

The 5-monobromo derivative **2a** obtained in this way was identical with the major product formed by direct bromination of **1a** with an equimolar amount of bromine in acetic acid.

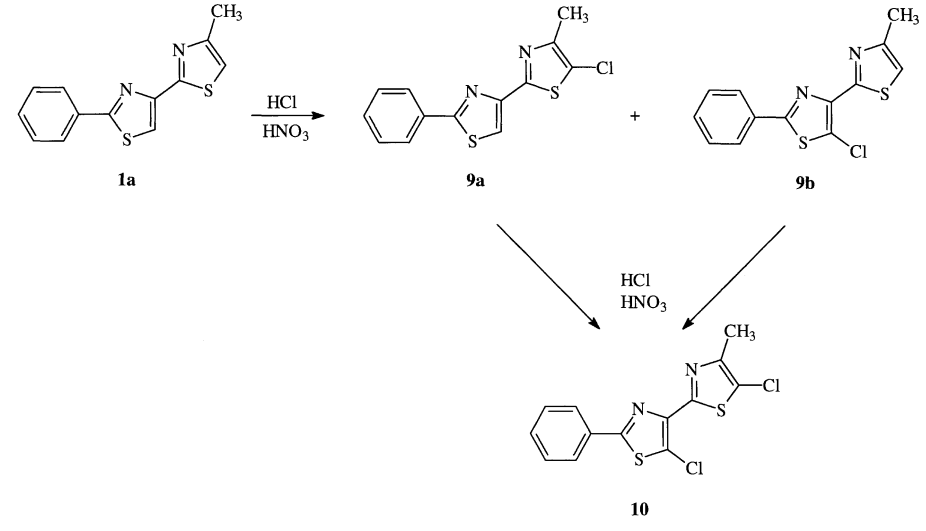
Chlorination of **1b** with a mixture of concentrated hydrochloric and nitric acid ($d = 1.42$) in equimolar amounts results in a selective electrophilic attack in position 5′ of thiazole ring A, giving 2′-phenyl-5′-chloro-4-chloromethyl-2,4′-bisthiazole (**6**). Hydrolysis of **1b** leads to 2′-phenyl-5′-chloro-4-hydroxymethyl-2,4′-bisthiazole (**7**), whose reaction with thionyl chloride affords the same compound **6** (Scheme 4).

By bubbling gaseous chlorine into an acetic solution of compound **1b** or **6**, 2′-phenyl-4-chloromethyl-5,5′-dichloro-2,4′-bisthiazole (**8**) was obtained. The ^{1}H NMR spectrum ($CDCl_3$) of **6** confirms the absence of the A thiazole proton ($\delta = 8.01$ ppm), whereas in the spectrum of **8** both signals of the thiazole rings A and B ($\delta = 7.37$ ppm) are absent. The ^{13}C NMR and mass spectra also confirm the structure of the 5,5′-dichloro derivative **8**.

Chlorination of 2′-phenyl-4-methyl-2,4′-bisthiazole (**1a**) with concentrated hydrochloric and nitric acid under the same conditions as used for **1b** yields a mixture of two isomeric monochloro derivatives (2′-phenyl-5-chloro-4-methyl-2,4′-bisthiazole (**9a**) and 2′-phenyl-5′-chloro-4-methyl-2,4′-bisthiazole (**9b**)) in a relative ratio of about 60:40. This-albeit low-regioselectivity of the reaction demonstrates again the higher reactivity of the position 5 of the thiazole ring B if substituted with a methyl group in position 4. Further chlorination of compounds



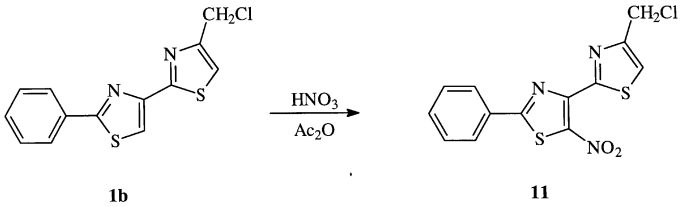
Scheme 4



Scheme 5

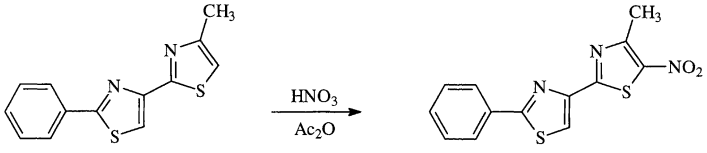
9a and **9b** with hydrochloric and nitric acid resulted in the formation of the dichloroderivative **10** (Scheme 5).

