Regioselective Synthesis of 5-Alkylthio- and 3-Alkylthioisoxazoles from Acylketene Dithioacetals[1]

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A regioselective synthesis of isomeric 5-alkylthio- and 3-alkylthioisoxazoles **3** and **4** has been developed from acylketene dithioacetals **2**. Thus the reaction of **2a–l** with hydroxylamine hydrochloride in the presence of sodium methoxide in refluxing methanol afforded 3-substituted 5-alkylthioisoxazoles **3a–l** in good yields. When compounds **2a–l** were reacted with hydroxylamine hydrochloride in the presence of sodium acetate/acetic acid (pH 2.2) in refluxing ethanol/benzene, 3-alkylthioisoxazoles **4a–l** were obtained regioselectively in good yields. Mass-spectral fragmentation and the mechanism of the formation of **3** and **4** are discussed.

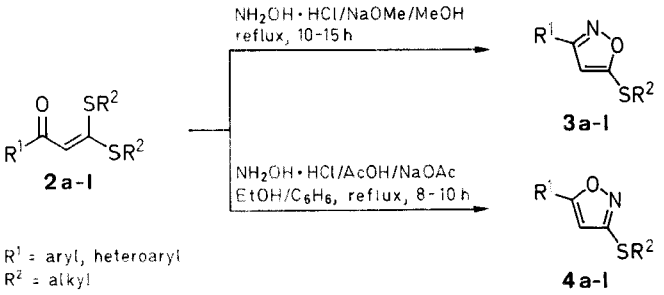
One of the useful general methods employed for the synthesis of substituted isoxazoles involves the cyclocondensation of hydroxylamine with C_3 units having 1,3-electrophilic centres. A wide structural variety of C_3 components has been used in these reactions with induction of regioselectivity, which is generally influenced either by altering the electrophilicity of the terminal C-atoms in the C–C–C component or by controlling the pH of the reaction medium and the reaction conditions.[2a,3]

Hydroxylamine, being an ambident nucleophile, has been shown to exist in the hydroxylamine (NH_2OH) form in neutral and weakly basic medium, while under strongly basic conditions the corresponding aminohydroxy anion (NH_2O^-) predominates.[4,5] The nucleophilicities of these species are centred at the N- and O-atoms, respectively. A detailed mechanistic study of the condensation of β-ketoesters with hydroxylamine to give either isoxazolin-3-one or its 5-one isomer at different pH and under different reaction conditions has also been reported.[6,7] The acylketene dithioacetals **2** can be regarded as masked β-ketoesters; their reaction with hydroxylamine is of interest, since this can yield either 3- or 5-alkylthioisoxazoles, depending on the reaction conditions. A literature survey revealed that the reaction of the doubly acitvated ketene dithioacetals **1a–d** with hydroxylamine to give the corresponding 3-methylthioisoxazoles has already been reported.[8–10] This reaction is apparently rendered possible by the enhanced electrophilicity of C-2 in **1** due to the presence of two electron-withdrawing substituents at C-1 which facilitate the attack of the nucleophilic N-atom of hydroxylamine at C-2.

1	R	R'	1	R	R'
a	–CN	–CN	c	COMe	COMe
b	–CN	CO_2Et	d	–CN	COAr

1

As already reported,[11] acylketene *S,N*-acetals react with hydroxylamine in a similar manner to give regioselectively 3-aminoisoxazoles by nucleophilic attack of the N-atom at C-2. This reaction may also be rationalized in terms of enhanced electrophilicity of C-2 in *S,N*-acetals due to delocalization of the lone pair of electrons at nitrogen over the 1,3-enone system[12] of **1**. We now report a highly regioselective synthesis of both 5-alkylthio- **3** and 3-alkylthioisoxazoles **4** by reaction of acylketene dithioacetals **2** with hydroxylamine hydrochloride at different pH values.



