Monosubstituted Oxazoles. 1. Synthesis of 5-Substituted Oxazoles by Directed Alkylation

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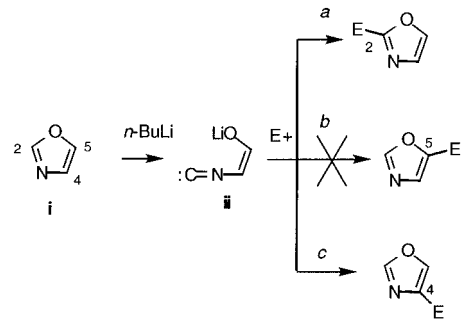
A general method is presented for synthesis of 2-(methylthio)-5-substituted oxazoles **2**. Deprotonation of the readily available 2-(methylthio)oxazole (**1**) with *n*-BuLi occurs smoothly in the presence of TMEDA and regiospecifically at C5. The organometallic **1a** added rapidly to aldehydes and other electrophiles to provide 5-substituted-2-(methylthio)oxazoles in very good to excellent yields. Reductive removal of the MeS group gave the desired 5-monosubstituted oxazoles **3** in good yield.

A number of oxazole-containing natural products have been isolated from marine invertebrates and microorganisms,[1−6] many of which exhibit potent biological activity. Syntheses of oxazole-containing natural products[7−12] has mostly concentrated on targets bearing the common biogenic 2,4-disubstituted oxazole. Surprisingly few methods are available for oxazoles *monosubstituted* at C5, a fact that is better understood with consideration of the complex chemistry of substituted oxazoles. Metalation on a preformed oxazole ring at C5 with strong base followed by electrophilic addition is limited to 2-substituted oxazoles with 4-carboxylate substituents.[13] Unfortunately, the intermediate organometallics are poor nucleophiles. Metalation of the parent oxazole at C5 is generally not possible if H2 is unsubstituted due to deprotonation of the more acidic H2 ($pK_A \sim 20$) leading to ring-opened isonitrile−enolate **ii** (Scheme 1).[14] Although the ambident nucleophile **ii** has been exploited for C−C bond formation, alkylation only occurs at C2 or C4.[15] Suppression of ring opening has been achieved by placement of a TMS group at C2[15,16] or use of oxazole−*N*-borane adducts to reduce electron density at nitrogen, but again alkylation is directed to C2.[17]

Scheme 1



We report here a solution to the problem of directed additions to C5 of oxazole by introduction of a 2-methylthio group to the oxazole ring. The surrogate MeS group allows low-temperature (−78 °C) metalation at C5, and the resulting 5-lithiooxazole smoothly reacts with aldehydes and other electrophiles to give 5-substituted oxazoles. The MeS group is then easily removed by reductive displacement. Since 2-(methylthio)oxazole (**1**) is readily prepared,[18] this two-step sequence allows convenient access to a variety of 5-oxazoles. In addition, we demonstrate that at room temperature the C2 MeS group can undergo displacement with the carbanion of isovaleronitrile to provide a 2-monosubstituted oxazole. Thus, the common precursor **1** can be *activated under nucleophilic or electrophilic conditions* for the tailored preparation of 5- or 2-monosubstituted oxazoles.

Results

Oxazole-2-thione, readily prepared from dihydroxymaleic acid and hydrogen thiocyanate,[18] was converted to 2-(methylthio)oxazole (**1**) by treatment with potassium hydride and methyl iodide (76%). The choice of base was important. Sodium hydride gave inferior yields and ethanolic alkali[19] produced mixtures of *S*- and *N*-methylated products. Deprotonation of **1** with *n*-BuLi in hexanes−THF followed by addition of benzaldehyde gave the 5-oxazolyl carbinol **2a** in modest yield (∼50%). After

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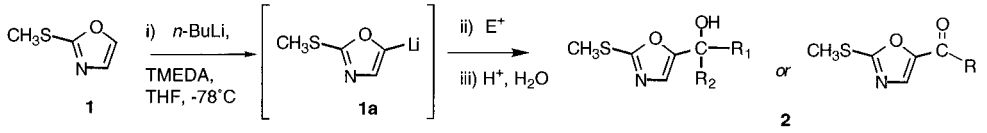
Table 1. Formation of 5-Substituted Oxazoles by Metalation of 1 and Electrophilic Addition