Concerning the nitration reaction of **1b** with nitric acid in acetic anhydride, only mononitration in position 5′ occured (Scheme 6). Further nitration of 2′-phenyl-4-chloromethyl-5′-nitro-2,4′-bisthiazole (**11**) was not successful, suggesting a deactivation of position 5 of the thiazole nucleus B induced by the presence of a nitro group in 5′. A steric effect may also be involved. The absence of the signal at $\delta = 8.01$ in the ^{1}H NMR spectrum ($CDCl_3$) of **11** is a proof of the nitration in that position.



1b **11**

Scheme 6



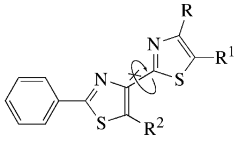
1a **12**

Scheme 7

Nitration of 2′-phenyl-4-methyl-2,4′-bisthiazole (**1a**) under the same conditions as used for **1b** leads to the 5-nitro isomer as a major product (Scheme 7). In its ^{1}H NMR spectrum ($CDCl_3$), the disappearance of the signal originating from the thiazole ring B ($\delta = 6.97$ ppm) was observed. The experimental results demonstrate the distinct influence of the methyl respectively chloromethyl-substituents in position 4, on the orientation of the electrophilic reagents in position 5 and 5′ of the 2,4′ bisthiazole system.

The electron donating methyl group increases the electronic density in position 5, promoting electrphilic attack at this position. In the case of the 4-chloromethyl derivative, the electron withdrawing inductive effect associated with its shielding steric effect for position 5 determines the preferential entry of electrophilic reagents in position 5′ of the thiazole ring A.

Compounds substituted in position 5′ of thiazole ring A demonstrate the existence of atropisomerism by a hindered rotation of the two thiazole rings about C^2-$C^{4'}$ (Fig. 1). Experimental evidence of this atropisomerism in the series of some 5′-substituted 2,4′-bisthiazole compounds was provided in the case of **3b** by ^{1}H NMR spectroscopy. The steric hindrance caused by the bromine atom in position 5′ results in an approximately perpendicular orientation of the two thiazole rings



R = CH_3, CH_2Cl; R^1 = Cl, Br, NO_2; R^2 = Cl, Br, NO_2

Fig. 1

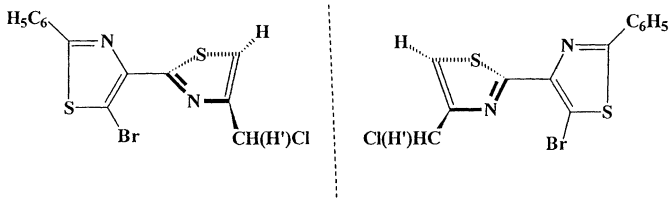


Fig. 2

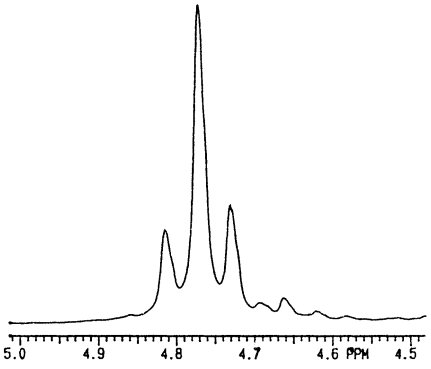


Fig. 3. ^{1}H NMR spectrum of **3b** (detail)

