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Synthesis of 2,4,5-Trisubstituted Thiazoles via Lawesson's Reagent-Mediated Chemoselective Thionation–Cyclization of Functionalized Enamides

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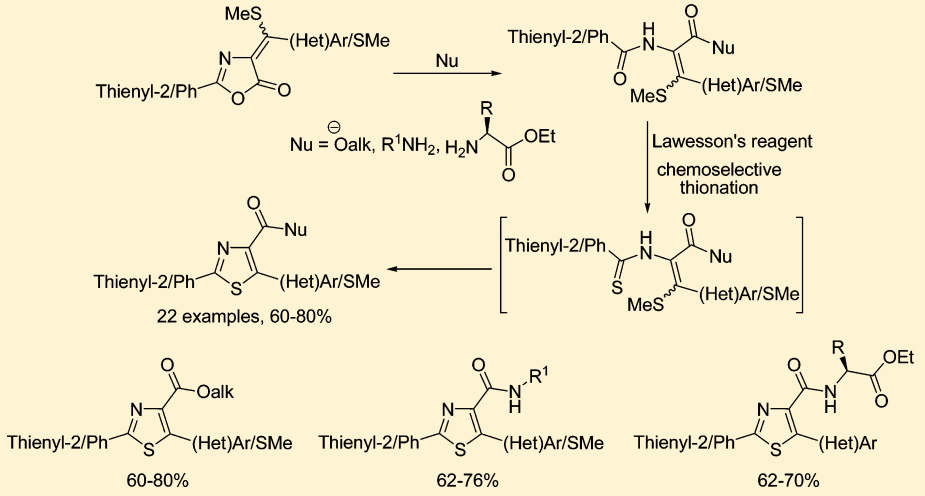
Supporting Information



ABSTRACT: An efficient route to 2-phenyl/(2-thienyl)-5-(het)aryl/(methylthio)-4-functionalized thiazoles via one-step chemoselective thionation–cyclization of highly functionalized enamides mediated by Lawesson's reagent is reported. These enamide precursors are obtained by nucleophilic ring-opening of 2-phenyl/(2-thienyl)-4-[bis(methylthio)/(methylthio)(het)-arylmethylene]-5-oxazolones with alkoxides and a variety of primary aromatic/aliphatic amines or amino acid esters, leading to the introduction of an ester, an N-substituted carboxamide, or a peptide functionality in the 4-position of the product thiazoles.

Thiazoles[1] are the most commonly encountered heterocycles among the compounds of biological interest found in the bioactive natural products of microbial and marine origin (particularly nonribosomal peptides) where they exhibit important biological activities[1,2a] such as antitumor, antifungal, antibiotic, antiviral, and antibacterial as well as acting as peptide mimetics[2a,b] and enzyme inhibitors.[2c−e] In nature, a thiazolium ring is the chemically active center of the coenzyme derived from vitamin B_1 (thiamine).[3] Synthetic thiazoles also occupy a prominent position in the drug-discovery process, and this ring system is found in several marketed drugs.[4] In addition, this class of compounds has broad applications, including use as functional materials,[5a] as liquid crystals for ferroelectric display,[5b] and as cosmetic sunscreens.[5c] Therefore, in view of the structural diversity of the complex naturally occurring thiazoles along with the broad application of synthetic analogs in various fields, new methods continue to be developed for thiazole synthesis.[1,6]

The two most common approaches for substituted thiazoles consist of either functionalization of a pre-existing core[1,7] or ring assembly from acyclic precursors.[1] Between these two approaches, the latter route has a greater potential for the rapid generation of diversity in functionalized thiazoles. Within this group, Hantzsch thiazole synthesis[8] (and its modified versions),[9] entailing the condensation of a suitably substituted α-haloketone (or its equivalents) with thioamide, has proven to be a powerful method for the synthesis of 2,4,5-substituted thiazoles. Other methods of synthesizing substituted thiazoles include the reaction of α-aminonitriles with CS_2, COS, isothiocyanates, and dithiocarboxlic acids.[4b,9h] The thionation–cyclization of α-acylaminoketones (or related precursors) with various thionation agents (e.g., P_2S_5, Lawesson's or Belleau's reagent, H_2S) (Gabriel synthesis) is also a promising method for the synthesis of substituted thiazoles.[10] However, this method is not well explored, probably because of the lack of availability of structural variants of α-acylaminocarbonyl compounds. Recently, Chen and co-workers have reported the synthesis of 2-substituted 4-phenyl-5-aminothiazoles in moderate yields, involving the thionation of α-acylglycinamides with either Lawesson's or Belleau's reagent and subsequent TFAA-mediated cyclization of thioamide intermediates.[11] Later, the

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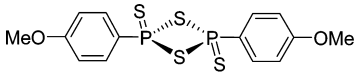
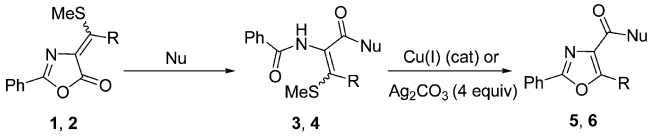
same group developed a four-component Ugi reaction using ammonia as the amine component, resulting in a simple one-step assembly of diamide precursors that were transformed into a library of 2,4-substituted 5-primary or secondary amino-thiazoles by thionation with Lawesson's reagent; however, this reaction gave moderate yields.[12] Sanz-Cervera and co-workers[13] have recently described the efficient fluorous and solution-phase synthesis of a small library of 2,5-substituted thiazole-4-carboxylic esters as potential antibacterial compounds through the thionation and cyclization of α-amido-β-ketoesters (obtained by double acylation of protected glycinates) with Lawesson's reagent.



Lawesson's Reagent (LR)

Our own interest in thiazole synthesis derives from our recently reported protocol for the efficient synthesis of 2-phenyl-5-(methylthio)/(het)aryl-4-functionlized oxazoles (**5** and **6**) from the common 2-phenyl-4-[(methylthio)-het(aryl)/bis(methylthio)methylene]-5-oxazolone precursors **1** and **2** (Scheme 1).[14,15] Oxazolones **1** and **2** are shown to

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



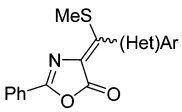
1, **2** **3**, **4** **5**, **6**

1, **3**, **5**, R= Substituted (het)aryl; **2**, **4**, **6**, R= SMe; Nu = $\overset{\ominus}{O}$Alk, NH(R^1R^2), R^3MgX

undergo facile ring-opening in the presence of various oxygen (alkoxides), nitrogen (primary/secondary amines), and carbon (Grignard reagents) nucleophiles, yielding functionalized enamide precursors, such as **3** or **4**, that on subsequent copper-catalyzed (for **3**) or silver carbonate-mediated (for **4**) 5-*endo* cyclization afford substituted oxazoles **5** and **6**, respectively, in high yields (Scheme 1).[14a,15a] In a continuation of this work along with our ongoing interest in the design and development of new synthesis methods for small molecule cheterocycles,[16] we further envisaged utilizing enamide precursors **3** and **4** to develop a synthesis method for 2,4,5-substituted thiazoles via thionation−cyclization of these intermediates in the presence of Lawesson's reagent (Schemes 2 and 3). In this Article, we now report the successful implementation of this strategy, providing an efficient chemoselective route for 2,4,5-functionalized thiazoles that display a high degree of diversity at various positions.

