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SHORT AND EFFICIENT SYNTHESIS OF 3-SUBSTITUTED 4-OXAZOLIN-2-THIONES AND THEIR REACTIVITY

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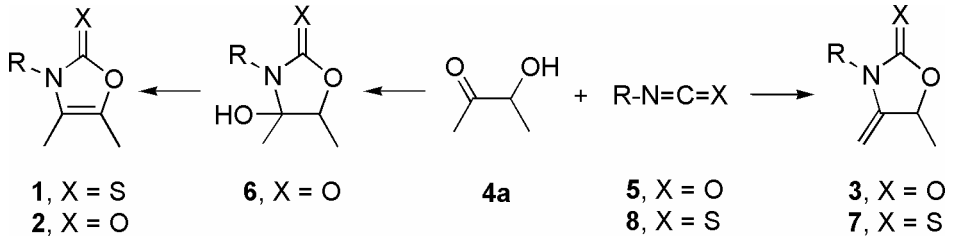
Abstract – A new synthesis of the substituted 4-oxazolin-2-thiones (**1**) and (**14**) is described by a regioselective tandem condensation reaction between α-ketols (**4a**-**4b**) and isothiocyanates (**8**). The use of dioxane as the solvent promotes the formation of the 4-methylene-1,3-oxazolidin-2-thiones (**7**), while the mixture of hemiaminals (**9**/**10**) is obtained in the presence of DMF; this mixture undergoes dehydration to give compounds (**1**). The latter are also prepared by an alternative solvent-free process by MW irradiation. Treatment of heterocycles (**1**) with alkyl iodides leads to the generation of the oxazolium iodides (**21**). The reactivity and regiochemistry of this process is explained in terms of FMO calculations.

INTRODUCTION

4-Oxazolidin-2-thiones have received much synthetic attention during the past decades because they have proved to be useful synthons[1] and valuable chiral auxiliaries.[2-7] In addition, they have also shown pharmacological activity.[8] These compounds are commonly prepared by condensation of carbon disulfide with β-aminoalcohols.[9] Although in principle these compounds might be prepared by asymmetric catalytic hydrogenation from 4-oxazolin-2-thiones (**1**),[10] or by functionalization of the endocyclic bond of the latter with an appropriate reagent,[11] it is somewhat surprising that the synthetic procedures for the preparation of (**1**) are scarce.[12] Compounds (**1**) have been obtained by treatment of the 4-oxazolin-2-ones (**2**) with phosphorous pentasulfide,[13] or with the Lawesson reagent in the case of their benzoxazol-2-thione analogues.[14] All previous attempts to prepare compounds (**1**) by direct condensation of α-ketols with isothiocyanates were unsuccessful.[13] The lack of synthetic methodology for the preparation of this interesting heterocyclic scaffold might be due to the difficulty of accessing to them from readily available starting materials and the absence of appropriate catalysts. A similar situation but

to a lesser extent is observed in the case of 4-oxazolin-2-ones (**2**), for which some synthetic approaches have been reported;[15-18] these molecules have also shown to be versatile chiral precursors.[11]

Recently, we described a regioselective method for the preparation of either 4-oxazolin-2-ones (**2**) or 4-methylene-2-oxazolidinones (**3**), involving a tandem condensation of 3-hydroxy-2-butanone (**4a**) with isocyanates (**5**) (Scheme 1).[19] The regioselectivity depended on the polarity of the solvent: dioxane was used for the preparation of the kinetic product (**3**), while DMF was the most efficient solvent for the generation of the thermodynamic product (**2**), via dehydration of the stable hemiaminal intermediates (**6**).

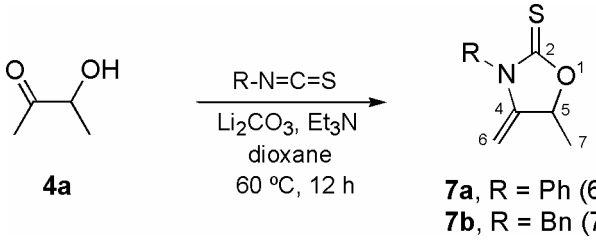


Scheme 1

As an extension of this methodology, herein we describe the synthesis of a series of the substituted 4-oxazolin-2-thiones (**1a**-**1g**), and the development of an alternative one-step synthesis of some of these compounds by direct irradiation of a mixture of the α-hydroxyketone (**4**) and the corresponding isothiocyanates (**8**) with microwaves (MW). An experimental and theoretical study of the reactivity of 4-oxazolin-2-thiones (**1**), towards Michael acceptors and alkyl halides is also reported.

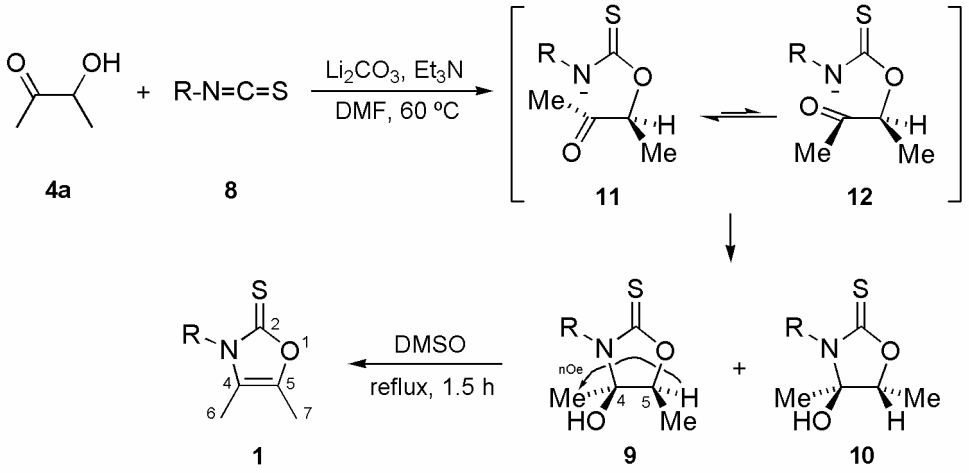
RESULTS AND DISCUSSION

The reaction of α-ketol (**4a**) with isocyanates (**5**) was found to proceed smoothly under mild conditions (Et_3N, Li_2CO_3, dioxane, room temperature, 12 h), to give the *N*-substituted 4-methylene-2-oxazolidinones (**3**) in fair yields (57-86%) as a single regioisomer (Scheme 1).[19] However, when isothioisocyanates (**8**) were used instead of **5**, under similar conditions, only starting materials were recovered. Better results were found when the reaction mixture was heated to 60 ºC for 12 h, yielding the *N*-substituted 4-methylene-1,3-oxazolidin-2-thiones (**7a**-**7b**) (Equation 1). Although the formation of isomers (**1a**-**1b**) and the decomposition of the starting materials reduced the reaction efficiency, the desired products were obtained in fairly good yields. If the temperature is increased, isomers (**1**) are obtained in larger amounts.[20]



[1]

As expected,[19] when DMF was employed as the solvent and the reaction was heated to 60 ºC for 12 h, hemiaminals were obtained in good yields as a mixture of two isomers (**9a-9g**/**10a-10g**) (Scheme 2, Table 1). It is worth mentioning that, in comparison with the milder temperature used (room temperature) in the preparation of hemiaminals (**6**), a higher temperature was applied in order to yield the products (Scheme 1). This difference is due to the well-known lower reactivity of isothiocyanates (**8**) with respect to isocyanates (**5**).[21,22]



Scheme 2

Compounds (**9a-9g**/**10a-10g**) were fully characterized by spectroscopy. The relative stereochemistry of the major isomer (**9**) was established by nOe experiments, which showed an enhancement of the signal of the methyl group Me-6 when the proton H-5 was irradiated. The preference for the *anti* isomer (**9**) might be explained in terms of thermodynamic control at the cyclization step of the thiocarbamate anion intermediates (**11**/**12**). The equilibrium between these conformational species is shifted towards the most stable isomer (**11**), whose methyl groups keep an *anti* relationship (Scheme 2).

