Inter- and Intramolecular Hetero Diels-Alder Reactions, 39[1]

Influence of Phenylthio and Alkylthio Substituents on the Reactivity of 1-Oxa-1,3-butadienes in Hetero Diels-Alder Reactions

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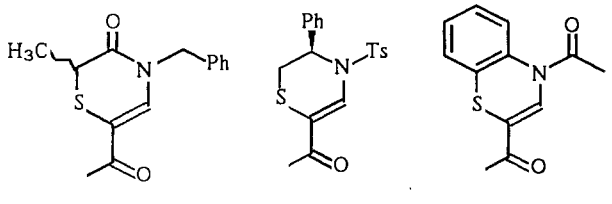
The synthesis of the cyclic enamino ketones **1**–**3** bearing an alkylthio or an phenylthio group and their reactivity in hetero Diels-Alder reactions with enol ethers is described. Only compound **3** with an phenylthio group undergoes a cycloaddition with **16a**–**d** to afford the diastereomeric adducts **17a**–**d** and **18a**–**d**. To estimate the activation by a phenylthio and alkylthio group semiempirical PM3/RHF calculations of the frontier orbital energies and coefficients of different enamine carbaldehydes have been performed.

We have recently shown that the intermolecular hetero Diels-Alder reaction of 1-oxa-1,3-butadienes bearing an acylamino group at C-3 and an electron-withdrawing group at C-1 or C-2 is an efficient route to 3-amino sugar derivatives[2]. In the reaction of these enamino ketones, which belongs to the inverse type, the overlap of the LUMO of the heterodiene with the HOMO of the dienophile is most important. Thus, electron-withdrawing groups, which lower the energy of the LUMO, increase the reaction rate. As electron-withdrawing groups the trichloromethyl, dichloromethyl, and the trifluoromethyl as well as the methoxycarbonyl group have been used[3]. Interestingly, enamino ketones with a phenylthio group[2a,c,4] at C-3 of the oxabutadiene moiety also show a high reacivity in hetero Diels-Alder reactions, whereas enamino ketones with an alkylthio group are much less reactive.

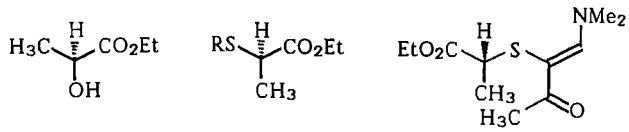
In this paper we describe our investigations of the understanding of this difference. We have synthesized the three cyclic enamino ketones **1**–**3** and have investigated their reactivity in cycloaddition reactions with enol ethers. The enamino ketones **1** and **2** bear an alkylthio group whereas enamino ketone **3** is activated by a phenylthio group at C-3 of the 1-oxabutadiene moiety. In all compounds the enamino group has the (*Z*) configuration.



1 **2** **3**

Synthesis and Cycloadditions of Enamino Ketones

Enamino ketone **1** is synthesized in four steps by starting from ethyl (*S*)-2-hydroxypropionate (**4**), which is converted into **5** by a Mitsunobu reaction[5] in 97% yield. Hydrolysis of the acetylthio group with K_2CO_3 in methanol[6] and reaction with chloroacetone lead to **6** in 91% yield. Condensation of **6** with dimethylformamide dimethyl acetal in tetrahydrofuran[7] affords 67% of **7**, which is cyclized with complete racemization by treatment with benzylamine in ethanol at reflux temperature to give *rac*-**1** in 63% yield.



4 **7**

	R
5	Ac
6	CH_2COCH_3

Enamino ketone **2** is prepared in four steps from (*R*)-2-amino-2-phenylethanol (**8**), which is first tosylated in pyridine[8] to give **9** in 73% yield. Subsequent S_N reaction with potassium thioacetate in acetone[9] affords 89% of **10**, which is transformed into **2** via **11** as described for **1**.

Similarly, the 1,4-benzothiazine derivative **3** is obtained in a four-step sequence from 2-mercaptoaniline (**12**) via **13**, **14**, and **15** in 44% yield. Interestingly, **14** reacts with dimethylformamide dimethyl acetal already at room temperature presumably due to a neighboring effect of the acetanilido group.

For the cycloadditions a solution of the dienes **1**–**3** and the dienophiles **16a**–**d** in toluene is heated for seven days at 125°C in a pressure flask. Only the diene **3** reacts under these conditions, whereas **1** and **2** can be recovered unchanged. At higher temperatures decomposition occurs. These results clearly show, that only the phenylthio group as compared to the alkylthio group has a sufficient activating effect on the 1-oxa-1,3-butadiene.