The desired 4-[(methylthio)-(het)arylmethylene]-2-phenyl/(2-thienyl)-5-oxazolone precursors **1a**−**j** and corresponding 4-[bis(methylthio)methylene] derivative **2** (Chart 1) were obtained in good yields according to our previously reported procedure.[14,15] We first examined the synthesis of 2-phenyl-5-(het)arylthiazole-4-carboxylates **8a**−**i** and corresponding 5-(methylthio)thiazole-4-carboxylate **9** via the thionation−cyclization of enamino esters **3a**−**i** and **4**, respectively, which were obtained in high yields by nucleophilic ring-opening of corresponding oxazolones **1** and **2** with various sodium alkoxides, as reported earlier (Scheme 2).[14a,15] The thionation−cyclization of enamide ester **3a** to thiazole-4-carboxylate **8a** was attempted first as a model substrate for the optimization of the reaction conditions. Thus, refluxing **3a** with 1 equiv of Lawesson's reagent in THF for a prolonged time yielded only unreacted starting material with no trace of thiazole **8a** (or thioamide **7a**). However, we found that a higher temperature reflux in toluene for 12 h resulted in efficient thionation as well as intramolecular cyclization of **3a**, furnishing ethyl 2-phenyl-4-(methoxyphenyl)thiazole-4-carboxylate **8a** in 68% yield. However, when **3a** was reacted with 2 equiv of Lawesson's reagent in refluxing toluene, the reaction was complete within 2 h, yielding **8a** in 70% yield (Scheme 2). Therefore, this optimized protocol (with 2 equiv of Lawesson's reagent) for the conversion of **3a** to **8a** was used throughout for the synthesis of other 5-(het)arylthiazole-4-carboxylates (**8b**−**i**), as shown in the Scheme 2. Thus the reaction was equally facile for the synthesis of other 5-arylthiazole-4-carboxylates (**8b**−**d**) that carry both electron-donating (**8b**−**c**) and electron-withdrawing (**8d**) substituents on the 5-aryl group. Interestingly, the thionation−cyclization of enamide *tert*-butyl carboxylate **3e** also proceeded smoothly without any side reactions, yielding corresponding *tert*-butyl thiazole-4-carboxylate **8e** in 75% yield. Similarly, enaminone carboxylic esters **3f**−**h** carrying various het(aryl) groups were also converted into corresponding 2-phenyl-5-(2-furyl)/(2-*N*-methylpyrrolyl)/(3-*N*-methylindolyl)-thiazoles **8f**−**h** in good yields under identical conditions that required prolonged refluxing (12 h) (Scheme 2). Further diversity at the 2- and 5-positions of product thiazoles **8** could be achieved by the synthesis of corresponding *n*-butyl 2,5-bis(2-thienyl)thiazole-4-carboxylate **8i** in 80% yield by the thionation−cyclization of enamino ester **3i** obtained by ring-opening of 2-thienyl-4-[methylthio(2-thienyl)methylene]-5-oxazolone **1h** with sodium *n*-butoxide (Scheme 2).[15b] The extension of the protocol to bis(methylthio)enamide carboxylate **4** (obtained by ring-opening of **2** with sodium ethoxide) also afforded the ethyl

Chart 1. 2-Phenyl/2-thienyl-4-[(methylthio)(het)aryl/bis(methylthio)methylene]-5-oxazolone Precursors 1a−j and 2



1a, Ar = 4-$MeOC_6H_4$

1b, Ar = 3,4-$(MeO)_2C_6H_3$

1c, Ar = 3,4-(methylenedioxy)C_6H_3

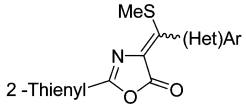
1d, Ar = 4-FC_6H_4

1e, (Het)Ar = 2-furyl

1f, (Het)Ar = 2-thienyl

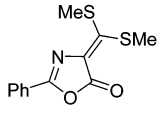
1g, (Het)Ar = 2-(N-methylpyrrolyl)

1h, (Het)Ar = 3-(N-methylindolyl)



1i, (Het)Ar= 2-thienyl

1j, Ar = 3,4-(methylenedioxy)C_6H_3



2

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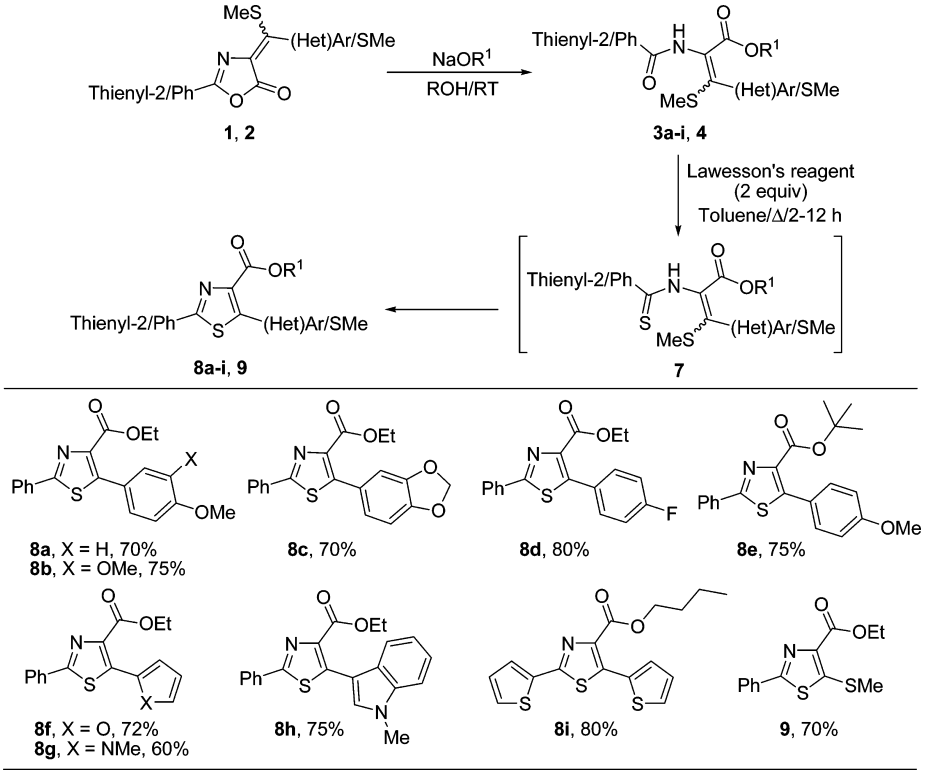
Scheme 2. Synthesis of 2-Phenyl/(2-thienyl)-5-(het)aryl/(methylthio)thiazole-4-carboxylates 8a−i and 9



2-phenyl-5-(methylthio)thiazole-4-carboxylate **9** in 70% yield (Scheme 2). The structures of all of these newly synthesized thiazoles were confirmed with the help of spectral and analytical data as well as by X-ray crystal structure analysis of thiazole ester **8b** (Figure S1, Supporting Information).

