4-Thiazoline-2-thiones. VI. The Conjugate Addition at the *S*- *vs.* *N*-Positions to Methyl Vinyl Ketone

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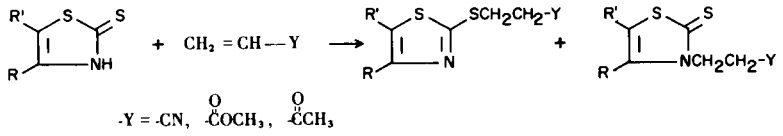
Recently, the base-catalyzed conjugate addition of 4-thiazoline-2-thiones to acrylonitrile or methyl acrylate was reported (1) to occur at either the *S*- or *N*-atoms of the -C(=S)-NH-moiety of the heterocycle (Equation 1, Chart I). In certain additions, a kinetically controlled formation of the *S*-adduct and a thermodynamically controlled formation of the *N*-adduct were assigned (Equation 2). Adducts of vinyl ketones previously have been found to be more active towards reversal than those of nitriles and esters (2,3) (Equation 2). In the present work, the site of the conjugate addition to methyl vinyl ketone (Equation 1) is reported as a function of the activity of the vinyl acceptor agent, the presence of a basic catalyst, and steric hindrance.

Summarized in Table I are the yields of the products of conjugate additions of 4-thiazoline-2-thiones after 2 hours of reflux in methanol. The results obtained in the presence of sodium methoxide allow comparison with the earlier reported additions to acrylonitrile and methyl acrylate. Thus, addition of 4-thiazoline-2-thione to methyl vinyl ketone yielded only a *N*-adduct, II (90%), as it did with acrylonitrile and methyl acrylate (1). However, 4-methyl- and 4,5-dimethyl-4-thiazoline-2-thione gave *N*-adducts, IV (85%) and VI (86%), respectively, in contrast to the predominant *S*-addition to acrylonitrile or methyl acrylate (1). 4-Phenyl-4-thiazoline-2-thione afforded the first observed example of its formation of a *N*-adduct, VIII (11%), although the *S*-adduct, VII (75%), predominated. 5-Acetyl-4-methyl- and 5-carbethoxy-4-methyl-4-thiazoline-2-thione gave only *N*-adducts, X (76%) and XII (75%), respectively, whereas the corresponding additions to acrylonitrile and methyl acrylate gave only *S*-adducts (1).

Equation 2 suggests that a *S*-adduct might be more readily obtained if the experimental conditions sufficiently slowed down the rate of reaction. Such increased selectivity in the isolation of the *S*-adducts of methyl vinyl

CHART I

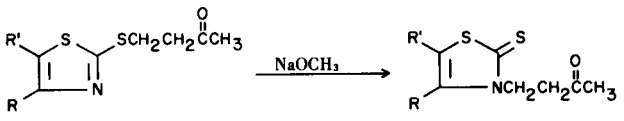
Equation 1



-Y = -CN, -COCH₃, -CCH₃

Equation 2 *S*-adduct ⇌ addendum ⇌ *N*-adduct

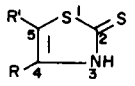
Equation 3



R = R' = H, or R = R' = CH_3

TABLE I

Yields of *S*- and *N*-Conjugate Additions of



to Methyl Vinyl Ketone (a)

R	R′	Adduct No.	% *S*-Addition in NaOMe-MeOH	% *S*-Addition in MeOH	Adduct No.	% *N*-Addition in NaOMe-MeOH	% *N*-Addition in MeOH
H	H	I	0	70 (b)	II	91	22 (b)
CH_3	H	III	0	(30) (c)	IV	85	0
CH_3	CH_3	V	0	34 (d)	VI	86	0
C_6H_5	H	VII	75 (e)	73	VIII	11 (e)	0
CH_3	$COCH_3$	IX	0	7 (f)	X	76	0
CH_3	$CO_2C_2H_5$	XI	0	9 (g)	XII	75	0
CO_2H	H	XIII	93	91			
$CO_2C_2H_5$	H	XIV	23 (h)	92 (i)			
p-$CH_3OC_6H_4$	H	XV	77	78			
p-$NO_2C_6H_4$	H	XVI	87	18			
$(CH_3)_3C$	H	XVII	90	85			