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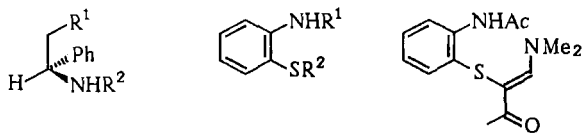
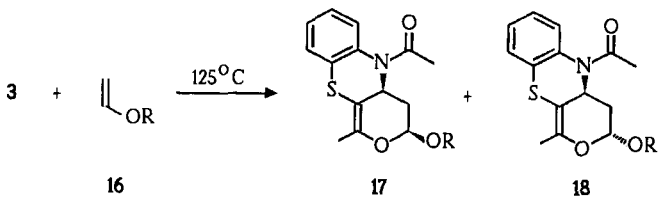


	R^1	R^2
8	OH	H
9	OTs	Ts
10	SAc	Ts
11	SCH_2COCH_3	Ts

	R^1	R^2
12	H	H
13	Ac	Ac
14	Ac	CH_2COCH_3

15

The yields and the selectivities of the cycloadditions of **3** and **16a–d** are given in Table 1.



16 17 18

	R
a	Me
b	Et
c	$CH_2CH(CH_3)_2$
d	tert-Bu

Table 1. Synthesis of **17a–d** and **18a–d** from **3** and **16**

17 + 18	a	b	c	d
Ratio **17**:**18**	4.5:1[a]	1.9:1[b]	2.4:1[a]	1:1.6[a]
Yield (%)	74	81	74	79

[a] Determined by ^{13}C-NMR spectroscopy of the crude product. – [b] Determined by HPLC.

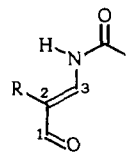
As found for the acyclic enamino ketones the *endo/exo* selectivity is low though the heterodiene is fixed in the (*Z*) configuration. The cycloaddition reaction of **3** with the enol ether **16d** bearing the bulky *tert*-butyl group is *exo*-selective because of a disfavoring of the *endo* transition structure due to steric interactions (**17d**:**18d** = 1:1.6); in contrast, the steric unhindered enol ether **16a** shows the highest *endo* selectivity (**17a**:**18a** = 4.5:1).

The configuration and the conformation of the cycloadducts **17a–d** and **18a–d** have been determined by ^1H-NMR spectroscopy. For all compounds the conformation with the acetamido group in a pseudoequatorial orientation is preferred. This can be deduced from the coupling constants for 3-H and 4-H in the ^1H-NMR spectra. 3-H in **17a–d** resonates at δ = 5.09–5.42 as a doublet of doublets with *J* = 10.0 and 2.5 Hz indicating an equatorial orientation of the alkoxy group. The signals for 3-H of **18a–d** are observed at δ = 4.95–5.34 with two small coupling constants of *J* = 2.5 Hz, which shows that the alkoxy group is axially orientated. 4-H_{ax} of **17a–d** gives a signal at δ = 1.59–1.64 as a doublet of doublets of doublets with three large coupling constants of *J* = 12.5, 11.0, and 10.0 Hz and 4-H_{ax} of **18a–d** at δ = 1.48–1.52 with two large and one small coupling constants of *J* = 12.5, 11.0, and 2.5 Hz. This clearly proves the pseudoequatiorial position of the acetamido group with an axially orientated 4a-H, in both the *exo* and *endo* products.

Semiempirical Calculations of Enamine Carbaldehydes

To confirm the results we had described earlier[2a] and the unexpected low reactivity of the alkylthio-substituted enamino ketones **1** and **2**, respectively, we have carried out calculations of frontier orbital energies and coefficients of an *N*-acetylenamine carbaldehyde bearing several different substituents at C-2. The results are given in Table 2.

Table 2. Calculated frontier orbital energies and coefficients with PM3/RHF



	HOMO					LUMO				
R	E[eV]	O	C1	C2	C3	E[eV]	O	C1	C2	C3
Me	-9.216	-0.225	0.030	0.583	0.321	-0.412	0.331	-0.368	-0.430	0.593
H	-9.376	-0.242	0.022	0.593	0.273	-0.437	0.334	-0.367	-0.427	0.595
OMe	-9.247	-0.218	0.032	0.576	0.307	-0.535	0.338	-0.374	-0.430	0.599
OPh	-9.270	-0.168	0.025	0.459	0.245	-0.645	0.323	-0.354	-0.431	0.608
SMe	-9.086	-0.130	0.023	0.370	0.203	-0.765	0.253	-0.265	-0.395	0.628
SPh	-9.565	-0.235	0.019	0.607	0.232	-0.867	0.239	-0.247	-0.389	0.632
CF_3	-9.972	-0.252	0.013	0.628	0.204	-1.056	0.271	-0.282	-0.416	0.652
CN	-9.672	-0.229	0.026	0.595	0.264	-1.128	0.261	-0.270	-0.403	0.641

The frontier orbital energies and coefficients have been calculated by using the semiempirical PM3/RHF[10] method. The given values always represent the *cisoid* conformation of each molecule. All other substituents have the orientation with the lowest energy. AM1/RHF[11] calculations give nearly the same relative results, though the absolute values are slightly different; for the missing AM1 sulfur parameters the MNDO[12] parameters have been used.

