Note

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

S. Vijay Kumar, G. Parameshwarappa, and Hiriyakkanavar Ila

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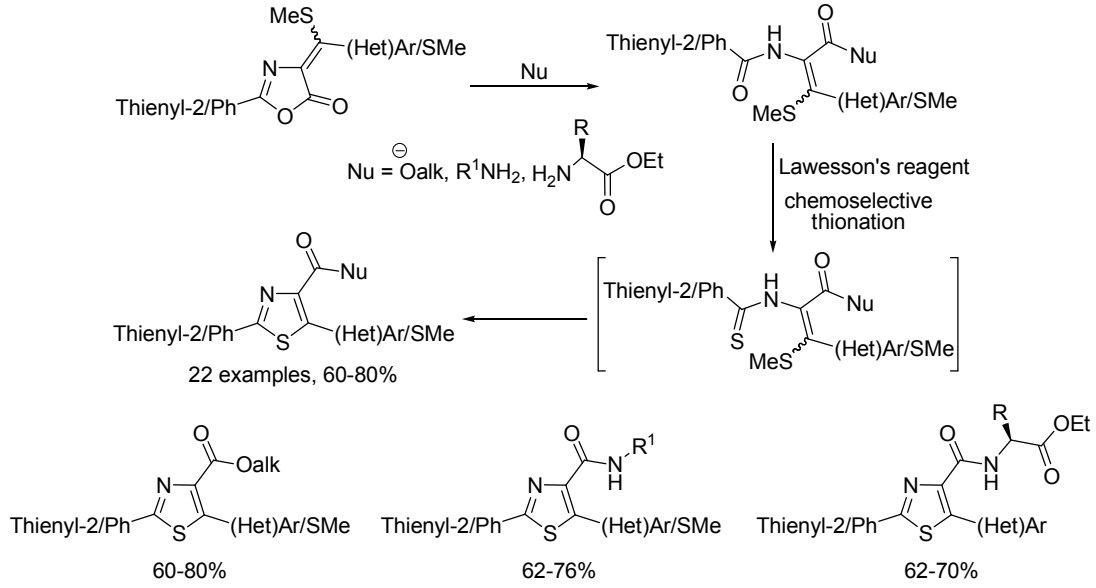
Synthesis of 2,4,5-Trisubstituted Thiazoles via Lawesson's Reagent Mediated Chemoselective Thionation-Cyclization of Functionalized Enamides

*S. Vijay Kumar, G. Parameshwarappa and H. Ila**

New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore-560064, Karnataka, India

E-mail: hila@jncasr.ac.in

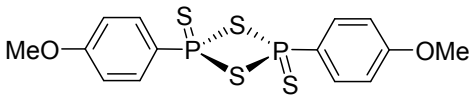


Abstract: An efficient route to 2-phenyl/(2-thienyl)-5-(het)aryl/(methylthio)-4-functionalized thiazoles via one step chemoselective thionation-cyclization of highly functionalized enamides, mediated by Lawesson's reagent has been reported. These enamide precursors are obtained by nucleophilic ring opening 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, thus leading to the introduction of an ester, N-substituted carboxamide or peptide functionality in the 4-position of the product thiazoles.

Thiazoles[1] are the most commonly encountered heterocycles among the compounds of biological interest and in bioactive natural products of microbial and marine origin (particularly non ribosomal peptides), exhibiting important biological activities,[1,2a] such as antitumor, antifungal, antibiotic, antiviral, antibacterial as well as peptide mimetic[2a-b] and enzyme inhibitors.[2c-e] In nature, thiazolium ring is chemically active centre in the coenzyme derived from vitamin B_1 (thiamine).[3] Synthetic thiazoles also occupy a prominent position in drug discovery process and this ring system is found in several marketed drugs.[4] Also, these class of compounds have found broad application as functional materials,[5a] liquid crystals for ferroelectric display[5b] and as cosmetic sunscreens.[5c] Therefore, in view of the structural diversity of complex naturally occurring thiazoles, along with 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 pre-existing core[1,7] or ring assembly from acyclic precursors.[1] Among the two, the latter route has greater potential for rapid generation of diversity in functionalized thiazoles. Within this group, Hantzsch thiazole synthesis[8] (and its modified versions)[9] entailing condensation of a suitably substituted α-haloketone (or its equivalents) with thioamide has proven to be a powerful method for synthesis of 2,4,5-substituted thiazoles. Other methods include reaction of α-aminonitriles with CS_2, COS, isothiocyanates and dithiocarboxlic acids.[4b,9h] Thionation-cyclization of α-acylaminoketones (or related precursors) with various thionation agents (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 much explored, probably due to the lack of availability of structural variants of α-acylaminocarbonyl compounds. Recently, Chen and co-workers have reported synthesis of 2-substituted-4-phenyl-5-aminothiazoles in moderate yields, involving thionation of α-acylglycinamides with either Lawesson's or Belleau's reagent and subsequent TFAA mediated cyclization of thioamide intermediates.[11] Same workers, later on developed a

