HIGH-PRESSURE DIELS-ALDER REACTIONS OF 1-METHOXYCARBONYL-3-METHYLTHIO- AND -3-PHENYLTHIOPYRROLE. AN EFFICIENT ENTRY TO 7-AZABICYCLO [2.2.1] HEPTANES.

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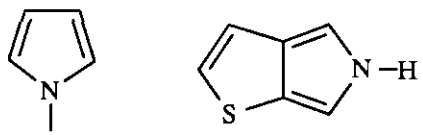
Abstract- The high pressure Diels-Alder reaction of new 3-thiosubstituted N-carbonyl-pyrrole derivatives 5 with electron-poor alkenes afforded 2-thiosubstituted 7-azabi-cyclo[2.2.1]hept-2-enes 9, 10 and 11 regiospecifically in high over-all yields.

In order to find a short entry into azabicycloheptanes which can easily be functionalized we have studied the cycloaddition of new 3-thiosubstituted pyrroles with electron-poor olefins.
It is already known that pyrrole and its derivatives show a poor reactivity in Diels-Alder reactions[1,2]. This relative inertness is ascribed to the partially aromatic character of the pyrrole system. A few cycloadducts have been reported when very reactive dienophiles were used (e.g. hexafluoroDewarbenzene, benzyne, allene dicarboxylates)[1,3].
It appeared that the use of a N-carbonyl substituent enhances the reactivity[4] probably by diminishing the aromatic character of the pyrrole ring. But even in these cases reactive dienophiles such as dimethyl acetylenedicarboxylate or benzyne have to be used.
Only a few pyrroles have been reported which are more reactive in Diels-Alder cycloaddition reactions than the N-carbonylpyrroles: the N-oxysubstituted pyrroles[5] 1 and 5H-thieno [2,3-c]pyrrole[6] 2.

Figure 1



1a: R=H
1b: R=COPh

1 2

Both react with N-phenylmaleimide. In the latter case, however, the reaction with the dienophile is not accompanied by loss of aromaticity, since the formed product is in fact a thiophene derivative.
It has also been demonstrated[2] that the application of external pressure is necessary for the cycloaddition of N-carbonylpyrroles with the reactive dienophile N-phenylmaleimide. These cycloadditions are accompanied by a large decrease in activation volume and are therefore strongly enhanced by pressure.

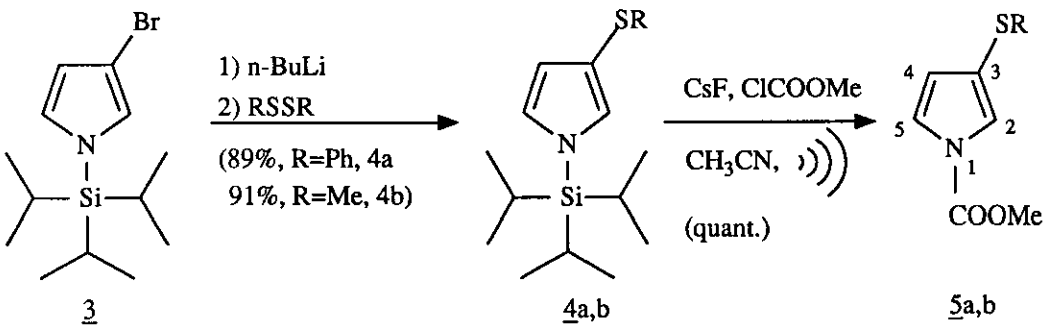
We envisaged that the introduction of alkyl- or aryl-thio groups as donating substituents should further enhance the reactivity toward electrophiles by raising the HOMO energy level of the pyrroles.

By exploring this concept we now report a new synthesis of some reactive 3-thio substituted pyrroles and their high pressure cycloadditions with dienophiles. For the first time it appeared to be possible to perform a high pressure Diels-Alder reaction of these pyrroles with alkenes having only one electron withdrawing substituent.

