JOC The Journal of Organic Chemistry

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Synthesis of 2,5-Bis(hetero)aryl 4′-Substituted 4,5′-Bisoxazoles via Copper(I)-Catalyzed Domino Reactions of Activated Methylene Isocyanides with 2-Phenyl- and 2-(2-Thienyl)-4-[(aryl/heteroaryl)(methylthio)methylene]oxazol-5(4*H*)-ones

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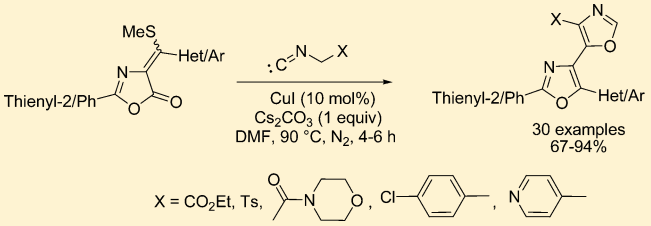
Supporting Information

ABSTRACT: An efficient straightforward synthesis of 2,5,4′-trisubstituted 4,5′-bisoxazoles via copper(I)-catalyzed domino reactions of 2-phenyl- and 2-(2-thienyl)-4-[(aryl/heteroaryl)-methylene]-5-oxazolones with activated methylene isocyanides has been reported. The overall domino process comprised of formation of one C−C and two C−O bonds involves initial nucleophilic ring opening of oxazolones by cupriomethylene isocyanides followed by sequential construction of two oxazole rings in the presence of copper catalyst. The broad substrate scope and excellent functional group compatibility of the reaction has been demonstrated by employing a variety of heteroaryl- and aryl-substituted oxazolones and activated methylene isocyanides, yielding bisoxazoles with three potential points of diversity. A probable mechanism for this novel copper-catalyzed domino process has been proposed.



INTRODUCTION

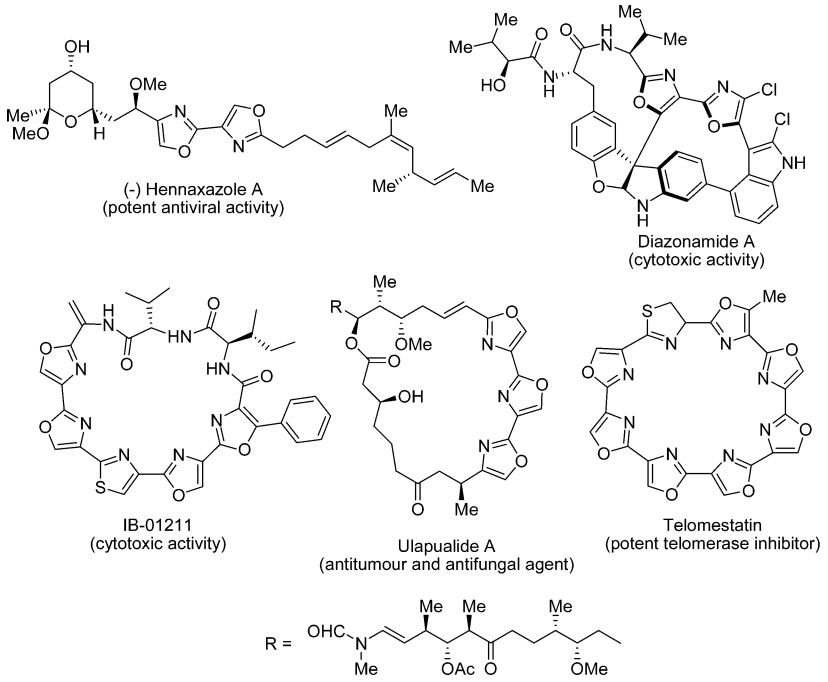
The oxazole heterocycle is a fundamental ring system found throughout in chemistry in areas such as natural products, pharmaceuticals, agrochemicals, peptidomimetics, and polymers.[1] Naturally occurring oxazoles range in structures from relatively simple 2,5-disubstituted derivatives (pimprinine and pimprinethine)[2] to more complex biologically important bis- and trisoxazoles containing cyclic peptides and macrolides.[1b−e] Examples include hennoxazole A[3] with a 2,4′-bisoxazole moiety displaying strong antiherpes simplex virus activity. Diazonamide A (cytotoxic activity),[4] Muscoride A,[5] and IB 01211[6] are other examples of natural products having two contiguous 2,4′-bisoxazole motifs in their cyclic frameworks. Macrolides such as ulapualide A,[7] mycalolide A,[8a,b] kabiramides[8b,c] with potent antifungal activity, and cyclic peptide YM-216391[9] (telomerase inhibitor) contain three contiguous 2,4′-oxazole rings. On the other hand, telomestatin,[10] a $C_2-C_{4'}$-linked macrocyclic heptaoxazole, has been shown to be the most powerful telomerase inhibitor described to date, which has found application in cancer chemotherapy. A few examples of biologically active bis-, tris-, and polyoxazoles are shown in Chart 1. These naturally occurring polyoxazoles display a $C_2-C_{4'}$ linkage as a result of their biosynthesis from amino acids such as serine and threonine.[1d,e,11] To the best of our knowledge, no example of a naturally occurring 4,5′-bisoxazole has been reported, and only a few examples of synthetic 2,2′-,[12a] 2,5′-,[12b] 4,4′-,[12c] 4,5′-,[13] and 5,5′-bisoxazoles[14] are known in the literature.

The unique and complex structure of these bis- and trisoxazole containing natural products and their important pharmacological properties have stimulated considerable interest in the synthesis of compounds containing directly linked 2,4′-bisoxazole (or tris- and polyoxazole) cores. Thus, a plethora of iterative methods have been reported for the construction of $C_2-C_{4'}$-linked polyoxazole subunits. Among them, the biomimetic cyclocondensation of serine derived peptide precursors to oxazoline and subsequent oxidation or dehydrative cyclization of acyclic amide intermediates is a popular approach to the polyoxazole moiety,[6,9,15] although chemoselective amide N−H insertion of rhodium carbenoids (derived from the dirhodium(II)-catalyzed reaction of diazocarbonyl compounds) has also been[1b−e] developed as a useful iterative oxazole synthesis.[16] The other isolated methods include intramolecular cyclization of α-alkynylglycine derivatives,[17] photolysis and pyrolysis of *N*-acylisoxazol-5-ones,[18] S_NAr substitution with the TosMIC anion in 2-chlorooxazole,[19] Pummerer[20] and Chan type[21] rearrangements and ring enlargement of *N*-acylaziridine derivatives,[22] and silver-mediated cross-condensation of amide and α-bromoketones.[23] Recently, metal-catalyzed reactions, i.e. Stille,[24a] Negishi,[24b] and especially Suzuki−Miyaura cross-coupling[12c,25] and direct arylation,[14,24c] have also been developed for the synthesis of bis- and trisoxazoles. Although they differ greatly in their synthetic strategies, these methods share a common linear approach involving a large number of consecutive steps; each time an oxazole ring needs to be introduced, it necessarily requires synthesis of complicated acyclic precursors prior to

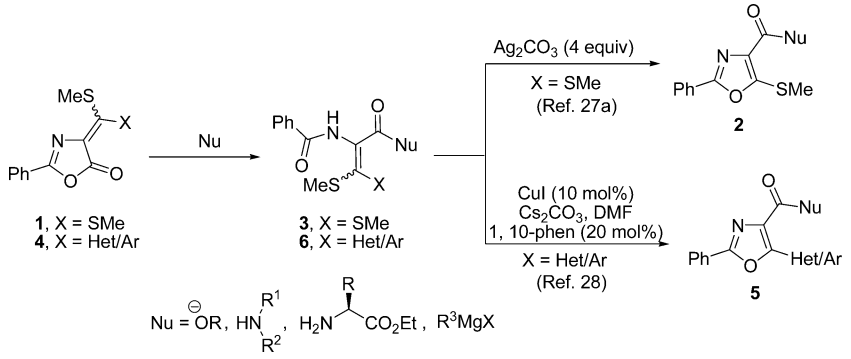
Received: February 12, 2013
Published: March 15, 2013

   dx.doi.org/10.1021/jo400317g | *J. Org. Chem.* 2013, 78, 3948−3960

Chart 1. Biologically Active Natural Products Incorporating Bis-, Tris-, and Polyoxazoles



Scheme 1. Synthesis of 2,4,5-Trisubstituted Oxazoles



cyclization. Therefore, more efficient improved methods for bisoxazole synthesis from readily available precursors are desirable.

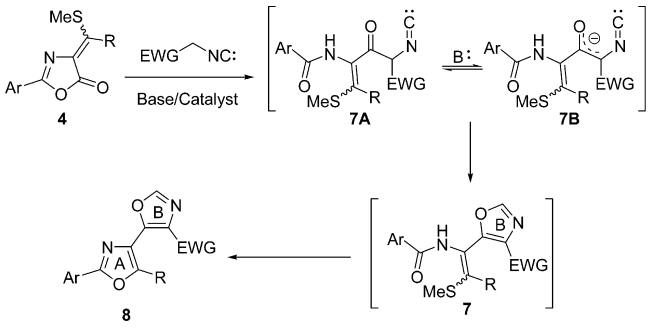
As part of our program to develop new synthetic methods for the construction of a wide range of small-molecule heterocyclic libraries with potential biological activity,[26] we have reported a substrate-controlled, diversity-oriented synthesis of 2-phenyl-5-(methylthio) 4-substituted oxazoles **2** and other heterocycles using the general 2-phenyl-4-bis(methylthio)methyleneoxazol-5(4*H*)-one **1** as a versatile synthetic template.[27] The overall strategy involves nucleophilic azalactone ring opening of **1** by various oxygen (alkoxide), nitrogen (amines), and carbon nucleophiles (Grignard reagents) followed by further synthetic transformations of the resulting open-chain enamide adducts **3** (Scheme 1).[27a,b] In continuation of these studies, as a further extension of this strategy, we have recently described the synthesis of a new class of 5-oxazolone-based synthons, i.e., 2-phenyl-4-[(aryl/heteroaryl)(methylthio)methylene]oxazol-5(4*H*)-ones **4**, and utilized them to develop a two-step synthesis of a variety of 5-aryl and 5-heteroaryl 4-functionalized oxazoles **5** and related natural products (Scheme 1).[28] The key step in this new protocol involves copper-catalyzed intramolecular cyclization of functionalized *β*-(methylthio)enamides **6**, which were obtained by ring opening of the newly synthesized oxazolone precursors **4** by various oxygen, nitrogen, and carbon nucleophiles (Scheme 1).[28]

