N'-Substituted *N*-Acyl- and *N*-Imidoyl-thioureas: Preparation and Conversion of *N',N'*-Disubstituted Compounds into 2-(*N,N*-Disubstituted Amino)thiazol-5-yl Ketones

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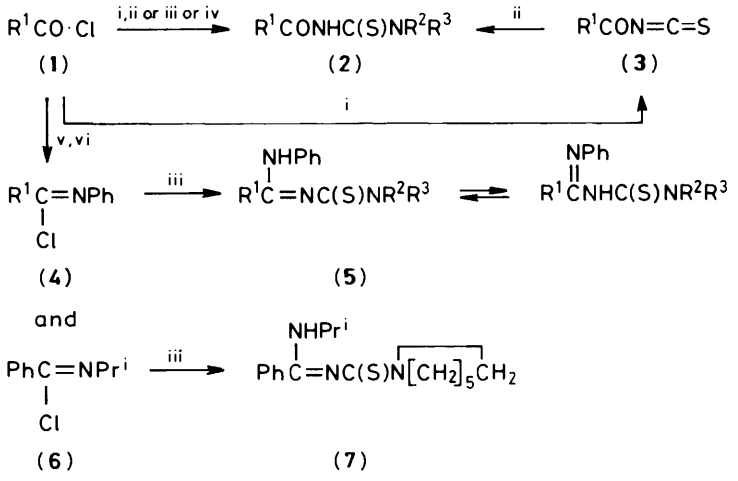
Known methods were developed to give convenient general procedures for preparing *N*-acyl-*N'*-mono- and -*N',N'*-disubstituted thioureas from acid chlorides, and related *N*-imidoyl thioureas from imidoyl chlorides. In the products from three acid chlorides and ammonium thiocyanate the acyl isothiocyanates did not appear to be accompanied by the isomeric thiocyanates.

Treatment of *N*-(anilino)benzylidene-*N',N'*-disubstituted thioureas with chloroacetone in the presence of triethylamine leads to 5-acetyl-4-phenyl-2-(*N,N*-disubstituted amino)thiazoles. In contrast, the corresponding *N*-benzoyl thioureas form only small amounts of these compounds; the main products are the 5-benzoyl-4-methyl isomers, and this unexpected outcome requires a revision of the literature. It is thought that formation of the 5-benzoyl-4-methylthiazoles involves N–C(4) fission of a cyclic intermediate to give an open-chain intermediate in which nucleophilic attack can occur at either the acetyl or the benzoyl group. One of the latter intermediates was generated directly from 2-acetyl-2-bromoacetophenone and *N*-methyl-*N*-phenylthiourea, and found to give the 5-benzoyl-4-methyl- and 5-acetyl-4-phenyl-thiazoles as the major and minor products, respectively.

The results in this report arise from a general investigation into the utilisation of *N'*-substituted *N*-acyl- and *N*-imidoyl-thioureas as starting materials in synthetic work. Initially, convenient methods for preparing a range of these substrates were established; the methods and the compounds are described here.

The second part of this paper is an account of further studies on, and a mechanistic interpretation of, a particular topic (already outlined[1]) involving some of these materials, *viz.*, the unexpected outcome of preparing thiazoles from *N',N'*-disubstituted *N*-benzoylthioureas and chloroacetone.

Scheme 1. Preparation of *N'*-substituted *N*-acyl- and *N*-imidoyl-thioureas



Reagents: i, NH_4SCN–Me_2CO, 40 °C; ii, R^2R^3NH–Me_2CO, 20 °C; iii, $Pb(SCN)_2$–PhMe, 80 °C, then R^2R^3NH–PhMe, 50 °C; iv, KSCN–MeCN, 5 °C, then R^2R^3NH–MeCN, 20 °C; v, $PhNH_2$ (or Pr^iNH_2)–Et_2O, 20 °C; vi, PCl_5, 90 °C.

R^1	R^2	R^3	R^2,R^3
A; Ph	**a**; H	Me	**h**; $CH_2CH(Me)$
B; C_6H_4OMe-*p*	**b**; H	Bu^t	**i**; $[CH_2]_3$
C; C_6H_4Cl-*p*	**c**; H	Ph	**j**; $[CH_2]_4$
D; $C_6H_4NO_2$-*p*	**d**; H	PhCH(Me)	**k**; $[CH_2]_5$
E; 2-Thienyl	**e**; Me	Me	**l**; $[CH_2]_2O[CH_2]_2$
F; Me	**f**; Me	Ph	**m**; $[CH_2]_6$
G; Bu^t	**g**; Me	$PhCH_2$	

