Diels–Alder Cycloaddtion Reactions of Enaminothiones with Ethyl Azodicarboxylate

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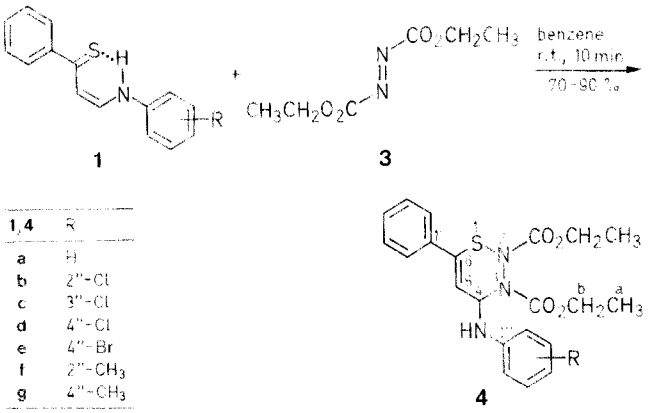
3-Arylamino-1-phenylpropene-1-thione and 3-dimethylamino-1-arylpropene-1-thione undergo [4 + 2] cycloaddition reactions with ethyl azodicarboxylate to yield 1,2,3-thiadiazine derivatives.

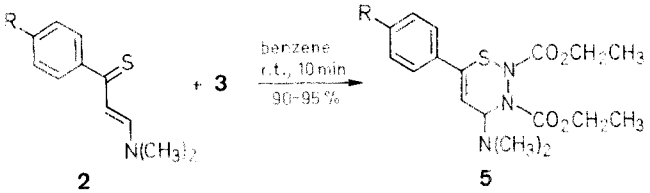
Enaminothiones **1** and **2** have been shown to be highly reactive synthones for the preparation of thiopyran derivatives via [4 + 2] cycloaddition reactions with C–C dienophiles.[1] The behavior of enaminothiones toward heterodienophiles has not yet been investigated.

We have now examined the reactions of enaminothiones with ethyl azodicarboxylate which is known to participate in Diels–Alder cycloadditions as a 4π as well as a 2π component.[2,3] Thus, treatment of 3-arylamino-1-phenylpropene-1-thiones **1** with an equivalent amount of ethyl azodicarboxylate (ethyl diazenedicarboxylate) **(3)** in dry benzene resulted in good yields (70–90%) of [4 + 2] cycloadducts which were characterized as the hitherto unknown diethyl 4-arylamino-6-phenyl-2,3-dihydro-4*H*-1,2,3-thiadiazine-2,3-dicarboxylates **4** on the basis of analytical and spectral data. The ^{1}H-NMR spectrum of **4a**, for example, showed the signals of the methyl protons "a" at higher field ($\delta = 0.83$) as compared to those of other methyl protons ($\delta = 1.33$), probably due to the shielding effect of the *N*-aryl group. The signal of the methylene protons "b" appears as a quartet only in the case of **4f**; in all other cases it appears as a multiplet and at higher field as compared to the signals of other methylene protons. This multiplicity cannot be well rationalized; it is possibly somehow due to non-equivalence of these methylene protons. The other methylene protons appear as a broad multiplet in cases where the signal of the NH proton and the quartet of the methylene protons are superimposed but the D_2O exchange spectra always showed this methylene signal as a clear quartet. The signal of the proton at C-4 appeared either as dd/m due to its splitting by NH and vinylic proton or as a doublet in the case of D_2O exchange. The coupling constant $J_{4,5} \approx 6$ Hz indicates the equatorial position for H-4.[4] Further structural proof for compound **4** was obtained from ^{13}C-NMR spectral assignments made with the help of coupled spectra (Table 2). The mass spectra of **4** in general showed absence of or a very weak molecular ion peak, and strong $M^+ - S$, $M^+ - CO_2Et$, $M^+ - 2CO_2Et$, and Ph–C≡C–H peaks.

The reactions of equimolecular amounts of 3-dimethylamino-1-arylpropene-1-thiones **2** and dienophile **3** under identical conditions followed by complete removal of the solvent resulted in a viscous mass the microanalysis of which was in satisfactory agreement with formula **5**. Final proof for structure **5** was obtained from mass-, IR-, and ^{1}H-NMR-spectral data (Table 1). The coupling constant $J_{4,5} \approx 3$ Hz indicates the axial position for H-4. The equatorial and axial positions for H-4 in the case of **4** and **5**, respectively, indicate the concerted nature of the cycloaddition of 2-aminovinylthiones **1** or **2** with ethyl azodicarboxylate. The difference in coupling constants $J_{4,5}$ cannot be attributed to the different amino functions at position 3, since in that case $J_{4,5}$ of thiadiazine **5** should have been greater than that of thiadiazine **4**.[5]



1,4	R
a	H
b	2″-Cl
c	3″-Cl
d	4″-Cl
e	4″-Br
f	2″-CH$_3$
g	4″-CH$_3$



2,5	R
a	H
b	Cl
c	Br
d	CH$_3$

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 297 IR spectrophotometer, ^{1}H-NMR spectra on a Varian EM 390 MHz spectrometer.

