Condensation of thiourea derivatives with carbonyl compounds: one-pot synthesis of *N*-alkyl-1,3-thiazol-2-amines and of 3-alkyl-1,3-thiazolimines

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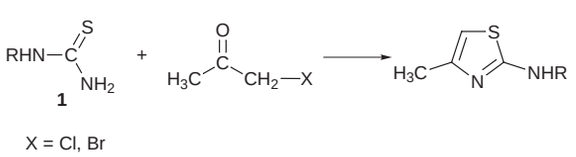
The reactions of ketones and *N*-substituted thioureas, in the presence of HCl (or HBr) and DMSO afford mixtures of the title compounds which are easily separated on a silica gel column. This method avoids the classical use of α-haloketones. The mechanism of these reactions involves the enolization of ketones and the activation of thiourea sulfur, probably by oxygen transfer from DMSO.

Introduction

We have reported[1] that mixtures of DMSO–H^+–halides produce an easy cyclization reaction of substituted thioamides or thioureas, affording 1,2,4-thiadiazole derivatives. These heterocyclic derivatives are interesting potential biocides[2] of low environmental impact. During our experiments we observed that some mixtures of *N*-substituted thioureas with HBr and DMSO, in acetone, afford 1,3-thiazole derivatives in high yields.

Usually, thiazol-2-amines are obtained[3] from thioureas or related compounds,[4] and α-haloketones, as indicated in Scheme 1, and 3-alkyl-1,3-thiazolimines are obtained from the corresponding thiazolamines and alkyl halides.[3]



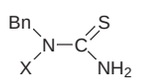
Scheme 1

We report some results on the cyclization of ketones and substituted thioureas in the presence of DMSO and hydrogen halides to give the title compounds without employment of α-haloketones.

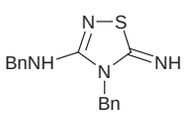
Results

Condensation of substituted thioureas with acetone

When the mixture of 2 equivalents of HCl (36%) (or HBr 48%) and DMSO (2 equivalents) is added to a solution in acetone of 1 equivalent of *N*-alkylthiourea, immediately a whitish solid separates. In the case of *N*-benzylthiourea **1b**, it was possible to collect and analyze this solid to which was tentatively assigned the structure of an *N*-chlorinated (or *N*-brominated) *N*-benzylthiourea (labelled as **2**, or **3** respectively, see Experimental section). Compound **3** is unreactive toward the acetone, also in the presence of HBr. When **3** is dissolved in DMSO and the solution is stirred at 40 °C for 20 h the thiadiazole derivative **4** is isolated in 95% yield.



2 X = Cl
3 X = Br



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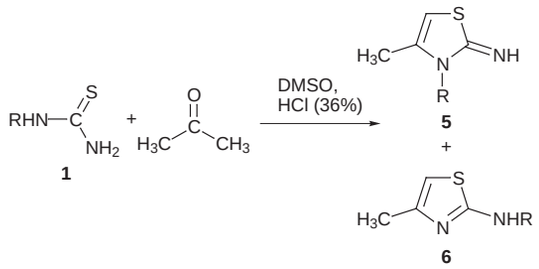
Compound **3** may be one of the possible intermediates of the cyclization reaction of thiourea derivatives (and of thioamides) that give the thiadiazole derivatives.[1]

The same solids **2** and **3** were also obtained (in acetone) from **1b** and *N*-chloro- and *N*-bromo-succinimide, respectively. ^{1}H NMR spectra (in DMSO-d_6) of **2**, **3** are very complicated and poorly reproducible, while ^{1}H NMR spectra in CD_3OD reproduce the spectrum of *N*-benzylthiourea **1b**. Aqueous solutions of both **2** and **3** liberate I_2 from KI solution and *N*-benzylthiourea is recovered. Addition of sodium carbonate to a solution of **2** or **3** in water quantitatively afforded **1b**. When **2** is dissolved in acetone and it is stirred at 40 °C for 10 days, the presence of **5b** and **6b** was not detected in the reaction mixtures (by TLC, eluant: Et_2O). In DMSO–acetone, both **2** and **3** give (after 8 days) traces of **5b** and **6b**. Probably **2** and **3** arise from reversible side reactions.

After further vigorous stirring of the original mixture containing **2** (or **3**), acetone and DMSO at 40 °C, **2** (or **3**) slowly dissolves, and a further crystalline solid **5** precipitates; the solution contains isomers **5** and **6** (Scheme 2). The structures of **5** and **6** were assigned on the basis of ^{1}H and ^{13}C NMR spectral data and by comparison (in some cases) with authentic samples prepared by literature procedures (see Experimental section). In particular, the NMR signal of H-5 of the thiazole moiety is representative of two isomers.[5] In addition, all products containing –NH–CH_2–Ar groups (as well as the –NH-2-butyl group) show the CH_2 signal as a broad singlet/doublet which becomes a sharp singlet after addition of deuterium oxide.[5] The structure of compound **5b** was ascertained by X-ray diffraction of **5b** hydrochloride (**5g**).



