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Nucleophilic Vinylic Substitutions of (*E*)- and (*Z*)-Ethyl 3-Aryl-3-chloro-2-cyanopropenoates with Thioureas. Synthesis of 1,3-Thiazin-4-ones

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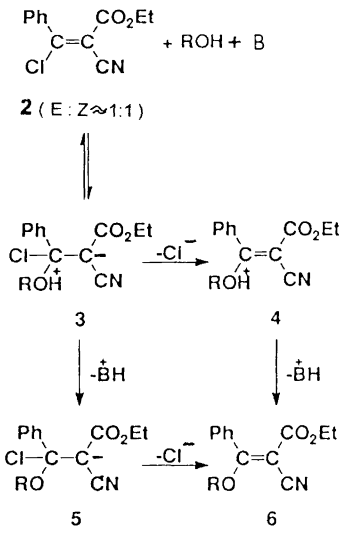
Some new substituted 1,3-thiazin-4-ones have been prepared by reacting (*E*)- and (*Z*)-ethyl 3-aryl-3-chloro-2-cyanopropenoates with thioureas. An interesting spiro compound 4′-cyano-5′-(4-methylphenyl)-3′*H*-spiro[fluorene-9,2′-thiophen]-3′-one was isolated in connection with the study of reaction mechanisms.

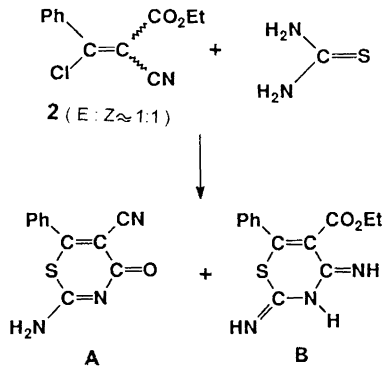
1,3-Thiazinones and related compounds show antibacterial activity[1] and are of interest as antibiotic agents[2] and radiation-sickness drugs.[3] A number of publications in the chemical literature describe various methods for the preparation of 1,3-thiazine and 1,3-thiazinone derivatives.[4–21] The kinetics and reaction mechanisms of nucleophilic vinylic substitutions have been thoroughly studied by Rappoport *et al.*[22]

In a previous study in this laboratory it was shown that (*E*)- and (*Z*)-ethyl 3-chloro-2-cyano-3-phenylpropenoate react with alcohols in the presence of bases to form only (*E*)-ethyl 3-alkoxy-2-cyano-3-phenylpropenoates independent of the configuration of the starting chloropropenoates (*Z*:*E* ≈ 1:1).[23] The formation of only one isomer may be the result of post isomerisation of the end products due to partial single bond character of the double bond or a kinetically controlled process due to the rotation of the C_α–C_β single bond of the intermediates **3** and/or **5** before the elimination of Cl^- to form the *E*-isomer (Scheme 1).

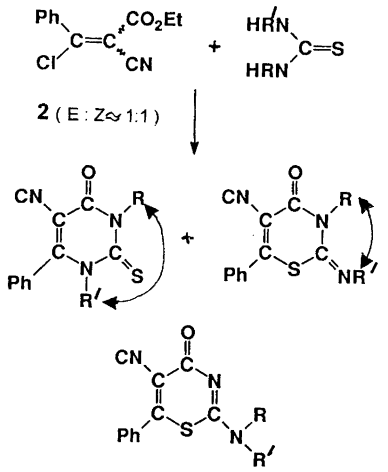
The present study was undertaken to elucidate the reaction pathway in similar nucleophilic vinylic substitutions and to develop a new method for the preparation of 1,3-thiazinones. For this purpose thioureas were chosen as reagents. The choice was based on the assumption



Scheme 1.



Scheme 2.



Scheme 3.

that thioureas with their multifunctionality could intercept one of the intermediates analogous to **3** and **5** shown in Scheme 1.