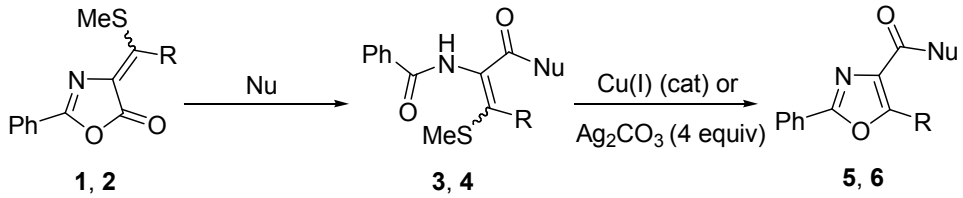
four component Ugi reaction using ammonia as amine component, for simple one step assembly of diamide precursors, which were transformed into 2,4-substituted 5-primary or secondary aminothiazoles library by thionation with Lawesson's reagent, although in moderate yields.[12] Sanz-Cervera and co-workers[13] have recently described an efficient fluorous and solution phase synthesis of small library of 2,5-substituted thiazole-4-carboxylic esters as potential antibacterials, involving 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 efficient synthesis of 2-phenyl-5-(methylthio)/(het)aryl-4-functionlized oxazoles **5-6** from common 2-phenyl-4-[(methylthio)-het(aryl)/bis(methylthio)methylene]-5-oxazolone precursors **1** and **2** (Scheme 1).[14,15] The oxazolones **1** and **2** are shown to 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**, which on subsequent copper catalyzed (for **3**) or silver carbonate mediated (for **4**) 5-*endo* cyclization, afford substituted oxazoles **5** or **6** respectively in high yields (Scheme 1).[14a,15a] In continuation of this work, along with our ongoing interest in design and

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



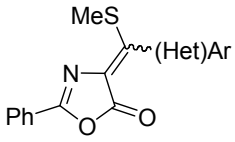
1, **2** **3**, **4** **5**, **6**

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

development of new synthetic methods for small molecule heterocycles,[16] we further envisaged to utilize these enamide precursors **3** and **4** for developing synthesis of 2,4,5-

substituted thiazoles via thionation-cyclization of these intermediates in the presence of Lawesson's reagent (Schemes 2 and 3). We now report in the present paper, successful implementation of this strategy, providing an efficient chemoselective route for 2,4,5-functionalized thiazoles, displaying high degree of diversity at various positions of product thiazoles.

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

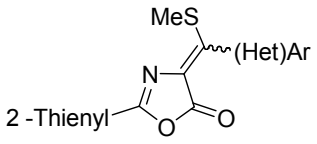
1d, Ar = 4-FC_6H_4

1e, (Het)Ar = 2-furyl

1f, (Het)Ar = 2-thienyl

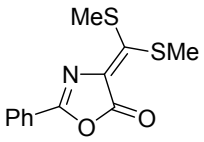
1g, (Het)Ar = 2-(N-methylpyrrolyl)