With the successful synthesis of 2,5-(het)arylthiazole-4-carboxylates **8** and **9** in hand, we next investigated the elaboration of this protocol for the synthesis of 2,5-(het)-arylthiazole-4-(N-aryl/alkyl)carboxamides **13a−k** and **14** by the one-step thionation−cyclization of corresponding enamides **10a−k** and **11** bearing a secondary amide functionality that was readily accessible by ring-opening of corresponding oxazolones **1** or **2** with primary aliphatic amines, aromatic amines, or amino acid esters, as reported earlier (Scheme 3).[14,15] It should be noted that enamide amide precursors **10** and **11** carry two secondary amide functionalities (though they are electronically different), and their transformation to corresponding thiazole-4-(N-substituted)carboxamides **13−14** in the presence of Lawesson's reagent is more challenging. This requires the chemoselective thionation of the enamide benzoylamino group, leading to enamide monothioamide intermediates **12** that upon intramolecular cyclization would afford desired thiazoles **13** and **14** (Scheme 3).

Therefore, we selected enamide anilide **10a** as the model substrate for the evaluation of the optimal conditions for its chemoselective thionation−cyclization to thiazole **13a** (Scheme 3). Initially, the thionation−cyclization of **10a** was conducted under reflux in toluene in the presence of 2 equiv of Lawesson's reagent under the previously described conditions for the conversion of enamide carboxylates **3** and **4** to thiazole 4-carboxylates **8** and **9** (Scheme 2). However, enamide amide intermediates **10** and **11** were found to be insoluble in toluene, and attempting the cyclization of **10a** to **13a** under toluene reflux for prolonged time (20 h) led to only the unreacted starting material. Interestingly, when **10a** was reacted with Lawesson's reagent (2 equiv) under reflux in THF for 12 h the analysis of the reaction mixture revealed the exclusive formation of only one product in reasonably good yield (65%), which to our delight was found to be desired 2-pheny-5-(4-methoxy-phenyl)-thiazole-4-(*N*-phenyl)carboxamide **13a** on the basis of its spectral and analytical data (Scheme 3).[17] Similarly, the other enamide anilide precursors **10b,c**, derived from ring-opening of oxazolones **1d,e** with 4-fluoroaniline, also underwent facile chemoselective monothionation−cyclization in the presence of Lawesson's reagent, furnishing corresponding 2-phenyl-5-(het)arylthiazole-4-carboxyanilides **13b,c** in good yields (Scheme 3). The structure of these thiazoles was further confirmed by X-ray crystal structure analysis of **13b** (Figure S2, Supporting Information). Similarly, 2,5-bis(2-thienyl)thiazole-4-carboxyanilide **13d** could also be obtained in 75% yield by the thionation−cyclization of enamide precursor **10d** (obtained by ring-opening of 2-(2-thienyl)-4-[(methylthio)(2-thienyl)-methylene]-5-oxazolone **1i** with 3,4,5-trimethoxyaniline). The versatility and scope of this chemoselective monothionation−cyclization protocol was further demonstrated by the efficient synthesis of 2-phenyl/(2-thienyl)-5-(het)arylthiazole-4-(*N*-alkyl)carboxamides **13e−g** in good yields from the respective enamide-*N*-(alkyl)amides **10e−g** under identical conditions (Scheme 3).

With the successful implementation of this strategy for the synthesis of 2,5-(het)arylthiazole-4-(*N*-aryl/alkyl)carboxamides **13a−g**, we further envisaged the interesting extension of this work for the synthesis of thiazole-based peptidomimetics such as **13h−k** that are known to display interesting biological activity.[2b,c] We were delighted to find that open-chain peptidoenamide precursors **10h−k** (obtained by ring-opening of **1** with various amino acid esters such as phenyalanine, valine, and tryptophan) were smoothly transformed into thiazole-based

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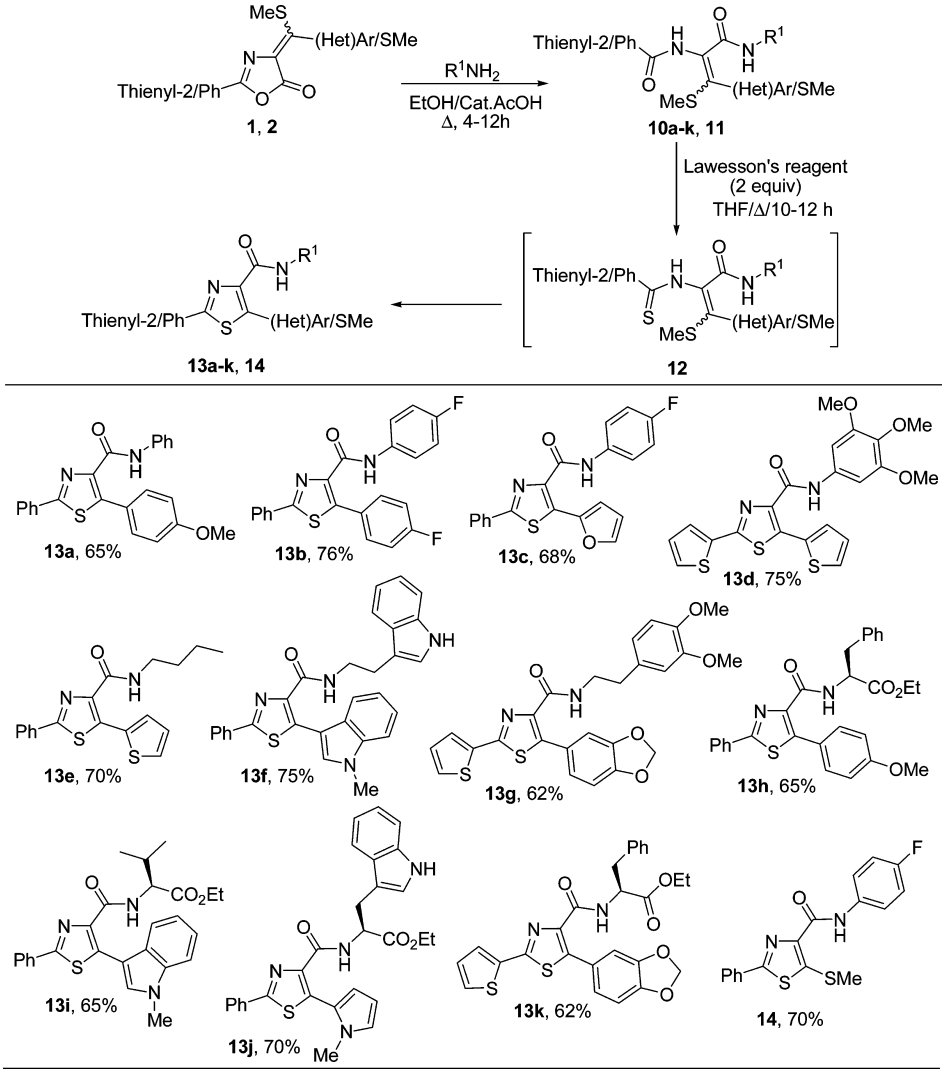
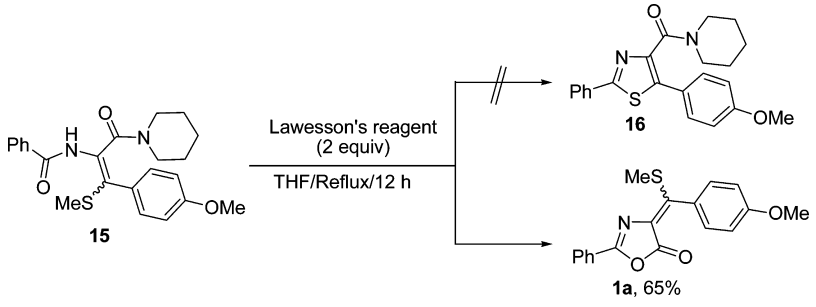
Scheme 3. Synthesis of N-Substituted 2-Phenyl/(2-Thienyl)-5-(het)aryl/(methylthio) Thiazole-4-carboxamides 13a–k and 14