During the course of these studies, we further anticipated that the use of activated methylene isocyanides[29] as the pronucleophiles, instead of common nucleophiles, in the ring opening of oxazolone precursors **1** or **4** would bring about a different kind of rearrangement−cyclization process. The rich chemistry of anionized *α*-isocyanoacetate and tosylmethyl isocyanide developed by Schollkopf[29a,b] and van Leusen,[30] respectively, is mainly due to the exploitation of nucleophilicity of the *α*-carbon atom, which can add to a variety of polar (hetero)multiple bonds, along with the electrophilicity of the divalent carbon atom of the isonitrile functionality resulting in efficient construction of C−C and C−X (X = C, N, O, S) bonds in a formal cycloaddition process to generate various heterocycles. In recent years, activated methylene isocyanides have emerged as versatile intermediates, participating in various types of base-mediated cocyclization reactions with various multiple bonds and other reactive species, leading to a diverse class of nitrogen heterocycles.[31,32]

dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

We have recently reported efficient syntheses of 2,3,4-substituted pyrroles[33] and imidazo[1,5-*a*]quinoxalines[34] by formal cycloaddition of activated methylene isocyanide anions to polarized ketene dithioacetals and 2,3-substituted quinoxalines, respectively. In continuation of these studies, along with our ongoing research interest in 5-oxazolone-derived synthetic templates,[27,28] we envisaged that nucleophilic ring opening of oxazolone **1** or **4** by an activated methylene isocyanide pronucleophile would give the acyclic intermediate **7A** having a *β*-ketoisonitrile moiety, which would undergo facile proton abstraction and subsequent intramolecular cyclization of the resulting enolate **7B** to the oxazole intermediate **7**, as observed earlier by Schollkopf and other workers in the acylation studies of isocyanoacetate anion with various acylating agents.[31b,35,36] It was further speculated that the resulting *α*-(5-oxazolyl)-*α*-benzoylamido intermediate **7** would also undergo cyclization via an intramolecular 5-*endo-trig* process in the presence of a base or metal catalyst with the formation of a second oxazole ring (A),[27,28] thus providing a facile access to novel 2,5,4′-substituted 4,5′-bisoxazoles **8** (Scheme 2).[37] We have

Scheme 2. Proposed Strategy for the Synthesis of Bisoxazoles 8



successfully achieved this goal and report in the present paper a novel copper-catalyzed domino reaction involving ring opening of 2-phenyl and 2-(2-thienyl)-4-[(heteroaryl/aryl)-(methylthio)methylene]-5-oxazolones **4** with various activated methylene isocyanide pronucleophiles and subsequent in situ intramolecular cyclization of the resulting diversely functionalized open-chain adducts **7**, thus providing a straightforward direct route to a wide range of 2,5,4′-substituted 4,5′-bisoxazoles **8** in excellent yields.

RESULTS AND DISCUSSION

The desired 2-phenyl-4-(heteroarylidene/arylidene)-5-oxazolone precursors **4a−f** were synthesized by condensation of 2-phenyloxazol-5(4*H*)-one **9a** with various aryl/heteroaryl dithioesters **10** in the presence of sodium hydride in DMF followed by alkylation of thiolate salts **11** with methyl iodide as reported earlier.[28] Further diversity in the 5-oxazolone framework was introduced by synthesis of the corresponding 2-[(2-thienyl)]-4-[(heteroaryl/aryl)(methylthio)]-5-oxazolones **4g,h** from the corresponding 2-(2-thienyl)-5-oxazolone **9b** following a similar procedure (Scheme 3).

The reaction of oxazolone **4a** with ethyl isocyanoacetate **12a** in the presence of various bases and Cu catalysts was selected as the model reaction for optimizing reaction conditions for the formation of bisoxazole **8aa** (Tables 1 and 2). Thus, when **4a** was reacted with **12a** in the presence of DBU as base at 60 °C for 10 h, analysis of the reaction mixture showed formation of

Scheme 3. Synthesis of 2-Phenyl- and 2-(2-Thienyl)-4-[(aryl/heteroaryl)methylthiomethylene]oxazol-5-ones (4a−h)

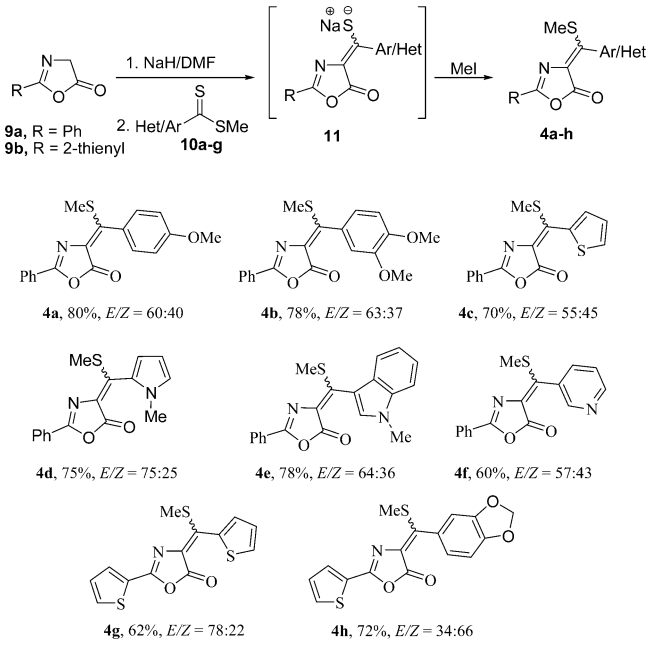
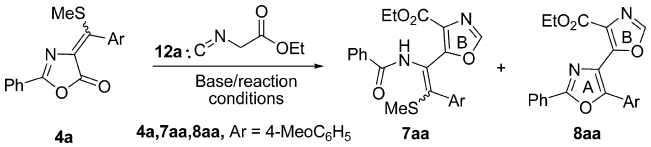


Table 1. Optimization of Reaction Conditions for the Formation of Bisoxazole 8aa from 4a and 12a in the Presence of Different Bases[a]



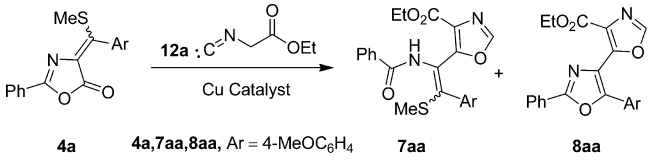
entry	base	solvent	*t* (h)	*T* (°C)	yield (%) 7aa	yield (%) 8aa
1	DBU	DMF	10	60	86	
2	*t*BuOK	THF	10	60	88	
3	NaH	DMF	10	60	84	
4	Cs_2CO_3	DMF	10	60	83	
5	Et_3N	THF	25	60	45 (41)[b]	
6	DBU	DMF	25	90	70	10
7	DBU	DMF	25	120		66
8	*t*BuOK	DMF	25	120		67
9	NaH	DMF	24	120		61
10	Cs_2CO_3	DMF	25	120		64

[a]Reaction conditions: **4a** (0.3 mmol), **12a** (1 equiv), and base (1 equiv) in 2 mL of solvent. [b]Yield of recovered **4a**.

only one product (86%), which was characterized as the acyclic adduct **7aa** bearing an oxazole B ring (Table 1, entry 1). Use of other bases such as potassium *tert*-butoxide, sodium hydride, and cesium carbonate, which are commonly employed in similar protocols, also yielded only the product **7aa** in 83−88% yields at lower temperature (entries 2−4, Table 1). On the other hand, use of a weaker base such as triethylamine furnished **7aa** in decreased yield (45%) along with unreacted **4a**, even after a prolonged reaction time (entry 5). Formation of oxazole derivative **7aa** from **4a** and **12a** is in line with our predicted course of reaction[35,36] involving nucleophilic ring opening of **4a** by isocyanoacetate anion followed by base-

dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

Table 2. Optimization of Reaction Conditions for the Formation of Bisoxazole 8aa from 4a and Isocyanoacetate 12a in the Presence of Copper Catalysts[a]



4a **4a,7aa,8aa**, Ar = 4-MeOC$_6$H$_4$ **7aa** **8aa**

					yield (%)	
entry	cat.	solvent	t (h)	T (°C)	**7aa**	**8aa**
1	Cu powder/PPh_3	dioxane	2	90	80	
2	Cu powder/phen	dioxane	2	90	78	
3	Cu powder/PPh_3	dioxane	12	100		68
4	Cu powder/phen	dioxane	17	100		65
5[b]	Cu_2O	DMF	24	100		61
6	Cu_2O/PPh_3	DMF	18	90		66
7	Cu_2O/phen	dioxane	20	100	72	22
8	CuCI/PPh_3	dioxane	20	100	trace	
9	CuBr/PPh_3	dioxane	25	100	70	10
10	CuI/PPh_3	DMF	20	90	25	55
11[c]	CuCI/Cs_2CO_3	DMF	10	90	15	70
12[c]	CuI/Cs_2CO_3	DMF	4	90		75
13[d]	CuI/PPh_3/ Cs_2CO_3	DMF	10	90		70
14[e]	CuI/Cs_2CO_3	DMF	10	90		70
15[f]	Ag_2CO_3	CH_3CN	20	80	38	52
16[g]	Cs_2CO_3	DMF	10	90	81	trace

[a]Reaction conditions: all reactions were performed with 0.3 mmol of **4a** and 1 equiv of **12a** in 2 mL of solvent. Catalyst (10 mol %) and ligand (20 mol %). [b]Cu_2O (10 mol %). [c]Catalyst (10 mol %) and Cs_2CO_3 (1 equiv). [d]CuI (10 mol %), PPh_3 (20 mol %) and Cs_2CO_3 (1 equiv). [e]Catalyst (5 mol %) and base (1 equiv). [f]Stoichiometric amount of Ag_2CO_3. [g]Cs_2CO_3 (1 equiv).

induced spontaneous intramolecular cyclization of the newly formed α-acylisocyanoacetate moiety in the initially formed open-chain intermediate **7aa** (Scheme 2). No trace of the desired bisoxazole **8aa** could be detected in the reaction mixture. However when the reaction of **4a** and **12a** in the presence of DBU was continued for a longer time (25 h) at higher temperature (90 °C), formation of **8aa** was observed, albeit in 10% yield along with **7aa** (70%) (Table 1, entry 6), whereas increasing the reaction temperature to 120 °C resulted in complete disappearance of **7aa**, furnishing the bisoxazole **8aa** in increased yield of 66% along with a polymeric mixture (Table 1, entry 7). Similarly, the bisoxazole **8aa** was observed as the exclusive product in 61−67% overall yield with *t*BuOK, NaH, or Cs_2CO_3 as base at higher temperatures and longer reaction times (Table 1, entries 8−10).

