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Access to 3-arylmethyl-5-(methylthio)isoxazoles via an initial ring-opening of 2-methylthio-4-nitrothiophene☆

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Abstract—The reactions of 1,1-bis(methylthio)-3-nitro-4-pyrrolidino-1,3-butadiene (deriving from the initial ring-opening of 2-methylthio-4-nitrothiophene with pyrrolidine and silver nitrate in EtOH) with arylmagnesium bromides result in the chemoselective replacement of the pyrrolidino group with the aryl moiety of the Grignards. The 4-aryl-1,1-bis(methylthio)-3-nitro-1,3-butadienes thus obtained are the key intermediates for the effective synthesis, through the corresponding reduction products 4-aryl-3-hydroximino-1,1-bis(methylthio)-1-butenes, of the previously unknown 3-arylmethyl-5-(methylthio)isoxazoles. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Among the numerous heterocyclic moieties of biological and pharmacological interest the isoxazole ring is endowed with a well acknowledged multi-faceted activity.[2] Its behaviour, e.g. as a bioisostere of the pyridine nucleus or of the carboxylic group[2a] or its involvement in peptidomimetics[2a,e] strongly depend on the presence of proper ring substituents; in this regard, 3,5-disubstitution undoubtedly represents a specific array which proves particularly useful and for which, therefore, a number of synthetic methodologies have been until recently developed.[2e,f,3,4]

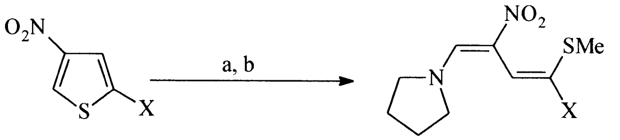
Within a project aimed at exploiting the highly functionalized building blocks deriving from the ring-opening of nitrothiophenes with primary or secondary amines[5,6] we have recently reported[5] that a number of 2-X-4-nitrothiophenes (**1**) are easily cleaved by pyrrolidine/$AgNO_3$ in ethanol to eventually furnish the polyfunctionalized 1,3-butadienes **2** in more than satisfactory absolute overall yields (Scheme 1).[7]

Herein we report on the high-yielding, three-step transformation of (*E*)-**2a** (X=SMe) into 3-arylmethyl-5-(methylthio)isoxazoles (**5**) involving (Scheme 2) (i) replacement of the pyrrolidino group with an aryl residue, (ii) reduction of the nitrovinyl moiety of **3** and (iii) cyclization of the resulting vinyloximes **4** accompanied by methanethiol elimination.

2. Results and discussion

2.1. Reactions of (*E*)-1,1-bis(methylthio)-3-nitro-4-pyrrolidino-1,3-butadiene [(*E*)-2a] with aryl Grignard reagents

Among the well-known potentialities of a *tert*-nitroenamine function such as that embedded in the butadiene **2a**,[8–10] the

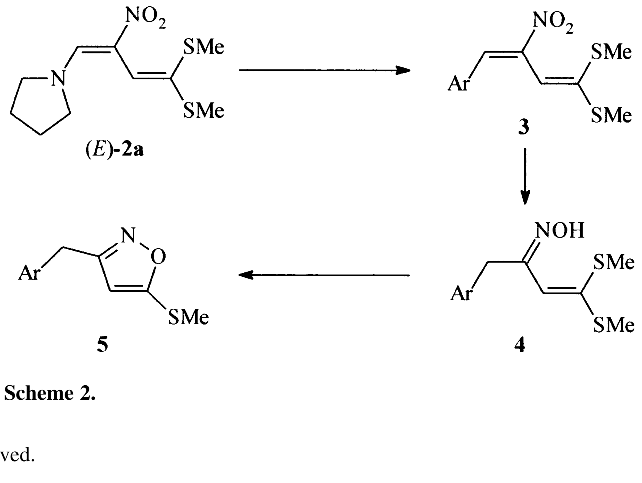


1

2
45–79% absolute overall yields

X = H, SPh, SO_2Ph, SMe, SO_2Me, COMe, COOMe, CN

Scheme 1. *Reagents and conditions*: (a) Pyrrolidine/$AgNO_3$, abs. EtOH, rt; (b) excess MeI, rt.



Scheme 2.

☆ See Ref. 1

Keywords: nitrothiophenes; ring-opening/ring-closure reactions; functionalized nitrobutadienes; 3,5-disubstituted isoxazoles.

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Table 1. Yields of (*E*)-**3a**–**i** from the reaction of (*E*)-**2a** with arylmagnesium bromides

Ar	Product	Yield (%)[a]
Ph	**3a**	65
p-MeC$_6$H$_4$	**3b**	88[b]
m-MeOC$_6$H$_4$	**3c**	97
p-MeOC$_6$H$_4$	**3d**	89
m-ClC$_6$H$_4$	**3e**	77
p-ClC$_6$H$_4$	**3f**	91
1-Naphthyl	**3g**	93
2-Naphthyl	**3h**	89
2-Thienyl	**3i**	88 (98)[c]

[**2a**]: ca. 0.08 M; ArMgBr: 1.1 mol equiv.; THF, −78°C; quenching into ice–CH$_2$Cl$_2$ with HCl equimolar with the Grignard.

[a] Isolated yields.