3-arylamino-1-phenylpropene-1-thiones[6] **1**, 3-dimethylamino-1-arylpropene-1-thiones[7] **2**, and ethyl azodicarboxylate were prepared according to known procedures.

4-Anilino-2,3-bis(ethoxycarbonyl)-6-phenyl-2,3-dihydro-4*H*-1,2,3-thiadiazine (4a); Typical Procedure:

To a stirred solution of 3-anilino-1-phenylpropene-1-thione (**1a**; 0.50 g, 0.002 mol) in dry benzene (15 mL) is added a solution of ethyl azodicarboxylate (0.35 g, 0.002 mol) in benzene (5 mL) and the mixture is stirred for 10 min at room temperature. The solvent is removed under reduced pressure and the oily residue is stirred with hexane (10 mL). The resultant solid product is isolated by suction and recrystallized from benzene/hexane (1:1); yield: 0.6 g (70%); mp 118°C.

$C_{21}H_{23}N_3O_4S$	calc.	C 61.02	H 5.56	N 10.17	S 7.72
(413.4)	found	60.75	5.35	10.20	7.75

IR (KBr): ν = 1730, 1715 (C=O); 1605 (C=C); 3375 cm^{-1} (NH).

^{1}H-NMR ($CDCl_3$): δ = 0.83 (t, 3H, 3H^a); 1.33 (t, 3H, CH_3); 4.04 (m, 2H^b); 4.36 (m, 2H, CH_2 and NH); 6.00 (d, 1H, $J_{4,5}$ = 6 Hz, H-5); 6.24 (m, 1H, H-4); 6.74 (d, 2H, H-2″ and H-6″); 7.30 (m, 8H$_{arom}$).

2,3-Bis(ethoxycarbonyl)-4-dimethylamino-6-phenyl-2,3-dihydro-4*H*-1,2,3-thiadiazine (5a); Typical Procedure:

A solution of ethyl azodicarboxylate (0.35 g, 0.002 mol) in dry benzene (10 mL) is added slowly to a stirred solution of 3-dimethylamino-1-phenylpropene-1-thione (**2a**; 0.38 g, 0.002 mol) in dry benzene (15 mL), and stirring is continued for 10 min at room temperature. The solvent is removed under reduced pressure and the remaining viscous mass is washed with cold petroleum ether (bp 40–60°C; 5 mL) and dried under reduced pressure; yield: 0.7 g (92%); oil.

$C_{17}H_{23}N_3O_4S$	calc.	C 55.89	H 6.30	N 11.51
(365)	found	55.96	6.24	11.57

MS: m/z = 365 (M^+).

IR (Neat): ν = 1735, 1725 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 1.30 (m, 6H, $2CH_3$); 2.33 [s, 6H, $N(CH_3)_2$]; 4.20 (m, 4H, CH_2); 5.50 (d, 1H, H-4); 5.90 (d, 1H, $J_{4,5}$ = 3 Hz, H-5); 7.13 (m, 5H$_{arom}$).