Table 1. Yields of the mixtures of hemiaminals (**9**/**10**), and mp of the major isomers (**9**), obtained from the reaction of α-ketol (**4a**) and isothiocyanates (**8a-8g**).

Entry	**8** (R)	**9/10**[a]	Yield (%)[b]	Mp (ºC)[c]
1	**8a** (Ph)	76:24	72	145-146
2	**8b** (Bn)	74:26	76	129-130
3	**8c** (C_6H_4-4-Cl)	74:26	66	oil
4	**8d** (C_6H_4-4-Me)	70:30	70	oil
5	**8e** (C_6H_4-4-OMe)	76:24	72	oil
6	**8f** (C_6H_4-3-Cl)	74:26	89	110-111
7	**8g** (C_6H_4-3-Me)	70:30	65	113-114

[a] Determined by ^{1}H NMR. [b] For the mixture of isomers after column chromatography. [c] Of the major isomer.

4-Oxazoline-2-thiones (**1a**-**1g**) were obtained in high yields (Table 2) through dehydration of the series of mixtures (**9**/**10**) by heating to 160 ºC in a DMSO solution (Scheme 2).[23] The process furnished exclusively the endocyclic elimination product, since the exocyclic products (**7**) were not detected by ^{1}H NMR of the crude mixture. In the ^{1}H and ^{13}C NMR spectra of all derivatives, the methyl group Me-6 on C-4 is shifted upfield with respect to the methyl group Me-7, as established by nOe and HETCOR experiments. This is probably due to the shielding effect of the aryl or benzyl group located at the nitrogen atom. The aromatic ring adopts a quasi-orthogonal conformation with respect to the heterocyclic ring, as confirmed by the X-ray diffraction data of the structure of **1f** (Figure 1).[24]

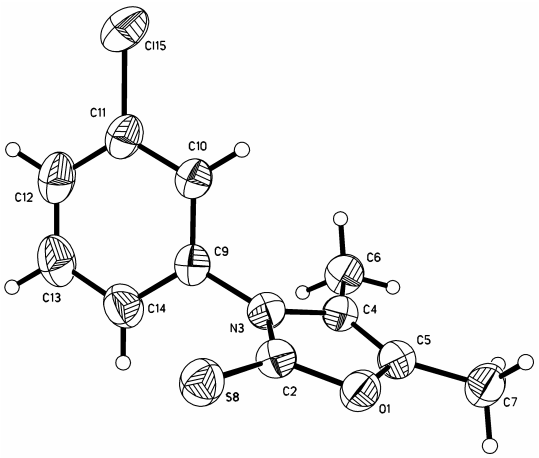


Figure 1. X-Ray structure of compound (**1f**) (ellipsoids with 30% probability).

In order to develop a one-pot procedure for the preparation of 4-oxazolin-2-thiones (**1)** through a cascade process that involves the condensation between 3-hydroxy-2-butanone (**4a**) and the isothiocyanates (**8a**, **8c**, **8e**, **8f**, and **8g**) (Scheme 2), followed by the cyclization, and dehydration reactions, we investigated the use of microwaves (MW)[25] at different irradiation powers and temperatures, either with solvent (xylene) or without it. Thus, we found that the most efficient reaction conditions consisted of the solvent-free irradiation of the mixture of the two reactants, in the presence of triethylamine, with MW (200 W) at 120 ºC for 90 min (Table 2, entries 8-12). Interestingly, in the case of **1a**, the tandem process was more efficient in overall yield than that involving two steps (Table 1, entry 1, and Table 2, entries 1 and 8), whereas in the case of **1e** the yield was similar (Table 2, entry 10). However, the reaction of isothiocyanates (**8c**, **8f**, and **8g**) provided the desired products (**1c**, **1f**, and **1g**) in lower yields (32-35%) (Table 2, entries 9, 11, and 12) with respect to those obtained by the first method (53-75%).

Table 2. Yields of compounds (**1**), obtained by dehydration of the mixtures of (**9**/**10**), or by MW radiation of a mixture of **4a** and **8**.[a]

Entry	Starting Material	**1** (R)	Yield (%)[b]
1	**9a**/**10a**	**1a** (Ph)	90
2	**9b**/**10b**	**1b** (Bn)	90
3	**9c**/**10c**	**1c** (C_6H_4-4-Cl)	85
4	**9d**/**10d**	**1d** (C_6H_4-4-Me)	82
5	**9e**/**10e**	**1e** (C_6H_4-4-OMe)	87
6	**9f**/**10f**	**1f** (C_6H_4-3-Cl)	84
7	**9g**/**10g**	**1g** (C_6H_4-3-Me)	82
8[c]	**8a**	**1a** (Ph)	69
9[c]	**8c**	**1c** (C_6H_4-4-Cl)	32
10[c]	**8e**	**1e** (C_6H_4-4-OMe)	58
11[c]	**8f**	**1f** (C_6H_4-3-Cl)	34
12[c]	**8g**	**1g** (C_6H_4-3-Me)	37

[a] In DMSO at 160 ºC for 1 h for the dehydration reaction of the mixture of the series **9**/**10**. [b] After purification by column chromatography or recrystallization. [c] Under MW irradiation (200 W) at 120 ºC for 90 min for the reaction of **4a** and isothiocyanates **8**, with Et_3N.

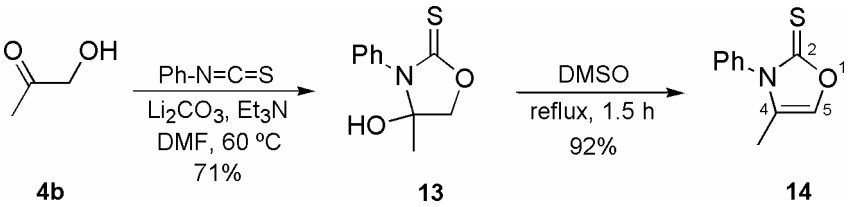
The exclusive endocyclic regioselectivity observed in both methods in the dehydration step suggests thermodynamic control, which is consistent with a carbenium ion intermediate.[23] The higher stability of regioisomer (**1**) with respect to **7** was confirmed by ab initio calculations (RHF/6-31G(d,p)), which showed a substantial energy difference for the pair (**1a**/**7a**) in favor of the *endo* double bond (Table 3). Moreover, DFT calculations (B3LYP/6-31G(d,p)) provided an even larger energy difference. These values are higher than those calculated for the 4-oxazolin-2-one pair (**2a**/**3a**) (Table 3), hence the isomerization process of the double bond towards the *endo* isomer (**1**) should be more favorable. It is worth noticing that the values of relative energies calculated here for the pair (**2a**/**3a**) are much higher than those previously calculated at lower levels of ab initio theory (HF/3-21G and HF/6-31G*).[19]

Table 3. Relative electronic energies including zero-point energy corrections (ΔE_0, kcal/mol) for the isomer pairs (**1a**/**7a**) and (**2a**/**3a**), calculated at the HF/6-31G(d,p) and B3LYP/6-31G(d,p) levels of theory.