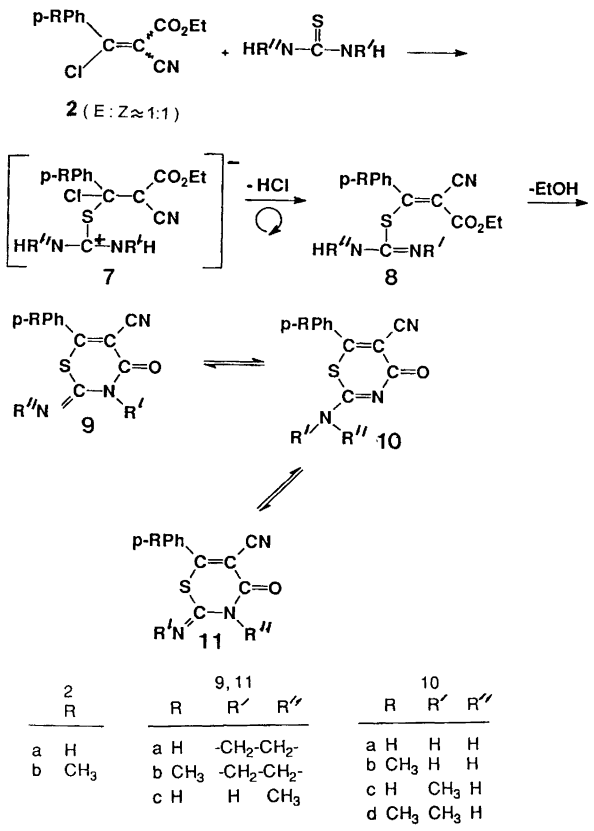
The *E*- and *Z*-isomers of **2** can form two 1,3-thiazines (**A** and **B**), in the reaction with thiourea, besides the tautomeric form of **A** and **B** (Scheme 2). The reactions with thioureas can proceed via *N*-nucleophilic and/or *S*-nucleophilic reactions to form pyrimidinones and/or thiazinones in cyclisation reactions. Five different products can be formed in reactions with unsymmetrical thioureas, if addition to the cyano group rather than to the ethoxycarbonyl group is not considered (Scheme 3).

Results and discussion

The reactions of the vinylic esters **2a** and **2b** ($E{:}Z \approx 1{:}1$) (Scheme 4) with thioureas were carried out with two equivalents of thioureas in THF at 60°C. With the thioureas studied in the present investigation only 1,3-thiazinones were formed. The reaction may proceed as shown in Scheme 4.

In the reaction with unsymmetrical thioureas, three different thiazinones can be formed and with symmetrical thioureas two tautomers **9** and **10** can be formed. In the reaction with 2-imidazolidinethione the imino tautomers **9** and **11** are the only possible 1,3-thiazinones. In this reaction **9** and **11** are identical. Intermediate **8** could not be detected in any of the reactions with thioureas. This shows that the cyclisation is fast in comparison with the substitution. The structures of the reaction products were deduced mainly from their NMR and mass spectra. The fragmentation pattern giving rise to the most abundant ions common to all 1,3-thiazinones studied in this work is shown below for **10d** (Fig. 1).

The reaction products from the reaction of methylthiourea with β-chloro esters **2b** were assigned the enamine structure **10d** because the aminomethyl group appeared as a doublet in the ^{1}H NMR spectrum ($J = 4.7$ Hz) and



2 R		9, 11 R	R′	R″	10 R	R′	R″
a	H	a	H	-CH_2-CH_2-	a	H	H	H
b	CH_3	b	CH_3	-CH_2-CH_2-	b	CH_3	H	H
		c	H	H	CH_3	c	H	CH_3	H
					d	CH_3	CH_3	H

Scheme 4.

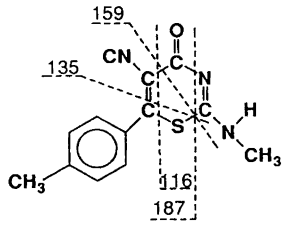
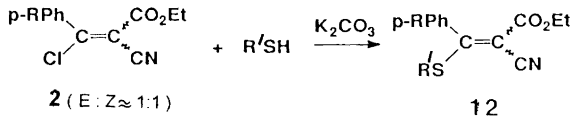


Fig. 1. General mass spectral fragmentation pattern for 1,3-thiazin-4-ones illustrated for **10d**.

