Tetrahedron Vol. 49, No. 16, pp. 3411-3424, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

A Novel Synthesis of 2-Imino-4-thiazolines via α-Bromoketimines

Norbert DE KIMPE[a,*] Mark BOELENS[a,#] and Jean-Paul DECLERCQ[b]

[a] Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, BELGIUM

[b] Laboratoire de Chimie Physique et de Cristallographie, Université Catholique de Louvain, Bâtiment Lavoisier, Place L. Pasteur, B-1348 Louvain-la-Neuve, Belgium

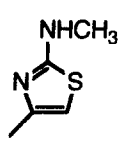
(*Received in UK* 29 *January* 1993)

Abstract

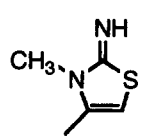
A novel straightforward synthesis of 2-imino-4-thiazolines has been performed by reaction of α-bromoketimines with potassium thiocyanate in acetonitrile. Contrary to other syntheses of these heterocycles, no side reactions were observed. The structural assignment of these relatively rare 2-imino-2,3-dihydrothiazoles was executed by spectroscopic means, by the synthesis of model compounds by an alternative route and by X-ray crystallographic analysis of an N-acetyl derivative, excluding any other isomeric possibility.

INTRODUCTION

The Hantzsch thiazole synthesis using the condensation of α-haloketones with thiourea was established a century ago.[1] The problem of isomerism of the heterocycles emerged soon when it was observed that the free base of the salt formed upon methylation of 2-amino-4-methylthiazole (obtained from chloroacetone and thiourea)[1] was isomeric with the free base resulting from the condensation of chloroacetone with N-methyl-



1



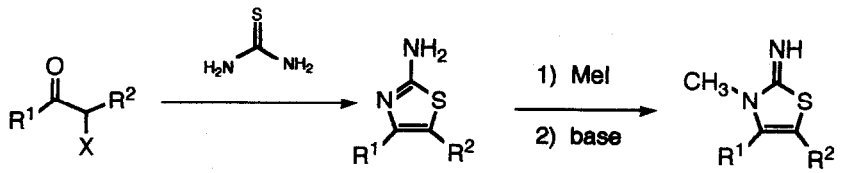
2

thiourea.[2] It was shown and later generally accepted that the former methylation product was 2-imino-3,4-dimethyl-4-thiazoline 2 and the latter 4-methyl-2-(methylamino)thiazole 1.

The condensation of α-haloketones with N-monosubstituted thioureas in the usual organic solvents has been studied extensively and led to 2-(N-substituted amino)thiazoles.[3,4] However, the same condensation

under acidic conditions gave rise to the isomeric 2-imino-4-thiazolines,[5,6] in addition to variable amounts of the aminothiazoles.[6]

While 2-(N-substituted amino)thiazoles are readily accessible under the neutral conditions discussed above, the isomeric 2-imino-4-thiazolines are not. The best entry to the latter heterocycles 5 involves the condensation of α-haloketones 3 with thiourea, followed by alkylation of the resulting 2-aminothiazole 4.[1,4,6-8]



3 X = Cl, Br 4 5

An alternative synthesis of 2-imino-4-thiazolines 5 consists of the condensation of α-haloketones with N-benzoyl N-substituted thioureas.[9] Less general approaches involve the reaction of ketones with N-alkyl rhodanamines[10] or bis-benzyl formamidine disulfide,[11] or the reaction of α-chloroketones with thiosemicarbazide in acid medium,[12-14] but the latter reaction was previously erroneously reported as giving rise to 2-amino-1,3,4-thiadiazines.[15,16] Some 2-imino-4-thiazolines are useful as schistosomicides[17,18] and cardiotonics, while some derivatives are active against trichomonides[17] or can be used as UV light stabilizers for polyolefins.[5] Recent patents claimed the use of 2-imino-4-thiazolines as acaricides and insecticides,[28] and plant growth regulators.[29] In this paper a new straightforward synthesis of 2-imino-4-thiazolines 7 will be disclosed, starting from readily accessible α-bromoketimines 6.