Scheme 4. Attempted Thionation–Cyclization of *N*-Piperidino-enamide Amide 15



peptidomimetics **13h–k** with a range of 5-(het)aryl groups in good yields under these optimized reaction conditions (Scheme 3). Finally, corresponding bis[(methylthio)methylene]-enamide anilide **11** (obtained by ring-opening of 4-bis-(methylthio) methyleneoxazolone **2** with 4-fluoroaniline) also afforded corresponding 2-phenyl-5-(methylthio)thiazole-4-(*N*-4-fluorophenyl)carboxyanilide **14** in 70% yield (Scheme 2).

Interestingly, the attempted thionation–cyclization of tertiary amide **15** (derived from ring-opening of **1a** with piperidine) did not furnish desired thiazole-5-tertiary-amide **16**. The isolated product was characterized as 2-phenl-4-[(4-methoxyarylidene)(methylthio)]oxazolone **1a**, which was formed by the thermal-eliminative cyclization of **14**, presumably because of steric reasons (Scheme 4).

We have devised a useful and highly regio- and chemoselective protocol for the synthesis of 2,4,5-trisubstituted thiazoles via the one-step thionation–cyclization of functionalized enamide precursors in the presence of Lawesson's reagent. These enamide intermediates are readily available in high yields by nucleophilic ring-opening of a number of 4-[(methylthio)-(het)arylmethylene]-5-oxazolones with alkoxides or a variety of primary aliphatic amines, aromatic amines,

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and amino acid esters, offering a wide range of functional-group diversity at the 4- and 5-positions of the product thiazoles. Furthermore, the remarkable chemoselectivity observed in the facile thionation of the benzoylamino group (over the other secondary amide moiety) in enamides **10** and **11** is particularly noteworthy because the selective conversion of an amide to a thioamide with various thionating agents is often not feasible for substrates composed of ketone, ester, and amide moieties.[10b,e] Additionally, the thionation−cyclization of amino acid-derived enamide precursors **10h−k** provides access to a range of potentially biologically relevant, thiazole-based chiral peptidomimetics. The broad scope and operational simplicity of the reaction along with the diversity of compatible starting materials makes this methodology attractive for the synthesis of biologically important thiazoles with an option for combinatorial synthesis.

Although it is not possible to give a definite explanation for the observed chemoselectivity in the thionation of enamide amides **10** and **11** with Lawesson's reagent, it appears that the enamide carbonyl group is more electrophilic (because of the delocalization of the nitrogen lone pair on the double bond) than the carbonyl group of the other secondary amide moiety, resulting in its undergoing a faster nucleophilic attack by the dissociated Lawesson's reagent followed by the facile intramolecular cyclization of the resulting thioamides to the corresponding thiazoles.[10b]

EXPERIMENTAL SECTION

Desired oxazolone precursors **1a−j** and **2** were prepared according to our earlier procedure.[14,15] Similarly, starting enamide esters **3a−i** and **4** were obtained by ring-opening corresponding oxazolones **1a−e**, **1g−i**, and **2** with appropriate alkoxides in alkanols as reported,[14a,15a] whereas enamide amide precursors **10a−k** and **11** were prepared by ring-opening the respective oxazolones **1a**, **1d−j**, and **2** with appropriate primary amines or amino acid esters.[14,15a] Known enamide esters **3a−c**, **3e**,**f**, **3h**, and **4** and enamide amides **10f**, **10h**, **10j**, and **11** were characterized by comparing their spectral data with those reported,[14a,15a] whereas the spectral and analytical data of unknown **3g**, **3i**, **10a−c**, **10g**, and **10k** is given below. A few enamides (**3d**, **10d**,**e**, and **10i**) were subjected to thionation−cyclization without further purification and characterization.

(*E*)-Ethyl 2-Benzamido-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)acrylate (3g). Brown semisolid (268 mg, 78%): R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3310, 1648, 1478, 1296; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.59−7.57 (m, 2H), 7.50−7.46 (m, 1H), 7.38 (t, J = 8.0 Hz, 2H), 6.71 (t, J = 2.4 Hz, 1H), 6.19−6.17 (m, 2H), 4.39 (q, J = 7.2 Hz, 2H), 3.59(s, 3H), 1.86 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 164.2, 133.5, 132.1, 130.5, 128.8, 127.3, 126.7, 124.9, 124.7, 110.5, 108.4, 61.7, 34.4, 15.9, 14.3; HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O_3S$ $[M + H]^+$ 345.1273, found 345.1256.

(*E*)-Butyl 3-(methylthio)-3-(thiophen-2-yl)-2-(thiophene-2-carboxamido)acrylate (3i). White solid (305 mg, 80%): mp 132−133 °C; R_f 0.5 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3312, 1712, 1650, 1511, 1244; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.51 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.46 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.41 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.27 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.11 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.05 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 4.32 (t, J = 6.8 Hz, 2H), 2.13 (s, 3H), 1.74 (quin, J = 6.8 Hz, 2H), 1.47 (sext, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.0, 138.7, 137.3, 131.7, 129.6, 128.8, 128.5, 128.2, 128.1, 128.0, 65.9, 30.6, 19.4, 17.6, 13.8; HRMS (ESI) m/z calcd for $C_{17}H_{19}NO_3S_3$ $[M + Na]^+$ 404.0425, found 404.0402.

(*E*) -*N*-(1-(4-Methoxyphenyl)-1-(methylthio)-3-oxo-3-(phenylamino)prop-1-en-2-yl) Benzamide (10a). White solid (394 mg, 85%): mp 112−113 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3270, 1634, 1250; ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (br s, 1H), 9.53 (br s, 1H), 7.68 (t, J = 8.8 Hz, 4H), 7.49 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.35−7.29 (m, 4H), 7.05 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.74 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 164.3, 159.1, 139.5, 138.5, 133.6, 131.6, 130.5, 128.6, 128.3, 127.7, 127.6, 123.2, 119.8, 113.8, 55.2, 15.7; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2O_3S$ $[M + H]^+$ 419.1429, found 419.1411.