Synthesis of 5-Alkylthioisoxazoles 3a–l

When benzoylketene dimethyl dithioacetal (**2a**) was submitted to the reaction with hydroxylamine hydrochloride (4 equiv) in the presence of sodium methoxide (6 equiv, pH 9) in boiling methanol, 5-methylthio-3-phenylisoxazole (**3a**) was obtained in 78% yield. The ^{1}H-NMR spectrum of **3a** (after work-up) did not indicate any trace of the isomeric 3-methylthioisoxazole (**4a**). The structure of **3a** was confirmed with the help of spectral and analytical data as well as by its alternative synthesis by a reported method[13] (superimposable IR and ^{1}H-NMR spectra). 5-Ethylthioisoxazole (**3b**) was prepared under identical conditions and its properties were found to be in agreement with those of a sample prepared by a reported method.[14,15] The hitherto unreported compounds **3c–l** were

Table 1. 5-Alkylthioisoxazoles **3** Prepared

Product	R^1	R^2	Reaction Time (h)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c] or Lit. Data	MS (70 eV)[d] *m/z* (%)
3a	Ph	Me	10	78	40 ($CHCl_3$/hexane)	39–40[13]	191 (M^+, 42); 144 (100); 116 (29); 77 (70)
3b	Ph	Et	15	58	viscous liquid	(bp 96–98/ 0.05 Torr)[14]	205 (M^+, 28); 144 (100); 116 (24); 77 (53)
3c	Ph	*n*-Pr	18	61	viscous liquid	$C_{12}H_{13}NOS$ (219.3)	219 (M^+, 39); 144 (100); 116 (21)
3d	4-MeC_6H_4	Me	15	77	51 ($CHCl_3$/hexane)	$C_{11}H_{11}NOS$ (205.3)	205 (M^+, 10); 158 (100); 130 (38); 91 (39)
3e	4-ClC_6H_4	Me	13	71	61 ($CHCl_3$/hexane)	$C_{10}H_8ClNOS$ (225.7)	227 (12), 225 (M^+, 31); 180 (36), 178 (100); 152 (16), 150 (50); 113 (9), 111 (22)
3f	4-$MeOC_6H_4$	Me	12	72	64 ($CHCl_3$/hexane)	$C_{11}H_{11}NO_2S$ (221.3)	221 (M^+, 37); 174 (100); 146 (86)
3g	4-BrC_6H_4	Me	10	71	95 ($CHCl_3$/hexane)	$C_{10}H_8BrNOS$ (270.1)	271 (30); 269 (M^+, 28); 224 (98); 222 (100); 196 (41); 194 (44); 157 (21); 155 (22)
3h	2,4-$Cl_2C_6H_3$	Me	15	70	48 ($CHCl_3$/hexane)	$C_{10}H_7Cl_2NOS$ (260.1)	261 (19); 259 (M^+, 26); 214 (73); 212 (100); 186 (30); 184 (53)
3i	4-$EtOC_6H_4$	Me	12	76	54–55 ($CHCl_3$/hexane)	$C_{12}H_{13}NO_2S$ (235.3)	235 (M^+, 33); 188 (100); 160 (29); 132 (70)
3j	2-naphthyl	Me	12	68	79 ($CHCl_3$/hexane)	$C_{14}H_{11}NOS$ (241.3)	241 (M^+, 37); 194 (100); 166 (43); 127 (91)
3k	4-pyridyl	Me	15	68	99 ($CHCl_3$/hexane)	$C_9H_8N_2OS$ (192.2)	192 (M^+, 100); 145 (100); 117 (29); 79 (90)
3l	2-furyl	Me	15	63	83 ($CHCl_3$/hexane)	$C_8H_7NO_2S$ (181.2)	181 (M^+, 96); 134 (100); 106 (74)

[a] Yield of pure isolated product based on **2**.
[b] Uncorrected, measured on a Thomas Hoover melting point apparatus.
[c] Satisfactory microanalyses: C ±0.28, H ±0.31, N ±0.27.
[d] Measured on a Jeol D-300 Mass spectrometer.

similarly obtained from acylketene dithioacetals **2c–l** and hydroxylamine hydrochloride. Also, when the reaction of **2a** with hydroxylamine hydrochloride (4 equiv) was performed using only an equivalent quantity of sodium methoxide (4 equiv) to neutralize the hydrochloride salt (pH 7), isoxazole **3a** was obtained in comparable yields. The use of other bases, such as potassium hydroxide, potassium carbonate, sodium acetate, or pyridine gave either a mixture of isomeric isoxazoles or other undesired product mixtures. However, when the reaction of **2a** with hydroxylamine hydrochloride was performed in the presence of barium hydroxide in boiling ethanol (pH 5.6), isoxazole **3a** was obtained exclusively in 70% yield, the isomeric isoxazole **4a** not being detectable in the reaction mixture. It was therefore apparent that the strength of the base employed was not a critical factor with regard to the observed regioselectivity.