entry	electrophile (E^+)	oxazole, equiv	E^+, equiv	TMEDA, equiv	product	yield (%)[a]
1	benzaldehyde	1.0	2.3	10.4	**2a**	84
2	*p*-anisaldehyde	1.0	2.2	10.0	**2b**	85
3	*p*-bromobenzaldehyde	1.0	2.2	10.4	**2c**	84
4	2-naphthaldehyde	1.0	2.0	10.3	**2d**	77
5	2-furaldehyde	2.0	1.0	16.2	**2e**	72
6	citral	1.0	2.2	10.5	**2f**	83[b]
7	decyl aldehyde	1.0	2.2	12.2	**2g**	73
8	pivaldehyde	1.0	2.1	10.4	**2h**	69
9	2,3-*O*-isopropylidene-D-glyceraldehyde	1.0	1.4	14.0	**2i**	60[c]
10	3-methyl-2-butanone	1.0	2.2	10.4	**2j**	39[d]
11	cyclohexanone	2.0	1.0	16.0	**2k**	53
12	benzoyl chloride	1.0	19.9	9.9	**2l**	38
13	pivaloyl chloride	1.0	15.9	9.9	**2m**	71
14	isovaleronitrile	1.0	2.2	9.9	**4**	33[e]

[a] Yield of isolated product. Each new compound gave satisfactory HRMS and/or elemental analysis, IR, ^{1}H NMR and ^{13}C NMR. [b] Δ^2*E*/*Z* ratio was 2:1 from *E*/*Z*-citral. [c] 2:1 diastereomeric ratio. [d] Based on recovered starting material, 24% yield. [e] 3-Methyl-2-(2′-oxazolyl)butanenitrile (**4**).

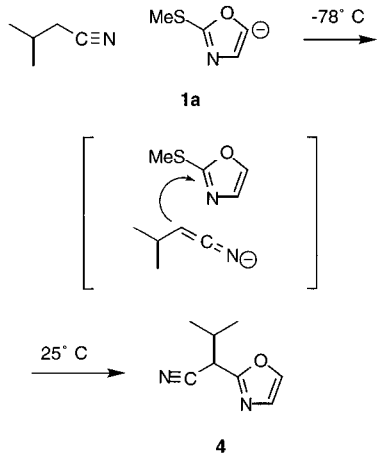
considerable experimentation, the optimum conditions were found to require TMEDA (10 equiv) during deprotonation at −78 °C followed by addition of carbanion **1a** to a solution of aldehyde at −78 °C, which improved the yield of **2a** to 84%.

The location of substitution of the oxazole ring in **2a** was confirmed by examination of the ^{1}H NMR spectrum, measurement of heteronuclear coupling constants, and deuterium quench experiments (see below). The product **2a** showed one aromatic singlet (δ 6.62) with a heteronuclear coupling constant of $^1J_{CH}$ = 195.8 Hz, most conveniently measured from ^{13}C satellites peaks in the ^{1}H NMR spectrum. It has been shown that magnitudes of coupling constants, $^1J_{CH}$, in the oxazole ring vary considerably with the electronic environment at different positions around the ring (C2, C4, or C5), but are essentially invariant with respect to alkyl substitution.[1,20] The relatively low value of $^1J_{CH}$ of the remaining oxazole ring proton signal in **2a** is consistent with substitution at C5 and not C4 (cf. oxazole, C4, $^1J_{CH}$ =194 Hz, C5, $^1J_{CH}$ = 210 Hz).[20]

Deprotonation−addition of **1a** was dependent upon the nature of the electrophile. Aldehydes reacted rapidly (complete in about 10 min) and gave high yields of carbinols (Table 1, entries 1−9). Interestingly, the reaction with *p*-bromobenzaldehyde showed no evidence of halogen−metal exchange products. With ketones the reaction was slower and did not always proceed to completion (Table 1, entries 10 and 11), perhaps due to competing enolization of ketone by proton exchange. Acid chlorides also reacted rapidly with the anion (Table 1, entries 12 and 13); however, a large excess of the acid chloride was required to compete against addition of a second equivalent of the anion of **1** to the ketone product. The reaction with acyl chlorides is uncomplicated by Cornforth-type rearrangement products.[21,22]

One example of addition to an alkanenitrile was explored (Table 1, entry 14; Scheme 2). Under standard

Scheme 2



conditions (−78 °C) no reaction with isovaleronitrile was observed (TLC), but upon allowing the mixture to warm to 25 °C over 16 h a new product (33%) could be isolated after workup and chromatography. The ^{1}H NMR spectrum of the product showed loss of the MeS group and addition of alkyl proton signals corresponding to isovaleronitrile, but some differences were apparent. In particular, the methyl groups were now diastereotopic as shown by two separate methyl signals (δ 1.11, d, J = 6.7 Hz; 1.12, d, J = 6.7 Hz), and the α-methylene protons were replaced by a one-proton doublet (δ 3.98, d, J = 6.7 Hz). The IR spectrum showed that the nitrile group had been retained (ν 2250 cm^{-1}), thus the structure of the product is **4**.