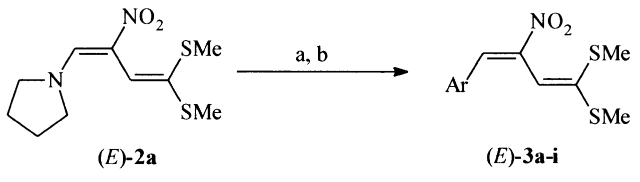
[b] Optimized yield from Ref. 5.

[c] Yield based on the reacted **2a**.

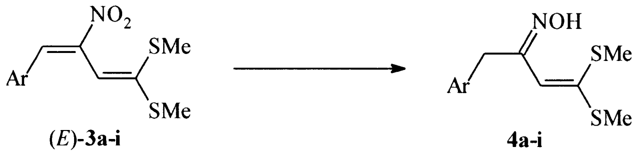
replacement of the dialkylamino group with the alkyl or aryl residue of an organometallic reagent represents an appealing C–C bond forming process which has been already successfully applied, in our laboratories, to the 1,4-bis(dialkylamino)-2,3-dinitro-1,3-butadienes deriving from the ring opening of 3,4-dinitrothiophene with secondary amines.[11–14] The possibility to extend the same methodology to **2a** for the preparation of **3** hinges upon the chemoselective reaction of the organometal with the nitroenamine system in spite of the presence of another functionality which can potentially compete for the organometal itself.[15,16]

Actually, following a preliminary result on the behaviour of **2a** towards *p*-tolylmagnesium bromide,[5] the data collected in Table 1, relevant to the reactions of the same substrate with 1.1 mol equiv. of selected arylmagnesium bromides in THF at −78°C (Scheme 3), should be regarded as more than satisfactory as far as both chemoselectivity and effectiveness of the desired replacement are concerned.[17] Occasional somewhat lower yields are to be ascribed to the intervention of competitive processes, possibly following the acidic quenching, whose identification goes beyond the scope of the present work.

As far as the stereochemistry of the nitrovinyl system is concerned, an (*E*)-configuration can be confidently assigned to the isolated products throughout the **3a**–**i** series on the grounds of the marked deshielding of the nitrovinylic proton *cis* to the nitrogroup. Thus, the average value for compounds **3a**,**c**–**i** (δ 8.1 ppm) is very similar to that (δ 8.0 ppm) for **3b**, to which the (*E*)-configuration has been previously assigned,[5] also based on a comparison with the parent **2a**. It is therefore possible to affirm that the formation of **3a**,**c**–**i** occurs with retention of configuration. Moreover, it should be recalled that the preference for the (*E*)-configuration in 1-aryl-2-nitrovinyl systems arising from substitution by Grignard reagents of the dialkylamino group of nitroenamines is well assessed.[11–13]



Scheme 3. *Reagents and conditions*: (a) [**2a**]: ca. 0.08 M in THF; ArMgBr: 1.1 mol equiv.; −78°C; (b) H$_3$O$^+$ quenching.



Scheme 4. *Reagents and conditions*: [**3**]: ca. 0.06 M in DMF/AcOH (15:1, v/v); Pb: 2.2–3.3 equiv.; rt.

2.2. Reduction of (*E*)-3a–i to the corresponding vinyloximes 4

The reduction of the nitrovinylic system of **3** has been performed by treatment with lead powder in an acetic acid/DMF mixture at room temperature (Scheme 4), with an adaptation of a methodology for nitroalkenes,[18] already successfully applied to 2,3-dinitro-1,3-butadienes.[12] The results (Table 2) are excellent throughout, yields of isolated α-hydroximino ketenedithioacetals **4** being always higher than 80%.

As to the stereochemistry of the ketoxime group, the ^{1}H and ^{13}C NMR spectroscopic analysis of the isolated products always indicates the presence of a single stereoisomer, although it does not allow to give the configurational assignment. Herein, though, the practical success of the following cyclization on the isolated oximes (see below) makes any further investigation on such stereochemical aspects irrelevant for the scope of the present work.[2f,3e]

2.3. Cyclization of vinyloximes 4a–i

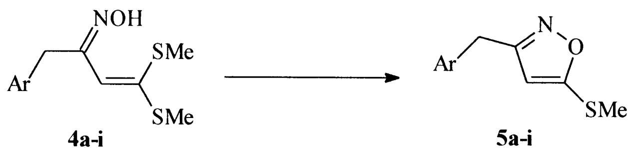
Although different systems for the desired transformation have been tested, excellent results have been eventually obtained by means of an adaptation of a method reported for structurally related compounds,[2f,3e] which makes use of an acidic ion-exchange resin in MeCN (Scheme 5). The figures in Table 3 clearly testify for a very efficient process which also overcomes, as anticipated above, any drawback related to the stereochemistry of the starting vinyloximes.

Table 2. Yields of **4a**–**i** from the reduction of (*E*)-**3a**–**i**

Ar	Product	Yield (%)[a]
Ph	**4a**	88
p-MeC$_6$H$_4$	**4b**	82
m-MeOC$_6$H$_4$	**4c**	90
p-MeOC$_6$H$_4$	**4d**	92
m-ClC$_6$H$_4$	**4e**	80
p-ClC$_6$H$_4$	**4f**	81
1-Naphthyl	**4g**	95
2-Naphthyl	**4h**	84
2-Thienyl	**4i**	83

[**3**]: ca. 0.06 M in DMF/AcOH (15:1, v/v); Pb: 2.2–3.3 equiv.; rt.