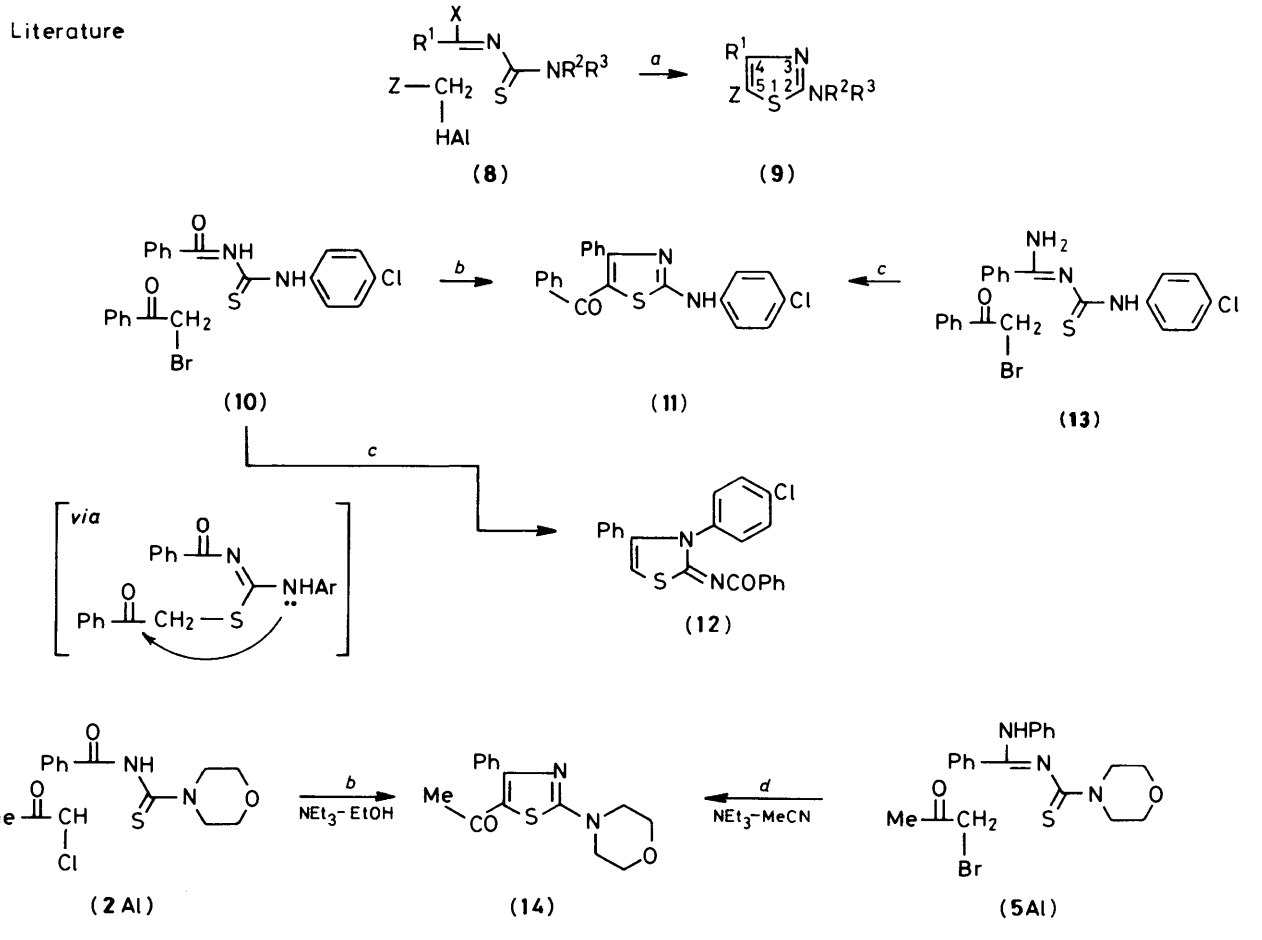
Compounds prepared (References are given to known compounds; the rest are new) **(2Aa)**,[4b] **(2Ab)**, **(2Ad)**, **(2Ae)**, **(2Af)**,[5] **(2Aj)**, **(2Ak)**, **(2Al)**,[15] **(2Am)**, **(2Be)**, **(2Bf)**, **(2Bl)**, **(2Cf)**, **(2Cl)**, **(2Dd)**, **(2Df)**, **(2Dl)**, **(2Eb)**, **(2Ed)**, **(2Ef)**, **(2Eg)**, **(2Eh)**, **(2Ei)**, **(2Ej)**, **(2Ek)**, **(2Em)**, **(2Fc)**,[2a] **(2Ff)**, **(2Fm)**, **(2Gd)**, **(2Ge)**, **(2Gf)**, **(2Gl)**, **(3A)**,[4b] **(3E)**, **(3G)**,[3] **(4A)**,[12a] **(4B)**,[12b] **(4C)**,[12c] **(4E)**, **(4G)**, **(5Af)**, **(5Al)**,[7] **(5Bf)**, **(5Cf)**, **(5El)**, **(5Gm)**, **(6)**,[10] **(7)**.

The original method for converting acid chlorides into acyl isothiocyanates, lead(II) thiocyanate in benzene,[2] is effective with many structural types.[3] Variations include the use of potassium[4a] or ammonium[5] thiocyanate in acetonitrile or acetone, and sodium thiocyanate in either of these solvents has been employed[6] for the corresponding reaction of imidoyl chlorides. Although the reaction of an amine with an acyl isothiocyanate may involve competition between nucleophilic attack at the carbonyl function and addition to the isothiocyanate group,[2a,4b] the latter generally predominates in non-polar solvents and *N*-acyl thioureas are formed. Similarly, imidoyl isothiocyanates afford *N*-imidoyl thioureas.[6,7]

Of the methods described for converting benzoyl chloride into *N*-benzoyl-*N'*-phenylthiourea the 'one-pot' technique[8] (with ammonium thiocyanate, then aniline, in acetone) appeared the most convenient. A simple procedure based on this was used to prepare all the acylthioureas (**2**) in Scheme 1 apart from those with R^1 = Ac or $C_6H_4NO_2$-*p*, and those with $R^2 = R^3$ = Me. Yields were high (79—89%) except for *N*-benzoyl-*N'*-methyl-thiourea (**2Aa**) (53%) which was formed by adding methylamine to benzoyl isothiocyanate at −2 °C. The unsatisfactory outcome of attempts to generate acetyl isothiocyanate in acetone was not unexpected;[4a,9] that of reactions between dimethylamine and acyl isothiocyanates stems from the marked tendency of this amine to form *N,N*-dimethylamides from solutions of the isothiocyanates in acetone. It was thought that both problems might be overcome by resorting to the original (lead thiocyanate) procedure and, as adumbrated in the early work,[2a] by adding the amines at a higher temperature. Under the conditions shown in Scheme 1 (but with the first stage at 60 °C for acetyl chloride and the second at 40 °C for dimethylamine) the six compounds of formula (**2**) with R^1 = Ac or $R^2 = R^3$ = Me were obtained in yields of 76—81%. Neither of the foregoing methods was suitable for preparative work with the very reactive *p*-nitrobenzoyl system ($R^1 = C_6H_4NO_2$-*p*). This isothiocyanate was generated more satisfactorily using potassium thiocyanate in acetonitrile at low temperature, but while the products (**2D**) from three 'favourable' amines were formed in *ca.* 60% yield the reactions with methylamine and dimethylamine led almost entirely to amides.