The anion formed by deprotonation of **1** under optimized conditions added smoothly to aldehydes, but when an excess of *n*-BuLi (~1.3 equiv) was used or the aldehyde was added to the preformed oxazole anion (inverse addition), signficant amounts of side-product due to "double alkylation" were observed. The second alkylation always occurred by deprotonation−addition to the MeS group (for example, product **5d**). Although standard conditions gave no products from addition to MeS group, the low acidity of the methylthio hydrogens raised the

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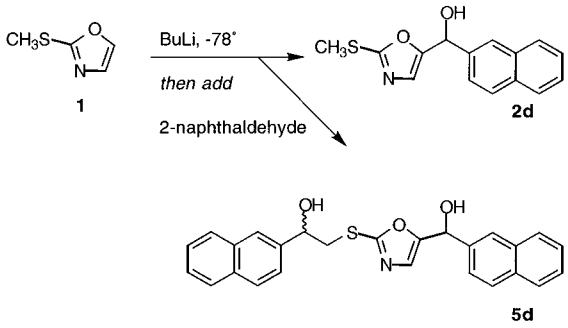
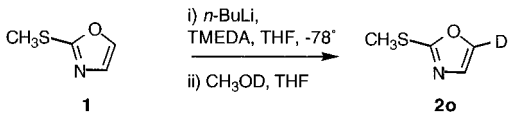


possibility that in the presence of excess lithioanion **1a** proton exchange with **1** may rearrange the anion at C5 with the α-anion of the MeS group, perhaps via a doubly charged intermediate. To examine the lability of the C5 anion, deuterium quench experiments were conducted. The anion was prepared under standard conditions (1.0 equiv of BuLi, TMEDA, −78 °C) and after 20 min a portion of this mixture was cannulated into a solution of CH_3OD at −78 °C. The carbanion solution was raised to −40 °C, and two additional aliquots were quenched with CH_3OD after a further 15 min and 100 min. For each sample, ^1H NMR integration and GCMS showed >90% deuterium incorporation at C5, but <5% incorporation at the MeS group (EIMS, *m*/*z* 100, $M^+ - Me$). This confirms that metalation occurred exclusively at C5 and, within the limits of detection, no deuterium incorporation was observed in the MeS group. Thus, the C5 carbanion **1a** does not appear to be kinetically labile under the conditions of the addition reaction.

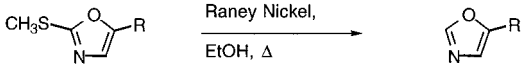


Reductive removal of the MeS group was carried out with several examples of **2** using one of two reagents: Raney nickel and nickel boride (created in situ from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$,[23] Table 2). Raney nickel in refluxing ethanol smoothly desulfurized the oxazole rings giving 5-monosubstituted oxazoles in good yields (59−68%). It was pleasing to note that the reductively sensitive benzylic alcohols **3a** and **3d** were formed in good yield without further deoxygenation to the corresponding 5-benzyl oxazoles. Although reactions involving Ni_2B were complete in a short time (<15 min), the yields were lower than those obtained with Raney nickel due to poor mass recovery from the insoluble Ni-containing residue.

Discussion

The preparation of 5-monosubstituted oxazoles by deprotonation−addition of 2-(methylthio)oxazole to aldehydes efficiently generates 5-substituted oxazoles in good yield. This method has an advantage over two literature methods for 5-substituted oxazoles, Schöllkopf condenstion of lithiated CH_3NC with esters[24] or condensation of triethyl formate with phenacylamines,[25,26] by allowing construction of C−C bonds at preformed oxazole rings. The secondary alcohol **2i** prepared from addition of **1** to a chiral aldehyde showed modest diastereoselectivity (2:1, entry 9, Table 1); however, this was not optimized.

Table 2. Reductive Desulfurization of 2 to 5-Substituted Oxazoles 3



entry	starting material (**2**)	product (**3**)	yield (%)[a]
1	**2a**	**3a**	68
2	**2d**	**3d**	60
3	**2g**	**3g**	60
4	**2h**	**3h**	59
5	**2k**	**3k**	60

[a] Yield of isolated product. Each new compound gave satisfactory HRMS and/or elemental analysis, IR, ^1H NMR, and ^{13}C NMR.