Synthesis of 3-Alkylthioisoxazoles 4a–l

When acylketene dithioacetal **2a** was submitted to the reaction with hydroxylamine hydrochloride in the presence of sodium acetate in a boiling mixture of acetic acid, ethanol, water, and benzene[16] (pH 2.2), the product isolated in 65% yield was characterized as 3-methylthio-5-phenylisoxazole (**4a**) on the basis of spectral and analytical data and by comparison of its melting point with that reported.[17] Similarly, the other 3-alkylthioisoxazoles **4b–l** were prepared from acylketene dithioacetals **2b–l** in 51–68% overall yields. In these reactions, the regioisomeric products **3** were not detected, except for the reactions of **2b** and **2c**, in which cases the ^{1}H-NMR spectra of the products showed the presence of a small amount (< 5%) of the corresponding 5-alkylthio isomers **3b** and **3c**, respectively, along with compounds **4b** or **4c** as the major products.

The isomeric isoxazoles **3** and **4** have the same R_f (benzene/hexane, 1:1) and their separation from mixtures was difficult to achieve by column chromatography. The ^{1}H-NMR spectra of **3** and **4** could be used to analyse the mixture of isomers formed from **2b** or **2c** since the SCH_3 and H-4 protons of **3** and **4** give close together but separated signals, although the independent spectra could not be used to correctly identify the respective regioisomer. A clear distinction of the 5- and 3-alkylthio regioisomers could be made by means of their mass-spectral fragmentation (Tables 1 and 2).[2b] The 5-alkylthioisoxazoles **3** show characteristic peaks due to loss of SR^2 and $COSR^2$ fragments ($M^+ - 47$ and $M^+ - 75$ in the case of 5-methylthio isomer) suggesting that the alkylthio group is adjacent to the ring O-atom. Similarly, the mass spectra of the 3-alkylthioisoxazoles exhibit a low-intensity peak for the ($M^+ - SR^2$) fragment whereas the base peak corresponds to the RCO fragment (m/z = 105 for **4a**), showing that the aryl group is adjacent to

