JOC Article
pubs.acs.org/joc

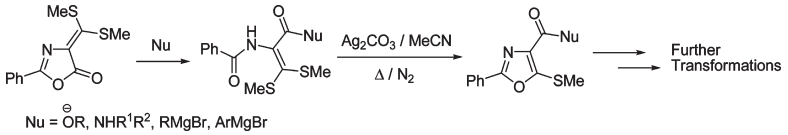
4-Bis(methylthio)methylene-2-phenyloxazol-5-one: Versatile Template for Synthesis of 2-Phenyl-4,5-functionalized Oxazoles§

Nimesh C. Misra[†,‡] and H. Ila*[,‡]

[†]*Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India, and* [‡]*New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore-560 064, India*

hila@jncasr.ac.in

Received May 13, 2010



4-Bis(methylthio)methylene-2-phenyloxazol-5-one has been shown to be a versatile template for the synthesis of various 2-phenyl-3,4-substituted oxazoles via nucleophilic ring-opening of oxazolone with various oxygen, nitrogen, and carbon nucleophiles and subsequent 5-*endo* cyclization of the resulting acyclic adducts in the presence of silver carbonate.

Introduction

During the past decade, a large number of natural products containing oxazole subunit have been isolated from marine invertebrates and microorganisms,[1] many of which (such as Diazonamide A,[2] Ulapualide A,[3] Virginiamycin M1,[4] Tentazole,[5] Hennoxazole A,[6] and Telomestatin[7]) display significant biological activities as cytotoxic, antifungal, antibacterial, antitumor, and antiviral agents. Also, 2,4- and 2,4,5-substituted oxazoles are frequently encountered structural motifs found in many pharmaceuticals, lead structures,[8] optical materials as scintillant molecules,[9] and fluorescent dyes[9] and are valuable precursors in many useful synthetic transformations. This has spurred renewed interest in the chemistry and synthesis of these heterocycles and led to the development of more general efficient synthetic methods for polyfunctional oxazoles.[10]

Methods for direct construction of oxazole ring range over a variety of reactions and starting materials. Some of the oldest and most widely used methods for substituted oxazoles include cyclodehydration of α-acylaminocarbonyl compounds (Robinson−Gabriel synthesis),[8a,11] the Cornforth and Cornforth

§Dedicated to Prof. Sukh Dev on his 85th birthday.

(1) (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (b) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 1195. (c) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249. (d) Lewis, J. R. *Nat. Prod. Rep.* **2000**, *17*, 154 and earlier reviews in this series.

(2) (a) Davies, J. R.; Kane, P. D.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 7305. (b) Cruz-Monserrate, Z.; Vervoort, H. C.; Bai, R. L.; Newman, D. J.; Howell, S. B.; Los, G.; Mullaney, J. T.; Williams, M. D.; Pettit, G. R.; Fenical, W.; Van Duyne, G. D.; Hamel, E. *Mol. Pharmacol.* **2003**, *63*, 1273. (c) Lindquist, N.; Fenical, W.; van duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.

(3) (a) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846. (b) Chattopadhyay, S. K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. I* **2000**, 2429.

(4) (a) Paris, J. M.; Barriere, J. C.; Smith, C.; Bost, P. E. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer Verlag: Berlin, Germany, 1990; pp 183−248. (b) Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301.

(5) (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (b) Jansen, R.; Kunze, B.; Wray, V.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Hofle, G. *Liebigs Ann. Chem.* **1991**, 707.

(6) (a) Ishiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173. (b) Higa, T.; Tamaka, J.-I.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227. (c) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558.

(7) (a) Shin-ya, K.; Wierzba, K.; Matsuo, K.; Ohtani, T.; Yamada, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1262. (b) Kim, M. Y.; Vankayalapati, H.; Shin-ya, K.; Wierzba, K.; Hurley, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 2098.

(8) (a) Morwick, T.; Hrapchak, M.; DeTuri, M.; Campbell, S. *Org. Lett.* **2002**, *4*, 2665. (b) Godfrey, A. G.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R.; Mitchell, D. *J. Org. Chem.* **2003**, *68*, 2623. (c) Liu, C.; Lin, J.; Sidney, P.; Leftheris, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1874. (d) Kuang, R.; Shue, H.-J.; Blythin, D. J.; Shih, N.-Y.; Gu, D.; Chen, X.; Schwerdt, S.; Lin, L.; Ting, P. C.; Zhu, X.; Aslanian, R.; Piwinski, J. J.; Xiao, L.; Prelusky, D.; Wu, P.; Zhang, J.; Zhang, X.; Celly, C. S.; Minnicozzi, M.; Billah, M.; et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5150.

(9) (a) Clapham, B.; Richard, A. J.; Wood, M. L.; Sutherland, A. J. *Tetrahedron Lett.* **1997**, *38*, 9061. (b) Dyer, A. In *An Introduction to Liquid Scintillation Coupling*: Heyden: London, UK, 1974; p 12. (c) Krasovitsky, B. M.; Bolotin, B. M. In *Organic Luminescent Material*; VCH: Weinheim, Germany, 1988.

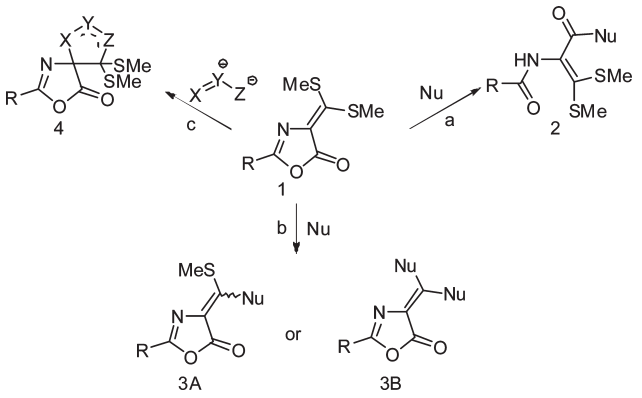
(10) (a) *Oxazoles: Synthesis, Reactions and Spectroscopy*; Palmer, D. C., Ed.; John Wiley and Sons: Hoboken, NJ, 2004; Part B, Vol. 60. (b) Oxazoles: Boyd, G. V. In *Science of Synthesis*; Schaumann, E., Ed.; George Thieme Verlag; Stuttgart, Germany, 2002; Vol. 11, p 383. (c) Hartner, F. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 3, p 261. (d) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (e) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (f) Boyd, G. V. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Elsevier Science Ltd.: London, UK, 1997; Vol. 9, p 1.