As expected the cyano and trifluoromethyl group as strong electron-withdrawing groups decrease the energy of the LUMO whereas the methyl group as an electron-donating group increases it. Alkoxy and phenoxy as well as alkylthio and phenylthio groups lower the energy of the LUMO due to –I and conjugation effects, whereby the phenylthio group causes the greatest change. Interestingly, the coefficients at C-3 for the two thio-substituted enamine carbaldehydes are quite similar; also the effect of the phenyl group as compared to the alkyl group on the LUMO in the *O*- and *S*-substituted enamine carbaldehydes is of the same magnitude (≈0.1 eV). The calculated difference for alkylthio and phenylthio substitution is in agreement with our experimental results, indicating that the energy of the LUMO

of enamine carbaldehydes or enamino ketones usable for cycloadditions should not be above $E = -0.8$ eV. These results also demonstrate that phenylthio is only a weakly activating group since enamino ketones with a CO_2Me group at C-2 or a CF_3, CO_2Me, and CCl_3 group, respectively, at C-1 show a much higher reactivity[2,3].

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Experimental

^1H and ^{13}C NMR: Varian XL-200, VXR-200, XL 100, and FT-80 A; multiplicities were determined with the APT-pulse sequence. – IR: Bruker IFS 25. – UV: Varian Cary 219. – Optical rotations: Perkin-Elmer 241. – Melting points: Kofler hot stage or Mettler FP 61. – Elemental analyses: Analytical laboratory of the university. – All solvents were distilled prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. All reactions were carried out under nitrogen and monitored by TLC (Macherey-Nagel, Polygram SIL G/UV_{254}). Products were isolated by column chromatography on silica gel (ICN Silica 63–200, 60 A, ICN Biomedicals).

Synthesis of (RS)-6-Acetyl-4-benzyl-2-methyl-2H-1,4-thiazin-3(4H)-one (**1**)

a) *Ethyl (R)-2-(Acetylthio)propionate* (**5**): To a stirred solution of triphenylphosphane (22.2 g, 84.6 mmol) in anhydrous tetrahydrofuran (200 ml) was added diisopropyl azodicarboxylate (17.1 g, 84.6 mmol) at 0°C. After stirring for 30 min at 0°C a solution of **4** (7.50 g, 63.5 mmol) and thioacetic acid (6.40 g, 84.6 mmol) in anhydrous tetrahydrofuran (50 ml) was added dropwise over a period of 15 min. Stirring was continued at 0°C for 1 h and for an additional h at room temp. to get a clear yellow solution. The solvent was removed in vacuo, and to the residue was added diethyl ether (150 ml). The solution was cooled at 0°C for 12 h and the precipitate (triphenylphosphane oxide) separated. The solvent was removed in vacuo and the residue purified by distillation to give 10.8 g (97%) of **5**, b.p. 107°C/15 Torr, $[\alpha]_D^{20} = 130.3$ ($c = 1$, MeOH). – UV (CH_3CN): λ_{max} (lg ε) = 229 nm (3.532). – IR (film): $\tilde{\nu} = 1735\ cm^{-1}$, 1695 (C=O). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.55 (d, $J = 7.5$ Hz, 3H, 3-H), 2.37 (s, 3H, $COCH_3$), 4.22 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 4.24 (q, $J = 7.5$ Hz, 1H, 2-H).

$C_7H_{12}O_3S$ (176.2) Calcd. C 47.71 H 6.86
Found C 47.83 H 6.97

b) *Ethyl (R)-2-(2-Oxopropylthio)propionate* (**6**): A mixture of **5** (5.00 g, 28.4 mmol) and potassium carbonate (2.00 g) in anhydrous methanol (50 ml) was stirred at room temp. for 30 min. After cooling to 0°C chloroacetone (2.26 ml, 28.4 mmol) was added dropwise, and the solution was stirred at room temp. for 1 h. The solvent was removed in vacuo, and to the residue was added diethyl ether (70 ml). The precipitate was filtered off, and after evaporation of the solvent in vacuo the residue was purified by distillation to give 4.91 g (91%) of **6**, b.p. 124°C/15 Torr, $[\alpha]_D^{20} = 111.1$ ($c = 1$, MeOH). – UV (CH_3CN): λ_{max} (lg ε) = 219 nm (3.864). – IR (film): $\tilde{\nu} = 1720\ cm^{-1}$ (C=O). – ^1H NMR ($CDCl_3$): δ = 1.30 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.45 (d, $J = 7.5$ Hz, 3H, 3-H), 2.30 (s, 3H, $COCH_3$), 3.46 (q, $J = 7.0$ Hz, 1H, 2-H), 3.40, 3.54 (AB system, $J = 18.0$ Hz, 2H, SCH_2), 4.21 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3).