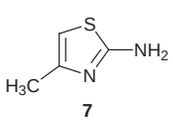
Compound series	R	Yield (%) 5	6
a	2-Butyl	0	74
b	Benzyl	70	25
c	*p*-Methylbenzyl	76	20
d	*p*-Methoxybenzyl	undetected	70
e	*p*-Chlorobenzyl	60	23
f	Methyl	40	6

Scheme 2

It is of interest to emphasize that in **5**, the more substituted nitrogen (which is the more hindered nitrogen) becomes included in the ring, while the unsubstituted amino group ends up in the exocyclic position. Usually in cyclization reactions the less hindered nitrogen is involved in the formation of the ring.

In order to investigate whether **5** and **6** are formed from the cyclization reaction or if they are from some isomerization reactions (**5** ↔ **6**) we checked the stability of **5** and **6** separately in the reaction medium. No conversion **5**↔ **6** was observed even after long reaction times (1 week) in DMSO–HCl mixtures.

Reaction between thiourea and acetone afforded, in the presence of the DMSO–HCl mixture, the 4-methylthiazol-2-amine (**7**) in low yields (15%).



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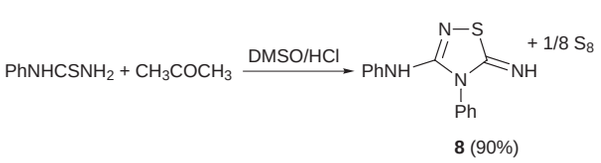
The condensation reaction between *N*-phenylthiourea and acetone afforded in high yields thiadiazole derivative **8**[1] (Scheme 3).



8 (90%)

Scheme 3

Table 1 collects data of some reactions between *N*-benzylthiourea **1b** and acetone under different experimental conditions. It is worthy of consideration that the mixture DMSO–HCl may be substituted by other reagents[6] (*N*-bromosuccinimide, *N*-chlorosuccinimide) but this gives lower conversion. The formation of **5b** and **6b** also in the presence of DMSO–$MeSO_3H$, and in the absence of halide ions (see Table 1), confirms that **2** and **3** are from a side reaction, while the acid catalysis is important.

X-Ray diffraction analysis of 5g

The molecular structure is shown in Fig. 1. The thiazole ring is planar and its displacement of bond distances and angles compares well with that of analogous compounds reported in the literature.[7] In particular the S–C bonds [S(1)–C(2) 1.718(2), S(1)–C(5) 1.727(3) Å] are intermediate between 1.808 Å for a single and 1.556 Å for a double bond. Also the N–C bonds [N(3)–C(2) 1.339(2), N(21)–C(2) 1.319(3) Å] are intermediate between single (1.47 Å) and double (1.29 Å) and are indicative of a high degree of π-delocalized bonding involving the S and N lone pairs. The N(21), C(31) and C(41) atoms are practically coplanar with the thiazole ring, the distances from the mean plane being 0.025(3), −0.045(2) and −0.0016(3) Å, respectively. The $N(21)^+$ iminium ion is involved in hydrogen bonds with Cl^- ion through its two hydrogen atoms, one intramolecular [N(21)]···Cl(1) 3.120(3), H(21)···Cl(1) 2.22(3) Å; N(21)–H(21)···Cl(1) 173(2)°] and the other intermolecular with Cl^- in the $-x$, $-y$, $1-z$ position [N(21)···Cl(1) 3.178(3), H(22)···Cl(1) 2.42(3) Å; N(21)–H(22)···Cl(1) 165(3)°]. Other contacts are consistent with van der Waals interactions.

The structure of Fig. 1 confirms[8] that (in the solid state) the exocyclic nitrogen is more basic than the endocyclic nitrogen since it is the only protonated nitrogen.

Table 1 Condensation reactions between *N*-benzylthiourea[a] and acetone at 30 °C

Reagent/mmol	HX/mmol	Reaction time	Yield (%) 5b	6b
DMSO (6.0)	HCl 37% (6.0)	4 d	70	25
DMSO (6.0)	—	4 d	n.r.[b]	n.r.
—	HCl 37% (6.0)	5 d	n.r.	n.r.
DMSO (6.0)	$MeSO_3H$ (6.0)	7 h	47	47
NCS (3.6)	—	10 d	13	10
NBS (3.6)	—	2 d	30	40

[a] 3.0 mmol of *N*-benzylthiourea. [b] n.r. = no reactions were observed.

