5-Alkenylthiazoles as In-Out Dienes in Polar [4+2] Cycloaddition Reactions

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5-Alkenyl-2-aminothiazoles react as in-out dienes with a wide range of electron-poor dienophiles leading to the corresponding cycloaddition products in good to excellent yields. The [4+2] cycloadditions of 5-alkenyl-2-aminothiazoles can be classified as site-selective since only the diene moiety including the formal C-C double bond of the heterocycle and that of the side-chain is involved. Calculations of the HOMO energy values of representative 5-alkenyl-2-aminothiazoles are disclosed. The cycloadditions are *endo*-selective with *N*-phenylmaleimide or maleic anhydride and regioselective when the reactions are conducted with non symmetrical dienophiles. Completely oxidized cycloadducts are obtained in the reactions of 5-alkenyl-2-aminothiazoles with naphthoquinone or DMAD. Unexpectedly, the reactions with PTAD are not stereospecific. A mechanism placed at the concerted/stepwise boundary is proposed.

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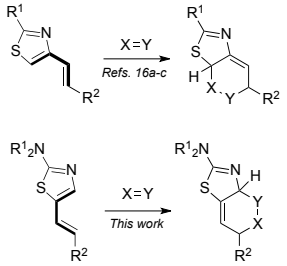
Introduction

The 1,3-thiazole ring plays an important role in nature and it is present in a high number of molecules with powerful biological activities.[1] For instance, thiazolo[5,4-*b*]pyridin-5(4*H*)-one derivatives are efficient HIV integrase strand transfer inhibitors,[2] whereas 2-aminothiazole derivatives are inhibitors of cdk5/p25 and thus, potentially useful for the treatment of Alzheimer's disease and other neurodegenerative disorders.[3] Likewise, 5-arylidene-2-imino-4-thiazolidinones exhibit significant levels of anti-inflammatory activity.[4] Recently, Kurth and coworkers have reported the synthesis of triazolobithiazole derivatives with cystic fibrosis corrector activity.[5] Because of the wide spectrum of activity shown by the thiazole moiety, the design of amenable synthetic approaches to new and complex thiazole derivatives is still an attractive challenge and a focus of great interest.

The Diels-Alder reaction is one of the most intensively studied organic processes, which affords six-membered products via carbon-carbon bond making.[6] The Diels-Alder reaction continues to play a central role in the construction of a large number of molecules of biological interest.[7] Synthetic plans that incorporate this reaction depend on our ability to effectively predict the relative reactivities of dienes and dienophiles.[7a] Thus, the Diels-Alder reaction is important not only from a synthetic standpoint but also from a theoretical view.[8]

An area of great interest in the Diels-Alder reaction involves the use of vinyl heterocycles as the dienic component.[9] Diverse polycyclic structures have been synthesized in this way from vinylfurans,[10] vinylindoles,[11] vinylpyrroles[12] and vinylimidazoles.[13] The reactivity of heterocyclic dienes is determined by the nature and number of heteroatoms and, in case of heteroaromatic compounds, also by their aromatic characters.[14] Evaluation of the reactivity of the parent compounds in the vinylheteroarene series is of general interest for predicting the outcome of Diels-Alder reactions and other pericyclic processes, especially with regard to synthesis planning.

Although it is generally assumed that thiazoles show unfavourable Diels-Alder reactions due to their considerable aromatic stabilization,[14-15] we have reported that 4-alkenylthiazoles behave as excellent dienes in [4+2] cycloadditions (Scheme 1).[16] They show a huge preference for the extra-annular cycloaddition due to the higher reactivity of the diene system including the side-chain double bond. This way of interacting allows substituted condensed heterocyclic systems to be synthesized.



Scheme 1. [4+2] cycloadditions of 4-alkenyl- and 5-alkenylthiazoles with a generic dienophile X=Y.

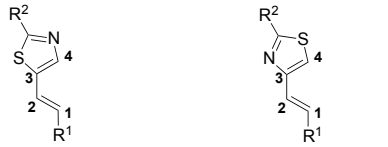
Recently, we have also established that an amino group at C-2 of the thiazole ring has a powerful activating effect,[16c] rendering electron density to the alkenylthiazole skeleton.[15a, 17] The [4+2] cycloadditions of 4-alkenylthiazoles emerges as a completely new methodology for the access to new polycyclic thiazole derivatives.

As a part of our program to expand the scope of this new methodology, we decided to investigate if 5-alkenylthiazoles behave as dienes in cycloaddition reactions as efficiently as their 4-alkenyl counterparts do (Scheme 1). For obvious reasons, the amino group at C-2 was preserved. Herein, we disclose our results regarding the synthesis and reactivity of 5-alkenyl-2-aminothiazoles as dienes in [4+2] cycloaddition reactions, including issues related to stereocontrol and regiochemistry. The operation of a concerted versus a stepwise mechanism is also thoroughly discussed.

Results and Discussion

HOMO energies of 5-vinylthiazole 1a and 5-alkenyl-2-aminothiazoles 1b,c

The HOMO energies of the 5-vinylthiazole **1a** and 5-alkenyl-2-aminothiazoles **1b,c** (Figure 1) were obtained through single-point Hartree-Fock (HF) calculations with the 6-31G basis set at the B3LYP/6-31G geometries, as this procedure has been shown to provide more accurate orbital energies than the B3LYP level.[18] The computed B3LYP/6-31G structures of thiazoles **1a-c** in their reactive *s-cis* conformations are shown in Figure 2. In Table 1 we summarize the HOMO energies and the $2p_z$ eigenvectors of the HOMOs of dienes **1a-c**. Besides, the HOMO energies and the $2p_z$ eigenvectors of the HOMOs of the 4-vinylthiazole **2a** and 4-alkenyl-2-aminothiazoles **2b,c** have been also included in Table 1 for comparison.



1a R^1 = H; R^2 = H
1b R^1 = H; R^2 = NH_2
1c R^1 = Ph; R^2 = NH_2

2a R^1 = H; R^2 = H
2b R^1 = H; R^2 = NH_2
2c R^1 = Ph; R^2 = NH_2

Figure 1. Structure of 5-alkenylthiazoles **1a-c** and 4-alkenylthiazoles **2a-c**.

Table 1. HOMO values for 5-alkenylthiazoles **1a-c** and 4-alkenylthiazoles **2a-c** in their respective *s-cis* conformations (for the numbering of the diene carbon atoms see Figure 1).

Entry	Diene	Eigenvalue (eV)	$2p_z$ coefficients			
			C_1	C_2	C_3	C_4
1	*s-cis*-**1a**	-8.71	-0.26	-0.19	0.27	0.29
2	*s-cis*-**1b**	-7.98	-0.23	-0.14	0.30	0.24
3	*s-cis*-**1c**	-7.18	-0.23	-0.20	0.22	0.21
4	*s-cis*-**2a**[a]	-8.65	-0.28	-0.20	0.25	0.29
5	*s-cis*-**2b**[b]	-7.98	-0.21	-0.14	0.23	0.33
6	*s-cis*-**2c**[b]	-7.40	-0.21	-0.22	0.17	0.27

[a] Data published in ref. [16a]. [b] Data published in ref. [16c].

The values included in Table 1 show that the change of the alkenyl substituent from carbon-4 to carbon-5 of the thiazole ring does not significantly affect the HOMO value. This observation is true for both, 2-unsubstituted (compare entries 1 and 4) and 2-aminothiazoles (compare entries 2 and 3 with 5 and 6). The data collected in Table 1 also demonstrate the same conclusion that we extracted previously:[16c] the HOMO energy values are enhanced by the presence of a phenyl group at R^1 (compare entries 2 and 3 and entries 5 and 6). Considering these results, 5-alkenyl-2-aminothiazole **1c** should be the most reactive diene.

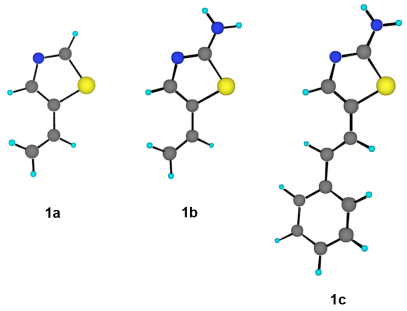
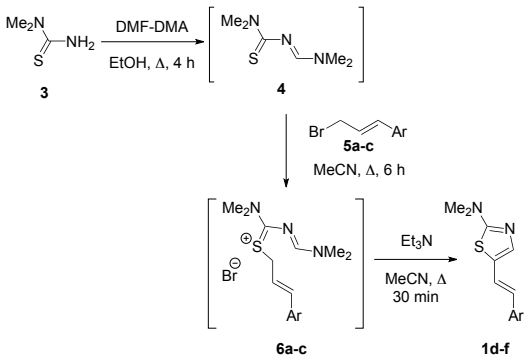


Figure 2. Computed B3LYP/6-31G geometries of 5-vinylthiazole **1a** and 5-alkenyl-2-aminothiazoles **1b,c** in their respective *s-cis* conformations.

Synthesis of 5-alkenyl-2-aminothiazoles 1d-f

On the basis of the preceding observations, 5-alkenyl-2-aminothiazoles **1d-f** were selected as the most appropriate dienes (Scheme 2). Our method of synthesizing thiazoles **1d-f** is based on a formerly reported method[19] for preparing related 2-amino-5-acylthiazoles, and it starts from *N*,*N*-dimethylthiourea (**3**). It comprises a three-step route in which none of the intermediates are isolated (Scheme 2). The first step was the reaction of **3** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA), which led to the iminothiourea **4** in quantitative yield. After removal of the solvent and the excess of DMF-DMA under reduced pressure, the ^{1}H NMR spectrum of the reaction mixture showed only resonances ascribable to the iminothiourea **4**. Among these signals are four singlets in the range of 3.06-3.50 ppm, attributable to the resonances of the four methyl groups and one more singlet at 8.75 ppm, assigned to the iminic hydrogen atom. The iminothiourea **4** was reacted with the corresponding cinnamyl bromides **5**, leading to the salts **6a-c**. Further *in situ* treatment of **6a-c** with triethylamine led to the thiazoles **1d-f** (Table 2).