Although many imidoyl chlorides have been involved in, for example, kinetic[10] and spectrometric[11] studies it is difficult to find details of their preparations elsewhere than in the very early work,[12] and there did not appear to be a clear account of a general preparative procedure. A simple method was therefore devised, and used to give the imidoyl chlorides (**4A**, **B**, **C**, **E**, and **G**) and (**6**) in *ca.* 90% yield. These were converted into substituted thioureas efficiently (*ca.* 80% yield) by the lead thiocyanate technique. Other methods were not studied; it may well be that the sodium thiocyanate procedures[6] would be equally successful. [Although the products (**5**) and (**7**) are represented in the Schemes as containing the ·C(NHR):N·CS· system there is the possibility of tautomerism involving the

Scheme 2. Preparation of 2-(*N*-substituted amino)thiazol-5-yl ketones



[a] Ref. 14a. [b] Ref. 15. [c] Ref. 14b [d] Ref. 7

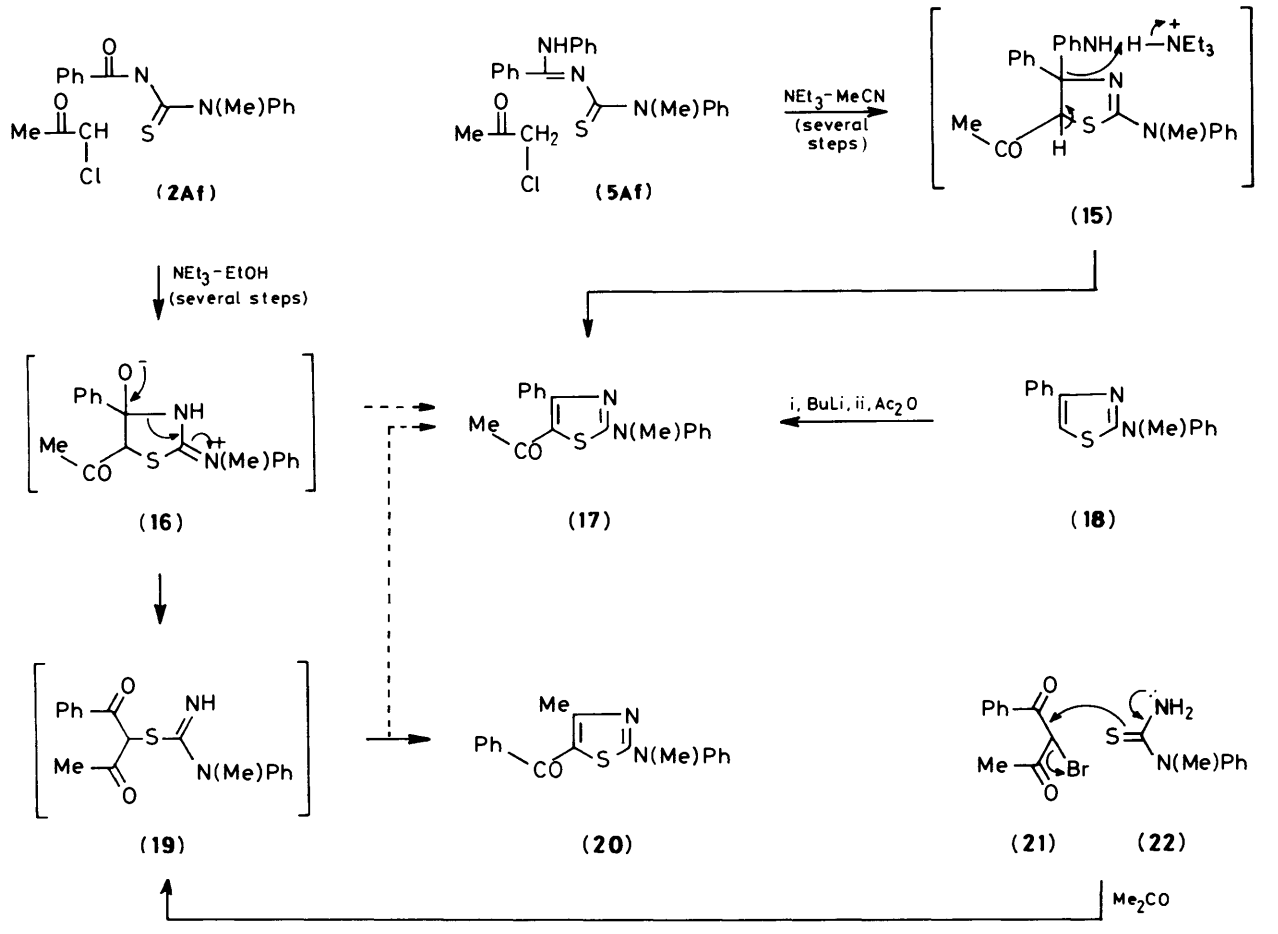
prototropic equilibrium shown in Scheme 2. This topic will be included in a later paper dealing with the spectrometric features of substituted thioureas.]

A point concerning the course of the reactions between acid chlorides and thiocyanate anions was also investigated. Dixon and Hawthorne[2] were the first to establish that the products isolated are isothiocyanates rather than thiocyanates, and it is generally accepted that the former are produced exclusively. However, with potassium thiocyanate in acetone ethoxy- and butoxy-carbonyl chloride are reported[9] to give thiocyanates and isothiocyanates in approximately equal amounts; although the thiocyanates can be distilled unchanged they isomerise to the isothiocyanates on contact with thiocyanate anions. The reactions of three acid chlorides (Scheme 1; R^1 = Ph, 2-Thienyl, and Bu^t) with ammonium thiocyanate were studied in detail. Under the standard conditions the acyl isothiocyanates (**3**) were formed in high yield, and characterised by strong bifurcated i.r. bands near 1 960 cm^{-1} (N=C=S). In a series of experiments the temperature and the proportions of the reactants were varied, and the usual procedure of adding the acid chloride to ammonium thiocyanate was reversed. The i.r. spectra of the total products showed no evidence for the presence of acyl thiocyanates, which may be expected[9] to have medium-intensity or weak bands at *ca.* 2 170 cm^{-1}. These results indicate either that isothiocyanates are the sole products or that isomerisation occurs much more easily with acyl thiocyanates than with the alkyloxycarbonyl analogues.[9]