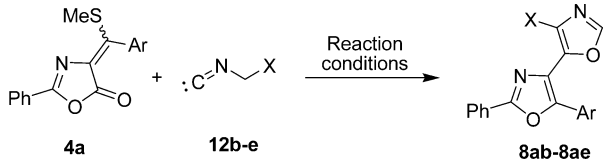
With the base-mediated tandem ring-opening cyclization of **4a** with isocyanoacetate **12a** to bisoxazole **8aa** in hand, we further became interested in its copper-catalyzed variant with a view to enhance the efficiency of the reaction under milder reaction conditions.[28] Recently, great progress has been made in the use of transition-metal-catalyzed reactions of activated methylene isocyanides with double and triple bonds.[31] Thus, de Meijere and co-workers[38a,b] and Yamamoto et al.[38c,d] have independently reported the copper-catalyzed formal cycloaddition reactions of isocyanoacetates and alkynes furnishing oligosubstituted pyrroles in good yields. Cai and co-workers have recently described novel copper-catalyzed domino reactions of activated methylene isocyanides with 1-(2-haloaryl)-2-yn-1-ones[39a] and *N*-(2-haloaryl)propiolamides,[39b] providing efficient synthesis of 4-oxoindeno[1,2-*b*]pyrroles and pyrrolo[3,2-*c*]quinolin-4-ones, respectively, via a formal [3 + 2] cycloaddition and subsequent intramolecular aryl C−C coupling of the resulting organocopper intermediate.

Encouraged by these findings, we conducted a detailed study of the reaction of oxazolone **4a** with ethyl isocyanoacetate (**12a**) and various copper catalysts, and the results are depicted in Table 2. A detailed survey of the screening of various combinations of catalysts and ligands revealed that most of the copper catalysts employed in these reactions demonstrated moderate to good activity in the formation of bisoxazole **8aa** under varying conditions, whereas CuI (10 mol %) in the presence of cesium carbonate in DMF turned out to most efficiently and effectively promote the formation of **8aa** within 4 h at 90 °C in 75% yield (Table 2, entry 12). With copper powder and Cu(I) oxide as catalysts, in the presence or absence of ligand, **8aa** was obtained in lower yields (61−68%) requiring higher temperature and prolonged reaction time (entries 3−6), whereas formation of only open-chain oxazole adduct **7aa** was observed at reduced temperature and time with copper powder under identical conditions (entries 1 and 2). On the other hand, in the presence of Cu_2O/phen, the bisoxazole **8aa** was obtained only in 22% yield along with open-chain adduct **7aa** as the major product (entry 7). Similarly, other copper catalysts such as CuCl, CuBr, and CuI in the presence of PPh_3 or Cs_2CO_3 also gave inferior results (entries 8−11), whereas a combination of CuI/PPh_3 and Cs_2CO_3 (entry 13) resulted in a significantly increased yield of **8aa** (entry 13).[40] Use of Ag_2CO_3 (in a stoichiometric amount) was found to be less effective and did not show complete conversion of **7aa** to **8aa** even after a prolonged time (entry 15). Similarly, decreasing the catalyst loading to 5 mol % of CuI gave **8aa** only in slightly reduced yield (70%), requiring a longer time (10 h) for completion of the reaction (entry 14). As a control experiment, when **4a** was reacted with **12a** in the absence of CuI, using 1 equiv of Cs_2CO_3 under conditions identical with those described in entry 14, the bisoxazole **8aa** was formed in only traces along with **7aa** as the major product (entry 16), thus showing that the presence of CuI as catalyst facilitates the formation of bisoxazole **8aa** from **7aa** (entry 16 vs entry 14).[40] Among the solvents we tested, DMF showed the best results, whereas other solvents such as 1,4-dioxane, toluene, acetonitrile and ethyl acetate (with CuI/Cs_2CO_3) gave the desired product **8aa** only in moderate yields.

The scope and limitations of this novel base-induced and copper-catalyzed domino reaction for bisoxazole synthesis was next examined by employing a variety of acceptor-substituted methylene isocyanides **12b−e** in the reaction with oxazolone **4a** (Table 3). The results of these studies reveal that the reaction of **4a** with tosylmethyl isocyanide (**12b**), *N*- morpholino-α-isocyanoacetamide (**12c**), 4-chlorobenzyl isocyanide (**12d**), and 4-pyridylmethyl isocyanide (**12e**) in the presence of bases such as potassium *tert*-butoxide and DBU afforded the corresponding 4′-substituted bisoxazoles **8ab−8ae** in moderate to good yields requiring higher temperature and longer reaction time (Table 3, entries 1−8). However, increased yields of bisoxazoles **8ab−8ae** (76−91%) were obtained under copper-catalyzed reaction conditions in the presence of CuI/Cs_2CO_3, which efficiently promoted the reaction at lower temperature (90 °C) within 4−6 h (Table 3, entries 9−12). Therefore, these optimized reaction conditions (CuI/Cs_2CO_3) were employed throughout in our subsequent studies.

dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

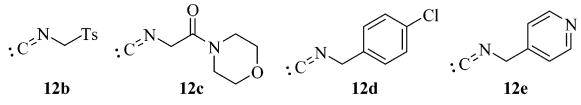
Table 3. Synthesis of Bisoxazoles 8ab−8ae Using 4a and Isocyanides 12b−e[a]

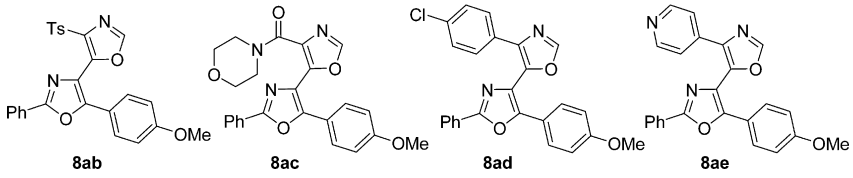


4a 12b-e 8ab-8ae

entry	CN 12 X	base/catalyst	t (h)	T(°C)	product 8	yield (%)
1	**12b**	*t*BuOK	12	140	**8ab**	69
2	**12b**	DBU	15	140	**8ab**	60
3	**12c**	*t*BuOK	24	140	**8ac**	58
4	**12c**	DBU	24	140	**8ac**	60
5	**12d**	*t*BuOK	16	140	**8ad**	60
6	**12d**	DBU	18	140	**8ad**	50
7	**12e**	*t*BuOK	28	140	**8ae**	55
8	**12e**	DBU	28	140	**8ae**	50
9[b]	**12b**	CuI/Cs_2CO_3	4	90	**8ab**	76
10[b]	**12c**	CuI/Cs_2CO_3	5	90	**8ac**	85
11[b]	**12d**	CuI/Cs_2CO_3	4	90	**8ad**	91
12[b]	**12e**	CuI/Cs_2CO_3	6	90	**8ae**	78

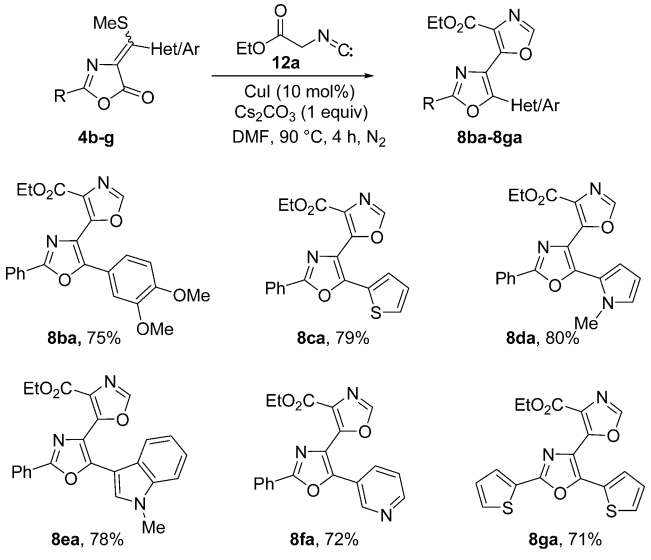
[a]Reaction conditions: **4a** (0.3 mmol), **12** (1 equiv) and base (1 equiv) in 2 mL of DMF. [b]Reaction conditions: CuI (10 mol %) and Cs_2CO_3 (1 equiv). [c]Structures of **8ab−8ae** and **12b−e** are as follows:





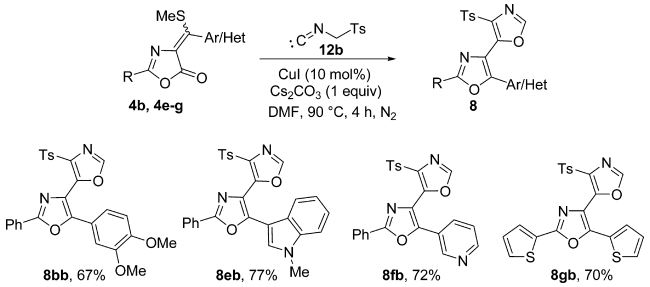
Having established the copper-catalyzed reaction conditions for the formation of bisoxazoles **8aa−8ae** from **4a** and **12a−e** (Table 3), the reaction of various substituted 2-phenyl and 2-(2-thienyl)-4-[(aryl/heteroaryl)(methylthio)methylene]oxazol-5(4*H*)-ones **4b−h** with activated methylene isocyanides **12a−e** was carried with a view to enhance the substrate scope of the reaction for a diversity-oriented synthesis of a variety of novel 2,5′-bisoxazoles carrying a wide range substituents at the 2-, 5-, and 4′- positions of two bisoxazole rings. These results are summarized in Schemes 4−8. Thus, 2-phenyl-5-(3,4-bismethoxyphenyl)-, 2-phenyl-5-(2-thienyl)-, 2-phenyl-5-[2-(1-*N*-methyl)pyrrolyl], and 2-phenyl-5-[3-(1-*N*-methyl)indolyl]-4′-carbethoxybisoxazoles (**8ba−8fa**) and the corresponding 2-thienyl derivative **8ga** were obtained in overall high yields, when ethyl isocyanoacetate **12a** was reacted with oxazolones **4b−g** under standard copper-catalyzed reaction conditions (Scheme 4). The novel domino reaction was found to be equally facile with tosylmethyl isocyanide **12b**, which readily reacts with oxazolones **4b** and **4e−g** under identical reaction conditions furnishing 2,5 bis(hetero)aryl-4′-tosyl-4,5′-bisoxazoles **8bb** and **8eb−8gb** in 67−77% yields (Scheme 5). Similarly the corresponding bisoxazoles **8cc**, **8ec**, **8fc**, and **8hc** carrying a 4′-(*N*-morpholino)amide functionality could also be prepared in excellent yields by employing *N*-(morpholino)-isocyanoacetamide **12c** as a reaction partner with oxazolones **4c,e,f,h**, respectively (Scheme 6). The versatility of the reaction