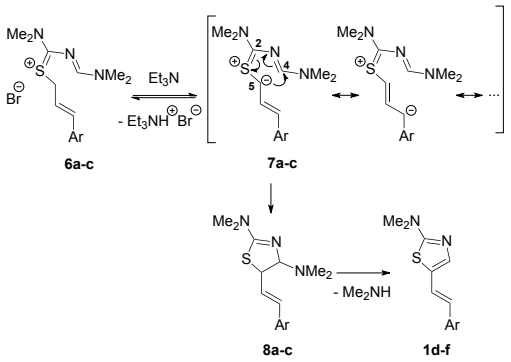
Scheme 2. Synthesis of 5-alkenyl-2-aminothiazoles **1d-f** from *N*,*N*-dimethylthiourea (**3**).

Table 2. Synthesis of 5-alkenyl-2-aminothiazoles **1d-f** from *N*,*N*-dimethylthiourea (**3**).

Entry	Ar	Compound	Yield (%)
1	Ph	**1d**	50
2	4-$O_2NC_6H_4$	**1e**	80
3	4-$MeOC_6H_4$	**1f**	13

As depicted in Table 2, higher yields were obtained when the phenyl group, labelled as Ar, contains an electron-acceptor functionality such as a nitro group (Table 2, entry 2). However, the global yield dropped to 13% if an electron-donating substituent, such as a methoxy group, is attached to the same position (Table 2, entry 3). In this latter case a great amount of unreacted iminothiourea intermediate (**4**) was recovered.

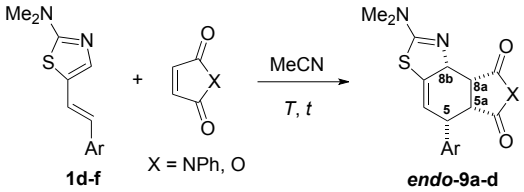
We assayed several modifications of this method for improving the yields, as a change in the number of equivalents of base, the use of an alternative one, *i.e.* DIPEA (diisopropyl ethyl amine) or an increase of the temperature of the reaction. However, the results were negative in all cases. We concluded that the high dependence of the yields of thiazoles **1c-d** on the electronic nature of the substituents at the Ar group, is probably related with the type of intermediates involved in the mechanism of this transformation. As shown in Scheme 3, the role of the Et_3N is the abstraction of a proton adjacent to the sulfur atom in the salts **6**, generating the corresponding sulfur ylides **7a-c**. The negative charge of **7** would be delocalized through the adjacent C-C double bond and the Ar group attached to it. The intramolecular nucleophilic addition of the ylidic carbon atom in **7** to the electrophilic C-4 should lead to the thiazolines **8**. In a final step, the elimination of dimethylamine in **8** would yield thiazoles **1**. Expectedly, the presence of an electron-acceptor functionality in Ar would favour not only the abstraction of the proton at C-5 by increasing their acidity through resonance effects, but also the initial nucleophilic substitution at the cinnamyl bromide for forming the sulfonium salts **6**.



Scheme 3. Mechanism of the transformation of intermediates **6a-c** into 5-alkenylthiazoles **1d-f**.

[4+2] cycloadditions of 5-alkenyl-2-aminothiazoles 1d-f

The HOMO values of the 5-alkenyl-2-aminothiazoles **1a-c** are higher than those of their 4-alkenylic counterparts[16c] and thus, we expected also higher reactivities. However, the reactions of thiazoles **1d-f** with *N*-phenylmaleimide (NPM) under analogous reaction conditions, *i.e.* acetonitrile at room temperature, led to low conversions of the starting materials even with long reaction times. Finally, we could obtain the cycloadducts ***endo*-9a-c** under refluxing acetonitrile in excellent yields (Scheme 4, Table 3, entries 1-3). The reaction of **1d** with maleic anhydride (MA) at room temperature gave the tetrahydrofuro[3,4-*e*]benzothiazole-6,8-dione ***endo*-9d** in good yield (Table 3, entry 4). The X-ray crystal structure of **9a** confirmed that the isolated stereoisomer is the result of an *endo* approach (see below).

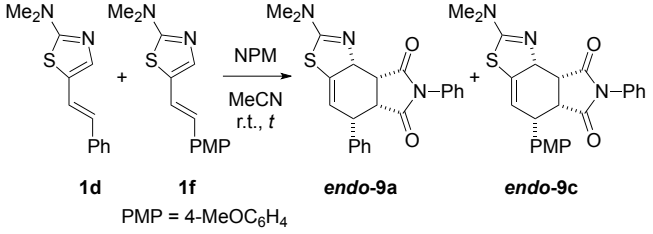


Scheme 4. Reactions of 5-alkenyl-2-aminothiazoles **1d-f** with NPM and MA (Ar, X, *T* and *t* defined in Table 3).

Table 3. Reactions of 5-alkenyl-2-aminothiazoles **1d-f** with NPM and MA.

Entry	Ar	X	*T* (ºC)	*t* (h)	Compound	Yield (%)
1	Ph	NPh	reflux	24	***endo*-9a**	97
2	4-$O_2NC_6H_4$	NPh	reflux	72	***endo*-9b**	98
3	4-$MeOC_6H_4$	NPh	reflux	24	***endo*-9c**	90
4	Ph	O	r.t.	24	***endo*-9d**	90

We conducted a competition experiment between thiazoles **1d** and **1f** to compare their relative reactivities toward NPM (Scheme 5). Thus, three equivalents of NPM were added to a solution containing equimolecular quantities of **1d** and **1f**. The reaction mixture was kept at room temperature and the ratio of ***endo*-9a**:***endo*-9c** was determined at different reaction times by ^{1}H NMR spectroscopy (Table 4). Our expectation was that the more electron-rich diene **1f** would react faster.[6a] However, as reflected in Table 4, the presence of a methoxy group in the aromatic group attached to the diene fragment does not affect its reactivity in a significant way.



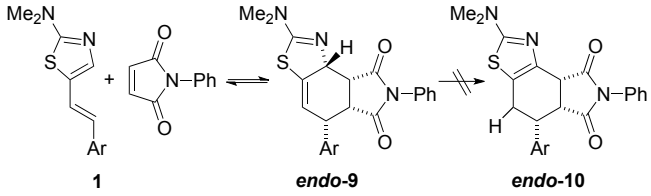
Scheme 5. Competition experiment between **1d** and **1f** toward NPM. The reaction time (*t*) is specified in Table 4.

Table 4. Competition experiment between **1d** and **1f** toward NPM.

Entry	*t* (h)	Conv. (%) [a,b]	***endo*-9a**:***endo*-9c**
1	15	9	48:52
2	24	11	47:53
3	48	15	46:54

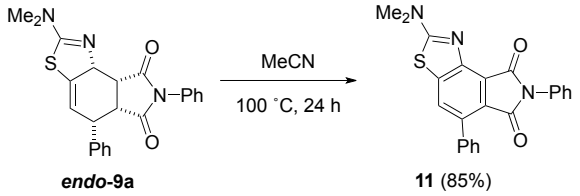
[a] Global conversion of **1d** plus **1f**. [b] Determined by ^{1}H-NMR analysis of characteristic signals directly on the reaction mixture (error ± 5% of the stated value).

Contrary to that observed for 4-alkenylthiazoles,[16a, 16c] primary cycloadducts ***endo*-9** were not prone to experience a further 1,3-hydrogen migration, in spite of the fact that this transformation would lead to the rearomatization of the thiazole ring (Scheme 6).



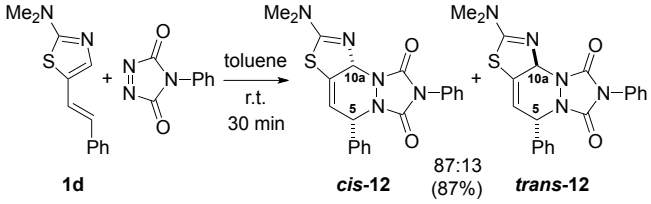
Scheme 6. [4+2] cycloaddition of a generic 5-alkenyl-2aminothiazole **1** and further 1,3-hydrogen migration step to give ***endo*-10**.

In order to promote the 1,3-hydrogen migration, the cycloadduct ***endo*-9a** was heated in acetonitrile solution at 100 ºC for 24 h (Scheme 7). In this way, the fully aromatized compound **11** was obtained.



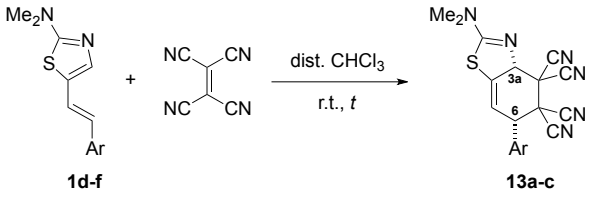
Scheme 7. Thermal treatment of ***endo*-9a**.

The reaction of **1d** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in toluene at room temperature led to a mixture of diastereoisomeric ***cis*-12** and ***trans*-12** in a 87:13 ratio (Scheme 8). In our hands, the separation of the two diastereomers by chromatographic techniques or crystallization could not be achieved due to their similar R_f values and solubilities.



Scheme 8. Reaction of 5-alkenyl-2-aminothiazole **1d** with PTAD.