(Fig. 2). The C^2-$C^{4'}$ axis represents the chiral element of the molecule, leading to the possible existence of two enantiomers for **3b**. The chirality of the molecule induces diastereotopicity for the two protons of the chloromethyl group. The ^{1}H NMR spectrum of compound **3b** (Fig. 3) shows an overlapping AB system looking like a triplet for these protons. The signal exhibits a large geminal coupling constant ($J = 12.3$ Hz) and at the same time a splitting corresponding to a coupling with the proton in position 5.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM 400 NMR spectrometer (solvent: $CDCl_3$ or *DMSO*-d_6); δ values are given in ppm relative to internal *TMS*. The mass spectra were recorded at 70 eV on a Trio MS 1000 spectrometer. IR spectra were measured as KBr disks on a FT-IR-Nicolet 205 spectrophotometer. Melting points were measured with an electrothermal melting point apparatus and are uncorrected. All compounds gave satisfactory elemental analyses (C, H, N) The syntheses of compounds **1a**, **b**, **5**, and **13** have already been reported [1].

General procedure for the bromination of compounds **1a**,**b**, **2a**,**b**, **3a**,**b**.

0.001 mol of **1a**,**b**, **2a**,**b**, or **3a**,**b** were dissolved in a minimum amount of glacial acetic acid or acetic anhydride. To the ice cooled solution, 0.06 ml (0.0012 mol) bromine were added dropwise under stirring. After one hour, the solution was poured into water; the obtained precipitate was filtered and washed with water. Purification of **2a**,**b** and **3a**,**b** by preparative thin layer chromatography was carried out using silica gel and different proportions of hexan-ethyl acetate-chloroform.

2a: M.p.: 182°C; $C_{13}H_9BrN_2S_2$ (337.27); ^{1}H NMR: 8.1 (s, 1H, H5′), 2.25 (s, 3H, CH_3), 8.01 (m, 2H, C_6H_5 (*o*)), 7.47 (m, 3H, C_6H_5 (*m*, *p*)).

2b: M.p.: 153–154°C; $C_{13}H_8BrClN_2S_2$ (371.71); ^{1}H NMR: 8.01 (s, 1H, H5′), 4.82 (s, 2H, CH_2Cl), 8.03 (m, 2H, C_6H_5 (*o*)), 7.48 (m, 3H, C_6H_5 (*m*, *p*)).

3a: M.p.: 129°C; $C_{13}H_9BrN_2S_2$ (337.27); ^{1}H NMR: 6.97 (s, 1H, H5), 2.32 (s, 3H, CH_3), 8.01 (m, 2H, C_6H_5 (*o*)), 7.47 (m, 3H, C_6H_5 (*m*, *p*)).

3b: M.p.: 135°C; $C_{13}H_8BrClN_2S_2$ (371.71); ^{1}H NMR: 7.37 (s, 1H, H5), 4.79 (s, 2H, CH_2Cl), 8.03 (m, 2H, C_6H_5 (*o*)), 7.48 (m, 3H, C_6H_5 (*m*, *p*)).

4a: M.p.: 148–150°C (ethanol-acetic acid); $C_{13}H_8Br_2N_2S_2$ (416.17).

4b: M.p.: 178°C (ethanol-acetic acid); $C_{13}H_7Br_2ClN_2S_2$ (450.61).

2′-Phenyl-5-bromo-4-methyl-2,4′-bisthiazone (**2a**)

0.29 g (0.001 mol) of **5** were dissolved in 60 ml 5% NaOH at 60°C, and 0.06 ml (0.0012 mol) bromine were added. Immediately 15 ml conc. HCl were added and the obtained compound was crystallized.

Yield 65%; m.p.: 182°C (ethanol-acetic acid); $C_{13}H_9BrN_2S_2$ (337.27); ^{1}H NMR: 8.1 (s, 1H, H5′), 2.25 (s, 3H, CH_3), 8.01 (m, 2H, C_6H_5 (*o*), 7.47 (m, 3H, C_6H_5 (*m*, *p*)).