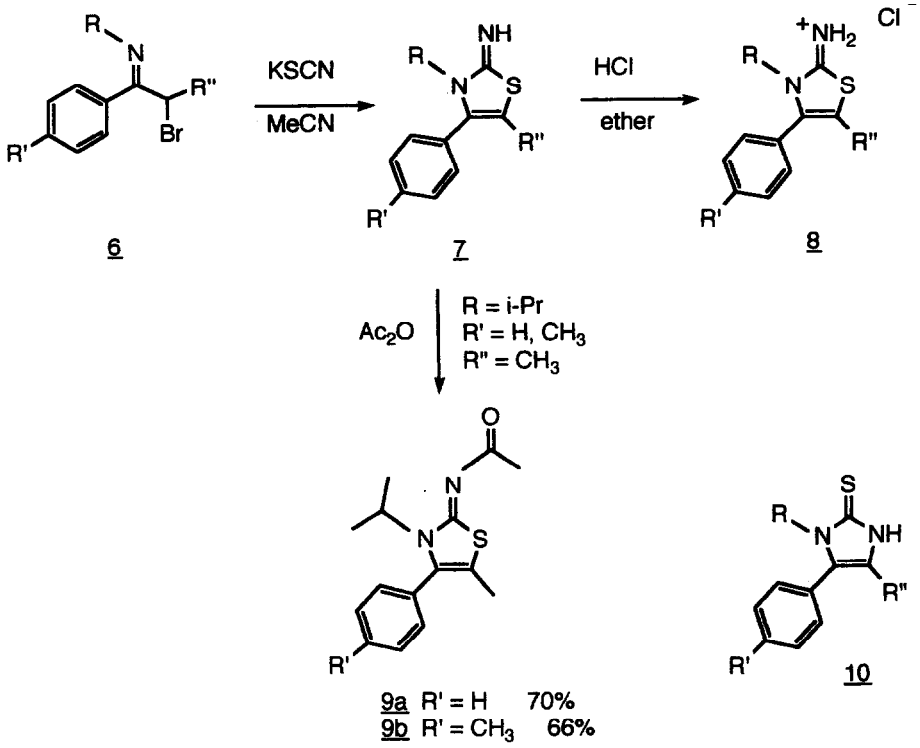
RESULTS AND DISCUSSION

The reaction of α-bromoketimines 6, easily prepared from the corresponding α-bromoketones with primary amines in the presence of titanium(IV) chloride,[20] with potassium thiocyanate in acetonitrile under reflux afforded 3-alkyl-2-imino-4-aryl-4-thiazolines 7 as dark oils (85-100% yield except for compound 7f which was prepared in 57% yield). High vacuum distillation (partial decomposition) gives the 2-imino-4-thiazolines 7 as yellow oils, but darkening occurs rapidly. These heterocycles can be converted into stable hydrochlorides 8 by reaction with gaseous hydrogen chloride in ether. An alternative procedure consists of the treatment of compounds 7 with aqueous hydrogen bromide and evaporation to dryness.[27] The synthesis of the 2-imino-4-thiazolines 7 and the corresponding hydrochlorides 8 is compiled in Table I.

Because of the fact that thiocyanate is an ambident nucleophile, care should be taken with regard to the final structure of the heterocycles. Spectrometric analysis (^{1}H NMR, ^{13}C NMR, IR and MS) revealed a net structure in which the bromine had been replaced by the nucleophile and in which an additional ring closure had taken place. Two structures match with these features, namely 2-imino-4-thiazolines 7 or 4-imidazoline-2-thiones 10. It is not evident from spectroscopic data which compound is actually formed. Therefore, some efforts have been performed to assure the structural assignment.

A salient feature of the known 2-imino-4-thiazolines is that they occur as oils (many times they are referred to as "dark oils").[6,7,26] Comparison with a known related 2-imino-4-thiazoline structure was perfor-

med in the following way. 2-Bromopropiophenone 11 was condensed with thiourea in absolute ethanol under reflux for two hours to afford 81% 2-amino-5-methyl-4-phenylthiazole hydrobromide 12.[7,21] The latter

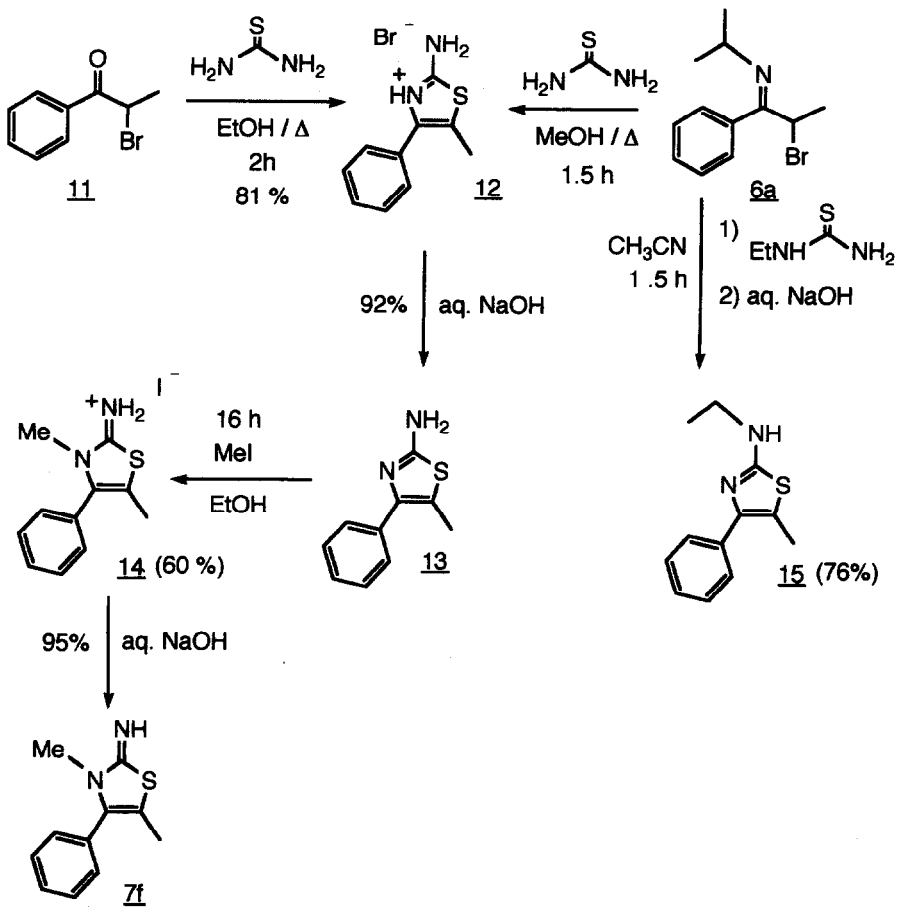


product was also obtained from the reaction of N-(2-bromo-1-phenyl-1-propylidene)isopropylamine 6a (R=i-Pr; R'=H; R"=Me) with thiourea in methanol under reflux for 1.5 h. The condensation of α-bromoketimine 6a with thiourea is comparable with the condensation of ß-chloro-ß-(ethoxycarbonyl)enamines[22] or α-chlorooximes[23] with thiourea, affording 2-amino-5-(ethoxycarbonyl)thiazoles or 2-aminothiazoles, respectively. The reaction of α-bromoketimines 6 with thiourea has no advantage over the use of α-bromoketones because the N-alkylamino moiety in the former is lost during the reaction. The same statement is applicable to the reaction of α-bromoketimines 6 with N-alkylthioureas. As exemplified for the condensation of α-bromoketimine 6a with N-ethylthiourea in acetonitrile under reflux, the N-alkylamino portion of the α-bromoketimine is lost while the N-alkylamino moiety of the thiourea derivative is retained in the final molecule as an alkylaminosubstituent at the 2-position, resulting in the formation of 2-(N-ethylamino)-5-methyl-4-phenylthiazole 15.

