The Hantzsch Thiazole Synthesis under Acidic Conditions: Change of Regioselectivity

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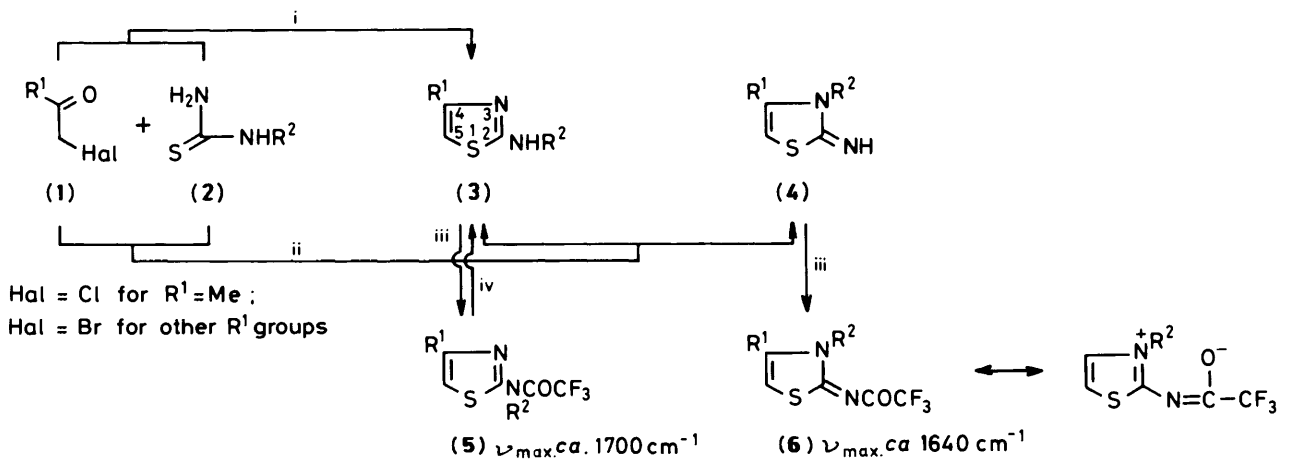
The condensation of α-halogeno ketones with *N*-monosubstituted thioureas *in neutral solvent* leads exclusively to 2-(*N*-substituted amino)thiazoles. In the present work it was shown that *under acidic conditions* mixtures of 2-(*N*-substituted amino)thiazoles and 3-substituted 2-imino-2,3-dihydrothiazoles are formed. (The isomers were distinguished by characteristic differences between their 5-H ^{1}H n.m.r. signals and the i.r. CO bands of their trifluoroacetate derivatives.) The proportions of the 2-imino-2,3-dihydrothiazoles in the mixtures are influenced by experimental features and by the structures of the starting materials. Reactions in 10M-HCl–EtOH (1:2) at 80 °C for 20 min were found to be the most efficient for generating 2-imino-2,3-dihydrothiazoles; in the most favourable case 2-imino-3,4-dimethyl-2,3-dihydrothiazole was obtained in 73% yield.

A possible explanation of the results is discussed.

The Hantzsch thiazole synthesis originated in the formulation[1] of 'rhodan propimin'[2] as 2-amino-4-methylthiazole, and the preparation[3] of this compound from chloroacetone and thiourea. Basification of the salt formed by methylating 2-amino-4-methylthiazole gave a base[1] which was isomeric with that[3] formed by condensing chloroacetone with *N*-methylthiourea; in showing that the former is 2-imino-3,4-dimethyl-2,3-dihydrothiazole and the latter 4-methyl-2-methylaminothiazole Traumann[3] made a fundamental observation about the orientation of substituents in thiazoles obtained by the Hantzsch synthesis. Subsequently[4] numerous α-halogeno ketones (**1**) have been treated with *N*-monosubstituted thioureas (**2**) *in neutral solvents* and, without exception, have given aminothiazoles (**3**) rather than iminodihydrothiazoles (**4**) (Scheme 1). (The evidence adduced for a contrary view[5] is unsatisfactory; whereas for some products, *e.g.* 2-anilino-4-arylthiazoles,[6] the structures have been rigorously established by independent syntheses based on 4-aryl-2-bromothiazoles.) There appears to have been only one instance[7] of a condensation *under acidic conditions*. Chloroacetone and *N*-phenylthiourea were heated

