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3-Amino-Substituted Isothiazole *S,S*-Dioxides as Dienophiles in Diels–Alder Cycloaddition Reactions with Cyclic, Acyclic and Heterocyclic Dienes[‡]

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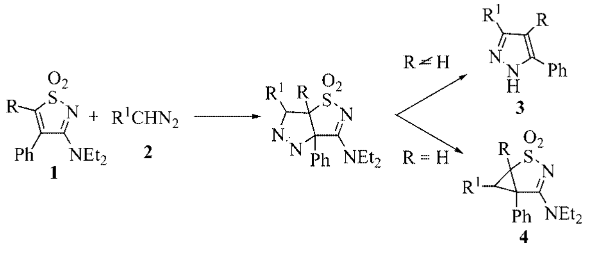
We report on the Diels–Alder reactions of differently substituted isothiazole dioxides with several kinds of dienes under diverse reaction conditions. Differences of reactivity and selectivity between the substituted isothiazoles are considered and the influence of the different reaction conditions on the outcome of the reactions discussed.

Introduction

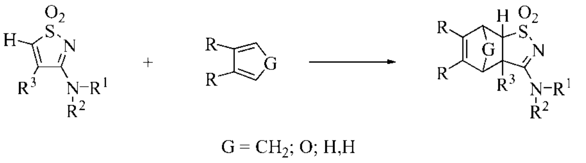
In the course of our studies on isothiazole *S,S*-dioxides we became interested in the preparation of anellated isothiazole dioxide derivatives.[1,2] 3-Amino-substituted isothiazole 1,1-dioxides are effective reaction partners for most dipoles in 1,3-cycloaddition reactions that form new heterocycles, all of which occur with high regioselectivity at the C-4=C-5 double bond.[3,4] These compounds are interesting starting materials for further transformations into different polyfunctionalized heterocycles, depending on their substitution pattern and reaction conditions, by the cleavage of one of the two rings present in the primary cycloadduct. As an example, Scheme 1 shows the two possible transformation pathways of the cycloadducts deriving from **1** and diazoalkanes **2**, which afford pyrazoles **3** or 2-thia-3-azabicyclo[3.1.0]hex-3-ene 2,2-dioxides **4** depending on the substitution at C-5 (Scheme 1).[5]



Scheme 1.

In continuation of our studies aiming to find new versatile 3-amino-substituted isothiazole dioxide derivatives, we report here on the use of the Diels–Alder reaction, which is one of the most powerful synthetic tools for the construction of six-membered ring systems and represents an attractive approach toward a range of bi- and tricyclic compounds containing the above fused heterocyclic nucleus.

The presence of the double bond in Diels–Alder cycloadducts, as well as the presence of the isothiazole ring, makes these compounds interesting substrates for further transformations. The rings of the bi- or tricyclic systems are, in principle, susceptible to cleavage, and which ring is cleaved easier depends on several factors, such as the reaction conditions and the substitution pattern. The combination of a Diels–Alder cycloaddition reaction and ring transformation could afford mono- or bicyclic compounds of both chemical and pharmacological interest. According to the above considerations, we began first of all to investigate the dienophilicity of 3-amino-substituted isothiazole dioxide systems toward different types of dienes under different reaction conditions (Scheme 2).



Scheme 2.

Two isothiazole derivatives, namely 3-(diethylamino)-4-(4-methoxyphenyl)isothiazole *S,S*-dioxide (**5**) and 3-(benzylamino)isothiazole *S,S*-dioxide (**6**; Figure 1) were used for these studies. Compounds **5** and **6** differ in their substitution at the C-4=C-5 double bond as an aryl substituent is present at C-4 in **5**. In principle, the lack of an aromatic ring at C-4 in compound **6** could influence the reactivity of the system substantially, both by altering the electronic distribution at the C-4=C-5 double bond and strongly reducing the steric hindrance. 2,3-Dimethylbutadiene (**7**), cy-

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[‡] Isothiazoles, XVI. Part XV: Ref.[2]

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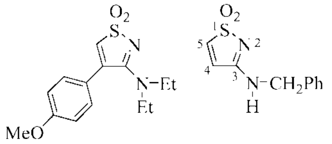
clopentadiene (**8**) and furan (**9**) were chosen as representatives of the main classes of dienes, i.e. acyclic, cyclic and heterocyclic ones, respectively. To achieve our synthetic target we investigated different reaction conditions, namely (i) thermally conducted, (ii) microwave- or ultrasound-assisted and (iii) Lewis acid mediated [$ZnCl_2$ and $Sc(OTf)_3$]. These studies revealed significant differences in reactivity between the compounds **5** and **6** and a marked influence of the reaction conditions on the outcome of the reaction, particularly in terms of stereoselectivity.