(*E*,*Z*)-*N*-(1-(4-Fluorophenyl)-3-(4-fluorophenylamino)-1-(methylthio)-3-oxoprop-1-en-2-yl) Benzamide (10b). White solid (E/Z = 50:50, 400 mg, 85%): mp 224−225 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3250, 1641, 1508; ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (br s, 0.5H), 9.86 (br s, 0.5H), 9.79 (br s, 0.5H), 9.58 (br s, 0.5H), 8.01 (d, J = 7.6 Hz, 1H), 7.73−7.59 (m, 3H), 7.55−7.48 (m, 1.5H), 7.42−7.40 (m, 2.5H), 7.32−7.14 (m, 4H), 7.00 (t, J = 8.8 Hz, 1H), 1.96 (s, 1.5H), 1.88 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.0, 164.0, 163.1, 162.9, 160.6, 160.5, 159.4, 157.0, 156.9, 138.7, 135.7, 135.4, 133.6, 133.5, 133.2, 132.1, 131.7, 131.53, 131.44, 131.2, 131.1, 130.8, 128.6, 128.3, 127.8, 127.7, 121.73, 121.66, 121.1, 121.0, 115.4, 115.3, 115.2, 115.1, 114.9; HRMS (ESI) m/z calcd for $C_{23}H_{18}F_2N_2O_2S$ $[M + Na]^+$ 447.0955, found 447.0938.

(*E*,*Z*)-*N*-(3-(4-Fluorophenylamino)-1-(furan-2-yl)-1-(methylthio)-3-oxoprop-1-en-2-yl) Benzamide (10c). Off-white solid (E/Z = 50:50, 382 mg, 87%): mp 120−122 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3268, 1634, 1509; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (br s, 0.5H), 8.32 (br s, 0.5H), 8.17 (br s, 0.5H), 7.91−7.89 (m, 1H), 7.86−7.84 (m, 1H), 7.63−7.54 (m, 3H), 7.49−7.44 (m, 2H), 7.42 (dd, J = 2.0 Hz, 0.8 Hz, 0.5H), 7.33 (dd, J = 9.2 Hz, 4.8 Hz, 1H), 7.00 (t, J = 8.4 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 6.79 (d, J = 3.2 Hz, 0.5H), 6.56 (dd, J = 3.6 Hz, 0.4 Hz, 0.5H), 6.52 (dd, J = 3.6 Hz, 1.6 Hz, 0.5H), 6.39 (dd, J = 3.6 Hz, 1.6 Hz, 0.5 H), 2.26 (s, 1.5H), 2.12 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.7, 162.7, 162.5, 161.0, 158.6, 151.5, 147.6, 144.3, 143.5, 133.9, 133.8, 133.6, 133.5, 133.4, 133.0, 132.9, 132.8, 132.68, 132.65, 129.0, 128.9, 127.8, 127.7, 122.5, 122.4, 122.3, 122.2, 118.2, 115.9, 115.73, 115.66, 115.5, 113.7, 113.6, 112.9, 112.3, 111.9, 19.3, 16.0; HRMS (ESI) m/z calcd for $C_{21}H_{17}FN_2O_3S$ $[M + Na]^+$ 419.0842, found 419.0833.

(*E*)-*N*-(3-(3,4-Dimethoxyphenethylamino)-1-(benzo[*d*][1,3]-dioxol-5-yl)-1-(methylthio)-3-oxoprop-1-en-2-yl)thiophene-2-carboxamide (10g). White solid (467 mg, 80%): mp 184−185 °C; R_f 0.4 (1:1 EtOAc/hexane); IR (KBr, cm^{-1}) 3251, 1626, 1480, 1243; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.40 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.32 (d, J = 3.2 Hz, 1H), 6.95 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 6.80−6.72 (m, 7H), 5.93 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.61 (q, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 161.2, 149.1, 148.3, 147.9, 147.7, 137.7, 131.8, 131.1, 129.5, 129.0, 127.9, 126.0, 122.6, 120.9, 112.3, 111.4, 109.1, 108.7, 101.5, 56.0, 41.3, 35.1, 16.3; HRMS (ESI) m/z calcd for $C_{26}H_{26}N_2O_6S_2$ $[M + H]^+$ 527.1311, found 527.1301

(*S*)-Ethyl 2-(3-(Benzo[*d*][1,3]dioxol-5-yl)-3-(methylthio)-2-(thiophene-2-carboxamido)acrylamido)-3-phenylpropanoate (10k). Off-white solid (449 mg, 75%): mp 184−185 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (KBr, cm^{-1}) 3403, 1735, 1665, 1511; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 7.78−7.75 (m, 2H), 7.55 (d, J = 3.2 Hz, 1H), 7.14 (s, 5H), 7.09 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.98 (s, 2H), 4.57 (q, J = 6.8 Hz, 1H), 4.04 (q, J = 7.2 Hz, 2H), 3.03 (dd, J = 6.0 Hz, 4.0 Hz, 2H), 1.75 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.6, 160.9, 146.9, 146.7, 138.8, 136.8, 131.4, 129.2, 129.1, 128.1, 127.8, 126.5, 122.6, 121.9, 108.6, 108.0, 101.1, 60.6, 53.5, 36.8, 15.9, 13.9; HRMS (ESI) m/z calcd for $C_{27}H_{26}N_2O_6S_2$ $[M + H]^+$ 539.1311, found 539.1288.

General Procedure for the Synthesis of 2-Phenyl/(2-thienyl)-5-(het)aryl/(methylthio)thiazole-4-carboxylates 8a−i and 9. To a solution of enamide ester **3** or **4** (0.5 mmol) in toluene (10 mL) was added Lawesson's reagent (0.4 g, 1.0 mmol), and the reaction mixture was refluxed with stirring for 2−3 (**8a−e**) or 10−12 h (**8f−i** and **9**) (monitored by TLC). The reaction mixture was then poured into ice-cold water (30 mL), extracted with EtOAc (3 × 30 mL), washed with brine (1 × 30 mL), and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give crude thiazoles that were

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purified by column chromatography over silica gel using EtOAc–hexane as eluent.

Ethyl 5-(4-Methoxyphenyl)-2-phenylthiazole-4-carboxylate (8a). White solid (118 mg, 70%): mp 126–127 °C; R_f 0.45 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1720, 1247, 1180; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.97 (m, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.46–7.44 (m, 3H), 6.95 (d, J = 8.8 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.6, 160.6, 146.2, 141.1, 133.1, 131.5, 130.6, 129.1, 126.9, 122.8, 113.8, 61.4, 55.5, 14.3; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_3S$ $[M + H]^+$ 340.1007, found 340.1008.

Ethyl 5-(3,4-Dimethoxyphenyl)-2-phenylthiazole-4-carboxylate (8b). Pale-yellow solid (138 mg, 75%): mp 140–141 °C; R_f 0.45 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1720, 1261, 1186; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.97 (m, 2H), 7.46–7.45 (m, 3H), 7.12 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.7, 150.1, 148.7, 146.0, 141.2, 133.0, 130.7, 129.1, 126.9, 123.0, 113.4, 110.9, 61.4, 56.2, 56.1, 14.3; HRMS (ESI) m/z calcd for $C_{20}H_{19}NO_4S$ $[M + Na]^+$ 392.0932, found 392.0932.