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



1i, (Het)Ar= 2-thienyl

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



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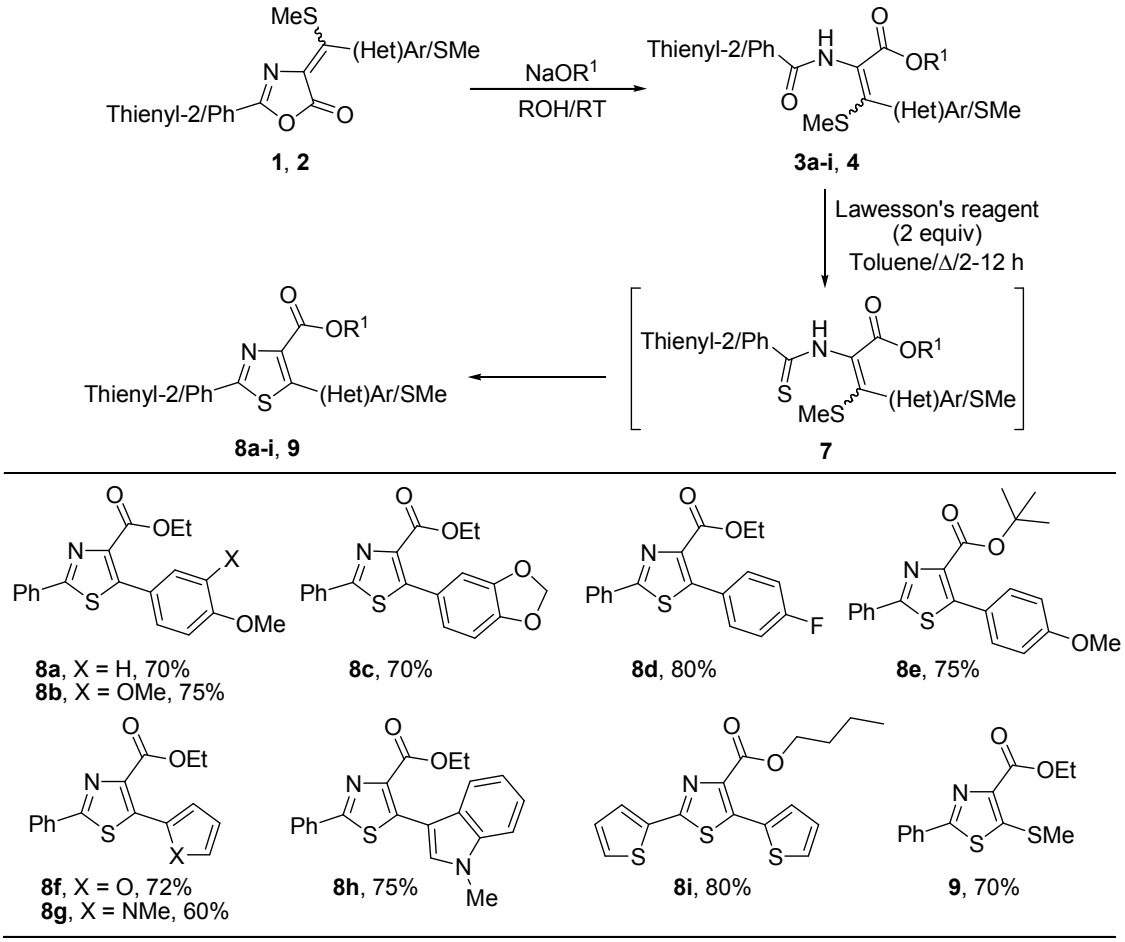
The desired 4-[(methylthio)-(het)arylmethylene]-2-phenyl/(2-thienyl)-5-oxazolones precursors **1a-j** or the corresponding 4-[bis(methylthio)methylene] derivative **2** (Chart 1) were obtained in good yields according to our previously reported procedure.[14-15] We first examined the synthesis of 2-phenyl-5-(het)arylthiazole-4-carboxylates **8a-i** and the corresponding 5-(methylthio)thiazole-4-carboxylate **9** via thionation-cyclization of the enamino esters **3a-i** and **4** respectively, which were obtained in high yields by nucleophilic ring opening of the corresponding oxazolones **1** or **2** with various sodium alkoxides, as reported earlier (Scheme 2).[14a,15] Thionation-cyclization of the enamide ester **3a** to thiazole-4-carboxylate **8a** was first attempted, as model substrate for optimization of reaction conditions. Thus, refluxing **3a** with 1 equiv of Lawesson's reagent in THF for prolonged time, yielded only unreacted starting material with no trace of thiazole **8a** (or thioamide **7a**). However we found, that higher temperature reflux in toluene for 12 h, resulted in efficient thionation as