$C_8H_{14}O_3S$ (190.3) Calcd. C 50.50 H 7.42 S 16.85
Found C 50.64 H 7.48 S 16.66

c) *Ethyl (R)-2-{1-[(Dimethylamino)methylen]-2-oxopropylthio}-propionate* (**7**): A stirred solution of **6** (4.00 g, 21.0 mmol) and dimethylformamide dimethyl acetal (5.00 g, 42.1 mmol) in anhydrous tetrahydrofuran (20 ml) was heated at reflux for 24 h. After evaporation of the solvent in vacuo the residue was purified by distillation to give 3.46 g (67%) of **7**, b.p. 143°C/0.1 Torr, $[\alpha]_D^{20} = 82.9$ ($c = 1$, MeOH). – UV (CH_3CN): λ_{max} (lg ε) = 302 nm (4.132). – IR (film): $\tilde{\nu} = 1729\ cm^{-1}$, 1640 (C=O), 1580 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.39 (d, $J = 7.0$ Hz, 3H, 3-H), 2.39 (s, 3H, $COCH_3$), 3.31 [s, 6H, $N(CH_3)_2$], 3.42 (q, $J = 7.0$ Hz, 1H, 2-H), 4.12 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 7.96 (s, 1H, 1′-H).

$C_{11}H_{19}NO_3S$ (245.3) Calcd. C 53.86 H 7.81 S 13.07
Found C 53.75 H 7.77 S 13.11

d) *Thiazinone* **1**: A stirred solution of **7** (1.50 g, 6.10 mmol) and benzylamine (0.65 g, 6.10 mmol) in anhydrous ethanol was heated at reflux for 24 h. After evaporation of the solvent in vacuo the residue was purified by column chromatography (ethyl acetate/hexane, 2:3) to yield 1.00 g (63%) of **1**, m.p. 99°C (diethyl ether), $R_f = 0.59$. – UV (CH_3CN): λ_{max} (lg ε) = 236 nm (3.736), 265 (3.707), 332 (3.877). – IR (KBr): $\tilde{\nu} = 1695\ cm^{-1}$, 1640 (C=O), 1605 (C=C). – ^1H NMR (C_6D_6): δ = 1.23 (d, $J = 7.0$ Hz, 3H, CH_3), 1.82 (s, 3H, 2′-H), 2.98 (q, $J = 7.0$ Hz, 1H, 2-H), 4.38, 4.52 (AB system, $J = 18.0$ Hz, 2H, NCH_2), 6.98 (s, 1H, 5-H), 7.08 (s, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.97 (CH_3), 25.44 (C-2′), 35.94 (C-2), 51.55 (NCH_2), 116.7 (C-6), 127.3, 127.9, 128.9 (CH-Ph), 135.9 (C-5), 136.1 (*i*-Ph), 165.4 (C-3), 192.7 (C-1′).

$C_{14}H_{15}NO_2S$ (261.3) Calcd. C 64.35 H 5.79 N 5.36 S 12.27
Found C 64.23 H 5.84 N 5.31 S 12.17

Synthesis of (R)-6-Acetyl-3,4-dihydro-3-phenyl-4-(p-tolylsulfonyl)-2H-1,4-thiazine (**2**)

a) *(R)-2-Phenyl-O-(p-tolylsulfonyl)-2-[(p-tolylsulfonyl)amino]-ethanol* (**9**): To a stirred solution of **8** (13.8 g, 0.10 mol) in pyridine (150 ml) was added at 0°C *p*-toluenesulfonyl chloride (42.0 g, 0.22 mol), and stirring was continued at 4°C for 1 d. The mixture was poured onto crushed ice (500 g), extracted with diethyl ether (5 × 100 ml), the combined organic extracts were washed with satd. aqueous $NaHCO_3$ (1 × 100 ml), brine (1 × 100 ml), and dried ($MgSO_4$). After evaporation of the solvent in vacuo the residue was purified by crystallization to give 32.5 g (73%) of **9**, m.p. 116°C (ethanol), $[\alpha]_D^{20} = -28.8$ ($c = 1$, chloroform). – UV (CH_3CN): λ_{max} (lg ε) = 226 nm (4.376), 263 (3.076). – IR (KBr): $\tilde{\nu} = 3306\ cm^{-1}$ (NH), 1598 (NH). – ^1H NMR ($CDCl_3$): δ = 2.38 (s, 3H, NTs-CH_3), 2.44 (s, 3H, OTs-CH_3), 4.14 (ABX system, $J = 16.0$, 6.0 Hz, 2H, 1-H), 4.42 (q, $J = 6.0$ Hz, 1H, 2-H), 5.22 (d, $J = 6.0$ Hz, 1H, NH), 6.98–7.24 (m, 7H, Ph, NTs-2-H), 7.29 (d, $J = 8.0$ Hz, 2H, OTs-2-H), 7.58 (d, $J = 8.0$ Hz, 2H, NTs-3-H), 7.64 (d, $J = 8.0$ Hz, 2H, OTs-3-H).