Recently 3-substituted pyrroles have been prepared through an electrophilic substitution reaction using a directing group on either the 1- or the 2-position[7]. After removal of the directing group, the 3-substituted pyrrole can be isolated. Following this route, Kozikowski[8] made the 3-bromopyrrole 3 using the bulky N-triisopropylsilyl directing group (scheme 1).

Compound 3 undergoes a rapid halogen-metal exchange with n-butyllithium in tetrahydrofuran to generate the corresponding 3-lithiopyrrole. Conversion of this species with the electrophilic diphenyl disulfide leads[8] to the corresponding 3-substituted pyrroles 4a in good yields.

Scheme 1

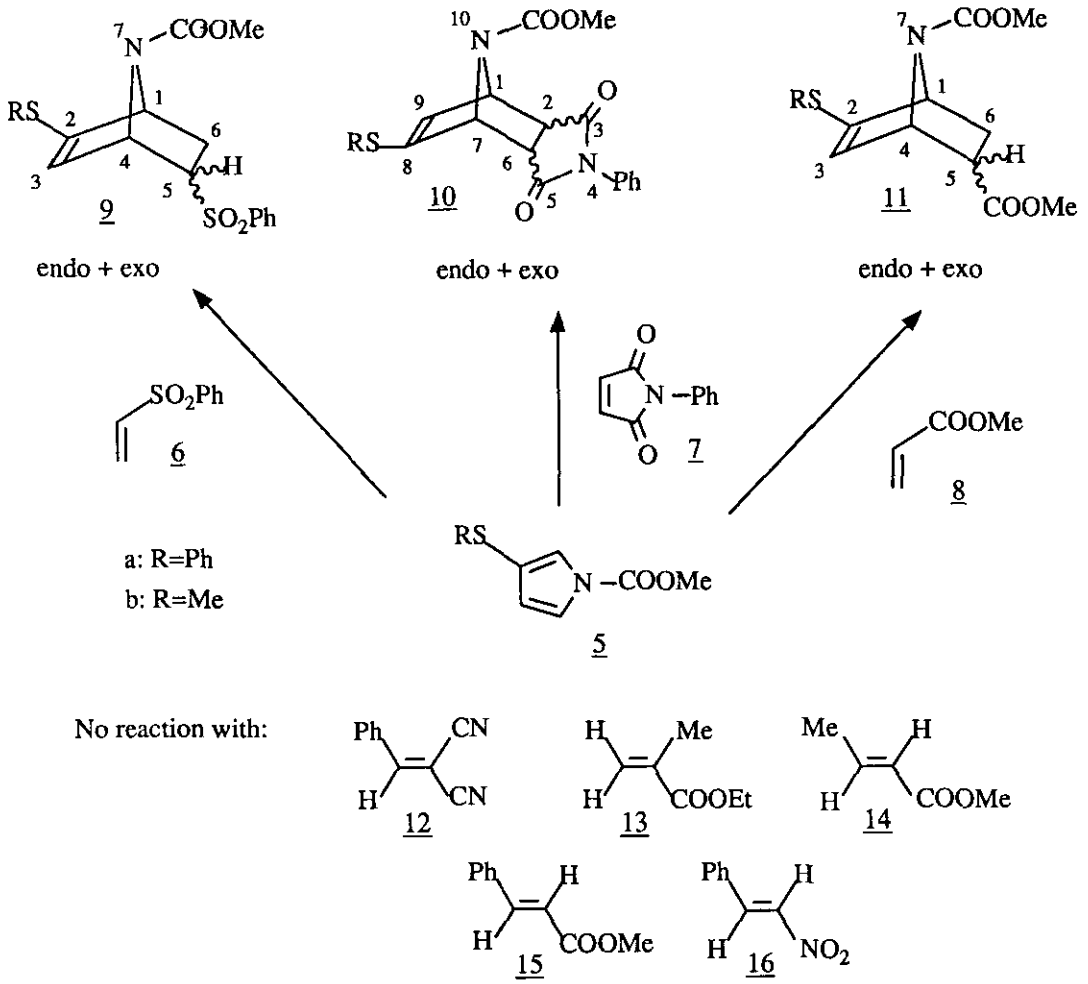


3 4a,b 5a,b

Following this route, after optimalizing the reaction conditions, we prepared in good yields not only the 3-phenylthiopyrrole 4a, but also via an analogous manner, the 3-methylthiopyrrole 4b. Subsequently we discovered a simple one-pot conversion of pyrroles 4 into the N-methoxycarbonylpyrroles 5. The silyl protecting group is removed with fluoride ion and the in situ formed pyrrolo-N-anion reacts with methyl chloroformate. The use of the extremely hygroscopic tetra-n-butylammonium fluoride resulted in only 50% conversion of 4 into 5. The combination of thoroughly dried cesium fluoride and acetonitrile as a solvent, using ultrasonic irradiation to disperse the salt, led to a quantitative conversion.

The cycloaddition reactions of pyrroles 5a and 5b and a variety of dienophiles were subsequently investigated (scheme 2). The reaction conditions were chosen as follows: temperatures between ambient and 50 ^{o}C, a pressure of about 12 Kbar and a reaction time of 16 hours, with acetonitrile as the standard solvent.

Scheme 2



High yields (ca. 80%) of the cycloadducts 9, 10 and 11 were obtained when the dienophiles 6, 7 and 8 were used. However, using other dienophiles which are sterically more hindered (14, 15 and 16) or less electron-poor (13 and 14) resulted only in the isolation of the reactants. It is surprising however that the strongly electron-poor dicyanostyrene 12 (in some Diels-Alder reactions an *excellent dienophile*) *does not react*[10].

The methylthio group is a stronger electron-donating substituent than the thiophenyl function. This becomes evident when the cycloaddition of 5a and 5b with 6 is stopped after 6 hours of reaction at ambient temperature and 12 Kbar of pressure. The reaction of 5a was only for 9% completed, whereas the reaction of 5b with 6 resulted in a 58% conversion to compound 9.