Table 3. Calculated Electrostatic Charges at C5 of Heterocyclic Carbanions (PM3, MacSpartan Plus)

parent heterocycle	δ^- at C5
oxazole	−0.86
2-(methylthio)oxazole	−0.88
2-ethyoxazole	−0.87
furan	−0.81
2-(methythio)furan	−0.82
2-ethyfuran	−0.81

The reaction of **1a** with aldehydes is relatively rapid, but somewhat slower with ketones, a tendency that suggests the nucleophilicity of **1a** is similar to that of 2-lithiofuran and may correlate with charge density at C5. This was briefly examined by molecular orbital calculations of the α-anions of **1**, 2-ethyloxazole, 2-ethylfuran, 2-methylthiofuran, and oxazole (PM3 level, MacSpartan Plus, Table 3). Examination of fractional electrostatic charge at each ring atom revealed that >80% of the fractional charge resided at the anionic carbon (C5 of **1**). The formal carbanion corresponding to **1a** has charge localized in an sp^2 orbital orthogonal to the π system and is not expected to be stabilized by classical resonance. All oxazoles anions examined gave comparable charge densities (range, −0.86 to −0.88) and were slightly higher than the corresponding furans (∼−0.81), suggesting a negligible electron-withdrawing effect of the SMe group on C5. While these calculations do not allow for solvent effects, stabilization by counterion, or coordination to the adjacent heteroatom, it supports the hypothesis that C5 lithiated 2-(methylthio)oxazole is at least as nucleophilic as lithiofuran in contrast with the poor nucleophilicity observed with 5-lithio 4-carboxylates.[13]

The differential reactivity of **1a** toward electrophiles indicates synthetic utility in selective addition reactions. Slower reaction of **1a** with ketones and poor reactivity with isovaleronitrile suggests that **1a** may add selectively at low temperature to aldehydes in the presence of ketones, nitriles, and perhaps esters. On the other hand, the formation of **4** from **1a** and isovaleronitrile indicates the α-nitrile carbanion is preferentially formed by proton transfer. The electrophilic nature of C2 is then revealed by addition−elimination of the α-nitrile carbanion to **1** and displacement of the MeS group to provide a moderate

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(unoptimized) yield of **4**. Thus, the MeS group, conveniently introduced in **1** as a robust surrogate group to direct electrophilic C−C bond formation at C5 by reaction with hard electrophiles (aldehydes), may also function as a leaving group for C−C bond formation at C2 under another set of conditions. This carbon−carbon bond-forming reaction complements the successful Vedejs modification for metalation−addition to 2-unsubstituted oxazoles.[17] We are now exploring both of these versatile properties in C−C bond-forming reactions of oxazoles.

Experimental Section

General. THF and ether were purified by distillation from sodium benzophenone ketyl. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ (unless stated otherwise) at 300 and 75 MHz and referenced to δ 7.26 and δ 77.00, respectively. Homonuclear *J* couplings were confirmed by COSY or single-frequency decoupling experiments. ^{13}C NMR signal chemical shift and multiplicity assignments (CH_3, methyl; CH_2, methylene; CH, methine; C, quaternary) were made from DEPT spectra. High-resolution mass spectra were provided by the University of California, Riverside, and the University of Minnesota Mass Spectrometry Laboratories. Other procedures are described elsewhere.[27]

2-(Methylthio)oxazole (1). Oxazole-2-thione (4.98 g, 49.3 mmol) in THF (125 mL) was added to hexane-washed KH (35% dispersion in oil, 6.38 g, 55.7 mmol) in THF (125 mL) at −60 °C, and, after 30 min, MeI was added. The reaction was stirred for 3.25 h and was quenched with NH_4Cl (aq, satd, 50 mL) and then diluted with H_2O (40 mL). The aqueous layer was extracted with Et_2O (3 × 800 mL), and the combined organic layers were dried ($MgSO_4$) and reduced to a yellow oil (6.6067 g). The crude material was purified by bulb-to-bulb distillation (70−100 °C, 28 mmHg) to give **1**[18] as a colorless oil (4.315 g; 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 3 H), 7.10 (s, 1 H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 128.1 (CH), 139.8 (CH), 161.1 (C); HREIMS found *m*/*z* 115.0090 (M^+), C_4H_5NOS requires 115.0092.

General Procedure for C-5 Alkylation. 1-Phenyl-1-[2′-(methylthio)oxazol-5′-yl]methanol (2a). 2-(Methylthio)oxazole (**1**) (0.2496 g, 2.17 mmol), TMEDA (3.4 mL, 22.5 mmol), and THF (5 mL) were added to a solution of *n*-BuLi (0.88 mL, 2.31 mmol) in THF (5 mL) at −78 °C. In a separate flask, benzaldehyde (0.50 mL, 4.92 mmol) was dissolved in THF (7 mL) and cooled to −78 °C. After 20 min, the oxazole anion of **1** was added to the aldehyde over 10 min via an insulated cannula. The mixture was stirred for an additional 12 min, quenched with $NaHCO_3$ (aq, satd, 3 mL), diluted with 10 mL H_2O, and extracted with EtOAc (3 × 125 mL). The organic layer was dried ($MgSO_4$) and reduced to a yellow oil which was purified by column chromatography (silica, 3:7 to 1:1 EtOAc:hexane) to give **2a** as a colorless oil (0.4008 g, 84%). IR (NaCl, neat) ν 3304 (OH), 1488 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 5.76 (s, 1 H), 6.62 (s, 1H, J_{C4-H4} = 195.8 Hz), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 68.04 (CH), 125.3 (CH), 126.5 (CH), 128.3 (CH), 128.5 (CH), 139.6 (C), 154.5 (C), 161.7 (C); HREIMS found *m*/*z* 221.0517 (M^+), $C_{11}H_{11}NO_2S$ requires 221.0511.