Scheme 1. Reactions of α-halogeno ketones with *N*-monosubstituted thioureas



Reagents: i, Me_2CO–$MgSO_4$, heat; ii, 10M-HCl–EtOH (1:2), 20 min at 80 °C; iii, $(CF_3CO)_2O$–PhMe, 20 °C; iv, EtOH, heat

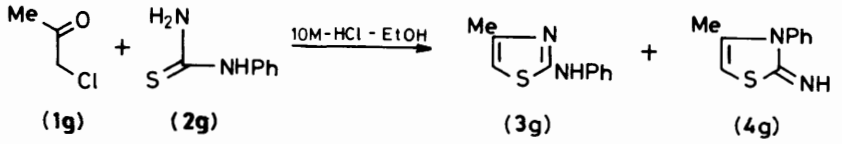
Results:

(1) + (2) $\xrightarrow{i}$ (**3a**—**k**), yields 85—95%
(1) + (2) $\xrightarrow{ii}$ mixtures of (**3a**—**k**) + (**4a**—**k**), combined yields 82—94%

	R¹	R²	Proportion (%) of (4) in mixtures
a;	Me	Me	80
b;	Pr^i	Me	65
c;	Bu^t	Me	45
d;	Ph	Me	69
e;	C_6H_4F-*p*	Me	64
f;	$C_6H_4NO_2$-*p*	Me	*ca.* 6
g;	Me	Ph	66
h;	Pr^i	Ph	20
i;	Ph	Ph	34
j;	C_6H_4F-*p*	Ph	32
k;	$C_6H_4NO_2$-*p*	Ph	*ca.* 3

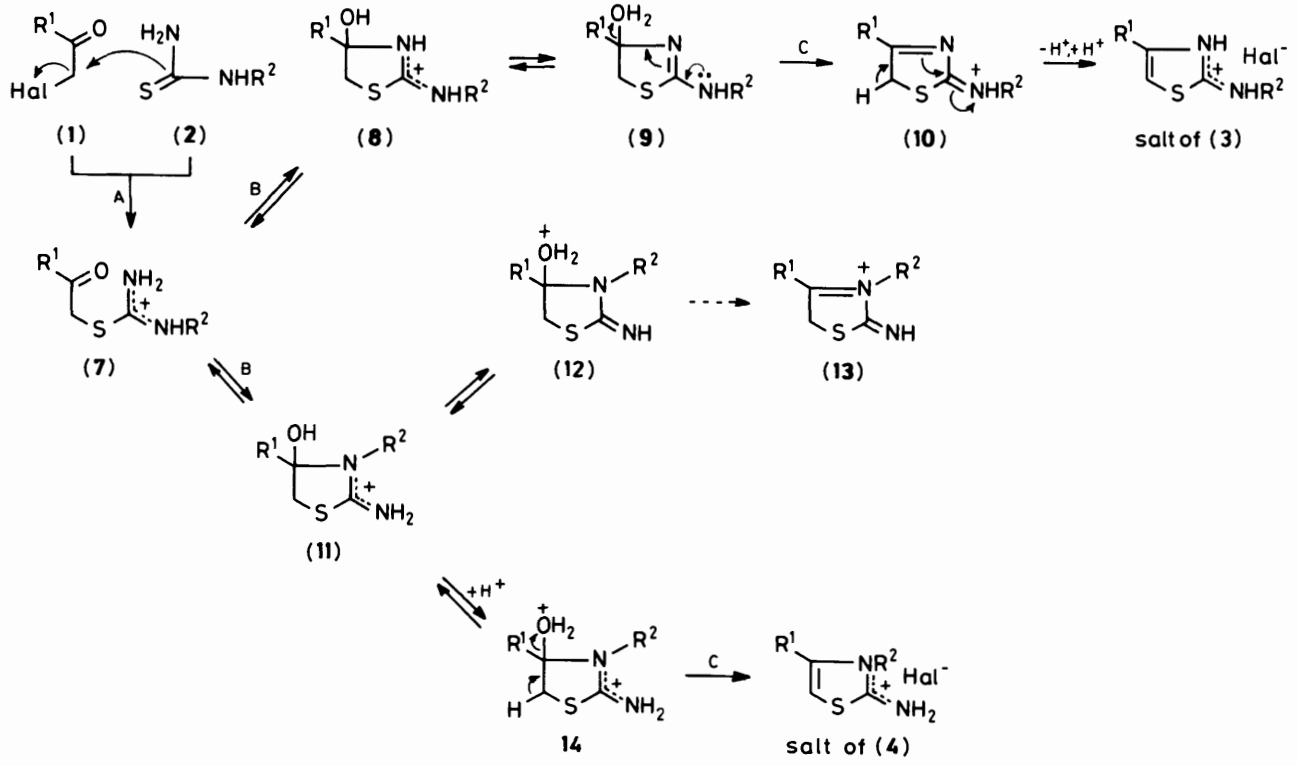
References to known compounds and the characterisations of known and new products are shown in Table 2 (Experimental section).