5-Alkenyl-2-aminothiazoles **1d-f** were reacted with tetracyanoethylene (TCNE) in distilled $CHCl_3$ to give the *cis* dihydrobenzothiazoles **13a-c** in excellent yields (Scheme 9, Table 5). Curiously, the use of commercial $CHCl_3$ lead to a mixture of unaltered starting materials.[20]

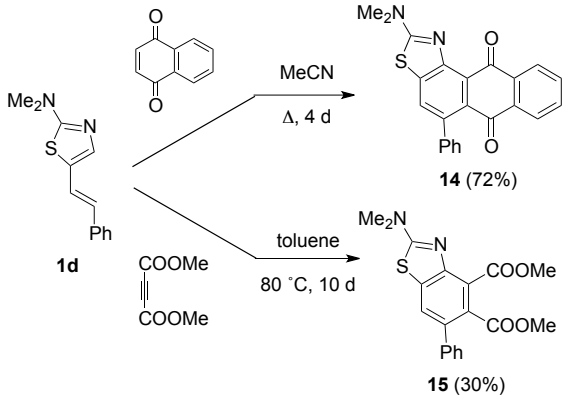


Scheme 9. Reaction of 5-alkenyl-2-aminothiazoles **1d-f** with TCNE (Ar and *t* specified in Table 5).

Table 5. Reaction of 5-alkenyl-2-aminothiazoles **1d-f** with TCNE.

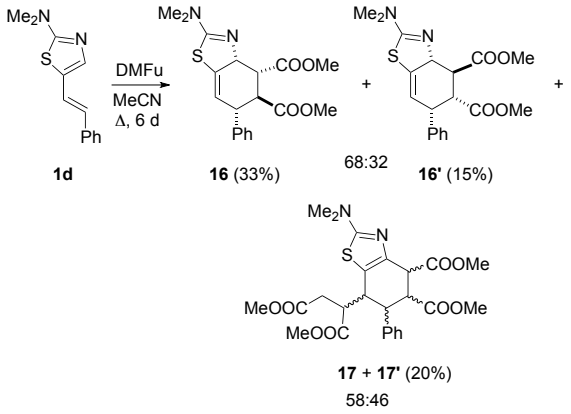
Entry	Ar	*t* (h)	Compound	Yield (%)
1	Ph	16	**13a**	97
2	4-$O_2NC_6H_4$	48	**13b**	91
3	4-$MeOC_6H_4$	24	**13c**	90

We also conducted the reaction of **1d** with naphthoquinone in acetonitrile under reflux to give **14** in 72% of yield (Scheme 10). The oxidation of the primary adduct under the reaction conditions should be favoured by the excess of naphthoquinone present in the reaction mixture. In addition, thiazole **1d** reacted with dimethyl acetylenedicarboxylate (DMAD) in toluene at 80 ºC leading to the dimethyl benzothiazol-4,5-dicarboxylate **15** in low yield (Scheme 10). Although other reaction conditions were assayed, *i.e.* toluene or acetonitrile under reflux, we could not improve this result. Similarly to other [4+2] cycloadditions with DMAD,[21] the completely oxidized benzothiazole **15** was the only reaction product.



Scheme 10. Reactions of 5-alkenyl-2-aminothiazole **1d** with naphthoquinone and DMAD.

Finally, the reaction of **1d** with dimethyl fumarate (DMFu) was conducted in acetonitrile under reflux to give a mixture of four tetrahydrobenzothiazoles, the two pairs of diastereomers **16**/**16'** and **17**/**17'** (Scheme 11). The two primary cycloadducts **16** and **16'** could be separated by chromatographic techniques and were isolated in 33% and 15% yield, respectively. The tetrahydrobenzothiazoles **17** and **17'** were isolated in a 58:46 ratio and 20% of global yield. Evidently, **17** and **17'** come from an ene reaction of **16** and **16'** with a second molecule of dimethyl fumarate. The reaction of more **1d** with dimethyl maleate under similar reaction conditions led to a complex mixture of unidentified products.

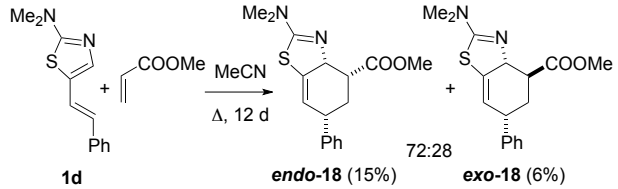


Scheme 11. Reaction of 5-alkenyl-2-aminothiazole **1d** with dimethyl fumarate.

This study confirms that the Diels-Alder reactions of 5-alkenyl-2-aminothiazoles **1** as dienes with NPM, MA, PTAD, TCNE, naphthoquinone, DMAD or dimethyl fumarate take place with the exclusive participation of the side-chain double bond (extra-annular addition). Therefore, these reactions may be qualified as site-selective.

Regioselectivity in the [4+2] cycloadditions of 5-alkenyl-2-aminothiazoles 1d-f with non symmetric dienophiles

According to FMO theory, the regiochemistry of a concerted pericylic Diels-Alder reaction is controlled by the complementarity of the frontier orbitals of diene and dienophile. Thus, the more effective overlapping takes place between the ends of both reagents with the highest coefficients.[6a] For 5-alkenyl-2-aminothiazoles **1a-c**, the coefficients of the end atoms of the dienic fragments are very similar in absolute value (Table 1). Thus, poor regioselectivities, if any, could be expected for the [4+2] cycloadditions of 5-alkenylthiazoles **1** with dienophiles. However, the reaction of **1d** with methyl acrylate gave only a mixture of ***endo*-18** and ***exo*-18**. The alternative regioisomeric products were not detected in the reaction mixture (Scheme 12). The diastereoisomeric cycloadducts ***endo*-18** and ***exo*-18** could be separated by chromatographic techniques. The reaction of **1d** with *trans*-β-nitrostyrene was tested under similar reaction conditions. However, the conversion after 6 days was extremely low. The addition of an excess of dienophile led to a very complex mixture of products.



Scheme 12. Reaction of 5-alkenyl-2-aminothiazole **1d** with methyl acrylate.

Structural and configurational assignment

The relative configuration of ***endo*-9a** was unequivocally established by single-crystal X-ray analysis (Supporting Information). The configurational assignment of compounds ***endo*-9b-d** was done by comparison of their ^{1}H NMR data with those of ***endo*-9a**. The coupling constants between protons H_5/H_{5a} and H_{8a}/H_{8b} (Scheme 4) were especially informative, ranging 5.6-6.6 Hz and 7.2-7.4 Hz, respectively. Additionally, the ^{1}H,^{1}H-NOESY spectrum of ***endo*-9b** (Supporting Information) supported the *cis* relative arrangement of the above mentioned protons.

The relative configurational assignment of the two stereogenic centers C_5 and C_{10a} in compound ***cis*-12** (Scheme 8) was done by comparison of the coupling constants between their methine protons with those reported for an analogous structure.[16b, 22] These protons show a mutual coupling constant in the range of 2.8 Hz, a typical value for assessing a *cis* relationship between H_5 and H_{10a}. Similarly, protons H_{3a} and H_6 in compounds **13a-c** coupled with constant values of around 3.3 Hz, typical for a *cis* arrangement (Scheme 9).

The relative stereochemistry of **16** and **16'** was established on the basis of the values of the coupling constants between the protons of the six-membered ring, and of significant cross-peaks in their respective ^{1}H,^{1}H-NOESY spectra (Figure 3). We worked out with the hypothesis that cycloadducts **16** and **16'** would possess in solution the half-chair conformation depicted in Figure 3. The most significant coupling constants for these assignments are those between protons H_{3a}/H_4, H_4/H_5 and H_5/H_6. For stereoisomer **16**, the coupling constant between H_{3a}/H_4 is 7.0 Hz, which indicates that H_4 adopts a pseudoequatorial position. Additionally, the coupling constant between H_4/H_5 is 4.8 Hz, pointing to a pseudoequatorial position also for H_5.[11d] For cycloadduct **16'**, the coupling constants between H_{3a}/H_4 and H_4/H_5 are 10.8 and 11.9 Hz, in agreement with a relative 1,2-*trans* disposition. The *J* value for H_5/H_6 is 6.8 Hz pointing to a *cis* arrangement of these two protons.[11d]

The most representative contacts observed in the ^{1}H,^{1}H-NOESY spectra of **16** and **16'** (Supporting Information) are also displayed in Figure 3. The ^{1}H,^{1}H-NOESY spectrum of **16** shows contacts between all protons placed at the six-membered ring, indicating their spatial proximity. The crosspeaks observed between the H_5/H_{ortho} and H_{3a}/H_6 agree well with the assignment based on the coupling constants. In the spectrum of **16'**, the most relevant contacts are those shown between protons H_{ortho}/H_4 and H_{3a}/H_5, suggesting that H_{3a} and H_5 adopt a 1,3-*cis* arrangement. Finally, the lack of a crosspeak between H_4/H_5 and also between H_{3a}/H_4 is in agreement with the consecutive 1,2-*trans* relationship for these three protons.

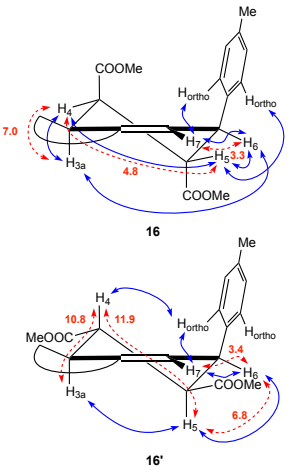


Figure 3. Significant coupling constants (red colour, dashed arrows) and NOE effects (blue colour, solid arrows) for the assignment of the relative configuration of cycloadducts **16** and **16'**.

For ***exo*-18**, the coupling constant between H_{3a}/H_4 is 10.5 Hz, indicating that they adopt a 1,2-transdiaxial arrangement (Figure 4).[11d] The same pair of protons are coupled with a constant value of 6.6 Hz in ***endo*-18**, which agree well with their 1,2-*cis* relationship.[11d] The key NOESY crosspeak to assign the *endo*/*exo* structure of cycloadducts **18** is that relating H_{3a} and H_4. Thus, whereas the spectrum of ***endo*-18** shows this contact, the spectrum of ***exo*-18** lacks it. Additionally, the NOESY spectrum of ***exo*-18** shows a crosspeak between H_{ortho}/H_4 indicating that the aromatic substituent and H_4 are placed in a relative 1,3-*cis* position. An analogous contact was not found in the spectrum of ***endo*-18**.