Oxime of 2-phenyl-5-bromo-4-formyl-thiazole (**14**)

2.05 g (0.01 mol) of **13** were dissolved in 20 ml of acetic acid. To the ice cooled solution, 0.6 ml (0.012 mol) bromine were added dropwise under stirring. After 30 minutes, the solution was poured into water; the obtained precipitate was filtered, washed with water, and crystallized.

Yield: 80%; m.p.: 182°C (ethanol); $C_{10}H_7BrN_2OS$ (283.16).

2-Phenyl-5-bromo-4-cyano-thiazole (**15**)

1 g (0.0036 mol) **14** was treated with 5 ml acetic anhydride and refluxed for one hour. After cooling, the precipitate was filtered, washed with water, and crystallized.

Yield: 50%; m.p.: 129°C (ethanol); $C_{10}H_5BrN_2S$ (265.2).

*2-Phenyl-5-bromo-4-thiocarbamido-thiazole (***16**)

0.5 g (0.0019 mol) **15** were dissolved in 10 ml absolute ethanol saturated with NH_3. H_2S was bubbled through the solution for 24 hours which then was boiled for 10 minutes. After cooling, the solution was poured into water; the resulting precipitate was filtered and crystallized.

Yield: 70%; m.p.: 132°C (ethanol); $C_{10}H_7BrN_2S_2$ (299.3).

2′-Phenyl-5′-bromo-4-chloromethyl-2,4′-bisthiazole (**3b**)

0.3 g (0.001 mol) of **16** were dissolved in the minimal amount of absolute ethanol and boiled for 1 hour after addition of 0.127 g (0.001 mol) of 1,3-dichloroacetone. After cooling, the solution was poured into water; the precipitate was filtered and crystallized.

Yield: 80%; m.p.: 135°C (acetic acid); $C_{13}H_8BrClN_2S_2$ (371.71); ^{1}H NMR: 7.37 (s, 1H, H5), 4.79 (s, 2H, CH_2Cl), 8.03 (m, 2H, C_6H_5 (*o*)), 7.48 (m, 3H, C_6H_5 (*m*, *p*)).

2′-Phenyl-5′-chloro-4-chloromethyl-2,4′-bisthiazole (**6**)

a) 0.29 g (0.001 mol) of **1b** were dissolved in 20 ml glacial acetic acid, and a mixture of 0.2 ml conc. HCl and 0.14 ml conc. HNO_3 63% ($d = 1.42$) was added. The solution was heated at 40°C for 10

minutes. After cooling, the precipitate was filtered, washed with water, and crystallized. The reaction may be also performed in acetic anhydride at room temperature.

Yield: 70%; m.p.: 153°C (ethanol-acetic acid); $C_{13}H_8Cl_2N_2S_2$ (327.25); ^{1}H NMR; 7.3 (s, 1H, H5), 4.9 (s, 2H, CH_2Cl), 8.1 (m, 2H, C_6H_5 (*o*)), 7.5–7.7 (m, 3H, C_6H_5 (*m*, *p*)).

b) 0.31 g (0.001 mol) of **7** were dissolved in 5 ml chloroform, and 3 ml thionyl chloride were added. After 30 minutes, the chloroform and the excess of thionyl chloride were removed by distillation; the remaining compound was crystallized.

Yield: 67% ; m.p.: 153–155°C (ethanol-acetic acid); $C_{13}H_8Cl_2N_2S_2$ (327.25).

2′-Phenyl-5′-chloro-4-hydroxymethyl-2,4′-bisthiazole (**7**)

0.29 g (0.001 mol) of **1b** were dissolved in 10 ml glacial acetic acid and then treated with 5 ml water and 5 ml HNO_3 ($d = 1.42$) and refluxed for 6 hours. After cooling, the precipitate was filtered, washed with water, and crystallized.

Yield: 80%; m.p.: 160 °C (ethanol); $C_{13}H_9ClN_2OS_2$ (308.80).

2′-Phenyl-4-chloromethyl-5,5′-dichloro-2,4′-bisthiazole (**8**)

0.29 g (0.001 mol) of **1b** or 0.327 g (0.001 mol) of **6** were dissolved in 10 ml acetic anhydride or glacial acetic acid. Chlorine was bubbled through the solution for 10 minutes. After 24 hours, the precipitate was filtered, washed with water, and crystallized.