Table 1.

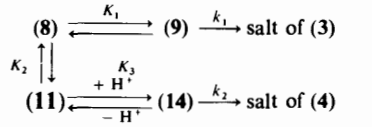


20 min at 80 °C			In 10M-HCl–EtOH (1:2) for 1 h	
10M-HCl–EtOH Ratio (by vol.)	Combined yield (%) (**3g**) + (**4g**)	Proportion (%) of (**4g**) in mixture	Temp. (°C)	Proportion (%) of (**4g**) in mixture
1:10	90	27	25	6
1:5	93	39	50	33
1:2	93	66	65	50
1:1	84	62	80	66
			90	61

Scheme 2. Suggested routes for formation of aminothiazoles (**3**) and iminodihydrothiazoles (**4**)



Simplified kinetic form based on assumption that rate constants of reactions (**9**) ⟶ (**8**) and (**14**) ⟶ (**11**) are much bigger than k_1 and k_2 respectively



$$\frac{\text{Rate of formation of (3)}}{\text{Rate of formation of (4)}} = \frac{k_1K_1K_2[H^+]}{k_2K_3}$$

in ethanolic hydrochloric acid; the solid (amount unspecified) which separated on cooling was represented, apparently soundly, as the hydrochloride of 2-imino-4-methyl-3-phenyl-2,3-dihydrothiazole (**4g**). The purpose of the present work was to examine this report and to study a range of Hantzsch reactions under acidic conditions.

Some general features which facilitated the investigation are as follows. The 5-H signals (δ *ca.* 6) of the aminothiazole (**3**)—iminodihydrothiazole (**4**) pairs differ by *ca.* 0.8 δ units, the resonances of the more aromatic aminothiazole systems being at lower field. Although several iminodihydrothiazoles were difficult to obtain in well-crystalline form and, therefore, were not fully purified, both the iminodihydrothiazoles and the aminothiazoles were readily characterised as their trifluoroacetates (**5**) and (**6**) which provide a second (i.r.) method for structural differentiation (Scheme 1). In the iminodihydro-

thiazole trifluoroacetates (**6**) the strong mesomeric effect operating to restore aromaticity leads to low CO wavenumbers; conversely in the aminothiazole derivatives (**5**), which were crystallised from non-hydroxylic solvents, the much higher double bond character is associated with easy nucleophilic displacement of the trifluoroacetyl group. [The trifluoroacetylation of 2-methylaminothiazoles in boiling chloroform was known to give derivatives of structure (**5**) but in some cases appreciable amounts of by-products resulting from reaction at the *endo-N* were formed.[8] Under the milder conditions used here the reactions were cleaner and afforded the *exo-N* products (**5**) more efficiently.]