(a) After 2 hours of reflux, unless otherwise indicated. (b) After 3 hours (trace of $CaCl_2$), *S*-addition was 87% and *N*-addition was 12%. (c) Since the product was unstable, the yield is based on an estimated λ max 281 mμ (ε, 15,400), (85%) after 24 hours. (d) After 24 hours, *S*-addition was 90% and *N*-addition, 0%. (e) Unchanged after 24 hours. (f) After 24 hours, *S*-addition was 40% and *N*-addition, 0%; after 72 hours (trace of $CaCl_2$), *S*-addition was 55% and *N*-addition, 0%. (g) After 24 hours, *S*-addition was 51% and *N*-addition, 0%. (h) After 24 hours, 62%. (i) Unchanged after 24 hours.

ketone was realized by omitting the catalyst. Thus, the reaction of 4-thiazoline-2-thione with methyl vinyl ketone in methanol gave the first reported example of *S*-addition of this heterocycle (*i.e.*, I, 70%) accompanied by *N*-addition (*i.e.*, II, 22%). In other examples, addition under similar conditions gave only the *S*-adducts, III, V, VII, IX, and XI. Yields of *S*-adducts were increased by use of longer reaction times (footnotes d, f, g, and h, Table I). 4-Thiazoline-2-thiones bearing electron-withdrawing groups, however, yielded only stable *S*-adducts (*i.e.*, XIII-XVI) in either the absence or the presence of sodium methoxide.

Sterically hindering substitution at the 4-position of the addendum favored isolation of a stable *S*-adduct. Thus, 4-*tert*-butyl-4-thiazoline-2-thione, unlike other 4-alkyl addenda studied, gave only the *S*-adduct, XVII, (85-90%) in either the absence or the presence of sodium methoxide. The same addendum failed to add to acrylonitrile in methanolic sodium methoxide in 2 hours, but afforded the *S*-adduct, XVIII (84%, Experimental), in 24 hours. An effect of possible steric hindrance in the vinyl acceptor agent also was noted. Thus, 4-carboxymethyl-4-thiazoline-2-thione failed to add to dimethyl benzalmalonate, but 4-thiazoline-2-thione added to diethyl methylenemalonate (see XIX, Experimental). In general, related heterocycles have failed to add to vinyl acceptor agents having β-phenyl group, *e.g.*, diethyl benzalmalonate and chalcone and their derivatives. However, examples of the addition of such heterocycles to diethyl methylenemalonate and to phenyl vinyl ketone and its derivatives have been reported (2).

Isolated, unstable *S*-adducts could be converted to

TABLE II

Physical Properties of Adducts

Adduct No.	Formula	M.P., °C. B.P., °C/μ	n_D^{25}	λ max (Methanol) mμ	ε x 10^3	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
I	$C_7H_9NOS_2$	56/3	1.5700	276	7.6	44.9	4.8	7.5	34.2	45.1	4.7	7.6	34.2
II		84/1	1.6310	317	14.0					45.1	4.9	7.6	34.4
III	$C_8H_{11}NOS_2$			(281)	(13.0)	47.7	5.5	7.0	31.9				
IV		84		321	13.6					47.6	5.6	7.1	32.1
V	$C_9H_{13}NOS_2$	100/65	1.5576	287	8.0	50.2	6.1	6.5	29.8	50.4	6.0	6.5	30.0
VI		114		325	15.0					50.4	5.9	6.4	29.7
VII	$C_{13}H_{13}NOS_2$	112/16	1.6365	274	13.0	59.2	5.0	5.3	24.3	59.1	5.0	5.2	24.4
VIII		113		323	19.3					59.0	4.9	5.2	24.2
IX	$C_{10}H_{13}NO_2S_2$	51		319	15.9	49.4	5.4	5.8	26.4	49.3	5.6	5.7	26.3
X		94		355	18.2					49.3	5.6	5.7	26.2
XI	$C_{11}H_{15}NO_3S_2$	107/10	1.5626	304	14.5	48.3	5.5	5.1	23.5	48.1	5.5	5.1	23.5
XII		75		341	19.4					48.2	5.4	5.2	23.4
XIII	$C_8H_9NO_3S_2$	167		282	6.4	41.5	3.9	6.1	27.7	41.7	4.1	6.0	27.8
XIV	$C_{10}H_{13}NO_3S_2$	75		280	6.1	46.3	5.1	5.4	24.7	46.3	5.2	5.2	24.8
XV	$C_{14}H_{15}NO_2S_2$	77		270	20.2	57.3	5.2	4.8	21.9	57.2	5.3	4.6	21.7
XVI	$C_{13}H_{12}N_2O_3S_2$	107		340	13.0	50.6	3.9	9.1	20.8	50.7	4.0	9.0	21.1
XVII	$C_{11}H_{17}NOS_2$	68/12	1.5347	278	6.8	54.3	7.0	5.8	26.3	54.1	6.9	5.6	26.4
XVIII	$C_{10}H_{14}N_2S_2$	66/2	1.5426	276	6.9	53.1	6.2	12.4	28.3	53.2	6.0	12.1	28.2
XIX	$C_{11}H_{15}NO_4S_2$	118/10	1.5568	318	13.3	45.7	5.2	4.8	22.1	45.5	5.1	4.9	22.0