	HF/6-31G(d,p)	B3LYP/6-31G(d,p)
ΔE_0 (**7a - 1a**)	6.05	9.14
ΔE_0 (**3a – 2a**)	2.01	6.03

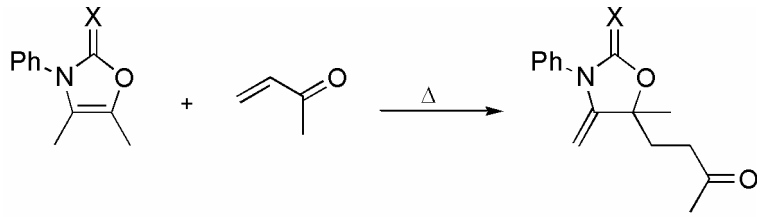
As an extension of our synthetic methodology, the 5-unsubstituted-4-oxazolin-2-thione (**14**) was prepared by reacting α-ketol (**4b**) with isothiocyanate (**8a**) through dehydration of the hemiaminal intermediates (**13**)

(Scheme 3). These transformations were also attempted under MW radiation, but only a complex mixture of products was obtained.



Scheme 3

4-Oxazolin-2-one (**2a**) (R = Ph) undergoes thermal (150 °C, 24 h) Michael addition to conjugated acceptors such as methyl vinyl ketone (**15**) to give the corresponding adduct 4-methylene-2-oxazolidinone (**16**) (Scheme 4).[19] To compare the reactivity of the thio compounds (**1**) with respect to **2** in the same type of reaction, we evaluated the addition of **1a** to **15** under similar conditions. However, the addition failed to provide the expected adduct (**17**), even when the reaction was carried out at higher temperatures (160-200 °C, 24 h) or under MW irradiation (400 W, 130 ºC, 6 h). Although other Michael acceptors such as acrolein (**18**) or methyl propiolate (**19**) were submitted to the same addition conditions with **1a**, none of the expected reaction products were detected. Even under more severe reaction conditions, only starting materials were recovered and a complex mixture of by-products was observed.



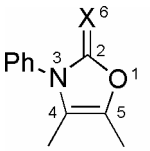
Scheme 4

The nucleophilicity of compounds (**2**) has been attributed to polarization of the endocyclic double bond by the nitrogen lone pair;[19,26] thus, in the above reactions these molecules behave formally as nucleophilic enamides. The difference in reactivity between **1** and **2** could be attributed to more efficient delocalization of the nitrogen lone pair towards de thiocarbonyl fragment, a fact that would reduce the nucleophilicity of the double bond. In order to evaluate this hypothesis by theoretical means, we calculated the energies of the MOs for the heterocycle (**1a**), comparing them with those of its analogue (**2a**). Geometries were optimized using the AM1 semiempirical method[27] and employed as starting points for ab initio optimization at the HF/6-31G(d,p) level of theory.[28] The HOMO and LUMO energies and the corresponding coefficients for each one of them and for the enone (**15**) are summarized in Table 4. From the FMO energies, it was found that the HOMO-heterocycle/LUMO-olefin interaction is preferred (Table 4). In principle, the heterocycle (**1a**) should be more reactive than the carbonyl analogue (**2a**) with **15**, due to the smaller energy gap

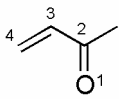
between the interacting FMOs (i.e., the HOMO of compound (**2a**) is more stable, see Table 4). This prediction is in contrast with the experimental results, since **2a** did react with **15**, but **1a** did not.

The sulfur atom seems to modify the delocalization of the electron density of the nitrogen lone-pair, resulting in a strong polarization towards the thiocarbonyl group. On the basis of coefficient distribution in the HOMO for heterocycles (**1a**) and (**2a**), one can observe that, unlike **2a** where the largest coefficient (C_5) is located at C-5 (where experimentally the addition takes place), in compound (**1a**) the largest coefficient is located at the sulfur atom (C_6). This suggests that the electron-density of the nitrogen lone-pair in **1a** is mainly delocalized towards the thiocarbonyl group, supporting the idea of a decrease of the nucleophilicity at C-5 in the oxazolidin-2-tiones (**1**) with respect to that in oxazolin-2-ones (**2**). Hence, in heterocycles (**1**), the electron-density should be polarized towards the sulfur atom, and as a result one could predict that in the reaction of **1a** with a proper electrophile, the interaction would take place at the sulfur atom S-6 and not at the carbon atom C-5. Therefore, we carried out the reaction of **1a** with alkyl halides. The reaction was successful with methyl iodide (**20a**) and ethyl iodide (**20b**) giving oxazolium iodides (**21a**) and (**21b**), respectively (Scheme 5),[13] supporting the MO prediction about the higher nucleophilicity of the thiocarbonyl group with respect to the enamide moiety. The formation of salts (**21a**) and (**21b**) suggests that the meso-ionic and aromatic resonance structure (**22**) is a major contributor to the chemical properties of compounds (**1**).[29]

Table 4. *Ab initio* HF/6-31G(d,p) energies (eV) and atomic coefficients (C_i) of the Frontier Molecular Orbitals for heterocycles (**1a**) and (**2a**), and MVK (**15**).



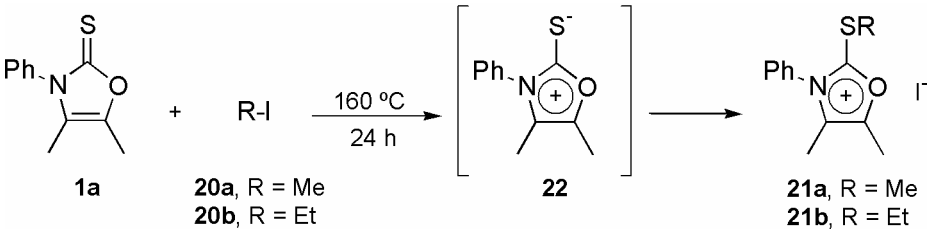
1a, X = S
2a, X = O



15

HOMO[a]								
Compd[b]	*E* (eV)	C_1	C_2	C_3	C_4	C_5	C_6	Δ*E* (HOMO-LUMO)[c]
1a	-7.8255	-0.1571	0.0065	-0.2330	0.1908	0.2256	0.5061	10.7469
2a	-8.3608	-0.1548	-0.0733	-0.2789	0.2776	0.3287	0.2204	11.2822
15	-10.4868	-0.2212	-0.0389	0.3663	0.3459			
LUMO[d]								
Compd[b]	*E* (eV)	C_1	C_2	C_3	C_4	C_5	C_6	Δ*E* (HOMO-LUMO)[e]
1a	5.0875	0.0762	0.1200	-0.1916	0.3705	-0.3547	-0.0519	15.5743
2a	5.3283	0.1581	-0.0729	-0.1038	0.3622	-0.3705	0.0489	15.8151
15	2.9214	0.2539	-0.2798	-0.2078	0.3108			

[a] Energies and coefficients of the HOMOs of **1a**, **2a**, and **15**. [b] The FMOs of the most stable planar *s-cis* conformer for **15**. [c] HOMO of the heterocycle and LUMO of **15**. [d] Energies and coefficients of 3NLUMO of **1a** and 2NLUMO **2a**, since the LUMOs and NLUMOs do not have a p_Z contribution at C-4 and C-5; LUMO of **15**. [e] HOMO of **15** and LUMO of the heterocycle.



