Formylation Products of Thioamides; Part 16:[1] Synthesis of 2-(2-Amino-1-phenylethenyl)thiazoles by Amine-Exchange Reactions or by New Ring Transformations of Pyrimidin-4(1*H*)-thiones

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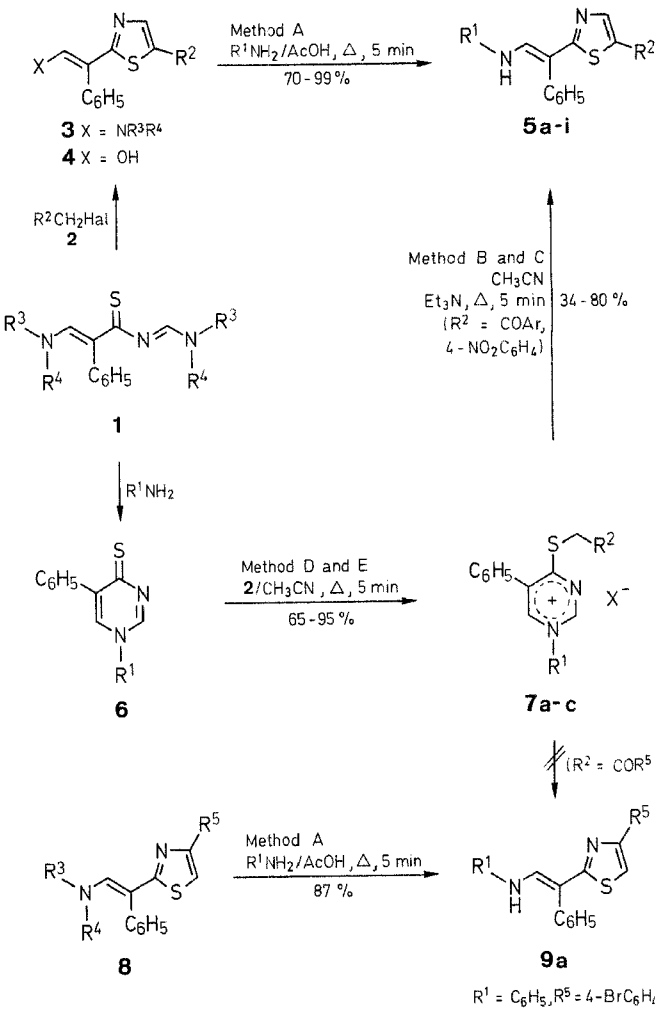
Substituted 2-(2-amino-1-phenylethenyl)- and 2-(2-hydroxy-1-phenylethenyl)thiazoles react with primary amines by amine-exchange and condensation, respectively, to give 2-(2-amino-1-phenylethenyl)thiazoles **5**, bearing monosubstituted amino groups. The same compounds can be synthesized by a new ring transformation of pyrimidin-4(1*H*)-thiones, achieved by their reaction with methyl halides substituted with electron withdrawing groups in the presence of a base.

Recently, we reported[2] the synthesis of 5-substituted 2-(2-amino-1-phenylethenyl)thiazoles **3** based on the reaction of *N*-(3-aminothioacryloyl)formamidines **1**[3] with methyl halides **2** possessing electron withdrawing substituents R^2 such as ArCO or 4-$NO_2C_6H_4$. This method produces only *N,N*-disubstituted compounds **3** (R^3, $R^4 \neq H$). *N*-Unsubstituted 2-(*β*-aminovinyl)thiazoles **12** (Scheme **B**) were synthesized by Singh et al.[4,5] by treating *S*-phenacylated pyrimidinthiones **10** with acids (nucleophilic attack of N-3 at C=O). The thiazolopyrimidinium salts **11** primarily formed suffer a subsequent hydrolytic ring cleavage and removal of the C-atom at position 2 of the pyrimidine nucleus. In this ring transformation of **10**, the pyrimidine unit acts as a S–C–N-synthon for the thiazole skeleton formed as the result of the reaction. The aminovinylthiazoles **12**, however, were not isolated but underwent further hydrolytic substitution of the amino group.

