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Halogenoarylation of Allyl Isothiocyanate: Synthesis of 2,5-Disubstituted 2-Thiazolines

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ABSTRACT: *A new approach to the synthesis of 2-R-5-benzyl-2-thiazolines with the use of chloro- and bromoarylation products of allyl isothiocyanate with arenediazonium halides was elaborated. The isothiocyanates obtained were reacted with ammonia, aliphatic or aromatic amines, and sodium methoxide. The use of ammonia or weakly basic amines in this reaction allowed. Intermediate thioureas to be isolated. On the basis of ^1H NMR spectra, amino–imino tautomerism of the synthesized 2,5-disubstituted 2-thiazolines were analyzed. 2-Arylamino-5-benzyl-2-thiazolines exist mainly in the Z-configuration of the imino form.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 517–525, 1999

INTRODUCTION

There are different approaches to the synthesis of 2-thiazoline derivatives [2a,b]. One of the most convenient methods is the cyclization of compounds containing the $CH(X)CH_2NHC(S)$ fragment that occurs when these compounds are heated or subjected to base catalysis. Another well-known method involves the addition of an electrophilic reagent to the double bond of the allylic fragment of the thiourea or related compound. In such cases, cyclization takes place either immediately or an adduct is formed first and then can easily be transformed into the 2-thiazoline.

Previously, allyl isothiocyanate or its dibromo derivative [3] was used as a starting compound for the preparation of 2,5-disubstituted 2-thiazolines, but this method is rather limited [2].

We offer a new approach to the synthesis of such compounds by the use of chloro- or bromoarylation products of allyl isothiocyanate in reaction with arenediazonium halides. Taking into account that Ar and Hal add to the double bond as the result of catalytic dediazoniation of arenediazonium halides in the presence of unsaturated compounds [4], we used this approach with allyl isothiocyanate to obtain suitable reagents for the synthesis of 2-thiazolines.

RESULTS AND DISCUSSION

We have found that the reaction of arenediazonium chlorides with allyl isothiocyanate in the presence of copper(II) chloride leads to the products of Ar and Cl addition to the carbon-carbon double bond [5,6]. In addition to these chlorides, arenediazonium bromides ($CuBr_2$ as the catalyst) react in the same manner but give lower yields of the desired products.

The chloro- and bromoarylation reactions were conducted in water-acetone (1:1) medium at pH 1 using a slight (10–15%) diazonium salt surplus. It was found (see Table 1 and Ref. [5]) that arenediazonium halides contained in the aromatic ring atoms of halogen or a nitro group provide greater yields of adducts.

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Synthesis of Heterocycles on the Basis of Anionoarylation Products of Unsaturated Compounds, Communication 6. For Communication 5 see Ref. [1].
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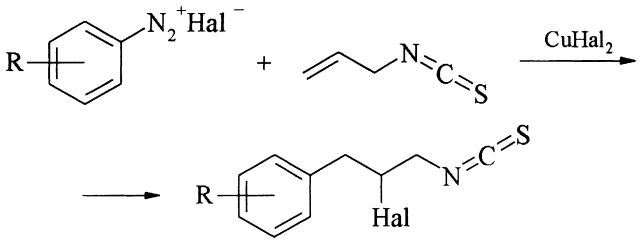


1a–g

a: R = 2-Cl, Hal = Cl; **b:** R = 2-Br, Hal = Cl;
c: R = 4-Br, Hal = Cl; **d:** R = 3-NO_2, Hal = Cl;
e: R = 4-NO_2, Hal = Cl; **f:** R = H, Hal = Br;
g: R = 2-Cl, Hal = Br

SCHEME 1

When equimolar quantities of ammonia, aromatic amines, or 4-aminoantipyrine were reacted with isothiocyanates **1,** monosubstituted and 1,3-disubstituted thioureas were formed (see Table 2).

Reactions with aromatic amines containing electron-withdrawing groups were affected under more severe conditions.

The 1,3-disubstituted thioureas obtained were easily cyclized in the presence of bases with formation of 2,5-disubstituted 2-thiazolines.

When using strongly basic aliphatic amines in the reaction with the isothiocyanates **1,** thioureas of the type **2** could not always be separated because they were partially cyclized during the reaction and separation of the formed mixtures was difficult. Probably this cyclization occurs faster than the addition of the amine to the C=N bond of the isothiocyanate. It is possible that the thiourea formed can also act as a catalyst for such a cyclization because the basicity of the nitrogen atom of C(S)NHMe, $C(S)NC_5H_{10}$ or $C(S)NC_4H_8O$ fragments is rather high.

Therefore, the optimal method of preparation of 2-thiazolines is heterocyclization of thioureas in situ. We used different bases (sodium ethoxide, potassium hydroxide, in ethanol and *N*-methylmorpholine) for such cyclizations. When strongly basic amines (methylamine, piperidine, or morpholine) were used as reagents it was necessary that they were present in surplus for the cyclization to take place (see Table 3).

The action of sodium methoxide on the previously described [5] 1-isothiocyanato-2-chloro-3-(4-tolyl)propane led to the formation of the 2-thiazoline with a methoxy group in position 2 of the thiazoline ring. In this case, the reaction occurred as an intramolecular nucleophilic substitution of the chlorine atom.