(11) (a) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2162. (b) Gabriel *Chem. Ber.* **1910**, *43*, 1283. (c) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642. (d) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901. (e) Roy, S.; Haque, S.; Gribble, G. W. *Synthesis* **2006**, 3948.

DOI: 10.1021/jo100941f Published on Web 07/16/2010

method[12] improved by Yokoyama,[13] the biomimetic dehydrative cyclization of β-hydroxy amides to oxazolines and their oxidative dehydrogenation,[14−16] the Hantsch-type reaction of α-halo/acyloxy carbonyl compounds with amides, the rhodium-catalyzed decomposition of α-diazocarbonyl compounds in the presence of nitriles,[18] and the photolysis/pyrolysis of α-acylisoxazolones.[19] However, these methods genuinely lack universality and suffer from one or more drawbacks such as modest to poor yields, harsh reaction conditions, longer reaction time, and reactive starting materials with limited stability, which make them incompatible for the range of tolerated functional groups in the target oxazole. Recently, several new synthetic protocols have been devised to overcome these drawbacks such as improved and modified Robinson−Gabriel synthesis (Wipf's dehydrating agent, $PPh_3/I_2/Et_3N$),[16] Rh-catalyzed NH insertion of amides to α-diazocarbonyl compounds,[20] direct conversion of ketones to oxazoles without isolation of reactive intermediates,[17b,21] cycloaddition of activated methylene isocyanides,[22] Ru[23a] and Cu[23b] catalyzed reactions, and Lewis acid[24a,b]/base,[24c] Pd,[25] gold[26,27] catalyzed cycloisomerization of propargyl amides along with the transition metal-catalyzed cross-coupling reactions on the built-in oxazole ring.[28] However, most of these reactions are inherently more specific in scope and lack generality. Therefore more robust, practical general methods for substituted oxazoles with wider scope for elaboration of various sites from readily available starting materials are very much desirable.

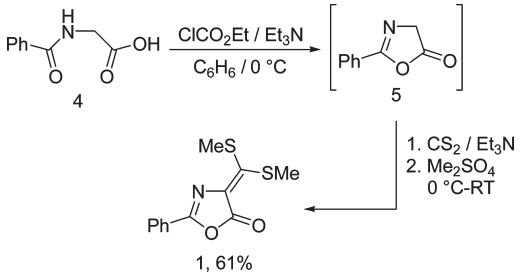
SCHEME 1. Diverse Reaction Pathways from 4-Bis(methylthio)-methylene-2-substituted Oxazol-5-one



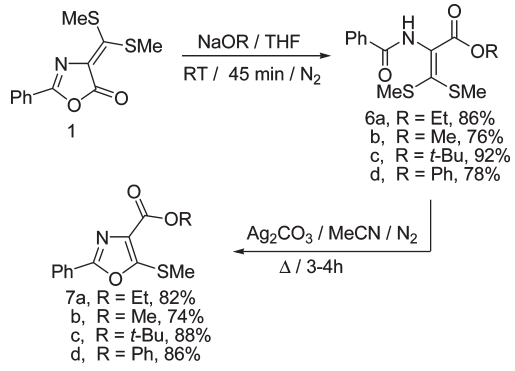
Our own interest in oxazole synthesis is driven by our long-standing research program aimed at devising new synthetic strategies for five- and six-membered heterocycles employing polarized ketene dithioacetals as versatile intermediates.[29,30] During the course of these studies, we set out to explore the feasibility of utilizing ketene dithioacetal **1** (R = Ph) derived from 2-phenyl-4,5-dihydrooxazol-5-one[31] as a versatile template to access a broad range of heterocycles with diverse functionalities. A close look at the structure of **1** reveals that it contains many reactive sites allowing for a diverse set of possible transformations. Thus, it was envisaged that the oxazolone ring in **1** could be readily opened by the regioselective attack of various carbon and hetero nucleophiles at the carbonyl group (1,2-addition, path a) to furnish acyclic polyfunctional intermediates **2** with multiple reactive sites, which can be exploited for the construction of diversly substituted heterocycles (Scheme 1). Alternatively, a conjugate

