Generation of a Thiazole *o*-Quinodimethane from an Imino Derivative and Its Intermolecular Diels–Alder Trapping with Alkynes or Quinones

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(*E*)-5-(*N*-Benzylformimidoyl)-4-methylthiazole 3 was prepared in good yield from 5-formyl-4-methylthiazole and benzylamine. Treatment of 3 with methylchloroformate in the presence of ethyldiisopropylamine in refluxing toluene has generated *o*-quinodimethane (*o*-QDM) 4. *In situ* trapping of the latter with acetylenic or quinonoid dienophiles directly afforded the aromatized products 5, 6, 7 and 9. An unprecedented elimination of *N*-carbomethoxybenzylamine occurred from the primary dihydro or tetrahydro cycloadducts. Starting from ethylpropynoate or juglone 8a, the single regioisomer 6 or 9a was obtained, while when using 2- or 3-bromojuglone 8b or 8c the reaction regiospecifically gave 9a or 9b. Calculations by the semi-empirical method PM3 indicated that the regiochemistry observed cannot be predicted by the frontier orbital coefficients theory for a concerted electrocyclic reaction, but is better explained by an attack of the nucleophilic end of diene 4 on the more electron deficient carbon of the dienophiles.

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

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**[5] 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.*[6] Thus, when a 2-methyl-3-iminoindole 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).

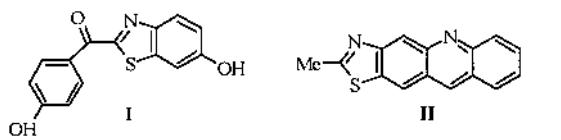

Chart 1

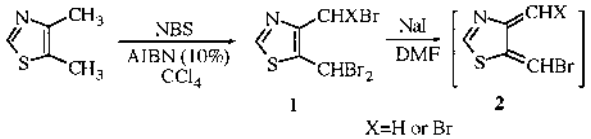

Chart 2

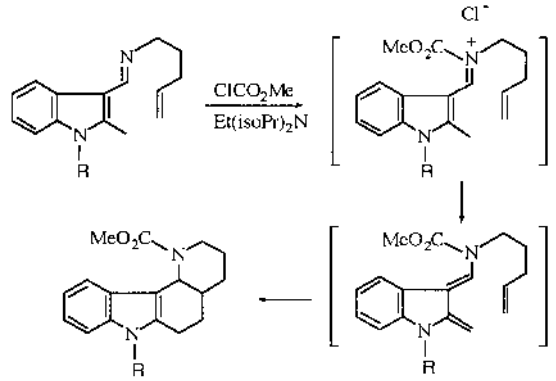

Chart 3

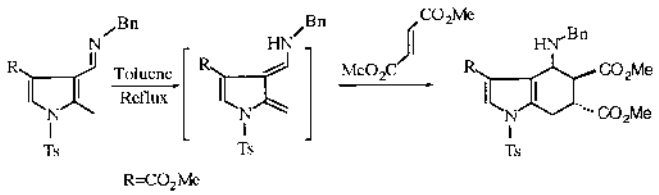

Chart 4

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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-regioisomer **9a**, while 2-bromojuglone **8b** gave the opposite 1,6-regioisomer **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.[4,14] On the other hand, the 1,9- and 1,6-regioisomers, **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–^{13}C HMBC technique performed on the acetyl derivative of **9a**.[3]

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 ΔE 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).