Scheme 5

CONCLUSION

A new efficient approach to the synthesis of substituted 4-oxazolin-2-thiones has been developed. Thus, 4,5-dimethyl-4-oxazolin-2-thiones (**1a**-**1g**) and the 5-unsubstituted-4-oxazolin-2-thione (**14**) were prepared by a regioselective tandem condensation reaction between α-ketols (**4a**-**4b**) and isothiocyanates (**8**). The polarity of the solvent plays an important role in the formation of either heterocycles (**7**) or the hemiaminal precursors (**9**/**10**), which are selectively dehydrated to the *endo* heterocyclic alkenes (**1**). The latter were also obtained in only one step by an alternative cascade process including condensation, cyclization, and dehydration reactions promoted by MW irradiation. These compounds proved to be inefficient nucleophilic enamides with some Michael acceptors (enones), although they reacted at the sulfur atom in the presence of alkyl iodides. This preference was rationalized by FMO calculations, which showed a polarization of the electron density toward the sulfur atom and not to the C-5 thioenamide atom.

EXPERIMENTAL

Melting points (uncorrected) were determined with an Electrothermal capillary melting-point apparatus. IR spectra were recorded on a Perkin Elmer 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury (300 MHz) instrument, with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra (MS) were taken, in electron impact mode, on Hewlett-Packard 5971A and Finnigan Trace GC Ultra spectrometers, and high-resolution mass spectra (HRMS), in FAB^+ mode, were obtained on a Jeol JMS-SX 102 spectrometer. X-Ray crystallographic structures were obtained on a Siemens P4 diffractometer. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ). Microwave (MW) irradiation was performed on a SEV/MIC-1 (Mexico) MW reactor. All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Dioxane and xylene were freshly distilled from sodium, and methylene chloride, DMF, and DMSO from calcium hydride prior to use. Li_2CO_3 was dried overnight at 120 °C before use. All other reagents were used without further purification.

General Procedure for the Preparation of N-Substituted 5-Methyl-4-methylene-2-oxazolidinthiones (7a-7b).

A solution of 3-hydroxy-2-butanone (**4a**) (0.31 g, 3.5 mmol) in dry dioxane (3 mL) was added to a

suspension of triethylamine (0.70 g, 7.0 mmol) and dry Li_2CO_3 (0.31 g, 4.2 mmol) in dry dioxane (2 mL), under an N_2 atmosphere at rt. The mixture was stirred for 30 min, and a solution of the isothiocyanate (**8**) (5.2 mmol) in dry dioxane (2 mL) was added dropwise. The mixture was stirred and heated to 60 ºC for 12 h, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel treated with triethylamine (10%) in hexane (30 g per gram of crude) (hexane/EtOAc, 9:1).

5-Methyl-4-methylene-3-phenyloxazolidine-2-thione (7a). The use of the general procedure with 0.7 g of **8a** gave 0.5 g (69%) of **7a** as pale yellow oil: R_f 0.58 (hexane/EtOAc, 7:3); IR (film) 1490, 1393, 1349, 1314, 1173, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, J = 6.6 Hz, 3H, Me-7), 3.97 (dd, J = 2.7, 2.5 Hz, 1H, H-6b), 4.12 (dd, J = 2.5, 2.2 Hz, 1H, H-6a), 5.37-5.46 (m, 1H, H-5), 7.23-7.41 (m, 2H, PhH), 7.43-7.49 (m, 3H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.9 (C-7), 80.0 (C-5), 84.8 (C-6), 127.9 (C-9), 129.1 (C-11), 129.7 (C-10), 135.0 (C-8), 149.0 (C-4), 187.7 (C-2); MS (70 eV) 205 (M^+, 42), 144 (34), 130 (100), 103 (23), 77 (54). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.20; H, 5.58; N, 6.97; S, 15.81.

3-Benzyl-5-methyl-4-methyleneoxazolidine-2-thione (7b). The use of the general procedure with 0.77 g of **8b** gave 0.61 g (79%) of **7b** as colorless oil: R_f 0.47 (hexane/EtOAc, 7:3); IR (film) 2928, 1662, 1440, 1408, 1376, 1243, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J = 6.5 Hz, 3H, Me-7), 4.17-4.20 (m, 1H, H-6b), 4.22-4.25 (m, 1H, H-6a), 4.97-5.12 (m, 2H, NCH_2Ph), 5.22-5.32 (m, 1H, H-5), 7.22-7.45 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.8 (C-7), 48.4 (NCH_2Ph), 79.2 (C-5), 84.7 (C-6), 126.6 (C-11), 127.3 (C-12), 128.7 (C-10), 134.0 (C-9), 146.0 (C-4), 188.0 (C-2); MS (70 eV) 219 (M^+, 78), 158 (48), 130 (30), 104 (33), 91 (100), 65 (29). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.75; H, 5.97; N, 6.39. Found: C, 65.72; H, 6.00; N, 6.78.

General Procedure for the Preparation of 3-Substituted 4-Hydroxy-4,5-dimethyloxazolidine-2-thiones, (9a-9g and 10a-10g).

A solution of 3-hydroxy-2-butanone (**4a**) (1.5 mol equiv) was added to a suspension of triethylamine (4.0 mol equiv) and dry Li_2CO_3 (4.0 mol equiv) in dry DMF (10 mL/g), under an N_2 atmosphere at rt. The mixture was stirred for 30 min, and a solution of the isocyanate (**3**) (1.0 mol equiv) in dry DMF (10 mL/g) was added dropwise. The mixture was stirred at 60 ºC for 12 h, filtered over celite (EtOAc, 3 x 20 mL), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel in hexane (30 g per gram of crude) (hexane/EtOAc, 9:1).

(4*R,5*S**)-4-Hydroxy-4,5-dimethyl-3-phenyloxazolidine-2-thione (9a). (4*R**,5*R**)-4-Hydroxy-4,5-**

dimethyl-3-phenyloxazolidine-2-thione (10a). The use of the general procedure with 1.32 g (0.015 mol) of **4a**, 2.96 g (0.04 mol) of Li_2CO_3, 4.04 g (0.04 mol) of triethylamine, and 1.35 g (0.01 mol) of **8a**, gave 1.6 g (72%) of a mixture of **9a**/**10a** (76:24), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.4 g of **9a** as colorless crystals. Data of **9a**: R_f 0.45 (hexane/EtOAc, 1:1); mp 145-146 °C; IR (CH_2Cl_2) 3319, 1496, 1420, 1290, 1208, 1067, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H, Me-6), 1.50 (d, *J* = 6.5 Hz, 3H, Me-7), 4.76 (q, *J* = 6.5 Hz, 1H, H-5), 5.83 (br s, 1H, OH), 7.37-7.50 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.7 (C-7), 23.3 (C-6), 84.9 (C-5), 91.8 (C-4), 128.8 (C-9), 129.4 (C-11), 130.0 (C-10), 137.1 (C-8), 188.6 (C-2); MS (70 eV) 207 (M^+-1, 1), 135 (100), 108 (3), 91 (4), 77 (70). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.00; H, 6.00; N, 6.38; S, 14.16. Data of **10a**: ^1H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10a**) from the spectrum of the mixture (**9a/10a**): δ 1.35 (s, Me-6), 1.45 (d, *J* = 6.6 Hz, Me-7), 4.89 (q, *J* = 6.6 Hz, H-5), 6.15 (br s, OH).