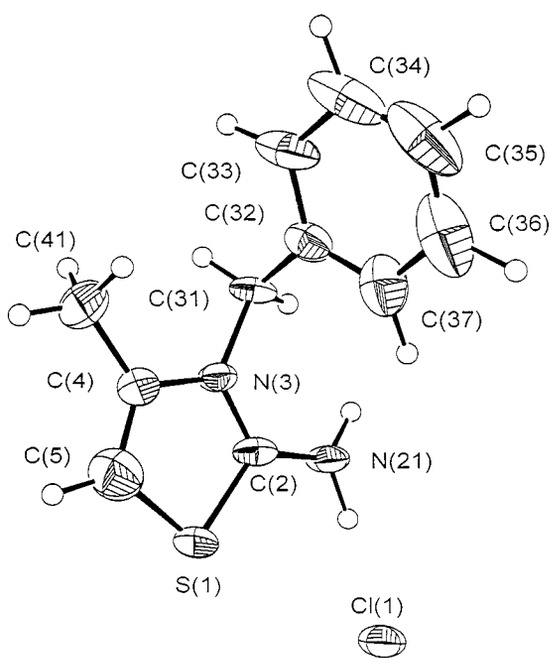


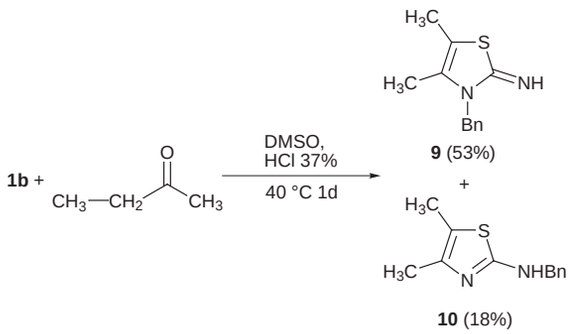
Fig. 1 Molecular structure of **5g** with labelling scheme. Displacement ellipsoids are plotted at the 50% probability level. H atoms are drawn as small circles of arbitrary radius.

Condensation of 1b with other ketones

In order to obtain information on the reaction mechanism of

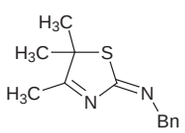
Scheme 2, we carried out some reactions with structurally different methyl ketones.

Condensation of *N*-benzylthiourea **1b** and butan-2-one affords the two thiazole derivatives **9** and **10** (Scheme 4).



Scheme 4

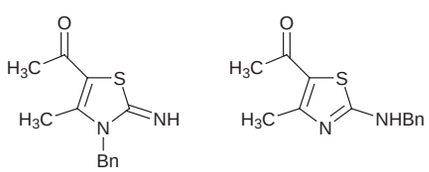
The condensation of **1b** with 3-methylbutan-2-one only affords thiazoline **11**. Structure **11** was assigned on the basis of ^{1}H and ^{13}C NMR and mass spectral data. These results indicate that the thiazole ring is formed by the attack of the S atom of the thiourea on the more substituted α carbon of the ketone.



11 40%

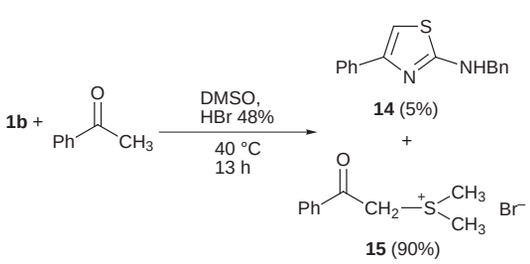
Thus, the ring closure occurs by the formation of an S–C5 bond between sulfur and C3 of butanone, and of an N–C4 bond between the nitrogen atom and the carbonyl carbon.

The reaction of **1b** with acetylacetone affords isomers **12** and **13**. In this case also, the more substituted α carbon of the ketone participates in the ring formation.



12 (46%) **13** (16%)

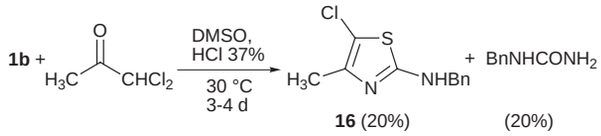
The reaction between **1b** and acetophenone is depicted in Scheme 5. In this case the side reaction of formation of



Scheme 5

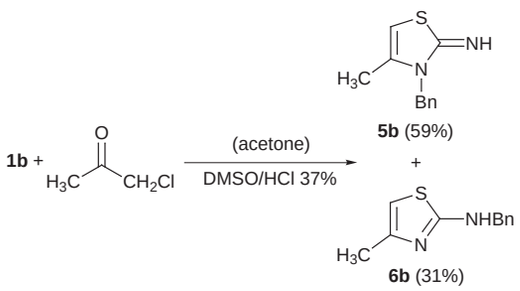
sulfonium bromide **15** predominates over the formation of the thiazole ring. Compound **15** is unable to yield thiazole derivatives.

The reaction between 1,1-dichloroacetone and **1b** affords thiazole derivative **16** in low yield. In this case the reaction of substitution of the thiourea sulfur by oxygen competes with the thiazole formation (Scheme 6). The benzylurea is obtained in low yield.



Scheme 6

1-Chloroacetone (in H_2O or in acetone) with **1b** (without DMSO and in the absence or in the presence of acid) affords the thiazole **6b** in almost quantitative yields. 1-Chloroacetone in acetone and in the presence of DMSO–HCl affords a mixture of isomers **5b** and **6b** (Scheme 7).



Scheme 7

The major product is the *N*-alkylthiazole derivative **5b**, which cannot arise from chloroacetone. This fact indicates that the only role for the chloroacetone could be in the synthesis of **6b**, but **6b** could also be synthesised from actone.

Discussion

In the mixtures of ketone and thiourea different reactions take place, affording several products which, in principle, may be considered intermediates toward compounds **5** and **6**. In particular, *N*-halogenothioureas **2** or **3** may be on the reaction pathway to give a thiazole ring, but attempts to obtain thiazole from **3** failed: probably, **2** and **3** are products of side reactions. However, **2** and **3** are on the reaction pathway to obtain 1,2,4-thiadiazole derivatives in a reaction pathway which competes with that previously proposed.[1]

Also the formation of alkyldimethylsulfonium halides (such as **15**) may be considered a side reaction which takes place when other reactions are slow.