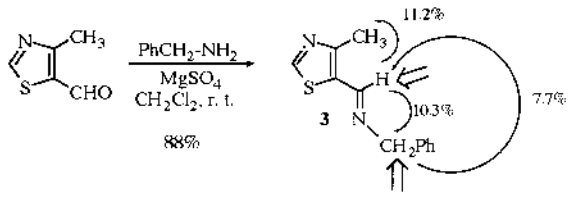

Chart 5

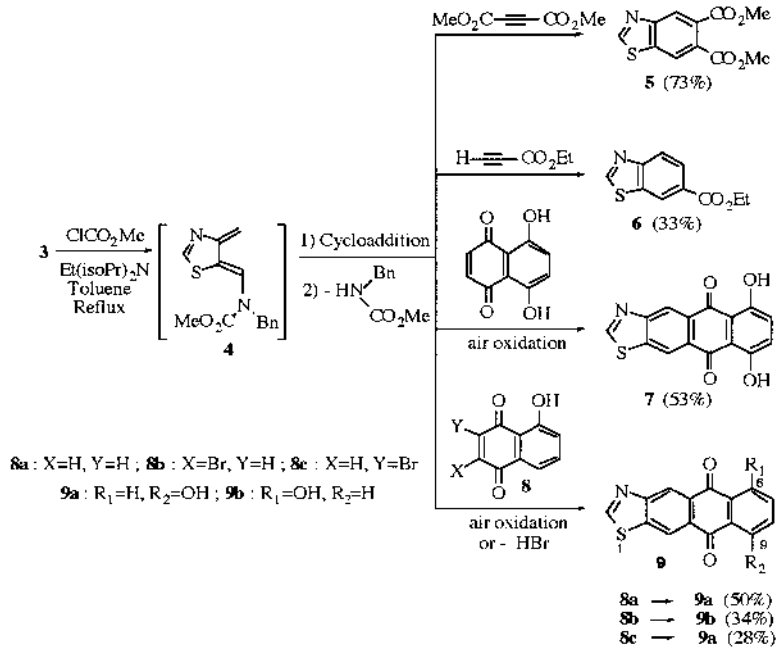

Chart 6

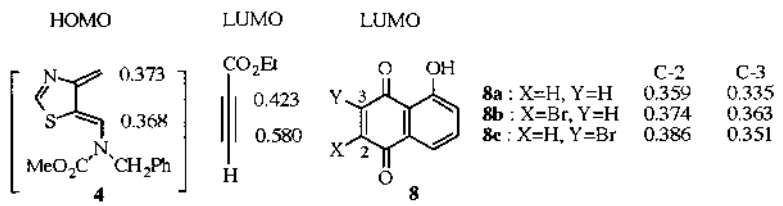

Chart 7

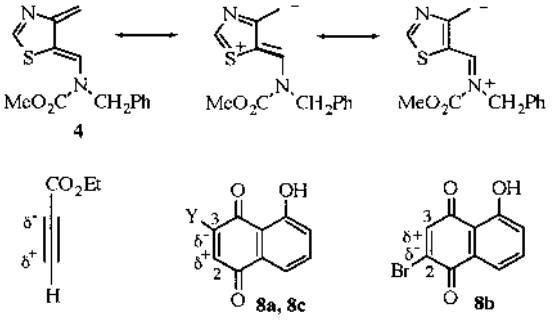

Chart 8

But, if we consider *o*-QDM **4** as a diene carbamate, the observed regioselectivity may result, in these cases, from an initial attack of the nucleophilic end of diene **4** on the more electron deficient carbon C-3 of ethyl propynoate, the C-2 of quinones **8a** or **8c** or the C-3 of 2-bromojuglone **8b** (Chart 8).

In conclusion, the generation of an *o*-QDM *via* the tautomerism of an imino derivative is a method generally employed in intramolecular Diels–Alder reactions. Its usefulness in intermolecular [4+2] cycloadditions is illustrated here by the preparation of a thiazole *o*-QDM and by its trapping with acetylenic or quinonoid dienophiles to directly provide aromatized cycloadducts through an original elimination of *N*-carbomethoxybenzylamine. Moreover, this procedure presents an advantage over that using polybromo derivatives to generate *o*-QDMs due to the stability of the benzylimine precursor and to the high regioselectivity or regiospecificity observed with the unsymmetrical dienophiles used. The regiochemistry observed with the latter and *o*-QDM **4** cannot be explained by the frontier orbital coefficients for a concerted electrocyclic reaction, but it is better accomodated by the polarity of the diene and the dienophiles.