2-(*N*,*N*-Disubstituted amino)thiazol-5-yl ketones were

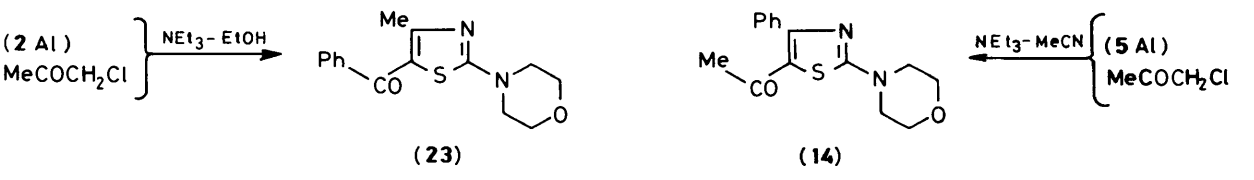
Scheme 3. Preparation of 2-(*N*,*N*-disubstituted amino)thiazol-5-yl ketones

Present results



Spectrometric comparison:

	(17)	(20)
m/z (abundance)	308 (M^+, 100), 293 (69), 43 (43)	308 (M^+, 100), 105 (43), 77 (69)
n.m.r. ($CDCl_3$)	δ_H 1.98 (s, MeCO)	2.41 (s, 4-Me)
	δ_C 158.5 (t, *J* 3.8 Hz, C-4), 190.5 [q, *J* 6.1 Hz, C(O)]	160.1 (q, *J* 6.8 Hz, C-4), 188.0 [t, *J* 3.6 Hz, C(O)]



required for structural studies.[13] It appeared that these could be obtained conveniently by the general approach[14a] (Scheme 2) in which the ends of a C–N–C–S chain [in formula (**8**)] are joined to a reactive methylene group, the carbon of the latter becoming C-5 of the thiazole system (**9**). In two applications 2-aminothiazol-5-yl ketones were reported as the products from condensations of *N*-benzoylthioureas,[15] such as (**10**) and (**2Al**), and of *N*-(α-anilino)benzylidenethioureas,[7] such as (**5Al**), with α-halogenoketones in the presence of triethylamine. Later it emerged[14b] that although the *N*-(α-amino)benzylidene-*N'*-monosubstituted thiourea (**13**) does give the thiazole (**11**) the reaction of the *N*-benzoyl-*N'*-monosubstituted thiourea (**10**) takes a different course and leads to the 2-benzoylimino-2,3-dihydrothiazole (**12**). Notwithstanding this complication no question has been raised hitherto about the nature of the products from *N',N'*-disubstituted thioureas [*e.g.* that the thiazole of structure (**14**) is formed from both the starting materials (**2Al**) and (**5Al**)].

In the present work (Scheme 3) the *N*-benzoylthiourea (**2Af**) was condensed with chloroacetone in the presence of triethylamine. Surprisingly, the product (65% yield after purification) was different from, but isomeric with, that obtained (in 78% yield) from the corresponding reaction of the *N*-(α-anilino)benzylidenethiourea (**5Af**). The major fragmentation peaks in the mass spectrum (Scheme 3) of the latter product correspond to $(M - Me)^+$ and Ac^+ ions, and those of the former to $PhCO^+$ and Ph^+ ions; further, the form and C–H coupling constants of the ^{13}C n.m.r. signals logically ascribed to the C-4 and C(O) atoms reveal the number of protons α and β to these centres. Thus, the *N*-(α-anilino)benzylidenethiourea (**5Af**) gives the 5-acetyl compound (**17**) but the unexpected isomer, the 5-benzoyl compound (**20**), is formed from the *N*-benzoylthiourea (**2Af**). These structures were confirmed by an unambiguous synthesis[13a] of the 5-acetyl isomer (**17**) from the parent thiazole (**18**), and a crystallographic examination[13b] of the 5-benzoyl product (**20**).

The 'rearrangement' (**2Af**)⟶(**20**), which occurs in the presence of 2 mol equiv. of triethylamine, is thought to proceed as portrayed in Scheme 3. Nucleophilic substitution[16] of chloroacetone by the sulphur of the thiourea (**2Af**) followed by an aldol condensation gives the intermediate (**16**), dehydration of which would lead to the 5-acetylthiazole (**17**). However, such a dehydration should be acid-catalysed[17] and, therefore, slower here than under the conditions of the standard Hantzsch thiazole synthesis. The alternative process involving fission of the N–C(4) bond supervenes, giving an open-chain intermediate (**19**) which provides the opportunity for subsequent ring closure at either carbonyl group. Reaction at the more electrophilic acetyl group predominates, and slow dehydration of the intermediate so formed leads to the 5-benzoyl isomer (**20**). This interpretation was supported by a second synthesis of the benzoyl isomer, from the bromodiketone (**21**) and *N*-methyl-*N*-phenylthiourea (**22**), in which the first step generates the intermediate (**19**). Careful examination of the total products showed that, as expected, the 5-benzoyl compound (**20**) is accompanied by the 5-acetyl isomer (**17**) as the minor product in both sequences. The ratios of the isomers are not the same [(**20**):(**17**) = 10:1 from (**2Af**), and 3:1 from (**21**) + (**22**)]; this difference will be discussed when studies of analogous systems are complete. [Conversion of an entity such as the intermediate (**16**) into a mixture of benzoyl and acetyl isomers, with the former predominating, by the mechanism in Scheme 3 closely parallels transformations[18] in the isoquinoline field, and there is also similarity to work[19] on the isomerisation of 2-acetylimino-3-phenacylthiazolidine.*]. In contrast, the *N*-benzimidoylthiourea (**5Af**) forms only the 5-acetyl isomer (**17**). Several factors may contribute to this difference but the salient feature is probably that the loss of aniline to form an early intermediate such as (**15**) is much faster than dehydration of the intermediate (**16**). The cyclic system (**15**), once formed, is thereby converted rapidly into the related thiazole (**17**).

Although it was thought[7] that the product from the *N*-(α-anilino)benzylidenethiourea (**5Al**) was identical with the compound obtained previously[15] from the *N*-benzoylthioureas (**2Al**) comparison of the experimental details argues against this: the melting points are 204 °C[7] and 150—153 °C.[15] Repetition of the work confirmed that the *N*-(α-anilino)benzylidenethiourea (**5Al**) gives a single product correctly formulated as the 5-acetyl compound (**14**). The main product from the *N*-benzoylthiourea (**2Al**) is, however, the 5-benzoyl compound (**23**) and this is accompanied by a small amount (12%) of the 5-acetyl isomer (**14**).

