51. Transformations in the Isoxazole Series: Synthesis of Substituted 2-Aminothiazoles

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Substitued *N*-(isoxazol-4-yl)thioureas **1** undergo a transformation in the presence of hexacarbonylmolybdenum and acid to yield functionalized thiazoles **3** in a one-pot reaction. In a few cases, 1,4,5-trisubstituted dihydroimidazolethiones **4** are also isolated as side products. Mechanistic considerations are outlined and scope and limitations of this new methodology discussed.

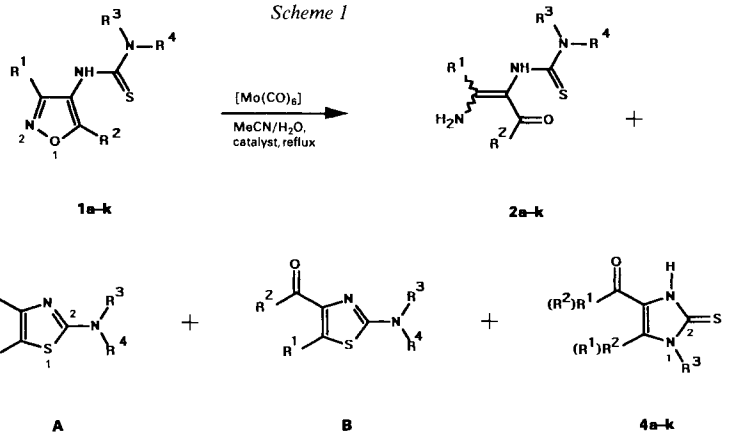
1. Introduction. – The isoxazole ring is a very useful masked functionality in organic syntheses [1]. It has been widely used in complex systems, *e.g.* in natural-product chemistry, to uncover a reactive amino-enone unit at a late step of a syntheses [2] or to exchange existing functionalities, as in the short synthesis of β-damascone from α-ionone [3]. These uses stem from the facility with which N–O bond cleavage can be effected. Recently, the preparative scope has included the synthesis of other N-containing five-membered heterocycles, *e.g.* pyrazoles [4] or triazoles [5], using isoxazoles substituted in the 4-position as synthons. In an elegant example of an intramolecular rearrangement, substituted imidazoles have been prepared regioselectively from 4-(acylamino)isoxazole derivatives [6], while isoxazole-oxazole conversions have also been reported [7] [8].

We have previously described the synthesis of 2-aminooxazole-4-carbonitriles in one step *via* the rearrangement of carbodiimides derived from 4-aminoisoxazoles [8]. In a further extension of this methodology, we now report the synthesis of substituted 2-aminothiazoles *via* the molecular rearrangement of *N*-(isoxazol-4-yl)thiourea derivatives **1**.

2. Results. – The normal conditions for ring opening of isoxazoles (catalytic hydrogenation, see *e.g.* [6]) were not applicable to thioureas such as **1**. We, therefore, sought a mild selective method to bring about this reaction. Several reports of N–O reductive scission exist in the literature[1]); we found that the use of $[Mo(CO)_6]$ in moist MeCN [10] proved to induce the desired cleavage of **1a** to **2a** cleanly; furthermore we could isolate form the same reaction the thiazole **3a** in low yield (see *Table 1, Entry 1*). The yield of **3a** could be improved greatly by increasing the reaction time (*Table 1, Entry 2*); **2a** is most likely the single intermediate to the formation of **3a** (*Entry 3*). Addition of 20%-equiv. of acid brought the reaction to completion in a much shorter time (*Entries 4–6*).

[1]) With samarium(II) iodide, see [9a]; with hexacarbonylmolybdenum, see [2] [10]; with dihydrolipoamide-iron(II), see [9b].

Scheme 1



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a	Me	Me	*t*-Bu	H	**g**	Me	Me	$PhCH_2$	H
b	Me	Me	Ph	H	**h**	Me	Me	Pr	H
c	Me	Me	4-$MeOC_6H_4$	H					
d	Me	Me	4-$MeCOC_6H_4$	H	**i**	i-Pr	i-Pr	i-Pr	H
e	Me	Me	Me	Me	**j**	Ph	Me	*t*-Bu	H
f	Me	Me	Ph	Me	**k**	4-ClC_6H_4	i-Pr	*t*-Bu	H

Table 1. *Preliminary Experiments with* **1a** *and* **2a**

Entry	Starting material	Catalyst[a])	Reaction time [h]	Yield [%][b])	
				2a	**3a**
1	**1a**	–	3	70	13
2	**1a**	–	30	20	61
3	**2a**	–	23	12	52
4	**1a**	HCl	20	traces	74
5	**1a**	$AlCl_3$	2.5	traces	67
6	**1a**	$SnCl_4$	1.5	–	68

[a]) *Ca.* 20%-equiv. b) Isolated yields after column chromatography.

Table 2. *Compounds Prepared*[a])

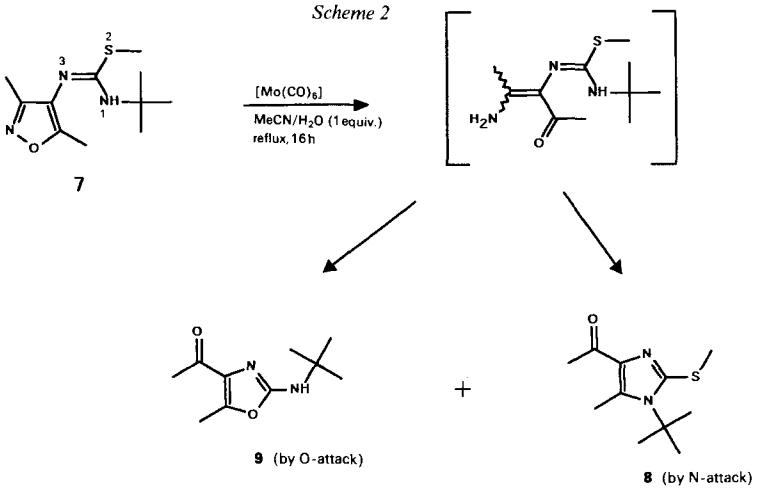
Starting material	Reaction time [h]	Yield [%][b])					Formation of **6** observed
		2	**3**	**4**	**8**	**9**	
1a	1.5	–	68	–	–	–	–
1b	3	–	16	15	–	–	+
1c	6	–	6	traces	–	–	+
1d	1.5	–	17	22	–	–	+
1e	1.5	–	56	–	–	–	–
1f	17	8	54	–	–	–	–
1g	1.5	–	3	6	–	–	+
1h	1.5	–	21	13	–	–	+
1i	1.5	–	61	–	–	–	–
1j[c])	48	27	49[d])	–	–	–	–
1k	1.5	–	70[e])	–	–	–	–
7[c])	16	–	–	–	18	58	–

[a]) $SnCl_4$ (20%-equiv.) as catalyst used. [b]) Isolated yields after column chromatography. [c]) No catalyst added. [d]) 14% of **A** and 35% of **B**. [e]) 17% of **A** and 53% of **B**.

After confirming the one-pot formation of the thiazoles **3 a–i** from **1a–i**, we investigated the use of unsymmetrically substituted isoxazoles **1**. We indeed found that from **1j** and **1k**, mixtures of products, *i.e.* **3jA/3jB** and **3kA/3kB**, were formed (*Table 2*, *Scheme 1*). In most cases, the yield of thiazole **3** was fair to good (*Table 2*); in a few instances, however, yields were reduced due to the formation of **4** and cleavage to **5** and **6** (see *Chapt. 4*).

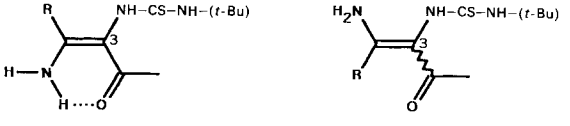
For comparison, we also studied the behaviour of one particular isothiourea derivative, **7** (see *Scheme 2*), and could isolate analogously imidazole **8** together with oxazole **9** as the main product (see *Table 2*).

Scheme 2



3. Structure Assignments. – The structure of all new compounds was established mainly by spectroscopic means.

Thioureas **2**. ^{1}H- and ^{13}C-NMR data for compound **2a** were initially inconclusive due to the high complexity of the spectra; a two-dimensional C,H experiment shows the existence of two isomers **2aA** and **2aB** (ratio of *ca.* 55:45), allowing for the unambiguous assignment of the signals. The major isomer is supposed to be **2aA** because of the possibility of a 6-ring H-bridging between the free NH_2 group and the C=O rest. This hypothesis is supported by the isolation of **2j** in a parallel experiment, which similarly shows two sets of signals in the NMR experiments, in a ratio of *ca.* 2:1. The major isomers **2aA** and **2jA** exhibit a typical chemical shift for C(3) of *ca.* 107



2aA R = Me
jA R = Ph

2aB R = Me
jB R = Ph

ppm, whereas the same C-atom in the minor isomers appears at *ca.* 103 ppm. It is interesting to note that during the melting-point determination of both **2a** and **2j**, two distinctly different melting ranges are observed. The only other isolated compound of this series, **2f**, melts sharply, and a single set of signals is observed in the NMR experiments.