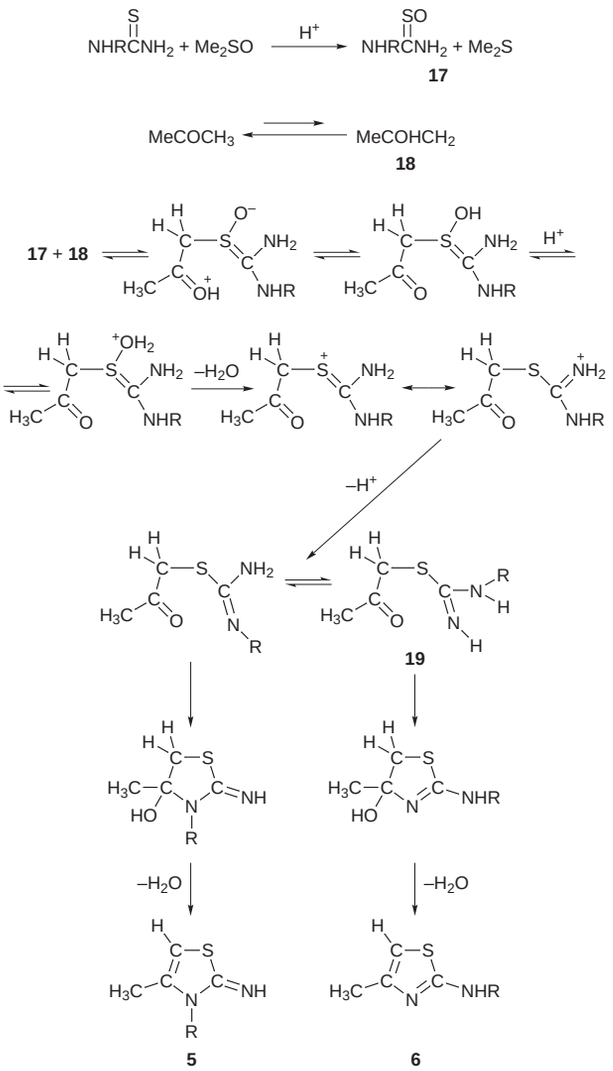
Data reported here strongly indicate the possibility that in our reaction mixtures the formation of a species involving positive halogen occurs, as tested by the formation of *N*-halogeno derivatives **2** and **3**.

Recently,[9] the mixture DMSO–H^+–Br^- has been indicated to be capable of brominating several substrates. Probably, the DMSO acts as an oxidizing reagent (in the acidic medium) to afford positive halonium ion. The possible presence of positive halonium ion (or molecular halogen) indicates that α-haloketones may be formed in the reaction mixtures, but from α-haloketones only the compounds **6** are obtained.[1,10]

The reaction also occurs in the presence of methansulfonic acid (without the presence of halides). Probably the first step is the activation of the thiourea by the DMSO in the presence of an acid as catalyst.

The formation of compounds **9**, **10**, **11**, **12**, **13** and **16** strongly indicates that the formation of the thiazole ring occurs between the sulfur atom and the α-carbon atom of the carbonyl group, and between the nitrogen atom and the carbonyl group in a situation in which the steric hindrance is insignificant. A possible reaction pathway is depicted in Scheme 8.

The reaction between the electrophilic sulfur atom (probably as an *S*-oxide[11]) and the α carbon of the enol form of the ketone produces an intermediate to **19**. This pathway explains the preference of the halogenated carbon (Scheme 6) or of the



Scheme 8

carbon with electron-withdrawing substituents (such as in the formation of **12** and **13**) to form the C–S bond. The tautomerism of ketones[12] explains the regioselectivity of the attack. The sulfur attack on the enol is possible if the sulfur is in an electrophilic form (such as in the *S*-oxide derivative).

In principle, both nitrogen atoms can attack the carbonyl group, but the substituted nitrogen is slightly more reactive than the unsubstituted nitrogen in forming the thiazole ring. It is known that the sp^2 nitrogen atom is a better base and nucleophile than the sp^3 nitrogen atom.[8,13] Probably, the ring closure occurs in a fast step, in which the steric requirements of nitrogen atoms are not very important, as in **19**.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50.3 or 75.46 MHz, respectively. Chemical shifts were measured in δ (ppm) and referenced to TMS. All compounds containing N*H* protons show a disappearance of the relevant signals in the ^{1}H NMR spectra, after addition of D_2O.

Solvents and reagents (Carlo Erba) were reagent grade. *N*-Substituted thioureas were prepared by the usual procedures. Reported yields (in mol%) are from weight determinations of the separate compounds. Melting points are uncorrected.

Halogenated *N*-benzylthioureas 2 and 3

When 6.0 mmol of HCl (37%) were added dropwise to solutions of 3.0 mmol of **1b** and 6.0 mmol of DMSO in acetone (5 mL) a whitish solid precipitates. This solid, probably, is *N*-chloro-*N*-benzylthiourea **2**. In the same way (from DMSO–HBr mixtures), *N*-bromo-*N*-benzylthiourea **3** is obtained. Compounds **2** and **3** are collected by filtration. All attempts to recrystallize these materials failed.