It is probable that the formation of such intermediates also occurs in the reaction with amines.

Compounds **1** reacted with allylamine to form thioureas that also turned into derivatives of 2-thiazoline during bromination in situ.

The IR spectra of compounds **1** showed wide bands of absorption between 2010 and 2240 cm^{-1} (valence oscillations of the N=C=S group).

For the derivatives of 2-aminothiazoline, amino-imino tautomerism is characteristic. The information about the shape of such compounds available in the literature is rather contradictory [7–12]. It is stated in the majority of the studies [8–10] that the amino-form is characteristic of 2-alkyl-substituted thiazolines and 2-aryl-substituted-imino forms, but in Ref. [9], strong arguments were presented confirming that in solution, 2-methylamino-5-methylthiazoline exists mainly in the imino-form. In order to study the possible thiazolidin-thiazoline tautomerism, we analyzed the ^{1}H NMR spectra of the **3a–v** compounds.

Of the synthesized thiazolines, only compounds **3p–u** had the amino form. It is known [8,13] that the double bond in the thiazoline ring (amino structure) deshields the protons of the methylene group 4-CH_2 to $\delta \sim 0.3$–0.6 ppm, and consequently the $\delta_{4\text{-}CH_2}$ value may be used for the determination of the structures of the tautomers. As seen in the data presented in Table 5 (compounds **3p–v**) and in the literature [8], the nature of the substituent near the exocyclic nitrogen atom has an insignificant influence on the chemical shift of the 4-CH_2 protons. The $\delta_{4\text{-}CH_2}$ values are very similar for compounds **3a–o** (where tautomerism is possible) and for thiazolines **3p–v,** so it is possible to assume that the compounds **3a–o** in solution (DMSO) are preliminary in the amino form. However, the peculiarities of the ^{1}H NMR spectra of the 2-arylamino-derivatives **3f–o** attracted our attention. The signals of the *para* protons of the aryl fragment are at the highest field. This supports the existence of the imino-form of compounds **3f–o** and the *Z*-configuration of the arylimino fragment [11,14,15] because in the *E*-configuration of this fragment and for the group NHAr, signals of the *ortho* protons should be displayed to high field.

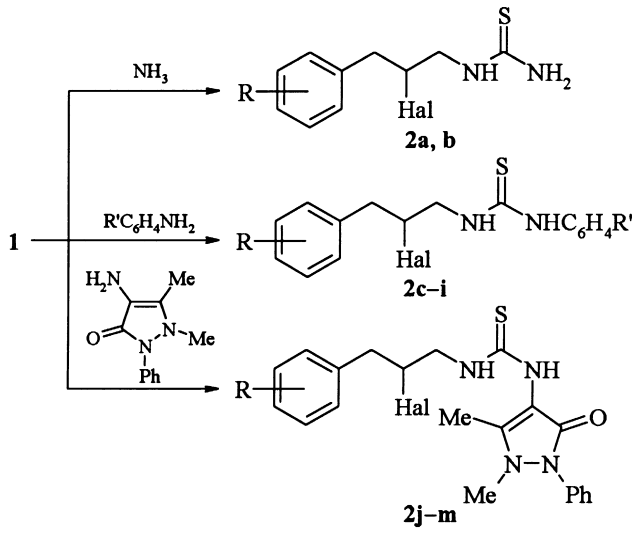
Chemical shifts of the *ortho*-protons of the ArN= fragment are in the range of 7.3–7.7 ppm, which also corresponds to the *Z*-isomer [14,15]. It is worth noting that the signals of these protons, as well as the signals of the methylene group protons in position 4, are revealed as noncharacteristic broad signals (see Table 5). This may support the fact that there is an equilibrium between amino- and imino-forms in solution (the latter prevailing) caused by fast prototropic migrations [12]. In this case, the observed signals of the *ortho* protons and the 4-CH_2

TABLE 1 Yields, Constants, and Analytical Data of the 1-Isothiocyanato-2-halo-3-arylpropanes **1a–g**

Compound	Reaction Temperature (°C)	*Yield* (%)	*B.P.* (°C/mm)	d_4^{20}	n_D^{20}	Formula	*Found %* (*Calcd %*) Hal	S
1a	10–15	47	138/1	1.2979	1.6026	$C_{10}H_9Cl_2NS$	28.5 (28.8)	13.3 (13.0)
1b	15–18	38	154/1	1.4793	1.6142	$C_{10}H_9BrClNS$	40.0 (39.7)	10.8 (11.0)
1c	0–5	40	157–58/1	1.4933	1.6226	$C_{10}H_9BrClNS$	39.6 (39.7)	11.3 (11.0)
1d	−5–+5	39	oil			$C_{10}H_9ClN_2O_2S$	14.0 (13.8)	12.7 (12.5)
1e	−5–+5	52	oil			$C_{10}H_9ClN_2O_2S$	13.7 (13.8)	12.3 (12.5)
1f	0–5	18	117–118/0.5	1.4045	1.6156	$C_{10}H_{10}BrNS$	31.3 (31.2)	12.7 (12.5)
1g	15–20	18	151–53/2	1.4873	1.6181	$C_{10}H_9BrClNS$	39.4 (39.7)	11.3 (11.0)