(4*R,5*S**)-3-Benzyl-4-hydroxy-4,5-dimethyloxazolidine-2-thione (9b). (4*R**,5*R**)-3-Benzyl-4-hydroxy-4,5-dimethyloxazolidine-2-thione (10b).** The use of the general procedure with 0.68 g (7.76 mmol) of **4a**, 1.55 g (0.021 mol) of Li_2CO_3, 2.12 g (0.021 mol) of triethylamine, and 0.77 g (5.17 mmol) of **8b**, gave 0.94 g (76%) of a mixture of **9b**/**10b** (74:26), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.47 g of **9b** as colorless crystals. Data of **9b**: R_f 0.40 (hexane/EtOAc, 7:3); mp 129-130 ºC; IR (CH_2Cl_2) 3286, 1460, 1417, 1351, 1247, 1143, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H, Me-6), 1.47 (d, *J* = 6.6 Hz, 3H, Me-7), 3.55 (br s, 1H, OH), 4.50 (q, *J* = 6.6 Hz, 1H, H-5), 4.65 (d, *J* = 15.9 Hz, 1H, H-8), 5.19 (d, *J* = 15.9 Hz, 1H, H-8), 7.25-7.41 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.6 (C-7), 23.8 (C-6), 47.3 (C-8), 83.9 (C-5), 90.8 (C-4), 127.4 (C-11), 127.6 (C-12), 128.6 (C-10), 136.7 (C-9), 188.9 (C-2); MS (70 eV) 219 (M^+-18, 1), 203 (8), 150 (11), 106 (23), 91 (100), 65 (12). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; Found: C, 60.91; H, 6.32; N, 6.55. Data of **10b**: ^1H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10b**) from the spectrum of the mixture (**9b/10b**): δ 1.26 (s, Me-6), 1.35 (d, *J* = 6.6 Hz, Me-7), 4.71 (d, *J* = 15.6 Hz, H-8), 5.10 (d, *J* = 15.6 Hz, H-8).

(4*R,5*S**)-3-(4-Chlorophenyl)-4-hydroxy-4,5-dimethyloxazolidine-2-thione (9c). (4*R**,5*R**)-3-(4-Chlorophenyl)-4-hydroxy-4,5-dimethyloxazolidine-2-thione (10c).** The use of the general procedure with 0.661 g (7.5 mmol) of **4a**, 1.48 g (0.02 mol) of Li_2CO_3, 2.02 g (0.02 mol) of triethylamine, and 0.85 g (5.0 mmol) of **8c**, gave 0.85 g (66%) of a mixture of **9c**/**10c** (74:26), which after a second column chromatography (hexane/EtOAc, 98:2) yielded 0.2 g of **9c** as a colorless oil. Data of **9c**: R_f 0.27 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3347, 1494, 1421, 1354, 1295, 1212, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H, Me-6), 1.50 (d, *J* = 6.6 Hz, 3H, Me-7), 4.00 (br s, 1H, OH), 4.67 (q, *J* = 6.6 Hz, 1H, H-5), 7.30-7.50 (m, 4H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.7 (C-7), 23.3 (C-6), 85.1 (C-5), 91.8

(C-4), 129.5 (C-9), 130.1 (C-10), 133.9 (C-11), 134.9 (C-8), 188.1 (C-2); MS (70 eV) 241 (M^+-18, 10), 239 (M^+-18, 30), 178 (15), 113 (10), 111 (30), 91 (100), 75 (25). Anal. Calcd for $C_{11}H_{12}NO_2SCl$: C, 51.26; H, 4.69; N, 5.43; Found: C, 51.08; H, 4.48; N, 5.66. Data of **10c**: ^{1}H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10c**) from the spectrum of the mixture (**9c/10c**): δ 1.28 (s, Me-6), 1.44 (d, *J* = 6.6 Hz, Me-7), 4.84 (q, *J* = 6.6 Hz, H-5).

(4*R,5*S**)-4-Hydroxy-4,5-dimethyl-3-(4-tolyl)oxazolidine-2-thione (9d). (4*R**,5*R**)-4-Hydroxy-4,5-dimethyl-3-(4-tolyl)oxazolidine-2-thione (10d).** The use of the general procedure with 0.792 g (0.009 mol) of **4a**, 1.78 g (0.024 mol) of Li_2CO_3, 2.42 g (0.024 mol) of triethylamine, and 0.894 g (0.006 mol) of **8d**, gave 0.995 g (70%) of a mixture of **9d**/**10d** (70:30), which after a second column chromatography (hexane/EtOAc, 98:2) yielded 0.55 g of **9d** as a colorless oil. Data of **9d**: R_f 0.25 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3301, 1514, 1420, 1353, 1296, 1210, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H, Me-6), 1.50 (d, *J* = 6.6 Hz, 3H, Me-7), 2.41 (s, 3H, CH_3Ar), 4.00-4.20 (br s, 1H, OH), 4.66 (q, *J* = 6.6 Hz, 1H, H-5), 7.18-7.38 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.8 (C-7), 21.2 (C-12), 23.5 (C-6), 84.9 (C-5), 91.6 (C-4), 129.5 (ArCH), 129.9 (ArCH), 132.7 (C-11), 138.9 (C-8), 188.2 (C-2); MS (70 eV) 219 (M^+-18, 100), 135 (55), 91 (60), 77 (10). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.73; N, 5.90. Found: C, 60.81; H, 6.52; N, 5.77. Data of **10d**: ^{1}H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10d**) from the spectrum of the mixture (**9d/10d**): δ 1.26 (s, 3H, Me-6), 1.43 (d, *J* = 6.6 Hz, 3H, Me-7), 4.85 (q, *J* = 6.6 Hz, H-5).