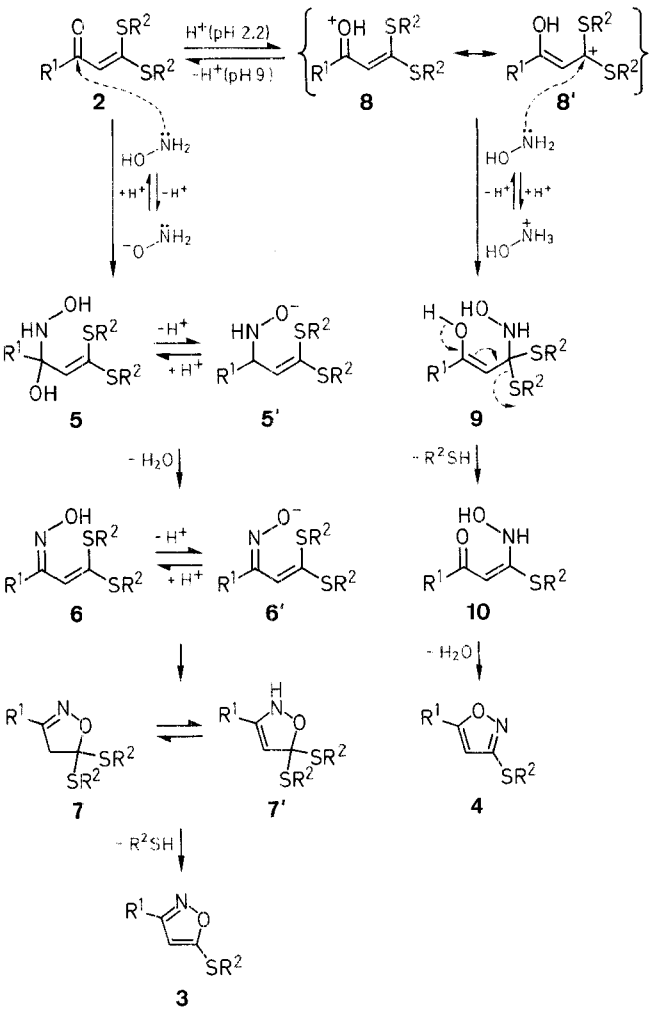


Table 2. 3-Alkylthioisoxazoles **4** Prepared

Product	R^1	R^2	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c] or Lit. Data	MS (70 eV)[d] m/z (%)
4a	Ph	Me	65	56–57 ($CHCl_3$/hexane)	56–57[17]	191 (M^+, 62); 144 (10); 105 (100)
4b	Ph	Et	63	50–51 ($CHCl_3$/hexane)	51–52[17]	205 (M^+, 100); 144 (50); 105 (100)
4c	Ph	*n*-Pr	64	41–42 ($CHCl_3$/hexane)	41–42[17]	219 (M^+, 16); 144 (24); 105 (100)
4d	4-MeC_6H_4	Me	68	64–65 ($CHCl_3$)	$C_{11}H_{11}NOS$ (205.3)	205 (M^+, 38); 158 (7); 119 (100)
4e	4-ClC_6H_4	Me	62	107–108 ($CHCl_3$/hexane)	$C_{10}H_8ClNOS$ (225.7)	227 (29); 225 (M^+, 79); 180 (2); 178 (5); 141 (65); 139 (100)
4f	4-$MeOC_6H_4$	Me	63	74–75 ($CHCl_3$/hexane)	$C_{11}H_{11}NO_2S$ (221.3)	221 (M^+, 42); 174 (10); 135 (100)
4g	4-BrC_6H_4	Me	63	120–121 ($CHCl_3$/hexane)	$C_{10}H_8BrNOS$ (270.1)	271 (48); 269 (M^+, 48); 224 (11); 222 (9); 185 (100); 183 (100)
4h	2,4-$Cl_2C_6H_3$	Me	58	110–111 ($CHCl_3$/hexane)	$C_{10}H_7Cl_2NOS$ (260.1)	261 (28); 259 (M^+, 41); 226 (11); 224 (28); 175 (90); 173 (100)
4i	4-$EtOC_6H_4$	Me	60	78–79 ($CHCl_3$/hexane)	$C_{12}H_{13}NO_2S$ (235.3)	235 (M^+, 56); 188 (4); 149 (100)
4j	2-naphthyl	Me	66	110–111 ($CHCl_3$/hexane)	$C_{14}H_{11}NOS$ (241.3)	241 (M^+, 53); 194 (8); 155 (100)
4k	4-pyridyl	Me	51	96–97 ($CHCl_3$/hexane)	$C_9H_8N_2OS$ (192.2)	192 (M^+, 74); 145 (19); 106 (100)
4l	2-furyl	Me	68	56–57 ($CHCl_3$/hexane)	$C_8H_7NO_2S$ (181.2)	181 (M^+, 40); 134 (30); 95 (42)

[a,b,d] See Table 1.

[c] Satisfactory microanalyses: C ±0.29, H ±0.30, N ±0.28.

ring O-atom. Thus, the crucial mass-spectral fragment in distinguishing **3** and **4** is the aroyl cation, which is not formed in the case of **3**.

In summary, the isomeric 5-alkylthio- **3** or 3-alkylthioisoxazoles **4** can be obtained at will from the same reactant by simply using the appropriate reaction conditions. The regioselective formation of **3** is achieved by using barium hydroxide or sodium methoxide, both in equivalent or excess amounts, in the pH range from 5 to 9. The predominant species up to pH 10 has been shown[6] to be the neutral hydroxylamine molecule; this proves that the role of the base in these reactions is limited to the release of free hydroxylamine from its salt; it does not exert an effect on **2** which is apparently converted into the isoxazole **3** via oxime **6**. On the other hand, in the presence of sodium