the amino hydrogen as a quartet with the same coupling constant. The reaction product from the reaction between **2a** and methylthiourea was assigned the structure **11c**. The amino methyl group appeared as a singlet at 2.94 ppm in the ^{1}H NMR spectrum. The amino methyl signal also remained a singlet in the spectrum taken in a mixture of trifluoroacetic acid and $CDCl_3$. This excludes the structure **9c**, because the nitrogen bearing the methyl group in **9c** is basic and should therefore be protonated in acidic solution and the methyl group should appear as a doublet. Such spin–spin coupling has been observed in the spectrum of 6-methoxycarbonyl-2-methylimino-2,3-dihydro-4*H*-1,3-thiazin-4-one.[6] The structure **10c** is also excluded because the amino methyl group should give a doublet in DMSO-d_6 as solvent as observed for **10d**.

There has to be a free rotation around the C_α–C_β bond

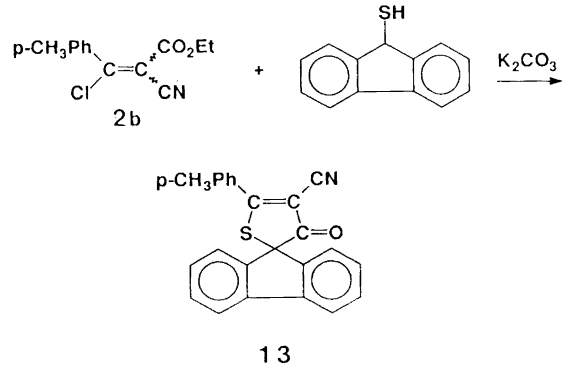


2 (E : Z ≈ 1:1)

12

2 R		12 R		R′
a	H	a	H	Heptyl
b	CH_3	b	CH_3	-"-
a	H	c	H	Fluorenyl

Scheme 5.



13

Scheme 6.

of intermediate **7** and the rotation has to progress through a situation where the amino group in thiourea and the ethoxycarbonyl group are close enough to each other to cyclize to 1,3-thiazinones.

Because the intermediate **8** could not be detected in the reactions with thioureas, some reactions of **2a** and **2b** were carried out with 1-heptanethiol and 9-fluorenethiol in the presence of potassium carbonate to study the ratio of *E*- and *Z*-isomers of the substitution products (Scheme 5).

The substitution products **12a–c** are analogous to intermediate **8** (Scheme 4) that could not be detected in the reactions with thioureas. In the reactions of **2a** and **2b** with 1-heptanethiol the ratio of the isomers with the heptylthio group and the ethoxycarbonyl group on the opposite sides of the carbon–carbon double bond (*E*-isomer) were 89 and 79%, respectively. In the reaction between **2a** and 9-fluorenethiol the ratios of *E*- and *Z*-isomers were 41 and 59%, respectively. The *E*–*Z* configurations were assigned on the basis of their NOESY 2D NMR spectra. In the reaction between **2b** and 9-fluorenethiol the reaction continued from the substitution stage with a cyclisation reaction shown in Scheme 6.

Because the substitution products **12a–c** (Scheme 5) contain *E*- as well as *Z*-isomers, and because *E*-isomers cannot cyclize to ring-closed products, it seems reasonable to conclude that the cyclisation takes place in a concerted addition elimination reaction during the rotation around the C_α–C_β bond of intermediate **7** (Scheme 4) and not after the formation of the intermediate analogous to **8** (Scheme 4) and **12** (Scheme 5). That these *E*-isomers could not be detected as intermediates in the reactions that gave ring-closed products supports this conclusion.

Experimental

General methods. Melting points are uncorrected. IR spectra were measured for KBr discs and are reported in cm^{-1}. NMR spectra were measured for samples either in DMSO-d_6 or $CDCl_3$ or in a mixture of $CDCl_3$ and CF_3CO_2H. ^1H NMR spectra were determined at 400 MHz on a Jeol GX-400 or at 90 MHz on a Jeol MX-90 spectrometer. ^{13}C NMR spectra were determined at 22.5 MHz or at 100.6 MHz on the same instruments as the ^1H NMR spectra. The *E*- and *Z*-configurations were determined on the basis of their NOESY 2D ^1H NMR spectra. The chemical shifts are expressed as ppm (δ) downfield from TMS. Electron ionization mass spectra (EIMS) were determined at 70 eV on a VG-7070E spectrometer equipped with a gas chromatograph (fused silica column, DB-1, 15 m × 0.53 mm i.d.). GLC analyses were performed on a similar column using temperature programming from 200 to 290 °C.