The reaction is regioselective as indicated in scheme 2. This is confirmed by nmr-decoupling experiments. Irradiation of proton H-4 (δ=4.98 ppm) of the endo product 11a causes decoupling of the protons H-3 and H-5.

Except for the formation of 10a and 10b no endo/exo selectivity was observed in these cycloadditions. The influence of the solvent on the endo/exo ratio of 10a, 10b and 11a determined by nmr measurements of the reaction mixtures is summarized in table 1.

Table 1: the influence of the solvent on the endo/exo ratio.

	endo/exo		
Solvent	10a	10b	11a
CH_3CN	8/1	9/1	1/1
CH_2Cl_2	8/1	9/1	1/1
C_6H_6	5/3	5/4	1/1
Et_2O	8/1	9/1	1/1

A special solvent effect has been found for benzene[9] in the cycloaddition of 5a and 5b with 7. The table shows that this is not caused by the polarity of the solvent.

EXPERIMENTAL

General Melting points are uncorrected. ^{1}H-Nmr spectra were taken in $CDCl_3$ solution on a Bruker WH-90 apparatus with tetramethylsilane (δ=0) as an internal standard. Mass spectra were obtained using a double-focusing G 7070E spectrometer. The mass spectra of the Diels-Alder cycloadducts showed in nearly all cases the patterns of the reactants (caused by retro Diels-Alder reactions during the measurement). Elemental analyses were performed with a Carlo Erba type 1106 elemental analyzer. All the obtained analyses were satisfactory (C,H,N; $\leq$ 0.4%). For chromatography Merck silica gel type 60 (size 70-230 mesh) was used, except when flash-chromatography was applied. In the latter case we used the same type silica gel size 230-400 mesh. Drying of organic solvents was done with sodium sulfate, unless noted otherwise. The THF used in the experiments was previously dried by destillation over sodium. Triisopropylsilyl chloride and the dienophiles were used as commercial products (obtained by Janssen Chimica). 1-Triisopropylsilylpyrrole was prepared as described in literature[11]. The high-pressure experiments were run in an apparatus equipped with a one-wall-piston cylinder for pressures up to 12 Kbar (1.2 GPa) having an initial volume of 70 ml. The vessel is closed from below with a steel stopper and from above with a mobile piston. Heating occurs by pumping oil between the vessel and a second