1-(4′-Methoxyphenyl)-1-[2′-(methylthio)oxazol-5′-yl]-methanol (2b). Yellow oil (85%); IR (NaCl, neat) ν 3332 (OH), 1614 cm^{-1} (C═C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.79 (s, 3 H), 5.70 (s, 1 H), 6.62 (s, 1H), 6.87 (d, 2 H, *J* = 8.6 Hz), 7.31 (d, 2 H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 55.2 (CH_3), 67.7 (CH), 113.8 (CH), 125.1 (CH), 127.8 (CH), 131.8 (C), 154.8 (C), 159.5 (C), 161.4 (C); HREIMS found *m*/*z* 251.0604 (M^+), $C_{12}H_{13}NO_3S$ requires 251.0616.

1-(4′-Bromophenyl)-1-[2′-(methylthio)oxazol-5′-yl]methanol (2c). Yellow oil (84%) which crystallized from ethyl acetate and hexane, mp 96−97 °C; IR (NaCl, neat) ν 3270 (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 5.58 (s, 1 H), 6.46 (s, 1H), 7.37 (d, 2 H, *J* = 8.3 Hz), 7.37 (d, 2 H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 67.0 (CH), 122.0 (C), 124.9 (CH), 128.1 (CH), 131.5 (CH), 138.6 (C), 154.1 (C), 161.8 (C); HREIMS found *m*/*z* 298.9607 (M^+), $C_{11}H_{10}BrNO_2S$ requires 298.9616. Anal. Calcd for $C_{11}H_{10}BrNO_2S$: C, 44.02; H, 3.36; N, 4.67; S, 10.68. Found: C, 44.30; H, 3.41; N, 4.49; S, 10.59.

1-[2′-(Methylthio)oxazol-5′-yl]-1-(2′-naphthyl)methanol (2d). Yellow oil (77%) which crystallized from ethyl acetate/hexane, mp 106−107 °C; IR (NaCl, neat) ν 3284 (OH), 1603 (C═C), 1487 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 5.29 (bs, 1 H), 5.85 (s, 1 H), 6.62 (s, 1H), 7.48 (m, 3 H), 7.84 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 67.6 (CH), 124.1 (CH), 124.9 (CH), 125.2 (CH), 125.9 (CH), 126.0 (CH), 127.4 (CH), 127.8 (CH), 128.1 (CH), 132.8 (C), 132.9 (C), 137.0 (C), 154.6 (C), 161.5 (C); HREIMS found *m*/*z* 271.0656 (M^+), $C_{15}H_{13}NO_2S$ requires 271.0667. Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.50; H, 4.91; N, 5.07; S, 11.64.

"Double alkylation" of 1a: Binaphthyl Diol 5d. The above reaction was repeated with 1.4 equiv of BuLi and addition of metalated **1** to aldehyde (2.2 equiv) at −40 °C. Silica gel chromatography gave **2d** (33%) in addition to a new compound **5d** (44%) which crystallized from ethyl acetate/hexane, mp 145−146 °C; IR (NaCl, neat) ν 3369 (OH), 1734, 1484 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (dd, 1 H, *J* = 13.7, 8.2 Hz), 3.57 (dd, 1 H, *J* = 13.7, 3.3 Hz), 5.10 (dd, 1 H, *J* = 8.2, 3.3 Hz), 5.55 (bs, 2 H), 5.90 (s, 1 H), 6.76 (s, 1H), 7.44 (m, 6 H), 7.82 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 40.7 (CH_2), 67.2 (CH), 72.0 (CH), 123.6 (CH), 124.1 (CH), 124.4 (CH), 124.5 (CH), 124.9 (CH), 125.3 (CH), 125.6 (CH), 125.7 (CH), 127.0 (CH), 127.1 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 132.4 (C), 132.5 (C), 132.6 (C), 137.7 (C), 155.1 (C), 160.0 (C); HRCIMS (NH_3) found *m*/*z* 428.1332 (MH^+), $C_{26}H_{21}NO_3S$ requires 428.1320.