(4*R,5*S**)-3-(4-Anisyl)-4-hydroxy-4,5-dimethyloxazolidine-2-thione (9e). (4*R**,5*R**)-3-(4-Anisyl)-4-hydroxy-4,5-dimethyloxazolidine-2-thione (10e).** The use of the general procedure with 0.792 g (0.009 mol) of **4a**, 1.78 g (0.024 mol) of Li_2CO_3, 2.42 g (0.024 mol) of triethylamine, and 0.991 g (0.006 mol) of **8e**, gave 1.1 g (72%) of a mixture of **9e**/**10e** (76:24), which after a second column chromatography (hexane/EtOAc, 98:2) yielded 0.6 g of **9e** as colorless oil. Data of **9e**: R_f 0.24 (hexane/EtOAc, 6:4); IR (CH_2Cl_2) 3320, 1513, 1430, 1295, 1249, 1211, 1069, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H, Me-6), 1.54 (d, *J* = 6.6 Hz, 3H, Me-7), 3.84 (s, 3H, OMe), 3.80-4.10 (br s, 1H, OH), 4.68 (q, *J* = 6.6 Hz, 1H, H-5), 6.93-7.01 (m, 2H, H-9), 7.24-7.32 (m, 2H, H-10); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.9 (C-7), 23.6 (C-6), 55.4 (OMe), 84.8 (C-5), 91.5 (C-4), 114.5 (C-10), 127.9 (C-8), 130.0 (C-9), 159.7 (C-11), 188.5 (C-2); MS (70 eV) 252 (M^+-1, 1), 149 (12), 127 (15), 113 (30), 99 (45), 85 (72), 71 (85), 57 (100). Anal Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.10; H, 6.15; N, 5.39. Data of **10e**: ^{1}H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10e**) from the spectrum of the mixture (**9e/10e**): δ 1.30 (s, Me-6), 1.46 (d, *J* = 6.9 Hz, Me-7), 3.81 (s, OMe), 4.88 (q, *J* = 6.9 Hz, H-5).

(4*R,5*S**)-3-(3-Chlorophenyl)-4-hydroxy-4,5-dimethyloxazolidine-2-thione (9f). (4*R**,5*R**)-3-(3-Chlorophenyl)-4-hydroxy-4,5-dimethyloxazolidine-2-thione (10f).** The use of the general procedure with 1.32 g (0.015 mol) of **4a**, 2.96 g (0.04 mol) of Li_2CO_3, 4.04 g (0.04 mol) of triethylamine, and 1.69 g (0.01 mol) of **8f**, gave 2.3 g (89%) of a mixture of **9f**/**10f** (74:26), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 1.6 g of **9f** as colorless crystals. Data of **9f**: R_f 0.25 (hexane/EtOAc, 7:3); mp 110-111 °C; IR (CH_2Cl_2) 3310, 1589, 1480, 1408, 1354, 1298, 1211, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H, Me-6), 1.53 (d, *J* = 6.6 Hz, 3H, Me-7), 4.20 (br s, 1H, OH), 4.69 (q, *J* = 6.6 Hz, 1H, H-5), 7.28-7.48 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.8 (C-7), 23.5 (C-6), 85.1 (C-5), 91.8 (C-4), 127.2 (C-13), 129.0 (C-11), 129.2 (C-9), 130.3 (C-12), 134.7 (C-10), 136.6 (C-8), 188.1 (C-2); MS (70 eV) 241 (M^+-18, 10), 239 (M^+-18, 30), 155 (17), 113 (8), 111 (25), 91 (100), 75 (25). Anal. Calcd for $C_{11}H_{12}NO_2SCl$: C, 51.26; H, 4.69; N, 5.43; Found: C, 51.24; H, 4.87; N, 5.60. Data of **10f**: ^1H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10f**) from the spectrum of the mixture (**9f**/**10f**): δ 1.32 (s, Me-6), 1.45 (d, *J* = 6.6 Hz, Me-7), 4.88 (q, *J* = 6.6 Hz, H-5)

(4*R,5*S**)-4-Hydroxy-4,5-dimethyl-3-(3-tolyl)oxazolidine-2-thione (9g). (4*R**,5*R**)-4-Hydroxy-4,5-dimethyl-3-(3-tolyl)oxazolidine-2-thione (10g).** The use of the general procedure with 0.792 g (0.009 mol) of **4a**, 1.78 g (0.024 mol) of Li_2CO_3, 2.42 g (0.024 mol) of triethylamine, and 0.894 g (0.006 mol) of **8g**, gave 0.919 g (65%) of a mixture of **9g**/**10g** (70:30), which after recrystallization (hexane/CH_2Cl_2, 1:1) yielded 0.41 g of **9g** as colorless crystals. Data of **9g**: R_f 0.23 (hexane/EtOAc, 7:3); mp 113-114 °C; IR (CH_2Cl_2) 3348, 1491, 1416, 1354, 1301, 1214, 1091, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H, Me-6), 1.53 (d, *J* = 6.6 Hz, 3H, Me-7), 2.38 (s, 3H, CH_3Ar), 4.25 (br s, 1H, OH), 4.67 (q, *J* = 6.6 Hz, 1H, H-5), 7.15-7.38 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.9 (C-7), 21.3 (CH_3Ar), 23.7 (C-6), 84.9 (C-5), 91.6 (C-4), 125.9 (C-13), 129.1 (C-12), 129.4 (C-9), 129.9 (C-11), 135.2 (C-10), 139.3 (C-8), 188.1 (C-2); MS (70 eV) 219 (M^+-18, 100), 218 (68), 135 (65), 118 (20), 91 (55), 65 (30). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 61.02; H, 6.60; N, 5.83. Data of **10g**: ^1H NMR (300 MHz, $CDCl_3$) signals attributed to the minor isomer (**10g**) from the spectrum of the mixture (**9g**/**10g**): δ 1.29 (s, 3H, Me-6), 1.45 (d, *J* = 6.6 Hz, 3H, Me-7), 4.88 (q, *J* = 6.6 Hz, H-5).

4-Hydroxy-4-methyl-3-phenyloxazolidine-2-thione (13). The use of the general procedure with 1.11 g (0.015 mol) of **4b**, 2.96 g (0.04 mol) of Li_2CO_3, 4.04 g (0.04 mol) of triethylamine, and 1.35 g (0.01 mol) of **8a**, gave 1.49 g (71%) of **13** as a colorless oil: R_f 0.18 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3422, 3307, 1658, 1497, 1424, 1303, 1230, 1134, 957, 760, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H, Me-6), 4.51 (d, *J* = 10.0 Hz, 1H, H-5), 4.68 (d, *J* = 10.0 Hz, 1H, H-5), 5.70 (br s, 1H, OH), 7.38-7.52 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.4 (C-6), 79.6 (C-5), 91.3 (C-4), 128.9 (C-10), 129.0 (C-8), 129.2 (C-9),

135.0 (C-7), 188.0 (C-2). HRMS (FAB$^+$) (mNBA) $[M + H]^+$ calcd for $C_{10}H_{12}NO_2S$: 210.0589. Found: 210.0595.

General Procedures for the preparation of 3-Substituted 4,5-Dimethyl-4-oxazoline-2-thiones (1a-1g).
Method A: A solution of alcohols (**9**/**10**) in dry DMSO was heated to 160 ºC for 1 h. Water was added (10 mL/mL of DMSO), and the solution was extracted with a mixture of hexane/EtOAc, 1:1 (2 x 10 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel (15 g per gram of crude) (hexane/EtOAc, 9:1).
Method B: In a screw-cap ACE pressure tube, under an N_2 atmosphere, a mixture of 0.88 g (0.01 mol) of **4a**, isothiocyanate (**8**) (0.01 mol), and 2.02 g (0.02 mol) of triethylamine was irradiated with MW (200 W) to 120 °C for 90 min. The mixture was diluted with CH_2Cl_2 (30 mL) and activated carbon (2 g) was added, then the mixture was stirred at room temperature for 2 h. The mixture was filtered through celite, and the filtrate was washed with a 5% aqueous solution of HCl (2 x 10 mL) and with water (10 mL). The organic layer was dried (Na_2SO_4), the solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel (30 g, hexane/EtOAc, 9:1).