Scheme 4. Synthesis of 2,5-Bis(heteroaryl/aryl)-4′-carbethoxy-4,5′-bisoxazoles 8



dx.doi.org/10.1021/jo400317g | *J. Org. Chem.* 2013, 78, 3948−3960

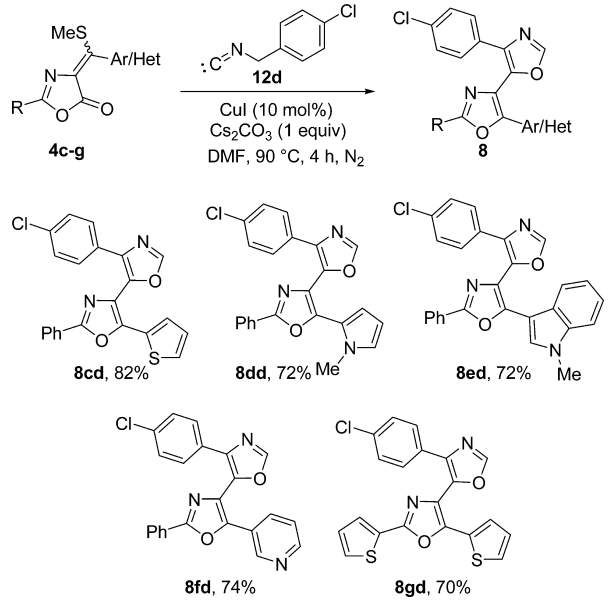
Scheme 5. Synthesis of 2,5-Bis(heteroaryl/aryl)-4′-tosyl-4,5′-bisoxazoles 8



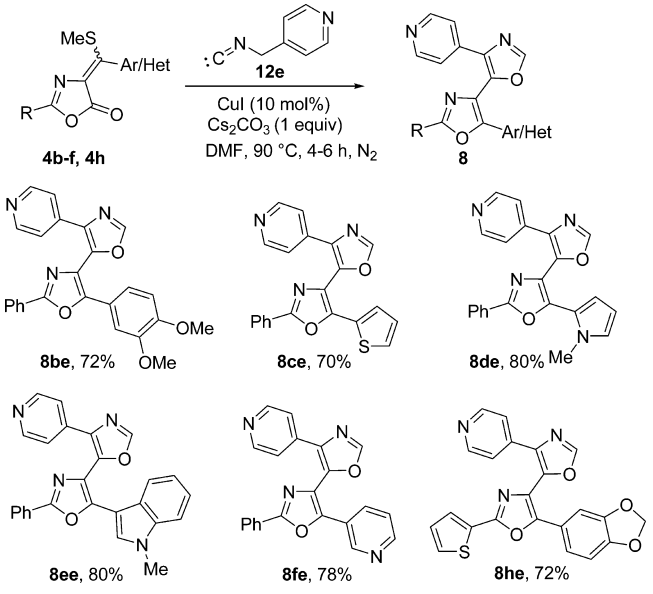
was further demonstrated by employing the less acidic 4-chlorobenzyl isocyanide **12d**, which also reacted smoothly with various 4-(aryl/heteroaryl)methyleneoxazolones **4c−g** under similar conditions, providing 2,5-bis(heteroaryl/aryl)-4′-(4-chlorophenyl)bisoxazoles **8cd−8gd** in excellent yields (Scheme 7). Further substituent diversity was introduced by installation of a 4-pyridyl moiety in the 4′-position of the bisoxazole framework by reacting 4-pyridylmethyl isocyanide **12e** with various oxazolones (**4b−f,h**) under identical conditions, yielding product bisoxazoles **8be−8fe** and **8he** in high yields (Scheme 8). The synthesis of these novel pyridyl-substituted bisoxazoles, especially the 5,4′-bis(pyridyl) derivative **8fe**, is particularly noteworthy, since the pyridyl group is an important pharmacophore in various pharmaceutically important compounds.

On the basis of our experimental observations and literature precedent, a plausible mechanism for this novel copper-catalyzed domino process leading to bisoxazoles **8** from oxazolones **4** and isocyanides **12** is depicted in Schemes 9 and 10. Thus, the initiating step appears to be the formation of α-cuprioisocyanide species **A** or its tautomer **A**[1] by reaction of isocyanides with CuI in the presence of base. Subsequent nucleophilic ring opening of the lactone ring of oxazolone **4** by intermediate **A** and/or **A**[1] generates the acyclic α-acylisonitrile intermediate **B**, which exists in equilibrium with the copper enolate **C** in the basic medium. The intermediate **C** undergoes facile intramolecular cyclization by attack on the isonitrile carbon to furnish the 2-oxazolocopper intermediate **D** (Scheme 9). The C−Cu bond in the intermediate **D** is protonated by isocyanide **12**, furnishing the initially formed oxazole (B ring) containing acyclic product **7** at lower temperature, with the regeneration of the copper intermediate **A** and/or **A**[1], thus completing the catalytic cycle for the formation of initial product **7**.

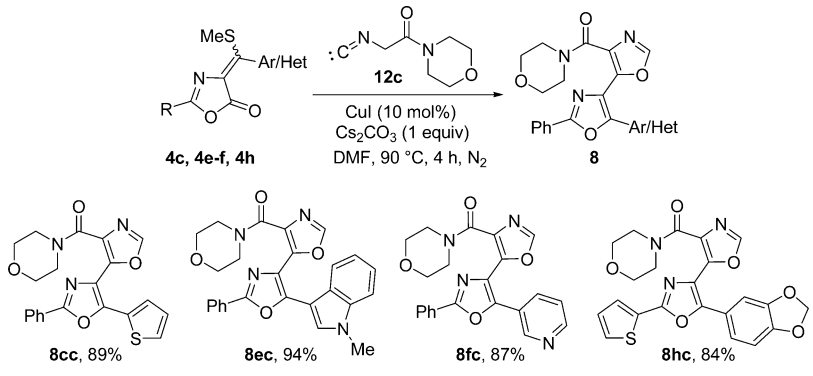
Scheme 7. Synthesis of 2,5-Bis(heteroaryl/aryl)-4′-(4-chlorophenyl)-4,5′-bisoxazoles 8



Scheme 8. Synthesis of 2,5-Bis(heteroaryl/aryl)-4′-(4-pyridyl)-4,5′-bisoxazoles 8

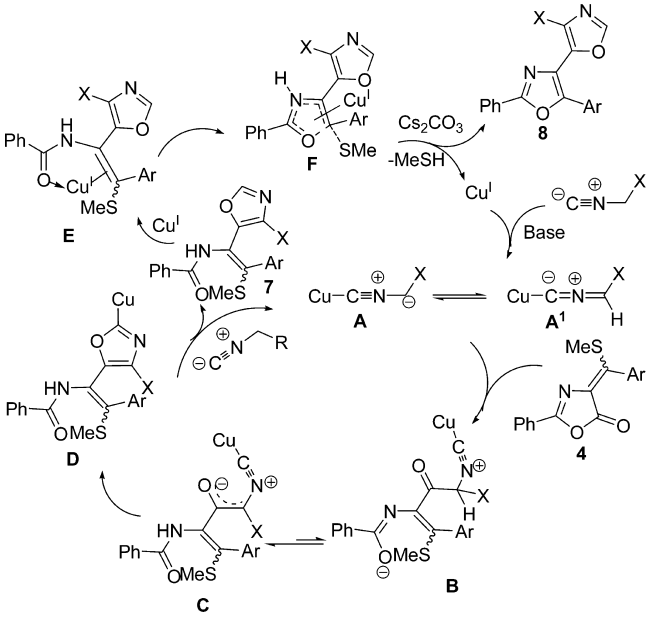


Scheme 6. Synthesis of 2,5-Bis(heteroaryl/aryl)-4′-(*N*-morpholinocarbonyl)-4,5′-bisoxazoles

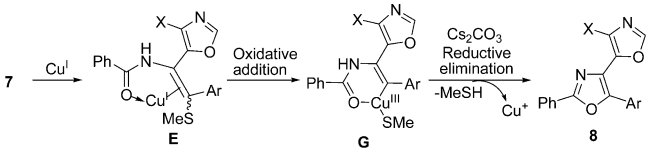


dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

Scheme 9. Proposed Mechanism for Cu(I)-Catalyzed Formation of Bisoxazoles 8 from 4

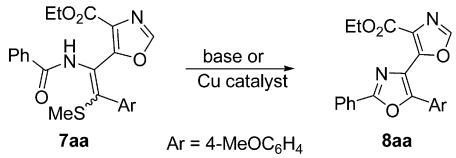


Scheme 10. Proposed Alternate Mechanism for Copper-Catalyzed Formation of Bisoxazoles 8 from Acyclic Precursors 7



Regarding the possible mechanism for the formation of a second oxazole ring (A) of the bisoxazole **8** from the intermediate **D** or **7** at higher temperature, our studies reveal that intramolecular cyclization of **7aa** to **8aa** is much more efficient in the presence of copper catalyst (CuI/Cs_2CO_3), giving bisoxazole **8aa** in 88% yield within 4 h (Table 4, entry 1), whereas under base-induced conditions (Cs_2CO_3/DMF), in the absence of CuI, the reaction was not complete even after 36 h, providing **8aa** in maximum yield of 65% along with unreacted starting material (Table 4, entries 2 and 3). Similarly, other bases such as potassium *tert*-butoxide or DBU also furnished **8aa** in lower yields, requiring more drastic reaction conditions (Table 4, entries 4 and 5). These observations evidently show that the formation of a second oxazole ring (A) of bisoxazole **8** by intramolecular cyclization of the intermediate **7** is facilitated in the presence of Cu(I) catalyst.

Table 4. Intramolecular Cyclization of Open-Chain Adduct 7aa to Bisoxazole 8aa



entry	reagent conditions[a]	solvent	T (°C)	t (h)	yield of **8aa** (%)
1	CuI/Cs_2CO_3	DMF	90	4	88
2	Cs_2CO_3	DMF	90	25	60 (24)[b]
3	Cs_2CO_3	DMF	90	36	65 (20)[b]
4	*t*BuOK	DMF	90	30	63
5	DBU	DMF	90	32	59

[a]Reaction conditions: catalyst (10 mol %), base (1 equiv). [b]Yield of recovered **7aa** given in parentheses.

On the basis of known mechanisms of Ullman -type condensations[41] along with the related mechanistic studies on the synthesis of benzoazoles by Cu(I)-catalyzed intramolecular cyclization of *o*-halobenzanilides,[42] we propose two possible mechanisms for the formation of the A ring of bisoxazole **8** via copper-catalyzed intramolecular cyclization of the β-(methylthio)vinylenamide functionality present in the intermediate **7** (Schemes 9 and 10).