Table 3. Spectral Data of Compounds **3** and **4**

Compound	IR (KBr)[a] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[c] δ
3a	1540, 1500, 1450, 1400	2.56 (s, 3H, SCH_3); 6.33 (s, 1H, H-4); 7.33–7.61 (m, $3H_{arom}$); 7.31–8.15 (m, $2H_{arom}$)	15.46 (SCH_3); 100.07 (C-4); 126.74, 128.90, 130.09 (CH_{phenyl}); 128.95 (C-1′$_{phenyl}$); 162.99 (C-3); 168.05 (C-5)
3b	1540, 1500, 1460, 1400	1.36 (t, 3H, J = 7, CH_3CH_2); 3.03 (q, 2H, J = 7, SCH_2CH_3); 6.33 (s, 1H, H-4); 7.25–7.46 (m, $3H_{arom}$); 7.53–7.82 (m, $2H_{arom}$)	15.14 (CH_3); 27.79 (SCH_2); 102.18 (C-4); 126.70, 128.90, 130.08 (CH_{phenyl}); 128.95 (C-1′$_{phenyl}$); 162.95 (C-3); 166.85 (C-5)
3c	1540, 1500, 1455, 1392	0.98 (t, 3H, J = 7, CH_3); 1.67 (sext, 2H, J = 7, $SCH_2CH_2CH_3$); 2.97 (t, 2H, J = 7, $SCH_2CH_2CH_3$); 6.36 (s, 1H, H-4); 7.25–7.58 (m, $3H_{arom}$); 7.60–7.86 (m, $2H_{arom}$)	
3d	1610, 1540, 1510, 1438, 1420	2.32 (s, 3H, CH_3); 2.50 (s, 3H, SCH_3); 6.22 (s, 1H, H-4); 7.14 (d, J = 8,$2H_{arom}$); 7.58 (d, J = 8,$2H_{arom}$)	
3e	1614, 1541, 1505, 1440, 1420	2.58 (s, 3H, SCH_3); 6.23 (s, 1H, H-4); 7.35 (d, J = 8,$2H_{arom}$); 7.66 (d, J = 8,$2H_{arom}$)	15.40 (SCH_3); 99.79 (C-4); 128.06, 129.18 (CH_{arom}); 127.23, 136.11 (C-1′, C-4′$_{phenyl}$); 162.01 (C-3); 168.48 (C-5)
3f	1620, 1522, 1446	2.52 (s, 3H, SCH_3); 3.72 (s, 3H, OCH_3); 6.18 (s, 1H, H-4); 6.84 (d, J = 8.5, $2H_{arom}$); 7.59 (d, J = 8.5, $2H_{arom}$)	15.44 (SCH_3); 55.32 (OCH_3); 99.86 (C-4); 114.27, 128.12 (CH_{arom}); 121.20, 161.03 (C-1′$_{phenyl}$, C-4′$_{phenyl}$); 162.59 (C-3); 167.67 (C-5)
3g	1595, 1535, 1490, 1430, 1418	2.61 (s, 3H, SCH_3); 6.28 (s, 1H, H-4); 7.58 (s, $4H_{arom}$)	
3h	1590, 1532, 1488, 1438	2.62 (s, 3H, SCH_3); 6.26 (s, 1H, H-4); 7.32 (dd, 1H, J = 7, 2, H-5′); 7.48 (d, 1H, J = 2, H-3′); 7.73 (d, 1H, J = 7, H-6′)	
3i	1620, 1525, 1446, 1418, 1394	1.42 (t, 3H, J = 7, OCH_2CH_3); 2.60 (s, 3H, SCH_3); 4.06 (q, 2H, J = 7, OCH_2CH_3); 6.22 (s, 1H, H-4); 6.85 (d, J = 9, $2H_{arom}$); 7.69 (d, J = 9, $2H_{arom}$)	
3j	1602, 1542, 1440, 1398	2.62 (s, 3H, SCH_3); 6.41 (s, 1H, H-4); 7.33–8.16 (m, $7H_{arom}$)	
3k	1600, 1530, 1520, 1437, 1394	2.56 (s, 3H, SCH_3); 6.33 (s, 1H, H-4); 7.60 (d, J = 8, $2H_{pyridyl}$); 6.73 (d, J = 8, $2H_{pyridyl}$)	
3l	1611, 1528, 1438	2.62 (s, 3H, SCH_3); 6.32 (s, 1H, H-4); 6.55 (dd, 1H, J = 3, 1.4, H-4′$_{furyl}$); 6.91 (d, 1H, J = 3, H-3′$_{furyl}$); 7.56 (d, 1H, J = 1.4, H-5′$_{furyl}$)	
4a	1600, 1580, 1560, 1482, 1440, 1402, 1340	2.58 (s, 3H, SCH_3); 6.27 (s, 1H, H-4); 7.17–7.45 (m, $3H_{arom}$); 7.49–7.79 (m, $2H_{arom}$)	13.90 (SCH_3); 99.07 (C-4); 125.79, 128.91, 130.27 (CH_{phenyl}); 127.18 (C-1′$_{phenyl}$); 160.89 (C-5); 169.89 (C-3)
4b	1600, 1581, 1562, 1482, 1440, 1400	1.44 (t, 3H, J = 7, CH_3CH_2); 3.10 (q, 2H, J = 7, SCH_2CH_3); 6.30 (s, 1H, H-4); 7.30–7.60 (m, $3H_{arom}$); 7.68–7.80 (m, $2H_{arom}$)	14.73 (CH_3CH_2); 25.86 (SCH_2CH_3); 102.22 (C-4); 125.80, 128.96, 130.30 (CH_{phenyl}); 127.16 (C-1′$_{phenyl}$); 160.16 (C-5); 169.71 (C-3)
4c	1600, 1580, 1561, 1480, 1440, 1340	1.03 (t, 3H, J = 7, $CH_3CH_2CH_2$); 1.78 (sext, 2H, J = 7, $CH_3CH_2CH_2$); 3.07 (t, 2H, J = 7, $SCH_2CH_2CH_3$); 6.28 (s, 1H, H-4); 7.24–7.52 (m, $3H_{arom}$); 7.52–7.80 (m, $2H_{arom}$)	
4d	1600, 1583, 1560, 1498, 1403, 1342	2.36 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 6.22 (s, 1H, H-4); 7.19 (d, J = 8.5, A_2B_2, $2H_{arom}$); 7.60 (d, J = 8.5, $2H_{arom}$)	
4e	1600, 1578, 1479, 1403, 1339	2.59 (s, 3H, SCH_3); 6.28 (s, 1H, H-4); 7.46 (d, J = 8, $2H_{arom}$); 7.72 (d, J = 8, $2H_{arom}$)	13.86 (SCH_3); 99.31 (C-4); 127.01, 129.24 (CH_{arom}); 126.97, 136.34 (C-1′$_{phenyl}$, C-4′$_{phenyl}$); 161.04 (C-5); 168.68 (C-3)
4f	1611, 1598, 1500, 1419, 1348	2.48 (s, 3H, SCH_3); 3.82 (s, 3H, OCH_3); 6.19 (s, 1H, H-4); 6.83 (d, J = 9, $2H_{arom}$); 7.70 (d, J = 9, $2H_{arom}$)	13.91 (SCH_3); 55.39 (OCH_3); 97.71 (C-4); 114.37, 127.44 (CH_{arom}); 119.96 (C-1′$_{phenyl}$); 160.83 (C-4′$_{phenyl}$); 161.20 (C-5); 169.91 (C-3)
4g	1600, 1476, 1398, 1340	2.58 (s, 3H, SCH_3); 6.28 (s, 1H, H-4); 7.56 (s, $4H_{arom}$)	
4h	1601, 1476, 1399, 1339	2.62 (s, 3H, SCH_3); 6.76 (s, 1H, H-4); 7.37 (dd, 1H, J = 8, 2, H-5′); 7.52 (d, 1H, J = 2, H-3′); 7.90 (d, 1H, J = 8, H-6′)	
4i	1600, 1500, 1402, 1321	1.40 (t, 3H, J = 7, OCH_2CH_3); 2.57 (s, 3H, SCH_3); 4.02 (q, 2H, J = 7, OCH_2CH_3); 6.15 (s, 1H, H-4); 6.85 (d, J = 8, A_2B_2, $2H_{arom}$); 7.59 (d, J = 8, A_2B_2, $2H_{arom}$)	