$C_{22}H_{23}NO_5S_2$ (445.6) Calcd. C 59.30 H 5.20
Found C 59.23 H 5.11

b) *(R)-S-Acetyl-2-phenyl-2-[(p-tolylsulfonyl)amino]ethanethiol* (**10**): A mixture of **9** (7.00 g, 15.7 mmol) and potassium thioacetate (2.00 g, 17.5 mmol) in anhydrous acetone (200 ml) was stirred at room temp. for 12 h. Filtration of the mixture, evaporation of the solvent from the filtrate and crystallization of the residue afforded 4.90 g (89%) of **10**, m.p. 115°C (ethanol), $[\alpha]_D^{20} = -73.6$ ($c = 1$, chloroform). – UV (CH_3CN): λ_{max} (lg ε) = 229 nm (4.191), 263 (2.806). – IR (KBr): $\tilde{\nu} = 3278\ cm^{-1}$ (NH), 1652 (C=O), 1600 (NH). – ^1H NMR ($CDCl_3$): δ = 2.26 (s, 3H, Ts-CH_3), 2.36 (s, 3H, $COCH_3$), 3.05, 3.14 (AB system, $J = 14.0$, 9.0 Hz, 2H, 1-H), 4.48

(m_c, 1H, 2-H), 5.30 (s, br, 1H, NH), 7.10–7.27 (m, 7H, Ph, Ts-2-H), 7.58 (d, J = 8.0 Hz, 2H, Ts-3-H).

$C_{17}H_{19}NO_3S_2$ (349.5) Calcd. C 58.42 H 5.48 S 18.35
Found C 58.53 H 5.50 S 18.30

c) *(R)-S-(2-Oxopropyl)-2-phenyl-2-[(p-tolylsulfonyl)amino]ethanethiol* (**11**): A mixture of **10** (4.13 g, 11.8 mmol) and potassium carbonate (0.85 g) in anhydrous methanol (50 ml) was stirred at room temp. for 30 min. After cooling to 0°C chloroacetone (1.09 g, 11.8 mmol) was added dropwise, and the solution was stirred at room temp. for 1 h. The solvent was removed in vacuo, and to the residue was added diethyl ether (60 ml). The precipitate was filtered off, and after evaporation of the solvent from the filtrate in vacuo the residue was purified by crystallization to give 2.62 g (61%) of **11**, m.p. 107°C (ethanol), $[\alpha]_D^{20}$ = −55.5 (c = 1, chloroform). – UV (CH_3CN): λ_{max} (lg ε) = 227 nm (4.023), 263 (2.803). – IR (KBr): $\tilde{\nu}$ = 3168 cm^{-1} (NH), 1706 (C=O), 1600 (NH). – ^1H NMR ($CDCl_3$): δ = 2.19 (s, 3H, Ts-CH_3), 2.36 (s, 3H, $COCH_3$), 2.81, 2.82 (AB system, J = 17.0, 7.5 Hz, 1H, 1-H), 3.01, 3.11 (AB system, J = 18.0 Hz, 1H, 1′-H), 4.44 (t, J = 7.5 Hz, 1H, 2-H), 5.54 (s, br, 1H, NH), 7.08–7.21 (m, 7H, Ph, Ts-2-H), 7.59 (d, J = 8.0 Hz, 2H, Ts-3-H).

$C_{18}H_{21}NO_3S$ (363.5) Calcd. C 59.48 H 5.82 S 17.64
Found C 59.63 H 5.82 S 17.30

d) *Thiazine* **2**: A solution of **11** (1.50 g, 4.10 mmol) and dimethylformamide dimethyl acetal (1.00 g, 8.30 mmol) in anhydrous tetrahydrofuran (30 ml) was heated at reflux for 24 h. Evaporation of the solvent and purification of the residue by column chromatography yielded **2** (0.95 g, 62%), m.p. 123°C (diethyl ether), R_f = 0.57, $[\alpha]_D^{20}$ = −33.5 (c = 1, chloroform). – UV (CH_3CN): λ_{max} (lg ε) = 223 nm (4.231), 315 (4.076). – IR (KBr): $\tilde{\nu}$ = 1658 cm^{-1} (C=O), 1592 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.39 (s, 3H, Ts-CH_3), 2.42 (s, 3H, $COCH_3$), 2.64 (dd, J = 14.0, 3.0 Hz, 1H, 2-H_{ax}), 2.90 (dd, J = 14.0, 3.0 Hz, 1H, 2-H_{eq}), 5.58 (t, J = 3.0 Hz, 1H, 3-H), 6.95–7.22 (m, 7H, Ph, Ts-2-H), 7.54 (d, J = 8.0 Hz, 2H, Ts-3-H), 8.37 (s, 1H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 21.48 (Ts-CH_3), 25.06 (C-2′), 30.67 (C-2), 55.62 (C-3), 115.9 (C-6), 126.1 (C-2-Ts), 127.1 (C-3-Ts), 127.7, 128.2, 129.9 (CH-Ph), 131.4 (C-5), 134.4 (C-4-Ts), 138.5 (*i*-Ph), 144.9 (C-1-Ts), 192.9 (C-1′).