5 **6**

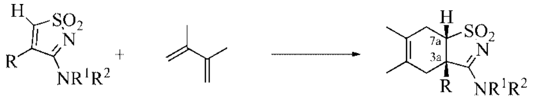
Figure 1. Isothiazole 1,1-dioxides **5** and **6**.

Results and Discussion

Diels–Alder Reaction Between Dienophiles 5/6 and 2,3-Dimethylbutadiene (7)

The [4+2] cycloaddition reactions between dienophiles **5** or **6** and diene **7**, mediated or not by Lewis acids, were performed at different temperatures and in both cases the influence of microwaves and ultrasound was examined. The results of these reactions are summarized in Table 1. Compound **6** did not undergo cycloaddition with **7**, neither at room temperature, nor in toluene at reflux, nor in a sealed tube at 110 °C (Entries 5–7), even when the diene was used in large excess. Similarly, isothiazole **5** did not react at room temperature (Entry 1) but afforded the cycloaddition product **10** when heated at 110 °C (Entry 2), with a substantial increase of the yields when the diene was used as the solvent (Entry 3). The application of non-conventional methods, such as ultrasound or microwaves, did not improve the reaction yields in the case of **5** and are inefficient for **6** (Entries 4 and 8).

It is well known that Diels–Alder reactions can be catalysed by a Lewis acid.[6] For this reason we selected two catalysts [ZnI_2 and $Sc(OTf)_3$] and repeated the cycloaddition reactions. The reactions between **5** and **7** either in toluene at reflux (Entry 10, 24 h) or in a sealed tube at 110 °C (Entry 11, 12 h), with ZnI_2 as the catalyst, gave the cycloadduct **10** in quantitative yields. Shortening of the reaction time could be achieved by using an excess of **7** under neat conditions (Entry 12, 2 h). Irradiation with microwaves did not result in any improvement of the reaction, neither in terms of yields, nor of reaction time (Entry 13). Similar results were obtained with **6**, which gave **11** (58–65% yield) when ZnI_2 was used (Entries 17 and 18). Turning to $Sc(OTf)_3$ as Lewis acid catalyst (Entries 14, 15 and 19) gave a notable increase of the reaction yield, particularly in the case of **6** (Entry 19; Scheme 3).



5,6 **7** **10,11**

5, **10**: R = MeO-C_6H_4; NR^1R^2 = NEt_2
6, **11**: R = H; NR^1R^2 = NHBn

Scheme 3.

Diels–Alder Reaction between Dienophiles 5/6 and Cyclopentadiene (8)

The cycloaddition of **5** and **6** with cyclopentadiene (**8**) was also studied under different reaction conditions in order to find the conditions suitable for controlling the *exo* and *endo* selectivity. When **8** was used as the diene, a mix-

Table 1. Diels–Alder reaction between dienophiles **5**/**6** and 2,3-dimethylbutadiene (**7**).

Entry	Reaction conditions[a]	Catalyst	Reagent	Time [h]	Adduct	Total yield [%]
1	CH_2Cl_2, 25 °C	–	**5**	96	**10**	–
2	toluene, 110 °C, sealed tube	–	**5**	21	**10**	32
3	110 °C, neat	–	**5**	10	**10**	96
4	110 °C, microwaves	–	**5**	4	**10**	61
5	CH_2Cl_2, 25 °C	–	**6**	96	**11**	–
6	110 °C, neat	–	**6**	48	**11**	–
7	toluene, 110 °C, sealed tube	–	**6**	48	**11**	–
8	50 °C, ultrasound	–	**6**	48	**11**	–
9	CH_2Cl_2, 25 °C	ZnI_2	**5**	96	**10**	–
10	toluene, 110 °C	ZnI_2	**5**	24	**10**	99
11	toluene, 110 °C, sealed tube	ZnI_2	**5**	12	**10**	99
12	110 °C, neat	ZnI_2	**5**	2	**10**	94
13	110 °C, microwaves	ZnI_2	**5**	4	**10**	60
14	110 °C, microwaves	$Sc(OTf)_3$	**5**	6	**10**	95
15	110 °C, neat	$Sc(OTf)_3$	**5**	10	**10**	95
16	CH_2Cl_2, 25 °C	ZnI_2	**6**	96	**11**	–
17	toluene, 110 °C	ZnI_2	**6**	5	**11**	65
18	toluene, 110 °C, sealed tube	ZnI_2	**6**	5	**11**	58
19	50 °C, ultrasound	$Sc(OTf)_3$	**6**	38	**11**	95

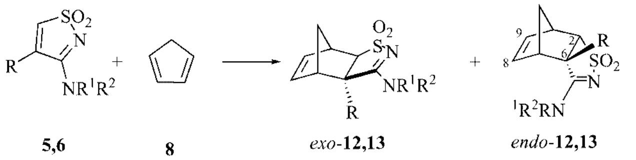
[a] An excess of diene was employed.