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



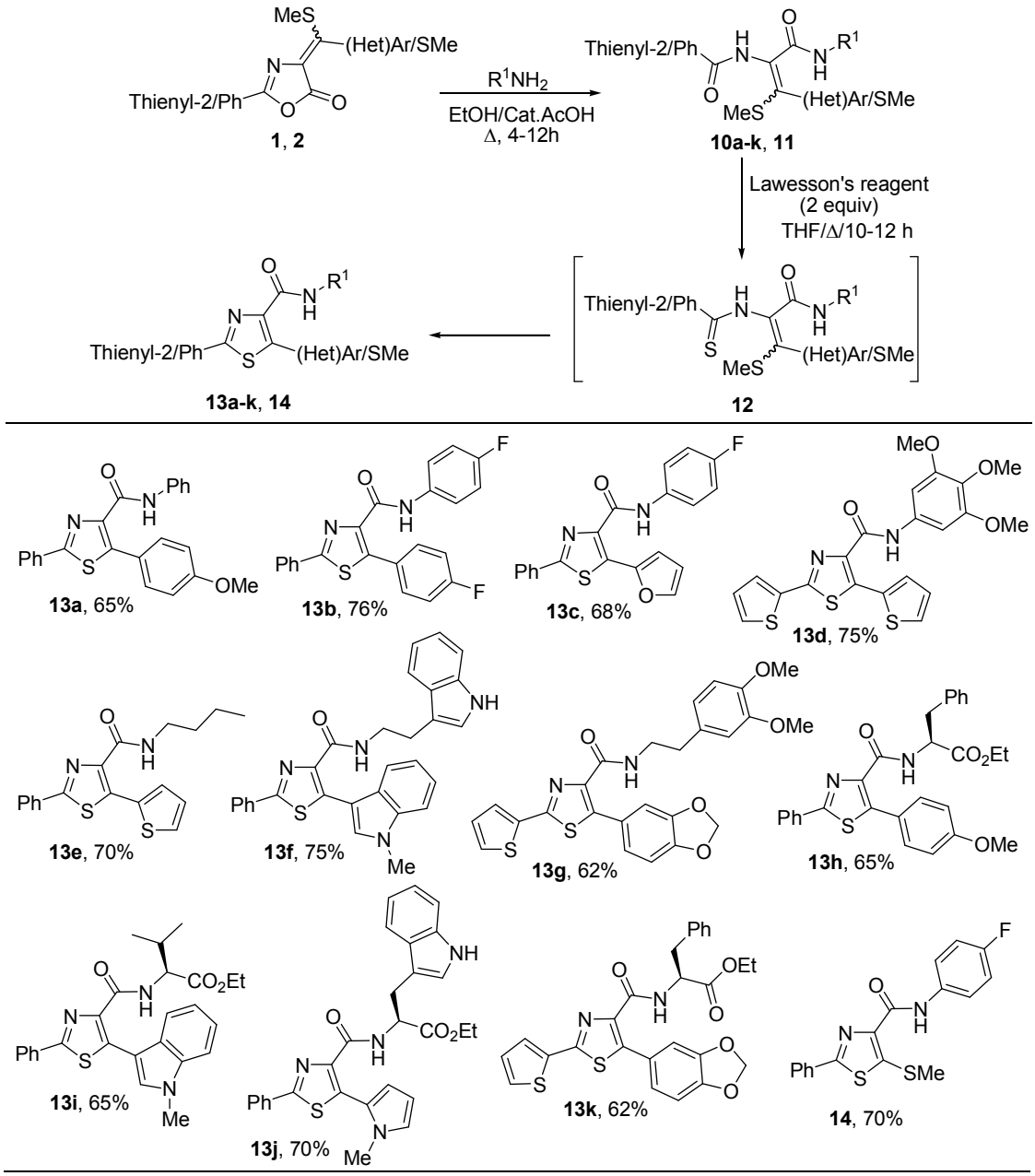
well as intramolecular cyclization of **3a**, furnishing ethyl 2-phenyl-4-(methoxyphenyl)thiazole-4-carboxylate **8a** in 68% yield. On the other hand, when **3a** was reacted with 2 equiv of Lawesson's reagent in refluxing toluene, reaction was complete within 2 h yielding **8a** in 70% yield (Scheme 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** carrying both electron donating (**8b-c**) and electron withdrawing (**8d**) substituents on 5-aryl group. Interestingly, the thionation-cyclization of the enamide *t*-butyl carboxylate **3e**, also