$C_{19}H_{19}NO_3S_2$ (373.5) Calcd. C 61.13 H 5.13 N 3.75 S 17.17
Found C 61.09 H 5.19 N 3.73 S 17.23

Synthesis of 2,4-Diacetyl-4H-1,4-benzothiazine (**3**)

a) *N-Acetyl-2-(acetylthio)aniline* (**13**): To a stirred solution of acetyl chloride (31.4 g, 0.40 mol) and pyridine (31.6 g, 0.40 mol) in anhydrous dichloromethane (250 ml) was added a solution of **12** (25.0 g, 0.20 mol) in dichloromethane (30 ml) over a period of 20 min. After stirring for 12 h at room temp., diethyl ether (200 ml) was added and the solution washed with 1 N HCl (1 × 200 ml), satd. aqueous $NaHCO_3$ (1 × 200 ml), and brine (1 × 200 ml) and dried (Na_2SO_4). Evaporation of the solvent and crystallization afforded **13** (37.2 g, 89%), m.p. 116°C (diethyl ether). – UV (CH_3CN): λ_{max} (lg ε) = 213 nm (4.394), 247 (4.081), 286 (3.377). – IR (KBr): $\tilde{\nu}$ = 3336 cm^{-1} (NH), 1690 (C=O), 1578 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.17 (s, 3H, $NCOCH_3$), 2.48 (s, 3H, $SCOCH_3$), 6.95–7.55 (m, 3H, Ph), 7.65 (br, 1H, NH), 8.05–8.40 (m, 1H, Ph).

$C_{10}H_{11}NO_2S$ (209.3) Calcd. C 57.39 H 5.30
Found C 57.52 H 5.39

b) *N-Acetyl-2-(2-oxopropylthio)aniline* (**14**): A mixture of **13** (10.0 g, 47.8 mmol) and potassium carbonate (3.30 g) in anhydrous methanol (80 ml) was stirred at room temp. for 30 min. After cooling to 0°C chloroacetone (3.80 g, 47.8 mmol) was added dropwise, and the solution was stirred at room temp. for 1 h. The solvent was removed in vacuo, and to the residue was added diethyl ether (100 ml). The precipitate was filtered off, and after evaporation of the solvent from the filtrate in vacuo the residue was purified by crystallization to give 9.80 g (92%) of **14**, m.p. 82°C (ethanol/hexane). – UV (CH_3CN): λ_{max} (lg ε) = 211 nm (4.303), 244 (4.092), 287 (3.335). – IR (KBr): $\tilde{\nu}$ = 3230 cm^{-1} (NH), 1712, 1656 (C=O), 1536 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.17 (s, 3H, $NCOCH_3$), 2.27 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 6.81–7.55 (m, 3H, Ph), 8.25 (m_c, 1H, Ph), 9.17 (br, 1H, NH).

$C_{11}H_{13}NO_2S$ (223.3) Calcd. C 59.17 H 5.87
Found C 59.21 H 5.98

c) *3-[2-(Acetylamino)phenylthio]-4-(dimethylamino)-3-buten-2-one* (**15**): A solution of **14** (5.00 g, 22.4 mmol) and dimethylformamide dimethyl acetal (2.94 g, 24.6 mmol) in anhydrous tetrahydrofuran (80 ml) was stirred at room temp. for 20 h. After evaporation of the solvent in vacuo the residue was purified by crystallization to give 5.38 g (86%) of **15**, m.p. 151°C (ethanol). – UV (CH_3CN): λ_{max} (lg ε) = 219 nm (4.298), 250 (4.163), 300 (4.230). – IR (KBr): $\tilde{\nu}$ = 3218 cm^{-1} (NH), 1686, 1632 (C=O), 1578, 1560 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.22 (s, 3H, $NCOCH_3$), 2.24 (s, 3H, 1-H), 3.29 [s, 6H, $N(CH_3)_2$], 6.95–7.25 (m, 3H, Ph), 7.81–8.02 (m, 2H, 4-H, Ph), 8.55 (br. 1H, NH).

$C_{14}H_{18}N_2O_2S$ (278.4) Calcd. C 60.40 H 6.52
Found C 60.38 H 6.58

d) *Benzothiazine* **3**: A solution of **15** (1.00 g, 3.59 mmol) and camphersulfonic acid (30.0 mg) in anhydrous toluene (30 ml) was heated at reflux for 24 h. After evaporation of the solvent in vacuo the residue was purified by column chromatography to yield **3** (0.52 g, 62%), m.p. 87°C (ethanol), R_f = 0.59. – UV (CH_3CN): λ_{max} (lg ε) = 216 nm (4.176), 238 (4.178), 351 (3.387). – IR (KBr): $\tilde{\nu}$ = 1676 cm^{-1}, 1666 (C=O), 1620 (C=C). – ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3H, $NCOCH_3$), 2.45 (s, 3H, 2′-H), 7.24 (s, 4H, Ph), 7.99 (s, 1H, 3-H). – ^{13}C NMR ($CDCl_3$): δ = 23.35 (CH_3), 26.03 (C-2′), 124.0, 127.0, 127.1 (CH-Ph), 127.5 (C-2), 128.4 (CH-Ph), 128.9, 135.7 (*i*-Ph), 136.9 (C-3), 168.6 (NCO), 192.1 (C-1′).