Table 2. Diels–Alder reaction between dienophiles **5**/**6** and **8**.

Entry	Reaction conditions[a]	Catalyst	Reagent	Time [h]	Adduct	Total yield [%] (*exo*/*endo*)
1	CH_2Cl_2, 25 °C	–	**5**	12	**12**	97 (1:4)
2	25 °C	–	**5**	16	**12**	>99 (1:4)
3	50 °C, ultrasound	–	**5**	6	**12**	>99 (1:4)
4	45 °C, microwaves	–	**5**	1.5	**12**	>99 (1:4)
5	CH_2Cl_2, 40 °C	–	**6**	5	**13**	79 (1:9)
6	25 °C	–	**6**	8	**13**	63 (1:9)
7	50 °C, ultrasound	–	**6**	5	**13**	80 (1:9)
8	45 °C, microwaves	–	**6**	0.5	**13**	66 (1:9)
9	25 °C	ZnI_2	**5**	12	**12**	99 (1:6)
10	25 °C	$Sc(OTf)_3$	**5**	5	**12**	99 (1:8)
11	50 °C, ultrasound	$Sc(OTf)_3$	**5**	1	**12**	99 (1:8)
12	45 °C, microwaves	$Sc(OTf)_3$	**5**	0.5	**12**	99 (1:8)
13	25 °C	ZnI_2	**6**	12	**13**	67 (1:16)
14	25 °C	$Sc(OTf)_3$	**6**	18	**13**	84 (0:1)
15	50 °C, ultrasound	$Sc(OTf)_3$	**6**	5	**13**	65 (0:1)
16	45 °C, microwaves	$Sc(OTf)_3$	**6**	1	**13**	70 (1:99)

[a] An excess of diene was employed.

ture of *exo*- and *endo*-**12** and *exo*- and *endo*-**13** was obtained from **5** or **6**, respectively (Table 2, Scheme 4).



5: R = MeO-C_6H_4; NR^1R^2 = NEt_2
6: R = H; NR^1R^2 = NHBn

12: R = MeO-C_6H_4; NR^1R^2 = NEt_2
13: R = H; NR^1R^2 = NHBn

Scheme 4.

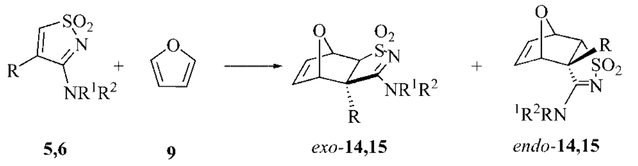
The reaction of **5** with **8** gave good yields under all reaction conditions tested. In contrast to the butadiene derivative, ultrasound and, above all, microwaves, dramatically accelerate the reaction rate with cyclopentadiene.

In the absence of catalyst, a 1:4 ratio of *exo* and *endo* diastereomers of **12** was obtained, whereas the use of a Lewis acid catalyst moved the diastereoselectivity toward the *endo* adduct: when ZnI_2 was used (Entry 9, Table 2) *exo*- and *endo*-**12** were obtained in a 1:6 ratio. A further improvement was found with $Sc(OTf)_3$, which exerts a marked influence on the stereochemical outcome of the reaction to afford *exo*/*endo*-**12** in a 1:8 ratio. An improvement in *endo* selectivity is particularly evident in the case of dienophile **6** in the uncatalysed reaction too (*exo*/*endo* = 1:9). With $Sc(OTf)_3$ as the catalyst, a complete *endo* selectivity was obtained both at room temperature (Entry 14) and when using ultrasound (Entry 15).

The *endo* or *exo* stereochemistry of the resulting adducts was determined from the chemical shifts in the ^1H NMR spectra and confirmed by performing NOE experiments. As an example, the main differences in the spectra of *endo*- and *exo*-**12** consist in the chemical shifts of the olefinic 8- and 9-H signals, which appear at δ = 6.18 and 6.60 ppm and at δ = 6.23 and 6.50 ppm, respectively, and the signals of the methylene bridge protons at δ = 1.95 and 2.02 ppm (*endo*-**12**) and at δ = 1.85 and 1.90 ppm (*exo*-**12**). Small differences can also be observed in the chemical shifts of the aromatic protons *ortho* to the methoxy group, which are more shielded in the *exo* isomer than in the corresponding *endo* one. Moreover, because of the shielding effect of the C-8=C-9 double bond, the chemical shift of the 2-H signal of the *exo* isomer exhibits an upfield shift of 0.5–0.6 ppm with respect to the corresponding signal of the *endo* isomer.[7]

Diels–Alder Reaction between Dienophiles 5/6 and Furan (9)

Compounds **5** and **6** did not afford adducts with furan (**9**) at room temperature (Scheme 5). Refluxing **5** and **6** in an excess of **9** with toluene or in the absence of co-solvent for several days afforded only traces of cycloaddition products together with a major amount of decomposition products and unaltered **5** or **6**. No improvements were observed when ultrasound or microwaves were applied.