Thiazoles **3**. The thiazole structure is easily confirmed by ^{13}C-NMR spectroscopy: C(2) shows no appreciable couplings ^nJ(C,H) in all cases investigated. Isomers **3A** and **3B** are assigned using IR data (C=O bands at *ca.* 1655 or 1690 cm^{-1}, resp.) and NMR spectroscopy.

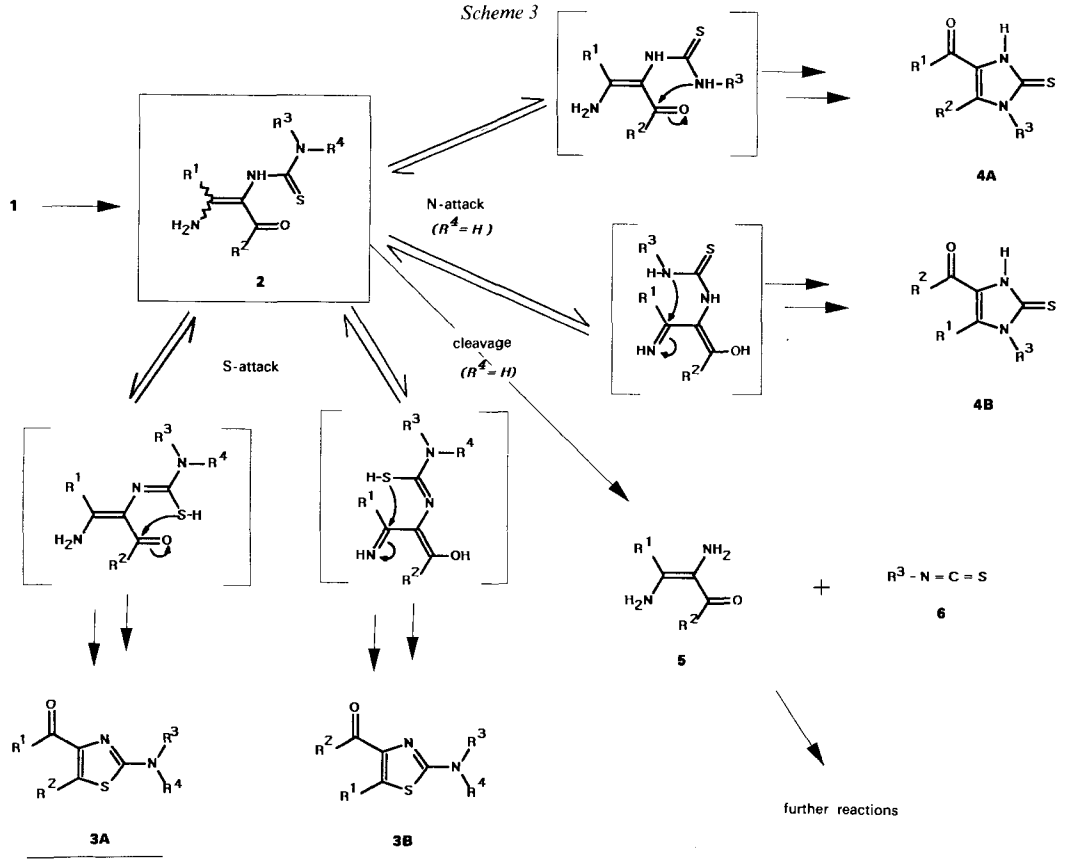
Dihydroimidazolethiones **4**. A slightly widened band at *ca.* 13 ppm in the ^{1}H-NMR spectrum ((D$_6$)DMSO) together with a C=O frequency at *ca.* 187 ppm suggests the existence of an intramolecular H-bridge; on the other hand, the ^{13}C-NMR shifts of the aromatic ring (*e.g.* in **4b**) are only consistent with a structure in which the Ph ring is attached directly to a ring N-atom. These facts together with mechanistic considerations help to postulate structure **4**. Published spectroscopic data for *N*-substituted dihydroimidazolethiones[2]) are consistent with the above interpretation.

Imidazole **8**. The structure of **8** is assigned on the basis of mechanistic considerations and of a similarity in analytical results with compound **9** and dihydroimidazolethiones **4**. It is interesting to note that, whereas the frequency of the C=O group in the IR spectrum is close to that of **4**, the chemical shift of the same group in the ^{13}C-NMR spectrum is found in the expected range (*ca.* 196 ppm), in contrast to the observed values for **4**.

Oxazole **9**. The IR frequency of the C=O group (1690 cm^{-1}) and NMR data support its structure; the chemical shifts and coupling constants in the ^{13}C-NMR spectrum are similar for the pertinent C-atoms to the published values for substituted 2-aminooxazole-4-carbonitriles [8].

4. Discussion. – Although the synthesis of compounds **3** was our main objective, isolation and characterisation of **4** has given us a better insight into the course of the ring-closure reaction and thus the potential scope thereof. After ring opening of **1** *via* Mo-complexation [10] to give the open structure **2**, the presence of the substituent R^4 on the molecule (see *Scheme 3*) has a great influence on the subsequent ring-closure step.

Scheme 3



[2]) For 1-alkyl-substituted and 1-phenyl-substituted dihydroimidazolethiones, see [11a] and [11b], respectively.

Should R^4 be different from H, only the S-attack pathway is open, and this leads to the single formation of thiazoles **3** (*cf. Table 2*); steric effects in R^3 and R^4 seem to play no role. However, if R^4 = H, several pathways are possible: *i*) S-attack to give thiazoles **3** as previously indicated (main route if R^3 is a bulky aliphatic group), *ii*) N-attack to give dihydroimidazolethiones **4**, and *iii*) cleavage to diamine **5** and isothiocyanate **6**. The formation of **4** and the cleavage pathway occur simultaneously (as proven by the isolation of **6b–d, g, h**), and since **5** is probably very prone to undergo further reactions before or during workup, this could explain the low yields of **3** and **4** obtained. Further unknown side reactions presumably occur, since the yields are, even in the best cases, not greater than 70%. The substitution pattern of the isoxazole ring of **1** (R^1 and R^2) has, on the other hand, no effect on the reaction outcome, and the isomer distribution **3A** *vs.* **3B** seems to be independent of the presence of catalyst (compare **1j** and **1k** in *Table 2*).

For preparative purposes, it is possible to separate **3** from **4** very easily by chromatography, so that a mixture **3**/**4** is also of great synthetic value. In the case of formation of both isomers **3A** and **3B**, chromatography also achieves a very good separation of the isomers. The scope of this methodology is, therefore, considerable; upon carefully selecting the substituents, it is possible to obtain **3** as a single reaction product or as a separable mixture with **4**. On the other hand, use of substituents R^3 or R^4 such as benzyl and aryl with electron-rich groups gives rise mainly to cleavage of intermediate **2**.

As expected, the use of isothioureas (*e.g.* **7**) does not lead to the formation of thiazoles; imidazole **8** (*via* N-attack; see *Scheme 2*) and oxazole **9** are the reaction products of **7**, and their formation supports the mechanistic considerations outlined above. The S-attack pathway is suppressed due to the leaving-group effect of the MeS substituent; however, O-attack leads to oxazole **9**. In sharp contrast to compound **2**, the equivalent intermediate (see *Scheme 2*) could not be detected. Although only one example was studied, this rearrangement concept should work with other appropriated S-containing side chains as well.

Thus, we have shown that thiourea derivatives in the isoxazole series (C(4) substitution) are useful intermediates for the synthesis of highly functionalized thiazoles; this methodology expands the synthetic interest of the isoxazole-ring system in organic chemistry and, since the carbonyl functionality is present in the 4-position of the thiazoles, offers a complementary route to the reported synthesis of thiazoles bearing the carbonyl group in the 5-position [12]. In a more general mechanistic context, this reaction belongs to the group of molecular heterocyclic rearrangements involving three side-chain atoms, of which only a few examples are known [13].

I greatly appreciate the fruitful discussions of NMR data with Dr. *H. Sauter* and Dr. *J. Schneider* of our analytical department as well as literature references offered by Dr. *T. Winkler* and the steady support and comments by Dr. *J. Ehrenfreund*. I am also indebted to Dr. *R. Hall* for valuable suggestions and improvement of the manuscript.