Table 3. (Continued)

Compound	IR (KBr)[a] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[c] δ
4j	1600, 1578, 1569, 1400, 1360, 1320	2.60 (s, 3H, SCH_3); 6.36 (s, 1H, H-4); 7.23–8.35 (m, 7H_{arom})	
4k	1598, 1540, 1388, 1350	2.61 (s, 3H, SCH_3); 6.46 (s, 1H, H-4); 7.53 (d, 2$H_{pyridyl}$); 8.67 (d, 2$H_{pyridyl}$)	
4l	1617, 1549, 1410, 1378, 1342	2.60 (s, 3H, SCH_3); 6.25 (s, 1H, H-4); 6.51 (dd, 1H, J = 3, 1.4, H-4′$_{furyl}$); 6.87 (d, 1H, J = 3, H-3′$_{furyl}$); 7.51 (d, 1H, J = 1.4, H-5′$_{furyl}$)	

[a] Recorded on a Perkin-Elmer 297 Infrared spectrophotometer.
[b] Recorded on a Varian EM-390 spectrometer.
[c] Recorded on a Bruker WP-80-DS (20.15 MHz) spectrometer.

acetate/acetic acid (pH 2.2), the dominant species is the hydroxylammonium ion with only a small amount of hydroxylamine being present; the latter adds regioselectively to the more electrophilic C-3 of **8** (protonated **2**) in the rate-determining step; cyclization then yields the 3-alkylthioisoxazoles **4**, while the hydroxylamine is regenerated in the equilibrium mixture.