Compound 2. Mp 159–162 °C. Anal. calc. for $C_8H_9N_2SCl$: C, 47.88; H, 4.52; N, 13.96; S, 15.98; Cl, 17.67%. Found: C, 47.59; H, 4.50; N, 13.76; S, 15.88; Cl, 17.55%.

Compound 3. Mp 189–191 °C. Anal. calc. for $C_8H_9N_2SBr$: C, 39.20; H, 3.70; N, 11.43; S, 13.08; Br, 32.6%. Found: C, 39.37; H, 3.64; N, 11.29; S, 12.97; Br, 32.53%.

Condensation reactions to give thiazole derivatives: typical procedure

A mixture of DMSO–HCl (2 equivalents, 1 : 1 molar ratio) and **1b** (1 equivalent) in acetone (2 mL per mmol of **1**) was vigorously stirred at 40 °C for 4 days, showing (TLC analysis, eluant Et_2O) the disappearance of the starting thiourea. Most of compound **5b** spontaneously precipitated (as the hydrochloride) and was filtered off. The remaining solution was concentrated (under vacuum) and poured into aqueous 10% KOH. The mixture was extracted with 20 mL of CH_2Cl_2, dried and the solvent was evaporated. The residue contains both **5b** and **6b** isomers which were separated on a silica gel column (eluant Et_2O–MeOH, 95 : 5).

Crystal structure of 5g †

A summary of the crystallographic work is given in Table 2. The intensities I_{hkl} were determined by analysing the reflection profiles by the Lehmann and Larsen procedure.[14] Corrections for Lorentz and polarization effects were performed; there were no corrections for polarization effects.

Atomic scattering factors were from International Tables for X-ray Crystallography.[15] Bibliographic searches were carried out using the Cambridge Structural database Files through the Servizio Italiano di Diffusione Dati Cristallografici, Parma, Italy.

N-(*sec*-Butyl)-4-methyl-1,3-thiazol-2-amine[19] (6a)

Oil, mp (picrate) 185–187 °C; δ_H(200 MHz; $CDCl_3$) 6.01 (1 H, q, *J* 1.1 Hz), 5.6 (1H, br s), 3.30–3.45 (1H, m), 2.21 (3H, d, *J* 1.1 Hz), 1.50–1.70 (2H, m), 1.24 (3H, d, *J* 6.4 Hz), 0.95 (3H, t, *J* 7.4 Hz); δ_C(50.3 MHz; $CDCl_3$) 170.2, 147.9, 100.1, 54.4, 29.9, 20.4, 17.0, 10.5; *m*/*z* 170 (M^+, 37%), 155 (14), 141 (100), 114 (77), 72 (16), 71 (14), 45 (13); HRMS: $C_8H_{14}N_2S$ requires 170.0878, found 170.0875. Found: C, 56.50; H, 8.33; N, 16.60; S, 18.74%. $C_8H_{14}N_2S$ requires C, 56.43; H, 8.29; N, 16.45; S, 18.83%.

3-Benzyl-4-methyl-2,3-dihydro-1,3-thiazol-2-iminium chloride (5g)

Mp 254–256 °C (MeOH); δ_H(200 MHz; DMSO-d_6) 9.82 (2H, br s), 7.5–7.1 (5H, m), 6.79 (1H, s), 5.36 (2H, s) 2.14 (3H, s); δ_C (50.3 MHz; DMSO-d_6) 169.4, 137.9, 133.7, 129.4, 128.5, 128.2, 102.7, 48.2, 13.4; *m*/*z* 204 (M^+, 49%), 189 (2), 127 (3), 113 (13), 106 (7), 100 (5), 91 (100), 65 (20), 36 (18). Found: C, 54.75; H, 5.50; N, 11.70; S, 13.28%. $C_{11}H_{13}ClN_2S$ requires: C, 54.88; H, 5.44; N, 11.64; S, 13.32; Cl, 14.73%.

3-Benzyl-4-methyl-1,3-thiazol-2(3*H*)-imine[20] (5b)

δ_H(200 MHz; $CDCl_3$) 7.12–7.35 (5H, m), 5.42 (1H, q, *J* 1.4 Hz) 4.96 (2H, s), 1.93 (3H, d, *J* 1.4 Hz); δ_C(50.3 MHz; $CDCl_3$) 166.2, 137.3, 135.3, 128.9, 127.4, 126.5, 92.6, 46.3, 15.2.

† CCDC reference number 207/313.

Table 2 Experimental data for the X-ray diffraction studies on crystalline compound **5g**

Formula	$C_{11}H_{13}N_2S^+Cl^-$
Cryst. habit	prism
Cryst. colour	colourless
FW $F(000)$	240.7 504
Cryst. system	monoclinic
Space group	$P2_1/c$
Cell parameters at 295 K	
a/Å	8.466(2)
b/Å	10.733(3)
c/Å	13.599(3)
α (°)	90
β (°)	98.5(1)
γ (°)	90
V/Å^3	1222.1(6)
Z	4
d_{calc}/g cm^{-3}	1.31
Cryst. dimensions/mm	0.43 × 0.29 × 0.34
Linear abs. coeff./cm^{-1}	41.1
Diffractometer	Siemens AED
Scan type	ω–2θ
Scan width (°)	*b*
Radiation	*c*
2θ range collection (°)	6–170
hkl range	$\pm h,k,l$
Unique total data	2623
Criterion of observation	$I > 2\sigma(I)$
Unique obs. data (NO)	1946
No. of refined par (NV)	188
Overdetermn ratio (NO/NV)	10.4
Absorption	*d*
Solution	*e*
H atoms	*f*
R	0.035
R_w	0.040
GOF	0.826
Largest shift/esd	0.3
Largest peak/e Å^{-3}	0.2
Computer and programs	*g*

