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PAPER

2-Phenyl-4-bis(methylthio)methyleneoxazol-5-one: versatile template for diversity oriented synthesis of heterocycles†‡

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4-Bis(methylthio)methylene-2-phenyloxazol-5-one (**1**) has been shown to be a versatile template for the synthesis of novel heterocyclic scaffolds. The key protocol involves nucleophilic ring opening of **1** with various primary aliphatic, aromatic amines and diamines to give open-chain amide adducts which are transformed into 4-bis(methylthio)methylene-2-phenyl-1-alkyl/arylimidazol-5-(4*H*)-ones (**5**) in good yields in the presence of anhydrous NaOAc/AcOH. Similarly, the amide adducts **4h–i** from 3,4-dimethoxyphenylethylamine and tryptamine undergo interesting rearrangement in the presence of $POCl_3$ to furnish 1-(2-phenyl-5-methylthio-4-thiazolyl)dihydroisoquinoline and β-carboline derivatives **8–9** in good yields. The amide adduct **14** from *o*-phenylenediamine on exposure to refluxing acetic acid or in the presence of Ag_2CO_3 affords substituted 3*H*-1,5-benzodiazepinone, 2-(5-methylthio-2-phenyl-4-oxazolyl)-1*H*-benzimidazole and trisubstituted oxazole (**15–17**), whereas the bis-adduct from ethylenediamine yields ethylene bridge tethered bis-imidazole **23** and bis-oxazole **24** under similar reaction conditions. Probable mechanisms for the formation of various products have been suggested.

Introduction

The imidazolone structural motif represents an important pharmacophore present in several therapeutics displaying a broad range of biological activity. In particular, imidazol-5-(4*H*)-one and its derivatives play a unique role in drug discovery[1] and crop protection[2] serving as privileged structures in combinatorial chemistry.[1d] Thus, compounds containing the imidazol-5-(4*H*)-one core are associated with antiviral (against both HSV and HIV),[1d] anticonvulsant,[3] immunosupressant,[4] protein kinase C (CDK-4) inhibitor,[1a] inflammation mediator,[1b] fungicidal and herbicidal[1d] and COX-2 inhibitor activity.[5] Some of these compounds act as antagonists against various receptors[6] such as angiotensin II receptor, dopamine CGRP, β_3-adrenergic and GABAA receptors.[6] Similarly, aplysinopsin, a naturally occurring 4-(indolylmethylene)-5-imidazolone derivative and its analogs display specific cytotoxicity for cancer cells,[7a–c] antileishmanial[7d] and anti-infective[7e] activity, and affect neurotransmission.[7a–b] Additionally, several imidazolone derivatives are used as intermediates in the synthesis of biologically active natural products including imidazoles.[6] Also, the 4-(aryl/heteroaryl)methyleneimidazolone moiety represents the main chromophore of green, blue and red fluorescent proteins (GFP, BFP, RFP).[6,8] α-Methyleneimidazolones also represent a highly electrophilic prosthetic group for chemical and biochemical studies.[9] Therefore, considerable interest has been evoked for the synthesis of such class of compounds in view of their broad range of biological activity and synthetic applications.[6,10]

Our own interest in the synthesis of imidazolone derivatives derives from our continued interest in the development of new general synthetic methods for five- and six-membered heterocycles using polarized ketene dithioacetals as versatile building blocks.[11–12] During the course of these studies, we have recently reported synthetic applications of 4-bis(methylthio)methylene-2-phenyloxazol-5-one (**1**) as a versatile template for the synthesis of 2-phenyl-4,5-substituted oxazoles.[13] The overall strategy involves nucleophilic lactone ring opening of **1** by various oxygen (alkoxides), nitrogen (amines) and carbon (Grignard reagents) nucleophiles to give open-chain adducts **2** in high yields followed by intramolecular 5-*endo* cyclization of **2** in the presence of silver carbonate to furnish 2,4,5-substituted oxazoles **3** in excellent yields (Scheme 1).[13] Facile ring opening of **1** by various nucleophiles, especially amines, further prompted us to envisage new synthetic transformations based on these open-chain amide adducts such as **4** leading to novel heterocycle scaffolds. We now report in the present paper, nucleophilic ring opening of **1** by various primary aliphatic/aromatic amines to **4** and their intramolecular cyclodehydration to novel 4-bis(methylthio)methylene-2-phenyl-1-alkyl/arylimidazol-5(4*H*)-ones **5** (Scheme 2). Synthetic transformations and rearrangements of a few open chain amides

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† Dedicated to Professor H. Junjappa on his 75th birthday.