Experimental

N.m.r., i.r., and u.v. spectra were recorded using solutions in $CDCl_3$, CCl_4, and EtOH, respectively. The i.r. spectra were obtained at a spectral slit-width of 1.5 cm^{-1}, the routine δ_H values at 90 MHz, and the δ_H and δ_C values of compounds (**17**) and (**20**) at 300 and 62.9 MHz, respectively. Me_2CO was stored over $CaCl_2$, and PhMe over Na; MeCN was distilled from P_2O_5. The metal cyanates were dried at 80 °C; immediately before use they were mixed with dry C_6H_6 and the solvent was removed at 80 °C/15 mmHg. The amines (except $MeNH_2$) were distilled, and stored over molecular sieves (previously heated at 100 °C/0.1 mmHg); $MeNH_2$ was passed through a vertical tube packed with KOH before being introduced into the reaction vessel. Light petroleum refers to the fraction, b.p. 80—100 °C, which was dried over Na and distilled.

Compounds (**2**)—(**7**) *in Scheme 1.*—The general procedures are illustrated by examples. Compounds (**2**), (**5**), and (**7**) are described first; these are followed by compounds (**3**), (**4**), and (**6**). Compounds (**2Ae**), (**2Be**), (**2Fc**), (**2Ff**), (**2Fm**), and (**2Ge**), all those of structure (**5**), and compound (**7**) were prepared using $Pb(SCN)_2$. Compounds (**2D**) were prepared using KCNS. All the other compounds of structure (**2**) were prepared using NH_4SCN.

Compounds (**2**) *using* NH_4SCN. *Example:* N-*Benzoyl*-N'-*t-butylthiourea* (**2Ab**).—A solution of PhCOCl (7.12 g) in Me_2CO (25 ml) was added during 15 min to a stirred solution of NH_4SCN (3.85 g) in Me_2CO (25 ml) at 40 °C. The mixture was stirred at 40 °C for a further 30 min and then cooled to 20 °C. A solution of Bu^tNH_2 (3.70 g) in Me_2SO (25 ml) was added during 15 min, stirring was continued for 2 h, and the mixture was poured into ice–water (150 ml). The material isolated with $CHCl_3$ was triturated with petroleum, collected, and crystallised from EtOH to give the *product* (10.61 g).

In the preparation of compound (**2Aa**) the mixture was kept at −2 °C while $MeNH_2$ (excess) was introduced as a gaseous stream.

Compounds (**2D**) *using* KSCN. *Example:* 4-[N-(*p-Nitrobenzoyl*)*thiocarbamoyl*]*morpholine* (**2Dl**).—A solution of *p*-nitrobenzoyl chloride (9.28 g) in MeCN (15 ml) was added during 15 min to a stirred solution of KSCN (5.82 g) in MeCN (100 ml) at 5 °C. After 45 min the mixture was filtered, and the filtrate was stirred at 20 °C. A solution of morpholine (4.35 g) in MeCN (10 ml) was added during 10 min, stirring was continued for 30 min, and the mixture was poured into brine (150 ml). The insoluble material was collected, dried, and crystallised from MeCN to give the *product* (8.92 g).

* We are grateful to Professor G. W. Kirby and to Dr. P. J. Taylor for bringing these points to our attention after the appearance of the preliminary publication (ref. 1).

Compounds (**2**), (**5**), *and* (**7**) *using* $Pb(SCN)_2$. *Example:* 4-[*Anilino*(2-*thienyl*)*methylenethiocarbamoyl*]*morpholine* (**5El**).—A solution of *N*-phenylthiophen-2-imidoyl chloride (**4E**) (3.80 g) in PhMe (10 ml) was added during 15 min to a suspension of $Pb(SCN)_2$ (3.21 g) in PhMe (35 ml) which was stirred vigorously (Hershberg stirrer) at 80 °C. After a further 40 min the mixture was filtered and the filtrate was stirred (magnetically) at 50 °C. A solution of morpholine (1.47 g) in PhMe (15 ml) was added during 20 min, and stirring was continued for 30 min at 50 °C. The heating bath was removed, the solution was stirred for a further 1 h, and the solvent was evaporated at 80 °C/15 mmHg. The residue was triturated with petroleum, collected, and crystallised from MeOH to give the *product* (4.36 g).

The first stage was carried out at 60 °C with acetyl chloride, and the second stage was carried out at 40 °C with dimethylamine.

Products (**2**), (**5**), *and* (**7**).—In the following list an abbreviated form is used. Thus, a full entry such as N-*benzoyl*-N′-*t-butylthiourea* (**2Ab**) (yield 89%), m.p. 125—126 °C (from EtOH) (Found: C, 60.9; H, 6.6; N, 12.0. $C_{12}H_{16}N_2OS$ requires C, 61.0; H, 6.8; N, 11.9%) is shortened to (**2AB**) (89), m.p. 125—126 (EtOH) (60.9, 6.6, 12.0. $C_{12}H_{16}N_2OS$, 61.0, 6.8, 11.9).