$C_{12}H_{11}NO_2S$ (233.3) Calcd. C 61.78 H 4.75
Found C 61.86 H 4.76

Synthesis of **17a–d** *and* **18a–d** *by Diels-Alder Reaction of* **3** *with the Dienophiles* **16a–d**. – *General Procedure:* To a solution of the diene **3** in anhydrous toluene (10 ml) were added the dienophiles **16a–d** (2 ml) and 2-*tert*-butyl-4-methylphenol (0.5 mol-%). The mixtures were heated at 125°C in a pressure flask for 7 d. After removal of the solvent in vacuo the crude products were purified by column chromatography (ethyl acetate/hexane, 1:1).

(3R,4aR*)- and (3S*,4aR*)-5-Acetyl-3,4,4a,5-tetrahydro-3-methoxy-1-methylpyrano[3,4-b][1,4]benzothiazine* (**17a**/**18a**): Reaction of **3** (500 mg, 2.14 mmol) with **16a** according to the general procedure afforded 110 mg of **3** and a mixture of **17a** and **18a** (360 mg, 74%), m.p. (mixture) 117°C (ethanol), R_f = 0.60. – UV (CH_3CN): λ_{max} (lg ε) = 220 nm (4.408), 247 (4.118). – IR (KBr): $\tilde{\nu}$ = 2998 cm^{-1}, 2932 (CH), 1646 (C=O), 1582, 1572 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.52 (m_c, 0.24H, 4-H_{ax}), 1.59 (ddd, J = 12.5, 11.0, 10.0 Hz, 0.76H, 4-H_{ax}), 1.97, 1.99 (2 d, J = 2.1 Hz, 3H, CH_3), 2.04 (s, 3H, $COCH_3$), 2.52 (m_c, 0.24H, 4-H_{eq}), 2.59 (ddd, J = 12.5, 5.5, 2.5 Hz, 0.76H, 4-H_{eq}), 3.48, 3.49 (2 s, 3H, OCH_3), 4.95 (t, J = 2.5 Hz, 0.24H, 3-H), 5.09 (dd, J = 10.0, 2.5 Hz, 0.76H, 3-H), 5.62 (m_c, 1H, 4a-H), 7.07–7.41 (m, 4H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 18.18 (CH_3), 23.23, 23.36 ($COCH_3$), 31.77, 33.49 (C-4), 52.77, 55.93 (C-4a), 55.79, 56.36 (OCH_3), 98.11, 100.1 (C-3), 102.1, 103.1 (C-10a), 126.3, 126.5, 126.6, 126.8, 126.9, 128.1, 128.2, 128.6 (CH-Ph), 136.7, 136.8, 138.1 (*i*-Ph), 150.6, 152.3 (C-1), 169.9, 170.0 (NCO).

$C_{15}H_{17}NO_3S$ (291.4) Calcd. C 61.83 H 5.88
Found C 61.97 H 5.87

(3R,4aR*)- and (3S*,4aR*)-5-Acetyl-3-ethoxy-3,4,4a,5-tetrahydro-1-methylpyrano[3,4-b][1,4]benzothiazine* (**17b**/**18b**): Reaction of **3** (500 mg, 2.14 mmol) with **16b** according to the general procedure afforded a mixture of **17b** and **18b** (547 mg, 84%), R_f = 0.60. – UV (CH_3CN): λ_{max} (lg ε) = 222 nm (4.346), 246 (4.087). – IR (film): $\tilde{\nu}$ = 2976 cm^{-1}, 2930 (CH), 1666 (C=O), 1584, 1570 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.21 (2 t, *J* = 7.5 Hz, 3H, OCH_2CH_3), 1.51 (ddd, *J* = 12.5, 11.0, 2.5 Hz, 0.33H, 4-H_{ax}), 1.62 (ddd, *J* = 12.5, 11.0, 10.0 Hz, 0.66H, 4-H_{ax}), 1.98 (2 d, *J* = 2.1 Hz, 3H, CH_3), 2.03 (s, 3H, $COCH_3$), 2.54 (m_c, 0.33H, 4-H_{eq}), 2.59 (ddd, *J* = 12.5, 5.5, 2.5 Hz, 0.66H, 4-H_{eq}), 3.50–3.97 (m, 2H, OCH_2), 5.06 (t, *J* = 2.5 Hz, 0.33H, 3-H), 5.18 (dd, *J* = 10.0, 2.5 Hz, 0.66H, 3-H), 5.62 (m_c, 1H, 4a-H), 7.07–7.41 (m, 4H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 15.11, 15.16 (OCH_2CH_3), 18.22, 18.26 (CH_3), 23.24, 23.39 ($COCH_3$), 31.95, 33.77 (C-4), 52.96, 55.99 (C-4a), 63.99, 64.72 (OCH_2), 96.77, 98.86 (C-3), 101.9, 102.9 (C-10a), 126.4, 126.5, 126.6, 126.7, 126.8, 127.0, 128.1, 128.6 (CH-Ph), 136.9, 137.1, 138.2, 138.5 (*i*-Ph), 150.7, 152.5 (C-1), 170.1 (NCO).

