DIELS-ALDER REACTIONS OF 1-DIMETHYLAMINO-1-AZA-1,3-DIENES WITH BENZO[*b*]THIOPHENE-4,7-QUINONES

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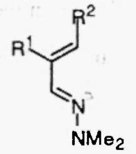
Abstract: The cycloaddition reactions of 1-dimethylamino-1-azabuta-1,3-dienes with benzo[*b*]thiophene-4,7-quinones substituted at 2- and 2,3-positions have been investigated. The reactions afforded thienoquinolinequinones or mixture of regioisomeric thienoquinolinequinones depending upon the substituents of the partners. The regiochemistry of the cycloadditions are in accord with the HOMOdiene/LUMOdienophile interactions.

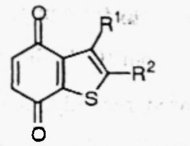
Introduction

The Diels-Alder reactions of 1-dimethylamino-1-aza-1,3-dienes with heterocyclic quinones represent an important and general strategy for the synthesis of fused *N*-heterocyclic quinones (1). A noteworthy feature of these cycloadditions is the relative high regioselectivity which could be predicted by FMO interactions. Despite the biological relevance of thiophen-containing compounds (2-6) and the facile access to benzo[*b*]thiophene-4,7-quinones (7-10) very few papers have adressed the [4+2] cycloaddition of these *S*-heterocyclic quinones with 1-aza-1,3-dienes. To date, we have reported the synthesis of the antiprotozoal active thienoquinolinquinones **8** and **9** *via* cycloaddition of quinones **4** and **5** with the corresponding 1-azadienes **1** and **2** (6). Most recently, Jackson and co-workers (11) have described the synthesis of a thiophene analogue of the antibiotic kuanoniamine A, through thienoquinolinquinone **10** prepared from azadiene **1** and quinone **6**.



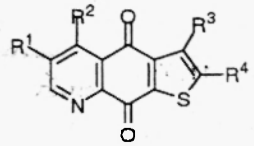
1-3

	R¹	R²
1	H	Me
2	Me	H
3	Me	Me



4-7

	R¹	R₂
4	H	H
5	Me	CO₂Me
6	H	CO₂Me
7	NHAc	CO₂Me



8-12

	R¹	R²	R³	R⁴
8	H	Me	H	H
9	Me	H	Me	CO₂Me
10	H	Me	H	CO₂Me
11	Me	H	H	CO₂Me
12	Me	H	NHAc	CO₂Me

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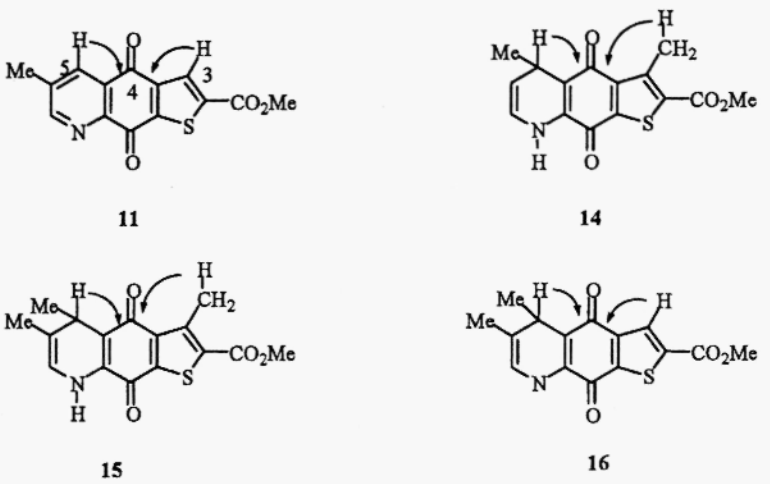
This communication describes results on the Diels-Alder cycloaddition reactions of 1-azadienes with benzo[*b*]thiophene-4,7-quinones. The results would provide information on the reactivity and regioselectivity of the cycloaddition and offer a facile entry into the thieno[3,2-*g*]quinolinequinones.

Results

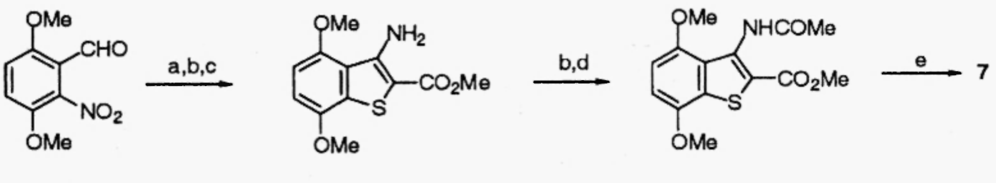
To know the influence of the substituents of the partners on the regioselectivity of the cycloadditions, dienes **1-3** and dienophiles **5-7**, were selected for this initial study. Benzo[*b*]thiophene-4,7-quinones **5** and **6**, prepared by oxidative deprotection of the corresponding dimethylethers (9), were reacted with azadiene **2** in dichloromethane under aerial conditions. In both cases thienoquinolinquinone **9** and **11** (12) were obtained as the sole regioisomer (Table 1, entries 1 and 2) in 75 and 70% yield, respectively (11).