wall. Reactions were performed in 1.5 ml Teflon ampules closed by screwed stainless steel stoppers. Four of these ampules can be inserted into the high pressure apparatus filled with n-hexane as a transmission medium.

3-Bromo-1-(triisopropylsilyl)pyrrole (3). We used a slight simplification on the procedure given in the literature[9], using the N-bromosuccinimide (NBS) as a solid material. A solution of 17.3 g 1-triisopropylsilyl pyrrole in 500 ml of dried THF cooled to -78 °C was kept under nitrogen. Then 13.5 g of NBS was added as a solid material in a single portion. The reaction mixture was stirred for 3 h before allowing to warm up to room temperature. After concentration of the reaction mixture under reduced pressure, carbon tetrachloride was added to precipitate the succinimide, and this mixture was filtered and washed. After concentration of the filtrates the resulting oil was chromatographed (with CCl_4 as eluent), yielding 22.0 g of 3 (94%) as a colorless oil. bp 97-99 °C (0.4 mm Hg).

3-Phenylthio-1-(triisopropylsilyl)pyrrole (4a). To 11.4 ml of a 1.6 M solution of n-butyllithium in hexane, cooled to -20 °C, was added 40 ml of dried THF. The mixture was cooled to -78 °C. A solution of 5.0 g (16.6 mmol) of 3 in 40 ml of dried THF was added dropwise during 15 min. The reaction mixture was kept at -78 °C for another 30 min and then 4.3 g (19.9 mmol) of diphenyl disulfide in 20 ml of dried THF was added. The solution was allowed to warm to room temperature and quenched with water (40 ml). After extraction with ether the extract was dried with $MgSO_4$ and concentrated under reduced pressure. Futher purification was done by chromatography ($CHCl_3$ 1/CCl_4 1). Crystallization (MeOH) gave 4.9 g of 4a (89%). mp 65-66 °C.

3-Methylthio-1-(triisopropylsilyl)pyrrole (4b). Procedure as described above, using 21 g of 3, 51 ml of BuLi-solution and 7.5 ml of dimethyl disulfide gave a product which was distilled at 125-130 °C (1.0 mm Hg). Yield 17.0 g (91%).

Analytical data: ^{1}H-Nmr: δ(ppm)= 1.05 (d, J=7Hz, 18H, iPr-H), 1.33 (m, partly hidden under doublet, 3H, iPr-H), 2.31 (s, 3H, SMe), 6.24 (br s, 1H), 6.71 (br s, 2H). High-resolution ms Calcd for $C_{14}H_{27}NSSi$ (M^+): 269.1633. Found 269.1629.

3-Phenylthio-1-methoxycarbonylpyrrole (5a). Acetonitrile was distilled over P_2O_5 shortly before use. The commercially available cesium fluoride is dried over P_2O_5 at room temperature and 15 mm Hg for several days. In a reaction vessel equipped with an argon inlet 1.22 g of cesium fluoride (8.0 mmol) was thoroughly heated under vacuum. Subsequently 0.76 g of methyl chloroformate (8.0 mmol), 2.4 g of 4a and 5 ml of dried acetonitrile were added. Reaction took place within 24 h of dispersing in a normal ultrasonic laboratorium cleaner, keeping the mixture under argon. The suspension was filtered, the residue washed several times with ether, the combined organic layers were washed with water, dried and concentrated in vacuo. The crude product was purified by chromatography on SiO_2/CCl_4 and was obtained as an oil. The yield was quantitative.