We have now tried to prepare *N*-monosubstituted 2-(2-amino-1-phenylethenyl)thiazoles **5** and **9** (Scheme **A**). The synthesis of the compounds **5** could easily be achieved by treating the 5-substituted thiazoles **3** or **4**,[2] possessing enamine (**3**) or enol (**4**) moities in the 2-position with the appropriate primary amine or its salt (Method A).[6] The substitution products **5** (Table) are formed in high yields independently of whether **3** (R^3R^4N = morpholino or pyrrolidino) or **4** is employed.

Furthermore we could demonstrate by the example **9a**, that 4-substituted 2-(2-amino-1-phenylethenyl)thiazoles **8**, like the 5-substituted compounds **3**, can undergo an amine exchange (Method A) to produce the 4-aryl-*N*-monosubstituted product **9a**.

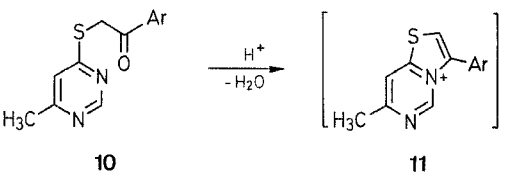
Adapting the idea of Singh et al.,[4,5] we have also tried to synthesize these 4-substituted 2-(2-amino-1-phenylethenyl) thiazoles **9** by the reaction of phenacyl halides (**2**; R^2 = ArCO) with pyrimidinthiones **6**, which can be produced from *N*-(3-aminothioacryloyl)-formamidines **1** and amines.[7] The *S*-alkylation of **6** takes place with ease. But the treatment of the resulting 4-phenacylthiopyrimidinium salts **7** (R^2 = ArCO) (Table) with acids leaves the compounds unchanged. In basic medium, however, aminovinylthiazoles could be obtained (Method B). To our surprise no 4-substituted compounds **9** (R^5 = Ar), but again their 5-aroyl substituted isomers **5** (R^2 = ArCO) are formed. The transformation of the pyrimidinthiones **6** to corresponding 5-substituted 2-(2-amino-1-phenylethenyl)thiazoles **5** is also possible with 4-nitrobenzyl bromide (**2**; R^2 = 4-$NO_2C_6H_4$) and is advantageously implemented without the isolation of the sometimes slowly crystallizing methylthiopyrimidinium salts **7** (Method C).[6] In general the yields

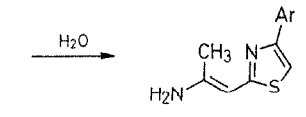


5	R^1	R^2
a	CH_3	4-BrC_6H_4CO
b	C_6H_5	4-BrC_6H_4CO
c	C_6H_5	4-$NO_2C_6H_4CO$
d	C_6H_5	CH_3CO
e	C_6H_5	4-$NO_2C_6H_4$
f	4-ClC_6H_4	4-ClC_6H_4CO
g	4-$CH_3C_6H_4$	4-ClC_6H_4CO
h	4-HOC_6H_4	4-ClC_6H_4CO
i	4-$HO_2CC_6H_4$	4-ClC_6H_4CO

7	R^1	R^2	X
a	$C_6H_5CH_2$	4-BrC_6H_4CO	Br
b	C_6H_5	4-BrC_6H_4CO	ClO_4
c	C_6H_5	4-$NO_2C_6H_4$	ClO_4

Scheme **A**





Scheme **B**

Table. 2-(2-Amino-1-phenylethenyl)thiazoles **5** and **9a** and Acceptor-Substituted Methylthiopyrimidinium Salts **7**