Experimental Part

1. *General.* Extracts were dried ($MgSO_4$) and evaporated at aspiration vacuum in a rotary evaporator. Flash column chromatography [14] (FC): silica gel (SiO_2 *60 Merck*, 0.040–0.063 mm, 230–400 mesh ASTM). M.p.: *Kofler* hot-plate apparatus. UV spectra (EtOH): *Perkin-Elmer-Lambda-5* UV/VIS apparatus. IR spectra: *Perkin-Elmer-157G* spectrometer. NMR spectra: *Varian-EM360L* (^{1}H, 60 MHz), *Bruker-AC-F250* (^{1}H, 250 MHz; ^{13}C, 62.5 MHz), or *Varian-XL-300* spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz); chemical shifts in ppm rel. to TMS as

Table 3. *NMR Data for Compounds* **2**

	^{1}H-NMR ((D$_6$)DMSO)[a])	^{13}C-NMR ((D$_6$)DMSO)[b])
2a	9.82 (br. *s*, NH); 9.67 (br. *s*, NH); 8.31 (*s*, NHCS); 7.92 (br. *s*, NH); 7.89 (*s*, NHCS); 7.46 (br. *s*, NH); 7.32 (*s*, NHCS); 5.86 (*s*, NHCS); 1.86 (*s*, 6 H); 1.80 (*s*, 3 H); 1.76 (*s*, 3 H); 1.43 (*s*, 18 H)	*major isomer:* 194.4 (CO); 161.2 (C(2)); 107.4 (C(1)); 26.5 (*Me*CO); *minor isomer:* 194.0 (CO); 162.8 (C(2)); 103.2 (C(1)); 26.1 (*Me*CO); *other signals:* 180.3, 183.3 (CS); 52.3, 52.2, 28.9, 28.8 (*t*-Bu); 18.4, 18.7 (C(3)).
2f	9.64 (br. *d*, NH); 7.69 (*s*, NHCS); 7.43 (br. *s*, NH); 7.55–7.28 (*m*, 5 arom. H); 3.56 (*s*, 3 H); 1.87 (*s*, 3 H); 1.76 (*s*, 3 H)	194.4 (CO); 184.0 (CS); 161.1 (C(2)); 144.4, 130.3, 127.9, 127.4 (arom C); 109.2 (C(1)); 43.6 (MeN); 26.7 (*Me*CO); 18.9 (C(3)).
2j[c])	10.10, 9.90 (2 br. *s*, 2 H); 8.35 (*s*, 1 H); 7.98 (br. *s*, 1 H); 7.81 (*s*, 2 H); 7.55–7.37 (*m*, 18 H); 7.16 (*s*, 2 H); 5.76 (*s*, 1 H); 2.01 (*s*, 6 H); 1.99 (*s*, 3 H); 1.35 (*s*, 18 H); 1.27 (*s*, 9 H)	*major isomer:* 197.0 (CO); 184.1 (CS); 159.6 (C(2)); 136.1, 128.9, 127.5 (arom. C); 106.8 (C(1)); 52.7, 28.9 (*t*-Bu); 26.8 (*Me*CO); *minor isomer:* 196.3 (CO); 179.6 (CS); 161.9 (C(2)); 134.7, 129.4, 127.5 (arom. C); 102.5 (C(1)); 52.2, 28.5 (*t*-Bu); 26.8 (*Me*CO)

[a]) At 300 MHz for **2a** and **2j**, at 250 MHz for **2f**. [b]) At 75 MHz for **2a** and **2j**, at 62.5 MHz for **2f**. [c]) The numbering of the main chain has been left unchanged to facilitate the comparison with Me-substituted compounds.

Table 4. *NMR Data* ($CDCl_3$) *for Compounds* **3**

	^{1}H-NMR[a])	^{13}C-NMR[b])
3a	4.80 (br. *s*, 1 H); 2.60 (*s*, 3 H); 2.50 (*s*, 3 H); 1.40 (*s*, 9 H)	195.6 (CO); 161.0 (C(2)); 144.1 (C(4)); 132.5 (C(5)); 52.9, 28.9 (*t*-Bu); 29.5 (*Me*CO); 12.7 (*Me*–C(5))
3b	7.4–7.3 (*m*, 4 H); 7.08 (*m*, 2 H); 2.66 (*s*, 3 H); 2.60 (*s*, 3 H)	195.8 (CO); 159.2 (C(2)); 144.3 (C(4)); 133.6 (C(5)); 140.4, 129.5, 123.0, 118.1 (arom. C); 29.6 (*Me*CO); 12.9 (*Me*–C(5))
3c[c])	7.30, 6.92 (2*m*, 5 H); 3.82 (*s*, 3 H); 2.62 (*s*, 3 H); 2.57 (*s*, 3 H)	
3d[d])	10.57 (*s*, 1 H); 7.94 (*d*, J = 9, 2 H); 7.75 (*d*, J = 9, 2 H); 2.61 (*s*, 3 H); 2.58 (*s*, 3 H); 2.52 (*s*, 3 H)	196.0 (*C*O–C(4)); 194.3 (*C*O–C(arom.)); 157.2 (C(2)); 143.8 (C(4)); 145.0, 129.9, 129.8, 115.9 (arom. C); 133.7 (C(5)); 29.4 (*Me*CO); 26.3 (*Me*CO–C(arom.)); 12.2 (*Me*–C(5))
3e	3.07 (*s*, 6 H); 2.60 (*s*, 3 H); 2.54 (*s*, 3 H)	195.5 (CO); 164.9 (C(2)); 144.6 (C(4)); 131.4 (C(5)); 39.3 (MeN); 28.7 (*Me*CO); 12.2 (*Me*–C(5))
3f	7.50–7.35 (*m*, 4 H); 7.30–7.20 (*m*, 1 H); 3.52 (*s*, 3 H); 2.58 (*s*, 3 H); 2.55 (*s*, 3 H)	195.6 (CO); 163.8 (C(2)); 144.4 (C(4)); 145.8, 129.4, 126.0, 124.3 (arom. C); 132.5 (C(5)); 39.3 (CH_2); 29.0 (*Me*CO); 12.4 (*Me*–C(5))
3g[c])	7.40–7.25 (*m*, 5 H); 5.45 (br. *s*, 1 H); 4.46 (*s*, 2 H); 2.58 (*s*, 3 H); 2.52 (*s*, 3 H)	
3h	5.02 (br. *s*, 1 H); 3.20 (br. *q*, 2 H); 2.60 (*s*, 3 H); 2.52 (*s*, 3 H); 1.68 (*sext.*, J = 7, 2 H); 1.00 (*t*, J = 7, 3 H)	195.6 (CO); 164.9 (C(2)); 144.3 (C(4)); 132.1 (C(5)); 47.9, 22.7, 11.4 (Pr); 29.5 (*Me*CO); 13.0 (*Me*–C(5))
3i	4.73 (br. *d*, J = 7, 1 H); 4.06 (*sept.* J = 7, 1 H); 3.70 (2*sept.*, 2 H); 3.60 (*sept.*, J = 7, 1 H); 1.27 (*d*, J = 7, 6 H); 1.22 (*d*, J = 7, 6 H); 1.14 (*d*, J = 7, 6 H)	201.9 (CO); 163.3 (C(2)); 147.1, 142.5 (C(4), C(5)); 47.6 (CN); 38.2 (*C*–CO); 27.5 (*C*–C(5)); 24.9, 22.9, 18.6 (6 Me)
3jA	8.1–7.9 (*m*, 2 H); 7.5–7.2 (*m*, 3 H); 5.10 (br. *s*, 1 H); 2.55 (*s*, 3 H); 1.35 (*s*, 9 H)	188.7 (CO); 161.6 (C(2)); 143.2 (C(4)); 133.2 (C(5)); 138.3, 132.2, 130.2, 127.8 (arom. C); 52.9, 28.9 (*t*-Bu); 12.9 (*Me*–C(5))
3jB	7.5–7.1 (*m*, 5 H); 5.15 (br. *s*, 1 H); 2.50 (*s*, 3 H); 1.40 (*s*, 9 H)	194.3 (CO); 163.0 (C(2)); 143.2 (C(4)); 133.6 (C(5)); 131.0, 129.9, 128.3, 128.0 (arom. C); 53.1, 28.9 (*t*-Bu); 29.9 (*Me*CO)
3kA	8.03, 7.40 (*AA'BB'*, J = 9); 4.85 (br. *s*, 1 H); 3.87 (*sept.*, J = 7, 1 H); 1.41 (*s*, 9 H); 1.32 (*d*, J = 7, 6 H)	
3kB	7.40, 7.32 (*AA'BB'*, J = 9); 4.92 (br. *s*, 1 H); 3.62 (*sept.*, J = 7, 1 H); 1.48 (*s*, 9 H); 1.14 (*d*, J = 7, 6 H)	201.2 (CO); 163.2 (C(2)); 142.9 (C(4)); 134.2 (C(5)); 132.4, 131.4, 128.9, 128.3 (arom. C); 53.3, 28.9 (*t*-Bu); 38.3, 18.5 (i-Pr)

[a]) At 60 MHz for **3a**, **3jA**, and **3jB**, at 250 MHz for **3b**–**h**, and at 300 MHz for **3i**, **3kA**, and **3kB**. [b]) At 75 MHz for **3a**, **3i**, **3jA**, **3jB**, and **3kB**, and at 62.5 MHz for **3b**, **3d**–**f**, and **3h**. [c]) Sample of *ca.* 80% purity. [d]) In (D$_6$)DMSO.