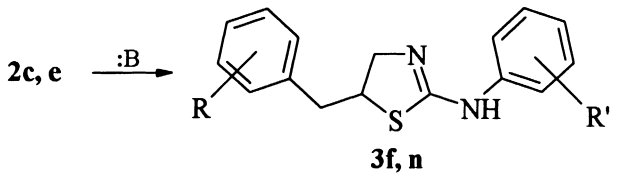
TABLE 2 Yields, Constants, and Analytical Data of the Monosubstituted and 1,3-Disubstituted Thioureas **2a–m**

Compound	*Yield* (%)	*M.P.* (°C) (*Solvent for Crystallization*)	*Formula*	*Found %* (*Calcd %*) *Hal*	*S*
2a	75	173 ($CHCl_3$)	$C_{11}H_{15}ClN_2S$	14.3 (14.6)	13.0 (13.2)
2b	70	189–190 (EtOH)	$C_{10}H_{12}BrClN_2S$	37.3 (37.5)	10.6 (10.4)
2c	66	93–94 (C_6H_6)	$C_{16}H_{16}Cl_2N_2S$	21.1 (20.9)	9.2 (9.5)
2d	91	198–199 (EtOH–C_6H_6)	$C_{16}H_{16}BrClN_2S$	30.3 (30.1)	8.1 (8.4)
2e	95	225 (EtOH)	$C_{16}H_{15}Br_2ClN_2S$	42.6 (42.2)	7.1 (6.9)
2f	78	228–229 (*n*-BuOH)	$C_{17}H_{16}BrClN_2O_2S$	26.7 (27.0)	7.4 (7.5)
2g	88	210–211 (EtOH)	$C_{16}H_{15}BrClN_3O_2S$	26.8 (26.9)	7.2 (7.5)
2h	81	187–188 (EtOH)	$C_{16}H_{17}BrClN_3O_2S_2$	25.2 (24.9)	13.6 (13.9)
2i	85	188–189 (EtOH–C_6H_6)	$C_{16}H_{16}BrN_3O_2S$	20.5 (20.3)	7.9 (8.1)
2j	66	219–220 (MeOH–C_6H_6)	$C_{22}H_{25}ClN_4OS$	8.4 (8.3)	7.6 (7.5)
2k	78	197–198 (MeOH–C_6H_6)	$C_{21}H_{22}Cl_2N_4OS$	16.0 (15.8)	7.3 (7.1)
21	90	241–242 (MeOH)	$C_{21}H_{22}BrClN_4OS$	23.5 (23.4)	6.2 (6.5)
2m	88	210–211 (MeOH–C_6H_6)	$C_{21}H_{23}BrN_4OS$	17.6 (17.4)	7.3 (7.0)



a: R = 4-Me, Hal = Cl; **b**: R = 4-Br, Hal = Cl;
c: R = 2-Cl, Hal = Cl, R′ = H; **d**: R = H, Hal = Cl, R′ = 4-Br;
e: R = R′ = 4-Br, Hal = Cl; **f**: R = 4-Br, Hal = Cl, R′ = 3-CO_2H;
g: R = 4-Br, Hal = Cl, R′ = 3-NO_2;
h: R = 4-Br, Hal = Cl, R′ = 4-SO_2NH_2;
i: R = H, Hal = Br, R′ = 4-NO_2; **j**: R = 4-Me, Hal = Cl;
k: R = 2-Cl, Hal = Cl; **l**: R = 4-Br, Hal = Cl;
m: R = H, Hal = Br

SCHEME 2



f: R = 2-Cl, R′ = H; **n**: R = R′ = 4-Br

SCHEME 3

group are averaged, leading to the loss of multiplicity of the signals and to their broadening.

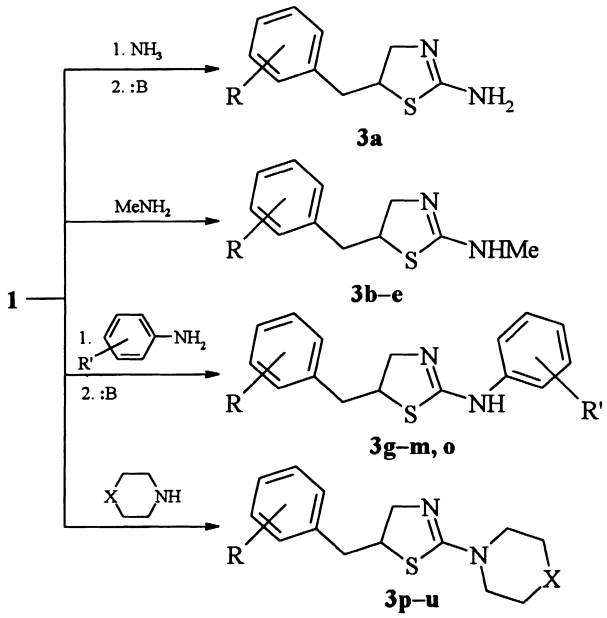
EXPERIMENTAL

The ^{1}H NMR spectra were obtained with a Bruker WP-300 spectrometer, with tetramethylsilane as the internal standard. The IR spectra of compounds **1** were recorded with a Specord 75 IR spectrometer in the form of a thin layer.