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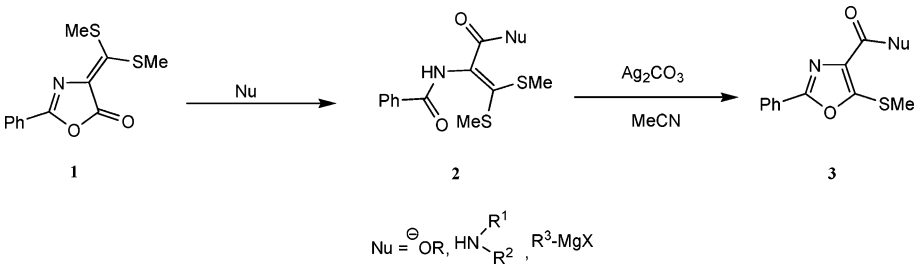
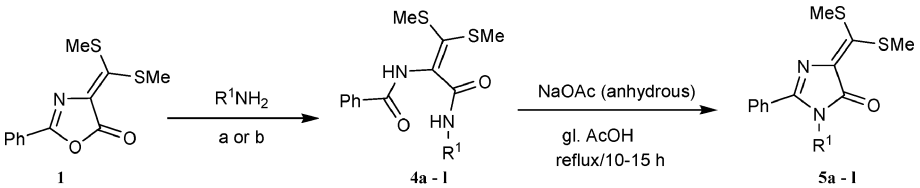


1 2 3

Scheme 1



1 4a - l 5a - l

Reagents and conditions: a, EtOH/RT/3-4 h; b, EtOH/AcOH (catalytic)/reflux/6-10 h.

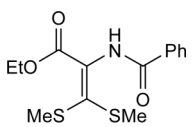
Scheme 2

from aromatic and aliphatic diamines to give novel heterocyclic scaffolds have also been reported.

Results and discussion

The ketene dithioacetal **1** was prepared from *N*-benzoylglycine, according to the modified procedure described in our previous paper.[13] Although we have reported earlier the reaction of a few primary amines with **1** in refluxing ethanol in the presence of a trace of acetic acid (entries 1 and 9, Table 1) to give the corresponding open-chain amide adducts (**4a** and **4i**), in our subsequent optimization studies, we found that most of the primary aliphatic amines smoothly react with **1** at room temperature in ethanol affording the acyclic amide adducts **4** in excellent yields (**4a**, **4d–i**, Table 1, entries 1, 4–9). The only exceptions were structurally crowded *i*-propyl and *t*-butyl amines which furnished the products **4b–c** in lower yields under these conditions along with the ethyl ester **6** as the side product formed by the ring opening of **1** by ethoxide ion (Table 1 entries 2–3). However, changing to a non-nucleophilic solvent such as THF afforded the amide adducts **4b–c** in high yields at room temperature (entries 2–3). On the other hand, the aromatic amines remained unreacted with **1** at room temperature in ethanol or THF and the amides **4j–l** were obtained in good yields only under refluxing ethanol in the presence of a trace of acetic acid (Table 1, entries 10–12).

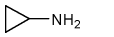
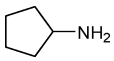
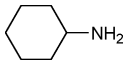
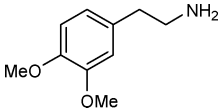
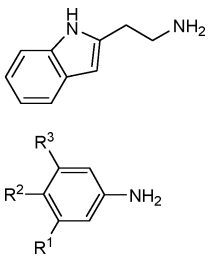
Intramolecular cyclodehydration of **4a** to imidazolone-4-dithioacetal **5a** was next attempted in the presence of various dehydrating agents (anhydrous $ZnCl_2$, K_2CO_3/EtOH, dry pyridine, anhydrous sodium acetate) and the best yield of **5a** (70%) was obtained when **4a** was exposed to freshly fused flame dehydrated sodium acetate in glacial acetic acid for 7 h (Table 1, entry 1). Similarly, the other open-chain amides **4d–l** from cyclic aliphatic amines, benzylamine and aromatic amines underwent smooth cyclodehydration under similar conditions furnishing the novel 1-*N*-substituted 2-pheyl-4-bis(methylthio)methylene-imidazol-5(4*H*)-ones **5d–l** in overall good yields (Table 1, entries 4–12). The adduct **4b** from *i*-propylamine, however, gave a low yield (48%) of imidazolone **5b** under these conditions (Table 1, entry 2), while no trace of 1-*N*-*t*-butylimidazolone **5c** was isolated on intramolecular cyclodehydration of the corresponding *N*-(*t*-butylamino) adduct **4c** (entry 3). In both of these reactions, the 4-bis(metylthio)methylene-5-oxazolone **1** was isolated in 38% and 60% yields, respectively (entries 2, 3). Apparently, the reaction takes different course because of steric reasons yielding **1** by intramolecular cyclization through the oxygen of the benzoylamino group in **4b–c** with concurrent elimination of bulkier amines as the major pathway.