Ethyl 5-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenylthiazole-4-carboxylate (8c). Pale-yellow solid (124 mg, 70%): mp 139–140 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1720, 1477, 1240, 1187; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H), 7.45–7.46 (m, 3H), 7.03–7.01 (m, 2H), 6.85 (dd, J = 6.8 Hz, 1.6 Hz, 1H), 6.03 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.5, 148.7, 147.7, 145.8, 141.4, 133.0, 130.7, 129.1, 126.9, 124.2, 124.1, 110.6, 108.3, 101.7, 61.5, 14.3; HRMS (ESI) m/z calcd for $C_{19}H_{15}NO_4S$ $[M + Na]^+$ 376.0619, found 376.0618.

Ethyl 5-(4-Fluorophenyl)-2-phenylthiazole-4-carboxylate (8d). White solid (130 mg, 80%): mp 158–160 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1716, 1195; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.97 (m, 2H), 7.51 (dd, J = 8.8 Hz, 5.2 Hz, 2H), 7.47–7.45 (m, 3H), 7.12 (t, J = 8.8 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 164.6, 162.3, 162.2, 144.9, 141.7, 132.8, 132.0, 131.9, 130.8, 129.1, 127.0, 126.63, 126.6, 115.6, 115.3, 61.5, 14.2; HRMS (ESI) m/z calcd for $C_{18}H_{14}FNO_2S$ $[M + H]^+$ 328.0808, found 328.0803.

***tert*-Butyl 5-(4-Methoxyphenyl)-2-phenylthiazole-4-carboxylate (8e).** Pale-yellow solid (138 mg, 75%): mp 99–100 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1718, 1251, 1153; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.45–7.41 (m, 5H), 6.95 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.8, 160.4, 144.5, 143.1, 133.1, 131.4, 130.5, 129.0, 126.9, 123.4, 113.8, 82.1, 55.6, 28.1; HRMS (ESI) m/z calcd for $C_{21}H_{21}NO_3S$ $[M + H]^+$ 368.1320, found 368.1312.

Ethyl 5-(Furan-2-yl)-2-phenylthiazole-4-carboxylate (8f). Brown solid (108 mg, 72%): mp 69–70 °C; R_f 0.65 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1712, 1317, 1226, 1186; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.97 (m, 2H), 7.54 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.47–7.43 (m, 3H), 6.56 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.6, 145.6, 143.9, 139.1, 136.1, 132.9, 130.7, 129.1, 126.9, 114.1, 112.8, 61.7, 14.5; HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_3S$ $[M + Na]^+$ 322.0514, found 322.0508.

Ethyl 5-(1-Methyl-1*H*-pyrrol-2-yl)-2-phenylthiazole-4-carboxylate (8g). Brown semisolid (94 mg, 60%): R_f 0.6 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 1720, 1465, 1189; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.97 (m, 2H), 7.46–7.45 (m, 3H), 6.81 (dd, J = 2.4 Hz, 2.0 Hz, 1H), 6.34 (dd, J = 3.6 Hz, 2.0 Hz, 1H), 6.22 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.54 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 161.9, 143.9, 136.8, 133.0, 130.8, 129.1, 127.0, 124.8, 121.0, 112.8, 108.4, 61.4, 34.7, 14.3; HRMS (ESI) m/z calcd for $C_{17}H_{16}N_2O_2S$ $[M + H]^+$ 313.1011, found 313.1005.

Ethyl 5-(1-Methyl-1*H*-indol-3-yl)-2-phenylthiazole-4-carboxylate (8h). Yellow solid (135 mg, 75%): mp 96–98 °C; R_f 0.5 (1:5 EtOAc/hexane); IR (KBr, cm^{-1}) 1708, 1469, 1190; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03–8.00 (m, 2H), 7.86–7.83 (m, 2H), 7.49–7.43 (m, 3H), 7.38 (d, J = 8.4 Hz, 1H), 7.31 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.25–7.22 (m, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.2, 140.5, 140.2, 137.1, 133.4, 131.9, 130.3, 129.1, 127.5, 126.9, 122.7, 120.9, 120.1, 109.9, 104.7, 61.4, 33.4, 14.4; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_2S$ $[M + Na]^+$ 385.0987, found 385.0985.

Butyl 2,5-Di(thiophen-2-yl)thiazole-4-carboxylate (8i). Yellow semisolid (140 mg, 80%): R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1716, 1464, 1186; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.47–7.43 (m, 3H), 7.09 (dd, J = 4.0 Hz, 2.4 Hz, 1H), 7.08 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 4.33 (t, J = 6.8 Hz, 2H), 1.71 (quin, J = 6.8 Hz, 2H), 1.37 (sext, J = 7.6 Hz, 2H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 159.0, 140.5, 137.9, 136.1, 130.5, 128.74, 128.69, 128.0, 127.6, 127.4, 65.5, 30.6, 19.1, 13.7; HRMS (ESI) m/z calcd for $C_{16}H_{15}NO_2S_3$ $[M + H]^+$ 350.0343, found 350.0335.

Ethyl 5-(Methylthio)-2-phenylthiazole-4-carboxylate (9). Yellow solid (98 mg, 70%): mp 82–83 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 1693, 1446, 1203, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.89 (m, 2H), 7.44–7.42 (m, 3H), 4.46 (q, J = 7.2 Hz, 2H), 2.66 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.6, 149.5, 139.4, 132.9, 130.4, 129.1, 126.6, 61.6, 20.3, 14.6; HRMS (ESI) m/z calcd for $C_{13}H_{13}NO_2S_2$ $[M + Na]^+$ 302.0285, found 302.0288.

General Procedure for the Synthesis of N-Substituted 2-(2-Thienyl)/phenyl-5-(het)aryl/(methylthio)thiazole-4-carboxamides 13a–k and 14. To a solution of enamide amide **10** or **11** (0.5 mmol) in THF (10 mL) was added Lawesson's reagent (0.4 g, 1.0 mmol), and the reaction mixture was refluxed with stirring for 10–12 h (monitored by TLC). The reaction mixture was then concentrated under reduced pressure, and the residue was diluted with water (30 mL), extracted with EtOAc (3 × 30 mL), washed with brine (1 × 30 mL), and dried over Na_2SO_4. The solvent was removed to give crude thiazoles that were purified by column chromatography over silica gel using EtOAc–hexane as eluent.

5-(4-Methoxyphenyl)-*N*,2-diphenylthiazole-4-carboxamide (13a). Yellow solid (125 mg, 65%): mp 167–168 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3362, 1681, 1602, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (br s, 1H), 7.99–7.97 (m, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.52–7.49 (m, 3H), 7.34 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.6, 159.7, 141.9, 138.2, 132.9, 131.9, 130.8, 129.3, 129.1, 126.6, 124.3, 123.4, 122.5, 120.1, 113.8, 55.5; HRMS (ESI) m/z calcd for $C_{23}H_{18}N_2O_2S$ $[M + Na]^+$ 409.0987, found 409.0984.