5: R = MeO-C_6H_4; NR^1R^2 = NEt_2
6: R = H; NR^1R^2 = NHBn

14: R = MeO-C_6H_4; NR^1R^2 = NEt_2
15: R = H; NR^1R^2 = NHBn

Scheme 5.

The reaction was successful when catalysed by ZnI_2 or $Sc(OTf)_3$. The reaction with ZnI_2 gave different results in terms of yields and selectivity depending on the reaction conditions. Thus, starting from **5** and operating at room temperature, only traces of a mixture of the two adducts *exo*- and *endo*-**14** were detected, the major component of the reaction mixture being the starting material (Entry 1, Table 3). Performing the reaction in an excess of furan with microwaves or ultrasound gave *exo*- and *endo*-**14** in a 1:5 ratio in poor (Entry 2) to satisfactory (Entry 3) yields,

Table 3. Diels–Alder reaction between dienophiles **5**/**6** and **9**.

Entry	Reaction conditions[a]	Catalyst	Reagent	Time [h]	Adduct	Total yield (%) (*exo*/*endo*)
1	25 °C	ZnI_2	**5**	96	**14**	traces
2	50 °C, microwaves	ZnI_2	**5**	6	**14**	45 (1:5)
3	50 °C, ultrasound	ZnI_2	**5**	17	**14**	70 (1:5)
4	70 °C, sealed tube	ZnI_2	**5**	30	**14**	99 (1:2)
5	25 °C	$Sc(OTf)_3$	**5**	48	**14**	65 (1:5)
6	25 °C	ZnI_2	**6**	96	**15**	50 (1:1)
7	25 °C	$Sc(OTf)_3$	**6**	96	**15**	95 (3:1)
8	80 °C, sealed tube	ZnI_2	**6**	1.5	**15**	87 (1:0)
9	50 °C, microwaves	$Sc(OTf)_3$	**6**	2	**15**	88 (1:0)

[a] An excess of diene was employed.

respectively (Scheme 5). Increasing the temperature gave an increase of the yields: operating at 70 °C, in a sealed tube with an excess of furan, gave cycloadducts **14** almost quantitatively (99% yields, Entry 4) with a 1:2 *exo*/*endo* ratio. It should be noted that a substantial change in the selectivity is apparent. Even though the *exo* adduct remains the minor component, it is obtained in much higher amounts than under the other conditions tested (Entry 4 vs. Entry 3). $Sc(OTf)_3$ is effective even at room temperature, giving a mixture of *exo*- and *endo*-**14** in 65% yield (1:5 ratio, Entry 5).

The catalytic cycloaddition reaction also occurs with **6**. Interestingly, a higher reactivity of **6** with respect to **5** was found and a considerable increase of the *exo* adduct was observed. In fact, performing the reaction at room temperature gave a 1:1 mixture of *exo*- and *endo*-**15** in 50% yield (Entry 6). $Sc(OTf)_3$ was more efficient and afforded cycloadducts **15** in 95% yield (3:1 ratio, Entry 7) at room temperature. Once again, increasing the temperature provoked a progressive increase of the *exo* adduct. At 80 °C in a sealed tube with ZnI_2 (Entry 8), or with microwaves and $Sc(OTf)_3$ (Entry 9), an 85–90% yield of *exo* adduct, as the sole reaction product, was obtained in less than 2 h.

We hypothesize that the *exo* selectivity observed in these cases is the result of a retro Diels–Alder process that favours the thermodynamically most stable *exo* adduct.[8] As a confirmation, a sample of a mixture of *exo*- and *endo*-**15** (1:5) was independently treated with furan in a sealed tube at 80 °C (Entry 8), and the reaction mixture was analysed by ^1H NMR spectroscopy every 30 min. The spectra show a progressive change of the *exo*/*endo* ratio in favour of the *exo* isomer, which indicates that a retro Diels–Alder reaction takes place.

The *endo* or *exo* stereochemistry of adducts **14** and **15** was determined by comparison with adducts **12** and **13** and confirmed by NMR experiments. One of the main features for these compounds is the upfield shift of the 2-H signal in the *exo* isomer relative to the corresponding signal of the *endo* isomer, thus confirming the shielding effect of the C-8=C-9 double bond in the *exo* isomer.