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 30 carefully centred reflections chosen from diverse regions of reciprocal space. [b] From (θ–0.6)° to [θ + (0.6 + $\Delta\theta$)]°; $\Delta\theta = (\lambda a_2 - \lambda a_1)/\lambda]\tan\theta$. [c] Ni-filtered Cu-K$\alpha$, λ = 1.54178 Å. [d] No. correction applied. [e] Direct methods. [f] Located in ΔF map and isotropically refined. [g] ENCORE e91, SHELX86,[16] SHELX76,[17] PARST.[18] $R = \Sigma|\Delta F|/\Sigma|F_o|$, $R_w = [\Sigma w(\Delta F^2)^2/\Sigma w(F_o^2)^2]^{\frac{1}{2}}$, GOF = $[\Sigma w|\Delta F|^2/(NO - NV)]^{\frac{1}{2}}$.

N-Benzyl-4-methyl-1,3-thiazol-2-amine[21] (6b)

Mp 91–93 °C (MeOH); δ_H(200 MHz; $CDCl_3$) 7.25–7.40 (5H, m), 6.3 (1H, br s), 6.02 (1H, q, *J* 1.1 Hz), 4.44 (2H, s), 2.17 (3H, d, *J* 1.1 Hz); δ_C(50.3 MHz; $CDCl_3$) 170.3, 148.9, 137.9, 128.8, 127.7, 127.6, 100.6, 49.9, 17.4; *m*/*z* 204 (M^+, 39%), 127 (3), 113 (5), 106 (8), 100 (6), 91 (100), 65 (12). Found: C, 64.60; H, 5.87; N, 13.68; S, 15.80%. $C_{11}H_{12}N_2S$ requires C, 64.67; H, 5.92; N, 13.71; S, 15.69%.

3-(4-Methylbenzyl)-4-methyl-1,3-thiazol-2(3*H*)-imine (5c)

Oil, mp (picrate) 174–176 °C; δ_H(200 MHz; $CDCl_3$) 7.05–7.15 (4H, m), 5.7 (1H, br s), 5.51 (1H, q, *J* 1.2 Hz), 4.96 (2H, s), 2.30 (3H, s), 1.97 (3H, d, *J* 1.2 Hz); δ_C(50.3 MHz; $CDCl_3$) 166.4, 138.9, 135.3, 133.6, 129.4, 126.2, 93.2, 46.2, 21.0, 14.9; *m*/*z* 218 (M^+, 31%), 105 (100), 86 (23), 84 (37), 78 (23), 63 (27); HRMS: $C_{12}H_{14}N_2S$ requires 218.0878, found 218.0875. Found: C, 65.91; H, 6.42; N, 12.79; S, 14.71%. $C_{12}H_{14}N_2S$ requires C, 66.02; H, 6.46; N, 12.83; S, 14.69%.

4-Methyl-*N*-(4-methylbenzyl)-1,3-thiazol-2-amine (6c)

Mp 120–121 °C (MeOH); δ_H(200 MHz; $CDCl_3$) 7.1–7.3 (4H, m), 6.1 (1H, br s), 6.03 (1H, q, *J* 1.1 Hz), 4.39 (2H, s), 2.34 (3H, s), 2.19 (3H, d, *J* 1.1 Hz); δ_C(50.3 MHz; $CDCl_3$) 170.3, 149.4, 137.9, 135.1, 129.9, 128.0, 101.1, 49.9, 21.3 17.5; *m*/*z* 218 (M^+, 30), 106 (8), 105 (100), 79 (7), 77 (9); HRMS: $C_{12}H_{14}N_2S$ requires 218.0878, found 218.0880. Found: C, 65.90; H, 6.56; N, 12.78; S, 14.63%. $C_{12}H_{14}N_2S$ requires C, 66.02; H, 6.46; N, 12.83; S, 14.69%.

N-(4-Methoxybenzyl)-4-methyl-1,3-thiazol-2-amine (6d)

Mp 88–91 °C (MeOH); δ_H(200 MHz; $CDCl_3$) 7.28 (2H, d, *J* 8.7 Hz), 6.87 (2H, d, *J* 8.7 Hz), 6.15 (1H, br s), 6.02 (1H, q, *J* 1.0 Hz), 4.36 (2H, s), 3.79 (3H, s), 2.17 (3H, d, *J* 1.0 Hz); δ_C(50.3 MHz; $CDCl_3$) 170.4, 159.7, 149.3, 130.2, 129.9, 114.5, 101.1, 55.6, 49.6, 17.5; *m*/*z* 234 (M^+, 13%), 137 (13), 122 (9), 121 (100), 78 (6), 77 (9), 43 (5); HRMS: $C_{12}H_{14}N_2OS$ requires 234.0827, found 234.0831. Found: C, 61.40; H, 6.09; N, 12.04%. $C_{12}H_{14}N_2OS$ requires C, 61.51; H, 6.02; N, 11.96%.