4,5-Dimethyl-3-phenyl-4-oxazoline-2-thione (1a). The use of **Method A** with 0.447 g (2.0 mmol) of **9a**/**10a** (76:24) gave 0.37 g (90%) of **1a** as an oil, which crystallized by adding EtOAc/hexane (2:1), to yield a white powder. The use of **Method B** with 1.35 g of **8a** gave 1.41 g (69%) of **1a** as white crystals: R_f 0.40 (hexane/EtOAc, 7:3); mp 78-80 °C; IR (CH_2Cl_2) 1758. 1704, 1596, 1497, 1437, 1395, 1346, 1293, 1177, 1098, 988, 757, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (q, J = 1.0 Hz, 3H, Me-6), 2.23 (q, J = 1.0 Hz, 3H, Me-7), 7.28-7.34 (m, 2H, PhH), 7.46-7.63 (m, 3H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.7 (C-6), 10.1 (C-7), 122.0 (C-4), 127.4 (C-9), 129.4 (C-11), 129.6 (C-10), 134.9 (C-8), 140.9 (C-5), 177.7 (C-2); MS (70 eV) 205 (M^+, 100), 204 (67), 176 (6), 162 (5), 144 (4), 121 (18), 77 (12). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.30; H, 5.48; N, 7.00; S, 15.77.

3-Benzyl-4,5-dimethyl-4-oxazoline-2-thione (1b). The use of **Method A** with 0.33 g (1.39 mmol) of **9a**/**10a** (74:26) gave 0.27 g (90%) of **1b** as a pale yellow oil; R_f 0.40 (hexane/EtOAc, 7:3); IR (film) 3038, 2924, 1428, 1362, 1254, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (br s, 3H, Me-6), 2.15 (br s, 3H, Me-7), 5.20 (s, 2H, H-8), 7.25-7.43 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.3 (C-6), 10.0 (C-7), 49.7 (C-8), 121.2 (C-4), 127.0 (C-11), 128.1 (C-12), 128.9 (C-10), 134.8 (C-9), 140.6 (C-5), 178.0 (C-2); MS (70 eV) 219 (M^+, 7), 186 (2), 128 (10), 91 (100), 65 (27). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.86; H, 5.85; N, 6.49.

3-(4-Chlorophenyl)-4,5-dimethyl-4-oxazoline-2-thione (1c). The use of **Method A** with 0.819 g (3.18 mmol) of **9c**/**10c** (76:24) gave 0.65 g (85%) of **1c** as an oil, which was crystallized by adding EtOAc/hexane

(2:1), to yield a white powder. The use of **Method B** with 1.7 g of **8c** gave 0.77 g (32%) of **1c** as white crystals: R_f 0.48 (hexane/EtOAc, 7:3); mp 107-108 °C; IR (CH_2Cl_2) 2922, 1762, 1704, 1492, 1393, 1345, 1291, 1209, 1176, 1094, 989, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (br s, 3H, Me-6), 2.23 (br s, 3H, Me-7), 7.25-7.32 (m, 2H, ArH), 7.48-7.55 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.8 (C-6), 10.1 (C-7), 121.8 (C-4), 129.0 (C-9), 130.0 (C-10), 133.5 (C-11), 135.5 (C-8), 141.1 (C-5), 178.0 (C-2); MS (70 eV) 241 (M^++2, 38), 239 (M^+, 100), 238 (35), 204 (4), 155 (52), 152 (22), 137 (10), 111 (38), 75 (33). Anal. Calcd for $C_{11}H_{10}NOSCl$: C, 55.11; H, 4.20; N, 5.84. Found: C, 55.33; H, 4.41; N, 6.03.

4,5-Dimethyl-3-(4-tolyl)-4-oxazoline-2-thione (1d). The use of **Method A** with 0.32 g (1.35 mmol) of **9d**/**10d** (70:30) gave 0.24 g (82%) of **1d** as a colorless oil, which was crystallized by adding EtOAc/hexane (2:1), to yield a white powder: R_f 0.35 (hexane/EtOAc, 7:3); mp 128-129 °C; IR (CH_2Cl_2) 2921, 1704, 1514, 1399, 1346, 1295, 1176, 1098, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (br s, 3H, Me-6), 2.23 (br s, 3H, Me-7), 2.42 (s, 3H, CH_3Ar), 7.17-7.23 (m, 2H, H-9), 7.30-7.37 (m, 2H, H-10); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.7 (C-6), 10.1 (C-7), 21.2 (CH_3Ar), 122.1 (C-4), 127.2 (C-9), 130.3 (C-10), 132.4 (C-8), 139.6 (C-11), 140.7 (C-5), 177.9 (C-2); MS (70 eV) 219 (M^+, 100), 218 (42), 204 (1), 176 (5), 158 (11), 135 (50), 132 (17), 91 (29), 65 (16). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.55; H, 6.15; N, 6.22.

3-(4-Anisyl)-4,5-dimethyl-4-oxazoline-2-thione (1e). The use of **Method A** with 0.94 g (3.71 mmol) of **9e**/**10e** (76:24) gave 0.76 g (87%) of **1e** as a colorless oil, which was crystallized by adding EtOAc/hexane (2:1), to yield a white powder. The use of **Method B** with 1.65 g of **8e** gave 1.36 g (58%) of **1e** as white crystals: R_f 0.45 (hexane/EtOAc, 6:4); mp 103-104 °C; IR (CH_2Cl_2) 2924, 1705, 1608, 1513, 1400, 1347, 1296, 1250, 1176, 1100, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (br s, 3H, Me-6), 2.23 (br s, 3H, Me-7), 3.85 (s, 3H, OMe), 7.00-7.06 (m, 2H, H-9), 7.20-7.26 (m, 2H, H-10); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.7 (C-6), 10.2 (C-7), 55.4 (OMe), 114.9 (C-10), 122.3 (C-4), 127.6 (C-8), 128.6 (C-9), 140.7 (C-5), 160.0 (C-11), 178.2 (C-2); MS (70 eV) 235 (M^+, 97), 220 (5), 202 (7), 174 (9), 151 (100), 134 (43), 92 (22), 77 (25). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.39; H, 5.32; N, 6.20.

3-(3-Chlorophenyl)-4,5-dimethyl-4-oxazoline-2-thione (1f). The use of **Method A** with 0.85 g (3.3 mmol) of **9f**/**10f** (74:26) gave 0.66 g (84%) of **1f** as a colorless oil, which was crystallized by adding EtOAc/hexane (2:1), to yield a white powder. The use of **Method B** with 1.70 g of **8f** gave 0.825 g (34%) of **1f** as white crystals: R_f 0.33 (hexane/EtOAc, 7:3); mp 116-117 °C; IR (CH_2Cl_2) 1760, 1705, 1591, 1481, 1392, 1345, 1294, 1180, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (br s, 3H, Me-6), 2.24 (br s, 3H, Me-7), 7.20-7.28 (m, 1H, H-13), 7.33-7.36 (m, 1H, H-9), 7.45-7.50 (m, 2H, H-11, H-12); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.8 (C-6), 10.2 (C-7), 121.8 (C-4), 126.0 (C-13), 128.0 (C-11), 129.9 (C-9), 130.7 (C-12),

135.2 (C-10), 136.1 (C-8), 141.2 (C-5), 178.0 (C-2); MS (70 eV) 241 (M^++2, 38), 239 (M^+, 100), 196 (6), 178 (12), 155 (36), 111 (50), 75 (45). Anal. Calcd for $C_{11}H_{10}NOSCl$: C, 55.11; H, 4.20; N, 5.84. Found: C, 55.01; H, 4.01; N, 5.97.

