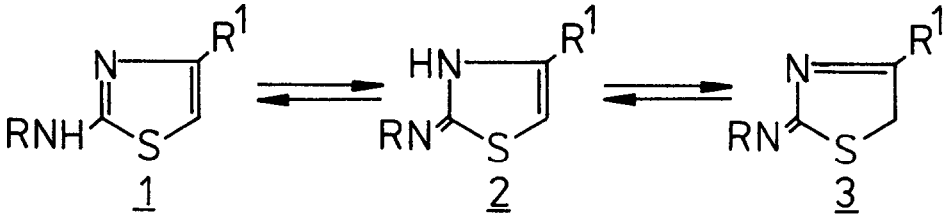
Tetrahedron Letters,Vol.26,No.15,pp 1835-1838,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

2-ARYLIMINO-3-THIAZOLINES - FORMATION OF UNUSUAL TAUTOMERS OF 2-ARYLAMINO-THIAZOLES BY A MODIFIED HANTZSCH SYNTHESIS

Jürgen Liebscher * and Elke Mitzner, Sektion Chemie, Humboldt-Universität zu Berlin, DDR-1040 Berlin, Hessische Str. 1-2

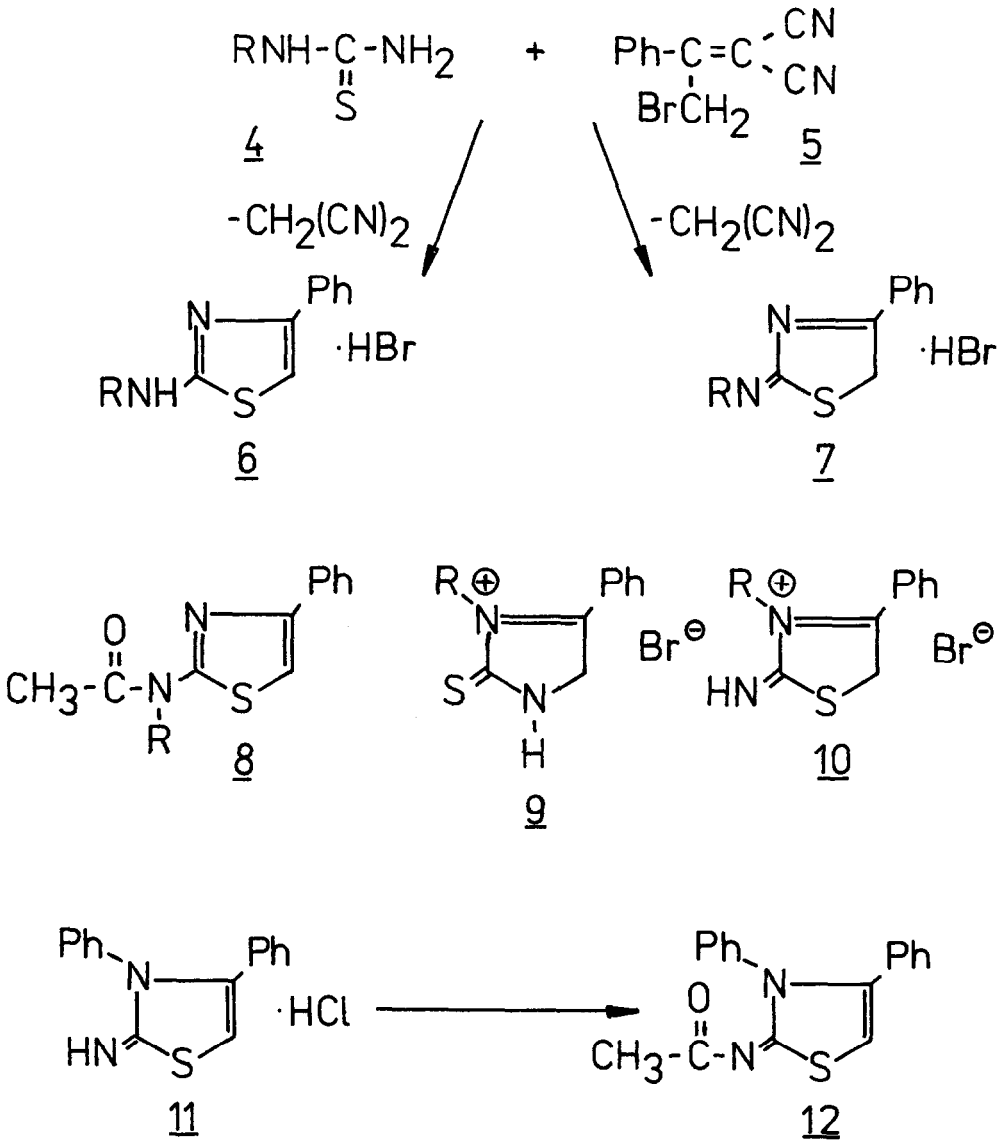
ABSTRACT: The reaction of thioureas with 3-bromomethyl-2-cyanocinnamonitrile gives the hydrobromides either of the 2-aminothiazoles or of the hitherto unknown 2-imino-3-thiazolines.