1-(2′-Furyl)-1-[2′-(methylthio)oxazol-5′-yl]methanol (2e). Yellow oil (72%); IR (NaCl, neat) ν 3269 (OH), 1487 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3 H), 5.75 (s, 1 H), 6.30 (m, 2 H), 6.80 (s, 1 H), 7.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 61.7 (CH), 107.8 (CH), 110.3 (CH), 125.3 (CH), 142.5 (CH), 152.2 (C), 161.6 (C); HREIMS found *m*/*z* 211.0299 (M^+), $C_9H_9NO_3S$ requires 211.0303.

1-[2′-(Methylthio)oxazol-5′-yl]-3,7-dimethylocta-2,6-dien-1-ol (2f). Clear oil (83%, 2:1 *E*:*Z*); IR (NaCl, neat) ν 3336 (OH), 1726, 1668 (C═C), 1490 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3 H), 1.59 (s, 3 H), 1.61 (s, 3 H), 2.00 (m, 4 H), 2.52 (s, 3 H), 4.99 (m, 1 H), 5.34 (m, 2 H), 6.72 (s, 1 H; *E*), 6.75 (s, 1 H, *Z*); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 16.5/17.5 (CH_3), 22.4/23.2 (CH_3), 25.4/25.5 (CH_3), 26.0/26.2 (CH_2), 32.2/ 39.2 (*Z*/*E*, CH_2), 62.0/62.4 (CH), 122.6 (CH), 123.4 (CH), 123.8 (CH), 131.7/132.3 (C), 140.6/140.9 (C), 154.6/154.7 (C), 160.9 (C); HRCIMS (NH_3) found *m*/*z* 268.1368 (MH^+), $C_{14}H_{22}NO_2S$ requires 268.1371.

1-[2′-(Methylthio)oxazol-5′-yl]-*n*-decanol (2g). Colorless solid (73%); IR (NaCl, neat) ν 3338 (OH), 1491 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (m, 3 H), 1.19 (s, 12 H), 1.36 (m, 2 H), 1.71 (m, 2 H), 2.52 (s, 3 H), 4.05 (bs, 1 H), 4.56 (t, 1 H, *J* = 6.8 Hz), 6.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 14.3 (CH_3), 22.5 (CH_2), 25.3 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 34.9 (CH_2), 65.3 (CH), 123.5 (CH), 155.6 (C), 160.6 (C); HRCIMS (NH_3) found *m*/*z* 272.1679 (MH^+), $C_{14}H_{26}NO_2S$ requires 272.1684.

1-[2′-(Methylthio)oxazol-5′-yl]-2,2-dimethylpropanol (2h). Colorless solid (69%); mp 71−73 °C (recrystallized from ethyl acetate/hexane); IR (NaCl, neat) ν 3285 (OH), 1490 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9 H), 2.53 (s, 3 H), 4.28 (s, 1 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 25.6 (CH_3), 35.3 (C), 74.0 (CH), 125.0 (CH), 154.5 (C), 160.1 (C); HRCIMS (NH_3) found *m*/*z* 202.0901 (MH^+), $C_9H_{16}NO_2S$ requires 202.0902.

1-[2′-(Methylthio)oxazol-5′-yl]-(2*R*)-2,3-*O*-Isopropylidenepropanol (2i). Yellow oil (60%, 2:1 ratio of diastereomers); IR (NaCl, neat) ν 3412 (OH), 1490 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36/1.39 (s, 3 H), 1.42/1.46 (s, 3 H), 2.63 (s, 3 H), 3.43 (bs, 1 H), 3.80 (m, 2 H), 4.02 (m, 1 H), 4.08 (m, 1 H), 4.34 (m, 1 H)/ 4.38 (m, 1 H), 4.63 (d, 1 H, *J* = 6.5 Hz)/4.75 (d,

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1 H, J = 5.9 Hz), 6.99/7.01 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 24.9 (CH_3), 26.3 (CH_3), 65.6/65.8 (CH_2), 66.7 (CH), 76.4/76.8 (CH), 109.5/109.9 (C), 125.1/125.4 (CH), 151.7/152.4 (C), 161.2/161.4 (C); HRCIMS (CH_4) found m/z 246.0796 (MH^+), $C_{10}H_{16}NO_4S$ requires 246.0800.

1-[2′-(Methylthio)oxazol-5′-yl]-2,2-dimethylpropanol (2j). Colorless solid (27%, 39% based on consumed starting material), recrystallized from ethyl acetate/hexane, mp 76−77 °C; IR (NaCl, neat) ν 3385 (OH), 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.8 Hz), 1.36 (s, 3 H), 2.01 (2 overlapping q, 1 H, J = 6.8 Hz), 2.52 (s, 3 H), 3.12 (bs, 1 H), 6.73 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 16.7 (CH_3), 17.3 (CH_3), 22.1 (CH_3), 36.6 (CH), 72.9 (C), 123.4 (CH), 158.1 (C), 159.9 (C); HREIMS found m/z 201.0816 (M^+), $C_9H_{15}NO_2S$ requires 201.0824. Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96; S, 15.93. Found: C, 53.88; H, 7.62; N, 6.82; S, 15.99.