Conclusions

In conclusion, we can state that isothiazoles **5** and **6** exhibit a reactivity that allows their complete reaction with acyclic, cyclic and heterocyclic dienes. To achieve high reaction yields the presence of a Lewis acid is required. $Sc(OTf)_3$ appears to be the most effective catalyst as it allows milder conditions and affords high yields of cycloadducts in all cases. Compound **5**, which is substituted with a *p*-methoxyphenyl group at C-4, is more reactive than the corresponding unsubstituted compound **6** in most cases.

A difference in the stereochemical outcome was also observed between the two dienophiles. Compound **5** gave a mixture of *exo* and *endo* adducts in all cases, with the latter being the preferred one. A major selectivity was found for the unsubstituted compound **6** depending on the kind of the diene. Thus, the reaction between **6** and cyclopentadiene affords *endo*-**13** as the sole reaction product and that with furan only *exo*-**15**.

The preferred formation of the *endo* isomer is not unexpected according to the "*endo* rule" of Diels–Alder reactions.[9] In our opinion, the formation of a significant amount of *exo* isomer in the case of the reaction of **5** with **8** could be ascribed to secondary orbital interactions between the diene and the aryl substituent on C-4, which are lacking in **6**, hence favouring an *exo* approach rather than an *endo* one (Figure 2).

As regards the inversion in selectivity observed with furan (i.e. *exo* selectivity), it is clearly the result, as discussed above, of a retro-cycloaddition reaction which produces the

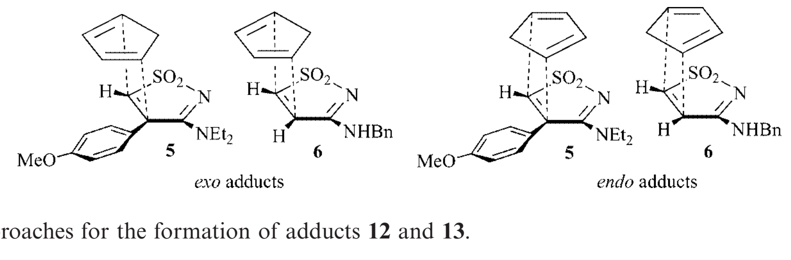


Figure 2. *exo* and *endo* approaches for the formation of adducts **12** and **13**.

thermodynamic *exo* adduct as the major (for **5**) or exclusive (for **6**) product.

Taken together, these studies have demonstrated the possibility of synthesizing polycyclic isothiazole dioxides with a different substitution pattern in high yields and with a high or complete stereoselectivity depending on the starting isothiazole and the reaction conditions.

Experimental Section

General Information: All reagents and solvents were obtained from commercial sources. Cyclopentadiene was distilled before use. Compounds **5** and **6** were synthesized according to the literature.[10,11] Column chromatography was performed on Kieselgel 60 (70–230 mesh ASTM) with ethyl acetate/cyclohexane as eluent. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 500 or a Varian Gemini 200 in the solvent indicated. IR spectra were recorded with a Jasco I.R. Report 100. Microwave experiments were conducted with an MLS GmbH/Milestone Ltd. instrument and mass spectra were recorded with a Finningan MD 800 instrument (70 eV). HPLC analyses were conducted with an HP 1050 instrument (DAD detector, Merck Hitachi L7100 injector, loop 20 µL).

General Procedure for the Cycloaddition Reactions of 5 and 6 With 7: A mixture of **5** or **6** (0.17 mmol) and **7** (2 mL) was treated under the conditions shown in Table 1 and the reaction checked by TLC and ^{1}H NMR spectroscopy. Excess **7** was evaporated under reduced pressure and the residue taken up with dichloromethane (20 mL) and washed with water (2 × 10 mL). The organic layer was separated, dried with Na_2SO_4, filtered and the solvents were evaporated to dryness to afford the cycloadducts **10** or **11**. Yields are reported in Table 1.