[a] Isolated yields.



Scheme 5. *Reagents and conditions*: **4**: 0.1 g in 5.5 ml MeCN; Amberlyst-15®: 0.1 g; reflux.

Table 3. Yields of **5a–i** from the intramolecular cyclization of **4a–i**

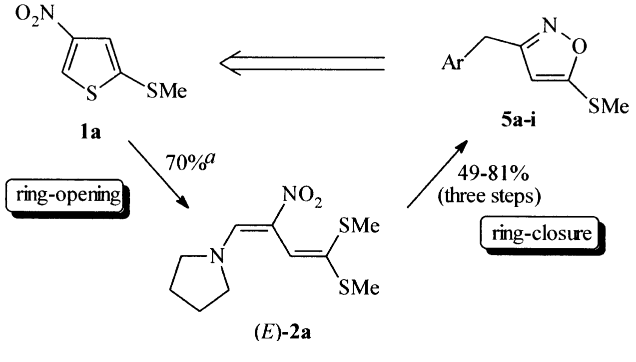
Ar	Product	Yield (%)[a]
Ph	**5a**	94
p-MeC_6H_4	**5b**	86
m-$MeOC_6H_4$	**5c**	93
p-$MeOC_6H_4$	**5d**	91
m-ClC_6H_4	**5e**	80
p-ClC_6H_4	**5f**	95
1-Naphthyl	**5g**	88
2-Naphthyl	**5h**	98
2-Thienyl	**5i**	87

4: 0.1 g in 5.5 ml MeCN; Amberlyst-15®: 0.1 g; reflux.
[a] Isolated yields.

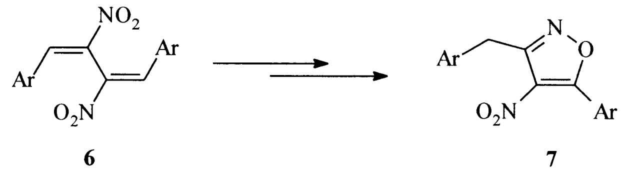
3. Conclusions

Overall, the results reported herein portray a useful ring–ring transformation in the heteroaromatic field whereby (Scheme 6) 2-methylthio-4-nitrothiophene (**1a**) is converted into the 3-arylmethyl-5-(methylthio)isoxazoles **5** by means of an initial ring-opening with pyrrolidine/$AgNO_3$ to yield the highly functionalized building-block **2a**. The key-step of the follow-up sequence to the final isoxazoles is represented by the displacement of the pyrrolidino group of **2a** through the reaction with arylmagnesium Grignards, which has proven to be, in the conditions employed, highly chemoselective and of wide applicability.

Further strong significance is attached to the **1a**→**5** protocol herein inasmuch as it allows the introduction of an arylmethyl side chain at the 3 position of the isoxazole nucleus. To our knowledge this goal, which surely makes the heterocyclic derivative amenable to further α-functionalization of presumably valuable interest in the perspective of a screening for pharmacological activity, has been only scantily achieved so far.[19] As a matter of fact, the only example relevant to the systematic access to a number of 3-(arylmethyl)isoxazoles comes from a previous report of ours,[20] where the 1,4-diaryl-2,3-dinitro-1,3-butadienes **6** (deriving from an initial ring-opening of 3,4-dinitrothiophene) were used as precursors of the isoxazoles **7** (Scheme 7).

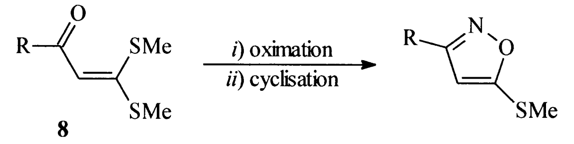


Scheme 6. (a) Yield based on the reacted substrate (Ref. 5).



Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 1-naphthyl, 2-thienyl

Scheme 7.



Scheme 8.

Actually, a number of drawbacks[4a,21] make some of the most common synthetic routes to isoxazoles unsuitable for the obtainment of 3-alkyl and, in particular, of 3-arylmethyl derivatives; to cite an example much akin to the methodology herein, for the until recently employed α-oxo ketenedithioacetals (**8**), precursors of 3-R-5-(methylthio)-isoxazoles (Scheme 8),[2f,3b,c,e] no efficient synthesis seems to have been devised when R is arylmethyl.[22,23]

Thus, besides the success in the obtainment of targets such as **5**, the results herein also suggest, in the light of the continuing interest attached to compounds **8** as synthetic intermediates,[22] the opportunity for a more detailed investigation on the potentialities of the nitrovinyl ketenedithioacetals **3** as convenient synthons of α-oxo ketenedithioacetals characterized by an array which cannot be otherwise easily assembled.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 spectrometer with TMS as internal reference; chemical shifts are expressed as δ ppm. IR Spectra were recorded on a Perkin–Elmer 881 Infrared Spectrophotometer as neat samples (for liquid compounds) or nujol mulls (for solids). Melting points were determined on a Büchi 535 apparatus and are uncorrected. Silica gel 230–400 mesh was used for column chromatography. All solvents were distilled before use; petroleum ether and light petroleum refer, respectively, to the fraction with bp 40–60°C and 80–100°C. Tetrahydrofuran (THF) was purified by standard methods and distilled over potassium benzophenone ketyl before use. Arylmagnesium bromides (ca. 1 M in THF) were prepared from the corresponding commercial aryl bromides using standard procedures and titrated just before use.[24] All other commercially available reagents were used as received.