Methylthiourea was prepared from methyl isothiocyanate and ammonia.[24] The other thioureas were purchased from Aldrich and were used without purification.

Ethyl 3-chloro-2-cyano-3-phenylpropenoate (**2a**) (*E*:*Z* ≈ 1:1) and ethyl 3-chloro-2-cyano-3-(4-methylphenyl)propenoate (**2b**) (*E*:*Z* ≈ 1:1) were prepared according to a method described in a previous article.[23]

9-Fluorenethiol was prepared from 9-bromofluorene and thiourea.[25]

2-Amino-5-cyano-6-phenyl-4H-1,3-thiazin-4-one (**10a**). A solution of thiourea (304 mg, 4 mmol) and **2a** (471 mg, 2 mmol) in dry THF (30 ml) was stirred at 60 °C under an argon atmosphere. A white precipitate was slowly formed after about 1 h. After 15 h at 60 °C the solvent was evaporated off under reduced pressure. The resulting precipitate was washed with water and diethyl ether. The solvent was filtered off and the product was recrystallized from a mixture of dichloromethane and ethanol (1:1). Yield 63%; m.p. 226–228 °C; IR: 2210, 1650, 1560; EIMS *m/z* (RA) 229 (M^+, 69%), 187 (92), 159 (100), 126 (13), 121 (45), 115 (12), 102 (47), 77 (30); ^1H NMR (DMSO-d_6): δ 9.05 (s, 1 H), 8.95 (s, 1 H), 7.60–7.70 (m, 5 H); ^{13}C NMR (DMSO-d_6): δ 165.70, 162.42, 161.18, 132.25, 129.36, 127.96, 114.88, 103.04; HRMC calc. for $C_{11}H_7N_3OS$, 229.0309; found 229.0296.

2-Amino-5-cyano-6-(4-methylphenyl)-4H-1,3-thiazin-4-one (**10b**). The reaction was carried out as above with thiourea (304 mg, 4 mmol) and **2b** (499 mg, 2 mmol) in 30 ml THF at 50 °C. Yield 66%; m.p. 210–212 °C; IR: 2220, 1660, 1560; EIMS *m/z* (RA) 243 (M^+, 75%), 201 (88), 173 (100), 172 (28), 142 (19), 141 (27), 135 (41), 102 (30), 91 (42); ^1H NMR (DMSO-d_6): δ 8.95 (s, 2 H), 7.57 (d,

2 H, $J = 9$ Hz), 7.42 (d, 2 H, $J = 9$ Hz), 2.4 (s, 3 H) ^{13}C NMR (DMSO-d_6): δ 165.91, 162.54, 161.27, 142.54, 130.42, 129.91, 115.06, 102.52; HRMS calc. for $C_{12}H_9N_3OS$ 243.0466; found 243.0440.

*5-Cyano-2-imino-6-phenyl-2,3-dihydro-4*H*-1,3-thiazin-4-one* (**11c**). The reaction was carried out as above with methythiourea (360 mg, 4 mmol) and **2a** (471 mg, 2 mmol). Yield 71%; m.p. 280°C; IR: 2220, 1630, 1565; EIMS *m/z* (RA) 243 (M^+, 100%), 187 (80), 159 (93), 121 (44), 116 (90), 77 (22); ^{1}H NMR (DMSO-d_6): δ 9.37 (s, 1 H), 7.70–7.60 (m, 5 H), 2.95 (s, 3 H); ^{13}C NMR (CF_3CO_2H–$CDCl_3$) δ 165.83, 162.25, 159.16, 135.44, 130.72, 130.34, 128.34, 111.11, 103.79, 31.64; HRMS calculated for $C_{12}H_9N_3OS$ 243.0466; found 243.0408.