Table 5. *NMR Data for Compounds* **4**

	^{1}H-NMR (250 MHz, (D$_6$)DMSO)	^{13}C-NMR (62.5 MHz, (D$_6$)DMSO)
4b	12.88 (br. *s*, 1 H); 7.60–7.50 (*m*, 3 H); 7.38–7.30 (*m*, 2 H); 2.43 (*s*, 3 H); 2.18 (*s*, 3 H)	187.0 (CO); 164.1 (CS); 135.2, 129.4, 129.3, 128.7 (arom. C); 134.7 (C(5)); 124.4 (C(4)); 28.5 (*Me*CO); 11.7 (*Me*–C(5))
4d	13.00 (br. *s*, 1 H); 8.12 (*d*, *J* = 9, 2 H); 7.54 (*d*, *J* = 9, 2 H); 2.66 (*s*, 3 H); 2.44 (*s*, 3 H) 2.20 (*s*, 3 H)	197.2 (*C*O–C(arom.)); 187.1 (*C*O–C(4)); 163.9 (CS); 139.0, 137.1, 129.2 (arom. C); 134.4 (C(5)); 124.7 (C(4)); 28.5 (*Me*CO); 26.9 (*Me*CO–C(arom.)); 11.6 (*Me*–C(5))
4g[a])	12.80 (br. *s*, 1 H); 7.40–7.20 (*m*, 5 H); 5.38 (*s*, 2 H); 2.40 (*s*, 3 H); 2.32 (*s*, 3 H)	187.0 (CO); 163.4 (CS); 136.1, 128.6, 127.5, 126.8 (arom. C); 134.4 (C(5)); 124.1 (C(4)); 46.4 (CH$_2$); 28.4 (*Me*CO); 10.9 (*Me*–C(5))
4h	12.68 (br. *s*, 1 H); 3.98 (*dd*, *J* = 6, 6, 2 H); 2.48 (*s*, 3 H); 2.38 (*s*, 3 H); 1.64 (*sext.*, *J* = 7, 2 H); 0.90 (*t*, *J* = 7, 3 H)	186.9 (CO); 162.4 (CS); 134.4 (C(5)); 123.7 (C(4)); 44.9 (CH$_2$N); 28.4 (*Me*CO); 21.1 (MeCH$_2$); 11.0 (*Me*–C(5)); 10.5 (*Me*CH$_2$)

[a]) Sample with *ca.* 80% purity.

Table 6. *Coupling Constants* ^nJ*(C,H) for* **8**, **9**, *and Selected Compounds* **3** *and* **4**

	^nJ(C,H)			
	C(2)	C(4)	C(5)	CO
3a	0	br. *q*	*J* = 7.5, *q*	*J* = 6.0, *q*
3jA	0	*J* = 4.0, *q*	*J* = 7.3, *q*	*J ca.* 4, *t*
3jB	0	br.	*J* = 4.5, *t*	*J* = 6.2, *q*
4d	*J* = 4.0, *d*	br.	*J* = 6.0, *q*	*J* = 6.0, *q*
8	*J* = 4.5, *q*	*J* = 4.0, 1.0, *qq*	*J* = 7.0, *q*	*J* = 6.0, *q*
9	0	br.	*J* = 7.8, *q*	*J* = 6.5, *q*

internal standard; coupling constants in Hz; NMR data for **2**–**4**, **8**, and **9**, see *Tables 3–6*. HR-MS: *Finnigan MAT 212/SS300* (ion source 70 eV at 200°, inlet at 60°).

2. *Starting Materials* **14** (see *Scheme 4*). 2.1. *Symmetrical Isoxazoles. 3,5-Dimethylisoxazole* (**10a**) was supplied by *Janssen* (Belgium) and used directly.

3,5-Diisopropylisoxazole (**10b**) was prepared by cyclisation of 2,6-dimethylheptane-3,5-dione [15] with NH_2OH in basic aq. EtOH [16]: To the soln. of dione (67.0 g, 0.429 mol) in EtOH (335 ml), a soln. of $NH_2OH \cdot HCl$ (46.2 g, 0.660 mol) in H_2O (500 ml) was added, followed by Na_2CO_3 (92.5 g, 0.430 mol) at r.t. within 30 min. After heating under reflux for 24 h, the major part of the solvent was evaporated and the residue worked up with Et_2O. The crude oily product (60.9 g) was fractionated (small *Vigreux* column) yielding pure **10b** (10.7 g; b.p. 86–89°/22 mbar) and the uncyclised oxime (41.3 g; b.p. 90–140°/22 mbar), which was treated with Na_2CO_3 (56.6 g) in EtOH (200 ml) and H_2O (300 ml) under reflux for 24 h, yielding a further 30.0 g of **10b** (overall yield 62%). UV: 214 (6720). IR (CCl_4): 2970*s*, 2930*m*, 2880*m*, 1600*s*, 1470*s*, 1420*m*, 1390*m*, 1370*m*, 1295*m*, 1180*m*, 1045*m*, 985*m*, 900*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 5.75 (*s*, 1 H); 3.05 (*sept.*, *J* = 7, 2 H); 1.28 (*d*, *J* = 7, 6 H); 1.25 (*d*, *J* = 7, 6 H). Anal. calc. for $C_9H_{15}NO$ (153.23): C 70.55, H 9.87, N 9.14; found: C 70.53, H 9.87, N 9.30.

3,5-Dimethyl-4-nitroisoxazole [17] (**11a**) *and 3,5-Diisopropyl-4-nitroisoxazole* (**11b**) were obtained from 3,5-disubstituted isoxazoles by nitration with HNO_3/H_2SO_4 at 110° according to [17].

11a: Yield 80%. M.p. 60–61°.

11b: Viscous pale yellow oil in 80% yield, after purification of the crude product by short-pad FC (AcOEt/hexane 1:10). UV: 204 (10680), 265 (5320). IR (CCl_4): 2980*m*, 2940*m*, 2880*w*, 1595*s*, 1515*s*, 1460*m*, 1430*m*, 1370*s*, 1265*w*, 1175*w*, 1130*m*, 1070*m*, 825*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 3.85 (*sept.*, *J* = 7, 1 H); 3.55 (*sept.*, *J* = 7, 1 H); 1.40 (*d*, *J* = 7, 6 H); 1.35 (*d*, *J* = 7, 6 H). Anal. calc. for $C_9H_{14}N_2O_3$ (198.22): C 54.54, H 7.12, N 14.13; found: C 54.65, H 7.06, N 14.10.

4-Amino-3,5-dimethylisoxazole [17] (**14a**) was obtained by reduction of **11a** with $Zn/NH_4Cl/H_2O$ at 0–5° (see [8]). Yield 82%. M.p. 51–53°. The crude product was used directly.

4-Amino-3,5-diisopropylisoxazole (**14b**) was obtained similarly from **11b**. Yield 60%, after FC (AcOEt/hexane 1:4). Pale yellow oil. UV: 248 (2500). IR (CCl_4): 3440*w* (br.), 3360*w* (br.), 2980*s*, 2940*m*, 1880*m*, 1650*m*, 1610*m*, 1475*s*, 1460*m*, 1385*m*, 1370*m*, 1245*m*, 1190*m*, 1055*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 3.7–2.6 (br. *s*, 2 H); 2.95 (*sept.*,

J = 7, 2 H); 1.25 (*d*, J = 7, 6 H); 1.22 (*d*, J = 7, 6 H). Anal. calc. for $C_9H_{16}N_2O$ (168.24): C 64.25, H 9.59, N 16.65; found: C 63.91, H 9.50, N 16.10.

2.2. *Asymmetrical Isoxazoles. 5-Methyl-4-nitro-3-phenylisoxazole* [20] (**11c**) *and 3-(4'-Chlorophenyl)-5-isopropyl-4-nitroisoxazole* (**11d**). Aromatic carbohydroximoyl chlorides **13** (obtained by chlorination in $CHCl_3$ of the corresponding oximes [18]) were condensed with α-nitroketones[3]) **12** to give 3-Ph-substituted 4-nitroisoxazoles [20].

11c: Yield 58%, after chromatography (AcOEt/hexane 1:10). M.p. 43–44°.