The reported[5] procedure for the synthesis of (*E*)-1,1-bis-(methylthio)-3-nitro-4-pyrrolidino-1,3-butadiene (**2a**) has been herein simplified without substantial variation of the yield: after the ring-opening process, the ethanolic mixture, containing the precipitated silver butadienethiolate, has been treated with 5 mol equiv. of MeI, avoiding both evaporation of solvent and use of a larger excess of MeI.

4.2. Reactions of the nitrovinylpyrrolidine 2a with arylmagnesium bromides

A solution of nitrovinylpyrrolidine **2a** (1 mmol) in THF (12 ml) was cooled to −78°C under argon and magnetic stirring. The calculated amount (1.1 mmol) of a freshly prepared solution (ca. 1 M) of arylmagnesium bromide in THF was slowly added by syringe and the reaction mixture left under stirring at the same temperature until disappearance of the substrate (ca. 15–45 min): the progress of the reaction being monitored by TLC. Quenching was performed by pouring the reaction solution, with vigorous shaking, into a mixture of dichloromethane with ice/water containing 1.1 mmol of HCl. After extraction with dichloromethane, the organic phase was washed with water, dried (Na_2SO_4) and concentrated in a rotary evaporator under reduced pressure. The products **3** were usually obtained in quite pure form by chromatography of the residue on a silica gel column eluted with a gradient of dichloromethane and diethyl ether.

(*E*)-4-(4-Methylphenyl)-1,1-bis(methylthio)-3-nitro-1,3-butadiene (**3b**) has been already described.[5]

4.2.1. (*E*)-1,1-Bis(methylthio)-3-nitro-4-phenyl-1,3-butadiene (3a). Yellow solid, mp 40.8–41.3°C (petroleum ether); ν_{max} 1639, 1541, 1511, 1311, 1211, 1282, 1049 cm^{-1}; ^{1}H NMR: δ 2.22 (3H, s), 2.48 (3H, s), 6.29 (1H, s), 7.42 (3H, m), 7.51 (2H, m), 7.96 (1H, s); ^{13}C NMR: δ 16.42, 16.84, 114.31, 128.87, 130.62, 130.65, 132.05, 134.36, 145.56, 147.30. Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.9; H, 4.9; N, 5.2%. Found: C, 53.8; H, 4.8; N, 5.3%.

4.2.2. (*E*)-4-(3-Methoxyphenyl)-1,1-bis(methylthio)-3-nitro-1,3-butadiene (3c). Yellow solid, mp 25.0–26.0°C (petroleum ether); ν_{max} 3000, 2919, 2832, 1642, 1597, 1575, 1514, 1485, 1463, 1430, 1321, 1260, 1195, 1172, 1161, 1037 cm^{-1}; ^{1}H NMR: δ 2.24 (3H, s), 2.48 (3H, s), 3.82 (3H, s), 6.30 (1H, s), 6.94 and 6.98 (1H in all, two m), 7.08 and 7.13 (2H in all, two m), 7.32 (1H, dd, J=7.4 and 8.0 Hz), 7.99 (1H, s); ^{13}C NMR δ: 16.47, 16.85, 55.25, 114.29, 115.07, 116.93, 123.51, 129.85, 133.21, 134.32, 145.59, 147.43, 159.69. Anal. Calcd for $C_{13}H_{15}NO_3S_2$: C, 52.5; H, 5.1; N, 4.7%. Found: C, 52.3; H, 5.2; N, 4.7%.

4.2.3. (*E*)-4-(4-Methoxyphenyl)-1,1-bis(methylthio)-3-nitro-1,3-butadiene (3d). Orange solid, mp 59.6–60.0°C (petroleum ether); ν_{max} 1634, 1600, 1565, 1547, 1488, 1442, 1423, 1303, 1259, 1216, 1176, 1117, 1050, 1028 cm^{-1}; ^{1}H NMR: δ 2.25 (3H, s), 2.50, (3H, s), 3.86 (3H, s), 6.30 (1H, s), 6.93 and 7.50 (2H each, AA′BB′, J=8.8 Hz), 7.98 (1H, s); ^{13}C NMR: δ 16.45, 16.90, 55.44, 114.49, 114.86, 124.43, 132.82, 134.59, 143.33, 146.60, 161.79. Anal. Calcd for $C_{13}H_{15}NO_3S_2$: C, 52.5; H, 5.1; N, 4.7%. Found: C, 52.5; H, 5.1; N, 4.8%.

4.2.4. (*E*)-4-(3-Chlorophenyl)-1,1-bis(methylthio)-3-nitro-1,3-butadiene (3e). Yellow oil; ν_{max} 3065, 2990, 2923, 2849, 1678, 1643, 1523, 1475, 1428, 1321, 1211, 1081 cm^{-1}; ^{1}H NMR: δ 2.24 (3H, s), 2.49 (3H, s), 6.28 (1H, s), 7.37 (3H, m), 7.50 (1H, m), 7.88 (1H, s); ^{13}C NMR: δ 16.40, 16.89, 113.38, 128.61, 130.08, 130.15, 130.44, 132.48, 133.87, 134.83, 146.52, 148.28. Anal. Calcd for $C_{12}H_{12}ClNO_2S_2$: C, 47.8; H, 4.0; N, 4.6%. Found: C, 47.6; H, 4.2; N, 4.5%.