(12) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96.
(13) (a) Yokoyama, M.; Menjo, Y.; Watanabe, M.; Togo, H. *Synthesis* **1994**, 1467. (b) Shin, C.-G.; Sato, Y.; Sugiyama, H.; Nanjo, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1788.
(14) Review on oxazolines: Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
(15) (a) Evans, D. L; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497. (b) Kashima, C.; Arao, H. *Synthesis* **1989**, 873. (c) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494. (d) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207. (e) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (f) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.
(16) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.
(17) (a) Liu, P.; Celatka, C. A.; Panek, J. S.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 5445. (b) Lee, J. C.; Choi, H. J.; Lee, Y. C. *Tetrahedron Lett.* **2003**, *44*, 123 and references cited therein.
(18) (a) Doyle, K. J.; Moody, C. J. *Synthesis* **1994**, 1021. (b) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657. (c) Clemencon, I. F.; Ganem, B. *Tetrahedron* **2007**, *63*, 8665. (d) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761.
(19) Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *J. Chem. Soc., Perkin Trans. I* **1997**, 2665 and 2659.
(20) (a) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. I* **1998**, 591. (b) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967. (c) Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840. (d) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett.* **2001**, *3*, 2173. See also oxazoles by azide decomposition: (e) Dhar, T. G. M.; Guo, J.; Shen, Z.; Pitts, W. J.; Gu, H. H.; Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Iwanowicz, E. J. *Org. Lett.* **2002**, *4*, 2091.
(21) (a) Lee, J. C.; Song, I.-G. *Tetrahedron Lett.* **2000**, *41*, 5891. (b) Lee, J. C.; Lee, Y. C. *Bull. Korean Chem. Soc.* **2003**, *24*, 893. (c) Kawano, Y.; Togo, H. *Synlett* **2008**, 217 and references cited therein. (d) Herrera, A.; Martinez-Alvarez, R.; Ramiro, P.; Molero, D.; Almy, J. *J. Org. Chem.* **2006**, *71*, 3026.
(22) (a) Barrett, A. G. M.; Cramp, S. M.; Hennessy, A. J.; Procopiou, P. A.; Roberts, R. S. *Org. Lett.* **2001**, *3*, 271. (b) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Org. Lett.* **2006**, *8*, 5231. (c) Atkins, J. M.; Vedejs, E. *Org. Lett.* **2005**, *7*, 3351. (d) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, 4076 and references cited therein. (e) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485.
(23) (a) Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951. (b) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521. (c) Schuh, K.; Glorius, F. *Synthesis* **2007**, 2297.
(24) (a) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593. (b) Coqueron, P.-Y.; Didier, C.; Ciufoleni, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411. (c) Nilsson, B. M.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285.
(25) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501.
(26) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712.
(27) (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (b) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537.
(28) (a) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495. (c) Besselievre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278. (d) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241. (e) Hoffman, T. J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 2400. (f) Araki, H.; Katoh, T.; Inoue, M. *Tetrahedron Lett.* **2007**, *48*, 3713. (g) Pippel, D. J.; Mapes, C. M.; Mani, N. S. *J. Org. Chem.* **2007**, *72*, 5828.
(29) Reviews: (a) Ila, H.; Junjappa, H.; Mohanta, P. K. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon Press: Oxford, UK, 2001; Vol 13, Chapter 1, pp 1−24. (b) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423.
(30) Recent papers: (a) Kumar, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 7046. (b) Singh, P. P.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 5496. (c) Kumar, S.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Org. Lett.* **2008**, *10*, 965. (d) Yadav, A. K.; Yadav, S. K. S.; Siddiqui, I.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Synlett* **2008**, 2674. (e) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246. (f) Yadav, A. K.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1388. (g) Sundaram, G. S. M.; Singh, B.; Venkatesh, C.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 5020. (h) Kumar, S.; Ila, H.; Junjappa, H. *Tetrahedron* **2009**, *63*, 10067.
(31) For a recent review on the chemistry of oxazol-5-(4*H*)-ones see: Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432.

SCHEME 2. Synthesis of 4-Bis(methylthio)methylene-2-phenyl-4,5-dihydrooxazol-5-one 1



SCHEME 3. Synthesis of 2-Phenyl-4-carboalkoxy/phenoxy-5-(methylthio)oxazoles 7a−d

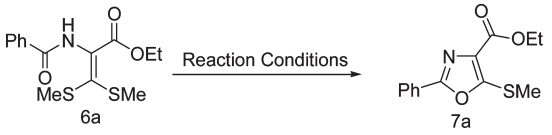


1,4-addition−elimination by a nucleophilic species (path b) or a dipolar cycloaddition on the activated bis(methylthio)-methylene double bond (path c) of **1** would provide substituted oxazolones **3**−**4** which could be further elaborated in the desired fashion to access a diverse array of heterocycles (Scheme 1). In the present work, we have focused on the former reactivity pattern of **1** (**1** → **2**) and herein report a practical general synthesis of novel 2-phenyl-4,5-substituted oxazoles from **1**.

Results and Discussion

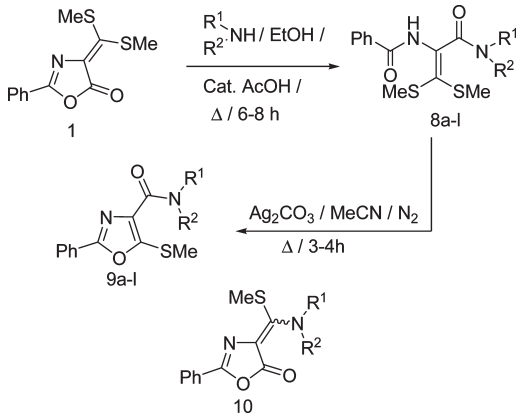
Our literature survey at this stage revealed that Brown and co-workers[32] have obtained 4-bis(methylthio)methylene-2-phenyl-4,5-dihydrooxazol-5-one **1** in 47% yield by treatment of 2-phenyloxazolone **5** with potassium *tert*-butoxide followed by addition of carbon disulfide and 2 equiv of methyl iodide. Subsequently, Mukerjee et al.[33] developed a one-pot method for the synthesis of **1** by subjecting hippuric acid **4** to intramolecular cyclodehydration in the presence of ethyl chloroformate and triethylamine in benzene followed by treatment of the in situ generated oxazolone **5** with either methyl bromide or methyl iodide (2 equiv) affording **1** in moderate to low yields (24−41%). We have synthesized **1** in improved yield of 61% by modification of the latter one-pot procedure as depicted in Scheme 2. Thus, the treatment of in situ generated oxazolone **5** with carbon disulfide in the presence of triethylamine followed by alkylation with dimethyl sulfate instead of methyl bromide or iodide furnished **1** in 61% yield (Scheme 2).