The reactions between chloroacetone and *N*-phenylthiourea were studied in detail. Heating in acetone gave only the aminothiazole (**3g**) (95%). Mixtures of products (**3g**) and (**4g**) were formed in ethanolic solutions containing various acids; of these none was better than hydrochloric acid for generating the iminodihydrothiazole (**4g**). The duration and temperature of the reaction and the concentration of hydrochloric acid were varied (Table 1). With 10M-HCl–EtOH ratios greater than 1:5 the reactions were complete within 1.5 h at 20 °C and 20 min at 80 °C. Increasing acid concentration (in runs of 20 min at 80 °C) favoured the iminodihydrothiazole but with a 10M-HCl–EtOH ratio greater than 1:2 the total yield and the proportion of the iminodihydrothiazole decreased. At a fixed acid concentration the proportion of the iminodihydrothiazole varied with the temperature, and reached a maximum at 80 °C. These results indicate that the iminodihydrothiazole (**4g**) decomposes slowly in very strong acid at 80 °C and in strong acid at higher temperatures. (The temperature effect accounts for the erratic results of some early experiments in which solutions were made up at room temperature and then heated to various temperatures.) Throughout the rest of the work the following procedure was adopted: the thiourea (**2**) and then the halogeno ketone (**1**) were added rapidly to a vigorously stirred mixture of 10M-HCl–EtOH (1:2) pre-heated to 80 °C, and after 20 min at this temperature the mixture was cooled quickly and basified.

As a preliminary it was established that the products from *N*-methyl- and *N*-phenyl-thiourea and a variety of α-halogeno ketones in a neutral medium consisted entirely of aminothiazoles (**3**) (Scheme 2). However, the standard acidic conditions led efficiently to mixtures in which the relative proportions of the aminothiazoles (**3**) and the iminodihydrothiazoles (**4**) varied widely. {The salts of the iminodihydrothiazoles are generally less soluble than those of the aminothiazoles, and in favourable cases the former can be obtained conveniently by cooling the acidic solutions. Isolation of 4-methyl-3-phenyl-2,3-dihydrothiazole hydrochloride [(**4g**)·HCl] in this way confirms the earlier work.[7]} From the results it transpires that the proportion of the iminodihydrothiazole decreases as the *N*-substituent (R^2) in the thiourea (**2**) changes from methyl to phenyl, the size of the aliphatic (R^1) group in the halogeno ketones increases, and the carbonyl group of the aromatic halogeno ketones becomes more electrophilic.

A report[9] that the iminodihydrothiazole (**4g**) isomerises to the aminothiazole (**3g**) on treatment with hydrochloric acid conflicts with the present results. Three pairs of products (**3d, g, j**) and (**4d, g, j**) were therefore subjected to the acidic preparative conditions. Each compound was recovered unchanged. Thus there is no interconversion of products and the present results do not arise from an interplay of kinetic *versus* thermodynamic control. A possible interpretation, outlined in Scheme 2, was developed by considering first the path by which the aminothiazole (**3**) is formed. Although mechanistic details remain obscure the Hantzsch synthesis is known[10,11] to involve a sequence of three stages which are incorporated into Scheme 2 as nucleophilic displacement of halogen by sulphur (A), cyclisation (B), and dehydration (C). (Some conversions represented as single steps may consist of more than one reaction. For example stage B could proceed by deprotonation, addition to the carbonyl group, and reprotonation.) Work on related systems[12] suggests that open chain and cyclic intermediates such as (**7**) and (**8**) should be readily interconverted. When even a neutral solvent is used the medium becomes acidic since the overall effect is that the reactants (**1**) and (**2**) give the aminothiazole (**3**) plus 1 mol equiv. of hydrogen halide. That dehydration (stage C) occurs from a protonated intermediate is likely on general grounds and is supported by direct evidence. Intermediates of type (**8**) have been isolated in a few cases[11]; while they are very easily dehydrated to the salts of aminothiazoles the free bases derived from them are much less susceptible to dehydration. Proton transfer to an intermediate such as (**9**) probably precedes dehydration, which is represented as generating a 3,4- rather than a 4,5-double bond because the former process should be assisted by electron release from the *exo*-nitrogen.