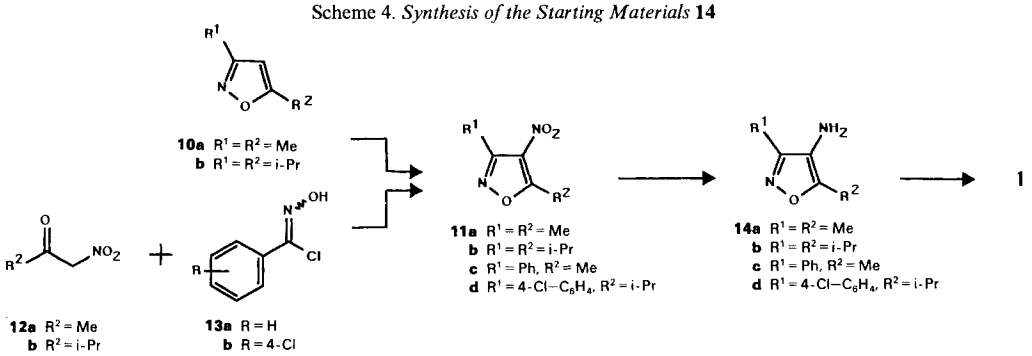
11d: Yield 53%, after FC (AcOEt/hexane 1:4). Colourless crystals. M.p. 74–77°. UV: 234 (17440), 262 (sh). IR (CCl_4): 2980*w*, 1605*s*, 1590*s*, 1510*s* (br.), 1430*m*, 1365*s*, 1185*m*, 1095*s*, 1065*m*, 1015*m*, 970*m*, 830*s*. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.45 (*s*, 4 H); 3.85 (*sept.*, J = 7, 1 H); 1.45 (*d*, J = 7, 6 H). Anal. calc. for $C_{12}H_{11}ClN_2O_3$ (266.68): C 54.05, H 4.16, N 10.50; found: C 54.13, H 4.29, N 10.33.

4-Amino-5-methyl-3-phenylisoxazole [21] (**14c**) *and 4-Amino-3-(4'-chlorophenyl)-5-isopropylisoxazole* (**14d**) were obtained as described above for **14a**.

14c: Yield 53%, after chromatography (AcOEt/hexane 1:2). M.p. 53–55°.

14d: Yield 62%, after FC (AcOEt/hexane 1:5→1:3). M.p. 50–52°. UV: 238 (12660), 278 (4600). IR ($CHCl_3$): 3420*w* (br.), 3340*w* (br.), 2970*m*, 1640*m*, 1605*m*, 1455*s* (br.), 1335*m*, 1090*s*, 1010*s*, 830*s*. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.75, 7.40 (*AA'B'B'*, J = 9); 3.15 (*sept.*, J = 7, 1 H); 2.75 (*s*, 2 H); 1.35 (*d*, J = 7, 6 H). Anal. calc. for $C_{12}H_{13}ClN_2O$ (236.70): C 60.89, H 5.54, Cl 14.98, N 11.84; found: C 60.73, H 5.59, Cl 14.75, N 11.94.

Scheme 4. *Synthesis of the Starting Materials* **14**



3. *Substituted* N-*(Isoxazolyl)thioureas* **1**. *General Procedure*. The 4-aminoisoxazoles **14** were converted to the corresponding crude isothiocyanates as previously described [8]. Crude isothiocyanate (30 mmol) was then dissolved in toluene (70 ml) and the amine (36 mmol) in toluene (25 ml) added at r.t. The mixture was then kept at 50° for 2 h. After cooling the crystals were filtered, washed with a few ml of toluene and then with hexane (10 ml) and dried. For **1d**, a slightly modified procedure was used.

N-*(*tert*-Butyl)*-N'-*(3,5-dimethylisoxazol-4-yl)thiourea* (**1a**). Yield 89%. M.p. 161–162°. UV: 211 (12790), 250 (12300). IR (KBr): 3450*m*, 3360*m*, 3320*s*, 3150*s*, 2980*s*, 2970*s*, 1680*m*, 1540*s*, 1400*s*, 1270*s*, 1240*s*, 1205*s*, 1170*s*, 790*m*, 650*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.70 (br. *s*, 1 H); 5.55 (br. *s*, 1 H); 2.35 (*s*, 3 H); 2.20 (*s*, 3 H); 1.48 (*s*, 9 H). Anal. calc. for $C_{10}H_{17}N_3OS$ (227.33): C 52.84, H 7.54, N 18.49, S 14.11; found: C 52.64, H 7.47, N 18.50, S 13.90.

N-*(3,5-Dimethylisoxazol-4-yl)*-N'-*phenylthiourea* (**1b**). Yield 82%. M.p. 189–191°. UV: 243 (14680), 268 (13400). IR (KBr): 3160*s*, 3000*s*, 1655*m*, 1590*m*, 1540*s*, 1510*s*, 1490*s*, 1310*s*, 1290*m*, 1250*s*, 1230*s*, 1200*m*, 690*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 9.96 (br. *s*, 1 H); 9.02 (br. *s*, 1 H); 7.47 (br. *d*, 2 H); 7.35 (*t*, J = 8, 2 H); 7.16 (*t*, J = 8, 1 H); 2.27 (*s*, 3 H); 2.13 (*s*, 3 H). Anal. calc. for $C_{12}H_{13}N_3OS$ (247.32): C 58.28, H 5.30, N 16.99, S 12.96; found: C 58.30, H 5.35, N 16.90, S 12.85.

N-*(3,5-Dimethylisoxazol-4-yl)*-N'-*(4'-methoxyphenyl)thiourea* (**1c**). Yield 91%. M.p. 192–194°. UV: 244 (15680). IR (KBr): 3360*m*, 3240*s*, 3160*s*, 2970*m*, 1540*s*, 1510*s*, 1440*m*, 1420*m*, 1360*m*, 1300*m*, 1240*s*, 1180*s*, 1030*s*, 830*s*, 735*m*, 610*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 9.75 (br. *s*, 1 H); 8.82 (br. *s*, 1 H); 7.30, 6.92 (*AA'BB'*, J = 9), 3.76 (*s*, 3 H); 2.26 (*s*, 3 H); 2.12 (*s*, 3 H). Anal. calc. for $C_{13}H_{15}N_3O_2S$ (277.34): C 56.30, H 5.45, N 15.15, S 11.56; found: C 56.37, H 5.51, N 14.94, S 11.30.

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[3]) Preparation of α-nitroalcohols in 44–53% yields according to [19a] and oxidation to α-nitroketones according to [19b]; the crude products **12** (*ca.* 90% yield) were used without further purifications.

N-(4'-Acetylphenyl)-N'-(3,5-dimethylisoxazol-4-yl)thiourea (**1d**). A soln. of 3,5-dimethyl-4-(isothiocyanato)isoxazol (crude; 6.00 g, *ca.* 39 mmol) in toluene (60 ml) was added to 4-aminoacetophenone (5.26 g, 38.9 mmol) in hot toluene (50 ml) and heated under reflux for 6 h. After cooling, a waxy solid was filtered out and crushed with cool toluene (10 ml), until it solidified completely. The brownish solid was filtered and washed with hexane: 4.85 g (43%). A small sample was recrystallized from toluene. M.p. 179–181°. IR (KBr): 3300*m*, 3180*m*, 3160*s*, 3080*m*, 3000*s*, 1670*s*, 1600*s*, 1535*s*, 1350*s*, 1315*s*, 1270*s*, 1245*s*, 1225*s*, 1200*m*, 1185*s*, 830*m*, 740*m*, 720*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 10.30 (br. *s*, 1 H); 9.28 (br. *s*, 1 H); 7.95, 7.72 (*AA'BB'*, J = 9); 2.56 (*s*, 3 H); 2.29 (*s*, 3 H); 2.13 (*s*, 3 H). MS: 289 (12, M^+), 255 (7), 213 (10), 212 (8), 178 (8), 161 (10), 145 (7), 130 (58), 120 (18), 102 (16), 91 (10), 71 (28), 43 (100).

N-(3,5-Dimethylisoxazol-4-yl)-N',N'-dimethylthiourea (**1e**). Yield 87%. M.p. 193–195°. UV: 208 (17000), 247 (14760). IR (KBr): 3290*m* (br.), 2920*m*, 1655*m*, 1540*s*, 1460*m*, 1380*m*, 1335*s*, 1285*m*, 1250*s*, 1150*m*, 870*m*, 720*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.52 (br. *s*, 1 H); 3.28 (*s*, 6H); 2.20 (*s*, 3 H); 2.07 (*s*, 3 H). Anal. calc. for $C_8H_{13}N_3OS$ (199.28): C 48.22, H 6.58, N 21.09, S 16.09; found: C 48.34, H 6.58, N 21.01, S 16.14.

N-(3,5-Dimethylisoxazol-4-yl)-N'-methyl-N'-phenylthiourea (**1f**). Yield 90%. M.p. 187–188°. UV: 253 (15640). IR (KBr): 3360*w*, 3260*m* (br.), 1665*m*, 1600*w*, 1515*s*, 1495*s*, 1345*s*, 1220*m*. 1110*m*, 695*s*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.20 (br. *s*, 1 H); 7.55–7.48 (*m*, 2H); 7.41–7.35 (*m*, 3 H); 3.58 (*s*, 3 H); 2.18 (*s*, 3 H); 2.08 (*s*, 3 H). Anal. calc. for $C_{13}H_{15}N_3OS$ (261,35): C 59.75, H 5.79, N 16.08, S 12.27; found: C 59.85, H 5.93, N 15.92, S 12.28.