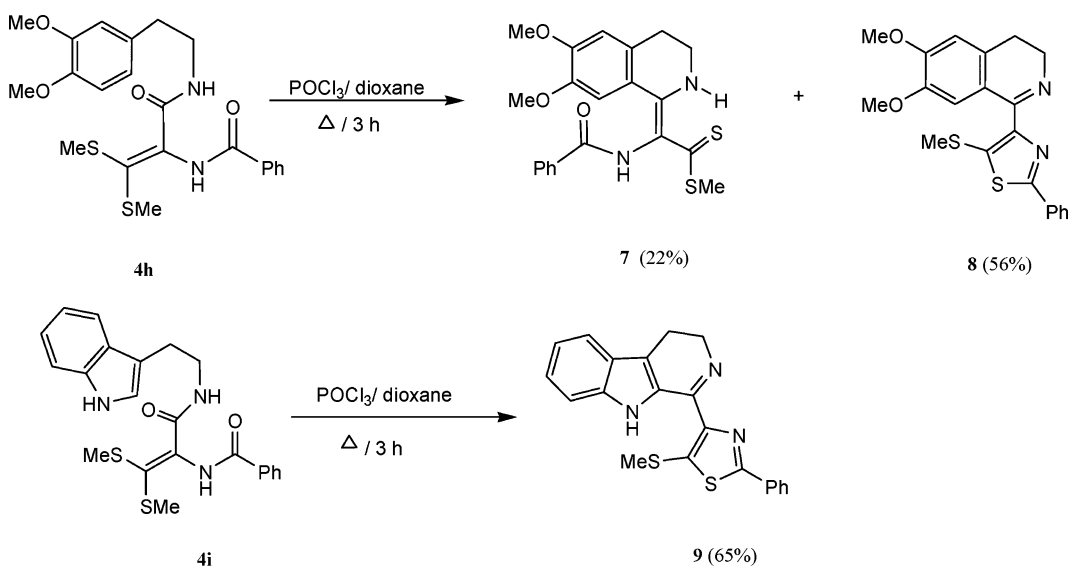
6

We next examined Bischler–Napieralski-type cyclization of open-chain amide adducts **4h** and **4i** from 3,4-dimethoxyphenylethylamine and tryptamine, in the presence of phosphorous oxychloride (Scheme 3). Since oxoketenedithioacetals are known to undergo partial hydrolysis to oxothioesters in the presence of Lewis acids,[14] we anticipated the formation of imidazo[5,1-*a*]isoquinoline derivatives such as A and B (Chart 1) through cascade dehydrative cyclization of **4h** and **4i** under these conditions.[15] However, when **4h** was reacted with phosphorous oxychloride (4 equiv.) in refluxing dioxane for 3 h, work-up of the reaction mixture furnished two products, which were characterized as the isoquinoline dithioester **7** (22%) and 6,7-dimethoxy-1-(5-methylthio-2-phenyl-4-thiazolyl)-3,4-dihydroisoquinoline **8** (56%) on the basis of spectral and analytical data. No trace of the desired imidazo[5,1-*a*]isoquinoline **A** could be detected from the reaction mixture (Scheme 3). Similarly, when open-chain amide adduct **4i** from tryptamine was exposed to $POCl_3$ under identical conditions, the only product isolated (65%) was identified as 1-(5-methylthio-2-phenyl-4-thiazolyl)-4,9-dihydro-3*H*-β-carboline **9** (Scheme 3). A probable mechanism for the formation of products **7** and **8**

Table 1 Synthesis of 4-bis(methythio)methylene-1-alkyl/cycloalkyl/aryl-2-phenylimidazol-5-ones (**5a–5l**)