It is proposed that the cyclic intermediates (**8**) and (**11**), which lead to the aminothiazole (**3**) and the iminodihydrothiazole (**4**) respectively, are formed in both the neutral solvent and the acidic media. Equilibration occurs *via* the open-chain form (**7**) and intermediate (**8**) predominates since the isomer (**11**) is destabilised by torsional strain (R^1, $OH \cdots R^2$). Although dehydration of intermediate (**9**), formed from its precursor (**8**) by proton transfer under the weakly acidic conditions generated in a neutral solvent, occurs readily, dehydration of the similar intermediate (**12**) is inhibited by the increased torsional strain ($R^1 \cdots R^2$) associated with the step (**12**) ⟶ (**13**). However, increasing the acidity of the medium is considered to generate a reactive dication, possibly with structure (**14**), in which the tendency for dehydration is further enhanced. Thus, loss of water and a proton, and formation of a 4,5-double bond leads directly to the stabilized system of the iminodihydrothiazole.

To obtain a simple kinetic expression for the relative rates of formation of the isomeric products assumptions have to be made; those in the lower part of Scheme 2 are reasonable possibilities. [If, for illustration only, the values $K_1 = 0.1$, $K_2 = 10$, and $K_3 = 0.1$ are used the condition for the formation of approximately equal amounts of the products (**3**) and (**4**) is that $k_2 = 30\ k_1$.] Increasing steric requirements of R^1 (Me to Bu^t) and/or R^2 (Me to Ph) should lower k_2, thus accounting for the observed decreases in the proportions of the iminodihydrothiazoles (**4**). The similar outcome caused by electron-withdrawing groups in R^1 may originate from lower concentrations of the dication (**14**).

Experimental

Petroleum refers to light petroleum (dried and distilled; b.p. 100—120 °C). The following procedures (i)—(v) describing the preparation and examination of compounds (**3g**), (**4g**), (**5g**), and (**6g**) were used in the other series of compounds to furnish the results in Scheme 1 and those reported in the text. The results in Table 1 were obtained by experiments based on procedure (ii). The products which were purified and fully characterised are shown in Table 2. The iminodihydrothiazoles (**4b**) (5 H, δ 5.46), (**4c**) (δ 5.44), and (**4h**) (δ 5.48) were not fully purified, but were characterised as their trifluoroacetates (**6b**), (**6c**), and (**6h**); the iminodihydrothiazoles (**4f**) {5 H of [$(CD_3)_2SO$] solution, δ 6.48} and (**4k**) (δ 5.89), formed in low yield, were not isolated or converted into derivatives.

Reactions between Chloroacetone and N*-Phenylthiourea.*—(i) A solution of chloroacetone (1.52 g) in dry Me_2CO (15 ml) was added during 15 min to a stirred suspension of anhydrous $MgSO_4$ (1 g) in dry Me_2CO (15 ml) containing *N*-phenylthiourea (2.50 g) which was boiling under reflux. After 1 h the