TABLE 1. Optimization of Reaction Conditions for Conversion of 6a to 7a



entry	reaction conditions	% yield of **7a**
1	Et_3N/C_6H_6/rt/24 h	68
2	Cs_2CO_3/dioxane/50 °C/24 h	58
3	MeOH/NaOH/3−4 days/rt	62
4	$CuBr_2/DBU/CH_2Cl_2$/rt	52
5	$CuBr_2/Cs_2CO_3$/dioxane/rt	46
6	$HgCl_2$/AcOH/reflux/4−5 h	64
7	$BF_3.Et_20/C_6H_6$/rt/24 h	48
8	Ag_2CO_3/CH_3CN/90 °C/2 h	82

SCHEME 4. Synthesis of 2-Phenyl-5-(methylthio)oxazole-4-carboxamides 9a−m

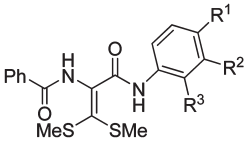
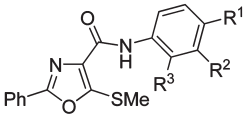
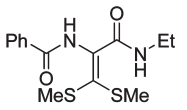
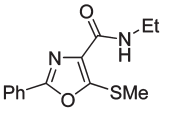
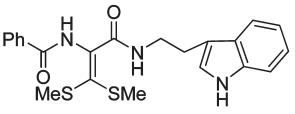
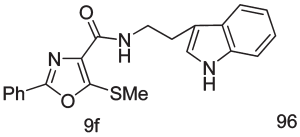
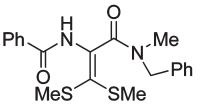
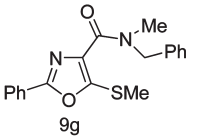
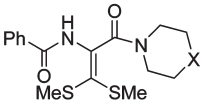
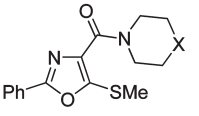
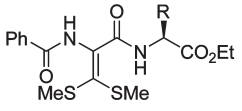
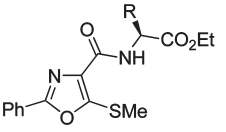


Mukerjee and co-workers have previously reported[34a] reaction of **1** with ethanolic (or methanolic) KOH to give acyclic adducts **6a**,**b** in good yields (Scheme 3); however, no attempts were made for further synthetic elaboration of these acyclic precursors. In our studies, **1** was allowed to react with sodium ethoxide in THF at room temperature, furnishing the corresponding ethyl α-[bis(methylthio)methylene]-*N*-benzoylglycinate **6a** in 86% yield (Scheme 3). Similarly the corresponding methyl, *tert*-butyl, and phenyl esters **6b**−**d** were obtained in high yields, when **1** was exposed to either sodium methoxide, *tert*-butoxide, or phenoxide, respectively, under the identical reaction conditions (Scheme 3).

We next evaluated intramolecular 5-*endo* cyclization of **6a** to the desired 2-phenyl-5-(methylthio)-4-carboethoxyoxazole (**7a**) under the influence of various cyclizing agents reported by the previous workers and the results are summarized in the Table 1. Thus treatment of **6a** with triethylamine in benzene under Yoshimura's conditions[13b] provided the desired **7a** in 68% yield (entry 1). The cyclization of **6a** to **7a** could also be effected in the presence of Cs_2CO_3/dioxane (entry 2),[35] MeOH/NaOH (entry 3),[35] $CuBr_2$/DBU (entry 4),[35] and $CuBr_2/Cs_2CO_3$ (entry 5)[36] furnishing the oxazole **7a**

(32) Brown, R. F. C.; Rae, I. D.; Sternhell, S. *Aust. J. Chem.* **1965**, *18*, 61.
(33) Ashare, R.; Roy, J.; Mukerjee, A. K. *Heterocycles* **1986**, *24*, 1325.
(34) (a) Tripathy, P. K.; Roy, J.; Mukerjee, A. K. *Indian J. Chem.* **1986**, *25B*, 1275. (b) Roy, J. *Indian J. Chem.* **1991**, *30B*, 433.
(35) Das, J.; Reid, J. A.; Kronenthal, D. R.; Singh, J.; Pansegrau, P. D.; Mueller, R. H. *Tetrahedron Lett.* **1992**, *33*, 7835.
(36) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2415.

TABLE 2. Synthesis of 2-Phenyl-5-(methylthio)oxazole-4-carboxamides 9a−m

Entry	8	% yield 8	9	% yield 9
				
1.	8a, $R^1 = R^2 = R^3 = H$	80	9a, $R^1 = R^2 = R^3 = H$	78
2.	8b, $R^1 = MeO$, $R^2 = R^3 = H$	86	9b, $R^1 = OMe$, $R^2 = R^3 = H$	84
3.	8c, $R^1 = F$, $R^2 = R^3 = H$	78	9c, $R^1 = F$, $R^2 = R^3 = H$	74
4.	8d, $R^1 = Me$, $R^2 = H$, $R^3 = Br$	72	9d, $R^1 = Me$, $R^2 = H$, $R^3 = Br$	92
5.	 8e	78	 9e	92
6.	 8f	84	 9f	96
7.	 8g	74	 9g	88
				
8.	8h, X = CH_2	72	9h, X = CH_2	90
9.	8i, X = NCH_2Ph	82	9i, X = NCH_2Ph	94
10.	8j, X = NCO_2Et	80	9j, X = NCO_2Et	86
				
11.	8k, R = $PhCH_2$	86	9k, R = $PhCH_2$	92
12.	8l, R = *i*-Pr	78	9l, R = *i*-Pr	94
13.	8m, R = CH_2CH_2SMe	74	9m, R = CH_2CH_2SMe	88

in maximum yield of 62%. Formation of **7a** in moderate to good yields was also observed when **6a** was reacted with either $HgCl_2$/AcOH (entry 6) or $BF_3.Et_2O$ (entry 7); however, the best yield (82%) of **7a** was obtained when the cyclization was conducted in the presence of an excess of silver carbonate (4 equiv) in refluxing acetonitrile under nitrogen atmosphere (entry 8).

These optimized reaction conditions were also followed for the cyclization of open chain esters **6b−d** affording the corresponding 2-phenyl-4-carboalkoxy/phenoxy-5-(methylthio)-oxazoles **7b−d** in 74−88% overall yields (Scheme 3).

We next investigated ring-opening of the oxazolone ring in **1** by various primary and secondary amines to the corresponding *N*-benzoylglycine carboxamide intermediates **8** and their subsequent intramolecular cyclization to the oxazole-4-carboxamides **9** with a view to add a further point of diversity at the 4-position of the oxazole ring. Our initial experiments under different neutral/acidic conditions met with only moderate success affording a mixture of amides **8** along with *N*,*S*- acetals **10** formed by conjugate 1,4-addition−elimination of amines. However, formation of exclusive ring-opened products **8** was observed when **1** was refluxed with amines in ethanol in the presence of a catalytic amount of AcOH for 7−8 h (Scheme 4). The generality of this optimized protocol is demonstrated in Table 2. Thus, the aromatic (entries 1−4) and aliphatic primary and secondary amines (entries 5−10) were all well accommodated yielding the open chain secondary and tertiary amide derivatives **8a−j** in excellent yields (entries 1−10).