N-adducts by further reaction. For example, treatment of the *S*-adducts, I and V, for 2 hours with methanolic sodium methoxide afforded the *N*-adducts, II (95%) and VI (87%), respectively (Equation 3). The *S*-adduct, III, tended to be unstable during isolation by high-vacuum distillation. When conjugate addition took place in methanol containing a trace of calcium chloride, the stability of III appeared to be enhanced. *S*-Adducts (*e.g.*, XIV) bearing an electron-withdrawing group remained unchanged after 24 hours of reflux in methanolic sodium methoxide.

In earlier work (1), the sites of *S*- and *N*-additions of 4,5-dimethyl-4-thiazoline-2-thione to methyl acrylate were confirmed by unequivocal syntheses. The two products obtained had λ max 287 mμ and λ max 326 mμ, respectively, in their U.V. spectra. By analogy, the adducts of this addendum and methyl vinyl ketone that had λ max 287 mμ and λ max 325 mμ were assigned *S*- and *N*-forms, respectively. S_N2-type alkylation reactions of the sodium salt of thiazolidine-2-thione have been reported to give, invariably, *S*-alkylation products (4). Products of the S_N2 alkylation of 4-thiazoline-2-thione (XX) and its 4-methyl (5), 4-phenyl (XXI) and 4-*tert*-butyl (XXII) derivatives by chloroacetone (Experimental) had λ max 271-279 mμ. The correspondingly assigned *S*-adducts of methyl vinyl ketone, I, III, VII, and XVII, similarly had λ max 274-281 mμ. All other assignments of structure were also made on the basis of U. V. spectra.

Characteristic data of new adducts are summarized in Table II (listed consecutively by adduct number and corresponding to those in Table I).

EXPERIMENTAL

Solid products were purified by recrystallization from methanol. Melting points were determined in soft-glass, capillary tubes and are corrected. Liquid products were purified by high-vacuum distillation by use of a stirred, oil-jacketed, 100-ml. Hickman still and an oil pump connected to a two-stage diffusion, glass ejector pump. Boiling points are uncorrected. Ultraviolet spectra were recorded on a Perkin-Elmer Ultraviolet-Visible Model 202 Spectrophotometer.

4-Thiazoline-2-thiones.

All 4-thiazoline-2-thiones employed were prepared as described previously (6-9).

General Procedures.

Typical preparations of the adducts of Tables I and II follow.

5-Carbethoxy-4-methyl-2-(3-oxobutylthio)thiazole, XI.

A solution of 35 g. (0.17 mole) of 5-carbethoxy-4-methyl-4-thiazoline-2-thione and 24.5 g. (0.35 mole) of methyl vinyl ketone in 400 ml. of methanol was refluxed for 2 hours. Removal of the volatile components *in vacuo* with warming gave a partially solid residue. The presence of XI could not be detected by the U. V. spectrum of the residue. Recrystallization of the solid from benzene yielded 27.9 g. of recovered 5-carbethoxy-4-methyl-4-thiazoline-2-thione, m.p. 152°. Concentration of the filtrate gave an amber oil, λ max 307 mμ (ε, 8,400). Distillation of the oil yielded 4.2 g. of XI and 1.8 g. of recovered 5-carbethoxy-4-methyl-4-thiazoline-2-thione, b.p. 137° at 8 μ; m.p. 152°, recrystallized from benzene.