Thus, the coordination of the amide functionality of **7** with cuprous ion first forms the chelated intermediate **E**,[43] which undergoes intramolecular nucleophilic substitution at the electrophilic double bond through the transition state intermediate **F** (Scheme 9). Subsequent Cs_2CO_3-assisted elimination of MeSH in the intermediate **F** and decomposition of the resulting bisoxazole−Cu complex furnishes the bisoxazole **8** along with the regenerated Cu(I) catalyst (Scheme 9). The present mechanism is similar to that proposed by Paine[41e] and later by Ma and co-workers in their detailed study of Cu(I)-catalyzed coupling reactions of aryl halides with α-amino acids, involving a π-complex intermediate.[44] Alternatively, the initially formed intermediate **E** can undergo oxidative addition, forming the Cu^{III}-containing transient intermediate **G** (Scheme 10). Subsequent reductive elimination of **G** in the presence of Cs_2CO_3 affords the bisoxazole **8** and Cu(I) catalyst.[41a−d,42a−c] In the absence of literature examples of Cu(I)-catalyzed coupling reactions of aryl/vinyl thioethers with nitrogen or oxygen nucleophiles, we prefer the former mechanism involving intramolecular nucleophilic substitution of the methylthio group in the intermediate **F** (Scheme 9). However, further study is required to investigate the detailed mechanism and role of the copper catalyst in this transformation.

CONCLUSION

In conclusion, we have demonstrated a novel, mild, and efficient Cu(I)-catalyzed domino process from readily accessible oxazolones **4** and activated methylene isocyanides **12**, providing a straightforward direct route for diversity-oriented synthesis of hitherto unreported 2,5,4′-trisubstituted 4,5′-bisoxazoles. The reaction displays broad substrate scope and excellent functional group compatibility by employing a wide range of substituted oxazolones and isocyanides furnishing bisoxazoles with three potential points of diversity. The overall domino process comprised of the formation of one C−C and two C−O bonds involves initial acylation of cupriomethylene isocyanides (α-cupriomethylene isocyanides) by nucleophilic ring opening of oxazolones followed by sequential construction of two oxazole rings in the presence of copper catalyst. It should be noted that although transition-metal-catalyzed synthesis of oxazolines by reaction of carbonyl compounds with activated methylene isocyanoacetate is a well-documented efficient methodology,[45] the analogous catalytic process for oxazole formation via α-acylation of activated methylene isocyanides has not been much explored.[46]

We believe that the synthesis reported herein can find application in a number of fields, including combinatorial and solid phase synthesis, as well as in automation, increasing the

dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

popularity of these novel bisoxazoles, in view of the medicinal importance of natural products containing this versatile scaffold.

EXPERIMENTAL SECTION

General Information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin-layer chromatography using Merck TLC silica gel plates and visualized with UV light. Flash chromatography was performed using Merck silica gel (100−200 mesh). Nuclear magnetic resonance spectra were recorded on a 400 MHz Fourier transform NMR spectrometer with $CDCl_3$, DMSO-d_6, or acetone-d_6 as solvent. Chemical shifts were reported in δ ppm (parts per million) using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6, and δ 2.05 for acetone-d_6 in ^{1}H NMR, δ 77.16 for $CDCl_3$ and δ 39.5 for DMSO-d_6 in ^{13}C NMR). Coupling constants were reported as J values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublets of doublets), td (triplet of doublets) m (multiplet) and br (broad). Infrared spectra were recorded with an FTIR instrument and HRMS on a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The desired activated methylene isocyanides **12a**,[47] **12c**,[48] **12d**,[49] and **12e**[50] were prepared according to the reported procedures, whereas the corresponding tosylmethyl isocyanide **12b** was commercially purchased. The dithioesters **10a−c**,[51a] **10g**,[51a] **10d,e**,[26e,51b] and **10f**[51c] required for the synthesis of 5-oxazolone precursors **4a−h** were prepared according to the reported methods in the literature.

General Procedure for the Synthesis of 2-Phenyl- and 2-(2-Thienyl)-4-[(aryl/heteroaryl)(methylthio)methylene]oxazol-5-ones (4a−h). The oxazalones **4a−h** were prepared following our earlier reported procedure[28] by reaction of the corresponding 2-phenyl- (**9a**) and 2-(2-thienyl)-oxazol-5-ones (**9b**) (3.0 mmol) with the appropriate heteroaryl/aryl dithioesters **10** (3.0 mmol) in the presence of sodium hydride (0.31 g, 7.8 mmol) in DMF (10 mL) followed by treatment with methyl iodide (0.28 mL, 4.5 mmol) and workup as reported.[28] 2-Phenyl-4-[(aryl/heteroaryl)(methylthio)-methylene]-5-oxazolones **4a−f** were characterized by comparison of their spectral and analytical data with those reported.[28] The spectral and analytical data of the unknown oxazolones **4g,h** are given below.

*(E/Z)-4-[(Methylthio)(2-thienyl)methylene]-2-(2-thienyl)oxazol-5(4H)-one (**4g**):* obtained from 2-(2-thienyl)oxazolone **9b** and dithioester **10c** (Ar = 2-thienyl) (*E*:*Z* = 78:22), brown solid (0.571 g, 62%); mp 128−130 °C; R_f = 0.5 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3101, 2926, 1771, 1616, 1396, 852, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 4.0 Hz, 1.2 Hz, 0.78H), 7.82−7.79 (m, 1H), 7.72 (dd, J = 4.8 Hz, 1.2 Hz, 0.78H), 7.63−7.60 (m, 1H), 7.59 (dd, J = 4.8 Hz, 1.2 Hz, 0.22H), 7.39 (dd, J = 3.6 Hz, 1.2 Hz, 0.22H), 7.21 (dd, J = 5.2 Hz, 4.0 Hz, 0.78H), 7.19−7.15 (m, 1.22H), 2.58 (s, 2.6H), 2.49 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 156.0, 144.4, 140.3, 134.3, 134.2, 132.4, 132.3, 131.9, 131.3, 130.7, 129.3, 129.0, 128.9, 128.7, 128.6, 128.22, 128.19, 19.9, 18.0; HRMS (ESI) m/z calcd for $C_{13}H_9NO_2S_3$ [M + H]$^+$ 307.9874, found 307.9859.

*(E/Z)-4-(Benzo[d][1,3]dioxol-5-yl(methylthio)methylene)-2-(2-thienyl)oxazol-5(4H)-one (**4h**):* obtained from oxazolone **9b** and dithioester **10g** (Ar = 3,4-methylenedioxyphenyl) (*E*:*Z* = 34:66), yellow solid (0.745 g, 72%); mp 126−128 °C; R_f = 0.4 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3102, 2926, 1772, 1608, 1476, 1425, 1205, 1028, 971, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 4.0 Hz, 1.2 Hz, 0.34H), 7.73 (dd, J = 3.6 Hz, 1.2 Hz, 0.66H), 7.60 (dd, J = 4.8 Hz, 1.2 Hz, 0.34H), 7.53 (dd, J = 4.8 Hz, 1.2 Hz, 0.66H), 7.15 (dd, J = 4.8 Hz, 3.6 Hz, 0.34H), 7.11 (dd, J = 5.0 Hz, 4.0 Hz, 0.66H), 7.01 (dd, J = 8.0 Hz, 1.6 Hz, 0.66H), 6.97 (d, J = 1.6 Hz, 0.66H), 6.94 (s, 0.34H), 6.92−6.89 (m, 0.66H), 6.86 (dd, J = 8.0 Hz, 1.6 Hz, 0.34H), 6.81 (d, J = 1.6 Hz, 0.34H), 6.06 (s, 1.32H), 6.05 (s, 0.68H), 2.26 (s, 1.02H), 2.22 (s, 1.98H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 161.9, 156.3, 156.1, 155.5, 155.4, 149.5, 149.3, 148.3, 148.1, 132.1, 131.7, 131.66, 131.4, 129.3, 129.1, 128.9, 128.5, 128.4, 128.1, 128.0, 126.3, 125.1, 123.7, 110.7, 109.6, 108.8, 108.6, 101.8, 17.3, 16.6; HRMS (ESI) m/z calcd for $C_{16}H_{11}NO_4S_2$ [M + H]$^+$ 346.0208, found 346.0192.

General Procedure for the Base-Induced Reaction of 4-[(4-Methoxyphenyl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one (4a) with Ethyl Isocyanoacetate (12a). To a stirred solution of oxazolone **4a** (97.6 mg, 0.3 mmol) and **12a** (33.9 mg, 0.3 mmol) in DMF or THF (2 mL) was added the appropriate base (DBU, *t*BuOK, NaH, Cs_2CO_3, Et_3N) (0.3 mmol), and the reaction mixture was further stirred at room temperature for 10−25 h (Table 1). It was then poured into saturated NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 25 mL), the extract was washed with water (2 × 30 mL) and brine (30 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a mixture of acyclic adduct **7aa** and bisoxazole **8aa**, which were purified by column chromatography on silica gel using EtOAc/hexane as eluent. The yields of products **7aa** and **8aa** isolated in various experiments are given in Table 1 (entries 1−10).

*(E/Z)-Ethyl 5-[1-benzamido-2-(4-methoxyphenyl)-2-(methylthio)-vinyl]oxazole-4-carboxylate (**7aa**):* obtained as a yellow solid (*E*:*Z* = 22:78); mp 104−106 °C; R_f = 0.35 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3262, 3135, 1700, 1662, 1605, 1574, 1511, 1479, 1285, 1246, 1171, 1095, 1045; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 0.38H), 7.96 (s, 0.62H), 7.90 (d, J = 6.8 Hz, 0.64H), 7.85 (s, 0.62H), 7.58−7.55 (m, 2.38H), 7.50−7.44 (m, 3H), 7.37−7.33 (m, 1.24H), 7.14 (dd, J = 6.4 Hz, 2.0 Hz, 0.76H), 6.96 (dt, J = 8.8 Hz, 2.4 Hz, 1.24H), 6.79 (dd, J = 7.0 Hz, 1.8 Hz, 0.76H), 4.37−4.27 (m, 2H), 3.83 (s, 1.86H), 3.78 (s, 1.14H), 1.98 (s, 1.14H), 1.92 (s, 1.86H), 1.37−1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 161.7, 161.6, 160.3, 159.8, 152.7, 152.3, 149.6, 149.3, 139.4, 138.9, 133.8, 133.6, 132.1, 132.0, 131.0, 130.9, 129.1, 128.8, 128.7, 127.6, 127.3, 127.2, 127.1, 119.1, 119.0, 114.6, 114.0, 61.4, 61.3, 55.5, 55.3, 16.0, 15.7, 14.4, 14.3; HRMS (ESI) m/z calcd for $C_{23}H_{22}N_2O_5S$ [M + Na]$^+$ 461.1147, found 461.1144.