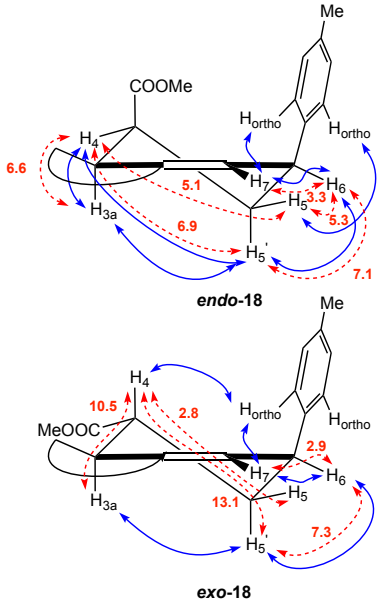
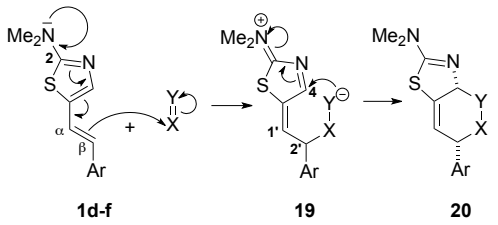


Figure 4. Significant coupling constants (red colour, dashed arrows) and NOE effects (blue colour, solid arrows) for the assignment of the relative configuration of cycloadducts ***endo*-18** and ***exo*-18**.

Proposed mechanism for the [4+2] cycloadditions of 5-alkenyl-2-aminothiazoles 1 with dienophiles

It is commonly accepted that in most of the Diels-Alder reactions the two new σ-bonds are formed in a concerted, although not necessarily synchronous, manner. Consistent with this mode of addition, Diels-Alder reactions are generally stereospecific.[6a, 23] The reactions of 5-alkenylthiazoles **1d-f** with NPM, MA, TCNE or DMFu are stereospecific, being in the two former cases highly *endo*-selective. In principle, a concerted mechanism with an asynchronous transition state, due to the non symmetric nature of the reagents, would agree with the observed results.[8b, 24] However, there are two relevant experimental observations clashing with the explanation of a concerted mechanism. First, the reaction of thiazole **1d** with PTAD lacks of stereospecificity (Scheme 8). The isolation of ***trans*-12** excludes thus, a pericyclic concerted mechanism at least for the reaction of thiazole **1d** with this highly reactive dienophile. More relevant is the fact that the coefficients at the end atoms of the dienic fragments in **1a-c** are very similar in absolute values (Table 1). Thus, poor regioselectivities if any would be expected on this basis, contrary to the observed results. That the adequate substitution on both diene and dienophile can favour the stabilization of charges of opposite signs and tune up the mechanism of the [4+2] cycloaddition from a concerted to a stepwise one is supported by previous works.[8b, 23-25] Thus, we propose that cycloadditions of thiazoles **1d-f** with dienophiles are probably close to the concerted/stepwise boundary, being the nature of the dienophile determinant to tip the scale in favour of one or another.

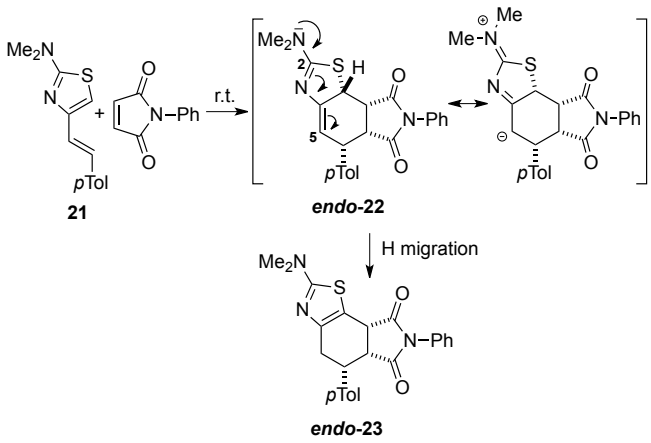
We propose the following stepwise mechanism to explain the reactions of thiazole **1d** with selected dienophiles such as PTAD or methyl acrylate, in which X=Y represents a generic asymmetric dienophile (Scheme 13). First, the nucleophilic addition of the alkenylic fragment, via its β-position, of thiazoles **1** to the most electron-deficient position of the dienophile (labelled as "X") may give the zwitterionic intermediate **19**. This process would be assisted by the lone pair of the amino group at C-2, which is partially delocalized into the heterocyclic ring and the exocyclic C-C double bond. The intramolecular cyclization of **19** by addition of the carbanionic "Y"-end to C-4 would then lead to the formal [4+2] cycloadduct **20**.



Scheme 13. Stepwise mechanism for the reactions of 5-alkenyl-2-aminothiazoles **1d-f** with dienophiles.

Assuming the stepwise mechanism depicted in Scheme 13, the zwitterionic intermediate resulting from the reaction of **1d** with PTAD would be enough long-lived due to the fact that the negative charge would be placed at the electronegative nitrogen atom. This fact would favour the rotation about the C1'-C2' bond before the intramolecular cyclization takes place, which finally would lead to the formation of small quantities of ***trans*-12**. The proposed stepwise mechanism depicted in Scheme 13 agrees not only with the observed high levels of regioselectivity but also with the structure of the isolated regioisomers. Thus, the formation of cycloadducts ***endo*-18** and ***exo*-18** would be the result of the nucleophilic addition of the alkenylic fragment of the thiazole **1d**, via its β-position, to the most electron-deficient position of the dienophile, *i.e.* the β-position of the C-C double bond of methyl acrylate. Therefore, the regioselectivity of the stepwise cycloadditions of 5-alkenyl-2-aminothiazoles with non symmetric dienophiles is apparently controlled by the resonance effect of the amino group at C-2 of the thiazole ring.

As it was pointed out previously, primary cycloadducts **20** are not prone to experience a further 1,3-hydrogen migration in spite of the fact that this transformation would induce the rearomatization of the thiazole ring (Schemes 6 and 7). This behaviour contrasts with that of cycloadducts resulting from a [4+2] cycloaddition of 4-alkenyl-2-aminothiazoles in which the 1,3-hydrogen migration takes place under very mild conditions. This transformation has been depicted in Scheme 14 taking **21** as a model.[16c] A plausible explanation for the unusual stability of cycloadducts **20** based on the different electronic properties of the sulfur and nitrogen atoms is given below.



Scheme 14. [4+2] cycloaddition of 4-alkenylthiazole **21** with NPM to give the primary adduct ***endo*-22**, which spontaneously experiences a further a 1,3-hydrogen migration.[16c]

The 1,3-hydrogen migration experienced by ***endo*-22** may be intermolecular since a concerted one is expected to have a very high activation barrier.[26] In a previous work[16c] we proposed that this hydrogen atom migrates with a positive charge density, being the negative charge generated at the carbon atom to which the proton was initially bonded, stabilized by the adjacent sulphur atom.[27] Additionally, the lone pair of the exocyclic nitrogen atom in ***endo*-22** would be delocalized over the unsaturated fragment of the intermediate bicyclic structure, increasing the basic character of C-5 and thus, facilitating the migration of the hydrogen atom as a proton (see the polar canonical form of ***endo*-22** in Scheme 14). In contrast, the negative density that would be generated as a consequence of the migration of a proton in the primary cycloadducts **20** would be placed adjacent to a nitrogen atom. This situation is much less favoured compared to that previously explained for ***endo*-22**. In fact, 5-methylenethiazolines are highly stable compounds and they only isomerize to the corresponding 5-methylthiazoles under acid or basic catalysis.[28] On the contrary, as far as we know, there are no examples in the literature describing the isolation of 4-methylenethiazolines. This fact is probably a consequence of 4-methylenethiazolines being prone to tautomerize to the corresponding 4-methylthiazoles.

Conclusions

5-Alkenyl-2-aminothiazoles **1d-f** have been synthesized in excellent yields and they behave as effective dienes in [4+2] cycloadditions. The reactions of **1** with classical electron-poor dienophiles are site-selective since only the diene moiety including the formal C-C and the side-chain double bonds is implicated (extra-annular addition). The reactions with cyclic dienophiles such as NPM or MA are *endo*-selective. The completely oxidized cycloadduct is obtained in the reactions of 5-alkenylthiazole **1d** with naphthoquinone or DMAD. The reaction of thiazole **1d** with PTAD is not stereospecific. However, the reaction of the same thiazole with methyl acrylate is highly regioselective. The collected data suggest a mechanism placed at the boundary between a concerted but highly asynchronous mechanism and a stepwise one. Presumably, the resonance effect of the amino group at C-2 of the thiazole ring is a key-controlling element for both, the reactivity and the regioselectivity observed in this type of cycloadditions.

The reactions of 5-alkenyl-2-aminothiazoles **1** with dienophiles described herein**,** complement those of their 4-alkenyl counterparts previously reported. Together they open up novel routes to a great variety of complex polycyclic thiazole derivatives.

Experimental Section

General. Melting points are not corrected. IR spectra were recorded as nujol emulsions. ^{1}H-NMR spectra were recorded at 300 or 401 MHz. ^{13}C-NMR spectra were measured at 50 or 75 MHz. Mass spectra were recorded on the EI (70 eV) or FAB$^+$ mode (3-nitrobenzyl alcohol as matrix).

X-Ray structure. CCDC-945001 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge form The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Cinnamyl bromides. Cinnamyl bromide is commercial. The 4-nitrocinnamyl[29] and 4-methoxycinnamyl[30] bromides were prepared following previously described methodologies.

Synthesis of the 5-alkenyl-2-aminothiazoles 1d-f. DMF-DMA (1.79 g; 15.0 mmol) was added to a solution of *N*,*N*-dimethylthiourea[15c] (1.04 g; 10.0 mmol) in ethanol (50 ml). The reaction mixture was stirred under reflux for 4 h. The solvent and the excess of DMF-DMA were removed under reduced pressure and the resulting residue was redissolved in acetonitrile (50 ml) to which the corresponding cinnamyl bromide (15.0 mmol) was added. The reaction mixture was kept under reflux for 6 h and after that, triethylamine (10 ml) was added and stirred at the same temperature for 30 min more. The solvent was evaporated until dryness. After addition of H_2O (30 ml), the reaction mixture was extracted with CH_2Cl_2 (3 × 30 ml). The organic extracts were dried under anhydrous $MgSO_4$, the solvent removed under reduced pressure and the residue purified by silica-gel column chromatography.