The experiment was repeated except that the duration of reflux was 24 hours. Distillation separated 24 g. of XI and 14.5 g. of 5-carbethoxy-4-methyl-4-thiazoline-2-thione.

No indication of the formation of the 3-adduct, XII, was evident in either experiment.

5-Carbethoxy-4-methyl-3-(3-oxobutyl)-4-thiazoline-2-thione, XII.

To 300 ml. of anhydrous methanol was added 0.2 g. of sodium. When the reaction of the sodium was complete, 20.3 g. (0.1 mole) of 5-carbethoxy-4-methyl-4-thiazoline-2-thione and 14.0 g. (0.2 mole) of methyl vinyl ketone were added, and the solution was refluxed for 2 hours (calcium chloride tube). The reaction mixture was cooled, treated with excess hydrogen chloride in methanol, and filtered. Concentration of the filtrate *in vacuo* yielded a crystalline product, 20.5 g. (75%), m.p. 75°. The melting point was unchanged on recrystallization.

Other Preparations.

4-*tert*-Butyl-2-(2-cyanoethylthio)thiazole, XVIII (Table II).

Treatment of 26.0 g. (0.15 mole) of 4-*tert*-butyl-4-thiazoline-2-thione and 15.9 g. (0.3 mole) of acrylonitrile in 300 ml. of methanol containing a catalytic amount of sodium methoxide for 24 hours by the procedure described to prepare XII afforded the adduct, XVIII, 28.4 g. (84%), purified by distillation.

3-(2-Dicarbethoxyethyl)-4-thiazoline-2-thione, XIX (Table II).

According to a previously reported method (2), a solution of 35.2 g. (0.3 mole) of 4-thiazoline-2-thione, 65.0 g. (0.38 mole) of redistilled diethyl methylenemalonate (b.p. 82° at 9 mm., n_D^{25} 1.4232) (10), and 200 ml. of glacial acetic acid was heated to boiling and then kept at room temperature overnight. Distillation yielded XIX, 62.0 g. (72%).

2-(2-Oxopropylthio)thiazole, XX.

To 300 ml. of anhydrous methanol was added 4.8 g. (0.21 mole) of sodium. When the reaction of the sodium was complete, 23.4 g. (0.2 mole) of 4-thiazoline-2-thione was added forming a solution. Chloroacetone (19.0 g., 0.205 mole) in 25 ml. of methanol was added dropwise with stirring during 10 minutes, resulting in an exothermic reaction (calcium chloride tube). The reaction mixture was heated under reflux for 15 minutes, cooled, and filtered. Removal of the methanol *in vacuo* from the filtrate afforded an oil, 34.2 g., λ max 274 mμ (ε, 7,200). Distillation gave pure XX, 27.6 g. (80%), b.p. 53° at 16 μ, n_D^{25} 1.5864, λ max 274 mμ (ε, 7,400).

Anal. Calcd. for $C_6H_7NOS_2$: C, 41.6; H, 4.2; N, 8.1; S, 37.0. Found: C, 41.6; H, 4.4; N, 7.8; S, 36.9.

2-(2-Oxopropylthio)-4-phenylthiazole, XXI.

Alkylation of 4-phenyl-4-thiazoline-2-thione by the preceding method gave XXI in 65% yield, b.p. 106° at 3 μ, n_D^{25} 1.6442, λ max 271 mμ (ε, 13,300).

Anal. Calcd. for $C_{12}H_{11}NOS_2$: C, 57.8; H, 4.4; N, 5.6; S, 25.7. Found: C, 57.6; H, 4.4; N, 5.5; S, 25.4.

4-*tert*-Butyl-2-(2-oxopropylthio)thiazole, XXII.

Alkylation of 4-*tert*-butyl-4-thiazoline-2-thione by the method described for XX gave XXII in 85% yield, b.p. 57° at 17 μ,

n_D^{25} 1.5417, λ max 275 mμ (ε, 6,900).

Anal. Calcd. for $C_{10}H_{15}NOS_2$: C, 52.4; H, 6.6; N, 6.1; S, 28.0. Found: C, 52.2; H, 6.4; N, 5.9; S, 28.2.

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