3-(4-Chlorobenzyl)-4-methyl-1,3-thiazol-2(3*H*)-imine (5e)

Mp 200–202 °C (hydrochloride, MeOH); δ_H(300 MHz; $CDCl_3$) 7.31 (2H, d, *J* 8.5), 7.18 (2H, d, *J* 8.5), 5.48 (1H, s), 4.97 (s, 2H), 1.98 (3H, s); δ_C(75.46 MHz; $CDCl_3$) 165.8, 135.8, 134.8, 133.2, 129.0, 127.9, 92.7, 45.7, 15.1; *m*/*z* 240 (M^+, 13%), 238 (34), 127 (33), 125 (100), 113 (16), 89 (15); HRMS: $C_{11}H_{11}N_2SCl$ requires 238.0331, found 238.0334. Found: C, 55.23; H, 4.60; N, 11.66; S, 13.30%. $C_{11}H_{11}ClN_2S$ requires C, 55.34; H, 4.64; N, 11.73; S, 13.43%.

N-(4-Chlorobenzyl)-4-methyl-1,3-thiazol-2-amine (6e)

Mp 139–141 °C (MeOH); δ_H(200 MHz; $CDCl_3$) 7.2–7.4 (4H, m), 6.06 (1H, q, *J* 1.1 Hz) 5.8 (1H, br s), 4.43 (2H, s), 2.21 (3H, d, *J* 1.1); δ_C(75.46 MHz; $CDCl_3$) 170.0, 148.8, 136.5, 133.5, 129.0, 100.8, 49.2, 17.4; *m*/*z* 240 (M^+, 12%), 238 (36), 140 (7), 127 (33), 125 (100), 113 (8), 89 (10); HRMS: $C_{11}H_{11}N_2SCl$ requires 238.0331, found 238.0340. Found: C, 55.23; H, 4.57; N, 11.63; S, 13.28%. $C_{11}H_{11}ClN_2S$ requires C, 55.34; H, 4.64; N, 11.73; S, 13.43%.

3,4-Dimethyl-1,3-thiazol-2(3*H*)-imine (5f)

Mp 45–47 °C (lit.,[22] 43–46 °C), mp 196–197 °C (picrate) (lit.,[21] 200 °C); δ_H(300 MHz; $CDCl_3$) 5.44 (1H, q, *J* 1.3 Hz), 3.25 (3H, s), 2.07 (3H, d, *J* 1.3 Hz); δ_C(75.46 MHz, $CDCl_3$) 166.5, 135.1, 92.1, 30.0, 15.3; *m*/*z* 128 (M^+, 38%), 86 (64), 84 (100), 71 (6), 56 (34); HRMS: $C_5H_8N_2S$ requires 128.0408, found 128.0411.

N,4-Dimethyl-1,3-thiazol-2-amine (6f)

Mp 226–228 °C (hydrochloride) (lit.,[23] 226–227 °C); δ_H(300 MHz; $CDCl_3$) 6.05 (1H, q, *J* 1.1 Hz), 2.94 (3H, s), 2.22 (3H, d, *J* 1.1 Hz); δ_C(75.46 MHz; $CDCl_3$) 171.0, 149.0, 100.8, 32.3, 17.5; *m*/*z* 128 (M^+, 100%), 100(49), 86 (16), 84 (26), 72 (31), 71 (40), 57 (17); HRMS: $C_5H_8N_2S$ requires 128.0408, found 128.0410.

4-Methyl-1,3-thiazol-2-amine (7)

Mp 44–45 °C (lit.,[24] 44–45 °C) (MeOH); δ_H(300 MHz; $CDCl_3$) 6.05 (1H, q, *J* 1.1 Hz), 5.3 (2H, br s), 2.20 (3H, d, *J* 1.1 Hz); *m*/*z* 114 (M^+, 100%), 72 (40), 71 (55), 45 (35), 42 (22).

3-Benzyl-4,5-dimethyl-1,3-thiazol-2(3*H*)-imine[21] (9)

Mp 147–149 °C (EtOH); δ_H(300 MHz; $CDCl_3$) 7.2–7.4 (5H, m), 6.0 (1H, br s), 4.96 (2H, s), 2.00 (3H, br s), 1.87 (3H, br s); δ_C(75.46 MHz; $CDCl_3$) 165.5, 143.0, 137.2, 128.8, 127.3, 126.3, 113.0, 46.9, 29.8, 11.86; *m*/*z* 218 (M^+, 30%), 127 (16), 106 (15), 91 (100), 65 (12); HRMS: $C_{12}H_{14}N_2S$ requires 218.0878, found 218.0880. Found: C, 66.22; H, 6.56; N, 12.74; S, 14.59%. $C_{12}H_{14}N_2S$ requires C, 66.02; H, 6.46; N, 12.83; S, 14.69%.

