Compounds with a benzothiazole nucleus in their structure are of interest since they possess significant biological properties. For instance, the aroylbenzothiazole I exhibits a hypolipemic property,\(^1\) while thiazolo [5,4-b] acridine II is known for its intercalating effect with DNA\(^2\) (Chart 1).

Strategies developed for the synthesis of such compounds often include construction of a thiazole nucleus. In order to diversify the synthetic approaches for these, we planned to access to the benzothiazole moiety through a [4+2] cycloaddition reaction between a thiazole analogue of o-quinodimethane (o-QDM) and an appropriate dienophile. In our previous papers,\(^3,4\) we described the use of polybrominated derivatives of 4,5-dimethylthiazole\(^1\) as precursors for thiazole o-QDMs\(^2\) (Chart 2). Although the generation and Diels–Alder trapping of the latter proceeded under mild conditions to afford [4+2] cycloadducts in good yields, the relative instability of polybromo derivatives\(^1\) would present some drawbacks for valuable synthetic applications.

In continuation of our investigation towards the use of thiazole o-QDMs to afford aromatized cycloadducts with appropriate dienophiles, we planned to develop the strategy devised by Magnus et al.\(^5\) Thus, when a 2-methyl-3-iminodione is treated with a suitable electrophile in the presence of a tertiary amine, the resulting iminium salt is converted to an indolo o-QDM after a proton loss. Then, the generated o-QDM undergoes an intramolecular Diels–Alder reaction. This strategy was extensively explored in the total synthesis of racemic indole alkaloids such as aspidospermidine,\(^7,8\) 16-methoxytabersonine,\(^9\) kopsanone and 10,22-dioxokopsane,\(^10,11\) and staurosporinone.\(^12\) This methodology is illustrated in Chart 3.

More recently, such imine tautomerism was extended to the generation of a pyrrole o-QDM\(^13\) which also underwent an intramolecular Diels–Alder reaction. The use of an electrophile was not necessary for the imine tautomerism which is initiated under thermal conditions. The o-QDM obtained gave, with dimethyl fumarate, a [4+2] cycloaddition providing the tetrahydro cycloadduct which constitutes, to our knowledge, the only example of intermolecular Diels–Alder trapping (Chart 4).

**Key words** thiazole; o-quinodimethane; Diels–Alder; alkyne; quinone

**Chart 1**

\[\begin{align*}
\text{I} & : \text{Aroylbenzothiazole} \\
\text{II} & : \text{Thiazolo [5,4-b] Acridine}
\end{align*}\]

**Chart 2**

\[\begin{align*}
\text{I} & \xrightarrow{\text{NBS}} \text{II} \\
\text{X} & = \text{H or Br}
\end{align*}\]

**Chart 3**

\[\begin{align*}
\text{Chart 3}
\end{align*}\]

**Chart 4**

\[\begin{align*}
\text{Chart 4}
\end{align*}\]

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In this context, we decided to evaluate the suitability of an iminothiazole derivative to afford directly aromatized cycloadducts from acetylenic or quinonoid dienophiles in the presence of an electrophile.

Results and Discussion

Thus, the treatment of 5-formyl-4-methylthiazole with benzylamine in the presence of magnesium sulfate gave the imine 3 as a single (E)-stereoisomer (Chart 5). Determination of the configuration of 3 was made by $^1$H-NMR Nuclear Overhauser Effect Difference experiments. First, irradiation at 8.50 ppm (imine proton) gave two responses: one on the methyl signal and the other one on the methylene group. On the other hand, irradiation of the methylene at 4.80 ppm afforded a response on the imine proton.

Then, the imine 3 was treated with methylchloroformate to afford the acyl iminium salt which gave the thiazole $o$-QDM 4 after proton removal. Then, the solution of 4 was reacted in situ with dienophiles to afford directly aromatized cycloadducts through a spontaneous and unprecedented elimination of N-carbomethoxybenzylamine (Chart 6). In the case of the unsymmetrical dienophiles, high regioselectivity was observed from ethyl propynoate or juglone 8a while regiospecificity was obtained from bromojuglones 8b and 8c. Moreover, starting from juglone 8a or its 3-bromo derivative 8c, we obtained the same 1,9-regiosomer 9a, while 2-bromojuglone 8b gave the opposite 1,6-regiosomer 9b. Assignment of the structure for compound 6 was made by comparison of its physical and $^1$H-NMR data with those of an authentic sample. On the other hand, the 1,9- and 1,6-regiosomers, 9a and 9b respectively, differ by $^1$H-NMR chemical shifts of H-4 and H-11. Their regiochemistry was previously assigned by a 2D $^1$H-$^1$C HMBC technique performed on the acetyl derivative of 9a.