1-[2′-(Methylthio)oxazol-5′-yl]cyclohexanol (2k). Colorless oil (53%) which crystallized from ethyl acetate/hexane, mp 85−86 °C; IR (NaCl, neat) ν 3314 (OH), 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (m, 5 H), 1.79 (m, 5 H), 2.60 (s, 3 H), 3.31 (bs, 1 H), 6.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 21.8 (CH_2), 25.2 (CH_2), 36.1 (CH_2), 68.7 (C), 122.7 (CH), 158.7 (C), 160.1 (C); HREIMS found m/z 213.0826 (M^+), $C_{10}H_{15}NO_2S$ requires 213.0824. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 56.59; H, 7.17; N, 6.49; S, 14.90.

2-(Methylthio)-5-benzoyloxazole (2l). Orange oil (38%) which crystallized from *tert*-butyl methyl ether/hexane, mp 62−63 °C; UV ($CHCl_3$) λ_{max} 258 (ϵ 7085), 311 (17810); IR (NaCl, neat) ν 1718 (C=O), 1653 (C=C), 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 3 H), 7.53 (m, 3 H), 7.73 (s, 1 H), 7.91 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 128.4 (CH), 128.5 (CH), 132.9 (CH), 136.4 (C), 137.3 (CH), 150.6 (C), 167.2 (C), 180.2 (C); HREIMS found m/z 219.0363 (M^+), $C_{11}H_9NO_2S$ requires 219.0354. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 59.92; H, 4.14; N, 6.35; S, 14.77.

[2′-(Methylthio)oxazol-5′-yl]-2,2-dimethylpropanone (2m). Yellow oil (71%) which crystallized from *n*-hexane, mp 58−59 °C; UV ($CHCl_3$) 292 (ϵ 13026); IR (NaCl, neat) ν 1669, 1552, 1451 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 2.63 (s, 3 H), 7.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 26.4 (CH_3), 43.0 (C), 135.2 (CH), 150.6 (C), 165.0 (C), 192.9 (C); HREIMS found m/z 199.0668 (M^+), $C_9H_{13}NO_2S$ requires 199.0667. Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03; S, 16.09. Found: C, 54.32; H, 6.46; N, 6.94; S, 16.02.

Addition−Elimination of Isovaleronitrile to 2-(Methylthio)oxazole. 3-Methyl-2-(2-oxazolyl)butanenitrile (4). The reaction was carried out as for addition to aldehydes, but the reaction mixture was allowed to warm to 25 °C over 16 h. Workup and chromatography of the product gave **4** as a yellow oil (33%); IR (NaCl, neat) ν 2250 (CN), 1571, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, 3 H, J = 6.7 Hz), 1.12 (d, 3 H, J = 6.7 Hz), 2.47 (dq, 1 H, J = 6.7 Hz), 3.98 (d, 1 H, J = 6.1 Hz), 7.14 (d, 1 H, J = 0.8 Hz), 7.71 (d, 1 H, J = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 19.0 (CH_3), 20.1 (CH_3), 31.5 (CH), 38.8 (CH), 115.7 (C), 127.6 (CH), 139.8 (CH), 157.2 (C); HRCIMS (NH_3) found m/z 151.0866 (MH^+), $C_8H_{11}N_2O$ requires 151.0871.

General Procedure for Reductive Displacement of the Methylthio Group. 1-(Oxazol-5′-yl)-1-phenylmethanol (3a). Compound **2a** (0.1071 g, 0.48 mmol) was dissolved in absolute EtOH. Raney nickel in EtOH was added, and the reaction mixture was refluxed for 1.5 h. The hot reaction mixture was filtered through Celite which was washed with hot absolute EtOH (500 mL). The solvent was removed to give a cloudy oil which was purified by column chromatography (1:1 ethyl acetate:hexane) to give **3a** (0.0575 g, 68%). IR (NaCl, neat) 3295 (OH), 1507, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (bs, 1 H), 5.83 (s, 1 H), 6.75 (s, 1 H), 7.30 (m, 5 H), 7.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 68.2 (CH), 123.5 (CH), 126.5 (CH), 128.5 (CH), 128.6 (CH), 139.8 (C), 151.1 (C), 153.5 (C); HREIMS found m/z 174.0565 (M^+), $C_{10}H_9NO_2$ requires 174.0555.