The nitrogen atom at the 3-position of 2-amino-5-methyl-4-phenylthiazole 13 was methylated with methyl iodide in absolute ethanol under reflux affording the hydroiodide of 2-imino-3,5-dimethyl-4-phenyl-4-thiazoline in 60% yield. Treatment with aqueous alkali provided access to the free base 7f. Both the hydroiodide 14 and the free base 7f exhibited ^{1}H NMR and ^{13}C NMR spectral characteristics which were in close agreement with the data of analogous 3-alkyl heterocycles 7. Especially the ^{13}C NMR data of the authentic 3-methyl derivatives 14 and 7f were indicative of a similar structure for the 3-alkyl derivatives 7.

Attempts to crystallize the salts of 2-imino-4-thiazolines in a suitable form for X-ray crystallographic

analysis failed. Therefore, efforts were conducted towards the preparation of a crystalline derivative. Acetylation of 2-aminothiazole derivatives is often problematic and can lead to different N-acetyl derivatives, the



regiochemistry of which being determined by the acetylation conditions (traces of mineral acids direct the acetylation in a different course than in the case of the presence of basic substances, e.g. sodium acetate).[24,25] This problem is prohibited in the title heterocycles of this article because the 3-position is blocked by N-alkylation, leaving the 2-imino functionality as the sole site for acetylation. Acetylation of compounds 7a and 7b was either performed with excess acetic anhydride under reflux without any solvent or with excess acetic anhydride in toluene at room temperature overnight (Table I).[4,6,8,25] The spectral characteristics of these two N-acetylimino derivatives 9a and 9b pointed again to a 2-imino-4-thiazoline structure, proving that no rearrangement had taken place.

The structure of the heterocycles resulting from the reaction of α-bromoketimines 6 with potassium thiocyanate was unambigously proven by the X-ray crystallographic analysis of the N-acetyl compound 9a, indicating the compound to be 2-(N-acetylimino)-3-isopropyl-5-methyl-4-phenyl-4-thiazoline. The X-ray

structure of compound 16a is given in figure 1 while the detailed X-ray data will be published in a forthcoming report.

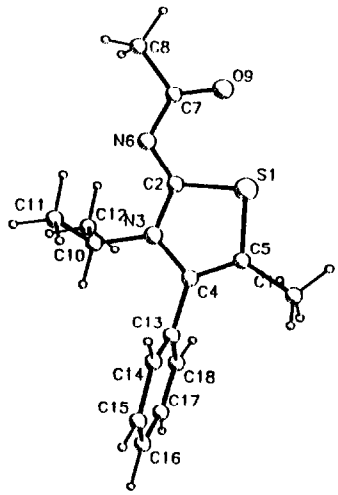
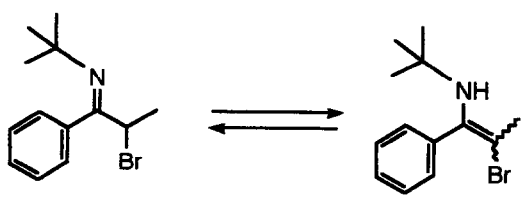


Figure 1 : X-ray structure of 2-(N-acetylimino)-4-thiazoline 9a.

As far as the examples show, the synthesis of 2-imino-4-thiazolines 7 is applicable to substrates having an alkyl substituent at the 3-position and the 5-position, and an aromatic substituent at the 4-position. One exception was noticed with the N-t-butyl ketimine derived from 2-bromopropiophenone. After the usual reaction time under reflux (1 hour, KSCN, CH_3CN) most of the starting material was still present but after 4 hours of reflux a very complex reaction mixture was formed from which no reaction products could be identified. It might be that this deviating reactivity finds its origin in the fact that the more sterically hindered α-bromoketimine 6h occurs in equilibrium with the less reactive enamine 16. Aliphatic α-chloroketimines, e.g. N-(3-chloro-2-butylidene)isopropylamine, did not react with potassium thiocyanate to afford the title 2-imino-4-thiazolines but instead a complex reaction mixture was formed. Also α-bromoaldimines, e.g. N-(2-bromo-2-methyl-1-propylidene)t-butylamine, although structurally not capable of giving rise

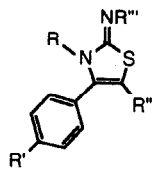


6h 16

to a 2-imino-4-thiazoline, on reaction with potassium thiocyanate in acetonitrile afforded a complex reaction mixture.

It was found that compounds 7 are preferably prepared by reaction of α-bromoketimines 6 with potassium thiocyanate in acetonitrile. When methanol was used as the solvent, the reactions were slower and methanol had the tendency to be incorporated in the organic substrates, leading to impure reaction products.

Table I. Synthesis of 3-Alkyl-4-aryl-2-imino-4-thiazolines 7, 9 and the corresponding Hydrochlorides 8



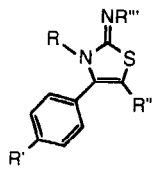
7 R''' = H

9 R''' = Ac

	R	R'	R''	R'''	%	Reaction Conditions	IR (NaCl) (cm^{-1})	Hydrochloride 8	
								%	mp. (°C)
7a	i-Pr	H	Me	H	100%	1.5E KSCN/MeCN Δ 1.5 h	1627 (m) 1570 (s)	77% 73%[c]	260 (decomp.) 280 (decomp.)[c]
7b	i-Pr	Me	Me	H	100%	1.5E KSCN/MeCN Δ 1.5 h	1550-1620 (br,s) 3300 (w)	80%	200 (decomp.)
7c	Et	Me	Me	H	85%[d]	1.5E KSCN/MeCN Δ 1.5 h	1625 (s) 1570 (s) 3300 (w)	78%[d]	130 (decomp.)
7d	i-Pr	H	Et	H	100%	1.5E KSCN/MeCN Δ 0.5 h	1625 (s) 1570 (s) 3330 (m)	100%	235 (subl.)
7e	i-Pr	H	Pr	H	100%	1.5E KSCN/MeCN Δ 1.2 h	1550 (s,br) 1630 (s,br) 3320 (w)	77%	200 (decomp.)
7f	Me	H	Me	H	57%	2-amino-5-methyl-4-phenyl thiazole + 2E MeI/EtOH	1628 (s,br) 1570 (s,br) 3430 (m)	60%[e]	204[e]
7g	cycloHex	H	Me	H	95%	1.5E KSCN/MeCN Δ 1.5 h	1630 (s,br) 1570 (s,br) 3320 (m)	86%[a]	235 (decomp.)
9a	i-Pr	H	Me	Ac	70% mp. 177°C	7a + excess Ac_2O/Δ 3.5 h	1590 (s) 1494 (s)	-	-
9b	i-Pr	Me	Me	Ac	66%[b] mp. 189°C	7b + 10E Ac_2O/toluene RT 23 h	1590 (s) 1491 (s)	-	-