10: M.p. 108 °C. ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, J = 7 Hz, 3 H, $\mathrm{CH_2C}\mathit{H}_3$), 1.26 (t, J = 7 Hz, 3 H, $\mathrm{CH_2C}\mathit{H}_3$), 1.75 (s, 3 H, 6-Me), 1.84 (s, 3 H, 5-Me), 2.17 (dd, J = 7.9, J = 18.4 Hz, 1 H, 7-H^{cis}), 2.59–2.67 (m, 3 H, 4-H, 7-H^{trans}), 2.96–3.04 (m, 2 H), 3.48–3.64 (m, 2 H, NCH_2), 3.55 (d, J = 7.9 Hz, 1 H, 7a-H), 3.82 (s, 3 H, OMe), 6.90 (d, J = 8.7 Hz, 2 H, ArH), 7.09 (d, J = 8.7 Hz, 2 H ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.8, 12.0 (CH_3), 18.0 (CH_3, 6-Me), 18.5 (CH_3, 5-Me), 25.5 (C-7), 34.8 (C-4), 42.4, 43.2 (NCH_2), 54.1 (C-3a), 54.6 (OCH_3), 65.3 (C-7a), 114.1, 126.1 (ArCH), 120.9, 123.7 (C-5, C-6), 133.0 (C^q), 158.2 (C-3), 170.9 (C^q) ppm. MS: *m*/*z* (%) = 377.3 (100). $C_{20}H_{28}N_2O_3S$ (376.51): calcd. C 63.80, H 7.50, N 7.44; found C 63.94, H 7.22, N 7.25.

11: M.p. 142 °C. ^{1}H NMR (CD_3COCD_3): δ = 1.67 (s, 3 H, 5-Me), 1.74 (s, 3 H, 6-Me), 2.19 (dd, J = 6.4, J = 15.6 Hz, 1 H, 4-H^{trans}), 2.27–2.32 (m, 2 H, 4-H^{cis}, 7-H^{cis}), 2.57 (d, J = 15.6 Hz, 1 H, 7-H^{trans}), 3.41–3.46 (m, 1 H, 3a-H), 3.53–3.57 (m, 1 H, 7a-H), 4.54 (dq, J = 5.2, J = 14.5, J = 36 Hz, 2 H, CH_2Ph), 6.22 (br. s, 1 H, NH), 7.28–7.38 (m, 5 H, ArH) ppm. ^{13}C NMR (CD_3COCD_3): δ = 18.2 (CH_3, 6-Me), 18.6 (CH_3, 5-Me), 27.7 (CH_2, C-7), 31.0 (CH_2, C-4), 43.1 (CH, C-3a), 46.7 (CH_2, CH_2Ph), 124.1 (C^q, C-Me), 125.6 (C^q, C-Me), 127.4, 127.5, 128.2 (CH, ArCH), 135.8 (C^q, ArC), 168.9 (C^q, C-3) ppm. MS: *m*/*z* (%) = 303.2 (100), 248.8 (20). $C_{16}H_{20}N_2O_2S$ (304.41): calcd. C 63.13, H 6.62, N 9.20; found C 63.02, H 6.50, N 8.95.

General Procedure for the Cycloaddition Reaction of 5 or 6 with 8: A mixture of **5** or **6** (0.17 mmol) and **8** (2 mL) was treated under the different conditions shown in Table 2 and the reaction checked by ^{1}H NMR spectroscopy. Excess cyclopentadiene was evaporated under reduced pressure and the residue was crystallized from ethyl acetate/cyclohexane (1:20) to afford the two cycloadducts **12** or chromatographed on a silica gel column using ethyl acetate/cyclohexane (100:0→0:100) to afford the cycloadducts **13**. Yields are reported in Table 2. The two pairs of diastereoisomers (*exo*-**12**/*endo*-**12** or *exo*-**13**/*endo*-**13**) were separated only by HPLC (chiral OD; 2-propanol/*n*-hexane, 30:70). Nevertheless, in the case of **12**, every signal could be assigned to the *exo* or *endo* isomer by the way of NMR experiments (NOESY, COSY, Hetcor). Therefore, for the sake of clarity, the NMR data of *exo*- and *endo*-**12** are described separately. As for **13**, *endo*-**13** was completely characterised while *exo*-**13** was obtained under the best conditions (see Table 2, Entry 32) only in traces and always as a mixture with a major amount of *endo*-**13**.

***endo*-12:** ^{1}H NMR ($CDCl_3$): δ = 0.70 (t, J = 7 Hz, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 1.13 (t, J = 7 Hz, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 2.02 (m, CH, 10-H), 1.95 (m, CH, 10-H), 3.15 (m, 2 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.26 (m, 2 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.43 (m, 1 H, 1-H), 3.68 (m, 1 H, 7-H), 3.81 (s, 3 H, *p*-MeO), 3.84 (1 H, 2-H), 6.18 (dd, J = 5.4, 2.9 Hz, 1 H, 8-H), 6.60 (dd, J = 5.4, 3.1 Hz, 1 H, 9-H), 6.91–7.39 (m, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_3, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 12.5 ($CH_3$, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 42.6 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 43.9 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 45.9 (CH, C-1), 47.3 (CH, C-7), 50.8 (CH_2, C-10), 55.4 (CH_3, *p*-MeO), 72.2 (C^q, C-6), 74.7 (CH, C-2), 114.8, 129.3 (CH, ArCH), 132.0 (C^q, ArC), 133.5 (CH, C-8), 139.4 (CH, C-9), 168.0 (C^q, C-5), 159.0 (C^q, ArC-OMe) ppm.