General Procedure for Obtaining 1-Isothiocyanato-2-halo-3-arylpropanes (**1a–g**)

The solution of arenediazonium chloride or bromide was added dropwise with stirring at −5°C to a mixture of acetone (75 mL), allyl isothiocyanate (9.7 mL, 0.1 mol), and copper(II) chloride or bromide (0.01 mol). The diazonium salt was prepared in the usual manner from 0.11 mol of the appropriate aromatic amine. The optimal reaction temperature was determined experimentally (see Table 1). When the nitrogen evolution ceased, the reaction mixture was diluted with 200 mL of water, extracted with three 50 mL portions of ether, and the combined extracts were dried ($MgSO_4$). The solvent was evaporated, and the residue was vacuum-distilled.

For isolation of the isothiocyanates **1d,e**, the formed chloroarene and the unreacted allyl isothiocyanate were separated by vacuum distillation after evaporation of the solvent. The residue was then dissolved in benzene and reprecipitated three times by addition of hexane.



a: R = 2-Cl; **b**: R = 2-Cl; **c**: R = 4-Me; **d**: R = 3-NO_2;
e: R = 4-NO_2; **g**: R = 4-Br, R′ = H; **h**: R = 3-NO_2, R′ = H;
i: R = 4-Br, R′ = 3-Me; **j**: R = 4-Br, R′ = 4-Me;
k: R = 3-NO_2, R′ = 4-Me; **l**: R = 4-Br, R′ = 4-OMe;
m: R = 4-Br, R′ = 4-Cl; **o**: R = H, R′ = 4-SO_2NH_2;
p: R = 2-Cl, X = CH_2; **q**: R = 4-Me, X = CH_2;
r: R = 4-Me, X = O; **s**: R = 2-Cl, X = O;
t: R = 3-NO_2, X = O; **u**: R = 4-NO_2, X = O

SCHEME 4

1-(2-Chloro-3-aryl)propylthioureas (**2a,b**)

A 25% water solution of ammonia (10 mmol) was added with stirring to a solution of the corresponding 1-isothiocyanato-2-chloro-3-arylpropane **1** (10 mmol) in acetone (5 mL). The mixture was main-

TABLE 3 Yields, Constants, and Analytical Data of the 2,5-Disubstituted 2-Thiazolines **3a–v**

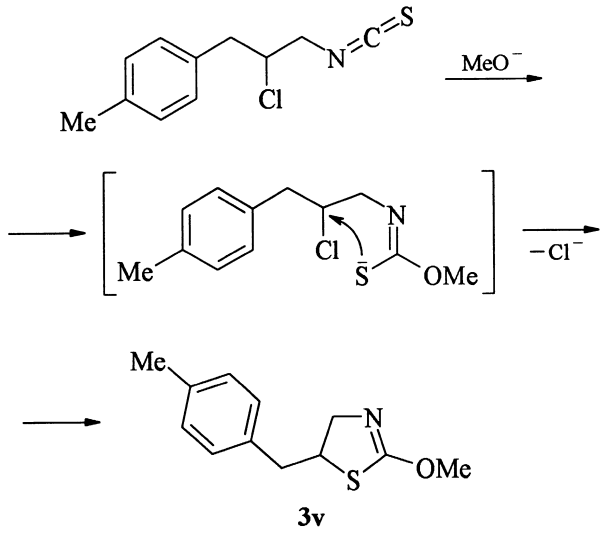
Compound	*Yield (%)*	*M.P. (°C) (Solvent for Crstallisation)*	*Formula*	*Found % (Calcd %)*	
				N	*S*
3a	65	92–93 (C_6H_6–cyclohexane)	$C_{10}H_{11}ClN_2S$	12.3 (12.4)	13.9 (14.1)
3b	89	77–78 (C_6H_{14})	$C_{11}H_{13}ClN_2S$	11.7 (11.6)	13.5 (13.3)
3c	85	116–117 (C_6H_6–C_6H_{14})	$C_{12}H_{16}N_2S$	12.9 (12.7)	14.7 (14.6)
3d	80	129–130 (C_6H_6–cyclohexane)	$C_{11}H_{13}N_3O_2S$	16.4 (16.7)	12.4 (12.8)
3e	74	146–147	$(C_6H_6)C_{11}H_{13}N_3O_2S$	16.6 (16.7)	12.9 (12.8)
3f	78	102–103 (cyclohexane)	$C_{16}H_{15}ClN_2S$	9.4 (9.2)	10.8 (10.6)
3g	81	167–168 (Me_2CO)	$C_{16}H_{15}BrN_2S$	8.2 (8.1)	9.0 (9.2)
3h	75	126–127 (C_6H_6–cyclohexane)	$C_{16}H_{15}N_3O_2S$	13.2 (13.4)	10.5 (10.2)
3i	79	125–126 (cyclohexane)	$C_{17}H_{17}BrN_2S$	7.9 (7.8)	8.7 (8.9)
3j	82	150 (cyclohexane–EtOH)	$C_{17}H_{17}BrN_2S$	7.8 (7.8)	9.0 (8.9)
3k	78	166–167 (C_6H_6–cyclohexane)	$C_{17}H_{17}N_3O_2S$	12.6 (12.8)	9.9 (9.8)
3l	72	143–144 (cyclohexane–EtOH)	$C_{17}H_{17}BrN_2OS$	7.5 (7.4)	8.7 (8.5)
3m	88	149–150 (C_6H_6–Me_2CO)	$C_{16}H_{14}BrClN_2S$	7.2 (7.3)	8.5 (8.4)
3n	79	157–158 (C_6H_6)	$C_{16}H_{14}Br_2N_2S$	6.7 (6.6)	7.3 (7.5)
3o	64	184–185 (C_6H_6–MeOH)	$C_{16}H_{17}N_3O_2S$	13.1 (13.3)	18.3 (18.5)
3p	77	b.p. 176–178°C/ 1 mm, n_D^{20} 1.5974	$C_{15}H_{19}ClN_2S$	9.3 (9.5)	10.6 (10.9)
3q	71	b.p. 200–202°C/1.5 mm, n_D^{20} 1.5867	$C_{16}H_{22}N_2S$	10.4 (10.2)	11.8(11.7)
3r	86	111–112 (C_6H_6–C_6H_{14})	$C_{15}H_{20}N_2OS$	10.3 (10.1)	11.5 (11.6)
3s	80	66–67 (petroleum ether)	$C_{14}H_{17}ClN_2OS$	9.2 (9.4)	10.7 (10.8)
3t	82	120–121 (C_6H_6–cyclohexane)	$C_{14}H_{17}N_3O_3S$	13.5 (13.7)	10.2 (10.4)
3u	73	103–104 (cyclohexane)	$C_{14}H_{17}N_3O_3S$	13.6 (13.7)	10.6 (10.4)
3v	93	b.p. 146–148°C/1.5 mm, n_D^{20} 1.5700	$C_{12}H_{15}NOS$	6.5 (6.3)	14.3 (14.5)