2-Dimethylamino-5-[(*E*)-2-phenylethenyl]thiazole (1d)*:* 1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.35); yield 50% (1.152 g); mp 106-107 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1567, 1520, 1489, 1418, 1305, 1265, 1118, 942, 930, 748, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.10 MHz) δ 3.13 (s, 6H, NMe_2), 6.47 (d, 1H, *J* = 15.9 Hz), 7.08 (d, 1H, *J* = 15.9 Hz), 7.16 (s, 1H, H_4), 7.17-7.21 (m, 1H), 7.27-7.33 (m, 2H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 40.1 (2×q, NMe_2), 119.8 (d), 125.75 (2×d), 125.76 (d), 126.7 (s, C_5), 126.9 (d), 128.6 (2×d), 137.4 (s), 140.0 (d, C_4), 169.9 (s, C_2); MS (EI, 70 eV) *m/z* (rel int) 230 (M^+, 100), 201 (25), 128 (24), 115 (28). Anal. Calcd for $C_{13}H_{14}N_2S$ (230.33): C, 67.79; H, 6.13; N, 12.16; S, 13.92. Found: C, 67.42; H, 6.52; N, 12.10; S, 13.81.

2-Dimethylamino-5-[(*E*)-2-(4-nitrophenyl)ethenyl]thiazole (1e)*:* 1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.20); yield 80% (2.203 g); mp 209-211 ºC (red needles, $CHCl_3/Et_2O$); IR (nujol) 1556, 1510, 1422, 1327, 1293, 1173, 1106, 928, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.17 (s, 6H, NMe_2), 6.45 (d, 1H, *J* = 15.8 Hz), 7.24-7.28 (m, 2H), 7.48 (d, 2H, *J* = 8.8 Hz), 8.16 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 40.2 (2×q, NMe_2), 122.7 (d), 124.2 (2×d), 124.5 (d), 125.78 (s, C_5), 125.81 (2×d), 143.0 (d, C_4), 144.3 (s), 145.9 (s), 170.8 (s, C_2); MS (EI, 70 eV) *m/z* (rel int) 275 (M^+, 100), 246 (38), 115 (30). Anal. Calcd for $C_{13}H_{13}N_3O_2S$ (275.33): C, 56.71; H, 4.76; N, 15.26; S, 11.65. Found: C, 56.53; H, 4.82; N, 15.10; S, 11.79.

2-Dimethylamino-5-[(*E*)-2-(4-methoxyphenyl)ethenyl]thiazole (1f)*:* 1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.33); yield 13% (0.339 g); mp 120-122 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1552, 1503, 1422, 1295, 1247, 1174, 1033, 944, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.13 (s, 6H, NMe_2), 3.81 (s, 3H, OMe), 6.44 (d, 1H, *J* = 15.9 Hz), 6.86 (d, 2H, *J* = 8.8 Hz), 6.94 (d, 1H, *J* = 15.9 Hz), 7.12 (s, 1H, H_4), 7.32 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 40.1 (2×q, NMe_2), 55.3 (q, OMe), 114.1 (2×d), 117.8 (d), 125.5 (d), 126.9 (2×d), 127.0 (s, C_5), 130.3 (s), 139.1 (d, C_4), 158.8 (s), 169.5 (s, C_2); MS (EI, 70 eV) *m/z* (rel int) 261 (M^+ + 1, 23), 260 (M^+, 100), 245 (75), 231 (21). Anal. Calcd for $C_{14}H_{16}N_2OS$ (260.36): C, 64.58; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.32; H, 6.32; N, 10.53; S, 12.41.

General procedure for the synthesis of *endo*-9a-c. A solution of the corresponding 5-alkenyl-2-aminothiazole **1** (0.650 mmol) and *N*-phenylmaleimide (0.338 g; 1.95 mmol) in acetonitrile (15 mL) was stirred under reflux (reaction time indicated in each case). The solvent was removed under reduced pressure and the residue purified by silica-gel column chromatography.

(5*R,5a*S**,8a*S**,8b*S**)-2-Dimethylamino-5,7-diphenyl-5,5a,8a,8b-tetrahydropyrrolo[3,4-*e*]benzothiazole-6,8-dione (*endo*-9a).** Reaction time: 24 h. EtOAc was used as eluent (R*f* = 0.18); yield 97% (0.254 g) ; mp 221-223 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1708, 1628, 1494, 1209, 1081, 758, 701, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.06 (s, 6H, NMe_2), 3.50 (dd, 1H, *J* = 8.5 Hz, *J* = 6.0 Hz, H_{5a}), 3.70 (m, 1H, H_5), 3.92 (dd, 1H, *J* = 8.5 Hz, *J* = 7.2 Hz, H_{8a}), 5.11 (dt, 1H, *J* = 6.7 Hz, *J* = 2.4 Hz, H_{8b}), 6.29 (t, 1H, *J* = 3.7 Hz, H_4), 7.11-7.13 (m, 2H), 7.28-7.40 (m,

8H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 39.9 (2×q, NMe_2), 43.5 (d, C_5), 44.7 (d, C_{8a}), 45.2 (d, C_{5a}), 74.6 (d, C_{8b}), 114.9 (d, C_4), 126.5 (2×d), 127.2 (d), 128.3 (2×d), 128.4 (d), 128.6 (2×d), 129.0 (2×d), 131.8 (s), 138.6 (s), 143.3 (s, C_{3a}), 161.0 (s, C_2), 173.2 (s, CO), 174.7 (s, CO); MS (EI, 70 eV) *m/z* (rel int) 403 (M^+, 37), 231 (38), 230 (100), 201 (28), 173 (30), 128 (28), 115 (23). Anal. Calcd for $C_{23}H_{21}N_3O_2S$ (403.50): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.09; H, 5.46; N, 10.38; S, 7.80.

(5*R,5a*S**,8a*S**,8b*S**)-2-Dimethylamino-5-(4-nitrophenyl)-7-phenyl-5,5a,8a,8b-tetrahydropyrrolo[3,4-*e*]benzothiazole-6,8-dione (*endo*-9b).** Reaction time: 72 h. 10:1 EtOAc/MeOH was used as eluent (R*f* = 0.32); yield 98% (0.286 g); mp 208-210 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1705, 1622, 1596, 1515, 1497, 1342, 1167, 1084, 888, 767, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.07 (s, 6H, NMe_2), 3.56 (dd, 1H, *J* = 8.6 Hz, *J* = 5.6 Hz, H_{5a}), 3.81 (m, 1H, H_5), 3.98 (dd, 1H, *J* = 8.6 Hz, *J* = 7.4 Hz, H_{8a}), 5.13 (dt, 1H, *J* = 6.9 Hz, *J* = 2.3 Hz, H_{8b}), 6.27 (t, 1H, *J* = 3.6 Hz, H_4), 7.10-7.12 (m, 2H), 7.31-7.36 (m, 1H), 7.38-7.42 (m, 2H), 7.54 (d, 2H, *J* = 8.8 Hz), 8.22 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 40.0 (2×q, NMe_2), 43.0 (d, C_5), 44.3 (d, C_{8a}), 45.0 (d, C_{5a}), 74.7 (d, C_{8b}), 113.0 (d, C_4), 123.5 (2×d), 126.4 (2×d), 128.6 (d), 129.1 (2×d), 129.5 (2×d), 131.5 (s), 144.7 (s, C_{3a}), 146.4 (s), 147.0 (s), 160.9 (s, C_2), 172.7 (s, CO), 174.6 (s, CO); MS (EI, 70 eV) *m/z* (rel int) 448 (M^+, 11), 275 (100), 246 (22), 173 (27). Anal. Calcd for $C_{23}H_{20}N_4O_4S$ (448.50): C, 61.59; H, 4.49; N, 12.49; S, 7.15. Found: C, 61.32; H, 4.63; N, 12.54; S, 7.30.

(5*R,5a*S**,8a*S**,8b*S**)-2-Dimethylamino-5-(4-methoxyphenyl)-7-phenyl-5,5a,8a,8b-tetrahydropyrrolo[3,4-*e*]benzothiazole-6,8-dione (*endo*-9c).** Reaction time: 24 h. 10:1 EtOAc/MeOH was used as eluent (R*f* = 0.30); yield 90% (0.254 g); mp 186-188 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1704, 1627, 1514, 1498, 1251, 1193, 1155, 1089, 1033, 830, 748, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.06 (s, 6H, NMe_2), 3.44 (dd, 1H, *J* = 8.5 Hz, *J* = 6.0 Hz, H_{5a}), 3.67 (m, 1H, H_5), 3.80 (s, 3H, OMe), 3.91 (dd, 1H, *J* = 8.5 Hz, *J* = 7.2 Hz, H_{8a}), 5.10 (dt, 1H, *J* = 6.6 Hz, *J* = 2.4 Hz, H_{8b}), 6.24 (t, 1H, *J* = 3.6 Hz, H_4), 6.90 (d, 2H, *J* = 8.7 Hz), 7.11-7.14 (m, 2H), 7.26 (d, 2H, *J* = 8.7 Hz), 7.29-7.33 (m, 1H), 7.37-7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 40.0 (2×q, NMe_2), 42.9 (d, C_5), 44.7 (d, C_{8a}), 45.3 (d, C_{5a}), 55.2 (q, OMe), 74.5 (d, C_{8b}), 113.7 (2×d), 115.4 (d, C_4), 126.5 (2×d), 128.4 (d), 129.0 (2×d), 129.6 (2×d), 130.6 (s), 131.8 (s), 143.0 (s, C_{3a}), 158.6 (s), 161.0 (s, C_2), 173.2 (s, CO), 174.8 (s, CO); MS (EI, 70 eV) *m/z* (rel int) 433 (M^+, 9), 261 (21), 260 (100), 245 (43), 173 (25). Anal. Calcd for $C_{24}H_{23}N_3O_3S$ (433.53): C, 66.49; H, 5.35; N, 9.69; S, 7.40. Found: C, 66.22; H, 5.62; N, 9.72; S, 7.45.