Product	Method	Yield (%)	m.p. (°C)[a] (Solvent)	Molecular Formula[b]	IR (Solvent)[c] ν(cm^{-1})	^{1}H-NMR (Solvent/TMS)[d] δ, J(Hz)
5a	A[e]	70	163–165 (MeCN)	$C_{19}H_{15}BrN_2OS$ (399.3)	1625, 1595, 1288[f]	3.00 (d, 3H); 6.59 (d, 1H, J = 12); 7.30 (m, 9H); 7.94 (s, 1H); 9.18 (m, 1H)[g]
5b	A[h]	99	137–139[k]	$C_{24}H_{17}BrN_2OS$	1630, 1609,	7.26 (m, 14H); 7.24 (d, 1H, J = 13); 8.14 (s,
	B[i]	80	(MeCN)	(461.4)	1595, 1270[f]	1H); 11.45 (d, 1H, J = 13)[g]
	C[j]	51				
5c	C[j]	70	157–160[l] (MeCN)	$C_{24}H_{17}N_3O_3S$ (427.5)	1635, 1610, 1595, 1270[m]	7.13 (m, 11H); 7.85 (d, 2H, J = 9); 8.10 (s, 1H); 11.44 (d, 1H, J = 12); 8.23 (d, 2H, J = 9)[g]
5d	C[n]	34	131–133 (MeOH)	$C_{19}H_{16}N_2OS$ (320.4)		2.35 (s, 3H); 7.09 (m, 11H); 8.13 (s, 1H); 11.38 (d, 1H, J = 12)[g]
5e[o]	A[p]	98	128–134[q]	$C_{23}H_{17}N_3O_2S$	1640, 1600,	7.23 (m, 15H); 8.03 (s, 2H); 8.14 (s, 1H);
	C[j]	40	(MeCN)	(399.5)	1595[f]	11.13 (d, 1H, J = 13)[g]
5f	A[p]	98	130–132 (MeCN)	$C_{24}H_{16}Cl_2N_2OS$ (451.4)	1630, 1605, 1270[f]	7.13 (m, 12H); 7.68 (d, 2H, J = 8); 8.06 (s, 1H); 11.33 (d, 1H, J = 12)[g]
5g	A[p]	87	124–126	$C_{25}H_{19}ClN_2OS$	1630, 1590,	2.20 (s, 3H); 7.11 (m, 14H); 7.68 (d, 2H);
	C[j]	70	(MeCN)	(431.0)	1270[f]	8.06 (s, 1H); 11.37 (d, 1H, J = 12.5)[g]
5h	A[p]	85	198–200 (MeCN)	$C_{24}H_{17}ClN_2O_2S$ (432.9)	1629, 1605, 1525, 1260[f]	–
5i	A[p]	98	228–230	$C_{25}H_{17}ClN_2O_3S$	–	–
	A[h]	97	(MeCN)	(461.0)		
7a	D[j]	65	189–203 (dec.) (MeOH)	$C_{25}H_{20}Br_2N_2OS$ (556.3)	–	5.04 (s, 2H); 5.63 (s, 2H); 7.50 (m, 12H); 7.99 (d, 2H, J = 11); 9.16 (s, 1H); 9.61 (s, 1H)[s]
7b	E[j]	84	128–142 (dec.) (MeOH)	$C_{24}H_{18}BrClN_2O_5S$ (561.9)	–	–
7c	E[j]	95	204–212 (dec.) (MeOH)	$C_{23}H_{18}ClN_3O_6S$ (500.0)	–	4.83 (s, 2H); 7.89 (m, 14H); 9.24 (d, 1H, J = 2); 9.85 (d, 1H, J = 2)[s]
9a	A[t]	87	164–166 (MeCN)	$C_{23}H_{17}BrN_2OS$ (433.4)		7.25 (m, 16H); 11.35 (d, 1H, J = 14)[g]

[a] Uncorrected, measured with heating block Boetius.
[b] Satisfactory microanalysis obtained: C ±0.49, H ±0.48, N ±0.29, S ±0.49.
[c] Recorded on a Perkin Elmer 580B Infrared spectrophotometer.
[d] Recorded on a Tesla BS 487K (80 MHz) spectrometer.
[e] NR^3R^4 in **3**: Pyrrolidino.
[f] In $CHCl_3$.
[g] In $CDCl_3$.
[h] Reactant: **4**.
[i] X^- in **7**: ClO_4^-.
[j] X in **2**: Br.
[k] Occurs in two crystal modifications, other modification: m.p. 142–143°C.
[l] Occurs in two crystal modifications, other modification: m.p. 170–177°C.
[m] In CCl_4.
[n] X in **2**: Cl.
[o] MS (70 eV): m/e (%) = 400 (27); 399 (M^+, 100); 398 (26); 352 (14); 193 (18); 104 (13); 93 (23); 89 (46); 77 (55); 51 (21).
[p] NR^3R^4 in **3**: Morpholino.
[q] Occurs in two crystal modifications, other modification: m.p. 154–159°C.
[r] MS (70 eV): m/e (%) = 306 (5); 278 (9); 274 (6); 273 (6); 246 (6); 245 (11); 106 (6); 105 (100); 92 (7); 91 (79); 89 (7); 77 (42)
[s] In DMSO-d_6.
[t] NR^3R^4 in **8**: Piperidino.