*5-Cyano-2-methylamino-6-(4-methylphenyl)-4*H*-1,3-thiazin-4-one* (**10d**). The reaction was performed as above with methylthiourea (360 mg, 4 mmol) and **2b** (499 mg, 2 mmol). Yield 61%; m.p. 280°C; IR: 2220, 1655, 1550; EIMS *m/z* (RA) 257 (M^+, 100%), 201 (81), 173 (88), 139 (15), 135 (28), 116 (68), 91 (25). ^{1}H NMR (DMSO-d_6): δ 9.227 (s, 1 H), 7.54 (d, 2 H, $J = 8.3$ Hz), 7.39 (d, 2 H, $J = 8.3$ Hz), 2.96 (d, 3 H, $J = 4.6$ Hz), 2.42 (s, 3 H) ^{13}C NMR (CF_3CO_2H–$CDCl_3$): δ 165.72, 164.89, 159.54, 147.25, 131.21, 128.23, 127.53, 111.45, 102.17, 31.48, 21.78; HRMS calc. for $C_{13}H_{11}N_3OS$, 257.0623; found 257.0619.

*6-Cyano-7-phenyl-2,3-dihydro-5*H*-imidazo[2,3-a][1,3]-thiazin-5-one* (**11a**). This compound was prepared from **2a** (471 mg, 2 mmol) and 2-imidazolidinethione (408 mg, 4 mmol). Yield 67%; m.p. 218–220°C; IR: 2210, 1660, 1530; EIMS *m/z* (RA) 255 (M^+, 100%), 254 (68), 188 (10), 159 (8), 127 (8), 121 (9), 100 (8), 72 (16), 68 (72), 41 (16); ^{1}H NMR (CF_3CO_2H–$CDCl_3$): δ 7.71–7.65 (m, 5 H), 4.63 (t, 2 H, $J = 8.8$ Hz), 4.38 (t, 2 H, $J = 8.8$ Hz); ^{13}C NMR (CF_3CO_2H–$CDCl_3$): δ 165.08, 162.71, 155.67, 135.72, 130.74, 129.98, 128.13, 110.95, 103.57, 47.02, 46.14; HRMS calculated for $C_{13}H_9N_3OS$, 255.0466; found 255.0477.

*6-Cyano-7-(4-methylphenyl)-2,3-dihydro-5*H*-imidazo[2,3-a]-[1,3]thiazin-5-one* (**11b**). Starting materials: 2-imidazolidinethione (408 mg, 4 mmol) and **2b** (499 mg, 2 mmol). Yield 68%; m.p. 210–212°C; IR: 2220, 1670, 1530; EIMS *m/z* (RA) 269 (M^+, 100%), 268 (72), 202 (16), 173 (4), 140 (13), 135 (8), 68 (47); ^{1}H NMR (CF_3CO_2H–$CDCl_3$): δ 7.61 (d, 2 H, $J = 6.4$), 7.48 (d, 2 H, $J = 6.4$), 4.62 (br, 2 H), 4.39 (br, 2 H); ^{13}C NMR (CF_3CO_2H–$CDCl_3$): δ 165.29, 162.98, 154.06, 148.41, 131.50, 128.25, 127.25, 111.59, 102.60, 47.14, 46.26, 21.24; HRMS calc. for $C_{14}H_{11}N_3OS$; 269.0622, found 269.0649.

(E)- and (Z)-Ethyl 2-cyano-3-phenyl-3-(heptylthio)propenoate (**12a**). A solution of 1-heptanethiol (264 mg, 2 mmol) and **2a** (471 mg, 2 mmol) in dry THF (30 ml) in the presence of potassium carbonate (0.6 g 4.3 mmol) was stirred at 60°C for 15 h. The solvent was evaporated off under reduced pressure. The residue was taken up in dichloromethane and washed with water. The organic phase was dried over sodium sulfate. Filtration and evaporation yielded 73%. (E:Z = 89:11%). The E-isomer gave the following spectroscopic data. IR (film on KBr disc): 2200, 1710; EIMS *m/z* 331 (M^+, 40%), 260 (59), 247 (100), 233 (38), 201 (39), 121 (66), 57 (38), 55 (39); ^{1}H NMR ($CDCl_3$): δ 7.2–7.53 (m, 5 H), 4.33 (q, 2 H), 2.34 (t, 2 H), 1.35 (t, 3 H), 1.10–1.25 (m, 10 H), 0.85 (t, 3 H); ^{13}C NMR ($CDCl_3$): δ 179.70, 162.71, 135.45, 129.83, 129.25, 127.0, 115.44, 99.41, 61.62, 34.02, 31.26, 28.68, 28.34, 28.28, 22.27, 14.04, 13.80; HRMS calc. for $C_{19}H_{25}NO_2S$, 331.1606; found 331.1600.