Experimental

Melting points were measured in a Büchi apparatus (capillary tube). The infrared (IR) spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. The ^{1}H-NMR spectra were recorded at 300 MHz on a Bruker AM 300 apparatus. Chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) as an internal standard. Coupling constants (J) values are given in Hz. Column chromatography was carried out with silica gel (60 Å, 35—70 μm). Elemental analysis was done at the Centre de Microanalyse at Solaize, France. The energies and coefficients of the molecular frontier orbitals were calculated from the MOPAC SYBYL program on an IBM Risk 6000 workstation.

5-Formyl-4-methylthiazole was prepared according to the procedure described by White and Spencer.[15] 2-Bromo-5-hydroxynaphthoquinone **8b** was prepared according to Grunwell *et al*.,[16] while 3-bromo-5-hydroxynaphthoquinone[17] **8c** was obtained by treating juglone **8a** with bromine in glacial acetic acid. Quinone **8c** was recrystallized from acetone before use.

(*E*)-5-(*N*-Benzylformimidoyl)-4-methylthiazole (3) To a stirred solution of 5-formyl-4-methylthiazole (0.7 g, 5.5 mmol) in CH_2Cl_2 (15 ml), were added $MgSO_4$ (1.3 g, 11 mmol) and then a solution of benzylamine (0.9 ml, 8.25 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred at room temperature for 24 h. After elimination of $MgSO_4$ by filtration, the filtrate was evaporated to dryness under a vacuum. The orange oil obtained was cooled at −18 °C until crystallization. Then, the solid was separated by filtration and washed with petroleum ether. Compound **3** was obtained in 88% yield (1.06 g); mp 76 °C (petroleum ether). IR (KBr): ν 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.70 (s, 1H, H-2), 8.50 (s, 1H, CH=N), 7.30 (m, 5H, H aromat.), 4.80 (s, 2H, CH_2), 2.60 (s, 3H, CH_3). *Anal*. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.38; H, 5.55; N, 12.79; S, 14.96.

General Procedure for the Generation of *o*-QDM 4 and Its Trapping 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 ethyldiisopropylamine (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 and purified by column chromatography on silica gel using 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.[3] The primary cycloadduct was not detected by TLC or by ^{1}H-NMR.

6-Ethoxycarbonylbenzothiazole (6) Starting with ethyl propynoate as the dienophile, its cycloaddition to **4** gave an unseparable mixture of compound **6** and *N*-carbomethoxybenzylamine eliminated from the initial 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 HBr/CH_3COOH (1 ml). Then, after cooling to 0 °C, a 10% solution of $NaHCO_3$ was added until a neutral pH was attained and the solution was extracted with 2×8 ml of Et_2O. 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 33% yield; mp 60 °C (lit.[14] 61—62 °C). IR (KBr): ν 1690, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.12 (s, 1H, H-2), 8.70 (dd, 1H, J=1.4, 0.7 Hz, H-7), 8.19 (dd, 1H, J=8.6, 1.4 Hz, H-5), 8.15 (dd, 1H, J=8.6, 0.7 Hz, H-4), 4.40 (q, 2H, J=7.1 Hz, CH_2), 1.40 (t, 3H, J=7.1 Hz, CH_3).

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 ethyldiisopropylamine (0.19 g, 1.5 mmol) and methylchloroformate (0.14 g, 1.5 mmol) in toluene (2 ml). Then, 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.[3]

9-Hydroxyanthra[2,3-*b*]thiazole-5,10-dione (9a)[3] Compound **9a** was obtained as a single 1,9-regioisomer from **8a** or **8c** according to the procedure described above, in 50% and 28% yields respectively; mp >300 °C. IR (KBr): ν 1670, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz, 70 °C): δ 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)[3] Compound **9b** was obtained as a single 1,6-regioisomer from **8b** according to the procedure described above, in 34% yield; mp >300 °C. IR (KBr): ν 1670, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 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

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