N-Benzyl-4,5-dimethyl-1,3-thiazol-2-amine (10)

Mp 114–116 °C (cyclohexane); δ_H(200 MHz; $CDCl_3$) 7.25–7.40 (5H, m), 5.25 (1H, br s), 4.42 (2H, s), 2.17 (3H, br s), 2.12 (3H,

br s); δ_C(75.46 MHz; $CDCl_3$) 166.2, 143.1, 138.0, 128.8, 127.7, 127.6, 113.5, 50.6, 14.2, 10.8; *m*/*z* 218 (M^+, 80%), 127 (21), 106 (18), 91 (100), 85 (17), 65 (12); HRMS: $C_{12}H_{14}N_2S$ requires 218.0878, found 218.0880. Found: C, 65.88; H, 6.54; N, 12.80%. $C_{12}H_{14}N_2S$ requires C, 66.02; H, 6.46; N, 12.83%.

_N_-Benzyl-_N_-[4,5,5-trimethyl-1,3-thiazol-2(5_H_)-ylidene]amine (11)

Oil; δ_H(300 MHz; $CDCl_3$) 7.2–7.5 (5H, m), 4.46 (2H, s), 2.28 (3H, s) 1.65 (6H, s); δ_C(75.46 MHz; $CDCl_3$) 191.8, 169.3, 139.6, 128.8, 128.2, 127.2, 67.4, 60.0, 28.5, 16.1; *m*/*z* 232 (M^+, 39%), 217 (62), 148 (15), 91 (100), 85 (17), 65 (15); HRMS: $C_{13}H_{16}N_2S$ requires 232.1034, found 232.1039. Found: C, 67.0; H, 6.88; N, 11.96; S, 13.75%. $C_{13}H_{16}N_2S$ requires C, 67.2; H, 6.94; N, 12.06; S, 13.80%.

1-(3-Benzyl-2-imino-4-methyl-2,3-dihydro-1,3-thiazol-5-yl)ethan-1-one (12)

Mp 93–95 °C (CH_2Cl_2); δ_H(300 MHz; $CDCl_3$) 7.1–7.4 (5H, m), 6.3 (1H, br s), 5.10 (2H, s), 2.43 (3H, s), 2.28 (3H, s); δ_C(75.46 MHz; $CDCl_3$) 188.8, 162.6, 146.2, 135.8, 129.0, 127.7, 126.4, 110.3, 46.5, 30.1, 14.4; *m*/*z* 246 (M^+, 25%) 231 (2), 203 (3), 155 (3), 91 (100), 65 (11), 43 (5); HRMS: $C_{13}H_{14}N_2OS$ requires 246.0827, found 246.0831. Found: C, 63.23; H, 5.70; N, 11.42%; $C_{13}H_{14}N_2OS$ requires C, 63.39; H, 5.73; N, 11.37%.

1-[2-(Benzylamino)-4-methyl-1,3-thiazol-5-yl]ethan-1-one (13)

Mp 118–120 °C (lit.,[21] 112 °C) (CH_2Cl_2); δ_H(300 MHz; $CDCl_3$) 7.3–7.4 (5H, m), 7.0 (1H, br s), 4.47 (2H, s), 2.47 (3H, s), 2.39 (3H, s); δ_C(75.46; $CDCl_3$) 188.0, 171.8, 157.9, 136.4, 128.9, 128.0, 127.5, 122.0, 48.9, 29.8, 18.4; *m*/*z* 246 (M^+, 45%), 231 (5), 149 (5), 106 (7), 91 (100), 65 (8), 43 (14); HRMS: $C_{13}H_{14}N_2OS$ requires 246.0827, found 246.0825. Found: C, 63.30; H, 5.70; N, 11.23%; $C_{13}H_{14}N_2OS$ requires C, 63.39; H, 5.73; N, 11.37%.

***N*-Benzyl-4-phenyl-1,3-thiazol-2-amine (14)**

Mp 100–102 °C (MeOH); δ_H(300 MHz; $CDCl_3$) 10.2 (1H, br s), 7.65–7.75 (3H, m), 7.3–7.5 (7H, m), 6.56 (1H, s), 4.57 (2H, d, *J* 5.8 Hz). Found: C, 72.00; H, 5.27; N, 10.45%; $C_{16}H_{14}N_2S$ requires C, 72.15; H, 5.30; N, 10.52%.

Phenacyldimethylsulfonium bromide (15)

Mp 136–138 °C (lit.,[25] 133–134 °C); δ_H(300 MHz; $CDCl_3$) 8.1–7.6 (5H, m), 5.60 (2H, s), 3.02 (6H, s); δ_C(75.46 MHz; $CDCl_3$) 191.5, 133.9, 135.2, 129.3, 128.8, 52.3, 24.7; *m*/*z* 200 (M^+, for C_8H_7OBr, 5%), 198 (5), 120 (3), 105 (100), 91 (10), 77 (38), 62 (23).

***N*-Benzyl-5-chloro-4-methyl-1,3-thiazol-2-amine (16)**

Oil; δ_H(300 MHz; $CDCl_3$) 7.3–7.4 (5H, m), 4.40 (2H, s), 2.13 (3H, s); δ_C(75.46 MHz; $CDCl_3$) 165.5, 144.5, 137.1, 128.8, 127.9, 127.6, 106.0, 49.4, 14.4; (*m*/*z*) 238 (M^+, 15%), 132 (5), 91 (100), 65 (10). Found: C, 55.18; H, 4.61; N, 11.65; S, 13.37; Cl, 14.78%; $C_{11}H_{11}ClN_2S$ requires C, 55.34; H, 4.64; N, 11.73; S, 13.43; Cl, 14.85%.

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