TABLE 4 ^{1}H NMR Data of the Thioureas **2**, δ (Multiplicity), J (Hz) (DMSO-d_6)

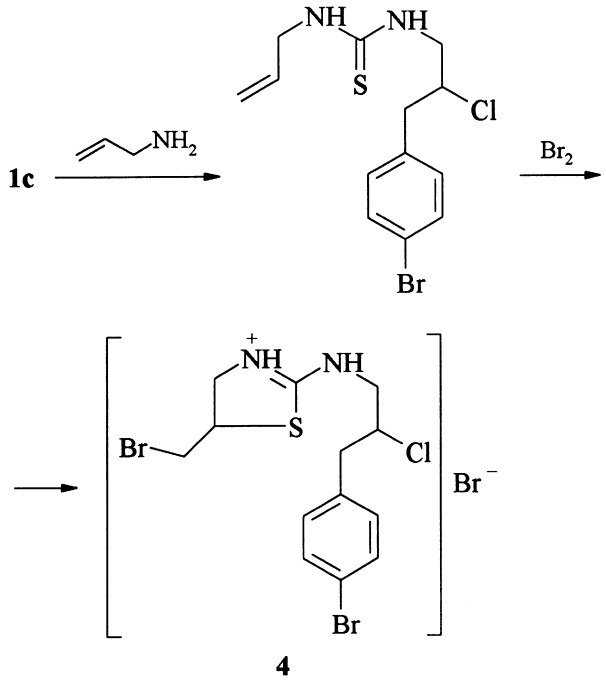
$RC_6H_4CH^AH^BCH^XCICH^CH^DNHC(S)NHR'$

Compound	*CH^AH^B*	*CH^{Xa}*	*CH^CH^D*	*RC_6H_4*	*R'*	*NHC(S)NH*
2a	2.93 (dd), 9, 3.06 (dd), 7, 14[b]	4.38	3.67 (dd), 5, 3.90 (dd), 7.5, 11.5[c]	2.28 (s) Me 7.15 (s) C_6H_4	9.59 (s)	
2c	3.20 (dd), 8.5, 3.30 (dd), 7, 14[b]	4.50	3.83 (dd), 5, 4.05 (dd), 7, 12[c]		7.30–7.50 (m)	11.45 (s)
2e	3.03 (dd), 9, 3.13 (dd), 7, 13[b]	4.45	3.78 (dd), 4, 4.00 (dd), 7, 12.5[c]	7.31 (d), 7.54 (d)	7.29 (d), 7.66 (d)	11.02 (s)[d]
2f	2.83 (dd), 9, 3.00 (dd), 6, 14[b]	4.13	3.76 (dd), 4, 3.92 (dd), 7, 12.5[c]	7.23 (d), 7.48 (d)	7.34 (t), 7.50 (d), 7.60 (d), 8.05 (s) C_6H_4 11.00 (s)[d], CO_2H	10.90 (s)
2g	3.06 (dd), 8, 3.16 (dd), 7, 13[b]	4.47	3.82 (dd), 4, 4.04 (dd), 7, 11.5[c]	7.31 (d), 7.53 (d)	7.76 (m), 8.15 (d), 8.27 (s)	11.15 (s)[d]
2h	3.01 (dd), 9, 3.11 (dd), 6, 14[b]	4.43	3.80 (dd), 4, 4.02 (dd), 9, 12.5[c]	7.28 (d), 7.54 (d)	7.50 (d), 7.86 (d) C_6H_4 7.44 (s)[d] NH_2	9.93 (s)[d]
2i	3.04 (dd), 8, 3.15 (dd), 7, 13.5[b]	4.47	3.86 (dd), 4.5, 4.07 (dd), 7.5, 12[c]	7.32 (m)	7.61 (d), 8.28 (d)	10.90 (s)[d]
2k	3.10–3.45 (m)[e]	4.54	3.82 (dd), 4, 4.06 (dd), 9, 12[c]	2.26 (s) 3.19 (s) 7.32–7.55 (m)	MeC=C MeN C_6H_4, Ph	11.10 (s)