Preparation of (5*R,5a*S**,8a*S**,8b*S**)-2-dimethylamino-5-phenyl-5,5a,8a,8b-tetrahydrofuro[3,4-*e*]benzothiazole-6,8-dione (*endo*-9d).** Maleic anhydride (0.191 g, 1.95 mmol) was added to a solution of the 5-alkenyl-2-dimethylaminothiazole **1d** (0.15 g, 0.65 mmol) in acetonitrile (15 ml). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated to dryness and the residue was purified by silica-gel column chromatography eluting with EtOAc (R*f* = 0.23); yield 90% (0.192 g); mp 173-175 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1782, 1628, 1248, 1083, 1045, 972, 936, 772, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.10 MHz) δ 3.07 (s, 6H, NMe_2), 3.55 (dd, 1H, *J* = 9.3 Hz, *J* = 6.6 Hz, H_{5a}), 3.67 (ddd, 1H, *J* = 6.3 Hz, *J* = 3.9 Hz, *J* = 1.8 Hz, H_5), 4.03 (dd, 1H, *J* = 9.3 Hz, *J* = 7.2 Hz, H_{8a}), 5.00 (dt, 1H, *J* = 6.6 Hz, *J* = 2.7 Hz, H_{8b}), 6.23 (t, 1H, *J* = 3.6 Hz, H_4), 7.29-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 39.9 (2×q, NMe_2), 43.0 (d, C_5), 45.6 (d), 45.7 (d), 73.5 (d, C_{8b}), 115.2 (d, C_4), 127.7 (d), 128.6 (4×d), 137.6 (s), 144.4 (s, C_{3a}), 161.7 (s, C_2), 168.0 (s, CO), 169.6 (s, CO); MS (FAB^+) m/z (%) 329 (M^+ + 1, 100). Anal. Calcd for $C_{17}H_{16}N_2O_3S$ (328.39): C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.83; H, 5.06; N, 8.38; S, 9.88.

Preparation of 2-dimethylamino-5,7-diphenyl-7*H*-pyrrolo[3,4-*e*]benzothiazole-6,8-dione (11). A solution of *endo*-**9a** (0.048 g, 0.12 mmol) in acetonitrile (5 ml) was stirred at 100ºC in a sealed tube for 24 h. The solvent was evaporated to dryness and the residue was purified by silica-gel column chromatography eluting with 1:1 EtOAc/*n*-hexane (R_f = 0.25); yield 85% (0.041 g); mp 264-266 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1709, 1618, 1573, 1548, 1167, 1133, 904, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.35 (s, 6H, NMe_2), 7.31-7.35 (m, 1H), 7.40-7.46 (m, 7H), 7.56-7.58 (m, 2H), 7.83 (s, 1H, H_4); ^{13}C NMR ($CDCl_3$, 100.81 MHz, *T* = 40 ºC) δ 40.5 (2×q, NMe_2), 118.2 (s), 125.7 (s), 126.8 (2×d), 127.5 (d), 127.6 (d), 128.0 (2×d), 128.1 (d), 128.8 (2×d), 129.6 (2×d), 132.2 (s), 133.4 (s), 136.9 (s), 140.5 (s), 149.2 (s), 166.1 (s), 167.1 (s), 172.4 (s); MS (EI, 70 eV) *m/z* (rel int) 400 (M^+ + 1, 24), 399 (M^+, 100), 370 (54). Anal. Calcd for $C_{23}H_{17}N_3O_2S$ (399.47): C, 69.15; H, 4.29; N, 10.52; S, 8.03. Found: C, 68.88; H, 4.42; N, 10.60; S, 8.09.

Reaction of the 5-alkenyl-2-aminothiazole 1d with PTAD. Preparation of (5*R,10a*S**)-2-dimethylamino-5,8-diphenyl-5,10a-dihydrothiazolo[4,5-*c*][1,2,4]triazolo[1,2-*a*]pyridazin-7,9-dione (*cis*-12) and (5*R**,10a*R**)-2-dimethylamino-5,8-diphenyl-5,10a-dihydrothiazolo[4,5-*c*][1,2,4]triazolo[1,2-*a*]pyridazin-7,9-dione (*trans*-12).** PTAD (0.075 g, 0.43 mmol) was added to a solution of the 5-alkenyl-2-aminothiazole **1d** (0.099 g, 0.43 mmol) in toluene (10 ml). The reaction mixture was stirred at room temperature for 30 min. The solid precipitate was filtered. More reaction product was obtained by removing the solvent under reduced pressure and further addition of Et_2O. A 87:13 mixture of the two *cis*/*trans* diastereomers was obtained; yield 87% (0.152 g); mp 167-168 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1773, 1719, 1625, 1406, 1261, 1138, 1108, 861, 760, 719, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.09 (s, 6H, NMe_2^m), 3.13 (s, 6H, NMe_2^M), 5.60 (dd, 1H, *J* = 5.1 Hz, *J* = 1.5 Hz, H_5^m), 5.64 (t, 1H, *J* = 3.2 Hz, H_5^M), 5.80 (dd, 1H, *J* = 3.6 Hz, *J* = 2.6 Hz, H_4^M), 5.90 (t, 1H, *J* = 2.4 Hz, H_{10a}^M), 5.97 (dd, 1H, *J* = 5.1 Hz, *J* = 2.5 Hz, H_4^m), 6.17 (br s, 1H, H_{10a}^m), 7.27-7.48 (m, 20H, $10H^M$ + $10H^m$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 39.4 (2×q, NMe_2^m), 39.5 (2×q, NMe_2^M), 57.5 (d, C_5^M), 59.5 (d, C_5^m), 82.6 (d, C_{10a}^m), 85.9 (d, C_{10a}^M), 118.1 (d, C_4^M), 120.0 (d, C_4^m), 125.3 (2×d, C^M), 125.5 (2×d, C^m), 127.9 (d, C^M), 128.0 (d, C^m), 128.2 (4×d, C^M + C^m), 128.8 (4×d, C^M + C^m), 128.9 (6×d, C^M + C^m), 131.1 (s, C^M), 136.3 (s, C^M), 137.5 (s, C^M), 150.5 (s, CO^M), 154.7 (s, CO^M), 162.4 (s, C_2^M). The six quaternary carbon atoms from the minor diastereomer could not be observed since the mixture decomposes after several hours in solution thus, we could not register a ^{13}C NMR spectrum with a higher number of scans; MS (EI, 70 eV) *m/z* (rel int) 405 (M^+, 76), 271 (39), 231 (65), 230 (63), 201 (22), 140 (50), 128 (26), 119 (100), 115 (40), 93 (22), 91 (44), 77 (25), 64 (24). Anal. Calcd for $C_{21}H_{19}N_5O_2S$ (405.48): C, 62.21; H, 4.72; N, 17.27; S, 7.91. Found: C, 61.95; H, 4.82; N, 17.32; S, 8.02.

General procedure for the synthesis of 13a-c. TCNE (0.250 g, 1.95 mmol) was added to a solution of the 5-alkenyl-2-aminothiazole **1** (0.65 mmol) in distilled $CHCl_3$ (15 ml). The reaction mixture was stirred at room temperature (reaction time indicated in each case). The solvent was removed under reduced pressure and the residue purified by silica-gel column chromatography.

(3a*R,6*S**)-4,4,5,5-Tetracyano-2-dimethylamino-6-phenyl-3a,6-dihydrobenzothiazole (13a).** Reaction time: 16 h. 1:2 EtOAc/*n*-hexane was used as eluent (R_f = 0.25); yield 97% (0.226 g); mp 157-158 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1619, 1257, 1078, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.09 (s, 6H, NMe_2), 4.55 (t, 1H, *J* = 3.3 Hz, H_6), 5.44 (t, 1H, *J* = 3.3 Hz, H_{3a}), 5.73 (t, 1H, *J* = 2.9 Hz, H_7), 7.43-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 39.8 (2×q, NMe_2), 45.7 (s), 46.5 (s), 49.7 (d, C_6), 74.3 (d, C_{3a}), 108.6 (s, CN), 109.0 (s, CN), 110.6 (s, CN), 110.7 (s, CN), 116.9 (d, C_7), 129.2 (2×d), 129.5 (2×d), 130.5 (d), 132.2 (s), 139.5 (s, C_{7a}), 162.4 (s, C_2); MS (FAB^+) m/z (%) 359 (M^+ + 1, 44). Anal. Calcd for $C_{19}H_{14}N_6S$ (358.42): C, 63.67; H, 3.94; N, 23.45; S, 8.95. Found: C, 63.37; H, 4.05; N, 23.55; S, 9.02.

(3a*R,6*S**)-4,4,5,5-Tetracyano-2-dimethylamino-6-(4-nitrophenyl)-3a,6-dihydrobenzothiazole (13b).** Reaction time: 48 h. 1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.48); yield 91% (0.239 g); mp 135-137 ºC (red prisms, $CHCl_3/Et_2O$); IR (nujol) 1627, 1523, 1352, 1268, 851, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.11 (s, 6H, NMe_2), 4.69 (t, 1H, *J* = 3.3 Hz, H_6), 5.45 (t, 1H, *J* = 3.3 Hz, H_{3a}), 5.71 (t, 1H, *J* = 2.9 Hz, H_7), 7.68 (d, 2H, *J* = 8.8 Hz), 8.36 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 39.9 (2×q, NMe_2), 45.5 (s), 45.8 (s), 49.3 (d, C_6), 74.4 (d, C_{3a}), 108.3 (s, CN), 108.7 (s, CN), 110.1 (s, CN), 110.3 (s, CN), 114.9 (d, C_7), 124.7 (2×d), 130.5 (2×d), 139.1 (s), 141.4 (s, C_{7a}), 149.2 (s), 162.2 (s, C_2); MS (FAB^+) m/z (%) 404 (M^+ + 1, 37). Anal. Calcd for $C_{19}H_{13}N_7O_2S$ (403.42): C, 56.57; H, 3.25; N, 24.30; S, 7.95. Found: C, 56.31; H, 3.38; N, 24.42; S, 7.89.