Analytical data: n_D^{20} = 1.5966. ^{1}H-Nmr: δ(ppm)= 3.91 (s, 3H, COOMe), 6.22 (dd, J_{AX}=3.6Hz, J_{BX}=2.2Hz, 1H, X part of ABX), 7.15 (br s, 5H, Ph), 7.28 (dd, J_{AB}=1.8Hz, J_{AX}=3.6Hz, 1H, A part of ABX), 7.41 (dd, J_{AB}=1.8Hz, J_{BX}=2.2Hz, 1H, B part of ABX). High-resolution ms Calcd for $C_{12}H_{11}NO_2S$ (M^+): 233.0510. Found: 233.0505.

3-Methylthio-1-methoxycarbonylpyrrole (5b). Procedure as described above. One batch contained 1.25 g of cesium fluoride, 0.8 g of methyl chloroformate, 2.0 g of 4b and 5 ml of dried acetonitrile. The crude product was destilled, bp 50 °C (1 mm Hg), the yield was quantitative.

Analytical data: ^{1}H-Nmr: δ(ppm)= 2.33 (s, 3H, SMe), 3.93 (s, 3H, COOMe), 6.20 (dd, J_{AX}=3.6Hz, J_{BX}=2.1Hz, 1H, X part of ABX), 7.11 (dd, J_{AB}=1.8Hz, J_{BX}=2.1Hz, 1H, B part of ABX), 7.20 (dd, J_{AB}=1.8Hz, J_{AX}=3.6Hz, 1H, A part of ABX). High-resolution ms Calcd for $C_7H_9NO_2S$ (M^+): 171.0354. Found: 171.0356.

The Diels-Alder reactions - general procedure. A mixture of 0.9 mmol of pyrrole 5, 1.3 mmol of dienophile and, in the case of the easily polymerizing compounds 6, 8 and 13-16 a crystal of hydroquinone, was dissolved in 1.5 ml of acetonitrile. The ampule was filled, closed and kept in the high pressure vessel at 12 Kbar and 50 °C for 16 h. Purification of the reaction products was achieved by flash-chromatography as indicated below. The endo/exo ratio is in all cases 1/1 except for 10a as indicated in table 1. Total yield was in all cases about 80%.

Phenyl 2-Phenylthio-7-methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene- 5-sulphone(9a). Chromatography (n-hexane 95/ THF 5) yielded endo-9a (Rf=0.20) and exo-9a (Rf=0.12), both as a waxy oil.

Analytical data: endo-9a. ^{1}H-Nmr: δ(ppm)= 1.83 (dd, $J_{6a,6b}$=12Hz, $J_{5,6a}$=5Hz, 1H, H-6a), 2.24 (ddd, $J_{6a,6b}$=12Hz, $J_{5,6b}$=8Hz, $J_{1,6b}$=4Hz, 1H, H-6b), 3.63 (s, 3H, OMe), 3.84 (ddd, $J_{5,6a}$=5Hz, $J_{5,6b}$=8Hz, $J_{4,5}$=2Hz, 1H, H-5), 4.62 (d, $J_{1,6}$=4Hz, 1H, H-1), 4.89 (dd, $J_{4,5}$=2Hz, $J_{3,4}$=2Hz, 1H, H-4), 6.13 (d, $J_{3,4}$=2Hz, 1H, H-3), 7.3-8.0 (m, 10H, Ph).