***N*,5-Bis(4-fluorophenyl)-2-phenylthiazole-4-carboxamide (13b).** Pale-yellow solid (148 mg, 76%): mp 208–209 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3352, 1680, 1228; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 7.99–7.96 (m, 2H), 7.69–7.63 (m, 4H), 7.51 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 7.04 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.7, 162.2, 160.8, 159.4, 158.4, 143.5, 142.3, 134.0, 133.9, 132.6, 132.4, 132.3, 131.1, 129.3, 126.7, 126.19, 126.15, 121.9, 121.8, 115.9, 115.7, 115.6, 115.3; HRMS (ESI) m/z calcd for $C_{22}H_{14}F_2N_2OS$ $[M + H]^+$ 393.0873, found 393.0854.

***N*-(4-Fluorophenyl)-5-(furan-2-yl)-2-phenylthiazole-4-carboxamide (13c).** Brown solid (123 mg, 68%): mp 120–122 °C; R_f 0.5 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3357, 1692, 1509, 1225; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (br s, 1H), 7.99–7.97 (m, 2H), 7.95 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.70 (dd, J = 8.8 Hz, 5.2 Hz, 2H), 7.52 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.51–7.48 (m, 3H), 7.09 (t, J = 8.8 Hz, 2H), 6.58 (dd, J = 3.6 Hz, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 159.6, 147.9, 143.7, 134.73, 134.70, 132.4, 131.7, 131.1, 129.3, 129.0, 127.93, 127.90, 126.7, 125.74, 125.7, 116.0, 115.8, 114.0, 112.2; HRMS (ESI) m/z calcd for $C_{20}H_{13}FN_2O_2S$ $[M + Na]^+$ 387.0579, found 387.0579.

2,5-Di(thiophen-2-yl)-*N*-(3,4,5-trimethoxyphenyl)thiazole-4-carboxamide (13d). Yellow semisolid (172 mg, 75%): R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3412, 1671, 1507, 1128; ^1H NMR

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(400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.71 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.54 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.48 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.46 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.13 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.09 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 6.98 (s, 2H), 3.89 (s, 6H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.4, 153.5, 140.9, 137.3, 135.9, 135.1, 134.0, 131.4, 130.8, 129.4, 128.9, 128.4, 128.0, 127.6, 98.2, 61.1, 56.4; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_4S_3$ $[M + H]^+$ 459.0507, found 459.0495.

_N_-Butyl-2-phenyl-5-(thiophen-2-yl)thiazole-4-carboxamide (13e). Brown solid (120 mg, 70%): mp 94–95 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3409, 1664, 1515; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.91 (m, 2H), 7.68 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.62 (br s, 1H), 7.48–7.46 (m, 3H), 7.43 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.06 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 3.46 (q, J = 7.2 Hz, 2H), 1.64 (quin, J = 7.2 Hz, 2H), 1.44 (sext, J = 7.6 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.9, 141.9, 136.9, 132.7, 131.4, 131.1, 130.8, 129.2, 129.1, 127.3, 126.6, 39.3, 32.0, 20.4, 14.0; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2OS_2$ $[M + Na]^+$ 365.0758, found 365.0758.

_N_-(2-(1_H_-Indol-3-yl)ethyl)-5-(1-methyl-1_H_-indol-3-yl)-2-phenylthiazole-4-carboxamide (13f). Yellow solid (178 mg, 75%): mp 159–160 °C; R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3401, 3293, 1652, 1523; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.12 (br s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.87–7.85 (m, 3H), 7.70 (d, J = 8.0 Hz, 1H), 7.45–7.43 (m, 3H), 7.39–7.35 (m, 2H), 7.30 (td, J = 8.0 Hz, 0.8 Hz, 1H), 7.24–7.19 (m, 2H), 7.13 (td, J = 8.0 Hz, 0.8 Hz, 1H), 7.08 (s, 1H), 3.84 (s, 3H), 3.80 (q, J = 7.2 Hz, 2H), 3.12 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 161.8, 141.4, 137.9, 137.1, 136.5, 133.6, 133.2, 130.2, 129.1, 127.6, 127.5, 126.5, 122.4, 122.3, 122.2, 120.7, 120.0, 119.6, 119.0, 113.5, 111.3, 109.9, 104.4, 40.0, 33.3, 25.7; HRMS (ESI) m/z calcd for $C_{29}H_{24}N_4OS$ $[M + Na]^+$ 499.1569, found 499.1567.

_N_-(3,4-Dimethoxyphenethyl)-5-(benzo[_d_][1,3]dioxol-5-yl)-2-(thiophen-2-yl)thiazole-4-carboxamide (13g). Yellow semisolid (153 mg, 62%); R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3406, 1665, 1507, 1236; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (br t, J = 6.0 Hz, 1H), 7.47 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.43 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.11–7.08 (m, 2H), 6.85–6.78 (m, 4H), 6.0 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.62 (q, J = 6.8 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.1, 149.2, 148.7, 147.8, 147.5, 142.6, 141.8, 136.5, 131.8, 128.5, 128.2, 127.4, 124.6, 123.6, 120.9, 112.2, 111.6, 111.1, 108.1, 101.6, 56.1, 56.0, 40.9, 35.7; HRMS (ESI) m/z calcd for $C_{25}H_{22}N_2O_5S_2$ $[M + H]^+$ 495.1048, found 495.1017.

(_S_)-Ethyl 2-(5-(4-Methoxyphenyl)-2-phenylthiazole-4-carboxamido)-3-phenylpropanoate (13h). Yellow solid (158 mg, 65%): mp 88–89 °C; R_f 0.45 (1:4 EtOAc/hexane); $[\alpha]_{25}^{D}$ = +35.1 (c 0.3, $CHCl_3$); IR (KBr, cm^{-1}) 3394, 1739, 1673, 1508; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br d, J = 8.4 Hz, 1H), 7.92–7.89 (m, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.47–7.45 (m, 3H), 7.32–7.22 (m, 5H), 6.94 (d, J = 8.8 Hz, 2H), 4.99 (dt, J = 8.4 Hz, 6.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.23 (dd, J = 14.0 Hz, 6.0 Hz, 1H), 3.19 (dd, J = 14.0 Hz, 6.0 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 164.2, 161.3, 160.5, 144.1, 141.5, 136.3, 132.9, 131.8, 130.6, 129.7, 129.1, 128.7, 127.2, 126.6, 122.5, 113.7, 61.5, 55.5, 53.2, 38.5, 14.2; HRMS (ESI) m/z calcd for $C_{28}H_{26}N_2O_4S$ $[M + Na]^+$ 509.1511, found 509.1512.