N-Benzoyl-*N*′-methylthiourea (**2Aa**) (53), m.p. 148—149 (MeOH) (lit.,[4b] 149—150). N-*Benzoyl*-N′-*butylthiourea* (**2Ab**) (89), m.p. 125—126 (EtOH) (60.9, 6.6, 12.0. $C_{12}H_{16}N_2OS$, 61.0, 6.8, 11.9). N-*Benzoyl*-N′-(1-*methylbenzyl*)*thiourea* (**2Ad**) (85), m.p. 78—79 (Pr^{i}OH) (67.7, 5.6, 9.7. $C_{16}H_{16}N_2OS$, 67.6, 5.6, 9.9). N-*Benzoyl*-N′,N′-*dimethylthiourea* (**2Ae**) (78), m.p. 134—135 (MeOH) (57.6, 5.9, 13.4. $C_{10}H_{12}N_2OS$, 57.7, 5.8, 13.5). *N*-Benzoyl-*N*′-methyl-*N*′-phenylthiourea (**2Af**) (84), m.p. 139—140 (MeOH) (lit.,[5] 138—139). 1-(N-*Benzoylthiocarbamoyl*)*pyrrolidine* (**2Aj**) (87), m.p. 123—124 (EtOH) (61.4, 6.0, 11.8. $C_{12}H_{14}N_2OS$, 61.5, 6.0, 12.0). 1-(N-*Benzoylthiocarbamoyl*)-*piperidine* (**2Ak**) (82), m.p. 122—123 (EtOH) (62.8, 6.5, 11.3. $C_{13}H_{16}N_2OS$, 62.9, 6.5, 11.3). 4-(*N*-Benzoylthiocarbamoyl)-morpholine (**2Al**) (88), m.p. 123—124 (EtOH) (reported[15] but not characterised) (57.4, 5.6, 11.3. Calc. for $C_{12}H_{14}N_2O_2S$: 57.6, 5.6, 11.2). 1-(N-Benzoylthiocarbamoyl)hexahydroazepine (**2Am**) (82), m.p. 95—96 (Pr^{i}OH) (64.0, 6.9, 10.5. $C_{14}H_{18}N_2OS$, 64.1, 6.9, 10.7). N-(p-*Methoxybenzoyl*)-N′,N′-*dimethylthiourea* (**2Be**) (76), m.p. 121—122 (Pr^{i}OH) (55.4, 5.9, 11.6. $C_{11}H_{14}N_2O_2S$, 55.5, 5.9, 11.8). N-(p-*Methoxybenzoyl*)-N′-*methyl*-N′-*phenylthiourea* (**2Bf**) (87), m.p. 122—123 (Pr^{i}OH) (64.1, 5.4, 9.2. $C_{16}H_{16}N_2O_2S$, 64.0, 5.4, 9.3). 4-N-(p-*Methoxybenzoyl*)-*thiocarbamoyl*]*morpholine* (**2Bl**) (86), m.p. 171—173 (EtOH) (55.75, 5.8, 10.0. $C_{13}H_{16}N_2O_3S$, 55.7, 5.8, 9.9). N-(p-*Chlorobenzoyl*)-N′-*phenylthiourea* (**2Cf**) (83), m.p. 129—131 (Pr^{i}OH) (59.1, 4.1, 9.3. $C_{15}H_{13}ClN_2OS$, 59.1, 4.3, 9.2). 4-[N-(p-*Chlorobenzoyl*)*thiocarbamoyl*]*morpholine* (**2Cl**) (89), m.p. 153—154 (EtOH) (50.4, 4.6, 9.7. $C_{12}H_{13}ClN_2O_2S$, 50.6, 4.6, 9.8). N-(1-*Methylbenzyl*)-N′-(p-*nitrobenzoyl*)*thiourea* (**2Dd**) (58), m.p. 108—109 (EtOH) (58.4, 4.6, 12.65. $C_{16}H_{15}N_3O_3S$, 58.3, 4.6, 12.8). N-*Methyl*-N-*phenyl*-N′-(p-*nitrobenzoyl*)*thiourea* (**2Df**) (61), m.p. 134—136 (EtOH) (57.2, 4.1, 13.3. $C_{15}H_{13}N_3O_3S$, 57.1, 4.2, 13.3). 4-[N-(p-*Nitrobenzoyl*)*thiocarbamoyl*]*morpholine* (**2Dl**) (60), m.p. 174—176 (MeCN) 48.9, 4.4, 14.1. $C_{12}H_{13}N_3O_4S$, 48.8, 4.4, 14.2). N-*t-Butyl*-N′-(2-*thenoyl*)*thiourea* (**2Eb**) (79), m.p. 131—132 (EtOH) (49.7, 5.7, 11.7. $C_{10}H_{14}N_2OS_2$, 49.6, 5.8, 11.6). N-(1-*Methylbenzyl*)-N′-(2-*thenoyl*)*thiourea* (**2Ed**) (80), 113—114 (EtOH) (58.0, 4.85, 9.6. $C_{14}H_{14}N_2OS_2$, 57.9, 4.9, 9.65). N-*Methyl*-N-*phenyl*-N′-(2-*thenoyl*)*thiourea* (**2Ef**) (84), 120—120.5 (EtOH) (56.5, 4.4, 10.2. $C_{13}H_{12}N_2OS_2$, 57.5, 4.4, 10.1). N-*Benzyl*-N-*methyl*-N′-(2-*thenoyl*)*thiourea* (**2Eg**) (86), 129—131 (EtOH) (57.95, 4.65, 9.5. $C_{14}H_{14}N_2OS_2$. 57.85, 4.9, 9.65). 2-*Methyl*-1-[N-(2-*thenoyl*)*thiocarbamoyl*]*aziridine* (**2Eh**) (79), m.p. 147—148 (EtOH) (47.8, 4.6, 12.2. $C_9H_{10}N_2OS_2$, 47.8, 4.45, 12.4). 1-[N-(2-*Thenoyl*)*thiocarbamoyl*]*azetidine* (**2Ei**) (82), 161—162 (EtOH) (47.8, 4.55, 12.7. $C_9H_{10}N_2OS_2$, 47.8, 4.45, 12.4). 1-[N-(2-*Thenoyl*)*thiocarbamoyl*]*pyrrolidine* (**2Ej**) (87), 150—151 (EtOH) (50.1, 4.8, 11.5. $C_{10}H_{12}N_2OS_2$, 50.0, 5.0, 11.7). 1-[N-(2-*Thenoyl*)*thiocarbamoyl*]*piperidine* (**2Ek**) (85, 119—120 (EtOH) (51.9, 5.5, 11.0. $C_{11}H_{14}N_2OS_2$, 51.9, 5.55, 11.0). 1-[N-(2-*Thenoyl*)*thiocarbamoyl*]*hexahydroazepine* (**2Em**) (82), 109—110 (EtOH) (53.5, 6.2, 10.3. $C_{12}H_{16}N_2OS_2$, 53.7, 6.0, 10.4). *N*-Acetyl-*N*′-phenylthiourea (**2Fc**) (76), m.p. 174—175 (EtOH) (lit.,[2a] 170—171). N-*Acetyl*-N′-*methyl*-N′-*phenylthiourea* (**2Ff**) (80), m.p. 119—121 (Pr^{i}OH) (57.5, 5.6, 13.6. $C_{10}H_{12}N_2OS$, 57.7, 5.8, 13.5). 1-(N-*Acetylthiocarbamoyl*)*hexahydroazepine* (**2Fm**) (76), m.p. 56—58 [flash chromatography on SiO_2 with pentane–Et_2O (3:1) as eluant] (*m/z* 200.0984. $C_9H_{16}N_2OS$, M^+, 200.0983). N-(1-*Methylbenzyl*)-N′-*pivaloylthiourea* (**2Gd**) (82), m.p. 103—104 (EtOH) (63.6, 7.6, 10.6. $C_{14}H_{20}N_2OS$, 63.7, 7.65, 10.6). N,N-*Dimethyl*-N′-*pivaloylthiourea* (**2Ge**) (76), m.p. 78—79 (petroleum) (51.2, 89.6, 15.1. $C_8H_{16}N_2OS$, 51.0, 8.6, 14.9). N-*Methyl*-N-*phenyl*-N′-*pivaloylthiourea* (**2Gf**) (86), m.p. 136—137 (EtOH) (62.5, 7.1, 11.0. $C_{13}H_{18}N_2OS$, 62.4, 7.25, 11.2). 4-(N-*Pivaloylthiocarbamoyl*)*morpholine* (**2Gl**) (88), m.p. 136—137 (51.8, 8.0, 12.1. $C_{10}H_{18}N_2O_2S$, 52.1, 7.9, 12.2). *N*-(α-*Anilino*)*benzylidene*-N′-*methyl*-N′-*phenylthiourea* (**5Af**) (81), m.p. 234—236 (EtOH) (73.2, 5.5, 12.3. $C_{21}H_{19}N_3S$, 73.0, 5.5, 12.2). 4-[(α-Anilino)benzylidenethiocarbamoyl]morpoline (**5Al**) (84), 133—134 (MeOH) (lit.,[7] 126). N-(α-*Anilino*-p-*methoxybenzylidene*)-N′-*methyl*-N′-*phenylthiourea* (**5Bf**) (82), 137—139 (EtOH) (70.5, 5.8, 11.3. $C_{22}H_{21}N_3OS$, 70.4, 5.6, 11.2). (α-N-*Anilino*-p-*chlorobenzylidene*)-N′-*methyl*-N′-*phenylthiourea* (**5Cf**) (79) 144—146 (Pr^{i}OH) (66.4, 4.6, 11.3. $C_{21}H_{18}ClN_3S$, 66.4, 4.8, 11.1). 4-[*Anilino*-(2-*thienyl*)*methylenecarbamoyl*]*morpholine* (**5El**) (78), m.p. 131—132 (MeOH) (57.8, 5.1, 12.7. $C_{16}H_{17}N_3OS_2$, 58.0, 5.2, 12.7). 1-[*Anilino*(*t-butyl*)-*methylenethiocarbamoyl*]*hexahydrozepine* (**5Gm**) (81), 99—101 (petroleum) (68.0, 8.7, 13.5. $C_{18}H_{27}N_3S$, 68.1, 8.6, 13.2). 1-[(α-*Isopropylaminobenzylidene*)*thiocarbamoyl*]*hexahydroazepine* (**7**) (82), 108—110 (Pr^{i}OH) (67.4, 8.2, 13.9. $C_{17}H_{25}N_3S$, 67.3, 8.3, 138.5).