[a] two steps from the corresponding α-bromoketimine; [b] overall yield from the corresponding α-bromoketimine; [c] hydrobromide 8a'; [d] compound 7c was only obtained in moderate purity (about 80%) and could not be further purified due to its instability; the purity of the hydrochloride is of the same order of magnitude; [e] hydroiodide.

Table II. ^{1}H NMR Data ($CDCl_3$) of 2-Imino-4-thiazolines 7 and 9

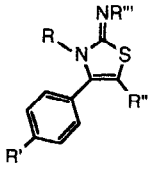


7 R''' = H

9 R''' = Ac

	R	R'	R''	R'''	δ_R	$\delta_{R''}$	$\delta_{NR'''}$	$\delta_{R'}$	δ_{aryl}
7a	i-Pr	H	Me	H	1.39 (6H,d,J=7Hz,Me_2) 4.03 (1H,septet,J=7Hz,CH)	1.81 (3H,s)	5.1 (1H,s,br)	-	7.2-7.6 (5H,m,C_6H_5)
7b	i-Pr	Me	Me	H	1.37 (6H,d,J=7Hz,Me_2) 4.01 (1H,septet,J=7Hz,CH)	1.76 (3H,s)	6.6 (1H,s,br)	2.35 (3H,s)	7.19 (4H,s,C_6H_4)
7c	Et	H	Me	H	1.06 (3H,t,J=6.5Hz,Me) 3.61 (2H,q,J=6.5Hz,CH_2)	1.89 (3H,s)	5.0 (1H,s,br)	-	7.1-7.6 (5H,m,C_6H_5)
7d	i-Pr	H	Et	H	1.40 (6H,d,J=6.7Hz,Me_2) 3.82 (1H,septet,J=6.7Hz,CH)	1.00 (3H,t,J=7Hz) 2.16 (2H,q,J=7Hz)	6.0 (1H,s,br)	-	7.1-7.6 (5H,m,C_6H_5)
7e	i-Pr	H	Pr	H	1.38 (6H,d,J=7Hz,Me) 4.01 (1H,septet,J=7Hz,CH)	2.16 (2H,~t,J=7Hz) 1.4 (2H,overlap) 0.8 (3H,~t,J=6Hz)	6.75 (1H,s,br)	-	7.1-7.6 (5H,m,C_6H_5)
7f	Me	H	Me	H	3.10 (3H,s,Me)	1.94 (3H,s)	5.8 (1H,s,br)	-	7.2-7.6 (5H,m,C_6H_5)
7g	cycloHex	H	Me	H	0.9-2.2 (10H,m,$(CH_2)_5$) 3.6 (1H,m,CH)	1.78 (3H,s)	6.3 (s,br)	-	7.2-7.7 (5H,m,C_6H_5)
9a	i-Pr	H	Me	Ac	1.54 (6H,d,J=7Hz,Me_2) 4.35 (1H,septet,J=7Hz,CH)	2.03 (3H,s)	2.28 (3H,s)	-	7.2-7.7 (5H,m,C_6H_5)
9b	i-Pr	Me	Me	Ac	1.50 (6H,d,J=7Hz,Me_2) 4.28 (1H,septet,J=7Hz,CH)	2.00 (3H,s)	2.25 (3H,s)	2.41 (s)	7.10 (2H,d,J=8Hz) 7.25 (2H,d,J=8Hz)

Table III. ^{13}C NMR Data ($CDCl_3$) of 2-Imino-4-thiazolines 7 and 9



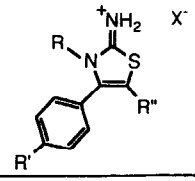
7 R''' = H

9 R''' = Ac

	R	R'	R''	R'''	$\delta_{R''}$	=C-R'' (s)	=C-N (s)	N-Substituent C_α	N-Substituent C_β	N-Substituent $C_{\gamma,\delta}$	Aryl Group C_q (s)	Aryl Group $C_{ortho/meta}$ (d)	Aryl Group C_{para}	C=N (s)	$\delta_{R'''}$
7a	i-Pr	H	Me	H	12.4(q)	106.5	135.1	49.9(d)	19.1(q)	-	131.9	128.6 130.2	128.8(d)	163.8	-
7b	i-Pr	Me	Me[a]	H	12.4(q)	106.1	130.3[b]	49.8(d)	19.2(q)	-	129.2[b]	129.2 130.3	138.7(s)	164.2	-
7c	Et	H	Me	H	11.6(q)	-[c]	-[c]	39.5(t)	13.2(q)	-	131.3	128.7 130.2	128.9(d)	164.5	-
7d	i-Pr	H	Et	H	15.1(q) 20.6(t)	113.7	134.2	49.6(d)	19.1(q)	-	132.2	128.8 130.2	128.8(d)	163.6	-
7e	i-Pr	H	Pr	H	13.4(q) 23.4(t) 29.1(t)	112.7	-[c]	49.8(d)	19.2(q)	-	-[c]	128.6 130.4	128.9(d)	163.9	-
7f	Me	H	Me	H	12.3(q)	106.7	134.7	32.4(q)	-	-	130.0	128.7 130.0	128.9(d)	165.1	-
7g	cycloHex	H	Me	H	12.4(q)	106.3	135.3	58.4(d)	28.9(t)	26.2(t) 25.0(t)	132.1	128.6 130.2	128.8(d)	164.4	-
9a	i-Pr	H	Me	Ac	12.3(q)	117.1	130.9	52.9(d)	19.5(q)	-	133.8	129.0 130.5	129.4(d)	165.3	179.4(s) 27.1(q)
9b	i-Pr	Me	Me	Ac	12.3(q)	117.0	133.9	52.8(d)	19.6(q)	-	128.0	129.7 130.4	139.4(s)	165.4	179.5(s) 27.1(q)

[a] The p.Methyl signal is situated at δ 21.3 ppm; [b] attribution may be interchanged; [c] could not be attributed.