N-Benzyl-N'-(3,5-dimethylisoxazol-4-yl)thiourea (**1g**). Yield 92%. M.p. 209–210°. UV: 248 (14360). IR (KBr): 3250*s*, 3180*s*, 3000*m*, 1640*m*, 1550*s*, 1520*s*, 1455*m*, 1455*m*, 1420*m*, 1235*s*, 1190*m*, 965*m*, 775*s*, 700*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.90 (br. *s*, 1 H); 8.30 (br. *s*, 1 H); 7.45–7.20 (*m*, 5 H); 4.72 (br. *d*, 2 H); 2.21 (*s*, 3 H); 2.07 (*s*, 3 H). Anal. calc. for $C_{13}H_{15}N_3OS$ (261.35): C 59.75, H 5.79, N 16.08, S 12.27; found: C 59.81, H 5.80, N 15.93, S 12.01.

N-(3,5-Dimethylisoxazol-4-yl)-N'-propylthiourea (**1h**). Yield 89%. M.p. 162–165°. UV: 247 (14640). IR (KBr): 3290*s*, 3160*s*, 2960*s*, 1640*m*, 1540*s*, 1520*s*, 1450*m*, 1420*m*, 1285*m*, 1240*s*, 1080*m*, 775*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.70 (br. *s*, 1 H); 7.80 (br. *s*, 1 H); 3.35 (br. *d*, 2 H); 2.20 (*s*, 3 H); 2.08 (*s*, 3 H); 1.52 (*sext.*, J = 7, 2 H); 0.86 (*t*, J = 7, 3 H). Anal. calc. for $C_9H_{15}N_3OS$ (213.30): C 50.68, H 7.09, N 19.70, S 15.03; found: C 50.60, H 7.37, N 19.91, S 14.77.

N-(3,5-Diisopropylisoxazol-4-yl)-N'-isopropylthiourea (**1i**). Yield 92%. M.p. 165–166°. UV: 207 (15240), 247 (14640). IR (KBr): 3600–2600*m* (br.), 3320*m*, 3160*s*, 2970*s*, 1620*w*, 1540*s*, 1510*s*, 1470*m*, 1270*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 8.35 (br. *s*, 1 H); 5.40 (br. *d*, J = 9, 1 H); 4.56 (*sept.*, J = 7, 1 H); 3.05 (2 *sept.*, 2 H); 1.25 (*d*, J = 7, 12 H); 1.18 (*d*, J = 7, 6 H). Anal. calc. for $C_{13}H_{23}N_3OS$ (269.41): C 57.96, H 8.61, N 15.60, S 11.90; found: C 57.91, H 8.64, N 15.85, S 12.00.

N'-(tert-Butyl)-N'-(5-methyl-3-phenylisoxazol-4-yl)thiourea (**1j**). Yield 94%. M.p. 163–164°. UV: 248 (17040). IR (KBr): 3370*m*, 3120*m*, 2970*m*, 1640*m*, 1530*s*, 1510*m*, 1450*m*, 1395*m*, 1270*s*, 1240*m*, 790*m*, 695*m*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 8.90 (br. *s*, 1 H); 8.2–7.7 (br. *m*, 6 H); 2.35 (*s*, 3 H); 1.45 (*s*, 9 H). Anal. calc. for $C_{15}H_{19}N_3OS$ (289.40): C 62.26, H 6.62, N 14.52, S 11.08; found: C 61.98, H 6.72, N 14.49, S 10.78.

N-(tert-Butyl)-N'-[3-(4'-chlorophenyl)-5-isopropylisoxazol-4-yl]thiourea (**1k**). Yield 84%. M.p. 162–164°. UV: 247 (22240). IR (KBr): 3300*m*, 3240*s*, 2970*s*, 1540*s*, 1515*s*, 1400*s*, 1265*m*, 1210*m*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 8.65 (br. *s*, 1 H); 7.75–7.30 (*m*, 5 H); 3.10 (*sept.*, J = 7, 1 H); 1.40 (*s*, 9H); 1.25 (*d*, J = 7, 6H). Anal. calc. for $C_{17}H_{22}ClN_3OS$ (351.90): C 58.02 H 6.30, N 11.94; found: C 57.78, H 6.68, N 12.06.

4. *Preliminary Experiments with* **1a** *and* **2a**. A soln. of **1a** (200 mg, 0.88 mmol) in MeCN (18 ml) was stirred and mixed with H_2O (*ca.* 0.016 ml, *ca.* 0.88 mmol) and [Mo(CO)$_6$] (116 mg, 0.44 mmol). If catalyst was used, *ca.* 20%-equiv. (*ca.* 0.025 ml $SnCl_4$, *ca.* 35 mg $AlCl_3$, or *ca.* 0.020 ml conc. HCl soln.) were added at last. The mixture was kept under light reflux for the time indicated in *Table 1*. After cooling, the suspension was filtered through a *Celite* pad, the solvent evaporated, and the residue worked up with AcOEt/$NaHCO_3$ soln. The crude product was submitted to FC (hexane/AcOEt 2:1→AcOEt): Yields of **2a** and **3a** in *Table 1*.

Similarly, **2a** (100 mg, 0.44 mmol) in MeCN (9 ml) and H_2O (*ca.* 0.008 ml, *ca.* 0.44 mol) was treated with [Mo(CO)$_6$] (58 mg, 0.22 mmol) at reflux for *ca.* 1 day (see *Table 1, Entry 3*). FC of the crude product gave **3a** (48 mg, 52%) and **2a** (12 mg, 12%).

N-(1-Acetyl-2-aminoprop-1-enyl)-N'-(tert-butyl)thiourea (**2a**). M.p. 173–175 and 196–200°. UV: 206 (12160), 250 (14540), 299 (10780). IR (KBr): 3300*s*, 3180*s*, 2970*s*, 1625*s*, 1605*s*, 1540*s*, 1515*s*, 1490*s*, 1395*s*, 1360*s*, 1290*s*, 1205*s*, 905*m*. MS: 230 (15), 229 (100, M^+), 212 (29), 196 (39), 156 (39), 149 (32), 140 (49), 114 (65), 97 (60), 86 (18), 71 (27), 57 (47), 43 (32), 41 (27). Anal. calc. for $C_{10}H_{19}N_3OS$ (229.34): C 52.37, H 8.35, N 18.33, S 13.98; found: C 52.65, H 8.58, N 18.06, S 13.64.

1-{2-[(tert-Butyl)amino]-5-methylthiazol-4-yl}ethan-1-one (**3a**). M.p. 126–127°. UV: 228 (16160), 254 (sh), 329 (3420). IR (CCl_4): 3440*w*, 2970*m*, 2930*m*, 1685*s*, 1640*w*, 1540*s* (br.), 1450*m*, 1420*m*, 1390*m*, 1365*m*, 1355*s*,

1315*m*, 1255*m*, 1205*s*, 950*w*. MS: 212 (29, M^+), 197 (7), 157 (8), 156 (100), 142 (5), 141 (70), 129 (5), 114 (7), 113 (10), 97 (6), 86 (6), 57 (23), 43 (21), 41 (21). Anal. calc. for $C_{10}H_{16}N_2OS$ (212.31): C 56.58, H 7.60, N 13.20, S 15.10; found: C 56.31, H 7.56, N 13.18, S 15.08.

5. *Thiazoles* **3**. *General Procedure*. To a soln. of **1** (4.40 mmol) in MeCN (90 ml) at r.t., $[Mo(CO)_6]$ (2.20 mmol) and H_2O (*ca.* 0.08 ml) were added. After 5 min stirring, anh. $SnCl_4$ (0.13 ml, *ca.* 1.0 mmol) was carefully introduced. The mixture was then kept under reflux for the time indicated in *Table 2*. After cooling, the solvent was evaporated, the residue taken up in AcOEt (or in solvent mixtures in a few cases), the slurry filtered through a small *Celite* pad, the filtrate evaporated, and the crude product (or mixture) worked up (AcOEt/$NaHCO_3$ soln.) and purified (or separated) by FC.

*1-{2-[(*tert*-Butyl)amino]-5-methylthiazol-4-yl}ethan-1-one* (**3a**). The crude product (0.74 g) was purified by FC (AcOEt/hexane 1:2): **3a** (0.63 g, 68%).

1-[5-Methyl-2-(phenylamino)thiazol-4-yl]ethan-1-one (**3b**). The product mixture after workup (0.60 g) was treated with AcOEt (2 ml), yielding a residue (0.16 g, 15%) consisting on practically pure **4b**. The soln. was evaporated and its residue purified by FC (AcOEt/hexane 1:5): small amount of phenyl isothiocyanate and **3b** (0.156 g, 16%).