4.2.5. (*E*)-4-(4-Chlorophenyl)-1,1-bis(methylthio)-3-nitro-1,3-butadiene (3f). Yellow-orange solid, mp 81.4–82.6°C (light petroleum); ν_{max} 1641, 1591, 1547, 1510, 1491, 1410, 1322, 1282, 1091, 1012 cm^{-1}; ^{1}H NMR: δ 2.25 (3H, s), 2.49 (3H, s), 6.25 (1H, s), 7.38 and 7.46 (2H each, AA′BB′, J=8.7 Hz), 7.91 (1H, s); ^{13}C NMR: δ 16.40, 16.87, 113.20, 129.23, 130.52, 131.72, 132.92, 136.73, 145.77, 147.88. Anal. Calcd for $C_{12}H_{12}ClNO_2S_2$: C, 47.8; H, 4.0; N, 4.6%. Found: C, 47.7; H, 4.2; N, 4.6%.

4.2.6. (*E*)-1,1-Bis(methylthio)-4-(1-naphthyl)-3-nitro-1,3-butadiene (3g). Orange oil; ν_{max} 3057, 2921, 1636, 1525, 1432, 1396, 1320, 1242, 1049 cm^{-1}; ^{1}H NMR: δ 2.03 (3H, s), 2.37 (3H, s), 6.31 (1H, s), 7.51 (4H, m), 7.90 (2H, m), 8.04 (1H, m), 8.58 (1H, s); ^{13}C NMR: δ 16.37, 16.86, 114.79, 123.91, 125.18, 126.54, 127.18, 127.82, 128.88, 129.45, 130.83, 131.69, 131.83, 133.60, 146.92, 147.36. Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.5; H, 4.8; N, 4.4%. Found: C, 60.6; H, 4.8; N, 4.5%.

4.2.7. (*E*)-1,1-Bis(methylthio)-4-(2-naphthyl)-3-nitro-1,3-butadiene (3h). Yellow-orange solid, mp 73.5–74.2°C (petroleum ether); ν_{max} 1619, 1553, 1513, 1314, 1183, 1035 cm^{-1}; ^{1}H NMR: δ 2.20 (3H, s), 2.51 (3H, s), 6.40 (1H, s), 7.55 and 7.61 [3H in all, m and dd (J=2.0 and 8.8 Hz) partially overlapping], 7.84 (3H, m), 8.01 (1H, s), 8.15 (1H, s); ^{13}C NMR: δ 16.45, 16.92, 114.30, 126.04, 126.90, 127.79, 127.93, 128.53, 128.77, 129.59, 132.45, 133.06, 134.06, 134.63, 145.44, 147.41. Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.5; H, 4.8; N, 4.4%. Found: C, 60.7; H, 4.9; N, 4.4%.

4.2.8. (*E*)-1,1-Bis(methylthio)-3-nitro-4-(2-thienyl)-1,3-butadiene (3i). Orange solid, mp 72.0–72.6°C (petroleum ether); ν_{max} 1626, 1537, 1510, 1492, 1416, 1321, 1298, 1238, 1217, 1051 cm^{-1}; ^{1}H NMR: δ 2.31 (3H, s), 2.55 (3H, s), 6.13 (1H, s), 7.15 (1H, dd, J=3.7 and 5.1 Hz), 7.46 (1H, d, J=3.8 Hz), 7.60 (1H, d, J=5.2 Hz), 8.28 (1H, s); ^{13}C NMR: δ 16.54, 16.73, 112.31, 127.94, 128.63, 133.11, 135.38, 135.71, 142.55, 149.83. Anal. Calcd for $C_{10}H_{11}NO_2S_3$: C, 43.9; H, 4.1; N, 5.1%. Found: C, 44.0; H, 4.2; N, 5.1%.

4.3. Reduction of compounds 3a–i to the corresponding vinyloximes 4a–i

In an Erlenmeyer flask, compounds **3a**–**i** (0.45 mmol) were dissolved in a preformed mixture of dimethylformamide (7 ml) and glacial acetic acid (0.47 ml). Under magnetic stirring and at room temperature, lead powder (0.2 g) was added in small portions and the mixture was stirred following the disappearance of substrate by TLC (petroleum ether/CH_2Cl_2 mixtures as eluant). Sometimes the addition of a second aliquot of lead (0.1 g) was needed in order to drive the reaction to completion within an overall 4–5 h time. Usual workup involved pouring the reaction mixture into water and extraction with Et_2O, followed by washing of the combined extracts with brine. After drying (Na_2SO_4) the organic layer and solvent removal under reduced pressure, the residue was chromatographed on a silica gel column (CH_2Cl_2 as eluant) to furnish the oximes **4** as single configurational isomers (^1H and ^{13}C NMR) in the yields reported in Table 2. In some instances the hydroximino protons were not clearly detectable in the ^1H NMR spectra.