11 **14** **15** **16**

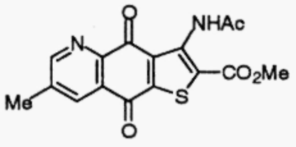
Figure 1. $^{n}J_{CH}$ correlations for compounds **11-16**

The relative location of the heterocyclic rings on the quinone nucleus for compounds **9** and **11** was assigned on the basis of the HMBC spectrum of **11**. The quaternary carbon at δ 178.3 ppm (C-4) showed $^{3}J_{CH}$ correlations with the protons at δ 8.29 (C-3) and 8.36 ppm (C-5) (Fig. 1). Quinone **7**, prepared recently in our laboratory from 2,5-dimethoxy-6-nitrobenzaldehyde according to Scheme 1 (13), was reacted with diene **2** in dichloromethane under aerial conditions.

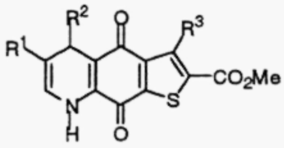


Scheme 1. *Reagents*: a) NH$_2$OH, NaOH, EtOH; b) Ac$_2$O, reflux; c) HSCH$_2$CO$_2$Me, KOH, DMF; d) HCl conc., MeOH, reflux; e) CAN, MeCN-H$_2$O

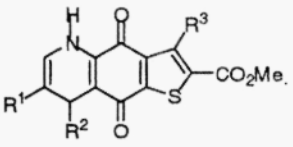
Cycloaddition reaction of quinone **7** with diene **2** gave a mixture of regioisomeric thienoquinolinquinones **12** and **13** in 65% yield and the ratio of the two regioisomers has been determined by relative integration of the NH protons (δ 9.26 and 9.46 ppm) (Table 1, entry 3). The regioisomers were purified by preparative TLC and the structure of the major regioisomer **12** was tentatively assigned on the basis of the regiochemistry of the reaction of diene **2** with quinone **6**.



13



14-16



17-19

	R^1	R^2	R^3
14,17	H	Me	Me
15,18	Me	Me	Me
16,19	Me	Me	H

Next the cycloaddition of diene **1** with quinone **5** was studied. Taking into account reports on the competitive addition reactions of dimethylamine with cycloaddition reactions of diene **1** with quinone **6** and thiazoloquinolinquinones (11,14) the reaction of **1** with **5** was carried out in acetonitrile-acetic anhydride under aerial conditions. The reaction afforded a mixture of dihydrothienoquinolinquinones **14** and **17** (Table 1, entry 4) and the ratio of the regioisomers was determined by relative integration of the vinyl protons at C-6 (δ 4.95 and 5.22 ppm). The major regioisomer **14** was isolated by preparative TLC and the structure was established by HMBC correlations (Fig. 1).

We have also examined the cycloaddition reaction of 1-dimethylamino-3,4-dimethyl-1-aza-1,3-butadiene **3** with quinones **5** and **6**. Azadiene **3** was prepared in 90% yield by condensation of 1,1-dimethylhydrazine with *trans*-2-methyl-2-butenal. The reaction of quinone **5** conducted in dichloromethane under aerial conditions afforded a mixture of dihydrothienoquinolinquinones **15** and **18** in 82% yield (Table 1, entry 5) together trace amounts of amination products (TLC).

The ratio of the regioisomers **15** and **18** was determined by integration of the vinyl protons at C-7 (δ 5.97 and 6.10 ppm). Recrystalization of the mixture **15** + **18** from methanol left pure the major regioisomer **15** (15). The structure of **15** was established by $^{3}J_{CH}$ and $^{4}J_{CH}$ correlations of the quaternary carbon C-4 at δ 181.3 ppm with the proton at δ 3.58 ppm (C-5) and the protons of the methyl group at δ 2.88 ppm (Fig. 1).

The reaction of diene **3** with quinone **6** carried out under aerial conditions afforded a complex mixture where regioisoimers **16** and **19** and their corresponding thienoquinolinquinones were detected by ^{1}H NMR. Nevertheless, when the cycloaddition of **3** with **6** was performed under nitrogen atmosphere a mixture of regioisomers **16** + **19** was obtained in 65% yield (Table 1, entry 6). The major regioisomer **16** was purified by washing the crude with methanol and the structure was established by HMBC correlations (Fig. 1).