The reaction was found to be equally facile with amino acid esters yielding acyclic dipeptide bis(methylthio)-methylene derivatives **8k−m** (Table 2, entries 11−13) in excellent yields. Interestingly the earlier cyclization conditions (Ag_2CO_3/CH_3CN) previously employed for the synthesis of 4-carboalkoxyoxazoles **6a−d** (Scheme 3) worked equally well for intramolecular 5-*endo* cyclization of acyclic

SCHEME 5. Synthesis of 4-Acyl-5-(methylthio)-2-phenyloxazoles 12a−d

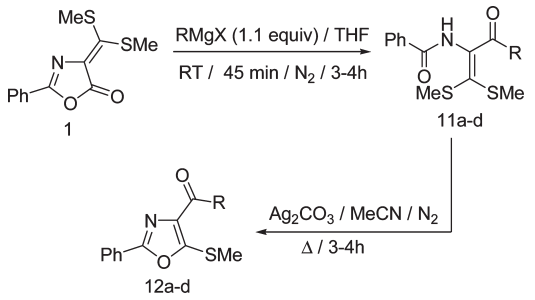


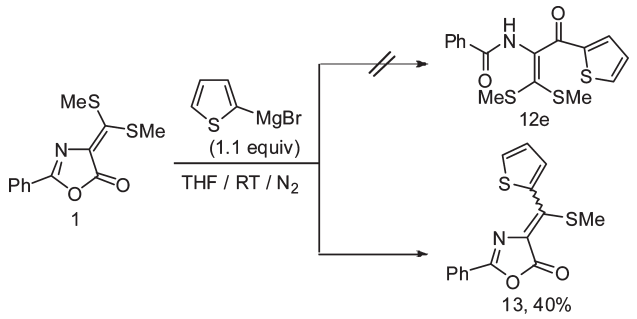
TABLE 3. Synthesis of 4-Acyl-5-(methylthio)-2-phenyloxazoles 12a−d

Entry	11	% Yield 11	12	%Yield 12
1.	11a	82	12a	92
2.	11b	86	12b	96
3.	11c, R = H	76	12c, R = H	98
4.	11d, R = OMe	84	12d, R = OMe	87

amides **8** to oxazole-4-carboxamides **9** (Scheme 4, Table 2). Thus, treatment of the anilide **8a** with silver carbonate in refluxing acetonitrile under earlier described conditions effected its smooth conversion to 5-(methylthio)-2-phenyloxazole-4-(*N*-phenyl)carboxamide **9a** in 78% yield (Table 2, entry 1). Similarly the other acyclic corboxamides from aromatic (**8b−d**, entries 2−4) and aliphatic primary (**8e−f**, entries 5−6) and secondary (**8g**, entry 7) amines and cyclic secondary amines (**8h−j**, entries 8−10) were smoothly transformed into the various oxazole-4-carboxamides **9b−j** in excellent yields under these optimal reaction conditions without formation of any side products involving alternate cyclization pathways. Similarly the amide derivatives **8k−m** derived from various amino acid esters could also be converted efficiently in excellent yields to the respective oxazole-4-carboxamides **9k−m** carrying an amino acid ester side chain (Table 2, entries 11−13).

Encouraged by our successful endeavor with the ring-opening of ketene *S*,*S*- acetal **1** with various alkoxide and amine nucleophiles, we further sought to examine the scope and generality of this sequential method for the synthesis of 4-acyl-5-(methylthio)-2-phenyloxazoles such as **12** by stepwise ring-opening of **1** by various alkyl/aryl Grignard reagents, followed by intramolecular cyclization of the resulting α-acyl-α-benzamido ketene dithioacetals **11** to the desired oxazoles **12** (Scheme 5). Thus when **1** was reacted with ethylmagnesium iodide at room temperature for 3−4 h, it was smoothly converted to the acyclic adduct **11a**, formed

SCHEME 6. Attempted Reaction of 1 with 2-Thienyl Grignard Reagent



SCHEME 7. Raney-Ni Dethiomethylation of 2-Phenyl-5-(methylthio)-4-substituted Oxazoles 7, 9, and 12

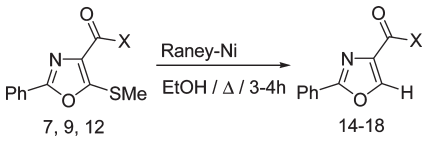


TABLE 4. Synthesis of 2,4-Substituted-5-unsubstituted Oxazoles 14−18

Entry	Substance	Dethiomethylated Compound	% Yield
1.	7a	14	92
2.	9c	15	94
3.	9j	16	88
4.	9k	17	86
5.	12b	18	90

by nucleophilic addition-ring-opening of **1** by ethyl Grignard reagent in highly regioselective fashion (Scheme 5, Table 3, entry 1). The nucleophilic ring-opening of **1** was found to be equally successful and regiospecific with other Grignard reagents, i.e. *n*-butylmagnesium bromide, phenyl, and 4-methoxyphenylmagnesium bromide, furnishing the open