Table 1. 4-Amino-2,3-bis(alkoxycarbonyl)-6-aryl-2,3-dihydro-4*H*-1,2,3-thiadiazine Derivatives **4** and **5** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (KBr) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J(Hz)
4a	70	118 (benzene/ hexane)	$C_{21}H_{23}N_3O_4S$ (413)	3375, 1730, 1715, 1605	0.83 (t, 3H, 3H^a); 1.33 (t, 3H, CH_3); 4.04 (m, 2H^b); 4.36 (m, 3H, CH_2 and NH); 6.00 (d, 1H, J = 6, H-5); 6.24 (m, 1H, H-4); 6.74 (d, 2H, J = 8, H-2″ and H-6″); 7.30 (m, 8H$_{arom}$)
4b	75	78 (benzene/ hexane)	$C_{21}H_{22}ClN_3O_4S$ (447.5)	3375, 1725, 1715, 1600	0.82 (t, 3H, 3H^a); 1.32 (t, 3H, CH_3); 3.90 (m, 2H^b); 4.33 (m, 3H, CH_2 and NH); 6.03 (d, 1H, J = 6, H-5); 6.26 (m, 1H, H-4); 7.02 (m, 9H$_{arom}$)
4c	75	144–146 (benzene/ hexane)	$C_{21}H_{22}ClN_3O_4S$ (447.5)	3375, 1730, 1715, 1600	0.93 (t, 3H, 3H^a); 1.43 (t, 3H, CH_3); 4.00 (m, 2H^b); 4.45 (q, 2H, CH_2); 4.56 (br, 1H, NH); 6.10 (d, 1H, J = 6, H-5); 6.24 (m, 1H, H-4); 7.17 (m, 9H$_{arom}$)
4d	88	138 (benzene/ hexane)	$C_{21}H_{22}ClN_3O_4S$ (447.5)	3380, 1740, 1720, 1600	0.86 (t, 3H, 3H^a); 1.33 (t, 3H, CH_3); 3.90 (m, 2H^b); 4.33 (q, 2H, CH_2); 4.56 (br, 1H, NH); 6.00 (d, 1H, J = 6, H-5); 6.23 (m, 1H, H-4); 6.76 (d, 2H, H-2″ and H-6″); 7.12 (d, 2H, $J_{2'',3'';5'',6''}$ = 8, H-3″ and H-5″); 7.30 (m, 5H$_{arom}$)
4e	92	140 (benzene/ hexane)	$C_{21}H_{22}BrN_3O_4S$ (492)	3385, 1740, 1720, 1600	0.92 (t, 3H, 3H^a); 1.40 (t, 3H, CH_3); 4.10 (m, 2H^b); 4.44 (q, 2H, CH_2); 4.58 (br, 1H, NH); 6.06 (d, 1H, J = 6, H-5); 6.26 (m, 1H, H-4); 6.80 (d, 2H, J = 8, H-2″ and H-6″); 7.40 (m, 7H, H-3″, H-5″, and 5H$_{arom}$)
4f	76	98–100 (benzene/ hexane)	$C_{22}H_{25}N_3O_4S$ (427)	3375, 1730, 1715, 1600	0.83 (t, 3H, 3H^a); 1.33 (t, 3H, CH_3); 2.13 (s, 3H, $C_6H_4CH_3$); 3.87 (q, 2H^b); 4.26 (m, 3H, CH_2 and NH); 6.06 (d, 1H, J = 6, H-5); 6.33 (m, 1H, H-4); 7.16 (m, 9H$_{arom}$)
4g	90	120–122 (benzene/ hexane)	$C_{22}H_{25}N_3O_4S$ (427)	3375, 1730, 1720, 1600	0.83 (t, 3H, 3H^a); 1.32 (t, 3H, CH_3); 2.25 (s, 3H, $C_6H_4CH_3$); 3.97 (m, 2H^b); 4.32 (q, 2H, CH_2); 4.17 (br, 1H, NH); 6.10 (d, 1H, J = 6, H-5); 6.28 (dd, 1H, H-4); 6.77 (d, 2H, H-2″ and H-6″); 7.04 (d, 2H, $J_{2'',3'';5'',6''}$ = 8, H-5″ and H-6″); 7.46 (m, 5H$_{arom}$)
5a	92	oil	$C_{17}H_{23}N_3O_4S$ (365)	1735, 1725	1.30 (m, 6H, 2CH_3); 2.33 [s, 6H, $-N(CH_3)_2$]; 4.20 (m, 4H, 2CH_2); 5.50 (d, 1H, J = 3, H-4); 5.90 (d, 1H, J = 3, H-5); 7.13 (m, 5H$_{arom}$)
5b	90	oil	$C_{17}H_{22}ClN_3O_4S$ (399.5)	1735, 1725	1.38 (m, 6H, 2CH_3); 2.42 [s, 6H, $N(CH_3)_2$]; 4.35 (m, 4H, 2CH_2); 5.57 (d, 1H, J = 3, H-4); 5.94 (d, 1H, J = 3, H-5); 7.40 (m, 4H$_{arom}$)
5c	90	oil	$C_{17}H_{22}BrN_3O_4S$ (444)	1740, 1730	1.33 (m, 6H, 2CH_3); 2.36 [s, 6H, $N(CH_3)_2$]; 4.23 (m, 4H, 2CH_2); 5.43 (d, 1H, J = 3, H-4); 5.90 (d, 1H, J = 3, H-5); 7.35 (m, 4H$_{arom}$)
5d	95	oil	$C_{18}H_{25}N_3O_4S$ (379)	1735, 1725	1.30 (m, 6H, 2CH_3); 2.30 [s, 6H, $N(CH_3)_2$]; 2.40 (s, 3H, $C_6H_4CH_3$); 4.20 (m, 4H, 2CH_2); 5.53 (d, 1H, J = 3, H-4); 5.90 (d, 1H, J = 3, H-5); 7.30 (m, 4H$_{arom}$)

[a] Satisfactory microanalyses: C ±1.08, H ±0.22, N ±0.28, S (only for **4a, f, g**) ±0.13.

Table 2. ^{13}C-NMR-Spectral Assignments for Compounds **4a** and **4f**

Compound	C=O	CH_3	CH_2	C-4	C-5	C-6	Aromatic Carbons
4a	154.74; 155.23	13.55; 14.47	63.11; 63.80	61.51	113.88	139.29	113.07 (C-2″, C-6″); 119.03 (C-4″); 134.47 (C-1′); 144.31 (C-1″); 127.03, 129.08, 130.08 (other C_{arom})
4f	155.26; 154.75	13.40; 14.47; 17.56	63.11; 63.72	61.51	113.10	139.35	111.83 (C-6″); 118.73 (C-4″); 121.98 (C-2″); 134.41 (C-1′); 144.90 (C-1″); 127.06, 129.07, 130.11 (other C_{arom})

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