2-Arylaminothiazoles may exist in three protomeric forms 1, 2 and 3. Evidence for the presence of form 3 has never been found /1, 2/.



Aiming the S-alkylation of thioureas 4 by means of 3-bromomethyl-2-cyano-cinnamonitrile 5 we found that surprisingly no S-alkylated thioureas are obtained but cyclized products while malodinitrile is eliminated. These cyclized products are either 2-aminothiazole hydrobromides 6 or their tautomeric 2-arylimino-3-thiazoline hydrobromides 7 which belong to the protomeric structure 3. The type of products obtained depends mainly on the substituent R and to some extend on the reaction conditions. N-Unsubstituted thiourea 4 (R=H) and N-allylthiourea 4 (R=allyl) formed the corresponding 2-aminothiazole hydrobromides 6 in all cases. Analogeous products 6 (R=aryl) were obtained if N-arylthioureas 4 (R=aryl) react with 3-bromomethyl-2-cyano-cinnamonitrile 5 in ethanol. If the latter reaction is carried out in acetone or chloroform at room temperature or by refluxing however 2-arylimino-3-thiazoline hydrobromides 7 (R=aryl) are isolated.

The structure of the 2-aminothiazole hydrobromides 6 can easily be proved by their independent synthesis from thioureas 4 and phenacyl bromide following the Hantzschprocedure /3, 4/. The hitherto unknown 2-arylimino-3-thiazoline hydrobromides 7 gave satisfactory results in the elemental analysis. The most important fact for the structural assignment of 7 is the appearance of a CH_2-signal in the ^{1}H-NMR spectra at about 4.40 ppm. The mass spectra of the corresponding compounds 6 and 7 show no remarkable differences. The 2-aminothiazole hydrobromides 6 possess a much stronger NH-peak in the



IR spectra than their tautomers 7. The 2-arylimino-3-thiazoline hydrobromides 7 are colourless crystalline compounds which are reasonably stable in the solid state. In solution however they are tautomerised to 2-arylamino-thiazole hydrobromides 6 which appear to be thermodynamically more stable. Hence it is not possible to recrystallise the 2-imino-3-thiazoline hydrobromides 7. The rate of this transformation depends on the substituent R and the nature of the solvent. The same tautomerisation probably also occurs during melting of 7 since melting ranges are observed. Furthermore the free bases of 6 and no 2-arylimino-3-thiazolines appear even after short times during attempts to deprotonate the 2-imino-3-thiazoline hydrobromides 7 by

triethylamine in acetonitrile. Like the 2-aminothiazole hydrobromides 6 /4, 5/ the protomers 7 are acetylated by acetic anhydride or acetic acid to give 2-acylaminothiazoles 8.

Alternative structures 9 and 10 for the products obtained by the reaction of thioureas 4 with the nitrile 5 can be ruled out due to the following facts. The products 7 evolve H_2S rather than methyl mercaptan when alkylated and subsequently hydrolyzed. The 3-substituted 2-imino-3-thiazolium salts 10 would be deprotonated by triethylamine in acetonitrile giving rise to the free bases of the protomeric 2-iminothiazoles like, for example the known compound 11 /4/. Acetylation of the latter has been described /4/. The structure of the corresponding acetylation product 12 has been proved by its independent synthesis from N-acetyl-N'-phenylthiourea and phenacyl bromide /6/. Finally 3,5-diphenyl substituted thiazole derivatives 11 and 12 give rise to an intense fragment peak of 180 ($Ph-\overset{+}{N}\equiv C-Ph$) in the MS which is missing in the cases of the 3-unsubstituted compounds 6 and 7.

The investigations of the isomerization rates of the transformation of the 7 to the corresponding 6 as well as of reactions of the 2-imino-3-thiazoline hydrobromides 7 are currently under way. These results will be published, together with a mechanistic proposal to account for the formation of 7, in a more detailed account.