(2_S_)-Ethyl 3-Methyl-2-(5-(1-methyl-1_H_-indol-3-yl)-2-phenylthiazole-4-carboxamido)butanoate (13i). Yellow solid (150 mg, 65%): mp 79–80 °C; R_f 0.45 (1:4 EtOAc/hexane); $[\alpha]_{25}^{D}$ = +22.3 (c 0.6, $CHCl_3$); IR (KBr, cm^{-1}) 3403, 1735, 1668, 1509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.20 (br d, J = 8.8 Hz 1H), 8.01–7.97 (m, 3H), 7.50–7.45 (m, 3H), 7.37–7.35 (m, 1H), 7.29 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.24 (td, J = 8.0 Hz, 1.2 Hz, 1H), 4.70 (dd, J = 9.2 Hz, 5.2 Hz, 1H), 4.29–4.20 (m, 2H), 3.87 (s, 3H), 2.36–2.28 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 162.5, 161.9, 140.9, 138.5, 137.1, 133.6, 133.2, 130.3, 129.1, 127.5, 126.5, 122.4, 120.8, 120.0, 109.9, 104.4, 61.3, 57.4, 33.4, 31.7, 19.3, 18.3, 14.4; HRMS (ESI) m/z calcd for $C_{26}H_{27}N_3O_3S$ $[M + Na]^+$ 484.1671, found 484.1670.

(2_S_)-Ethyl 3-(1_H_-Indol-3-yl)-2-(5-(1-methyl-1_H_-pyrrol-2-yl)-2-phenylthiazole-4-carboxamido)propanoate (13j). Brown solid (174 mg, 70%): mp 88–89 °C; R_f 0.45 (1:4 EtOAc/hexane); $[\alpha]_{25}^{D}$ = −6.0 (c 0.3, $CHCl_3$); IR (KBr, cm^{-1}) 3376, 1735, 1664, 1517; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 8.03 (br d, J = 8.4 Hz 1H), 7.79–7.77 (m, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.45–7.42 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 8.4 Hz, 1.2 Hz, 1H), 7.10–7.05 (m, 2H), 6.7 (dd, J = 2.8 Hz, 2.0 Hz, 1H), 6.34 (dd, J = 3.6 Hz, 2.0 Hz, 1H), 6.19 (dd, J = 3.6 Hz, 2.8 Hz, 1H), 5.03 (dt, J = 8.4 Hz, 5.6 Hz, 1H), 4.16–4.10 (m, 2H), 3.50 (s, 3H), 3.40 (dd, J = 5.6 Hz, 3.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 165.7, 160.9, 144.2, 136.3, 133.9, 132.8, 130.7, 129.1, 127.9, 126.7, 125.0, 123.0, 122.3, 121.0, 119.9, 119.0, 112.7, 111.3, 110.6, 108.2, 61.5, 53.2, 34.9, 28.0, 14.2; HRMS (ESI) m/z calcd for $C_{28}H_{26}N_4O_3S$ $[M + Na]^+$ 521.1623, found 521.1624.

(2_S_)-Ethyl 2-(5-(Benzo[_d_][1,3]dioxol-5-yl)-2-(thiophen-2-yl)-thiazole-4-carboxamido)-3-phenylpropanoate (13k). Yellow semisolid (156 mg, 62%): R_f 0.45 (1:4 EtOAc/hexane); $[\alpha]_{25}^{D}$ = +47.2 (c 0.3, $CHCl_3$); IR (KBr, cm^{-1}) 3391, 1737, 1672, 1502, 1250; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br d, J = 8.4 Hz, 1H), 7.48 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.44 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.34–7.30 (m, 2H), 7.27–7.22 (m, 3H), 7.12 (d, J = 1.6 Hz, 1H), 7.09 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.0 (s, 2H), 4.95 (dt, J = 8.4 Hz, 6.0 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.20 (dd, J = 6.0 Hz, 4.0 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 160.9, 158.2, 148.7, 147.5, 143.1, 141.2, 136.6, 136.2, 129.6, 128.8, 128.6, 128.1, 127.4, 127.2, 124.5, 123.5, 111.0, 108.1, 101.6, 61.5, 53.3, 38.5, 14.2; HRMS (ESI) m/z calcd for $C_{26}H_{22}N_2O_5S_2$ $[M + H]^+$ 507.1048, found 507.1046.

_N_-(4-Fluorophenyl)-5-(methylthio)-2-phenylthiazole-4-carboxamide (14). Off-white solid (120 mg, 70%): mp 185–186 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3374, 1664, 1509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.1 (br s, 1H), 7.89–7.87 (m, 2H), 7.69 (dd, J = 8.8 Hz, 4.8 Hz, 2H), 7.47–7.45 (m, 3H), 7.05 (dd, J = 8.6 Hz, 8.8 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.7, 160.3, 158.2, 146.1, 140.9, 134.1, 134.0, 132.7, 130.6, 129.3, 126.2, 121.5, 121.4, 115.9, 115.6, 20.4; HRMS (ESI) m/z calcd for $C_{17}H_{13}FN_2OS_2$ $[M + Na]^+$ 367.0351, found 367.0354.

5-(4-Methoxyphenyl)-_N_,2-diphenylthiazole-4-carbothioamide (17). Red solid (132 mg, 66%): mp 130–132 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3440, 1594, 1550, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.85 (br s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.81–7.78 (m, 2H), 7.50–7.48 (m, 4H), 7.40–7.39 (m, 3H), 7.30–7.27 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 163.6, 161.5, 145.8, 141.7, 141.2, 140.2, 133.1, 131.8, 130.1, 130.0, 129.1, 126.7, 126.3, 121.4, 112.6, 55.6; HRMS (ESI) m/z calcd for $C_{23}H_{18}N_2OS_2$ $[M + H]^+$ 403.0939, found 403.0920.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra, ORTEP X-ray crystal structure displays, and CIF crystallographic data for **8b** and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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DEDICATION

Dedicated to Professor Sukh Dev on his 90th birthday.

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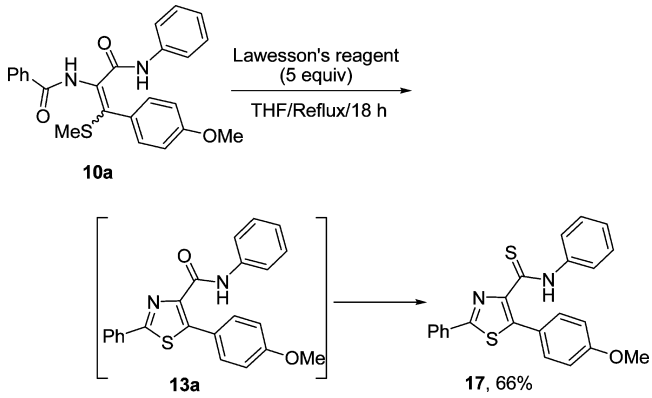
(17) In the case of thionation−cyclization of all enamide amides **10a−k** and **11** with Lawesson's reagent, the formation of some polymeric product was observed along with the corresponding product thiazole-4-carboxamides **13a−k** and **14**. When enamide anilide **10a** was reacted with an excess of Lawesson's reagent (5 equiv) under refluxing THF for 18 h, the reaction showed the initial formation of thiazole-4-anilide **13a**, which was slowly converted to thiazole-4-thioanilide **17** in 66% yield. Similarly, when thiazole **13a** was reacted with Lawesson's reagent (2 equiv) for 8 h under refluxing THF, thioanilide **17** was obtained in 65% yield.



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