Data of **3b**: M.p. 141–143°. UV: 220 (sh), 282 (19160), 320 (sh). IR (CCl_4): 3340*w*, 3420*w*, 1690*m*, 1610*m*, 1550*s*, 1500*m*, 1465*w*, 1440*m*, 1360*m*, 1310*m* (br.), 1200*m*. MS: 233 (17), 232 (100, M^+), 217 (45), 189 (36), 150 (26), 136 (12), 129 (15), 104 (20), 93 (13), 77 (44). 55 (22), 51 (19), 43 (38). Anal. calc. for $C_{12}H_{12}N_2OS$ (232.30): C 62.05, H 5.21, N 12.06, S 13.80; found: C 62.37, H 5.33, N 11.93, S 13.44.

*4-Acetyl-1,3-dihydro-5-methyl-1-phenyl-2*H*-imidazole-2-thione* (**4b**): M.p. > 240°. UV: 222 (9720), 270 (8760), 323 (9000). IR (KBr): 3440*m* (br.), 3050*s*, 2930*s*, 1660*s*, 1600*s*, 1500*s*, 1480*s*, 1410*s*, 1380*s*, 1345*s*, 1290*s*, 1210*s*, 1080*m*, 965*m*, 730*s*, 690*s*, 620*s*. MS: 233 (13), 232 (100, M^+), 231 (32), 217 (25), 189 (10), 131 (13), 118 (15), 93 (20), 77 (39), 51 (18), 44 (30), 43 (44). Anal. calc. for $C_{12}H_{12}N_2OS$ (232.31): C 62.04, H 5.21, N 12.06, S 13.80; found: (corrected for 3.05% ash): C 62.05, H 5.38, N 12.19, S 13.68.

1-{2-[(4'-Methoxyphenyl)amino]-5-methylthiazol-4-yl}ethan-1-one (**3c**). The crude product was treated with AcOEt/MeCN 2:1 (200 ml). The insoluble part was discarded, the filtered soln. evaporated, and the new residue treated with cool AcOEt (200 ml). The resulting solid (1.30 g) was shown to be a mixture of many components (NMR). The filtrate was evaporated (0.72 g) and separated by FC (AcOEt/hexane 1:3): 4-methoxyphenyl isothiocyanate (40 mg) and **3c** (80 mg, *ca.* 80% pure, *ca.* 6%). IR (CCl_4): 3450*w*, 3420*w*, 3010*w*, 2960*w*, 2940*w*, 2840*w*, 1685*s*, 1645*m*, 1550*s*, 1510*s*, 1250*s*, 1040*m*.

1-{2-[(4'-Acetylphenyl)amino]-5-methylthiazole-4-yl}ethan-1-one (**3d**). The residue was treated with AcOEt/MeCN 1:1 and the filtrate evaporated. The crude product (1.35 g) was purified by FC (AcOEt/hexane 2:1→5:1): **3d** (0.25 g, washed with AcOEt (2 ml); 0.21 g, 17%) and **4d** (0.26 g, 22%).

Data of **3d**: M.p. 222–226°. UV: 227 (16440), 335 (30880). IR (KBr): 3450*w* (br.), 3320*s*, 3200*m*, 1680*s*, 1665*s*, 1605*s*, 1540*s*, 1280*s*, 1255*s*, 1180*s*. MS: 274 (61, M^+), 260 (12), 259 (78), 231 (10), 189 (13), 122 (18), 43 (100).

*4-Acetyl-1-(4'-acetylphenyl)-1,3-dihydro-5-methyl-2*H*-imidazole-2-thione* (**4d**): M.p. 225–242°. UV: 240 (16240), 319 (8760). IR (KBr): 3440*w*, 3050*m*, 2920*m*, 1690*s*, 1655*s*, 1595*s*, 1485*s*, 1410*s*, 1380*s*, 1345*m*, 1295*m*, 1260*s*, 1210*m*. MS: 275 (21), 274 (100, M^+), 273 (38), 259 (24), 231 (18), 120 (19), 43 (83).

1-[2-(Dimethylamino)-5-methylthiazol-4-yl]ethan-1-one (**3e**). FC (AcOEt/hexane 1:2) of the crude product (0.59 g) gave **3e** (0.45 g, 56%). M.p. 50–52°. UV: 227 (17240), 250 (sh), 325 (3560). IR (CCl_4): 3340*w*, 2920*m*, 2880*w*, 1685*s*, 1565*s*, 1425*s*, 1355*s*, 1320*s*, 1190*m*, 1140*m*. MS: 184 (100, M^+), 169 (37), 155 (39), 151 (14), 141 (12), 88 (29), 72 (23), 56 (15), 44 (55), 43 (39), 42 (19). Anal. calc. for $C_8H_{12}N_2OS$ (184.26): C 52.15, H 6.56, N 15.20, S 17.40; found: C 52.02, H 6.62, N 15.09, S 17.50.

*1-[5-Methyl-2-(*N*-methyl-*N*-phenylamino)thiazol-4-yl]ethan-1-one* (**3f**). The residue (0.89 g) was submitted to FC (AcOEt/hexane 1:5→AcOEt): **3f** (0.58 g, 54%) as an oil which solidified quickly and **2f** (0.09 g, 8%).

Data of **3f**: M.p. 50–56°. UV: 228 (18160), 281 (10440), 320 (sh). IR (CCl_4): 3460*w*, 2920*w*, 1680*s*, 1535*s*, 1495*s*, 1415*m*, 1365*s*, 1320*m*, 1265*m*, 1200*s*, 695*s*. MS: 247 (15), 246 (100, M^+), 245 (22), 203 (11), 154 (20), 106 (21), 93 (16), 91 (18), 77 (35). Anal. calc. for $C_{13}H_{14}N_2OS$ (246.33): C 63.39, H 5.73, N 11.37, S 13.02; found: C 63.40, H 5.71, N 11.41, S 12.98.

N-(1-Acetyl-2-aminoprop-1-enyl)-N'-methyl-N'-phenylthiourea (**2f**): M.p. 174–177°.

1-[2-(Benzylamino)-5-methylthiazol-4-yl]ethan-1-one (**3g**). The crude product (0.95 g) was separated by FC (AcOEt/hexane 1:2→2:1): benzyl isothiocyanate (80 mg), **3g** (35 mg, 3%; a very viscous oil which solidified 1 week later), and **4g** (70 mg, *ca.* 80% purity, 6%). **3g**: IR (CCl_4): 3440*w*, 3040*w*, 2930*w*, 1685*s*, 1560*s*, 1360*m*, 705*m*.

1-[5-Methyl-2-(propylamino)thiazol-4-yl]ethan-1-one (**3h**). The residue (0.98 g) was separated by FC (AcOEt/hexane 2:1→5:1): **3h** (0.23 g; oil: solid after a few h; after repeated FC, 0.185 g, 21%) and **4h** (0.11 g, 13%).

Data of **3h**: M.p. 38–44°. UV: 227 (15320), 246 (sh), 326 (3280). IR (CCl_4): 3440*w*, 2970*m*, 2940*m*, 2880*m*, 1685*s*, 1560*s*, 1365*s*, 1320*m*, 1200*m*. MS: 198 (84, M^+), 183 (21), 169 (68), 156 (100), 155 (26), 151 (40), 141 (42), 127 (14), 113 (16), 86 (15), 59 (30), 43 (90), 41 (39).

*4-Acetyl-1,3-dihydro-5-methyl-1-propyl-2*H*-imidazole-2-thione* (**4h**): M.p. 146–150°. UV: 224 (5560), 263 (12640), 324 (9640). IR (KBr): 3440*m*, 3060*m*, 2960*m*, 1660*s*, 1600*m*, 1490*s*, 1410*s*, 1335*s*, 1130*m*, 965*m*, 810*m*. MS: 199 (13), 198 (100, M^+), 183 (16), 165 (48), 156 (65), 141 (85), 113 (16), 69 (20), 43 (50), 42 (30), 41 (22).

1-[5-Isopropyl-2-(isopropylamino)thiazol-4-yl]-2-methylpropan-1-one (**3i**). The crude product (1.10 g) yielded, after FC (AcOEt/hexane 1:5), pure **3i** (0.635 g, 61%). M.p. 93–96°. UV: 227 (15220), 248 (sh), 327 (3620). IR (CCl_4): 3440*w*, 2970*m*, 2930*m*, 2870*w*, 1680*s*, 1550*s*, 1465*m*, 1345*w*, 1210*w*, 1000*m*. MS: 255 (12), 254 (61, M^+), 239 (57), 225 (13), 212 (9), 211 (42), 197 (13), 184 (17), 183 (18), 179 (8), 169 (33), 156 (10), 141 (30), 82 (19), 43 (100), 41 (59). Anal. calc. for $C_{13}H_{22}N_2OS$ (254.39): C 61.38, H 8.72, N 11.01, S 12.60; found: C 61.18, H 8.85, N 11.18, S 12.57.