Yield: 90% m.p.: 163°C (ethanol); $C_{13}H_7Cl_3N_2S_2$ (361.69); ^{1}H NMR: 4.8 (s, 2H, CH_2Cl), 7.9 (m, 2H, C_6H_5 (*o*)), 7.45–7.55 (m, 3H, C_6H_5 (*m*, *p*)); MS: $m/z = 360$, 325, 289, 222, 105.

2′-Phenyl-5-chloro-4-methyl-2,4′-bisthiazole (**9a**) *and 2′-Phenyl-5′-chloro-4-methyl-2,4′-bisthiazole* (**9b**)

0.11 g (0.00042 mol) of **1a** were dissolved in 15 ml acetic anhydride, and a mixture of 0.2 ml conc. HCl and 0.15 ml HNO_3 63% ($d = 1.42$) was added. After about 10 minutes, a precipitate was formed. It was filtered and washed with water. From the crude product, the isomers **9a** and **9b** were separated by preparative thin layer chromatography using silicagel and a mixture of heptane-ethylacetate = 7:3.

9a: Yield: 50%; m.p.: 178°C; $C_{13}H_9ClN_2S_2$ (292.81); ^{1}H NMR: 7.88 (s, 1H, H5′), 2.41 (s, 3H, CH_3), 7.98–8.02 (m, 2H, C_6H_5 (*o*)), 7.46–7.49 (m, 3H, C_6H_5 (*m*, *p*)).

9b: Yield: 30%; m.p.: 153°C; $C_{13}H_9ClN_2S_2$ (292.81); ^{1}H NMR: 2.18 (s, 3H, CH_3), 7.88–7.92 (m, 2H, C_6H_5 (*o*)), 7.48 (m, 4H, C_6H_5 (*m*, *p*), H5).

2′-Phenyl-5,5′-dichloro-4-methyl-2,4′-bisthiazole (**10**)

10 was obtained by the procedure described for **9a**, **b**, starting from **9a**.

Yield: 70%; m.p.: 190°C (ethanol-acetic acid); $C_{13}H_8Cl_2N_2S_2$ (327.25); ^{1}H NMR: 2.49 (s, 3H, CH_3), 7.90 (m, 2H, C_6H_5 (*o*)), 7.47 (m, 3H, C_6H_5 (*m*, *p*)).

2′-Phenyl-4-chloromethyl-5′-nitro-2,4′-bisthiazole (**11**)

0.292 g (0.001 mol) of **1b** were dissolved in 6 ml acetic anhydride, and 0.15 ml HNO_3 63% ($d = 1.42$) were added. After about 7 hours, a precipitate was formed. It was filtered, washed with water, and crystallized.

Yield: 80%; m.p.: 144°C (ethanol-acetic acid); $C_{13}H_8ClN_3O_2S_2$ (337.81); ^{1}H NMR: 7.70 (s, 1H, H5), 4.85–4.9 (s, 2H, CH_2Cl), 8–8.1 (m, 2H, C_6H_5 (*o*)), 7.5–7.6 (m, 3H, C_6H_5 (*m*, *p*)); MS: *m*/*z* = 337, 292, 189, 186, 154, 83, 77.

2′-Phenyl-4-methyl-5-nitro-2,4′-bisthiazole (**12**)

0.260 g (0.001 mol) of **1a** were dissolved in **15** ml acetic anhydride, and 0.12 ml HNO_3 63% ($d = 1.42$) were added. After 24 hours, a precipitate was formed. It was filtered, washed with water, and crystallized.

Yield: 60%; m.p.: 105–107°C (ethanol-acetic acid); $C_{13}H_9N_3O_2S_2$ (303.37); ^{1}H NMR: 7.30 (s, 1H, H5′), 2.65 (s, 3H, CH_3), 8–8.05 (m, 2H, C_6H_5 (*o*)), 7.5–7.6 (m, 3H, C_6H_5 (*m*, *p*)).

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