SCHEME 8. Synthesis of 5-Amino-2-phenyl-4-substituted Oxazoles

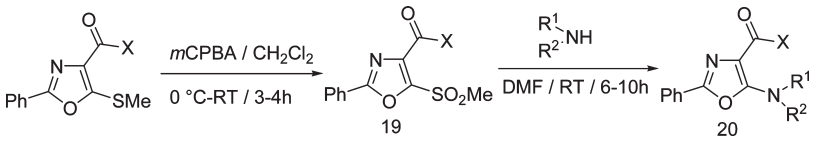
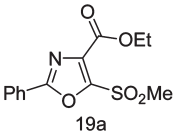
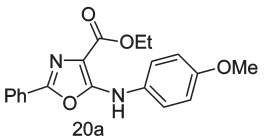
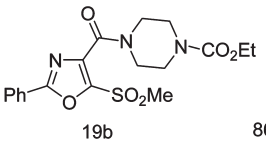
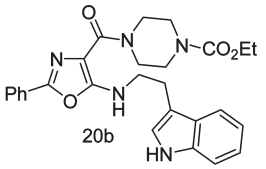
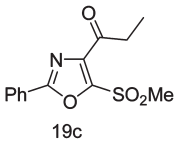
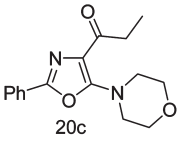
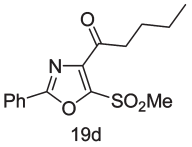
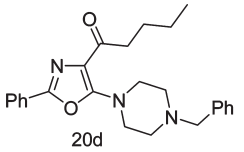
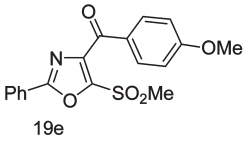
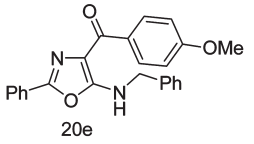


TABLE 5. Synthesis of 5-Amino-2-phenyl-4-substituted Oxazoles

Entry	Oxazole	19	% Yield 19	20	% Yield 20
1.	6a	 19a	91	 20a	78
2.	9j	 19b	86	 20b	82
3.	12a	 19c	94	 20c	92
4.	12b	 19d	88	 20d	88
5.	12d	 19e	92	 20e	90

chain α-acyl-α-benzamido ketene dithioacetals in 76−86% overall yields (Table 3, entries 2−4). The open chain adducts **11a**−**d** underwent facile cyclization to the desired 2-phenyl-5-(methylthio)-4-acyloxazoles **12a**−**d** in excellent yields when exposed to silver carbonate in refluxing acetonitrile under earlier described reaction conditions (Scheme 5, Table 3, entries 1−4). On the other hand, when **1** was subjected to addition with 2-thienylmagnesium bromide under identical reaction conditions, workup of the reaction gave an intractable mixture of products from which only one pure compound could be isolated (40%), which was characterized as 4-((methylthio)(2-thienyl)methylene)-2-phenyloxazol-5(4*H*)-one **13**, apparently formed by conjugate 1,4-addition−elimination of 2-thienyl Grignard reagent to **1** (Scheme 6).

A few of the selected newly synthesized 2-phenyl-5-(methylthio)-4-substituted oxazoles were subjected to Raney-Ni induced reductive dethiomethylation with a view to synthesize 2,4-substituted-5-unsubstituted oxazoles which are not readily accessible by usual cyclocondensation reactions, because of the sensitivity of α-aminoacyl aldehydes to harsh oxidizing and dehydrating conditions.[8a,37] Thus treatment of the oxazoles **7a**, **9c**, **9j**, **9k**, and **12b** with Raney-Ni in refluxing ethanol for 3−4 h furnished the corresponding 5-unsubstituted oxazoles **14**−**18** in excellent yields (Scheme 7, Table 4, entries 1−5).

To further expand the generality and scope of this oxazole synthesis, the 5-(methylthio) functionality in a few of these substituted oxazoles was transformed into the more labile 5-(methylsulfonyl) group by oxidation with *m*-chloroperbenzoic acid providing the corresponding 2-phenyl-4-substituted-5-(methylsulfonyl)oxazoles **19** in excellent yields (Scheme 8, Table 5). Nucleophilic displacement of the 5-(methylsulfonyl) group in **19** by various primary and secondary amines afforded novel 2,4,5-substituted oxazoles **20** that displayed additional diversity at the 5-position of the oxazole ring (Scheme 8, Table 5).

Conclusion

In summary, a rapid highly efficient synthesis of 2-phenyl-4,5-substituted oxazoles, which offers a wide range of

(37) Kreisberg, J. D.; Magnus, P.; Shinde, S. *Tetrahedron Lett*. **2002**, *43*, 7393.

functional group and substituent diversity at 4,5-positions[38] and utilizes readily available 2-phenyl-4-bis(methylthio)methylene-5-oxazolone **1** as a general template, has been reported. This novel two-step procedure involves silver carbonate assisted 5-*endo* cyclization of α-acyl/carboalkoxy/carbamoyl-α-(benzoylamino) ketene dithioacetals as the key step. It should be noted that only a few examples are known in the literature employing a similar cyclization approach for oxazoles that usually utilizes 2-acylamino-3-bromoacrylate precursors involving multistep synthesis.[13b,35,36] The easy desulfurization of the methylthio group at the C-5 position allows the synthesis of difficultly accessible 2,4-substituted (5-unsubstituted) oxazoles (Scheme 7, Table 4) in excellent yields. Alternatively, *m*-CPBA oxidation of the 5-(methylthio) group permits the preparation of 5-(methylsulfonyl) oxazoles, which undergo facile displacement by various amines to provide further diversity at the 5-position of the oxazole ring (Scheme 8, Table 5). The simplicity and synthetic versatility of the present method should make it a useful compliment to the existing methods for the multisubstituted oxazoles. The broader scope of this reaction is currently under investigation.

Experimental Section

General details are described in Supporting Information. The known *S*,*S*-acetal **1** was prepared by modification of the reported procedure.[33] The unknown 5-methylsulfonyl oxazoles **19a**−**e** were prepared by the *m*CPBA oxidation of corresponding 5-methylthiooxazoles **6a**, **9i**, **12a**,**b**, or **12d** in CH_2Cl_2.

General Procedure for the Synthesis of α-[Bis(methylthio)-methylene]-*N*-benzoylglycinates 6a−d. A suspension of corresponding sodium alkoxide (5.0 mmol) in THF (10 mL) and 4-bis(methylthio)methylene-5-oxazolone (0.9 g, 3.4 mmol) was stirred at room temperature under nitrogen atmosphere. Progress of the reaction was monitored by TLC. It was then poured into saturated NH_4Cl solution (100 mL). The mixture was extracted with chloroform (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and distilled under reduced pressure to give crude products, which were purified by column chromatography over silica gel with hexane−EtOAc as eluent.