***exo*-12:** ^{1}H NMR ($CDCl_3$): δ = 0.52 (m, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 1.12 (t, J = 7 Hz, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 1.85, 1.90 (2 m, 2 H, 10-H), 3.15 (m, 2 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.26 (m, 3 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$, 2-H), 3.45 (m, 1 H, 1-H), 3.60 (m, 1 H, 7-H), 3.78 (s, 3 H, *p*-MeO), 6.23 (dd, J = 5.5, 2.9 Hz, 1 H, 9-H), 6.53 (dd, J = 5.5, 2.7 Hz, 1 H, 8-H), 6.86–7.39 (m, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.5 (CH_3, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 12.7 ($CH_3$, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 43.2 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 44.9 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 45.7 (CH, C-1), 46.3 (CH_2, C-10), 47.8 (CH, C-7), 55.3 (CH_3, *p*-MeO), 69.9 (C^q, C-6), 73.4 (CH, C-2), 114.3, 127.7 (CH, ArCH), 131.8 (C^q, ArC-OMe), 137.0 (CH, C-9), 137.7 (CH, C-8), 158.9 (C^q, ArC-OMe), 168.2 (C^q, C-5) ppm. MS (ESI): *m*/*z* (%) = 383.3 (100) [M^+ + Na] $C_{19}H_{24}N_2O_3S$ (360.47): calcd. C 63.31, H 6.71, N 7.77; found C 63.10, H 6.80, N 7.45.

***endo*-13:** M.p. 154 °C. IR (KBr tablet): $\tilde{\nu}_{max}$ = 3294.7 (NH) cm^{-1}. ^{1}H NMR (CD_3COCD_3): δ = 1.65 (m, 2 H, 10-H), 3.32 (m, 1 H, 1-H), 3.43 (m, 1 H, 7-H), 4.02 (dd, J = 4, 8.3 Hz, 1 H, 2-H), 4.13 (dd, J = 4, 8.3 Hz, 1 H, 6-H), 4.45 (m, 2 H, CH_2Ph), 6.05 (m, 1 H, 8-H), 6.31 (m, 1 H, 9-H), 7.34–7.44 (m, 5 H, ArH), 7.66 (br. s, 1 H, NH) ppm. ^{13}C NMR (CD_3COCD_3): δ = 44.5 (CH, C-1), 44.8 (CH, C-7), 45.7 (CH_2, C-10), 51.0 (CH_2, CH_2Ph), 52.9 (CH, C-6), 62.8 (CH, C-2), 126.7, 126.9, 127.3 (CH, ArCH), 131.9 (CH, C-9), 135.8 (CH, C-8), 137.2 (C^q, ArC), 166.5 (C^q, C-5) ppm. MS: *m*/*z* (%) = 288.9 (20), 222.9 (100). $C_{15}H_{16}N_2O_2S$ (288.36): calcd. C 62.48, H 5.59, N 9.71; found C 62.79, H 5.65, N 9.47.

General Procedure for the Cycloaddition Reactions of 5 and 6 with 9: A mixture of **5** or **6** (0.17 mmol) and **9** (2 mL) was treated under the different conditions shown in Table 3 and the reaction checked by TLC and ^{1}H NMR spectroscopy. The excess furan was evaporated under reduced pressure and the residue was chromatographed on a silica gel column using ethyl acetate/cyclohexane (100:0→0:100, highlighting by ninhydrin) to afford the cycloadduct *endo*-**14** in pure form and *exo*-**14** always as a mixture with *endo*-**14**. Concerning **15**, *exo*-**15** was completely characterised, whereas *endo*-**15** was always obtained as a mixture with *exo*-**15**. Yields are reported in Table 3.