1-(Oxazol-5′-yl)-1-(2-naphthyl)methanol (3d). Off-white solid (60%); mp 102−103 °C (recrystallized from chloroform/hexane); IR (NaCl, neat) ν 3270 (OH), 1603 (C=C), 1508 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (bs, 1 H), 5.99 (s, 1 H), 6.80 (s, 1 H), 7.47 (m, 3 H), 7.74 (s, 1 H), 7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 67.9 (CH), 123.1 (CH), 124.1 (CH), 125.3 (CH), 126.1 (CH), 126.2 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 132.9 (C), 133.0 (C), 137.2 (C), 151.0 (CH), 153.6 (C); HREIMS found m/z 225.0800 (M^+), $C_{14}H_{11}NO_2$ requires 225.0790. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.12; H, 4.99; N, 6.06.

1-(Oxazol-5′-yl)decanol (3 g). Yellow oil (60%); mp 62−64 °C (recrystallized from ethyl acetate/hexane); IR (NaCl, neat) ν 3364 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3 H), 1.25 (m, 12 H), 1.46 (m, 2 H), 1.84 (m, 2 H), 2.65 (bs, 1 H), 4.76 (t, 1 H, J = 6.8 Hz), 6.97 (s, 1 H), 7.84 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.3, 29.3, 29.5, 31.8, 35.3, 65.9, 122.5, 150.6, 154.2; HRCIMS found m/z 226.1808 (MH^+), $C_{13}H_{24}NO_2$ requires 226.1807. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.56; H, 10.03; N, 6.20.

1-(Oxazol-5′-yl)-2,2-dimethylpropanol (3h). Yellow oil (59%); mp 57−58 °C (recrystallized from ethyl acetate/hexane); IR (NaCl, neat) ν 3330 (OH), 1508, 1479 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9 H), 3.50 (bs, 1 H), 4.41 (s, 1 H), 6.87 (s, 1 H), 7.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_3), 35.5 (C), 74.2 (CH), 123.4 (CH), 150.2 (C), 153.3 (C); HRCIMS (i-C_4H_9) found m/z 156.1025 (MH^+), $C_8H_{14}NO_2$ requires 156.1025. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.00; H, 8.43; N, 9.08.

1-(Oxazol-5′-yl)cyclohexanol (3k). White solid (60%); mp 76−77 °C (recrystallized from ethyl acetate/hexane); IR (NaCl, neat) ν 3355 (OH), 1648, 1505, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (m, 4 H), 1.74 (m, 2 H), 1.91 (m, 4 H), 2.89 (bs, 1 H), 6.91 (s, 1 H), 7.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8 (CH_2), 25.2 (CH_2), 36.3 (CH_2), 68.9 (CH), 121.2 (CH), 150.2 (CH), 157.5 (C); HRCIMS (i-C_4H_9) found m/z 168.1025 (MH^+), $C_9H_{14}NO_2$ requires 168.1024. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.61; H, 7.82; N, 8.28.

Deuterium Incorporation Experiment. **2-(Methylthio)oxazole-5-*d* (2o).** Compound **1** (0.2984 g, 2.59 mmol), TMEDA (4.0 mL, 26.5 mmol), and THF (8 mL) were added to *n*-BuLi (1.0 mL, 2.62 mmol) and THF (7 mL) at −78 °C. After 15 min, approximately one-third of the reaction mixture was transferred via an insulated cannula to CH_3OD (1 mL) in Et_2O (5 mL) at −78 °C (sample 1). The temperature of the remaining reaction mixture was raised to −40 °C, and after another 15 min, approximately one-third of the reaction mixture was transferred to a mixture of CH_3OD (1 mL) and Et_2O (5 mL) at −78 °C using an insulated cannula (sample 2). The remaining reaction mixture was stirred for an additional 1.7 h at −40 °C after which it was quenched by addition of CH_3OD (1 mL, sample 3). Each of the three samples was dried ($MgSO_4$), concentrated under vacuum, and purified by column chromatography (silica, elution with Et_2O). The ^{1}H NMR signal of H5 was integrated and compared to the H4 integral. Comparison of the integrations of H5 to H4 gave the following results (atom % deuterium): sample 1 (96%); sample 2 (94%); sample 3 (90%). Comparison of NMR integrations of H4 to the MeS group indicated that in each case the ratio was 1:3 (∼±5% error). GC/MS (column DB-5, 30 m; T_i 50 °C, t_i 1 min, ramp 10 °C/min, T_f 280 °C, t_f 5 min) gave % deuteration. sample 1 (89%); sample 2 (95%); sample 3 (86%) error ±2%.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of **1**, **2a**−**m**, **3a**, **3d**, **3g**, **3h**, **3k**, **4**, and **5d** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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