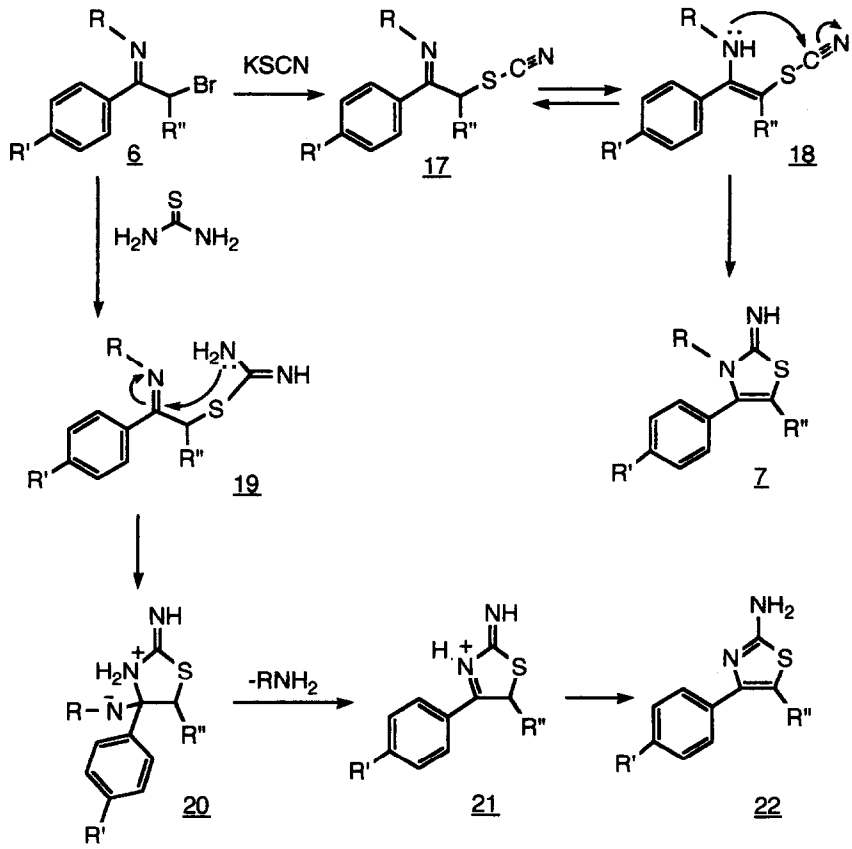
Table IV. ^{13}C NMR Data of 2-Imino-4-thiazoline Hydrohalides 8, 14



	Solvent	R	R′	R"	X	$\delta_{R''}$	=C-R" (s)	=C-N (s)	N-Substituent C_α	N-Substituent C_β	N-Substituent $C_{\gamma,\delta}$	$\delta_{R'}$	Aryl Group C_q (s)	Aryl Group $C_{ortho/meta}$ (d)	Aryl Group C_{para}	C=N (s)
8a	D_2O (ref. dioxane δ 67.4)	i-Pr	H	Me	Cl	12.0 (q)	117.7	129.5	53.6 (d)	18.71 (q)	-	-	137.8	130.1 131.5	131.2 (d)	166.9
8b	dmso-d_6	i-Pr	Me	Me	Cl	11.6 (q)	115.4	125.9[a]	52.2 (d)	18.4 (q)	-	20.9 (q)	136.1[a]	129.6 130.6	139.9[a] (s)	165.4
8c	dmso-d_6	Et	H	Me	Cl	-	115.7	127.9	-	14.5 (q)	-	-	135.3	129.1 130.5	-[b]	165.7
8d	dmso-d_6	i-Pr	H	Et	Cl	14.8 (q) 19.5 (t)	122.3	-[b]	52.7 (d)	18.4 (q)	-	-	135.3	129.0 129.1	128.8 (d)	165.3
8e	dmso-d_6	i-Pr	H	Pr	Cl	13.1 (q) 23.0 (t) 27.7 (t)	120.8	128.9	52.1 (d)	18.5 (q)	-	-	135.9	129.0 129.1	128.9 (d)	165.5
14	$CDCl_3$	Me	H	Me	I	12.6 (q)	117.0	127.3	37.4 (q)	-	-	-	136.1	129.3 130.6	128.1	165.9
8g	dmso-d_6	cycloHex	H	Me	Cl	11.6 (q)	115.6	-[b]	60.4 (d)	28.1 (t)	25.3 (d) 23.5 (d)	-	136.1	130.1 130.7	129.0 (d)	165.7
8a′	dmso-d_6	i-Pr	H	Me	Br	11.8 (q)	115.8	128.9	52.4 (d)	18.5 (q)	-	-	136.2	129.2 130.8	132.7 (d)	165.4

[a] the attribution may be interchanged; [b] signal covered by the broadened aromatic signals.

From the mechanistic point of view, the formation of 2-imino-4-thiazolines 7 from α-bromoketimines 6 can be interpreted as arising from nucleophilic substitution of the bromide by the sulphur atom of thiocya-



nate followed by intramolecular addition of the enamino nitrogen (see structure 18) across the carbon-nitrogen triple bond. In similar way, thiourea substitutes the bromide in α-bromoketimine 6a but, by the subsequent intramolecular nucleophilic addition, the ketimino function is attacked, leading to expulsion of the aliphatic amine. Finally, tautomerism of 21 produces the 2-aminothiazole 22.