4.3.1. 3-Hydroximino-1,1-bis(methylthio)-4-phenyl-1-butene (4a). Pale-yellow solid, mp 58.4–58.9°C (petroleum ether/CH_2Cl_2); ν_{max} 3264, 1619, 1598, 1526, 1491, 1434, 1332, 1299, 1244, 1016 cm^{-1}; ^1H NMR: δ 2.23 (3H, s), 2.35 (3H, s), 3.93 (2H, s), 5.74 (1H, s), 7.24 (5H, m); ^{13}C NMR: δ 16.45, 17.23, 34.38, 117.91, 126.39, 128.52, 129.05, 136.82, 142.40, 155.91. Anal. Calcd for $C_{12}H_{15}NOS_2$: C, 56.9; H, 6.0; N, 5.5%. Found: C, 57.0; H, 6.0; N, 5.4%.

4.3.2. 3-Hydroximino-4-(4-methylphenyl)-1,1-bis(methylthio)-1-butene (4b). Pale-yellow solid, mp 51.6–52.8°C (taken up with petroleum ether); ν_{max} 3293, 1669, 1608, 1546, 1512, 1428, 1322, 1296, 1240, 1227, 1014 cm^{-1}; ^1H NMR: δ 2.24 (3H, s), 2.31 (3H, s), 2.36 (3H, s), 3.89 (2H, s), 5.76, (1H, s), 7.19, (4H, app s); ^{13}C NMR: δ 16.48, 17.23, 21.03, 33.96, 118.31, 128.89, 129.16, 133.65, 135.85, 142.12, 155.88. Anal. Calcd for $C_{13}H_{17}NOS_2$: C, 58.4; H, 6.4; N, 5.2%. Found: C, 58.4; H, 6.5; N, 5.3%.

4.3.3. 3-Hydroximino-4-(3-methoxyphenyl)-1,1-bis(methylthio)-1-butene (4c). Yellow oil; ν_{max} 3301, 2994, 2919, 2832, 1595, 1584, 1530, 1487, 1429, 1316, 1258, 1148, 1047, 1011 cm^{-1}; ^1H NMR: δ 2.24 (3H, s), 2.37 (3H, s), 3.79 (3H, s), 3.91 (2H, s), 5.76 (1H, s), 6.78 (3H, m), 7.20 (1H, dt, J=1.0 and 7.5 Hz), ca. 8.40 (1H, br s); ^{13}C NMR: δ 16.42, 17.11, 34.35, 55.09, 111.76, 114.66, 118.28, 121.41, 129.31, 138.28, 142.12, 155.15, 159.62. Anal. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.1; H, 6.0; N, 4.9%. Found: C, 55.2; H, 6.2; N, 5.0%.

4.3.4. 3-Hydroximino-4-(4-methoxyphenyl)-1,1-bis(methylthio)-1-butene (4d). Pale-yellow oil; ν_{max} 3302, 2994, 2919, 2833, 1610, 1584, 1509, 1463, 1432, 1300, 1248, 1177, 1105, 1035 cm^{-1}; ^1H NMR: δ 2.24 (3H, s), 2.36 (3H, s), 3.78 (3H, s), 3.87 (2H, s), 5.76 (1H, s), 6.83 and 7.14 (2H each, AA$'$BB$'$, J=8.7 Hz); ^{13}C NMR: δ 16.47, 17.24, 33.47, 55.23, 113.91, 118.21, 128.79, 130.02, 142.15, 156.05, 158.16. Anal. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.1; H, 6.0; N, 4.9%. Found: C, 55.2; H, 6.1; N, 5.0%.

4.3.5. 4-(3-Chlorophenyl)-3-hydroximino-1,1-bis(methylthio)-1-butene (4e). Pale-yellow solid, mp 65.4–66.8°C (petroleum ether/CH_2Cl_2); ν_{max} 3255, 1595, 1566, 1525, 1433, 1243, 1078, 1020 cm^{-1}; ^1H NMR: δ 2.27 (3H, s), 2.37 (3H, s), 3.92 (2H, s), 5.76 (1H, s), 7.16 (4H, m); ^{13}C NMR: δ 16.58, 17.30, 34.07, 117.87, 126.66, 127.21, 129.15, 129.74, 134.28, 138.89, 143.06, 155.09. Anal. Calcd for $C_{12}H_{14}ClNOS_2$: C, 50.2; H, 4.9; N, 4.9%. Found: C, 50.3; H, 5.0; N, 4.9%.

4.3.6. 4-(4-Chlorophenyl)-3-hydroximino-1,1-bis(methylthio)-1-butene (4f). Pale-yellow solid, mp 106.0–106.3°C (light petroleum); ν_{max} 3270, 1626, 1544, 1486, 1429, 1415, 1298, 1244, 1159, 1105, 1089, 1007 cm^{-1}; ^1H NMR: δ 2.27 (3H, s), 2.37 (3H, s), 3.90 (2H, s), 5.74 (1H, s), 7.16 and 7.26 (2H each, AA$'$BB$'$, J=8.6 Hz), ca. 8.1 (1H, br s); ^{13}C NMR: δ 16.47, 17.25, 33.72, 117.67, 128.59, 130.32, 132.19, 135.30, 142.93, 155.38. Anal. Calcd for $C_{12}H_{14}ClNOS_2$: C, 50.1; H, 4.9; N, 4.9%. Found: C, 50.2; H, 4.9; N, 5.0%.