(E)- and (Z)-Ethyl 2-cyano-(4-methylphenyl)-3-(heptylthio)-propenoate (**12b**). Starting materials: 1-heptanethiol (264 mg, 2 mmol), **2a** (299 mg, 2 mmol) and potassium carbonate (600 mg). The reaction conditions were the same as above. Yield 76% (E:Z = 79:21). The E-isomer gave the following spectroscopic data. IR (film on KBr disc): 2200, 1710; EIMS *m/z* 345 (M^+, 47%), 274 (49), 261 (90), 247 (62), 215 (37), 201 (27), 142 (32), 135 (100), 57 (47), 55 (40); ^{1}H NMR ($CDCl_3$): δ 7.29 (d, 2 H, $J = 7.8$ Hz), 7.12 (d, 2 H, $J = 7.8$ Hz), 4.32 (q, 2 H), 2.40 (s, 3 H), 2.36 (t, 2 H), 1.35 (t, 3 H), 1.00–1.25 (m, 10 H), 0.84 (t, 3 H); ^{13}C NMR ($CDCl_3$): δ 180.14, 162.80, 140.09, 132.60, 129.89, 127.28, 115.66, 99.35, 61.55, 34.11, 31.29, 28.74, 28.31, 22.30, 21.24, 14.07, 13.80; HRMS calc. for $C_{20}H_{27}NO_2S$ 345.1763; found 345.1762.

(E)- and (Z)-Ethyl 2-cyano-3-(9-fluorenylthio)-3-phenylpropenoate (**12c**). Starting materials: 9-fluorenethiol (396 mg, 2 mmol) **2a** (271 mg, 2 mmol) and potassium carbonate (600 mg). The same reaction conditions as above. Yield 68%, (E:Z = 41:59). The Z-isomer was separated from the E-isomer by repeated recrystallisation from ethanol. The Z-form gave the following spectroscopic data: m.p. 150–152°C; IR (KBr disc): 2210, 1715, 1710; EIMS *m/z* 397 (M^+, 17%), 352 (4), 324 (10), 197 (6), 165 (100); ^{1}H NMR ($CDCl_3$): δ 7.12–7.57 (m, 13 H), 4.89 (s, H), 4.05 (q, 2 H), 1.09 (t, 3 H); ^{13}C NMR ($CDCl_3$): δ 174.85, 160.71, 142.73, 140.55, 134.02, 130.31, 129.31, 128.68, 128.10, 127.79, 125.24, 120.21, 115.35, 101.99, 61.92, 50.54, 13.83; HRMS calc. for $C_{25}H_{19}NO_2S$ 397.1137; found 397.1142;

*4'-Cyano-5,5'-(-4-methylphenyl)-3'*H*-spiro[fluorene-9,2'-thiophen]-3'-one* (**13**). Starting materials: 9-fluorenethiol (396 mg, 2 mmol), **2b** (499 mg, 2 mmol) and potassium carbonate. The same reaction conditions as above. On evaporation of the dichloromethane at reduced pressure a light brown precipitate was formed. The yield was 62% after recrystallisation from ethanol. M.p. 260–262°C; IR (KBr disc): 2230, 1680, 1600; EIMS *m/z* (RA) 365 (M^+, 100%), 337 (43), 336 (27), 322 (40), 290 (18), 246 (11), 196 (34), 152 (11); ^{1}H NMR ($CDCl_3$): δ 6.68–770 (m, 15 H), 2.17 (s, 3 H) ^{13}C NMR ($CDCl_3$): δ 191.10, 179.44,

142.64, 141.98, 140.94, 130.17, 129.71, 129.47, 121.91, 121.03, 115.66, 112.59, 21.42; HRMS calc. for $C_{24}H_{15}NOS$ 365.0874; found 365.0862.

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