EXPERIMENTAL SECTION

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer. ^{1}H NMR spectra were measured with a Varian T-60 NMR spectrometer while ^{13}C NMR spectra were recorded with a Varian FT-80 NMR spectrometer. Mass spectra were obtained with a Varian-MAT 112 mass spectrometer using the direct inlet system (70 eV). Melting points were recorded with a Kofler hotstage and are uncorrected. All α-bromoketimines 6 were synthesized according to our previously published method.[20] The spectrometric data of two representative new α-bromoketimines is given below.

N-(2-Bromo-1-phenyl-1-butylidene)isopropylamine 6d (R=i-Pr; R'=H; R"=Et)

Yield : 87% (> 98% pure by GLC); bp 60-63°C/0.05 mmHg.

IR (NaCl) : $\nu_{C=N}$ 1635 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.03 (3H,t,J=6Hz); 1.03 and 1.07 (6H,2d,J=6Hz,Me_2); 1.6-2.4 (2H,m,CH_2); 3.38 (1H,septet,J=6Hz,NCH); 4.63 (1H,dxd,J=6.5Hz,J=8Hz,CHBr); 7.1-7.5 (5H,m, C_6H_5). ^{13}C NMR ($CDCl_3$) : δ 23.29 and 23.47 (each q,Me_2); 12.51 (q,Me); 28.94 (t,CH_2); 60.23 (d,NCH); 52.46 (d); 128.59 (d,CH_{para}); 127.56 and 128.10 (each d,CH_{ortho} and CH_{meta}); 135.59 (s,$C_{quat.}$); 166.14 (s,C=N). Mass spectrum m/z (%) : 267/9 (M^+; 1); 266/8(1); 252/4(1); 239/41(4); 188(8); 187(5); 162(2); 150(2); 146(14); 131(2); 130(2); 115(4); 104(100); 90(5); 77(9); 50(4); 43(9); 41(10).

N-(2-bromo-1-phenyl-1-propylidene)t-butylamine 6h

According to the procedure described in our previous paper,[20] 8.52 g (0.04 mol) 2-bromopropiophenone 11, 11.68 g (0.16 mol) t-butylamine and 5.13 g (0.027 mol) titanium(IV) chloride in 80 ml benzene were refluxed for two hours. Workup with aqueous sodium hydroxide afforded N-t-butyl α-bromoketimine 6h in 84% yield after distillation, bp. 56-60°C/0.01 mmHg. Shortly after distillation : ratio 6h : 16 about 1:1 (CCl_4; ^1H NMR); after equilibration : ratio 6h : 16 7:3. ^1H NMR (CCl_4), α-bromoketimine 6h : δ 1.03 (9H,s,t-Bu); 1.75 (3H,d,J=6.5Hz,Me); 4.70 (1H,q,J=6.5Hz,CHBr); 7.2-7.5 (5H,m,C_6H_5). ß-Bromoenamine 16 : δ 0.96 (9H,s, t-Bu); 2.15 (3H,s,Me); 3.9 (1H,s,broad,NH); 7.2-7.5 (5H,m,C_6H_5). IR (NaCl) : 3340 cm^{-1} (w, ν_{NH}); 1620 and 1640-1655 cm^{-1} ($\nu_{C=N}$ and $\nu_{C=C}$). Mass spectrum, m/z (%) : 267/69 (M^+; 18); 252/54(10); 211/13(36); 160(49); 132(42); 115(29); 105(46); 104(100); 91(8); 77(29); 57(93); 51(13); 41(29).

Synthesis of 3,5-Dialkyl-4-aryl-2-imino-5-methyl-4-thiazolines 7

A solution of 0.01 mol of α-bromoketimine 6 in 25 ml of acetonitrile was treated with 0.015 mol of potassium thiocyanate. The heterogeneous mixture was stirred under reflux for the time indicated in Table I during which potassium thiocyanate gradually dissolved and potassium bromide precipitated from the colored solution. The reaction mixture was cooled and poured into 150 ml of 1N sodium hydroxide. Extraction with dichloromethane gave an essentially colorless aqueous phase and a dark colored organic phase. A second extraction with a small portion of dichloromethane was executed and the combined organic phases were dried ($MgSO_4$). Evaporation under vacuo afforded a dark syrup which was treated with dry ether (in order to remove some potassium thiocyanate), filtered, evaporated under vacuo to leave a dark oil, which consisted of pure 2-imino-4-thiazoline 7 as evidenced by ^1H NMR analysis. These compounds are preferably converted into their stable hydrochlorides (vide infra), as they decompose to tarry materials on standing.

Synthesis of Hydrochlorides of 3,5-Dialkyl-4-aryl-2-imino-4-thiazolines (compounds 8)

A stirred solution of 0.01 mol of 3,5-dialkyl-4-aryl-2-imino-4-thiazolines 7 in 40 ml of dry ether was treated dropwise with a solution of dry hydrogen chloride in ether until no further precipitation occurred. After standing overnight, the precipitated hydrochloride was isolated by filtration, washed five times with dry ether and dried under vacuum. The hydrochlorides 8 thus obtained as free flowing yellow to orange powders are stable when kept in a closed vessel. Detailed information on salts 8 is given in Tables I and IV.

Elemental analyses of hydrochlorides 8

Compound 7a : 58.09% C calcd., 57.19% C found; 6.37% H calcd., 6.57% H found; 13.19% Cl calcd., 13.13% Cl found; 10.42% N calcd., 10.29% N found. Compound 7b : 9.90% N calcd., 10.14% N found; 12.53% Cl calcd., 12.39% Cl found. Compound 7d : 9.90% N calcd., 10.19% N found; 12.53% Cl calcd., 12.69% Cl found. Compound 7e : 60.69% C calcd., 60.74% C found; 7.13% H calcd., 7.33% H found; 11.94% Cl calcd., 11.70% Cl found; 9.44% N calcd., 9.25% N found. Compound 7g : 9.07% N calcd., 9.29% N found; 11.48% Cl calcd., 11.31% Cl found.