Table 2. Characterisation of products

Compd.	M.p. (°C) or B.p.* (°C/mmHg) Found	Literature	δ(5-H) ($CDCl_3$)	$\nu_{max.}$ (cm^{-1}) (CCl_4)	Found (%) (Required) C	H	N
4-Methyl-2-methylaminothiazole (**3a**)	72—73 (petroleum)	71.5—72.5[a]	6.10				
2-Imino-3,4-dimethyl-2,3-dihydrothiazole (**4a**)	43—46 (EtOAc–C_6H_{12})	47.5[b]	5.45				
4-Methyl-2-(*N*-methyl)trifluoroacetamidothiazole (**5a**)	70—71 (petroleum)	69—70[c]		1 703			
3,4-Dimethyl-2-trifluoroacetylimino-2,3-dihydrothiazole (**6a**)	180—181 (MeOH)	174—175[c]		1 641			
4-*Isopropyl-2-methylaminothiazole* (**3b**) ($C_7H_{12}N_2S$)	124—126/16*		6.10		53.7 (53.8)	7.7 (7.7)	17.9 (17.9)
2-*Imino-4-isopropyl-3-methyl-2,3-dihydrothiazole hydrochloride* (**4b**)·HCl ($C_7H_{13}ClN_2S$)	262—264 (decomp.) (MeOH)		6.55		43.7 (43.6)	6.7 (6.8)	14.4 (14.5)
4-*Isopropyl-2-(N-methyl)trifluoroacetamidothiazole* (**5b**) ($C_9H_{11}F_3NOS$)	84—86 (EtOAc—petroleum)			1 701	42.9 (42.85)	4.4 (4.4)	11.0 (11.1)
4-*Isopropyl-3-methyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6b**) ($C_9H_{11}F_3N_2OS$)	195—197 (EtOAc–petroleum)			1 640	42.8 (42.85)	4.3 (4.4)	11.2 (11.1)
4-t-Butyl-2-methylaminothiazole (**3c**)	91—93 (MeOH–H_2O)	92—93[d]	6.08				
4-t-*Butyl-2-(N-methyl)trifluoroacetamidothiazole* (**5c**) ($C_{10}H_{13}F_3N_2OS$)	134—136 (EtOAc–petroleum)			1 699	45.3 (45.1)	4.8 (4.9)	10.5 (10.5)
4-t-*Butyl-3-methyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6c**) ($C_{10}H_{13}F_3N_2OS$)	136—138 (EtOAc–petroleum)			1 640	45.2 (45.1)	5.0 (4.9)	10.6 (10.5)
2-Methylamino-4-phenylthiazole (**3d**)	134—135 (MeOH–H_2O)	136—137[e]	6.70				
2-Imino-3-methyl-4-phenyl-2,3-dihydrothiazole (**4d**)	79—80 (EtOAc–C_6H_{12})	86[f]	5.75				
2-(N-*Methyl)trifluoroacetamido-4-phenylthiazole* (**5d**) ($C_{12}H_9F_3N_2OS$)	175—177 (EtOAc–petroleum)			1 697	50.0 (50.3)	3.4 (3.2)	9.7 (9.8)
3-*Methyl-4-phenyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6d**) ($C_{12}H_9F_3NOS$)	170—172 (EtOAc–petroleum)			1 638	50.2 (50.3)	3.5 (3.2)	9.7 (9.8)
4-(4-*Fluorophenyl*)-2-*methylaminothiazole* (**3e**) ($C_{10}H_9FN_2S$)	137—138 (MeOH–H_2O)		6.53		57.4 (57.7)	4.45 (4.4)	13.4 (13.45)
4-(4-*Fluorophenyl*)-2-*imino-3-methyl-2,3-dihydrothiazole* (**4e**) ($C_{10}H_9FN_2S$)	70—72 (C_6H_{12})		5.67		57.6 (57.7)	4.3 (4.4)	13.2 (13.45)
4-(4-*Fluorophenyl*)-2-(N-*methyl*)*trifluoroacetamidothiazole* (**5e**) ($C_{12}H_8F_4N_2OS$)	187—188 (EtOAc–petroleum)			1 698	47.5 (47.4)	2.5 (2.65)	9.3 (9.2)
4-(4-*Fluorophenyl*)-3-*methyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6e**) ($C_{12}H_8F_4N_2OS$)	195—196 (EtOAc–petroleum)			1 639	47.6 (47.4)	2.3 (2.65)	9.2 (9.2)
2-*Methylamino-4-(4-nitrophenyl)thiazole* (**3f**) ($C_{10}H_9N_3O_2S$)	183—185 (MeOH–H_2O)			7.38 [$(CD_3)_2SO$]	50.8 (51.05)	3.8 (3.9)	17.7 (17.9)
2-(N-*Methyl)trifluoroacetamido-4-(4-nitrophenyl)-thiazole* (**5f**) ($C_{12}H_8F_3N_3O_3S$)	158—159 (EtOAc–petroleum)			1 701	43.7 (43.5)	2.4 (2.4)	12.8 (12.7)
4-Methyl-2-phenylaminothiazole (**3g**)	86—87 (MeOH–H_2O)	88[g]	6.11				
2-Imino-4-methyl-3-phenyl-2,3-dihydrothiazole (**4g**)	84—85 (EtOAc–EtOH)	80,[h] 85—86[i]	5.55				
2-Imino-4-methyl-3-phenyl-2,3-dihydrothiazole hydrochloride (**4g**)·HCl	250—254 (decomp.) (EtOH)	253 (decomp.)[h]					
4-*Methyl-2-(N-phenyl)trifluoroacetamidothiazole* (**5g**) ($C_{12}H_9F_3N_2OS$)	143—144 (petroleum)			1 705	50.5 (50.3)	3.1 (3.2)	9.9 (9.8)
4-*Methyl-3-phenyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6g**) ($C_{12}H_9F_3N_2OS$)	196—198 (MeOH)			1 635	50.45 (50.3)	3.1 (3.2)	9.8 (9.8)
4-*Methyl-2-phenylimino-3-trifluoroacetyl-2,3-dihydrothiazole* ($C_{12}H_9F_3N_2OS$)	133—135 (petroleum)		6.21	1 640	50.1 (50.3)	3.0 (3.2)	9.7 (9.8)
4-*Isopropyl-2-phenylaminothiazole* (**3h**) ($C_{12}H_{14}N_2S$)	145—147/2*		6.13		65.8 (66.0)	6.6 (6.5)	12.7 (12.8)
4-*Isopropyl-2-(N-phenyl)trifluoroacetamidothiazole* (**5h**) ($C_{14}H_{13}F_3N_2OS$)	136—138 (EtOAc–petroleum)			1 704	53.6 (53.5)	4.2 (4.2)	8.8 (8.9)
4-*Isopropyl-3-phenyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6h**) ($C_{14}H_{13}F_3N_2OS$)	186—188 (MeOH)			1 641	53.8 (53.5)	4.4 (4.2)	8.9 (8.9)
4-Phenyl-2-phenylaminothiazole (**3i**)	136—137 (EtOH)	136[i]	6.82				
2-Imino-3,4-diphenyl-2,3-dihydrothiazole (**4i**)	109—111 (EtOAc)	111,[h] 84[j]	5.91				
4-*Phenyl-2-(N-phenyl)trifluoroacetamidothiazole* (**5i**) ($C_{17}H_{11}F_3N_2OS$)	219—220 (petroleum)			1 705	58.7 (58.6)	3.1 (3.2)	7.8 (8.0)
3,4-*Diphenyl-2-trifluoroacetylimino-2,3-dihydrothiazole* (**6i**) ($C_{17}H_{11}F_3N_2OS$)	221—222 (MeOH)			1 638	58.5 (58.6)	3.1 (3.2)	7.7 (8.0)
4-(4-Fluorophenyl)-2-phenylaminothiazole (**3j**)	111—112 (EtOH)	108—110[k]	6.78				
4-(4-*Fluorophenyl*)-2-*imino-3-phenyl-2,3-dihydrothiazole* (**4j**) ($C_{15}H_{11}FN_2S$)	142—143 (EtOAc–C_6H_{12})		5.88		66.8 (66.6)	3.9 (4.1)	10.6 (10.4)