Ethyl 2-benzamido-3,3-bis(methylthio)acrylate (6a):[34a] white solid (0.90 g, 86%); mp 116−118 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (cm^{-1}) (KBr) 3239, 1720, 1644, 1480, 1305, 1178; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 7.83 (m, 2H), 7.47−7.54 (m, 3H), 4.40 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 163.7, 135.0, 132.5, 128.8, 128.8, 127.4, 121.5, 61.9, 17.6, 16.3, 13.9; HRMS (ESI) calcd for $C_{14}H_{18}NO_3S_2$ [M + H^+] 312.0728, found 312.0726.

General Procedure for the Synthesis of Anilides (8a−m). A mixture of 4-bis(methylthio)methylene-5-oxazolone (0.53 g, 2.0 mmol), the corresponding amine (2.0 mmol), and a catalytic amount of glacial acetic acid (0.2 mL) in absolute ethanol was heated to reflux with constant stirring. Progress of the reaction was monitored by TLC. Solvent was evaporated under reduced pressure to give crude products, which were purified by column chromatography over silica gel with hexane−EtOAc as eluent.

***N*-(3-(4-Benzylpiperazin-1-yl)-1,1-bis(methylthio)-3-oxoprop-1-en-2-yl)benzamide (8i):** white solid (0.72 g, 82%); mp 182−184 °C; R_f 0.2 (3:2 EtOAc:hexane); IR (cm^{-1}) (KBr) 3241, 2918, 1660, 1616, 1474, 1291; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.84 (d, J = 6.8 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.48 (dd, J = 7.6, 7.1 Hz, 2H), 7.37−7.26 (m, 5H), 3.77 (s, 2H), 3.64−3.56 (m, 4H), 2.68−2.61 (m, 4H), 2.35 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 163.3, 132.7, 132.6, 132.5, 130.2, 130.2, 128.9, 128.77, 128.75, 127.4, 127.3, 62.1, 51.6, 51.2, 16.8, 16.2; HRMS (ESI) calcd for $C_{23}H_{28}N_3O_2S_2$ [M + H^+] 442.1623, found 442.1628.

General Procedure for the Synthesis of *N*-(1,1-Bis(methylthio)-3-oxo)benzamides (11a−d). To a stirred solution of 4-bis-(methylthio)methylene-5-oxazolone (0.53 g, 2.0 mmol) in THF (10 mL) was added dropwise at room temperature the corresponding alkyl/aryl/hetaryl Grignard reagent (2.3 mmol) under nitrogen atmosphere. Progress of the reaction was monitored by TLC. It was then poured into ice cooled water (100 mL). The mixture was extracted with chloroform (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and distilled under reduced pressure to give crude products, which were purified by column chromatography over silica gel with hexane−EtOAc as eluent.

***N*-(3-(4-Methoxyphenyl)-1,1-bis(methylthio)-3-oxoprop-1-en-2-yl)benzamide (11d):** white solid (0.62 g, 84%); mp 152−154 °C; R_f 0.5 (1:9 EtOAc:hexane); IR (cm^{-1}) (KBr) 3296, 2922, 1653, 1595, 1466, 1258; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.53−7.49 (m, 1H), 7.44−7.40 (m, 2H), 6.93 (d, J = 4.6 Hz, 2H), 3.38 (s, 3H), 2.38 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 163.4, 163.1, 140.6, 132.4, 132.3, 131.0, 130.3, 128.7, 127.5, 118.4, 113.8, 55.4, 17.0, 16.3; HRMS (ESI) calcd for $C_{19}H_{20}NO_3S_2$ [M + H^+] 374.0884, found 374.0886.

General Procedure for the Synthesis of Oxazoles 7a−d, 9a−m, and 12a−d via Ag_2CO_3-Mediated 5-*endo* Cyclization of Open Chain Acrylates/Anilides/Benzamides 6a−d, 8a−m, and 11a−d. A suspension of corresponding acyclic acrylate/anilide/benzamide (1.0 mmol) and Ag_2CO_3 (1.1 g, 4.0 mmol) in 20 mL of CH_3CN was heated to reflux under nitrogen atmosphere with constant stirring. Progress of the reaction was monitored by TLC. Ag_2CO_3 was filtered off by sintered funnel and the filtrate was concentrated under reduced pressure to give the crude products, which were purified by column chromatography over silica gel with hexane−EtOAc as eluent.

Ethyl 5-(methylthio)-2-phenyloxazole-4-carboxylate (7a): white solid (0.21 g, 82%); mp 70−72 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (cm^{-1}) (KBr) 2985, 1676, 1517, 1380, 1217, 1163; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97−7.94 (m, 2H), 7.39−7.37 (m, 3H), 4.35 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 161.2, 155.2, 131.3, 129.2, 129.0, 126.8, 126.7, 61.6, 14.9, 14.8; HRMS (ESI) calcd for $C_{13}H_{14}NO_3S$ [M + H^+] 264.0694, found 264.0698.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-5-(methylthio)-2-phenyloxazole-4-carboxamide (9f):** white solid (0.36 g, 96%); mp 162−164 °C; R_f 0.2 (2:3 EtOAc:hexane); IR (cm^{-1}) (KBr) 3410, 3287, 2925, 1653, 1564, 1501, 1225; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.94−7.92 (m, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.45−7.44 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.22−7.10 (m, 3H), 7.1 (s, 1H), 3.77 (t, J = 6.6 Hz, 2H), 3.08 (t, J = 7.1 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 150.4, 136.4, 131.7, 130.7, 128.8, 127.3, 126.2, 122.2, 119.3, 118.8, 112.9, 111.2, 39.5, 25.6, 15.2; HRMS (ESI) calcd for $C_{21}H_{20}N_3O_2S$ [M + H^+] 378.1276, found 378.1282.