An alternative synthesis of a stable salt of 2-imino-4-thiazolines 7 consisted of treatment of the free base with an excess of concentrated hydrobromic acid followed by evaporation of water in vacuo. Final drying occurred in high vacuo and in the dessicator (see Tables I and IV for the hydrobromide 8a').

Regeneration of 2-Imino-4-thiazolines 7 from the Corresponding Hydrochlorides 8

A solution of 0.01 mol of salt 8 in 60 ml of dichloromethane was treated with 30 ml 1N sodium hydroxide in a separatory funnel. After vigorous shaking the dark organic phase was isolated and washed with 30 ml of water. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford the free bases 7 as dark colored syrups in yields exceeding 90%.

Reaction of α-Bromoketimine 6a with Thiourea

A solution of 1.27 g (0.005 mol) α-bromoketimine 6a (R=i-Pr; R'=H; R"=Me) and 0,42 g (0.0055 mol) of thiourea in 15 ml of dry methanol was refluxed for 1.5 h. The reaction mixture was poured into excess 1N sodium hydroxide, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give 0,68 g (72%) of pure 2-amino-4-phenyl-5-methylthiazole 13. Recrystallization was performed in chloroform. Mp. 118°C (Lit.[7] mp. 118-119°C). This compound was identical in all aspects with a sample prepared from 2-bromopropiophenone 11 and thiourea in ethanol under reflux for two hours, according to the procedure of Dickey.[21] From 0.01 mol of 2-bromopropiophenone 11 there was obtained 2.2 g (81%) 2-amino-4-phenyl-5-methylthiazole hydrobromide 12, mp. 175° (EtOH) (Lit.[21] mp. 172-175°C). The hydrobromide 12 was converted into thiazole 13 upon treatment with aqueous alkali and extraction with dichloromethane (92% yield).

Condensation of α-bromoketimine 6a with N-Ethylthiourea

A solution of 0.76 g (0.003 mol) of α-bromoketimine 6a and 0.47 g (0.0045 mol) of N-ethylthiourea in 10 ml of acetonitrile was refluxed for 1.5 hours. The reaction mixture was poured into water, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to leave 0.50 g (76%) of crystalline 2-(N-ethylamino)-5-methyl-4-phenylthiazole 15, mp. 99°C (ether). ^1H NMR ($CDCl_3$) : 1.04 (3H,t,J=7.5Hz,Me); 3.10 (2H,q, J=7.5Hz); 2.33 (3H,s,Me); 6.5 (1H,s,broad,NH); 7.2-7.7 (5H,m,C_6H_5). IR (KBr) : 3220 cm^{-1} (ν_{NH}); 1600 cm^{-1} ($\nu_{arom.}$). ^{13}C NMR ($CDCl_3$) : 12.27 (q,Me); 14.50 (q,Me); 40.77 (t,CH_2); 128.10 and 128.53 (each d,CH ortho and meta); 127.03 (d,CH para); 135.78 (s,$C_{quat.}$); 146.41 (s, C-4); 114.70 (s,C-5); 166.85 (s,C-2). MS m/z (%) : 218 (M^+; 100); 203(57); 190(30); 176(21); 147(33); 104(21); 44(33); 40(21).

Synthesis of 3,5-Dimethyl-2-imino-4-phenyl-4-thiazoline Hydroiodide 14

A solution of 0.36 g (0.002 mol) of 2-amino-5-methyl-4-phenylthiazole 13 in 5 ml of absolute ethanol was treated with 0.57 g (0.004 mol) of methyl iodide. After reflux overnight, the reaction mixture was

evaporated in vacuo and the residue was triturated with dry ether to afford 0.40 g (60%) of 3,5-dimethyl-2-imino-4-phenyl-4-thiazoline hydroiodide 14 as a light yellow powder (Table I). The free base 7f was obtained by trituration of the hydroiodide 14 with aqueous 1N sodium hydroxide and extraction with dichloromethane. After drying ($MgSO_4$), evaporation of the solvent afforded the free base as a dark oil in 95% yield. ^1H NMR and ^{13}C NMR are compiled in Tables II and III. Mass spectrum (direct inlet) : m/z (%) 204 (M^+; 100); 203(63); 160(21); 147(10); 146(17); 117(35); 114(13); 102(10); 77(26).

Synthesis of 2-(N-Acetylimino)-3-isopropyl-5-methyl-4-phenyl-4-thiazoline 9a

As described above, 0.27 g (1 mmol) of the hydrochloride of 2-imino-4-thiazoline 7a (R=i-Pr; R'=H; R"=Me) was converted into the free base by treatment with aqueous alkali. After drying ($MgSO_4$) and evaporation of the dichloromethane, the residual oil, consisting of the pure free base 7a, was triturated with 3 ml of acetic anhydride. After 3.5 hours of reflux, the excess acetic anhydride was evaporated under vacuo and the residue was treated with dry ether/pentane (1:1). Crystallisation at -20°C afforded 0.19 g (70%) of pure 9a as well-formed colorless crystals, mp. 177°C. ^1H NMR, ^{13}C NMR and IR data are compiled in Tables I, II and III. Mass spectrum : m/z (%) 274 (M^+; 30); 273(13); 232(20); 217(27); 190(100); 189(9); 148(14); 147(18); 115(13); 104(14); 43(38); 41(14).

Elemental analysis : 10.21% N calcd., 10.02% N found.

Preparation of 2-(N-acetylimino)-3-isopropyl-5-methyl-4-(4-methylphenyl)-4-thiazoline 9b

Essentially as described in the previous experiment, 0.28 g (0.001 mol) of the hydrochloride of 2-imino-4-thiazoline 7b (R=i-Pr; R"=Me; R'=Me) was converted with aqueous alkali into the free base 7b, which was treated with 1.02 g (0.01 mol) of acetic anhydride in 10 ml of dry toluene. The homogeneous reaction mixture was left at room temperature for 23 h after which it was poured into aqueous potassium carbonate and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to leave 0.19 g (66%) of pure crystalline 2-(N-acetylimino)-4-thiazoline 9b. Recrystallization from pentane : ether (1:1) afforded well-formed crystals, mp. 189°C. ^1H NMR, ^{13}C NMR and IR data are compiled in Tables I, II and III. Mass spectrum, m/z (%) : 288 (M^+; 56); 287(18); 246(21); 230(50); 204(100); 162(12); 161(12); 118(9); 91(12); 43(37).