*2-Phenyl-5-(4-methoxyphenyl)-4′-carbethoxy-4,5′-bisoxazole (**8aa**):* obtained as a pale yellow solid; mp 128−130 °C; R_f = 0.5 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3129, 2977, 2931, 2842, 1712, 1505, 1256, 1174, 1091, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.12 (m, 2H), 8.05 (s, 1H), 7.53(d, J = 8.8 Hz, 2H), 7.51−7.49 (m, 3H), 6.92 (d, J = 8.8 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 160.3, 159.3, 152.8, 150.2, 147.1, 131.2, 129.5, 129.4, 127.4, 126.2, 126.0, 121.8, 119.3, 114.7, 60.7, 55.4, 13.6; HRMS (ESI) m/z calcd for $C_{22}H_{18}N_2O_5$ [M + Na]$^+$ 413.1113, found 413.1115.

General Procedure for Copper(I)-Catalyzed Domino Reactions of 2-Phenyl- and 2-(2-Thienyl)-4-[(aryl/heteroaryl)-(methylthio)methylene]-5-oxazolones (4a−h) with Activated Methylene Isocyanides (12a−e): Synthesis of 2,5-Bis(aryl/heteroaryl) 4′-Substituted 4,5′-Bisoxazoles (8aa−8he). To a stirred solution of the corresponding 5-oxazolone **4** (0.3 mmol) and appropriate activated methylene isocyanides **12** (0.3 mmol) in DMF (2 mL) was added CuI (5.7 mg, 10 mol %) under a nitrogen atmosphere, followed by addition of Cs_2CO_3 (97.7 mg, 0.3 mmol). The reaction mixture was then stirred at 90 °C for 4−6 h (monitored by TLC). It was then poured into saturated NH_4Cl (50 mL) solution and extracted with EtOAc (3 × 25 mL), the extract was washed with water (2 × 30 mL) and brine (30 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give crude bisoxazoles **8aa−8he**, which were purified by column chromatography over silica gel using EtOAc/hexane as eluent.

*2-Phenyl-5-(4-methoxyphenyl)-4′-carbethoxy-4,5′-bisoxazole (**8aa**):* obtained from oxazolone **4a** and isocyanide **12a**, as a pale yellow solid (89.9 mg, 75%) (under copper-catalyzed conditions); spectral and analytical data have been given earlier.

*2-Phenyl-5-(3,4-dimethoxyphenyl)-4′-carbethoxy-4,5′-bisoxazole (**8ba**):* obtained from oxazolone **4b** and isocyanide **12a**, pale yellow solid (88.7 mg, 75%); mp 112−114 °C; R_f = 0.52 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3116, 2932, 2837, 1716, 1511, 1256, 1098, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.13 (m, 2H), 8.06 (s, 1H),

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7.51−7.50 (m, 3H), 7.19 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.3, 151.0, 150.9, 150.5, 149.3, 131.0, 130.3, 129.0, 127.5, 126.8, 126.7, 122.4, 120.5, 119.3, 111.4, 108.8, 61.5, 56.1, 56.0, 14.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}N_2O_6$ $[M + Na]^+$ 443.1219, found 443.1225.

*2-Phenyl-5-(2-thienyl)-4′-carbethoxy-4,5′-bisoxazole (**8ca**):* obtained from oxazolone **4c** and isocyanide **12a**, gray solid (96.0 mg, 79%); mp 138−140 °C; R_f = 0.5 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3111, 2928, 1725, 1297, 1184, 1079, 1026, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 8.07 (s, 1H), 7.52−7.50 (m, 3H), 7.40 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.36 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.08 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.3, 151.1, 147.2, 146.7, 131.2, 131.0, 129.1, 128.8, 128.0, 127.7, 126.9, 126.8, 126.5, 122.8, 61.5, 14.1; HRMS (ESI) m/z calcd for $C_{19}H_{14}N_2O_4S$ $[M + Na]^+$ 389.0572, found 389.0573.

*2-Phenyl-5-(1-methyl-2-pyrrolyl)-4′-carbethoxy-4,5′-bisoxazole (**8da**):* obtained from oxazolone **4d** and isocyanide **12a**, gray solid (97.4 mg, 80%); mp 136−138 °C; R_f = 0.52 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3116, 2996, 1727, 1511, 1180, 1085, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.08 (m, 2H), 7.99 (s, 1H), 7.50−7.49 (m, 3H), 6.78 (dd, J = 2.6 Hz, 1.6 Hz, 1H), 6.30 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.13 (dd, J = 3.6 Hz, 2.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.6, 150.6, 147.8, 145.0, 131.0, 129.7, 129.1, 126.9, 126.6, 126.3, 124.2, 120.1, 112.8, 109.0, 61.4, 36.0, 14.2; HRMS (ESI) m/z calcd for $C_{20}H_{17}N_3O_4$ $[M + Na]^+$ 386.1117, found 386.1116.

*2-Phenyl-5-(1-methyl-3-indolyl)-4′-carbethoxy-4,5′-bisoxazole (**8ea**):* obtained from oxazolone **4e** and isocyanide **12a**, white solid (92.5 mg, 78%); mp 168−170 °C; R_f = 0.35 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3105, 2978, 1706, 1587, 1410, 1278, 1203, 1114, 731; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.13−8.11 (m, 2H), 7.78 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.64−7.56 (m, 4H), 7.30 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.7, 150.6, 148.9, 148.7, 137.0, 130.7, 130.0, 129.1, 128.5, 127.2, 126.5, 125.5, 123.2, 121.5, 121.0, 120.8, 110.0, 103.5, 61.4, 33.4, 14.1; HRMS (ESI) m/z calcd for $C_{24}H_{19}N_3O_4$ $[M + Na]^+$ 436.1273, found 436.1276.

*2-Phenyl-5-(3-pyridyl)-4′-carbethoxy-4,5′-bisoxazole (**8fa**):* obtained from oxazolone **4f** and isocyanide **12a**, brown solid (87.8 mg, 72%); mp 146−148 °C; R_f = 0.5 (6/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3079, 2925, 1719, 1417, 1297, 1095, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 1.6 Hz, 1H), 8.62 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.16−8.14 (m, 2H), 8.08 (s, 1H), 7.89−7.86 (ddd, J = 8.0 Hz, 2.2 Hz, 0.8 Hz, 1H), 7.53−7.52 (m, 3H), 7.35 (ddd, J = 8.0 Hz, 4.8 Hz, 0.8 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 160.6, 151.2, 150.4, 148.1, 147.5, 147.1, 133.0, 131.5, 130.7, 129.2, 126.9, 126.4, 125.1, 124.2, 123.6, 61.6, 14.1; HRMS (ESI) m/z calcd for $C_{20}H_{15}N_3O_4$ $[M + Na]^+$ 384.0960, found 384.0964.

*2,5-Bis(2-thienyl)-4′-carbethoxy-4,5′-bisoxazole (**8ga**):* obtained from oxazolone **4g** and isocyanide **12a**, brown solid (79.3 mg, 71%); mp 163−165 °C; R_f = 0.2 (4/6 EtOAc/hexane); IR (KBr, cm^{-1}) 3101, 2933, 2852, 1727, 1587, 1175, 1050, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.80 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.51 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 7.39 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.35 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.16 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.07 (dd, J = 4.8 Hz, 3.6 Hz, 1H) 4.21 (q, J = 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 156.6, 151.2, 146.9, 146.1, 131.1, 129.5, 128.9, 128.7, 128.5, 128.2, 127.9, 127.7, 126.9, 122.6, 61.5, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{12}N_2O_4S_2$ $[M + H]^+$ 373.0317, found 373.0304.

*2-Phenyl-5-(4-methoxyphenyl)-4′-(4-tosyl)-4,5′-bisoxazole (**8ab**):* obtained from oxazolone **4a** and isocyanide **12b**, pale yellow solid (106.0 mg, 73%); mp 183−185 °C; R_f = 0.54 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3148, 2929, 2862, 1499, 1334, 1264, 1148, 1091; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.14−8.11 (m, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.65−7.61 (m, 3H), 7.48 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.3, 151.9, 151.0, 146.1, 145.1, 139.3, 136.8, 131.0, 129.8, 129.1, 128.9, 128.2, 126.9, 126.6, 120.7, 119.7, 114.6, 55.5, 21.8; HRMS (ESI) m/z calcd for $C_{26}H_{20}N_2O_5S$ $[M + Na]^+$ 495.0991, found 495.0994.

*2-Phenyl-5-(3,4-dimethoxyphenyl)-4′-(4-tosyl)-4,5′-bisoxazole (**8bb**):* obtained from oxazolone **4b** and isocyanide **12b**, pale yellow solid (94.7 mg, 67%); mp 188−190 °C; R_f = 0.52 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3015, 2932, 2829, 1511, 1340, 1264, 1142, 1021; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.16−8.13 (m, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.65−7.62 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 151.9, 151.1, 150.7, 149.4, 146.1, 145.2, 139.5, 136.7, 131.1, 129.8, 129.1, 128.8, 126.8, 126.7, 120.9, 119.81, 119.79, 111.5, 109.3, 56.1, 56.0, 21.8; HRMS (ESI) m/z calcd for $C_{27}H_{22}N_2O_6S$ $[M + Na]^+$ 525.1096, found 525.1093.

*2-Phenyl-5-(1-methyl-3-indolyl)-4′-(4-tosyl)-4,5′-bisoxazole (**8eb**):* obtained from oxazolone **4e** and isocyanide **12b**, pale yellow solid (109.5 mg, 77%); mp 216−218 °C; R_f = 0.45 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3130, 3066, 1649, 1574, 1328, 1152, 913; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.46 (s, 1H), 8.24−8.21 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 6.8 Hz, 1.6 Hz, 2H), 7.66−7.57 (m, 4H), 7.54 (d, J = 8.4 Hz, 1H), 7.35−7.30 (m, 3H), 7.25−7.21 (m, 1H), 3.86 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 153.0, 149.2, 145.2, 145.0, 137.6, 136.7, 136.4, 131.0, 130.2, 129.8, 129.5, 127.9, 126.3, 125.9, 124.5, 122.7, 121.4, 119.7, 118.4, 110.8, 100.9, 33.0, 21.1; HRMS (ESI) m/z calcd for $C_{28}H_{21}N_3O_4S$ $[M + Na]^+$ 518.1150, found 518.1155.