Exo-9a. ^{1}H-Nmr: δ(ppm)= 1.74 (dd, $J_{6a,6b}$=13Hz, $J_{5,6a}$=9Hz, 1H, H-6a), 2.29 (ddd, $J_{6a,6b}$=13Hz, $J_{5,6b}$=4Hz, $J_{1,6b}$=4Hz, H-6b), 3.13 (dd, $J_{5,6b}$=4Hz, $J_{5,6a}$=9Hz, 1H, H-5), 3.62 (s, 3H, OMe), 4.56 (d, $J_{1,6b}$=4Hz, 1H, H-1), 5.11 (d, $J_{3,4}$=3Hz, 1H, H-4), 6.00 (d, $J_{3,4}$=3Hz, 1H, H-3), 7.3-8.0 (m, 10H, Ph).
Note: H-6a=endo-H6 and H-6b=exo-H6.

Phenyl 2-Methylthio-7-methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene- 5-sulphone (9b). Chromatography (n-hexane 70/dichloromethane 20/chloroform 5/THF 5) yielded exo-9b (Rf=0.18) and endo-9b (Rf=0.11), both as an oil.

Analytical data: endo-9b. ^{1}H-Nmr: δ(ppm)= 1.71 (dd, $J_{6a,6b}$=12Hz, $J_{5,6a}$=4Hz, 1H, H-6a), 2.1 (ddd, $J_{6a,6b}$=12Hz, $J_{5,6b}$=9Hz, $J_{1,6b}$=4Hz, 1H, H-6b), 2.22 (s, 3H, SMe), 3.20 (ddd, $J_{5,6a}$=4Hz, $J_{5,6b}$=9Hz, $J_{4,5}$=4Hz, 1H, H-5), 3.62 (s, 3H, OMe), 4.61 (d, $J_{1,6b}$=4Hz, 1H, H-1), 4.94 (dd, $J_{4,5}$=4Hz, $J_{3,4}$=2Hz, 1H, H-4), 5.63 (d, $J_{3,4}$=2Hz, 1H, H-3), 8.2-8.9 (m, 5H, Ph).

Exo-9b. ^{1}H-Nmr: δ(ppm)= 1.72 (dd, $J_{6a,6b}$=12Hz, $J_{5,6a}$=4Hz, 1H, H-6a), 2.24 (s, 3H, SMe), 2.3 (ddd, $J_{6a,6b}$=12Hz, $J_{5,6b}$=9Hz, $J_{1,6b}$=4Hz, 1H, H-6b), 3.14 (dd, $J_{5,6a}$=4Hz, $J_{5,6b}$=9Hz, 1H, H-5), 3.61 (s, 3H, OMe), 4.63 (d, $J_{1,6b}$=4Hz, 1H, H-1), 5.09 (d, $J_{3,4}$=2Hz, 1H, H-4), 5.67 (d, $J_{3,4}$=2Hz, 1H, H-3), 7.62 (m, 5H, Ph).

Note: H-6a=endo-H6 and H-6b=exo-H6.

4-Phenyl-8-phenylthio-10-methoxycarbonyl-4,10-diazatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione(10a)
Chromatography (CH_2Cl_2) yielded only endo-10a (Rf=0.23).

Analytical data: mp 135-137 °C. ^{1}H-Nmr: δ(ppm)= 3.02 and 3.15 (AB, J_{AB}=5.5Hz, 2H, H-2 and

H-6), 3.66 (s, 3H, OMe), 4.96 (broad s, 1H, H-7), 5.24 (broad s, $J_{1,9}$=2Hz, 1H, H-1), 6.30 (d, $J_{1,9}$=2Hz, H-9), 7.2-7.5 (m, 10H, Ph).

Methyl 2-Phenylthio-7-methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene-5-carboxylate (11a). Chromatography (n-hexane 95/THF 5) yielded endo-11a (Rf=0.13) and exo-11a (Rf=0.07).