(3a*R,6*S**)-4,4,5,5-Tetracyano-2-dimethylamino-6-(4-methoxyphenyl)-3a,6-dihydrobenzothiazole (13c).** Reaction time: 24 h. 1:1 EtOAc/*n*-hexane was used as eluent (R_f = 0.40); yield 90% (0.227 g); mp 162-163 ºC (colourles prisms, $CHCl_3/Et_2O$); IR (nujol) 1617, 1513, 1309, 1260, 1180, 1076, 1023, 850, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.91 MHz) δ 3.09 (s, 6H, NMe_2), 3.85 (s, 3H, OMe), 4.51 (t, 1H, *J* = 3.3 Hz, H_6), 5.43 (t, 1H, *J* = 3.3 Hz, H_{3a}), 5.71 (t, 1H, *J* = 2.9 Hz, H_7), 6.98 (d, 2H, *J* = 8.8 Hz), 7.36 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 39.8 (2×q, NMe_2), 45.6 (s), 46.7 (s), 49.3 (d, C_6), 55.4 (q, OMe), 74.3 (d, C_{3a}), 108.7 (s, CN), 109.2 (s, CN), 110.69 (s, CN), 110.71 (s, CN), 114.9 (2×d), 117.3 (d, C_7), 123.8 (s), 130.5 (2×d), 139.2 (s, C_{7a}), 161.1 (s), 162.4 (s, C_2); MS (FAB^+) m/z (%) 389 (M^+ + 1, 44). Anal. Calcd for $C_{20}H_{16}N_6OS$ (388.45): C, 61.84; H, 4.15; N, 21.63; S, 8.25. Found: C, 61.49; H, 4.29; N, 21.84; S, 8.20.

Preparation of the 2-dimethylamino-5-phenylanthra[1,2-*d*]thiazol-6,11-dione (14): Naphthoquinone (0.308 g, 1.95 mmol) was added to a solution of the 5-alkenyl-2-dimethylaminothiazole **1d** (0.15 g, 0.65 mmol) in acetonitrile (15 ml). The reaction mixture was stirred under reflux for 4 d. The solvent was evaporated to dryness and 1 *M* NaOH aqueous solution (10 ml) was added to the residue, which was later extracted with CH_2Cl_2 (3 × 5 ml). The organic extracts were dried over anhydrous $MgSO_4$ and after filtration of the inorganic salts, the solvent was removed under reduced pressure and the residue purified by silica-gel column chromatography eluting with 1:1 EtOAc/*n*-hexane (R*f* = 0.25); yield 72% (0.180 g); mp 291-292 ºC (orange prisms, $CHCl_3/Et_2O$); IR (nujol) 1670, 1594, 1562, 1408,

1350, 1258, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 3.39 (s, 6H, NMe_2), 7.31-7.33 (m, 2H), 7.38-7.47 (m, 3H), 7.66 (td, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.73 (td, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.75 (s, 1H, H_4), 8.04 (dd, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 8.30 (dd, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 40.4 (2×q, NMe_2), 122.9 (s), 126.6 (d), 126.7 (d), 126.8 (d), 128.1 (2×d), 128.2 (2×d), 128.8 (d, C_4), 130.1 (s), 133.2 (d), 133.5 (d), 134.0 (s), 134.1 (s), 136.7 (s), 139.9 (s), 142.9 (s), 152.2 (s), 171.7 (s), 183.4 (s, CO), 184.4 (s, CO); MS (EI, 70 eV) m/z (%) 385 (M^+ + 1, 27), 384 (M^+, 100), 383 (71), 369 (39), 368 (22), 355 (48), 354 (72), 341 (22), 340 (46). Anal. Calcd for $C_{23}H_{16}N_2O_2S$ (384.46): C, 71.85; H, 4.19; N, 7.29; S, 8.34. Found: C, 71.52; H, 4.43; N, 7.35; S, 8.36.

Preparation of the dimethyl 2-dimethylamino-6-phenylbenzothiazole-4,5-dicarboxylate (15): DMAD (0.371 g, 2.61 mmol) was added to a solution of the 5-alkenyl-2-dimethylaminothiazole **1d** (0.20 g, 0.87 mmol) in dry toluene (15 ml). The reaction mixture was stirred at 80 ºC for 10 d. The solvent was evaporated to dryness and the residue purified by silica-gel column chromatography eluting with 1:1 EtOAc/*n*-hexane (R*f* = 0.23); yield 30% (0.097 g); mp 175-177 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1730, 1599, 1563, 1534, 1415, 1307, 1238, 1214, 1120, 1093, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 3.24 (s, 6H, NMe_2), 3.60 (s, 3H, COOMe), 3.97 (s, 3H, COOMe), 7.31-7.41 (m, 5H), 7.65 (s, 1H, H_7); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 40.2 (2×q, NMe_2), 52.2 (q, COO<u>Me</u>), 52.6 (q, COO<u>Me</u>), 121.9 (s), 124.0 (d), 127.3 (d), 128.2 (2×d), 128.5 (2×d), 129.9 (s), 133.4 (s), 134.7 (s), 140.3 (s), 150.3 (s), 167.5 (s), 168.9 (s), 169.7 (s); MS (EI, 70 eV) m/z (%) 371 (M^+ + 1, 22), 370 (M^+, 100), 339 (46), 323 (37), 309 (23), 252 (62). Anal. Calcd for $C_{19}H_{18}N_2O_4S$ (370.43): C, 61.61; H, 4.90; N, 7.56; S, 8.66. Found: C, 61.24; H, 5.03; N, 7.83; S, 8.55.

Reaction of the 5-alkenyl-2-aminothiazole 1d with dimethyl fumarate. Dimethyl fumarate (1.877 g, 13.02 mmol) was added to a solution of the 5-alkenyl-2-aminothiazole **1d** (0.20 g, 0.87 mmol) in acetonitrile (15 ml). The reaction mixture was stirred under reflux for 6 d. The solvent was removed under reduced pressure and the residue purified by silica-gel column chromatography eluting with 3:1 → 1:1 CH_2Cl_2/EtOAc to give compounds **16**, **16'**, **17** and **17'**.

Dimethyl (3a*R,4*R**,5*S**,6*S**)-2-dimethylamino-6-phenyl-3a,4,5,6-tetrahydrobenzothiazole-4,5-dicarboxylate (16).** *R*$_f$ = 0.10 in 3:1 CH_2Cl_2/EtOAc; yield 33% (0.108 g); mp 121-123 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1736, 1618, 1435, 1267, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 3.00 (s, 6H, NMe_2), 2.99-3.03 (m, 1H, H_5), 3.50 (s, 3H, COOMe), 3.57 (s, 3H, COOMe), 3.68-3.72 (m, 1H, H_6), 3.82 (dd, 1H, *J* = 7.0 Hz, *J* = 4.8 Hz, H_4), 4.83 (dt, 1H, *J* = 7.0 Hz, *J* = 3.0 Hz, H_{3a}), 5.81 (t, 1H, *J* = 3.3 Hz, H_7), 7.20-7.24 (m, 3H), 7.28-7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 39.7 (2×q, NMe_2), 43.6 (d, C_6), 46.1 (d, C_4), 49.4 (d, C_5), 51.4 (q, COO<u>Me</u>), 52.1 (q, COO<u>Me</u>), 72.2 (d, C_{3a}), 118.0 (d, C_7), 126.8 (d), 128.0 (2×d), 128.5 (2×d), 141.3 (s), 143.2 (s), 161.5 (s, C_2), 171.9 (s, <u>C</u>OOMe), 174.2 (s, <u>C</u>OOMe); MS (EI, 70 eV) m/z (%) 374 (M^+, 7), 314 (27), 281 (24), 255 (30), 230 (21), 212 (23), 115 (25), 77 (23), 71 (23), 69 (43), 59 (100), 57 (28), 55 (23). Anal. Calcd for $C_{19}H_{22}N_2O_4S$ (374.46): C, 60.94; H, 5.92; N, 7.48; S, 8.56. Found: C, 60.79; H, 6.05; N, 7.42; S, 8.50.

Dimethyl (3a*R,4*S**,5*R**,6*S**)-2-dimethylamino-6-phenyl-3a,4,5,6-tetrahydrobenzothiazole-4,5-dicarboxylate (16').** *R*$_f$ = 0.23 in 3:1 CH_2Cl_2/EtOAc; yield 15% (0.049 g); mp 130-131 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1728, 1622, 1319, 1263, 1197, 1147 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 2.97 (dd, 1H, *J* = 11.9 Hz, *J* = 10.8 Hz, H_4), 3.01 (s, 6H, NMe_2), 3.39 (s, 3H, COOMe), 3.49 (dd, 1H, *J* = 11.9 Hz, *J* = 6.8 Hz, H_5), 3.73 (s, 3H, COOMe), 4.02 (dt, 1H, *J* = 6.8 Hz, *J* = 3.4 Hz, H_6), 4.64 (dt, 1H, *J* = 10.8 Hz, *J* = 2.8 Hz, H_{3a}), 5.56 (t, 1H, *J* = 3.4 Hz, H_7), 7.12-7.15 (m, 2H), 7.21-7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 39.4 (2×q, NMe_2), 43.9 (d, C_4), 44.1 (d, C_6), 47.8 (d, C_5), 51.4 (q, COO<u>Me</u>), 51.9 (q, COO<u>Me</u>), 75.7 (d, C_{3a}), 118.9 (d, C_7), 127.6 (d), 128.2 (2×d), 129.0 (2×d), 139.4 (s), 141.1 (s), 160.9 (s, C_2), 171.7 (s, <u>C</u>OOMe), 174.9 (s, <u>C</u>OOMe); MS (EI, 70 eV) m/z (%) 374 (M^+, 25), 315 (49), 283 (31), 255 (62), 230 (51), 115 (41), 77 (33), 69 (40), 59 (100). Anal. Calcd for $C_{19}H_{22}N_2O_4S$ (374.46): C, 60.94; H, 5.92; N, 7.48; S, 8.56. Found: C, 60.73; H, 5.99; N, 7.38; S, 8.88.