achieved with Method B and C are lower than is Method A. After treatment with base the benzyl substituted mercaptopyrimidinium salt **7a** (R^1 = benzyl) gave a red oil, from which no crystalline product **5** ($R^1 = CH_2C_6H_5$; R^2 = 4-BrC_6H_4CO) could be isolated.

The synthesis of the 5-substituted 2-(2-amino-1-phenylethenyl)thiazoles **5** from pyrimidinthiones **6** and acceptor substituted methyl halides **2** presents a new type of ring transformations of pyrimidines. The pyrimidine acts as S–C–N–C-synthon for the final heterocyclic ring rather than as a S–C–N[4,5,8,9] or as a C–C–C-synthon[10] as is known in other cases. Since for steric reasons the formation of the thiazole ring cannot directly occur by nucleophilic attack of the deprotonated S–CH_2-group of the 4-alkylthiopyrimidinium salt **7** at the C-atom in position 2 of the pyrimidine ring, we assume a primary ring opening reaction initiated by the attack of base at the pyrimidine ring C-atom at position 2.

The 2-(2-amino-1-phenylethenyl)thiazoles **5** are stable crystalline compounds. In contrast to their colorless precursors **7** they are intensively colored (yellow to red). Their structures are confirmed by microanalysis and their spectroscopic data (Table). Their ^{1}H-NMR spectra, for example, are very similar to those of the *N,N*-disubstituted 2-(2-amino-1-phenylethenyl)thiazoles **3**[2] indicating that the *N*-monosubstituted compounds also exist in the enamine form rather than in the tautomeric azomethine form. It has to be mentioned that each of the compounds **5b, 5c** and **5e** appear in different crystalline forms possessing identical ^{1}H-NMR and IR spectra as well as R_f-values, but different colors and different melting points, depending on the method employed for their synthesis. This phenomenon, which is to be reported in more detail later, probably also appears in other cases since the aminovinylthiazoles **5** often show melting ranges instead of sharp melting points.

2-Aminovinylthiazoles 5 and 9a; General Procedures:

Method A: To a suspension of *N,N*-disubstituted 2-aminovinylthiazole **3** (10 mmol) in glacial AcOH (20 mL) the appropriate primary amine (12 mmol) or its corresponding hydrochloride (in case of aliphatic amines) is added. The mixture is heated to boiling for 5 min, cooled and diluted with water (30 mL). The product is filtered by suction and recrystallized.

Method B: A mixture of substituted mercaptopyrimidinium salt **7** (10 mmol), MeCN (20 mL) and triethyl amine (1.1 g, 11 mmol) is heated to boiling for 5 min. After cooling to room temperature the mixture is diluted with water (30 mL). After oily product has solidified, it is filtered by suction and recrystallized.

Method C: A mixture of pyrimidinthione **6** (10 mmol), acceptor substituted methyl halide **2** (10 mmol) and MeCN (20 mL) is heated to boiling for 3 min. After the addition of triethylamine (1 g, 10 mmol) the heating is continued for 5 min. The deep red-colored solution is worked up according to Method B.

Substituted Mercaptopyrimidinium Salts 7; General Procedures:

Method D: Pyrimidinthione **6** (10 mmol) is added to a solution of the acceptor-substituted methyl halide **2** (10 mmol) in MeCN (20 mL). The mixture is heated to boiling for 5 min. After cooling to room temperature ether (50 mL) is added. The product is filtered by suction and recrystallized from MeOH.

Method E: According to Method D, but instead of ether, 70% $HClO_4$ (1.5 mL) is added. The pyrimidinium salt **7** precipitates after dilution with water.

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