Table 2 (*continued*)

Compd.	M.p. (°C) or B.p.* (°C/mmHg) Found	Literature	δ(5-H) ($CDCl_3$)	$\nu_{max.}$ (cm^{-1}) (CCl_4)	Found (%) (Required) C	H	N
4-(4-*Fluorophenyl*)-3-*phenyl*-2-*trifluoroacetyl*-*imino*-2,3-*dihydrothiazole* (**6j**) ($C_{17}H_{10}F_4N_2OS$)	200—201 (EtOH)			1 637	55.9 (55.7)	2.6 (2.75)	7.7 (7.65)
4-(4-Nitrophenyl)-2-phenylaminothiazole (**3k**)	206—208 (MeOH–H_2O)	202[l]	6.80				
4-(4-*Nitrophenyl*)-2-(N-*phenyl*)*trifluoroacet*-*amidothiazole* (**5k**) ($C_{17}H_{10}F_3N_3O_3S$)	186—188 (EtOAc–petroleum)			1 705	51.6 (51.9)	2.4 (2.6)	10.9 (10.7)

[a] R. Burtles, F. L. Pyman, and J. Roylance, *J. Chem. Soc.*, 1925, 581. [b] Ref. 3. [c] Ref. 8. [d] J. B. Dickey, E. B. Towne, and G. F. Wright, *J. Org. Chem.*, 1955, **20**, 499. [e] C. P. Joshua and P. N. Nambisan, *Indian J. Chem.*, 1973, **11**, 118. [f] Ref. 5. [g] I. Y. Postovski and I. B. Lundina, *Zh. Obshch. Khim.*, 1959, **29**, 608. [h] Ref. 7. [i] Ref. 9. [j] Ref. 6. [k] K. C. Joshi and S. Giri, *J. Indian Chem. Soc.*, 1962, **39**, 17. [l] M. V. Bhatt, B. H. Iyer, and P. C. Guha, *Curr. Sci.*, 1948, **17**, 298.