$C_{16}H_{19}NO_3S$ (305.4) Calcd. C 62.99 H 6.28
Found C 62.81 H 6.38

(3R,4aR*)- and (3S*,4aR*)-5-Acetyl-3,4,4a,5-tetrahydro-3-isobutoxy-1-methylpyrano[3,4-b][1,4]benzothiazine* (**17c**/**18c**): Reaction of **3** (500 mg, 2.14 mmol) with **16c** according to the general procedure afforded a mixture of **17c** and **18c** (529 mg, 74%), R_f = 0.61. – UV (CH_3CN): λ_{max} (lg ε) = 222 nm (4.291), 239 (4.112). – IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2928 (CH), 1668, 1658 (C=O), 1580, 1572 (C=C). – ^1H NMR ($CDCl_3$): δ = 0.82–0.98 [m, 6H, $CH(CH_3)_2$], 1.51 (m_c, 0.4H, 4-H_{ax}), 1.64 (ddd, *J* = 12.5, 11.0, 10.0 Hz, 0.6H, 4-H_{ax}), 1.97, 1.99 (2 d, *J* = 2.1 Hz, 3H, CH_3), 2.04 (s, 3H, $COCH_3$), 2.57 (m_c, 0.4H, 4-H_{eq}), 2.60 (ddd, *J* = 12.5, 5.5, 2.5 Hz, 0.6H, 4-H_{eq}), 3.20–3.70 (m, 2H, OCH_2), 5.06 (t, *J* = 2.5 Hz, 0.4H, 3-H), 5.18 (dd, *J* = 10.0, 2.5 Hz, 0.6H, 3-H), 5.66 (m_c, 1H, 4a-H), 7.07–7.45 (m, 4H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 18.17, 18.27 (CH_3), 19.14, 19.21, 19.24, 19.37 [$(CH_3)_2$], 23.24, 23.37 ($COCH_3$), 28.39, 28.45 (CH), 31.96, 33.71 (C-4), 53.00, 56.01 (C-4a), 75.16, 76.03 (OCH_2), 97.14, 99.26 (C-3), 101.8, 102.9 (C-10a), 126.3, 126.5, 126.6, 128.1, 128.2, 128.6 (CH-Ph), 136.9, 138.2 (*i*-Ph), 150.7, 152.6 (C-1), 169.9, 170.0 (NCO).

$C_{18}H_{23}NO_3S$ (333.4) Calcd. C 64.85 H 6.95
Found C 65.01 H 6.98

(3R,4aR*)- and (3S*,4aR*)-5-Acetyl-3-tert-butoxy-3,4,4a,5-tetrahydro-1-methylpyrano[3,4-b][1,4]benzothiazine* (**17d**/**18d**): Reaction of **3** (500 mg, 2.14 mmol) with **16d** according to the general procedure afforded a mixture of **17d** and **18d** (565 mg, 79%), m.p. (mixture) 119 °C (ethanol), R_f = 0.48. – UV (CH_2CN): λ_{max} (lg ε) = 222 nm (4.307), 246 (4.047). – IR (KBr): $\tilde{\nu}$ = 2978 cm^{-1}, 2934 (CH), 1664 (C=O), 1582, 1570 (C=C9. – ^1H NMR ($CDCl_3$): δ = 1.25, 1.26 [2 s, 9H, $OC(CH_3)_3$], 1.48 (m_c, 0.64H, 4-H_{ax}), 1.64 (m_c, 0.36H, 4-H_{ax}), 1.95 (d, *J* = 2.1 Hz, 3H, CH_3), 2.04 (s, 3H, $COCH_3$), 2.34–2.52 (m, 1H, 4-H_{eq}), 5.34 (t, *J* = 2.5 Hz, 0.64H, 3-H), 5.42 (dd, *J* = 10.0, 2.5 Hz, 0.36H, 3-H), 5.68 (m_c, 1H, 4a-H), 7.02–7.44 (m, 4H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 18.42, 18.53 (CH_3), 23.24, 23.41 ($COCH_3$), 28.64, 28.70 [$OC(CH_3)_3$], 31.16, 34.88 (C-4), 53.24, 56.19 (C-4a), 74.99, 75.96 [$OC(CH_3)_3$], 91.68, 93.59 (C-3), 101.1, 102.2 (C-10a), 126.3, 126.5, 126.7, 128.1, 128.2, 128.6 (CH-Ph), 137.2, 137.4, 138.2, 138.6 (*i*-Ph), 150.8, 153.1 (C-1), 170.0 (NCO).

$C_{18}H_{23}NO_3S$ (333.4) Calcd. C 64.85 H 6.95
Found C 64.95 H 7.01

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