[a]Quintet.
[b]J_{AB}.
[c]J_{CD}.
[d]Broad signals.
[e]Superposition of two dd of CH^AH^B and s of MeN in R′.



SCHEME 5



SCHEME 6

tained for 5 hours at room temperature, and water (50 mL) was added. Trituration of the oil gave a solid product that was washed with diethyl ether and crystallized from the appropriate solvent (see Table 2).

1-Phenyl-3-[2-chloro-3-(2-chlorophenyl)propyl]thiourea (**2c**)

Aniline (10 mmol) was added with stirring to a solution of 1-isothiocyanato-2-chloro-3-(2-chlorophenyl)propane (**1a**) (10 mmol) in acetone (5 mL). The reaction mixture was maintained for 12 hours at room temperature, water (20 mL) was added, and the mixture was acidified with HCl (5% solution) until a pH of 3 was obtained. The product was filtered off and crystallized from benzene. Thioureas **2d,e** were obtained similarly.

1-(3-Carboxyphenyl)-3-[2-chloro-3-(4-bromophenyl)propyl]thiourea (**2f**)

meta-Aminobenzoic acid (5 mmol) was added to a solution of compound **1c** in ethanol (5 mL). The mixture was refluxed for 5 hours and cooled, the solvent was evaporated, and the residue was crystallized from *n*-butanol. Thioureas *2g–i* were obtained similarly.

1-(1-Phenyl-2,3-dimethylpyrazol-5-on-4-yl)-3-(3-aryl-2-halopropyl)thio-ureas (**2j–m**)

The corresponding isothiocyanate **1** (10 mmol) was added to a solution of 4-aminoantipyrine (10 mmol) in benzene (10 mL). The mixture was refluxed for 30 minutes and cooled, the upper layer was separated off, the residue was triturated, and the solid product that was obtained was crystallized from the appropriate solvent (see Table 2).

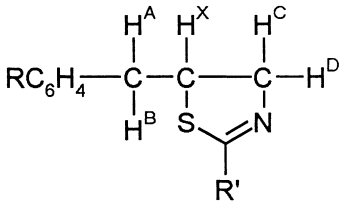
2-Amino-5-(2-chlorobenzyl)-2-thiazoline (**3a**)

Isothiocyanate **1a** (5 mmol) was dissolved in diethyl ether (5 mL), and this solution was saturated with gaseous ammonia for 5 minutes. The reaction mixture was maintained for 12 hours at room temperature, and a precipitate was filtered off and dissolved in anhydrous ethyl alcohol (5 mL). Sodium ethoxide (5 mmol) in ethanol (5 mL) was added with stirring to this mixture. Then, over a period of 10 minutes water (20 mL) was added, and the mixture was acidified with HCl (5% solution) to a pH of 2. The organic phase was extracted with benzene. NaOH (5% solution) was added to the aqueous phase to a pH of 10, and the product was extracted with benzene (15 mL). The extract was dried ($MgSO_4$), the solvent was evaporated, and the residue was crystallized from benzene–cyclohexane.

2-Methylamino-5-benzyl-2-thiazolines (**3b–e**)

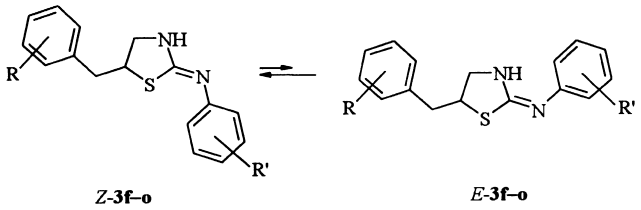
Methylamine (25 mmol) (the 25% aqueous solution) was added with stirring to a solution of the corresponding isothiocyanate **1** (10 mmol) in acetone or acetonitrile (15 mL). The reaction mixture was maintained for 1 hour at room temperature, diluted

TABLE 5 ^{1}H NMR Data of the 2-Thiazolines **3**, δ (Multiplicity), J (Hz) (DMSO-d_6)