Dimethyl 2-dimethylamino-7-[1,2-bis(methoxycarbonyl)ethyl]-6-phenyl-4,5,6,7-tetrahydrobenzothiazole-4,5-dicarboxylates (17 and 17'). *R*$_f$ = 0.36 in 3:1 CH_2Cl_2/EtOAc; yield 20% (a 58:46 mixture of diastereomers) (0.090 g); mp 125-127 ºC (colourless prisms, $CHCl_3/Et_2O$); IR (nujol) 1735, 1554, 1342, 1265, 1200, 1164, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 2.23-2.28 (m, 2H, $H^M + H^m$), 2.68 (dd, 1H, *J* = 16.9 Hz, *J* = 10.3 Hz, H^M), 2.90-2.98 (m, 2H, $H^M + H^m$), 3.02 (s, 6H, $NMe_2{}^M$), 3.03 (s, 6H, $NMe_2{}^m$), 3.06 (s, 3H, $COOMe^m$), 3.06-3.12 (m, 2H, $H^M + H^m$), 3.17 (td, 1H, *J* = 8.5 Hz, *J* = 2.7 Hz, H^m), 3.22 (s, 3H, $COOMe^m$), 3.26 (s, 3H, $COOMe^M$), 3.34 (dd, 1H, *J* = 11.7 Hz, *J* = 10.8 Hz, H^m), 3.43 (dd, 1H, *J* = 11.8 Hz, *J* = 10.9 Hz, H^M), 3.62 (s, 3H, $COOMe^m$), 3.66 (s, 3H, $COOMe^M$), 3.68 (s, 3H, $COOMe^M$), 3.74 (s, 3H, $COOMe^m$), 3.75 (s, 3H, $COOMe^M$), 3.93-3.98 (m, 2H, , $H^M + H^m$), 4.01-4.06 (m, 2H, $H^M + H^m$), 7.19-7.29 (m, 6H), 7.32-7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 30.6 (t), 30.7 (t), 39.83 (2×q), 39.84 (2×q), 42.2 (d), 42.3 (d), 42.5 (d), 45.3 (d), 46.1 (d), 47.4 (d), 47.6 (d), 47.9 (d), 50.5 (d), 51.3 (d), 51.4 (q), 51.5 (q), 51.6 (q), 51.76 (q), 51.82 (q), 52.16 (q), 52.17 (q), 52.3 (q), 116.9 (s), 118.9 (s), 127.6 (d), 127.8 (2×d), 128.1 (2×d), 128.4 (2×d), 128.7 (2×d), 129.1 (d), 138.1 (s), 138.8 (s), 143.85 (s), 143.90 (s), 169.6 (s), 170.0 (s), 171.5 (s), 172.1 (s), 172.3 (s), 172.4 (s), 172.6 (s), 172.7 (s), 173.8 (2×s); MS (EI, 70 eV) m/z (%) 518 (M^+, 23), 373 (50), 341 (27), 313 (22), 281 (62), 255 (26), 254 (20), 211 (39), 114 (35), 59 (100). Anal. Calcd for $C_{25}H_{30}N_2O_8S$ (518.59): C, 57.90; H, 5.83; N, 5.40; S, 6.18. Found: C, 57.53; H, 5.95; N, 5.62; S, 6.07.

Reaction of the 5-alkenyl-2-aminothiazole 1d with methyl acrylate. Methyl acrylate (1.12 g, 13.1 mmol) was added to a solution of the 5-alkenyl-2-aminothiazole **1d** (0.20, 0.87 mmol) in acetonitrile (15 ml). The reaction mixture was stirred under reflux for 12 d. The solvent was removed under reduced pressure and the residue purified by silica-gel column chromatography eluting with 2:1 → 4:1 EtOAc/*n*-hexane to give a mixture of ***exo*-18** and ***endo*-18**.

Methyl (3a*R,4*R**,6*S**)-2-Dimethylamino-6-phenyl-3a,4,5,6-tetrahydrobenzothiazol-4-carboxylate (*endo*-18).** *R*$_f$ = 0.07 in 2:1 EtOAc/*n*-hexane; yield 15% (0.041 g); mp 101-103 ºC (colourless prisms, $CHCl_3$/ Et_2O); IR (nujol) 1741, 1624, 1448, 1304, 1263, 1186, 1165, 1099, 1069, 1018, 772, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 2.07 (dt, 1H, *J* = 13.9 Hz, *J* = 5.3 Hz, H_5), 2.39 (dt, 1H, *J* = 13.9 Hz, *J* = 7.1 Hz, $H_{5'}$), 2.99 (s, 6H, NMe_2), 3.36 (s, 3H, COOMe), 3.42 (m, 1H, H_6), 3.47 (td, 1H, *J* = 6.7 Hz, *J* = 4.9 Hz, H_4), 4.77 (dt, 1H, *J* = 6.4 Hz, *J* = 3.3 Hz, H_{3a}), 5.84 (t, 1H, *J* = 3.3 Hz, H_7), 7.16-7.21 (m, 3H), 7.27-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 32.9 (t, C_5), 39.7 (2×q, NMe_2), 40.4 (d, C_6), 41.8 (d, C_4), 50.8 (q, COO<u>Me</u>), 73.6 (d, C_{3a}), 118.8 (d, C_7), 126.3 (d), 127.9 (2×d), 128.3 (2×d), 141.7 (s), 145.2 (s), 161.1 (s, C_2), 172.9 (s, <u>C</u>OOMe); MS (FAB^+) m/z (%) 318 (M^+ + 2, 21), 317 (M^+ + 1, 100). Anal. Calcd for $C_{17}H_{20}N_2O_2S$ (316.42): C, 64.53; H, 6.37; N, 8.85; S, 10.13. Found: C, 64.35; H, 6.50; N, 9.02; S, 10.05.

Methyl (3a*R,4*S**,6*S**)-2-Dimethylamino-6-phenyl-3a,4,5,6-tetrahydrobenzothiazol-4-carboxylate (*exo*-18).** *R*$_f$ = 0.24 in 2:1 EtOAc/*n*-hexane; yield 6% (0.017 g); mp 110-112 ºC (colourless prisms, $CHCl_3$/*n*-hexane); IR (nujol) 1737, 1615, 1435, 1261, 1192, 1167, 1105, 1032, 733, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400.91 MHz) δ 1.97 (dm, 1H, *J* = 13.1 Hz, H_5), 2.36 (td, 1H, *J* = 13.1 Hz, *J* = 7.3 Hz, $H_{5'}$), 2.63 (ddd, 1H, *J* = 13.1 Hz, *J* = 10.5 Hz, *J* = 2.8 Hz, H_4), 2.99 (s, 6H, NMe_2), 3.64-3.67 (m, 1H, H_6), 3.69 (s, 3H, COOMe), 4.71 (dt, 1H, *J* = 10.5 Hz, *J* = 2.9 Hz, H_{3a}), 5.60 (t, 1H, *J* = 2.9 Hz, H_7), 7.19-7.24 (m, 3H), 7.29-7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.81 MHz) δ 33.7 (t, C_5), 39.4 (2×q, NMe_2), 40.9 (d, C_6), 42.3 (d, C_4), 51.8 (q, COO<u>Me</u>), 74.8 (d, C_{3a}), 119.7 (d, C_7), 126.6 (d), 128.0 (2×d), 128.5 (2×d), 141.8 (s), 144.7 (s), 160.9 (s, C_2), 175.3 (s, <u>C</u>OOMe); MS (EI, 70 eV) m/z (%) 317 (M^+ + 1, 25), 316 (M^+, 100), 257 (62), 256 (42), 255 (78), 230 (33), 212 (85), 201 (27), 181 (21), 154 (47), 128 (32), 115 (31), 88 (27). Anal. Calcd for $C_{17}H_{20}N_2O_2S$ (316.42): C, 64.53; H, 6.37; N, 8.85; S, 10.13. Found: C, 64.27; H, 6.52; N, 8.99; S, 9.98.

Supporting Information (see footnote on the first page of this article): It contains the ^1H,^1H-NOESY spectra of ***endo*-9b**, **16, 16', *endo*-18** and ***exo*-18**, the X-ray structure of ***endo*-9a**, the cartesian coordinates, electronic energies and imaginary frequencies of 5-alkenylthiazoles **1a-c** optimized at the B3LYP/6-31+G level and copies of the ^1H NMR and ^{13}C NMR for all new compounds.

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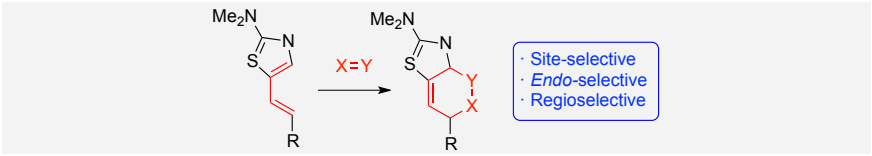

5-Alkenyl-2-aminothiazoles behave as active in-out dienes in [4+2] cycloadditions with a wide range of dienophiles. These processes are *endo*-selective with certain dienophiles of cyclic nature. Additionally, the reactions with non symmetric dienophiles are regioselective. The results point to a mechanism placed at the boundary between a highly asynchronous concerted mechanism and a stepwise one.

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5-Alkenylthiazoles as In-Out Dienes in Polar [4+2] Cycloaddition Reactions

Keywords: Cycloaddition / Nitrogen heterocycles / Cyclization / Zwitterions / / Reaction Mechanisms