proceeded smoothly without any side reactions, yielding the corresponding *t*-butyl thiazole-4-carboxylate **8e** in 75% yield. Similarly, the enaminone carboxylic esters **3f-h** carrying various het(aryl) groups, were also converted into the corresponding 2-phenyl-5-(2-furyl)/(2-*N*-methylpyrrolyl)/(3-*N*-methylindolyl)thiazoles **8f-h** in good yields, under identical conditions, requiring prolonged refluxing (12 h) (Scheme 2). Further diversity at the 2 and 5 positions of the product thiazoles **8** could be achieved by synthesis of the corresponding *n*-butyl 2,5-bis(2-thienyl)thiazole-4-carboxylate **8i** in 80% yield by thionation-cyclization of enaminoester **3i** obtained by ring opening of 2-thienyl-4-[methylthio(2-thienyl)methylene]-5-oxazolone **1h** with sodium *n*-butoxide (Scheme 2).[15b] Extension of the protocol to bis(methylthio)enamide carboxylate **4** (obtained by ring opening of **2** with sodium ethoxide) also afforded the ethyl 2-phenyl-5-(methylthio)thiazole-4-carboxylate **9** in 70% yield (Scheme 2). The structures of all these newly synthesized thiazoles were confirmed with the help of spectral and analytical data and also by X-ray crystal structure analysis of thiazole ester **8b** (Figure S1, Supporting Information).

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

We therefore selected enamide-anilide **10a** as the model substrate for evaluation of optimal conditions, for its chemoselective thionation-cyclization to the thiazole **13a** (Scheme 3). To begin with, the thionation-cyclization of **10a** was conducted in refluxing toluene in the

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



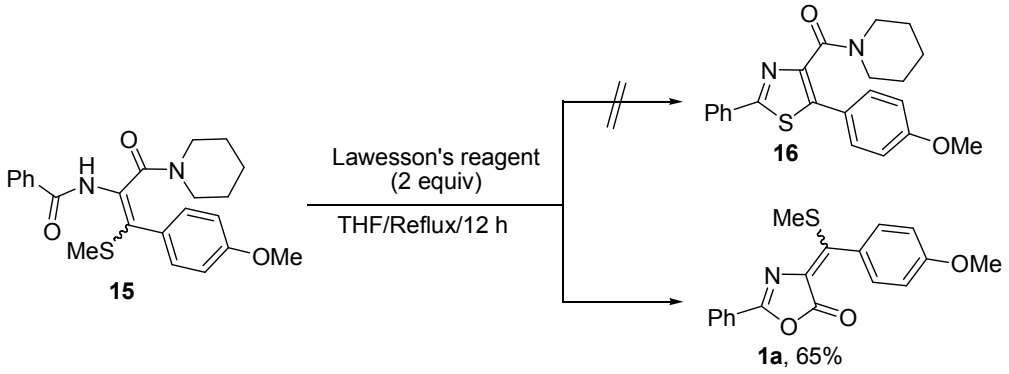
presence of 2 equivalents of Lawesson's reagent, under previously described conditions for the conversion of enamide carboxylates **3-4** to thiazole 4-carboxylates **8-9** (Scheme 2). However these enamide- amide intermediates **10-11** were found to be insoluble in toluene and attempted cyclization of **10a** to **13a** under toluene reflux for prolonged time (20 h) led only to the unreacted starting material. On the other hand, when **10a** was reacted with Lawesson's reagent (2 equiv) in refluxing THF for 12 h, analysis of reaction mixture revealed exclusive formation of only one product in reasonably good yield (65%), which to our delight, was found to be the desired 2-pheny-5-(4-methoxyphenyl)-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 the corresponding 2-phenyl-5-(het)arylthiazole-4-carboxyanilides **13b-c** in good yields (Scheme 3).The structure of these thiazoles were further confirmed by X-ray crystal structure analysis of **13b** (Figure S-2, Supporting Information). Similarly, the 2,5-bis(2-thienyl)thiazole-4-carboxyanilide **13d** could also be obtained in 75% yield, by thionation-cyclization of the 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 the scope of this chemoselective monothionation-cyclization protocol was further demonstrated by 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 the 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 of interesting extension of this work for the synthesis of thiazole based peptidomimetics such as **13h-k**, which are known to display interesting biological activity.[2b-c] We were indeed delighted to