(4-Benzylpiperazin-1-yl)(5-(methylthio)-2-phenyloxazol-4-yl)-methanone (9i): white solid (0.36 g, 94%); mp 136−138 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (cm^{-1}) (KBr) 3037, 2921, 1610, 1514, 1437, 1231; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.97 (m, 2H), 7.45 (t, J = 3.4 Hz, 3H), 7.35−7.26 (m, 5H), 4.15 (s, 2H), 3.81 (br s, 2H), 3.57 (br s, 2H), 2.61 (s, 3H), 2.56 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 159.9, 152.2, 136.6, 133.1, 130.6, 129.3, 128.8, 128.3, 127.5, 126.5,, 126.1, 62.7, 53.2, 52.7,

(38) Although we have focused our studies only on 2-phenyl-4-bis-(methylthio)methylene-5-oxazolone **1** as the model substrate, these reactions may be extended to other 2-aryl/heteroaryl/alkyl oxazolones, thus adding further diversity at the 2-position of newly synthesized oxazoles.

46.1, 42.1, 29.6, 15.6; HRMS (ESI) calcd for $C_{22}H_{24}N_3O_2S$ [M + H^+] 394.1589, found 394.1594.

(*S*)-Ethyl 2-(5-(methylthio)-2-phenyloxazole-4-carboxamido)-3-phenylpropanoate (9k): white solid (0.38 g, 92%); mp 116−118 °C; R_f 0.6 (3:7 EtOAc:hexane); IR (cm^{-1}) (KBr) 3341, 2986, 1733, 1659, 1564, 1514; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 6.5 Hz, 3.1 Hz, 2H), 7.46−7.45 (m, 3H), 7.40 (d, J = 8.4 Hz, 1H), 7.29−7.18 (m, 5H), 5.02 (q, J = 6.3 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.22 (d, J = 6.1 Hz, 2H), 2.65 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 160.7, 160.4, 151.1, 136.1, 131.3, 130.9, 129.5, 128.9, 128.6, 127.1, 126.5, 126.4, 61.6, 53.1, 38.5, 15.3, 14.2; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_4S$ [M + H^+] 411.1378, found 411.1378. Anal. Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.37; H, 5.37; N, 6.78.

(4-Methoxyphenyl)(5-(methylthio)-2-phenyloxazol-4-yl)methanone (12d): yellow solid (0.28 g, 87%); mp 134−136 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (cm^{-1}) (KBr) 2927, 1596, 1492, 1445, 1347, 1260, 906; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 7.0 Hz, 2.1 Hz, 2H), 8.04−8.01 (m, 2H), 7.47−7.45 (m, 3H), 6.97 (dd, J = 7.1 Hz, 2.0 Hz, 2H), 3.86 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 163.3, 159.5, 157.3, 135.9, 132.9, 132.6, 130.6, 129.9, 128.8, 126.7, 126.2, 113.5, 55.4, 14.2; HRMS (ESI) calcd for $C_{18}H_{16}NO_3S$ [M + H^+] 326.0851, found 326.0856.

General Procedure for Raney-Ni Dethiomethylation of 5-(Methylthio)-2-phenyl-4-substituted Oxazoles: Synthesis of Corresponding 5-Unsubstituted Oxazoles 14−18. Raney-Ni (W_2) (ca. 0.5 g) was added to an ethanolic solution (20 mL) of the corresponding oxazole (1 mmol), and the suspension was heated at reflux with stirring for 2−3 h (monitored by TLC). It was then filtered through a sintered glass funnel and washed with hot ethanol. The filtrate was concentrated to afford a viscous residue, which was purified by column chromatography over silica gel with hexane−EtOAc (4:1) as eluent to give the pure products.

Ethyl 4-(2-phenyloxazole-4-carbonyl)piperazine-1-carboxylate (16): white solid (0.29 g, 88%); mp 128−130 °C; R_f 0.2 (2:3 EtOAc:hexane); IR (cm^{-1}) (neat) 2924, 2857, 1700, 1629, 1431, 1247, 1231; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.93−7.92 (m, 2H), 7.42−7.41 (m, 3H), 4.14 (br s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.70 (br s, 2H), 3.53 (br s, 4H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 160.3, 155.9, 153.5, 132.9, 131.2, 129.3, 126.9, 126.5, 62.1, 46.8, 44.5, 42.6, 15.1; HRMS (ESI) calcd for $C_{17}H_{19}N_3O_4$ [M^+] 329.1376, found 329.1378.

General Procedure for the Synthesis of 5-Aminooxazoles 20a−e via Reaction of 5-Methylsulfonyloxazoles 19a−e with Primary/Secondary Amines. A mixture of the corresponding 5-methylsulfonyloxazole (1.0 mmol) and the corresponding primary/secondary amine (2.2 mmol) in DMF (20 mL) was stirred at room temperature under nitrogen atmosphere. Progress of the reaction was monitored by TLC. It was then poured into ice cooled water (100 mL). The mixture was extracted with chloroform (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and distilled under reduced pressure to give crude products, which were purified by column chromatography over silica gel with hexane−EtOAc as eluent.

1-(5-(4-Benzylpiperazin-1-yl)-2-phenyloxazol-4-yl)pentan-1-one (20d): white solid (0.35 g, 88%); mp 58−60 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (cm^{-1}) (KBr) 2955, 2928, 1662, 1614, 1598, 1452; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 6.4 Hz, 2H), 7.40−7.37 (m, 2H), 7.27 (m, 6H), 3.77 (t, J = 4.9 Hz, 4H), 3.56 (s, 2H), 2.96 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 4.9 Hz, 4H), 1.67−1.62 (m, 2H), 1.41−1.36 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 157.4, 149.3, 137.2, 129.6, 129.3, 128.7, 128.3, 127.4, 127.1, 125.5, 117.1, 62.9, 52.5, 47.9, 39.6, 26.9, 22.6, 13.9; HRMS (ESI) calcd for $C_{25}H_{30}N_3O_2$ [M + H^+] 404.2338, found 404.2338.

Acknowledgment. N.C.M. thanks CSIR, New Delhi, for a Research Associateship and H.I. thanks the Indian National Science Academy, New Delhi for the INSA Senior Scientist position at JNCASR, Bangalore. Financial assistance under the DST project is also acknowledged.

Supporting Information Available: General experimental procedures, characterization data, and copies of ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.