Elemental analysis : 9.71% N calcd., 9.59% N found.

REFERENCES

* De Kimpe, N. : Research Director of the Belgian "National Fund for Scientific Research"

* M. Boelens : Research Assistant of the I.W.O.N.L.

1. Hantzsch, A.; Weber, J.H. Ber. Dsch. Chem. Ges., **1887** *20*, 3118.
2. Traumann, V. Justus Liebigs Ann. Chem., **1888**, *249*, 31-53.
3. Vernin, G. Thiazole and its Derivatives, Metzger, J.V., Ed., J. Wiley and Sons, New York, Part 1, Chapter 2, **1979**.
4. Birkinshaw, T.N.; Harkin, S.A.; Kaye, P.T.; Meakins, G.D.; Smith, A.K. J. Chem. Soc. Perkin I, **1982**, 939-943.
5. a) Beyer, H.; Ruhlig, G. Chem. Ber., **1956**, *89*, 107-114.

b) Bloom, M.S.; Newland, G.C. U.S. 3,391,106 (Cl. 260-45.8), 02 Jul 1968, Appl. 13 Aug 1965; Chem. Abstr., **1968**, *69*, 36758.

6. Bramley, S.E.; Dupplin, V.; Goberdhan, D.G.C.; Meakins, G.D. J. Chem. Soc. Perkin Trans. I, **1987**, 639-643.
7. Wilson, W.; Woodger, R. J. Chem. Soc., **1955**, 2943-2948.
8. Krasovskii, V.A.; Burmistrov, S.I. Khim. Geterotsikl. Soedin., **1969**, 56-58; Chem. Abstr., **1969**, *70*, 115051.
9. Murav'eva, K.M.; Shchukina, M.N.; Arkhangel'skaya, N.V. Khim. Geterotsikl. Soedin., **1967**, 1036-1039; Chem. Abstr., **1968**, *69*, 52055. See also : Jurasek, A.; Safar, P.; Zvak, V. Chem. Pap., **1988**, *41*, 693-702; Chem. Abstr., **1988**, *109*, 37772.
10. Schmitz, E.; Striegler, H. J. prakt. Chem., **1970**, *312*, 359-365.
11. Bhattacharya, A.K. J. Indian Chem. Soc., **1967**, *44*, 57-63.
12. Beyer, H.; Lässig, W.; Bulka, E. Chem. Ber., **1954**, *87*, 1385-1392.
13. Beyer, H.; Lässig, W.; Bulka, E.; Behrens, D. Chem. Ber., **1954**, *87*, 1392-1401.
14. Beyer, H.; Wolter, G. Chem. Ber., **1956**, *89*, 1652-1658.
15. McLean, J.; Wilson, F.J. J. Chem. Soc., **1937**, 556-559.
16. Beyer, H.; Lässig, W.; Ruhlig, G. Chem. Ber., **1953**, *86*, 764-769.
17. Werbel L.M. (Parke, Davis and Co.), Ger. Offen. 1,927,448 (Cl. CO7d, A61k), 04 Dec 1969, US Appl. 31 May 1968 - 10 Mar 1969; Chem. Abstr., **1970**, *72*, 55437.
18. Werbel, L.M.; Degnan, M.B.; Harger, G.F.; Capps, D.B.; Islip, P.J.; Closier, M.D. J. Med. Chem., **1972**, *15*, 955-963.
19. Rudorf, W.D.; Haase, C. Ger. (East) DD 240,544 (Cl. CO7D277/12), 04 Nov 1986, Appl. 280, 132, 30 Aug 1985; Chem. Abstr., **1987**, *107*, 154324.
20. De Kimpe, N.; Verhé, R.; De Buyck, L.; Moëns, L.; Schamp, N. Synthesis **1982**, 43-46.
21. Dickey, J.B.; Towne, E.B.; Wright, G.F. J. Org. Chem., **1955**, *20*, 499-510.
22. Böhme, H.; Braun, R. Liebigs Ann. Chem., **1971**, *744*, 27-32.
23. Beger, J.; Thong, P.D. Ger. (East) 127, 813 (Cl. CO7D277/38), 12 Oct 1977, Appl. 194, 779, 14 Sept 1976; Chem. Abstr., **1978**, *88*, 121164.
24. Lundina, I.B.; Postovskii, I.Y. Trudy Ural. Politekh. Inst. im. S.M. Kirova, **1959**, 15-35; Chem. Abstr., **1961**, *55*, 9380b.
25. Posotovskii, I.Y. Lundina, I.B. Zhur. Obshch. Khim., **1959**, *29*, 608; Chem. Abstr., **1960**, *54*, 1499.
26. Goerdeler, J.; Roth, W. Chem. Ber., **1963**, *96*, 534-549.
27. For a study on the protonation site of 2-imino-4-thiazolines and 2-aminothiazoles, see : Forlani, L.; De Maria, P. J. Chem. Soc., Perkin Trans. II, **1982**, 535-537.
28. Nagasaki, F.; Yamada, T.; Takahashi, E.; Kitagawa, Y.; Hatano R. (Nippon Soda Co., Ltd.), Jpn. Kokai Tokkyo Koho JP 63,250,371 [88,250,371] (Cl. CO7D277/42), 18 Oct 1988, Appl. 87/82,455, 03 Apr 1987; Chem. Abstr., **1989**, *110*, 192810.
29. Hoelzel, H.; Creuzburg, D.; Stohr, P.; Dehne, H.; Teller, J.; Kranz, L.; Luthardt, H.; Roethling, T.; Kaestner A. (VEB Chemiekombinat Bitterfeld), Ger. (East) DD 258, 168 (Cl. AO1N43/78), 13 Jul 1988, Appl. 300, 359, 02 Mar 1987; Chem. Abstr., **1989**, *111*, 2681g.