Table: Thiazole Derivatives 6, 7, 8, 11, and 12

	R	m.p.[°C]	^{1}H-NMR (DMSO-d_6, 80 MHz) δ[ppm]	yield[%]
6a[a]	C_6H_5	194-195 (ethanol)	5.30 (br; NH_2), 6.72-7.90 (m; 11H)	72[b][c] 78[d]
6b[e]	4-ClC_6H_4	187-190[f]	5.55 (br; NH_2), 7.21-7.90 (m; 10H)	73[d]
6c[g]	H	147-148 (ethanol)		92[b]
6d	CH_2=$CHCH_2$	70[h] (ethanol)		81[b]
7a[i]	C_6H_5	274-290[f]	[j] 4.39 (s; CH_2), 4.94 (s; NH), 6.76-7.86 (m; 2 C_6H_5)	96[b][k]
7b[l]	4-ClC_6H_4	187-197[f]	[j] 4.40 (s; CH_2), 5.16 (br; NH), 7.22-7.75 (m; C_6H_5, C_6H_4)	82[b][k]
8a[m]	C_6H_5	133-135 (ethanol)	[n] 1.92 (s; 3 H), 7.00-7.50 (m; 11 H)	76[o] 74[p]
11[q]	--	273 (ethanol)	3.27 (br; NH_2), 6.94-7.32 (m; 11H)	68
12[r]	--	213-214 (ethanol)	[n] 2.09 (s; 3 H), 6.51 (s; 1 H), 7.01-7.22 (m; 10 H)	56[s] 60[t]

footnotes of the table

a) IR(in KBr) ν_{NH}=3300 cm^{-1}; UV(CH_3OH) λ_{max}[nm]: 241(4.23), 281(4.26), 299 sh (4.20); MS: 253(21), 252(100,M^+), 251(62), 150(20), 149(15), 134(52), 104 (31), 90(21), 89(25), 82(23), 80(22), 77(44). ref. /4/ m.p. 189°C

b) reactant: 5 c) in ethanol d) reactant: phenacyl bromide

e) IR(in KBr) ν_{NH}=3300 cm^{-1}; UV(CH_3OH) λ_{max}[nm]: 243(4.20), 285(4.27), 300 (4.27). f) without recrystallisation

g) ref. /7/ m.p. 151-152°C h) m.p. of the free base

i) MS: 253(19), 252(100,M^+), 251(63), 150(23), 149(18), 134(47), 104(27), 90 (18), 89(19), 77(24).

j) The integration does not fully fit the required values. There is a gradual change of the spectrum with the time due to tautomerisation.

k) in acetone l) UV(CH_3OH) λ_{max}[nm]: 259 sh (4.19), 264(4.20), 306 sh (3.85) m) ref. /4/ m.p. 135°C; UV(CH_3CN) λ_{max}[nm]: 234(4.34), 270(4.20); MS: 294(18), 253(21), 252(100), 251(46), 149(15), 134(51), 104(24), 90(15), 89(18), 77(44).

n) in $CDCl_3$ o) reactant: 7a p) reactant: 6a

q) synthesis according ref. /4/; m.p. of the free base: 111°C; MS: 253(13), 252(55,M^+), 251(100), 180(39), 134(17), 89(15), 77(92).

r) ref. /4/ m.p. 210°C; UV(CH_3CN) λ_{max}[nm]: 224 sh (4.19), 310(4.16); MS: 294 (40,M^+), 279(100), 251(19), 180(20), 134(18), 77(68).

s) reactant: 11 t) reactants: N-acetyl-N'-phenylthiourea + phenacyl bromide

REFERENCES:

/1/ M. Chanon, Chem. Heterocycl. Compounds 34 (part II), 2 .

/2/ B. Barone, M. Chanon, R. Gallo, Chem. Heterocycl. Compounds 34 (part II), 31 .

/3/ G. Vernin, Chem. Heterocycl. Compounds 34 (part I), 232 .

/4/ H. Beyer, G. Ruhlig, Chem. Ber. 89, 111 (1955) .

/5/ B. Barone, M. Chanon, R. Gallo, Chem. Heterocycl. Compounds 34 (part II), 52 .

/6/ R. J. S. Beer, D. Mc Monagle, M. S. S. Siddiqui, A. Hordvik, K. Jynge, Tetrahedron 35, 1199 (1979) .

/7/ C. King, F. M. Miller, J. Am. Chem. Soc. 71, 367 (1949) .

(Received in Germany 10 December 1984)