***endo*-14:** M.p. 144 °C. IR (KBr tablet): $\tilde{\nu}_{max}$ = 3436.3 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 7 Hz, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 1.20 (t, *J* = 7 Hz, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 2.96–3.17 (m, 2 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.36–3.50 (m, 2 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.81 (s, 3 H, *p*-MeO), 3.98 (d, *J* = 5 Hz, 1 H, 2-H), 5.34 (d, *J* = 5 Hz, 1 H, 1-H), 5.46 (s, 1 H, 7-H), 6.50 (dd, *J* = 1.5, 5.5 Hz, 1 H, 8-H), 6.89–6.94 (m, 3 H, 9-H, ArH), 7.30 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.5 (CH_3, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 13.0 ($CH_3$, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 43.6 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 43.8 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 55.8 ($CH_3$, *p*-MeO), 71.0 (C^q, C-6), 73.5 (CH, C-2), 80.1 (CH, C-1), 84.7 (CH, C-7), 115.4, 127.4 (CH, ArCH), 130.6 (C^q, ArC), 134.4 (CH, C-8), 139.2 (CH, C-9), 159.7 (C^q, ArC-OMe-*p*), 166.9 (C^q, C-5) ppm. MS (ESI): *m*/*z* (%) = 385.1 (100) [$M^+ + Na$]. $C_{18}H_{22}N_2O_4S$ (362.44): calcd. C 59.65, H 6.12, N 7.73; found C 59.77, H 6.32, N 7.54.

***exo*-14:** ^{1}H NMR ($CDCl_3$): δ = 0.53 (m, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 1.20 (m, 3 H, $\mathrm{NCH_2C}\mathit{H}_3$), 3.20–3.31 (m, 1 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.33–3.45 (m, 2 H, 2-H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.35 (s, 1 H, 2-H), 3.50–3.60 (m, 2 H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_3}$), 3.78 (s, 3 H, *p*-MeO), 5.55, 5.56 (2 br. s, 2 H, 1-H, 7-H), 6.60, 6.85 (2 dd, *J* = 1.6, 5.8 Hz, 1 H, 8-H, 9-H), 6.90 (d, *J* = 9 Hz, 2 H, ArH), 7.33 (d, *J* = 9 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.9 (CH_3, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 11.9 ($CH_3$, $\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$), 42.5 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 44.4 ($CH_2$, $\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$), 71.2 (C^q, C-6), 71.4 (CH, C-2), 80.8, 81.9 (CH, C-1, C-7), 113.0, 128.4 (CH, ArCH), 128.9 (C^q, ArC), 136.1, 136.4 (CH, C-8, C-9), 158.4 (C^q, ArC-OMe-*p*), 166.1 (C^q, C-5) ppm.

***endo*-15:** ^{1}H NMR (CD_3COCD_3): δ = 4.12–4.16 (m, 1 H, 2-H), 4.30–4.35 (m, 1 H, 6-H), 4.43 (d, *J* = 5.5 Hz, 2 H, CH_2Ph), 5.30 (m, 2 H, 1-H, 7-H), 6.41 (d, *J* = 5.8 Hz, 1 H, 8-H), 6.62 (d, *J* = 5.8 Hz, 1 H, 9-H), 7.31–7.38 (m, 5 H, ArH), 7.91 (br. s, 1 H, NH) ppm. ^{13}C NMR (CD_3COCD_3): δ = 46.8 (CH_2, CH_2Ph), 54.5 (CH, C-6), 62.6 (CH, C-2), 79.2 (CH, C-1/C-7), 80.1 (CH, C-1/C-7), 127.8, 128.29, 128.8 (CH, ArCH), 133.4 (CH, C-8), 136.6 (CH, C-9), 137.7 (C^q, ArC), 165.3 (C^q, C-5) ppm.

***exo*-15:** M.p. 168 °C. IR (KBr tablet): $\tilde{\nu}_{max}$ = 3436.2, 3336.9 (NH) cm^{-1}. ^{1}H NMR (CD_3COCD_3): δ = 3.52 (d, *J* = 6.9 Hz, 1 H, 2-H), 3.78 (d, *J* = 6.9 Hz, 1 H, 6-H), 4.54 (d, *J* = 5.5 Hz, 2 H, CH_2Ph), 5.34 (m, 2 H, 1-H, 7-H), 6.53 (dd, *J* = 1.7, 5.7 Hz, 1 H, 8-H), 6.62 (dd, *J* = 1.7, 5.7 Hz, 1 H, 9-H), 7.32–7.40 (m, 5 H, ArH), 7.89 (br. s, 1 H, NH) ppm. ^{13}C NMR (CD_3COCD_3): δ = 46.8 (CH_2, CH_2Ph), 54.6 (CH, C-6), 62.9 (CH, C-2), 80.9 (CH, C-1), 82.1 (CH, C-7), 127.7, 128.08, 128.8 (CH, ArCH), 137.4 (CH, C-9), 137.5 (CH, C-8), 137.8 (C^q, ArC), 166.2 (Cq, C-5) ppm. MS (ESI): *m*/*z* (%) = 313.4 [$M^+ + Na$]. $C_{14}H_{14}N_2O_3S$ (290.34): calcd. C 57.92, H 4.86, N 9.65; found C 58.12, H 4.66, N 9.43.

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