Table 1. Diels-Alder reaction of azadienes **1-3** with quinones **5-7**

Entry	Azadiene	Quinone	Yield (%)	Products	Ratio
1	**2**	**5**	75	**9**	-
2	**2**	**6**	70	**11**	-
3	**2**	**7**	65	**12 + 13**	2:1
4	**1**	**5**	47	**14 + 17**	2:1
5	**3**	**5**	82	**15 + 18**	4:1
6	**3**	**6**	65	**16 + 19**	4:1

Discussions

The results indicate that the cycloaddition of 1-dimethylamino-1-azabutadienes **1-3** with benzo[*b*]thiophene-4,7-quinones **5-7** occurs under a regioselective manner to give thienoquinolinquinones or dihydrothienoquinolinquinones depending upon the substituent at 4-position in the 1-azadienes. Calculations of the primary and secondary HOMO coefficients of dienes **1-3** show that the HOMO is heavily concentrated on the C-2 and C-4. For quinones **5-7** the calculations indicate a small difference between the primary LUMO coefficients at C-5 and C-6 and a relative large difference between those at C-4 and C-7.

These facts lead to the prediction that the favored regioisomer in the cycloadditions probably is generated through a transition state allowed by primary and secondary orbital interactions. In Figure 2 are shown examples of primary and secondary HOMO-LUMO coefficients for compounds **2**, **3**, **6**, and **7** performed by semiempirical calculations (16).

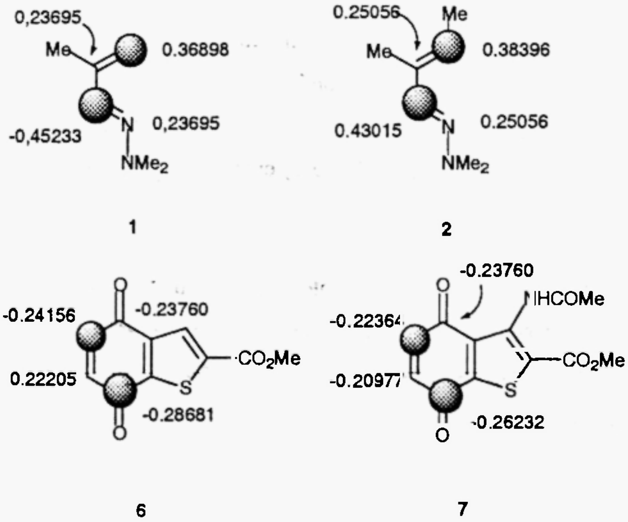


Figure 2. HOMO-LUMO eigenvector coefficients for compounds **2**, **3**, **6**, and **7**

Conclusions

The Diels-Alder cycloaddition reactions between 1-azadienes and benzo[*b*]thiophene-4,7-quinones are regiocontrolled providing access to thieno[3,2-*g*]quinolinequinones derivatives. The regioselectivity of these cycloadditions depends on the substituents of the partners and the structure of the favored regioisomers is predicted by FMO interactions. Further studies on the scope of these cycloaddition and antiprotozoan activity of thieno[3,2-*g*]quinolinequinones derivatives are ongoing in our laboratory.

Acknowledgement

Financial support is gratefully acknowledged to FONDECYT (Grant 8980003 and 2990099).

References and Notes

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(12) Selected data for compound **11**: yellow crystals mp> 250 °C; IR. ν_{max} (cm^{-1}) 2950, 1725, 1610,1620; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.89 (d, 1H, *J* = 2.1 Hz, H-5), 8.36 (d, 1H, *J* = 2.1 Hz, H-7), 8.29 (s, 1H, H-3), 3.99 (s, 3H, CO_2Me), 2.57 (s, 3H, 6-CH_3);^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.3, 176.5, 161.2, 155.2, 149.0, 147.0, 141.7, 141.3, 139.3, 135.3, 131.1, 130.0, 53.2, 19.0; elemental analysis: $C_{14}H_9N O_4S$; calcd. C,58.53; H, 3.13; N, 4.87; S, 11.15; found: C, 58.82; H, 2.98; N, 4.10; S, 10.99.

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(15) Selected data for compound **15**: navy blue crystals; as a result of its thermal instability, a satisfactory mp for this compound could not be obtained; IR. ν_{max} (cm^{-1}) 3400, 1710, 1656; ^{1}H NMR (CDCl$_3$, 200 MHz): δ 6.65 (br s, 1H, NH), 5.97 (dq, 1H, *J* = 5.8; 1.4 Hz, H-7), 3.92 (s, 3H, CO$_2$Me), 3.58 (q, 1H, *J* = 6.6 Hz, H-5), 2.88 (s, 3H, 3-Me), 1.77 (d, 3H, *J* = 1.4 Hz, 6-Me), 1.15 (d, 3H, *J* = 6.6 Hz, 5-Me); ^{13}C NMR (CDCl$_3$, 50 MHz): δ 181.3, 176.0, 162.3, 147.2, 141.5, 140.0, 138.8, 134.9, 118.4; 118.0, 113.2, 52.5 30.7, 20.4, 18.4, 14.6; elemental analysis $C_{16}H_{15}NO_4S$; calcd. C, 60.56; H, 4.73; N, 4.42; S, 10.09; found: C, 59.99; H, 4.93; N, 4.21; S, 10.16.

(16) The HOMO and LUMO eigenvector coefficients were performed using the semiempirical PM3 method implemented in the Spartan package. SPARTAN version 5.1.3, Wavefunction Inc., Von Karman Ave. 370, 18401 Irvine, CA, 1999.

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