The Imidoyl Chlorides (**4**) *and* (**6**).—A solution of 2-thenoyl chloride (7.33 g) in dry Et_2O (100 ml) was added during 20 min to a stirred solution of $PhNH_2$ (9.35 g) in Et_2O (150 ml), and stirring was continued for a further 20 min. The mixture was diluted with water, and the Et_2O layer was separated and washed with 2M $NaHCO_3$ and water, dried, and evaporated to give *N*-phenylthiophen-2-carboxamide (8.64 g), m.p. 170—171 °C (lit.,[20] 143—144 °C), *m/z* 203 (M^+, 35%) and 111 (100). This amide (4.04 g) and a magnetic 'flea' were placed in the bulb of a distillation apparatus, and the bulb was immersed in an oil-bath. PCl_5 (4.16 g) was added, the pressure was reduced to 700 mmHg, and the oil was heated to 90 °C. The mixture, which soon melted, was stirred at 90 °C for 20 min while HCl vapour was removed. The pressure was reduced to 15 mmHg (to remove $POCl_3$) and then to 1.5 mmHg, and the temperature of the oil-bath was raised slowly. N-*Phenylthiophen*-2-*carbimidoyl chloride* (**4E**) distilled as a yellow oil (4.01 g), b.p. 107—109 °C/1.5 mmHg (Found: C, 59.5; H, 3.4; N, 6.2. $C_{11}H_8ClNS$ requires C, 59.6; H, 3.6; N, 6.3%), *m/z* 221 (M^+, 30%) and 186 (100).

The following imidoyl chlorides were prepared similarly, the final pressure being adjusted so that the products distilled without decomposition: *N*-phenylbenzimidoyl chloride (**4A**) (92%), b.p. 199—201 °C/15 mmHg, m.p. 42—44 °C (lit.,[12a] 39—40 °C); *p*-methoxy-*N*-phenylbenzimidoyl chloride (**4B**) (87%), b.p. 126—128 °C/0.1 mmHg (lit.,[12b] m.p. 70 °C, b.p. 220—230 °C/17 mmHg with almost complete decomposition); *p*-chloro-*N*-phenylbenzimidoyl chloride (**4C**) (89%), b.p. 118—120 °C/0.3 mmHg, m.p. 69—70 °C (lit.,[12c] 68 °C); N-*phenyl*-

pivalimidoyl chloride (**4G**) (90%), b.p. 125—127 °C/1 mmHg (Found: C, 67.5; H, 7.5; N, 7.2. $C_{11}H_{14}ClN$ requires C, 67.5; H, 7.2; N, 7.15%), *m/z* 195 (M^+, 15%) and 104 (100); *N*-isopropylbenzimidoyl chloride (**6**) (91%), b.p. 101—102 °C/15 mmHg (lit.,[10] 52—54 °C/ 1 mmHg).