Analytical data: endo-11a. mp 96-97 °C. ^{1}H-Nmr: δ(ppm)= 1.73 (dd, $J_{6a,6b}$=12.5Hz, $J_{5,6a}$=4.5Hz, 1H, H-6a), 2.18 (ddd, $J_{6a,6b}$=12.5Hz, $J_{5,6b}$=9Hz, $J_{1,6b}$=4.5Hz, 1H, H-6b), 3.27 (ddd, $J_{5,6a}$=4.5Hz, $J_{5,6b}$=9Hz, $J_{4,5}$=4.5Hz, 1H, H-5), 3.62 (s, 6H, OMe), 4.61 (d, $J_{1,6b}$=4.5Hz, 1H, H-1), 4.98 (dd, $J_{4,5}$=4.5Hz, $J_{3,4}$=2Hz, 1H, H-4), 5.92 (d, $J_{3,4}$=2Hz, 1H, H-3), 7.2-7.4 (m, 5H, Ph).

Exo-11a. mp 79-80 °C. ^{1}H-Nmr: δ(ppm)= 1.64 (dd, $J_{6a,6b}$=9Hz, $J_{5,6a}$=4Hz, 1H, H-6a), 2.29 (ddd, $J_{6a,6b}$=9Hz, $J_{5,6b}$=4Hz, $J_{1,6b}$=4Hz,1H, H-6b), 2.48 (dd, $J_{5,6a}$=4Hz, $J_{5,6b}$=4Hz, 1H, H-5), 3.57 (s, 3H, OMe), 3.66 (s, 3H, OMe), 4.59 (d, $J_{1,6b}$=4Hz, 1H, H-1), 5.01 (d, $J_{3,4}$=2Hz, 1H, H-4), 6.12 (d, $J_{3,4}$=2Hz, 1H, H-3), 7.26 (s, 5H, Ph).

Note: H-6a=endo-H6 and H-6b=exo-H6.

Methyl 2-Methylthio-7-methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene-5-carboxylate (11b). Chromatography (n-hexane 93/THF 7) yielded endo-11b (Rf=0.20) and exo-11b (Rf=0.12). Further purification was done by crystallization from petroleum ether (40-60).

Analytical data: endo-11b. mp 49-50 °C. ^{1}H-Nmr: δ(ppm)= 1.68 (dd, $J_{6a,6b}$=8Hz, $J_{5,6a}$=4Hz, 1H, H-6a), 2.24 (s, 3H, SMe), 2.0-2.4 (m, partly hidden under singlet, 1H, H-6b), 3.21 (ddd, $J_{5,6a}$=8Hz, $J_{5,6b}$=4Hz, $J_{4,5}$=4Hz, 1H, H-5), 3.64 (s, 3H, N-COOMe), 3.73 (s, 3H, C-COOMe), 4.60 (d, $J_{1,6b}$=4Hz, 1H, H-1), 4.96 (m, $J_{3,4}$=2Hz, $J_{4,5}$=4Hz, 1H, H-4), 5.62 (d, $J_{3,4}$=2Hz, 1H, H-3).

Exo-11b: mp 60-62 °C. ^{1}H-Nmr: δ(ppm)= 1.59 (dd, $J_{6a,6b}$=11Hz, $J_{5,6a}$=8Hz, 1H, H-6a), 2.24 (s, 3H, SMe), 2.3 (m, partly hidden under singlet, 1H, H-6b), 2.51 (dd, $J_{5,6a}$=8Hz, $J_{5,6b}$=4Hz 1H, H-5), 3.61 (s, 3H, C-COOMe), 3.71 (s, 3H, N-COOMe), 4.62 (d, $J_{1,6b}$=4Hz, 1H, H-1), 5.02 (d, $J_{3,4}$=2Hz, 1H, H-4), 5.76 (d, $J_{3,4}$=2Hz, 1H, H-3).

Note: H-6a=endo-H6 and H-6b=exo-H6.

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9. This unexpected behaviour was also found by Isaacs et al.[2] in an analogous reaction and it is now further investigated.
10. This may be ascribed to an unfavourable overlap between the diene and dienophile in this case, because the distance between the diene ends in 5 is relative short whereas the C=C bond in 12 is relatively long.
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