The reactions described here provide a facile entry to 3- and 5-alkylthioisoxazoles from easily accessible acylketene dithioacetals. Some of the 5-alkylthio-3-arylisoxazoles **3** have been found to exhibit anthelmintic activity.[18,19]

The required acylketene dithioacetals **2a–l** were prepared according to the earlier reported procedure.[20]

5-Alkylthio-3-arylisoxazoles 3a–l; General Procedure:
Hydroxylamine hydrochloride (2.80 g, 0.04 mol) is added to a stirred suspension of NaOMe [prepared by dissolving Na (1.38 g, 0.06 mol) in absolute MeOH (30 mL)] and stirring is continued for 10 min. The acylketene dithioacetal **2** (0.01 mol) is added and the mixture is refluxed with stirring for 10–15 h. Methanol is removed under reduced pressure and the residue is poured into ice-cold H_2O (200 mL). In most cases (**3a, 3d–l**), the isoxazoles **3** separate as pale-colored solids which are isolated by suction and which are pure enough for recording of their spectra. [The ^{1}H-NMR spectra of **3a–l** thus obtained do not show any trace of the isomeric isoxazoles **4** as indicated by the sharp signals of the SCH_3 and H-4 protons]. Products **3a, 3d–l** are recrystallized from $CHCl_3$/hexane for element analysis.

In the case of isoxazoles **3b** and **3c**, the mixture obtained after pouring the reaction mixture into ice-cold H_2O, is extracted with $CHCl_3$ (2 × 50 mL), and the organic layer is washed with H_2O (1 × 100 mL), dried (Na_2SO_4), and evaporated to give **3b** or **3c**, respectively, as orange viscous liquids which are pure enough for recording of their spectra. The orange viscous liquids are passed through a small column of neutral alumina using CCl_4 as eluent to give the analytically pure products **3b** or **3c**.

3-Methylthio-5-phenylisoxazole (3a); Typical Procedure using Barium Hydroxide as Base:
Hydroxylamine hydrochloride (2.80 g, 0.04 mol) is added to a stirred suspension of $Ba(OH)_2$ (10.30 g, 0.06 mol) in 95% EtOH (30 mL) followed by the addition of benzoylketene dimethyl dithioacetal (**2a**: 2.24 g, 0.01 mol). The mixture is refluxed with stirring for 4 h, EtOH is then removed under reduced pressure, the residue is poured into ice-cold H_2O (200 mL), and this mixture is acidified with dilute AcOH (5%, 15 mL). The isoxazole **3a** thus obtained is isolated by suction and passed through a neutral alumina column using CCl_4 as solvent; yield: 1.30 g (70%); mp 40–41 °C (Lit.[13] mp 39–40 °C).

3-Alkylthio-5-arylisoxazoles 4a–l; General Procedure:
To a stirred solution of the acylketene dithioacetal **2** (0.01 mol) in benzene (100 mL) + AcOH (100 mL), a solution of NaOAc (2.80 g, 0.034 mol) and $NH_2OH \cdot HCl$ (2.80 g, 0.04 mol) in H_2O (10 mL) is added. The mixture is made homogenous by the addition of EtOH (55 mL) and refluxed for 8–10 h. It is then evaporated to dryness under reduced pressure, and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ layer is washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and evaporated to give a dark brown residue, which on TLC (silica gel, benzene as mobile phase) shows only one spot corresponding to the isoxazole **4** (R_f 0.75) and some polymeric impurities at the base. The brown residue is filtered through a small neutral alumina column using EtOAc/hexane (1:20) as eluent to give the isoxazole **4** which is pure enough for spectral measurements. [The ^{1}H-NMR spectra of the products **4a, 4d–l** thus obtained do not show the presence of the regioisomers **3**, whereas in the case of isoxazoles **4b** and **4c** the presence of traces (< 5%) of the isomeric isoxazoles **3b** and **3c**, respectively, is observed.] Products **4a–l** are recrystallized from $CHCl_3$/hexane for element analyses.

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