The Isothiocyanates (**3**).—The Me_2CO used in these experiments was dried over $CaCl_2$, distilled, and stored over $CaCl_2$. A solution of 2-thenoyl chloride (7.41 g) in Me_2CO (25 ml) was added during 30 min to a stirred solution of NH_4SCN (3.75 g) in Me_2CO (50 ml) at 20 °C, and stirring was continued for a further 30 min. The mixture was filtered, and the filtrate was washed with Me_2CO. The filtrate and washings were combined, and evaporated. Dry C_6H_6 (60 ml) was added, and the small amount of insoluble material was filtered off. Evaporation of the filtrate gave an oil (7.96 g) which, on distillation, afforded 2-*thenoyl isothiocyanate* (**3E**) (7.12 g), b.p. 132—133 °C/15 mmHg (Found: C, 42.35; H, 1.7; N, 8.1. $C_6H_3NOS_2$ requires C, 42.6; H, 1.8; N, 8.3%), *m/z* 169 (M^+, 2%) and 111 (100). The i.r. spectra of the oil and the product were very similar, with strong bands at 1 995, 1 955, and 1 696 cm^{-1} but no absorption at *ca.* 2 170 cm^{-1}. In a series of experiments the temperature was varied (over the range 10—50 °C), the amount of NH_4SCN was increased (to 5.62 g), and the NH_4SCN solution was added to the 2-thenoyl chloride solution. None of the total products showed i.r. absorption at *ca.* 2 170 cm^{-1} and all gave the isothiocyanate (**3E**) in good yield.

Similar results were obtained in studies of the reactions between PhCOCl and NH_4SCN [which, at 20 °C, gave benzoyl isothiocyanate (**3A**) (78%), b.p. 72—74 °C/0.3 mmHg (lit.,[4b] 58—62 °C/0.03 mmHg), $\nu_{max.}$ 1 975, 1 937, and 1 700 cm^{-1}] and between Bu^tCOCl and NH_4SCN [which, at 20 °C, gave the isothiocyanate (**3G**) (79%), b.p. 63—65 °C/25 mmHg (lit.,[3] 163—166 °C/760 mmHg), $\nu_{max.}$ 1 998, 1 965, and 1 725 cm^{-1}].

Treatment of solutions of the isocyanates (**3**) in Me_2CO at 20 °C with the appropriate amines gave the products (**2Af**), (**2Al**), (**2Ef**), (**2Em**), (**2Gf**), and (**2Gl**) in yields of 90—93%.

Condensations with Chloroacetone.—(*a*) A stirred solution of *N*-(α-anilino)benzylidene-*N'*-methyl-*N'*-phenylthiourea (**5Af**) (1.34 g), chloroacetone (0.36 g), and NEt_3 (0.78 g) in MeCN (20 ml) was boiled under reflux for 2 h, cooled, and poured into brine. Extraction with Et_2O gave an oil (1.12), δ 1.98 (3 H, s, MeCO) but no signal at δ *ca.* 2.4. Crystallisation from MeOH afforded 5-acetyl-2-(*N*-methylanilino)-4-phenylthiazole (**17**) (0.93 g), m.p. and mixed m.p. with an authentic sample[13a] 153—154 °C, $\nu_{max.}$ 1 635 cm^{-1}.

(*b*) The procedure of experiment (*a*) with 4-[(α-anilino)benzylidenethiocarbamoyl]morpholine (**5Al**) (1.62 g), chloroacetone (0.46 g), and NEt_3 (1.01 g) in MeCN (25 ml) gave a yellow solid (1.32 g), δ 1.97 (3 H, s, MeCO) but no signal at δ *ca.* 2.4. Crystallisation from EtOH afforded 4-(5-acetyl-4-phenylthiazol-2-yl)morpholine (**14**) (1.08 g,), m.p. 210—211 °C (lit.,[7] δ 1.90, m.p. 204 °C).

(*c*) The procedure of experiment (*a*) with *N*-benzoyl-*N'*-methyl-*N'*-phenylthiourea (**2Af**) (2.98 g), chloroacetone (1.02 g) and NEt_3 (2.23 g) in EtOH (40 ml) gave an oil (3.20 g), ^1H n.m.r. signals at 2.41 (s), and 1.98 (s) with ratio 10:1. Two crystallisations from MeOH afforded *5-benzoyl-4-methyl*-2-(*N-methylanilino)thiazole* (**20**) (2.21 g), m.p. 77—78 °C (Found: C, *69.9*; *H, 5.3*; N, *8.9*. $C_{18}H_{16}N_2OS$ requires C, 70.1; H, 5.2; N, 9.1%), $\nu_{max.}$ 1 633 cm^{-1}.

(*d*) The procedure of experiment (*a*) with 4-(*N*-benzoylthiocarbamoyl)morpholine (**2Al**) (1.25 g), chloroacetone (0.46 g), NEt_3 (1.01 g) in EtOH (20 ml) gave a yellow solid (1.36 g), ^1H n.m.r. signals at δ 2.39 (s) and 197 (s) with ratio 8:1. Two crystallisations from EtOH afforded 4-(5-benzoyl-4-methylthiazol-2-yl)morpholine (**23**) (0.95 g), m.p. 151—152 °C (Found: C, 62.3; H, 5.6; N, 9.9. Calc. for $C_{15}H_{16}N_2O_2S$: C, 62.5; H, 5.6; N, 9.7%) [lit.,[15] m.p. 150—153 °C for the product formulated as the isomer (**14**)].

Second Preparation of the Thiazole (**20**).—A solution of Br_2 (6.06 g) in CCl_4 (40 ml) was added during 45 min to a vigorously stirred dispersion of 2-acetylacetophenone (6.16 g) in CCl_4 (40 ml)–water (40 ml) at 0 °C. The layers were separated, and the aqueous layer was extracted with CCl_4. The CCl_4 phases were combined, washed with brine, and dried ($MgSO_4$). Evaporation at 20 °C/12 mmHg gave an oil (7.57 g) which solidified at −10 °C. ^1H N.m.r. examination showed this to be mainly (*ca.* 91%) the keto form of 2-acetyl-2-bromoacetophenone (**21**), δ 6.59 (1 H, s, CHBr) and 2.47 (3 H, s, MeCO).

A stirred solution of the foregoing oil (1.41 g) and *N*-methyl-*N*-phenylthiourea (**22**) (0.92 g) in Me_2CO (30 ml) was boiled under reflux for 30 min, cooled, and poured into brine. Basification with 18M NH_3 and extraction with Et_2O gave an oil (1.63 g), ^1H n.m.r. signals at 2.41 (s) and 1.98 (s) with ratio 3:1. Crystallisation from MeOH afforded the 5-benzoylthiazole (**20**) (1.31 g), m.p. and mixed m.p. 76—78 °C.

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