mixture was cooled, poured into brine (80 ml), and basified with 18M-NH_3. Extraction with EtOAc gave crude material (2.97 g; δ 6.11; no signal at δ 5.55). Crystallisation from MeOH–H_2O afforded the iminothiazole (**3g**), first crop (2.10 g), m.p. 86—87 °C, and second crop (0.72 g), m.p. 85—86 °C.

(ii) *N*-Phenylthiourea (2.62 g) and then a solution of chloroacetone (1.64 g) in 10M-HCl (3 ml)–EtOH (6 ml) were added to a mixture of 10M-HCl (5.5 ml)–EtOH (11 ml) which was stirred at 80 °C. After 20 min the solution was cooled quickly, poured into brine (60 ml), and basified with 18M-NH_3. Extraction with EtOAc gave crude material (3.10 g, signals at δ 6.11 and 5.55 with relative areas 1:1.95) which was chromatographed on neutral Al_2O_3 (150 g). Elution with $CHCl_3$ afforded the aminothiazole (**3g**) (0.98 g). Elution with $CHCl_3$–EtOH (11:1) gave the iminodihydrothiazole (**4g**) (1.94 g, m.p. 79—80 °C, after crystallisation from EtOAc–EtOH); δ 5.55.

(iii) The foregoing experiment was repeated using *N*-phenylthiourea (3.93 g), chloroacetone (2.46 g) in 10M-HCl (3 ml)–EtOH (6 ml), and 10M-HCl (3 ml)–EtOH (6 ml). The solution was heated for 20 min at 80 °C, then cooled slowly. The insoluble material was collected and crystallised from EtOH to give 4-methyl-3-phenyl-2,3-dihydrothiazole hydrochloride [(**4g**)·HCl] (2.07 g), m.p. 250—254 °C (decomp.). Basification with 18M-NH_3 and extraction with EtOAc afforded the iminodihydrothiazole (**4g**) (1.48 g).

(iv) A solution of the iminodihydrothiazole (**4g**) (1.52 g) in 10M-HCl (8 ml)–EtOH (16 ml) was stirred at 80 °C for 20 min. Work-up as in the foregoing experiment gave the starting material (**4g**) (1.46 g) identified by comparison with an authentic specimen. Similarly, the aminothiazole (**3g**) was unchanged (96% recovery).

(v) Trifluoroacetic anhydride (2.5 g) was added to a solution of the aminothiazole (**3g**) (1.05 g) in dry PhMe (15 ml) which was stirred at 20 °C. After 24 h the solution was poured into brine (50 ml)–$CHCl_3$ (50 ml), and the mixture was basified with 2M-$NaHCO_3$. Separation of the layers and extraction of the aqueous layer with more $CHCl_3$ gave, from the combined $CHCl_3$ layers, material (1.52 g) shown by ^1H n.m.r. examination to contain two products (9:1). Crystallisation from petroleum (35 ml) gave 4-*methyl*-2-*phenylimino*-3-*trifluoroacetyl*-2,3-*dihydrothiazole* (75 mg), m.p. 133—135 °C. The filtrate was concentrated (to *ca.* 15 ml) and cooled, and the insoluble material was collected and recrystallised from petroleum to give the *trifluoroacetylamidothiazole* (**5g**) (1.12 g), 143—144 °C. Similarly, the iminodihydrothiazole (**4g**) (1.15 g) gave, as the sole product, the *trifluoroacetyliminodihydrothiazole* (**6g**) (1.59 g), m.p. 196—198 °C, after crystallisation from petroleum. A solution of the trifluoroacetate (**5g**) in EtOH was boiled under reflux for 15 min. Dilution with water and cooling afforded the aminothiazole (**3g**). The trifluoroacetate (**6g**) was not affected by this treatment.

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