4.3.7. 3-Hydroximino-1,1-bis(methylthio)-4-(1-naphthyl)-1-butene (4g). White solid, mp 113.6–114.9°C (light petroleum); ν_{max} 3266, 1597, 1519, 1422, 1245, 1016 cm^{-1}; ^1H NMR: δ 1.94 (3H, s), 2.31 (3H, s), 4.36 (2H, s), 5.53 (1H, s), 7.33 (1H, br d, J=5.9 Hz), 7.50 (3H, m), 7.76 (1H, br d, J=7.7 Hz), 7.85 (1H, m), 8.01 (1H, m); ^{13}C NMR: δ 16.31, 16.87, 31.99, 116.87, 124.02, 125.50, 125.77, 126.22, 127.10, 127.43, 128.61, 132.30, 132.94, 133.72, 142.29, 155.45. Anal. Calcd for $C_{16}H_{17}NOS_2$: C, 63.3; H, 5.6; N, 4.6%. Found: C, 63.4; H, 5.7; N, 4.7%.

4.3.8. 3-Hydroximino-1,1-bis(methylthio)-4-(2-naphthyl)-1-butene (4h). Pale-yellow solid, mp 98.5–99.0°C (light petroleum); ν_{max} 3264, 1611, 1599, 1529, 1425, 1244, 1016 cm^{-1}; ^1H NMR: δ 2.20 (3H, s), 2.35 (3H, s), 4.10 (2H, s), 5.81 (1H, s), 7.42 (3H, m), 7.66 (1H, s), 7.79 (3H, m); ^{13}C NMR: δ 16.49, 17.25, 34.51, 118.07, 125.46, 126.01, 127.30, 127.56, 127.61, 128.10, 132.18, 133.58, 134.34, 142.55, 155.75. Anal. Calcd for $C_{16}H_{17}NOS_2$: C, 63.3; H, 5.6; N, 4.6%. Found: C, 63.5; H, 5.7; N, 4.7%.

4.3.9. 3-Hydroximino-1,1-bis(methylthio)-4-(2-thienyl)-1-butene (4i). Pale-yellow solid, mp 60.2–61.2°C (petroleum ether/CH_2Cl_2); ν_{max} 3255, 1608, 1530, 1421, 1332, 1290, 1257, 1228, 1134, 1010 cm^{-1}; ^1H NMR: δ 2.28 (3H, s), 2.39 (3H, s), 4.12 (2H, s), 5.81 (1H, s), 6.90 (2H, m), 7.15 (1H, dd, J=1.4 and 5.3 Hz), ca. 8.5 (1H, br s); ^{13}C NMR: δ 16.52, 17.21, 28.62, 117.18, 124.26, 126.24, 126.81, 138.51, 142.93, 154.81. Anal. Calcd for $C_{10}H_{13}NOS_3$: C, 46.3; H, 5.1; N, 5.4%. Found: C, 46.5; H, 5.1; N, 5.5%.

4.4. Cyclization of compounds 4a–i to the isoxazoles 5a–i

The acidic ion-exchange resin (Amberlyst-15®, special for non-aqueous systems, 0.1 g) was added to a solution of **4** (0.1 g) in dry acetonitrile (5.5 ml) and the mixture was heated to reflux under stirring. The progress of the reaction (generally complete in 15 min) was monitored by TLC (petroleum ether/Et_2O mixtures as eluants). The resin was filtered off and washed three times by stirring for 30 min in anhydrous Et_2O. The combined ethereal washings were reunited to the acetonitrile solution. After solvent evaporation under reduced pressure, chromatography on silica gel (petroleum ether/Et_2O mixtures as eluant) allowed to isolate pure isoxazoles **5** in the yields reported in Table 3.

4.4.1. 3-Benzyl-5-(methylthio)isoxazole (5a). Low-melting pale-yellow solid; ν_{max} 3144, 1601, 1547, 1494, 1446, 1413, 1404, 1320, 1210, 1091, 1073, 1031 cm^{-1}; ^1H NMR: δ 2.52 (3H, s), 3.96 (2H, s), 5.82 (1H, s), 7.30 (5H, m); ^{13}C NMR: δ 15.21, 32.37, 101.69, 126.85, 128.69, 128.75, 136.97, 163.62, 167.55. Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.4; H, 5.4; N, 6.8%. Found: C, 64.6; H, 5.5; N, 6.7%.

4.4.2. 3-[(4-Methylphenyl)methyl]-5-(methylthio)isoxazole (5b). Yellow oil; ν_{max} 3136, 3018, 2921, 1551, 1513, 1444, 1320, 1209, 1083 cm^{-1}; ^{1}H NMR: δ 2.32 (3H, s), 2.51 (3H, s), 3.91 (2H, s), 5.80 (1H, s), 7.12 (4H, s); ^{13}C NMR: δ 15.27, 21.04, 32.02, 101.74, 128.89, 129.43, 133.97, 136.53, 163.92, 167.49. Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.7; H, 6.0; N, 6.4%. Found: C, 65.8; H, 6.2; N, 6.4 %.

4.4.3. 3-[(3-Methoxyphenyl)methyl]-5-(methylthio)isoxazole (5c). Pale-yellow oil; ν_{max} 3134, 1600, 1585, 1550, 1488, 1454, 1413, 1314, 1287, 1259, 1209, 1150, 1081, 1046 cm^{-1}; ^{1}H NMR: δ 2.53 (3H, s), 3.79 (3H, s), 3.93 (2H, s), 5.83 (1H, s), 6.81 (3H, m), 7.23 (1H, m); ^{13}C NMR: δ 15.26, 32.44, 55.21, 101.72, 112.29, 114.53, 121.14, 129.73, 138.54, 159.87, 163.54, 167.60. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.3; H, 5.6; N, 6.0%. Found: C, 61.2; H, 5.8; N, 6.0%.