Compound	CH^AH^B	CH^X	CH^CH^D	RC_6H_4		*R′*
3a	2.92 (dd), 8.5, 3.06 (dd), 7, 13[a]	4.14 (m)	3.65 (dd), 3.5, 3.79 (dd), 7, 14[b]	7.24–7.44 (m)	6.29 (s)[c]	NH_2
3b	2.90 (dd), 9, 3.05 (dd), 6.5, 13[a]	4.13 (m)	3.69 (dd), 5, 3.81 (dd), 6, 12[b]	7.23–7.45 (m)	2.71 (s) 6.64 (s)[c]	NMe NH
3c[d]	2.88 (dd), 8, 2.95 (dd), 6.5, 14[a]	4.07 (m)[e]	3.86 (dd), 4.5, 3.96 (dd), 5.5, 13[b]	2.33 (s) Me 7.08 (d), 7.12 (d) C_6H_4	2.93 (s)	NMe
3d	2.92 (dd), 9.5, 3.10 (dd), 5, 14[a]	4.17 (m)	3.69 (dd), 6, 3.83 (dd), 8, 12.5[b]	7.60 (t), 7.72 (d), 8.09 (d), 8.12 (s)	2.69 (s) 6.61 (s)[c]	NMe NH
3e	2.91 (dd), 9, 3.10 (dd), 6.5, 14[a]	4.16 (m)	3.67 (dd), 3, 3.83 (dd), 7, 12[b]	7.53 (d), 8.15 (d)	2.69 (s) 6.61 (s)[c]	NMe NH
3f	2.99 (dd), 8.7, 3.14 (dd), 6.5, 14.1[a]	4.17 (m)	3.79 (dd), 3, 3.92 (dd), 6.5, 12.5[b]	7.20–7.46 (m) 6.92 (t) 8.91 (s)		$2C_6H_4$ 4-H in R′ NH
3g	2.80 (dd), 9, 2.98 (dd), 7, 13.5[a]	4.09 (m)	3.88 (s)[c]	7.22 (d), 7.48 (d)	6.90 (t) 7.21 (m), 7.60 (s)[c] 9.28 (s)[c]	4-H in R′ Ph NH
3i	2.80 (dd), 9.5, 2.98 (dd), 7, 13.5[a]	4.09 (m)	3.79 (dd), 4, 3.86 (dd), 6, 12[b]	7.23 (d), 7.49 (d)	2.24 (s) 6.73 (d) 7.10 (t) 7.30 (s)[c] 9.09 (s)[c]	Me 4-H in R′ 3-H in R′ 2-H in R′ NH
3j	2.78 (dd), 6.5, 2.98 (dd), 4, 13.5[a]	4.09 (m)	3.76 (s)[c] 3.86 (s)[c]	7.22 (d), 7.49 (d)	2.21 (s) 7.03 (d), 7.30 (s)[c] 9.09 (s)[c]	C_6H_4 NH
3k	2.99 (dd), 9.5, 3.15 (dd), 6, 14[a]	4.18 (m)	3.82 (s)[c] 3.91 (s)[c]	7.61 (t), 7.74 (d), 8.10 (d), 8.16 (s)	2.22 (s) 7.03 (d), 7.32 (s)[s] 8.94 (s)[c]	Me C_6H_4 NH
3l	2.80 (dd), 9, 2.99 (dd), 7, 13[a]	4.08 (m)	3.84 (s)[c]	7.22 (d), 7.49 (d)	3.68 (s) 6.80 (d), 7.30 (s)[c] 8.85 (s)[c]	OMe C_6H_4 NH
3m	2.81 (dd), 9.5, 2.99 (dd), 8.5, 13.2[a]	4.12 (m)	3.90 (s)[c]	7.23 (d), 7.48 (d)	7.26 (d), 7.63 (s)[c] 9.45 (s)[c]	C_6H_4 NH
3n	2.81 (dd), 9.5, 2.99 (dd), 7.5, 13[a]	4.13 (m)	3.91 (s)[c]	7.23 (d), 7.49 (d)	7.39 (d), 7.56 (s)[c] 9.44 (s)[c]	C_6H_4 NH
3o	2.68 (dd), 9.5, 3.03 (dd), 6, 13[a]	4.17 (m)	3.96 (s)[c]	7.27 (m)	7.68 (d), 7.70 (s)[c] 7.16 (s) 9.71 (a)[c]	C_6H_4 SO_2NH_2 NH
3p	2.92 (dd), 8, 3.13 (dd), 6, 14[a]	4.11 (m)	3.79 (dd), 4, 3.82 (dd), 6, 11[b]	7.14–7.47 (m)	1.48 (s)[c] 3.28 (t)	$(CH_2)_3$ $N(CH_2)_2$
3r	2.76 (dd), 7.8, 2.89 (dd), 6.9, 14[a]	4.14 (m)	3.70 (dd), 5.1, 3.87 (dd), 7.5, 13.5[b]	2.26 (s) Me 7.10 (s) C_6H_4	3.26 (t) 3.57 (t)	$N(CH_2)_2$ $O(CH_2)_2$
3s	2.95 (dd), 8.4, 3.06 (dd), 6.5, 14.1[a]	4.22 (m)	3.78 (dd), 4.7, 3.88 (dd), 7.2, 13.7[b]	7.24–7.46 (m)	3.28 (t) 3.58 (t)	$N(CH_2)_2$ $O(CH_2)_2$
3t	2.97 (dd), 8.1, 3.10 (dd), 6.3, 13.8[a]	4.25 (m)	3.77 (dd), 4.2, 3.90 (dd), 7.2, 13.8[b]	7.60 (t), 7.73 (d), 8.09 (d), 8.14 (s)	3.26 (t) 3.55 (t)	$N(CH_2)_2$ $O(CH_2)_2$
3u	2.96 (dd), 8.7, 3.11 (dd), 6.2, 13.7[a]	4.26 (m)	3.76 (dd), 4.5, 3.91 (dd), 7, 13.5[b]	7.54 (d), 8.15 (d)	3.25 (t) 3.56 (t)	$N(CH_2)_2$ $O(CH_2)_2$
3v[f]	2.87 (dd), 8.5, 2.98 (dd), 6, 14[a]	4.28 (m)	3.75 (dd), 5.5, 3.93 (dd), 7.5, 13.8[b]	2.28 (s) Me 7.12 (s) C_6H_4	3.83 (s)	OMe