*2-Phenyl-5-(3-pyridyl)-4′-(4-tosyl)-4,5′-bisoxazole (**8fb**):* obtained from oxazolone **4f** and isocyanide **12b**, brown solid (107.8 mg, 72%); mp 190−192 °C; R_f = 0.56 (6/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3123, 2928, 1335, 1152, 705, 667, 598; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 1.6 Hz, 1H), 8.66 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.16−8.14 (m, 2H), 8.00 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.89 (ddd, J = 9.0 Hz, 2.0 Hz, 0.8 Hz 1H), 7.57−7.53 (m, 3H), 7.38 (ddd, J = 9.0 Hz, 4.8 Hz, 0.4 Hz, 1H), 7.3 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 153.9, 150.6, 148.6, 146.6, 145.5, 143.7, 138.6, 136.0, 133.6, 131.8, 130.0, 129.5, 128.0, 126.6, 125.6, 124.2, 123.0, 122.8, 21.1; HRMS (ESI) m/z calcd for $C_{24}H_{17}N_3O_4S$ $[M + Na]^+$ 466.0837, found 466.0838.

*2,5-Bis(2-thienyl)-4′-(4-tosyl)-4,5′-bisoxazole (**8gb**):* obtained from oxazolone **4g** and isocyanide **12b**, off-white solid (95.4 mg, 70%); mp 128−130 °C; R_f = 0.5 (4/6 EtOAc/hexane); IR (KBr, cm^{-1}) 3109, 2954, 1587, 1330, 1153, 712, 602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 2H), 7.99 (s, 1H), 7.79 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.53 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.43 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 7.39 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H),7.18 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 7.09 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 150.9, 146.8, 145.2, 144.8, 139.9, 136.8, 129.8, 129.6, 129.1, 129.0, 128.8, 128.34, 128.26, 128.1, 128.0, 127.6, 121.3, 21.8; HRMS (ESI) m/z calcd for $C_{21}H_{14}N_2O_4S_3$ $[M + H]^+$ 455.0194, found 455.0174.

*2-Phenyl-5-(4-methoxyphenyl)-4′-(N-morpholinocarbonyl)-4,5′-bisoxazole (**8ac**):* obtained from oxazolone **4a** and isocyanide **12c**, yellow solid (112.6 mg, 85%); mp 163−165 °C; R_f = 0.2 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3142, 2960, 2852, 1630, 1505, 1436, 1253, 1121, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.98 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.51−7.47 (m, 3H), 6.98 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.70−3.56 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 160.3, 159.4, 151.6, 148.3, 142.0, 131.3, 131.1, 129.3, 128.2, 126.07, 126.0, 122.7, 119.2, 114.4, 66.0, 65.8, 55.4, 46.7, 41.7; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_3O_5$ $[M + Na]^+$ 454.1379, found 454.1383.

*2-Phenyl-5-(2-thienyl)-4′-(N-morpholinocarbonyl)-4,5′-bisoxazole (**8cc**):* obtained from oxazolone **4c** and isocyanide **12c**, gray solid (120.3 mg, 89%); mp 218−220 °C; R_f = 0.25 (8/2 EtOAc/hexane); IR (KBr, cm^{-1}) 3105, 2902, 2859, 1625, 1498, 1114, 919, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 2H), 8.02 (s, 1H), 7.66 (dd, J =

dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

3.6 Hz, 1.2 Hz, 1H), 7.50−7.49 (m, 3H), 7.46 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.14 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 3.76 (br s, 4H), 3.66 (br s, 2H), 3.59 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 159.5, 151.8, 143.4, 141.0, 131.8, 131.5, 129.4, 129.1, 128.3, 127.9, 127.6, 126.2, 125.6, 123.2, 66.1, 65.8, 46.7, 41.8; HRMS (ESI) m/z calcd for $C_{21}H_{17}N_3O_4S$ [M + Na]$^+$ 430.0837, found 430.0833.

*2-Phenyl-5-(1-methyl-3-indolyl)-4′-(N-morpholinocarbonyl)-4,5′-bisoxazole (**8ec**):* obtained from oxazolone **4e** and isocyanide **12c**, yellow solid (122.6 mg, 94%); mp 220−222 °C; R_f = 0.2 (9/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3135, 2902, 2852, 1625, 1568, 1114, 737; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.32 (s, 1H), 8.19−8.16 (m, 2H), 8.04 (s, 1H), 8.00 (dt, J = 7.2 Hz, 1.2 Hz, 1H), 7.63−7.54 (m, 4H), 7.34−7.30 (m, 1H), 7.26−7.22 (m, 1H), 3.97 (s, 3H), 3.58 (br s, 4H), 3.48 (br s, 2H), 3.41 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 158.7, 151.3, 146.0, 141.9, 136.7, 130.9, 130.4, 130.3, 129.4, 126.3, 125.8, 125.0, 122.6, 121.4, 121.1, 120.0, 110.7, 101.3, 66.0, 65.8, 46.7, 41.8, 33.1; HRMS (ESI) m/z calcd for $C_{26}H_{22}N_4O_4$ [M + Na]$^+$ 477.1539, found 477.1535.

*2-Phenyl-5-(3-pyridyl)-4′-(N-morpholinocarbonyl)-4,5′-bisoxazole (**8fc**):* obtained from oxazolone **4f** and isocyanide **12c**, pale yellow solid (118.1 mg, 87%); mp 210−212 °C; R_f = 0.40 (1/1 DCM/acetone); IR (KBr, cm^{-1}) 3092, 2978, 2865, 1625, 1505, 1108, 957; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.66 (br s, 1H), 8.12−8.09 (m, 2H), 8.04 (br d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.54−7.49 (m, 3H), 7.44−7.41 (m, 1H), 3.76−3.67 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 161.6, 150.3, 150.1, 147.7, 146.1, 143.5, 134.0, 132.7, 131.5, 129.1, 126.9, 126.4, 125.9, 123.7, 66.9, 66.7, 47.5, 42.5; HRMS (ESI) m/z calcd for $C_{22}H_{18}N_4O_4$ [M + Na]$^+$ 425.1226, found 425.1228.

*2-(2-Thienyl)-5-(benzo[d][1,3]dioxol-5-yl)-4′-(N-morpholinocarbonyl)-4,5′-bisoxazole (**8hc**):* obtained from oxazolone **4h** and isocyanide **12c**, pale yellow solid (113.7 mg, 84%); mp 188−190 °C; R_f = 0.30 (8/2 EtOAc/hexane); IR (KBr, cm^{-1}) 3096, 2926, 2844, 1640, 1501, 1457, 1243, 1104, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.73 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.48 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.23 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.15−7.13 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.04 (s, 2H), 3.75−3.60 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 156.8, 150.0, 148.9, 148.4, 148.1, 143.4, 132.2, 129.2, 129.1, 128.6, 128.2, 123.2, 121.5, 121.2, 108.9, 107.1, 101.7, 66.8, 66.7, 47.4, 42.5; HRMS (ESI) m/z calcd for $C_{22}H_{17}N_3O_6S$ [M + H]$^+$ 452.0916, found 452.0903.

*2-Phenyl-5-(4-methoxyphenyl)-4′-(4-chlorophenyl)-4,5′-bisoxazole (**8ad**):* obtained from oxazolone **4a** and isocyanide **12d**, white solid (120.0 mg, 91%); mp 158−160 °C; R_f = 0.53 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3129, 2829, 1607, 1511, 1256, 1180, 1091, 931, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.13 (m, 2H), 8.05 (s, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.52−7.49 (m, 3H), 7.45 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 160.3, 150.8, 149.4, 138.6, 136.9, 134.1, 130.8, 129.4, 128.9, 128.5, 128.4, 127.5, 126.8, 126.5, 123.4, 119.8, 114.2, 55.4; HRMS (ESI) m/z calcd for $C_{25}H_{17}ClN_2O_3$ [M + Na]$^+$ 451.0825, found 451.0821.

*2-Phenyl-5-(2-thienyl)-4′-(4-chlorophenyl)-4,5′-bisoxazole (**8cd**):* obtained from oxazolone **4a** and isocyanide **12d**, white solid (110.1 mg, 82%); mp 150−152 °C; R_f = 0.65 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3085, 2991, 1561, 1518, 1479, 1089, 837, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.12 (m, 2H), 8.08 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.53−7.51 (m, 3H), 7.35 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.30−7.28 (m, 3H), 7.01 (dd, J = 5.2 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 151.0, 145.3, 137.81, 137.76, 134.4, 131.2, 129.6, 129.1, 128.7, 128.6, 128.0, 127.7, 126.84, 126.79, 126.6, 124.2; HRMS (ESI) m/z calcd for $C_{22}H_{13}ClN_2O_2S$ [M + Na]$^+$ 427.0284, found 427.0286.

*2-Phenyl-5-(1-methyl-2-pyrrolyl)-4′-(4-chlorophenyl)-4,5′-bisoxazole (**8dd**):* obtained from oxazolone **4d** and isocyanide **12d**, off-white solid (96.9 mg, 72%); mp 116−118 °C; R_f = 0.6 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3117, 2928, 2852, 1518, 1486, 1089, 932, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.99 (s, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.51−7.50 (m, 3H), 7.29 (d, J = 8.6 Hz, 2H), 6.71 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 6.28 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.087 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 150.5, 143.0, 138.5, 136.8, 134.0, 130.9, 129.6, 129.0, 128.7, 128.3, 126.8, 126.4, 126.0, 125.5, 119.7, 113.2, 108.8, 35.7; HRMS (ESI) m/z calcd for $C_{23}H_{16}ClN_3O_2$ [M + Na]$^+$ 424.0829, found 424.0829.

*2-Phenyl-5-(1-methyl-3-indolyl)-4′-(4-chlorophenyl)-4,5′-bisoxazole (**8ed**):* obtained from oxazolone **4e** and isocyanide **12d**, reddish brown solid (93.4 mg, 72%); mp 165−167 °C; R_f = 0.5 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3130, 3054, 2928, 1574, 1479, 1102, 907, 731; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.37 (s, 1H), 8.21−8.18 (m, 2H), 7.96−7.90 (m, 3H), 7.64−7.57 (m, 4H), 7.48 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 7.33−7.27 (m, 3H), 7.24−7.19 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.7, 147.0, 139.3, 136.9, 136.2, 133.9, 130.7, 129.8, 129.1, 128.8, 128.6, 128.4, 127.3, 126.5, 125.5, 123.1, 122.4, 121.3, 120.8, 109.9, 103.0, 33.2; HRMS (ESI) m/z calcd for $C_{27}H_{18}ClN_3O_2$ [M + Na]$^+$ 474.0985, found 474.0982.