*2-[(*tert*-Butyl)amino]-5-methylthiazol-4-yl Phenyl Ketone* (**3jA**) *and 1-{2-[(*tert*-Butyl)amino]-5-phenylthiazol-4-yl}ethan-1-one* (**3jB**). The reaction was performed on a 3.1-mmol scale without catalyst. For the workup, a large amount of AcOEt was needed due to solubility problems. The residue (1.05 g) was treated with cool AcOEt (10 ml) leaving **2j** as a solid (0.24 g, 27%). The filtrate was evaporated and the crude oil separated by FC (AcOEt/hexane 1:10): **3jA** (0.12 g, 14%; yellow wax) and **3jB** (0.30 g, 35%; oil which became solid).

Data of **3jA**: UV: 254 (15920), 358 (3400). IR (CCl_4): 3440*w*, 2980*m*, 1650*s*, 1550*s*, 1450*m*, 1330*m*, 1235*s*, 725*m*, 690*m*. MS: 275 (12), 274 (62, M^+), 219 (14), 218 (63), 217 (100), 105 (18), 77 (23), 57 (16).

Data of **3jB**: M.p. 88–91°. UV: 234 (17800), 350 (5560). IR (CCl_4): 3440*w*, 2970*m*, 1690*s*, 1545*s*, 1480*m*, 1370*m*, 1355*m*, 1260*m*, 1220*m*, 1180*m*, 1155*m*, 910*m*, 695*m*. MS: 275 (5), 274 (76, M^+), 219 (18), 218 (100), 217 (53), 203 (46), 57 (17), 43 (24), 41 (12). Anal. calc. for $C_{15}H_{18}N_2OS$ (274.38); C 65.66, H 6.61, N 10.21, S 11.69; found: C 65.06, H 6.58, N 10.26, S 11.61.

N-*(1-Acetyl-2-amino-2-phenylethenyl)-*N′-*(*tert*-butyl)thiourea* (**2j**): M.p. 139–143 and 170–173° (dec.). IR (KBr): 3320*s*, 3180*s*, 2970*s*, 1610*s*, 1530*s*, 1510*s*, 1475*s*, 1395*s*, 1365*s*, 1270*s*, 970*m*, 705*m*. MS: 292 (18), 291 (100, M^+), 274 (15), 158 (25), 218 (38), 202 (33), 176 (94), 175 (50), 133 (42), 106 (15), 104 (20), 77 (12), 57 (38), 43 (85).

*2-[(*tert*-Butyl)amino]-5-isopropylthiazol-4-yl 4-Chlorophenyl Ketone* (**3kA**) *and 1-{2-[(*tert*-Butyl)amino]-5-(4′-chlorophenyl)thiazol-4-yl}-2-methylpropan-1-one* (**3kB**). The reaction was performed on a 2.20-mmol scale. The crude product (0.70 g) was purified by FC (AcOEt/hexane 1:5) giving 0.52 g (70%) of **3kA**/**3kB**. Thereof, 310 mg were further chromatographed: 72 mg of **3kA** and 210 mg of **3kB**.

Data of **3kA**: M.p. 120–125°. UV: 217 (14280), 261 (18980), 366 (3940). IR ($CCCl_4$): 3440*w*, 2980*m*, 1655*s*, 1590*m*, 1550*s*, 1490*m*, 1370m, 1325*s*, 1225*s*, 1175*m*, 995*m*. MS: 338 (31), 337 (16), 336 (81, M^+), 282 (24), 281 (20), 280 (63), 279 (36), 267 (20), 265 (53), 230 (18), 153 (21), 141 (19), 140 (19), 139 (21), 111 (39), 113 (15), 82 (16), 75 (24), 57 (65), 43 (20), 41 (100).

Data of **3kB**: M.p. 174–179°. UV: 233 (18620), 242 (sh), 353 (6480). IR (CCl_4): 3440*w*, 2980*s*, 1690*s*, 1545*s*, 1480*m*, 1370*w*, 1220*m*, 1185*m*, 1100*m*, 1070*w*, 1020*w*, 970*w*. MS: 338 (16), 336 (49, M^+), 282 (20), 280 (67), 239 (34), 237 (89), 202 (19), 155 (10), 71 (9), 70 (17), 57 (78), 55 (13), 43 (79), 41 (100).

6. *Reaction with Isothiourea* **7**. 6.1. *1-(*tert*-Butyl)-3-(3,5-dimethylisoxazol-4-yl)-2-methylisothiourea* (**7**). A soln. of **1a** (6.00 g, 26.4 mmol) in EtOH (85 ml) was mixed with MeI (4.30 g, 30.4 mmol) and heated under reflux for 4 h. After cooling and evaporation, the residue was taken up in CH_2Cl_2 and worked up with $NaHCO_3$ and sat. NaCl soln. The crude product, already solid, was purified by FC (AcOEt/hexane 1:4): pure **7** (5.50 g, 86%). M.p. 77–79°. UV: 203 (12960), 248 (sh). IR (CCl_4): 3440*w*, 2960*m*, 2920*m*, 1650*s*, 1600*s*, 1485*s*, 1450*s*, 1390*m*, 1365*m*, 1245*m*, 1210*m*, 1155*s*, 895*w*, 875*w*. ^{1}H-NMR (60 MHz, $CDCl_3$): 4.40 (br. *s*, 1 H); 2.20 (*s*, 3 H); 2.17 (*s*, 3 H); 2.10 (*s*, 3 H); 1.40 (*s*, 9 H). Anal. calc. for $C_{11}H_{19}N_3OS$ (241.35): C 54.74, H 7.94, N 17.41, S 13.29; found: C 55.02, H 8.01, N 17.31, S 12.99.

6.2. *Formation of* **8** *and* **9**. A mixture of **7** (0.53 g, 2.20 mmol), MeCN (45 ml), and H_2O (0.08 ml, *ca.* 4.4 mmol) was treated with $[Mo(CO)_6]$ (0.29 g, 1.10 mmol), heated under reflux for 16 h, and worked up as described in the general procedure of *Exper. 5*. The crude product (0.45 g) was separated by FC (AcOEt/hexane 1:7): **8** (0.090 g, 18%) and **9** (0.250 g, 58%) of very similar R_f.

*1-[1-(*tert*-Butyl)-5-methyl-2-(methylthio)-1*H*-imidazole-4-yl]ethan-1-one* (**8**): Yellowish oil. UV: 215 (14160), 246 (sh), 294 (7000). IR (CCl_4): 2980*w*, 2930*w*, 1670*s*, 1640*m*, 1550*m*, 1450*m*, 1360*m*, 1285*s*, 1200*s*, 1010*m*, 945*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.75 (*s*, 3 H); 2.60 (*s*, 3 H); 2.45 (*s*, 3 H); 1.75 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.4 (*q*, $J = 6$, CO); 143.0 (*q*, $J = 4.5$, C(2)); 137.3 (*qq*, $J = 4$, 1, C(4)); 136.9 (*q*, $J = 7$, C(5)); 59.9 (*m*, $(CH_3)_3C$); 31.2 (*m*, $(CH_3)_3C$); 27.9 (*q*, $J = 127$, CH_3CO); 17.3 (*q*, $J = 141.5$, CH_3S); 14.9 (*q*, $J = 129$, $CH_3C(5)$). MS: 226 (27, M^+), 170 (100), 155 (69), 137 (77), 57 (41), 43 (16), 41 (25).

*1-{2-[(*tert*-Butyl)amino]-5-methyloxazol-4-yl}ethan-1-one* (**9**): M.p. 75–80°. UV: 218 (12320), 300 (3520). IR (CCl_4): 3440*m*, 2970*m*, 2920*m*, 1690*s*, 1640*s*, 1600*m*, 1500*m*, 1365*s*, 1285*m*, 1230*m*, 1190*s*, 1070*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 4.50 (br. *s*, 1 H); 2.50 (*s*, 3 H); 2.45 (*s*, 3 H); 1.40 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 195.3 (*q*, $J = 6.5$, CO); 156.7 (*s*, C(2)); 147.5 (*q*, $J = 8$, C(5)); 133.7 (br. *m*, C(4)); 51.8 (*m*, $(CH_3)_3C$); 29.1 (*m*, $(CH_3)_3C$); 28.0 (*q*, $J = 127.5$, CH_3CO); 11.9 (*q*, $J = 129.5$, $CH_3C(5)$). MS: 196 (25, M^+), 141 (8), 140 (100), 125 (38), 122 (10), 99 (7), 97 (11), 70 (10), 57 (38), 55 (14), 43 (29), 41 (22). Anal. calc. for $C_{10}H_{16}N_2O_2$ (196.25): C 61.20, H 8.22, N 14.27, O 16.30; found: C 60.97, H 8.39, N 14.16, O 16.12.

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