[a] J_{AB}
[b] J_{CD}.
[c] Broad signals.
[d] $CDCl_3$.
[e] Superposition of the signals of H^x and NH in R′
[f] $(CD_3)_2CO$.



Z-**3f–o** *E*-**3f–o**

SCHEME 7

with water (30 mL), and acidified with HCl (5% solution) to a pH of 2. The organic phase was extracted with benzene, NaOH (5% solution) was added to the aqueous phase to a pH of 10, and the precipitate was filtered off and crystallized from the appropriate solvent (see Table 3).

2-Phenylamino-5-(2-chlorobenzyl)-2-thiazoline (**3f**)

Potassium hydroxide (5 mmol) in ethyl alcohol (5 mL) was added with stirring to the solution of thiourea **2c** (5 mmol) in ethyl alcohol (8 mL). After 10 minutes water (30 mL) was added to the reaction mixture, and the precipitate was filtered off and crystallized from cyclohexane. 2-(4-Bromophenyl) amino-5-(4-bromobenzyl)-2-thiazoline (**3n**) was obtained similarly.

2-Arylamino-5-benzyl-2-thiazolines (**3g–m**)

The aromatic amine (5 mmol) was added with stirring to a solution of the corresponding isothiocyanate **1** (5 mmol) in acetone (8 mL). The reaction mixture was maintained at room temperature for 12 hours, and a solution of *N*-methylmorpholine (5 mmol) in acetone (3 mL) was then added with stirring. The precipitate of the *N*-methylmorpholine hydrochloride was formed immediately. After 10 minutes, water (40 mL) was added to this mixture, and the precipitate was filtered off and crystallized from the appropriate solvent (see Table 3).

2-(4-Sulfamidophenylamino)-5-benzyl-2-thiazoline (**3o**)

1-Isothiocyanato-2-chloro-3-phenylpropane [5] (5 mmol) was added to a solution of 4-aminophenylsulfamide (5 mmol) in ethyl alcohol (10 mL), and the reaction mixture was refluxed for 5 hours. After the mixture was cooled, a solution of potassium hydroxide (5 mmol) in ethyl alcohol (5 mL) was added with stirring. After 10 minutes the reaction mixture was diluted with water (30 mL), and the precipitate was filtered off and crystallized from benzene–methanol.

2-Piperidino-5-benzyl-2-thiazolines (**3p,q**)

A mixture of piperidine (8 mL), the corresponding isothiocyanate **1** (10 mmol), and water (8 mL) was refluxed for 1 hour. The reaction mixture was cooled to 20°C, and water (50 mL) was added. The organic layer was extracted with diethyl ether (50 mL), the extract was dried ($MgSO_4$), and the solvent was evaporated. The residue was vacuum-distilled.

2-Morpholino-5-benzyl-2-thiazolines (**3r–u**)

Morpholine (22 mmol) was added with stirring to a solution of the corresponding isothiocyanate **1** (10 mmol) in acetone (8 mL). After 10 minutes, water (40 mL) was added to this reaction mixture, and the precipitate of the thiazoline was filtered off, air dried, and crystallized from the appropriate solvent (see Table 3).

2-Methoxy-5-(4-methylbenzyl)-2-thiazoline (**3v**)

A mixture of sodium methoxide (10 mmol), 1-isothiocyanato-2-chloro-3-(4-tolyl)propane [5] (10 mmol), and anhydrous methanol (30 mL) was refluxed for 1 hour. After the mixture was cooled to room temperature, water (50 mL) was added to the reaction mixture, and the organic layer was extracted with diethyl ether (50 mL). The extract was dried over $MgSO_4$, the solvent evaporated, and the oily residue was vacuum-distilled.

2-[2-Chloro-3-(4-bromophenyl)propylamino]-5-bromomethyl-2-thiazoline hydrobromide (**4**)

Allylamine (10 mmol) was added with stirring at 10°C to a solution of the isothiocyanate **1c** (10 mmol) in chloroform (10 mL). The reaction mixture was stirred for an additional 10 minutes cooled to 0°C, and at this temperature, a solution of bromine (10 mmol) in chloroform (10 mL) was added with stirring. Filtration of the mixture and washing of the precipitate with chloroform gave 3.9 g (77%) of product **4**; m.p. 151–152°C. Found, 30.5% C, 3.3% H, 5.3% N, and 6.5% S. $C_{13}H_{16}Br_3ClN_2S$. Calcd, 30.8% C, 3.2% H, 5.5% N and 6.3% S.

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