4.4.4. 3-([4-Methoxyphenyl)methyl]-5-(methylthio)isoxazole (5d). Yellow solid, mp 39.7–41.0°C (petroleum ether); ν_{max} 3140, 1607, 1584, 1551, 1507, 1453, 1412, 1323, 1301, 1246, 1211, 1178, 1155, 1105, 1087, 1025 cm^{-1}; ^{1}H NMR: δ 2.53 (3H, s), 3.79 (3H, s), 3.90 (2H, s), 5.80 (1H, s), 6.85 and 7.16 (2H each, AA′BB′, J=8.6 Hz); ^{13}C NMR: δ 15.29, 31.58, 55.29, 101.71, 114.16, 129.08, 129.83, 158.57, 164.08, 167.50. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.3; H, 5.6; N, 6.0%. Found: C, 61.3; H, 5.6; N, 6.0%.

4.4.5. 3-[(3-Chlorophenyl)methyl]-5-(methylthio)isoxazole (5e). Pale-yellow oil; ν_{max} 3138, 2929, 1598, 1573, 1549, 1475, 1437, 1320, 1203, 1078, 1001 cm^{-1}; ^{1}H NMR: δ 2.54 (3H, s), 3.94 (2H, s), 5.82 (1H, s), 7.13 (1H, m), 7.23 (3H, m); ^{13}C NMR: δ 15.19, 32.02, 101.50, 126.96, 127.15, 128.87, 129.95, 134.48, 138.92, 162.89, 167.96. Anal. Calcd for $C_{11}H_{10}ClNOS$: C, 55.1; H, 4.2; N, 5.8%. Found: C, 55.3; H, 4.4; N, 5.6%.

4.4.6. 3-[(4-Chlorophenyl)methyl]-5-(methylthio)isoxazole (5f). White solid, mp 79.2–79.6°C (petroleum ether); ν_{max} 3144, 1547, 1486, 1445, 1411, 1207, 1109, 1088, 1014 cm^{-1}; ^{1}H NMR: δ 2.53 (3H, s), 3.93 (2H, s), 5.80 (1H, s), 7.17 and 7.29 (2H each, AA′BB′, J=8.4 Hz); ^{13}C NMR: δ 15.24, 31.81, 101.52, 128.90, 130.15, 132.88, 135.46, 163.22, 167.95. Anal. Calcd for $C_{11}H_{10}ClNOS$: C, 55.1; H, 4.2; N, 5.8%. Found: C, 55.0; H, 4.4; N, 5.8%.

4.4.7. 5-Methylthio-3-[(1-naphthyl)methyl]isoxazole (5g). Yellow oil; ν_{max} 3123, 1596, 1537, 1508, 1432, 1409, 1354, 1325, 1260, 1210, 1163, 1154, 1139, 1082, 1018 cm^{-1}; ^{1}H NMR: δ 2.47 (3H, s), 4.41 (2H, s), 5.72 (1H, s), 7.49 (4H, m), 7.83 (2H, m), 8.07 (1H, m); ^{13}C NMR: δ 15.20, 30.08, 101.82, 123.79, 125.53, 125.90, 126.44, 127.17, 128.01, 128.76, 131.87, 132.96, 133.94, 163.72, 167.54. Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.6; H, 5.1; N, 5.5%. Found C, 70.7; H, 5.2; N, 5.5%.

4.4.8. 5-Methylthio-3-[(2-naphthyl)methyl]isoxazole (5h). White solid, mp 40.9–41.5°C (petroleum ether); ν_{max} 3134, 1598, 1549, 1446, 1411, 1323, 1211, 1088 cm^{-1}; ^{1}H NMR: δ 2.51 (3H, s), 4.13 (2H, s), 5.84 (1H, s), 7.35 (1H, dd, J=1.8 and 8.4 Hz), 7.48 (2H, m), 7.70 (1H, s), 7.81 (3H, m); ^{13}C NMR: δ 15.25, 32.60, 101.79, 125.81, 126.27, 127.01, 127.30, 127.58, 127.69, 128.49, 132.38, 133.51, 134.49, 163.65, 167.74. Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.6; H, 5.1; N, 5.5%. Found C, 70.8; H, 5.3; N, 5.4%.

4.4.9. 5-Methylthio-3-[(2-thienyl)methyl]isoxazole (5i). Pale-yellow oil; ν_{max} 3133, 2925, 1551, 1441, 1320, 1252, 1208, 1077, 1038 cm^{-1}; ^{1}H NMR: δ 2.54 (3H, s), 4.17 (2H, s), 5.93 (1H, s), 6.92 (2H, m), 7.19 (1H, dd, J=1.5 and 5.0 Hz); ^{13}C NMR: δ 15.27, 26.70, 101.61, 124.70, 126.17, 127.08, 138.91, 163.06, 167.85. Anal. Calcd for $C_9H_9NOS_2$: C, 51.2; H, 4.3; N, 6.6%. Found: C, 51.4; H, 4.5; N, 6.5%.

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