find that open- chain peptidoenamide precursors **10h-k** (obtained by ring opening of **1** with various amino acid esters i.e., phenyalanine, valine and tryptophan) were smoothly transformed into thiazole based peptidomimetics **13h-k**, with a range of 5-(het)aryl groups, in good yields, under these optimized reaction conditions (Scheme 3). Finally the corresponding bis[(methylthio)methylene]enamide anilide **11** (obtained by ring opening of 4-bis(methylthio) methyleneoxazolone **2** with 4-fluoroaniline) also afforded the corresponding 2-phenyl-5-(methylthio)thiazole-4-(N-4-flurophenyl)carboxyanilide **14** in 70% yield (Scheme 2).

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

Scheme 4. Attempted Thionation-cyclization of N-piperidino-enamide-amide 15



In conclusion, we have devised a highly regio- and chemoselective, useful protocol for the synthesis of 2,4,5-trisubstituted thiazoles via 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, aromatic amines and amino acid esters, offering wide range of functional group diversity at 4- and 5-positions of the product thiazoles. Also, the remarkable chemoselectivity observed in the

facile thionation of benzoylamino group (over the other secondary amide moiety) in enamides **10-11**, is particularly noteworthy, since, selective conversion of an amide to thioamide with various thionating agents is often not feasible for substrates, comprised of ketone, esters and amide moieties.[10b,10e] Additionally, thionation-cyclization of the aminoacid 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 option for combinatorial synthesis.

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

Experimental Section

The desired oxazolone precursors **1a-j** and **2** were prepared according to our earlier procedure.[14,15] Similarly, all the starting enamide esters **3a-i** and **4** were obtained by ring opening of the corresponding oxazolones **1a-e**, **1g-i** or **2** with appropriate alkoxides in alkanols as reported,[14a,15a] whereas, the enamide amide precursors **10a-k** and **11** were prepared by ring opening of the respective oxazolones **1a,1d-j** or **2** with appropriate primary amines or amino acid esters.[14,15a] The known enamide esters **3a-c, 3e-f, 3h, 4** and the enamide amides **10f**, **10h**, **10j** and **11** were characterized by comparison of their spectral data with those reported,[14a,15a] whereas the spectral and analytical data of the unknown **3g, 3i, 10a-c**,

10g and **10k** is given below. A few of the 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; ^{1}H 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; ^{1}H 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 (sex, 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; ^{1}H 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). (*E*:*Z* = 50:50), white solid (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). (*E*:*Z* = 50:50), off-white solid (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; ^{1}H 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), Lawesson's reagent (0.4 g, 1.0 mmol) was added and the reaction mixture was refluxed with stirring for 2-3 (for **8a-e**) or 10-12 h (for **8f-i** and **9**) (monitored by TLC). It was then poured into ice-cold water (30 mL), extracted with EtOAc (3 x 30 mL), washed with brine (1 x 30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude thiazoles, which were 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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.

***t*-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 (sex, 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), Lawesson's reagent (0.4 g, 1.0 mmol) was added and the reaction mixture was refluxed with stirring for 10-12 h (monitored by TLC). It was then concentrated under reduced pressure and the residue was diluted with water (30 mL), extracted with EtOAc (3 x 30 mL), washed with brine (1 x 30 mL), dried over Na_2SO_4, followed by removal of the solvent to give crude thiazoles, which 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; ^{1}H 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; ^{1}H 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 64.1, 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; ^{1}H NMR (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; ^1H 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 (sex, 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H

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; ^1H 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.

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Supporting Information. Figures giving ^1H NMR and ^{13}C NMR spectra and ORTEP X-ray crystal structure displays and CIF files giving 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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17. In the case of thionation-cyclization of all the enamide- amides **10a-k** and **11** with Lawesson's reagent, formation of some polymeric product was observed, along with the corresponding product thiazole -4- carboxamides **13a-k** and **14**.

When the enamide-anilide **10a** was reacted with excess of Lawesson's reagent (5 equiv) in refluxing THF for prolonged time (18 hr), monitoring of reaction showed initial formation of thiazole-4-anilide **13a**, which was slowly converted to the thiazole -4-thioanilide **17** in 66% yield. Similarly, when the thiazole **13a** was reacted with Lawesson's reagent (2 equiv) for 8 hr in refluxing THF, the thioanilide **17** was obtained in 65 % yield.