4,5-Dimethyl-3-(3-tolyl)-4-oxazoline-2-thione (1g). The use of **Method A** with 0.29 g (1.22 mmol) of **9g**/**10g** (83:17) gave 0.22 g (82%) of **1g** as a colorless oil, which was crystallized by adding EtOAc/hexane (2:1), to yield a white powder. The use of **Method B** with 1.49 g of **8g** gave 0.81 g (37%) of **1g** as white crystals: R_f 0.35 (hexane/EtOAc, 7:3); mp 97-98 °C; IR (CH_2Cl_2) 2921, 1759, 1705, 1492, 1392, 1344, 1296, 1218, 1155, 1096, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (br s, 3H, Me-6), 2.23 (br s, 3H, Me-7), 2.42 (s, 3H, CH_3Ar), 7.07-7.14 (m, 2H, H-9, H-13), 7.28-7.32 (m, 1H, H-11), 7.38-7.46 (m, 1H, H-12); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.8 (C-6), 10.2 (C-7), 21.3 (CH_3Ar), 122.1 (C-4), 124.5 (C-13), 128.0 (C-12), 129.5 (C-9), 130.4 (C-11), 135.0 (C-8), 139.9 (C-10), 140.9 (C-5), 177.9 (C-2); MS (70 eV) 219 (M^+, 100), 218 (62), 204 (2), 176 (6), 135 (50), 91 (40), 77 (5), 65 (29). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.99; H, 6.15; N, 6.18.

4-Methyl-3-phenyl-4-oxazoline-2-thione (14). The use of **Method A** with 0.229 g (1.0 mmol) of **13** gave 0.176 g (92%) of **14** as a colorless oil, which was crystallized by adding EtOAc/hexane (2:1), to yield a white powder. R_f 0.38 (hexane/EtOAc, 7:3); mp 102-103 °C; IR (CH_2Cl_2) 1654, 1595, 1497, 1389, 1343, 1251, 1125, 1073, 957, 766, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (d, J = 1.6 Hz, 3H, Me-6), 7.20 (q, J = 1.6 Hz, 1H, Me-5), 7.32-7.37 (m, 2H, PhH), 7.51-7.58 (m, 3H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 9.2 (C-6), 127.6 (C-8), 128.3 (C-4), 129.7 (C-10), 129.8 (C-9), 131.8 (C-5), 134.5 (C-7), 179.5 (C-2); HRMS (FAB^+) (mNBA) $[M + H]^+$ calcd for $C_{10}H_{10}NOS$: 192.0483. Found: 192.0493.

4,5-Dimethyl-3-phenyl-2-thiomethyloxazolium iodide (21a). In a screw-cap ACE pressure tube, under an N_2 atmosphere, a mixture of 0.30 g (1.46 mmol) of **1a** and 0.415 g (2.92 mmol) of methyl iodide in dry xylene (3 mL) was heated to 160 °C for 24 h in the darkness. The solid was filtered under an N_2 atmosphere, and recrystallized (hexane/CH_2Cl_2, 1:2), giving 0.23 g (46%) of **21a** as a highly hygroscopic beige powder: R_f 0.26 (CH_2Cl_2/MeOH, 9:1); mp 124-125 °C; IR (CH_2Cl_2) 2921, 1699, 1600, 1505, 1416, 1400, 1367, 1296, 1174, 993, 759, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (br s, 3H, Me-6), 2.57 (br s, 3H, Me-7), 3.00 (s, 3H, MeS), 7.60-7.70 (m, 3H, PhH), 7.78-7.85 (m, 2H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.3 (C-6), 11.4 (C-7), 15.8 (MeS), 126.8 (C-9), 127.7 (C-4), 130.1 (C-5), 130.7 (C-10), 132.1 (C-11), 149.9 (C-8), 164.8 (C-2); MS (70 eV) 347 (M^+, 1), 206 (23), 205 (25), 121 (15), 104 (15), 77 (100). HRMS (FAB^+) $[M - I]^+$ (mNBA) calcd for $C_{12}H_{14}NOS$: 220.0796. Found: 220.0787.

4,5-Dimethyl-3-phenyl-2-thioethyloxazolium iodide (21b). The use of the method of preparation of **21a**

with 0.205 g (1.0 mmol) of **1a** and 0.312 g (2.0 mmol) of ethyl iodide gave 0.22 g (61%) of **21b** as a highly hygroscopic beige powder: R_f 0.41 (CH_2Cl_2/MeOH, 9:1); mp 107-108 °C; IR (CH_2Cl_2) 2923, 2853, 1744, 1610, 1500, 1362, 1292, 1264, 1165, 750, 618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$S), 2.09 (br s, 3H, Me-6), 2.59 (br s, 3H, Me-7), 3.61 (q, *J* = 7.4 Hz, 2H, CH$_3$C*H*$_2$S), 7.60-7.72 (m, 3H, PhH), 7.76-7.82 (m, 2H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.6 (C-6), 11.6 (C-7), 14.2 (*C*H$_3$CH$_2$S), 28.9 (CH$_3$*C*H$_2$S), 126.9 (C-9), 127.9 (C-4), 130.3 (C-5), 130.8 (C-10), 132.2 (C-11), 150.1 (C-8), 164.8 (C-2). HRMS (FAB$^+$) [M - H]$^+$ (mNBA) calcd for $C_{13}H_{15}NOIS$: 359.9925. Found: 359.9954.

Single-Crystal X-ray Crystallography. 4-Oxazolin-2-thione (**1f**) was obtained as colorless crystals (hexane/CH_2Cl_2, 6:1). These were mounted on glass fibers. Crystallographic measurements were performed with Cu Kα radiation (λ = 1.54178 Å; graphite monochromator) at room temperature. Three standard reflections were monitored periodically; they showed no appreciable change during data collection. Unit cell parameters were obtained from least-squares refinement of 40 reflections in the range 22.92<2θ<56.32°. Intensities were corrected for Lorentz and polarization effects. No absorption corrections were applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined. Unit weights were used in the refinement. Structures were solved using SHELXTL[30] on a personal computer. Data of **1f**: Formula: $C_{11}H_{10}ClNOS$; molecular weight: 239.71; cryst. syst.: monoclinic; space group: $P2_1/n$; unit cell parameters: *a*, 9.6982 (10), *b*, 10.6248 (8), *c*, 11.9173 (9) (Å); *α*, 90, *β*, 108.745 (9), *γ*, 90 (deg); temp. (°K): 293 (2); *V* = 1162.8 (2) (Å^3); Z: 4; *D* = 1.369 (mg/m^3); reflections collected (10.28<2θ<113.98°): 2132; independent reflections: 1568; R_1: 0.0698; GOF: 1.049.

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