The observed regioselectivity is discussed in connection with the results of semi-empirical PM3 calculations. In the trapping of $o$-QDM 4 with unsymmetrical dienophiles, we have considered the frontier molecular orbital (FMO) model using HOMO (diene) and LUMO (dienophiles) due to the calculation of their corresponding energies. Thus, for all the reactions with normal electron demand, the $\Delta E$ are lower than those of the reactions with inverse electron demand. Calculations of the FMO coefficients for $o$-QDM 4 indicate that the coefficient values are very close. So, the high regioselectivity observed with ethyl propynoate and juglone 8a or the regiospecificity obtained with the bromo quinones 8b or 8c cannot be explained by FMO considerations (Chart 7).
with Acetylenic Dienophiles

To a stirred solution of imine 3 (0.108 g, 0.5 mmol) and the corresponding dienophile (1 mmol) in toluene (8 ml) were added ethylidniosopropylamine (0.19 g, 1.5 mmol) and methylchloroformate (0.14 g, 1.5 mmol) in toluene (2 ml). The mixture was refluxed for 30 min. After cooling to room temperature and filtration, the filtrate was concentrated under a vacuum. The orange oil obtained was cooled and washed with petroleum ether. The residue was purified by column chromatography on silica gel eluting with EtOAc/petroleum ether (5:5) as the eluent.

5.6-Bis(methoxycarbonyl)benzothiazole (5) Trapping 4 with dimethyl acetylenedicarboxylate afforded the directly aromatized product 5 in 73% yield identical with a sample of 5 previously prepared. The primary cycloadduct was not detected by TLC or by $^1$H-NMR.

6-Ethoxycarbonylbenzothiazole (6) Starting with ethyl propynoate as the diene, its cycloaddition to 4 gave an unseparable mixture of compound 6 and N-carboxybenzothiazene eliminated from the primary adduct. To remove the carbamate from the reaction mixture, the latter was stirred at room temperature for 24 h with a 33% solution of NaHCO$_3$ and then added until a neutral pH was attained and the solution was extracted with 2×8 ml of Et$_2$O. The organic layer was washed with water, dried over MgSO$_4$ and concentrated under a vacuum. The white solid obtained after recrystallization from petroleum ether was compound 6 in 88% yield; mp 1620 cm$^{-1}$ 60 °C (lit. 14) 61—62 °C). IR (KBr): $\delta$ 9.12 (s, 1H, H-2), 8.80 (dd, 1H, J=1.4, 0.7 Hz, H-7), 8.19 (dd, 1H, J=8.6, 1.4 Hz, H-5), 8.40 (4H, J=7.1 Hz, CH$_3$). 1H-NMR (CDCl$_3$, 300 MHz): $\delta$ 10.75 (s, 1H, H-2), 8.75 (d, 1H, J=8.3 Hz, H-8).

6.9-Dihydroxyanthra[2,3-b]thiazole-5,10-dione (7) To a stirred solution of imine 3 (0.108 g, 0.5 mmol) and 5,8-dihydroxynaphthoquinone (0.094 g, 0.5 mmol) in toluene (6 ml) were added ethylidniosopropylamine (0.19 g, 1.5 mmol) and methylchloroformate (0.14 g, 1.5 mmol) in toluene (2 ml). The reaction mixture was refluxed for 1 h, cooled at room temperature and evaporated to dryness. The residue was dissolved in EtOAc and adsorbed on about ten times its weight of silica gel by evaporating the solvent. This loaded adsorbent was then added to the top of a conventional column chromatography on silica gel and eluted with EtOAc/petroleum ether (4/6). Compound 7 was obtained in an overall yield of 53%. It is identical with a sample prepared according to reference.

9-Hydroxyanthra[2,3-b]thiazole-5,10-dione (9a) Compound 9a was obtained as a single 1,9-regiosomer from 8a or 8c according to the procedure described above, in 50% and 28% yields respectively; mp $>$300°C. $^1$H-NMR (CDCl$_3$): $\delta$ 1670, 1645 cm$^{-1}$; $\delta$ 12.50 (s, 1H, OH), 9.75 (s, 1H, H-2), 9.17 (s, 1H, H-11), 8.77 (s, 1H, H-4), 7.75 (m, 2H, H-6, H-7), 7.45 (d, 1H, J=8.3 Hz, H-8).

6-Hydroxyanthra[2,3-b]thiazole-5,10-dione (9b) Compound 9b was obtained as a single 1,8-regiosomer from 8b according to the procedure described above, in 34% yield; mp $>$300°C. $^1$H-NMR (CDCl$_3$): $\delta$ 1620 cm$^{-1}$ 300 MHz): $\delta$ 12.50 (s, 1H, OH), 9.75 (s, 1H, H-2), 9.06 (s, 1H, H-11), 8.75 (s, 1H, H-4), 7.80 (m, 2H, H-8, H-9), 7.40 (d, 1H, J=8.3 Hz, H-8).

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References and Notes

3) The primary cyanoadduct was not detected by TLC or by $^1$H-NMR.