*2-Phenyl-5-(3-pyridyl)-4′-(4-chlorophenyl)-4,5′-bisoxazole (**8fd**):* obtained from oxazolone **4f** and isocyanide **12d**, pale yellow solid (99.8 mg, 74%); mp 148−150 °C; R_f = 0.42 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3142, 3035, 1662, 1555, 1518, 1089, 938, 699; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.88 (d, J = 2.1 Hz, 1H), 8.56 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 8.44 (s, 1H), 8.23−8.20 (m, 2H), 8.04−8.01 (ddd, J = 8.0 Hz, 2.1 Hz, 1.2 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.63−7.60 (m, 3H), 7.42 (ddd, J = 8.0 Hz, 4.8 Hz, 1.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 151.1, 150.1, 147.2, 146.2, 137.8, 137.7, 134.6, 133.1, 131.5, 129.3, 129.2, 128.8, 128.7, 126.9, 126.8, 126.5, 123.9, 123.5; HRMS (ESI) m/z calcd for $C_{23}H_{14}ClN_3O_2$ [M + H]$^+$ 400.0853, found 400.0857.

*2,5-Bis(2-thienyl)-4′-(4-chlorophenyl)-4,5′-bisoxazole (**8gd**):* obtained from oxazolone **4g** and isocyanide **12d**, pale yellow solid (87.5 mg, 71%); mp 158−160 °C; R_f = 0.5 (2/8 EtOAc/hexane); IR (KBr, cm^{-1}) 3101, 2926, 2859, 1720, 1602, 1521, 1234, 1094, 837, 712; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.91 (dd, J = 5.1 Hz, 1.2 Hz, 1H), 7.89 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.71 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.41 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.30 (dd, J = 5.1 Hz, 4.0 Hz, 1H), 7.13 (dd, J = 4.8 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 151.1, 144.8, 137.9, 137.5, 130.4, 129.54, 129.49, 128.97, 128.93, 128.7, 128.6, 128.3, 128.2, 127.9, 127.7, 126.8, 124.0; HRMS (ESI) m/z calcd for $C_{20}H_{11}ClN_2O_2S_2$ [M + H]$^+$ 411.0029, found 411.0015.

*2-Phenyl-5-(4-methoxyphenyl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8ae**):* obtained from oxazolone **4a** and isocyanide **12e**, off-white solid (92.5 mg, 78%); mp 158−160 °C; R_f = 0.2 (4/6 EtOAc/hexane); IR (KBr, cm^{-1}) 2947, 2933, 2845, 1734, 1602, 1433, 1271, 1168, 845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.9 Hz, 2H), 8.13−8.16 (m, 2H), 8.08 (s, 1H), 7.73 (dd, J = 4.9 Hz, 1.6 Hz, 2H), 7.50−7.54 (m 3H), 7.49 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.6, 151.1, 150.0, 146.1, 141.0, 138.5, 135.6, 131.1, 129.1, 127.7, 126.8, 126.7, 123.1, 121.4, 119.8, 114.5, 55.2; HRMS (ESI) m/z calcd for $C_{24}H_{17}N_3O_3$ [M + H]$^+$ 396.1348, found 396.1337.

*2-Phenyl-5-(3,4-dimethoxyphenyl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8be**):* obtained from oxazolone **4b** and isocyanide **12e**, yellow solid (86.1 mg, 72%); mp 159−161 °C; R_f = 0.4 (7/3 EtOAc/hexane); IR (KBr, cm^{-1}) 3060, 2934, 2840, 1599, 1511, 1259, 1026, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 4.8 Hz, 1.6 Hz, 2H), 8.16−8.14 (m, 2H), 8.09 (s, 1H), 7.74 (dd, J = 4.8 Hz, 1.6 Hz, 2H), 7.54−7.52 (m, 3H), 7.16 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.1, 150.5, 150.1, 150.0, 149.3, 141.1, 138.5, 135.8, 131.2, 139.1, 126.8, 126.7, 123.2, 121.3, 119.8, 119.6, 111.5, 109.1, 56.1, 56.0; HRMS (ESI) m/z calcd for $C_{25}H_{19}N_3O_4$ [M + H]$^+$ 426.1454, found 426.1454.

*2-Phenyl-5-(2-thienyl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8ce**):* obtained from oxazolone **4c** and isocyanide **12e**, gray solid (86.2 mg, 70%); mp 128−130 °C; R_f = 0.55 (7/3 EtOAc/hexane); IR (KBr, cm^{-1}) 3085, 3060, 2928, 1662, 1599, 1410, 906, 705, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 6.0 Hz, 2H), 8.15−8.12 (m, 2H), 8.12 (s, 1H), 7.78 (dd, J = 4.8 Hz, 1.6 Hz, 2H), 7.55−7.51 (m, 3H), 7.38 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.34 (dd, J = 3.6 Hz, 1.2 Hz, 1H),

dx.doi.org/10.1021/jo400317g | J. Org. Chem. 2013, 78, 3948−3960

7.032 (dd, J = 5.2 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.1, 150.0, 145.7, 140.2, 138.6, 136.3, 131.4, 129.2, 128.4, 128.04, 128.01, 127.1, 126.8, 126.5, 123.7, 121.6; HRMS (ESI) m/z calcd for $C_{21}H_{13}N_3O_2S$ $[M + H]^+$ 372.0807, found 372.0809.

*2-Phenyl-5-(1-methyl-2-pyrrolyl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8de**):* obtained from oxazolone **4d** and isocyanide **12e**, brown solid (98.8 mg, 80%); mp 148−150 °C; R_f = 0.53 (7/3 EtOAc/hexane); IR (KBr, cm^{-1}) 3092, 3061, 3006,1611, 1572, 1486, 1094, 937; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.8 Hz, 1.4 Hz, 2H), 8.10−8.08 (m, 2H), 8.02 (s, 1H), 7.78 (dd, J = 4.8 Hz, 1.4 Hz, 2H), 7.53−7.50 (m, 3H), 6.73 (dd, J = 2.8 Hz, 1.6 Hz, 1H), 6.32 (dd, J = 4.0 Hz, 1.6 Hz, 1H), 6.09 (dd, J = 4.0 Hz, 2.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 150.7, 149.7, 143.4, 140.7, 138.6, 135.3, 131.0, 129.0, 126.6, 126.4, 126.2, 125.0, 121.6, 119.5, 113.4, 108.9, 35.8; HRMS (ESI) m/z calcd for $C_{22}H_{16}N_4O_2$ $[M + H]^+$ 369.1352, found 369.1354.

*2-Phenyl-5-(1-methyl-3-indolyl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8ee**):* obtained from oxazolone **4e** and isocyanide **12e**, yellow solid (96.0 mg, 80%); mp 188−190 °C; R_f = 0.33 (7/3 EtOAc/hexane); IR (KBr, cm^{-1}) 3061, 2810, 1619, 1580, 1486, 1376, 1110, 898; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.51 (dd, J = 4.6 Hz, 1.6 Hz, 2H), 8.12 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 4.6 Hz, 1.6 Hz, 2H), 7.72 (s, 1H), 7.65−7.59 (m, 3H), 7.52 (d, J = 8.4 Hz, 1H), 7.29 (td, J = 7.7 Hz, 1.2 Hz, 1H), 7.22 (td, J = 7.7 Hz, 1.2 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.8, 149.7, 147.5, 141.7, 138.8, 137.0, 134.8, 130.8, 129.1, 128.8, 127.2, 126.5, 125.4, 123.2, 122.0, 121.49, 121.46, 120.8, 110.1, 103.0, 33.4; HRMS (ESI) m/z calcd for $C_{26}H_{18}N_4O_2$ $[M + H]^+$ 419.1508, found 419.1511.

*2-Phenyl-5-(3-pyridyl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8fe**):* obtained from oxazolone **4f** and isocyanide **12e**, pale yellow solid (96.4 mg, 78%); mp 138−140 °C; R_f = 0.40 (0.5/9.5 MeOH/DCM); IR (KBr, cm^{-1}) 3091, 3040, 1607, 1550, 1480, 1402, 1091, 938, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (br d, J = 2.0 Hz, 1H), 8.59−8.57 (m, 3H), 8.17−8.15 (m, 2H), 8.09 (s, 1H), 7.86 (ddd, J = 8.0 Hz, 2.2 Hz, 1.6 Hz, 1H), 7.79 (dd, J = 4.4 Hz, 1.6 Hz, 2H), 7.57−7.52 (m, 3H), 7.31 (ddd, J = 8.0 Hz, 5.0 Hz, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 151.2, 150.3, 150.1, 147.4, 146.7, 140.0, 138.3, 136.4, 133.3, 131.7, 129.3, 126.9, 126.4 126.3, 123.8, 123.6, 121.7; HRMS (ESI) m/z calcd for $C_{22}H_{14}N_4O_2$ $[M + H]^+$ 367.1195, found 367.1193.

*2-(2-Thienyl)-5-(benzo[d][1,3]dioxol-5-yl)-4′-(4-pyridyl)-4,5′-bisoxazole (**8he**):* obtained from oxazolone **4h** and isocyanide **12e**, off-white solid (89.7 mg, 72%); mp 167−169 °C; R_f = 0.40 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3388, 3094, 2903, 1609, 1506, 1477, 1249, 1035, 720; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.54 (br s, 2H), 7.93 (dd, J = 3.6 Hz, 1.0 Hz, 1H), 7.85 (dd, J = 5.2 Hz, 1.0 Hz, 1H), 7.67 (d, J = 3.6 Hz, 2H), 7.29 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.06−7.04 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 151.3, 149.2, 149.1, 149.0, 148.2, 140.8, 139.1, 135.5, 129.5, 128.9, 128.8, 128.3, 123.1, 120.9, 120.7, 108.9, 106.3, 101.7; HRMS (ESI) m/z calcd for $C_{22}H_{13}N_3O_4S$ $[M + H]^+$ 416.0705, found 416.0705.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. C. N. R. Rao, FRS, for encouragement, the Council of Scientific and Industrial Research (CSIR) for fellowships (to S.Y. and A.A.), New Delhi, and JNCASR, Bangalore, for financial support and the Indian National Science Academy, New Delhi, for an INSA Senior Scientist position (to H.I.).

■ DEDICATION

Dedicated to Professor Yoshinori Yamamoto on his 70th Birthday.

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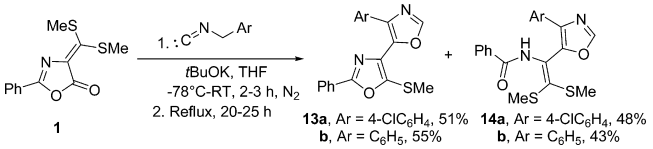

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