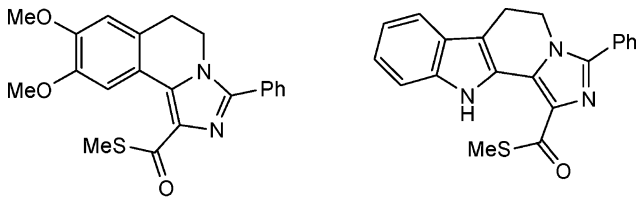
Entry	Primary amine	Reaction conditions	**4**	% Yield **4**	**5**	% Yield **5**[d]
1	$EtNH_2$	a	**4a**	85	**5a**	70
2	*i*-$PrNH_2$	b	**4b**	80[b] (59)[a]	**5b**	48 (38)[e]
3	*t*-$BuNH_2$	b	**4c**	81[b] (30)[a]	**5c**	0 (60)[e]
4		a	**4d**	78	**5d**	67
5		a	**4e**	75	**5e**	65
6		a	**4f**	78	**5f**	64
7	$PhCH_2NH_2$	a	**4g**	78	**5g**	59
8		a	**4h**	76	**5h**	58
9		a	**4i**	85	**5i**	61
10	R^2 = Me; R^1 = R^3 = H	c	**4j**	70	**5j**	58
11	R^1 = R^2 = MeO; R^3 = H	c	**4k**	69	**5k**	65
12	R^1 = R^3 = H; R^2 = OMe	c	**4l**	65	**5l**	64

Reaction conditions:[a] EtOH/RT/3–4 h. [b] THF/RT, 4 h for **4b**, 24 h for **4c**. [c] EtOH/gl. AcOH (catalytic)/Δ, 6–10h. [d] Yields of pure isolated compounds. [e] Yield of **1**.



Scheme 3

from **4h** is shown in the Scheme 4. Thus **4h** undergoes Bischler–Napieralski-type cyclization in the presence of $POCl_3$ to give dihydroisoquinoline intermediate **10** having a substituted ketene dithioacetal moiety at the 1-position. The intermediate **10** appears to undergo further $POCl_3$ assisted dethiomethylation through intermediate **11** to give dithioester **7** which was isolated as the minor product from cyclization of **4h**. Subsequent intramolecular cyclization of **7** in the presence of $POCl_3$ furnishes the observed product thiazole **8** through the intermediate **12** as depicted in Scheme 4.[16] The corresponding 1-(4-thiazolyl)-β-carboline **9** is also

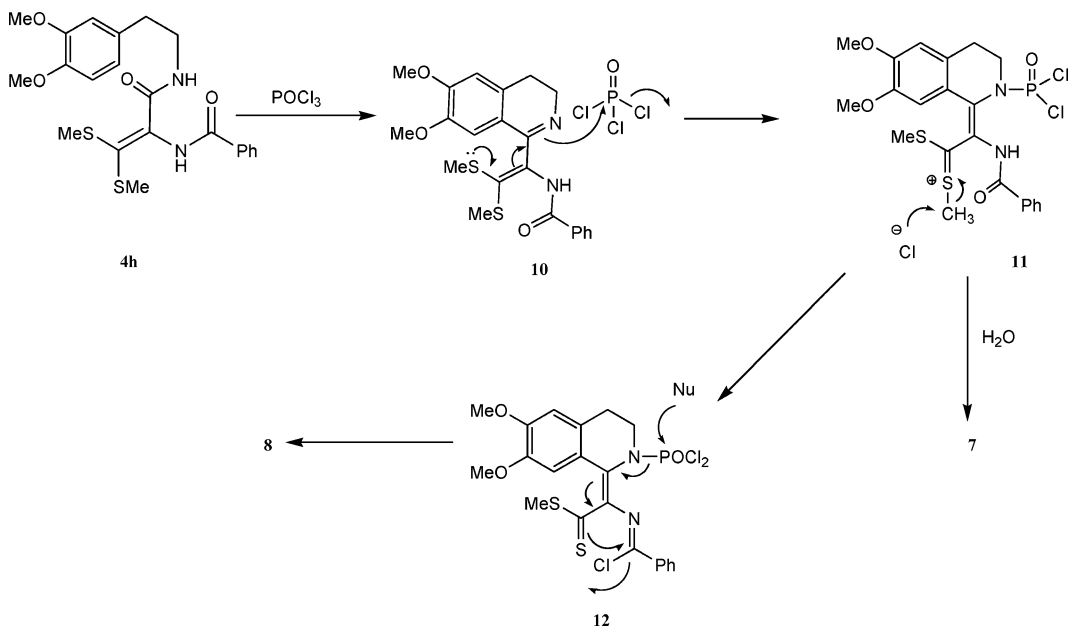


A B

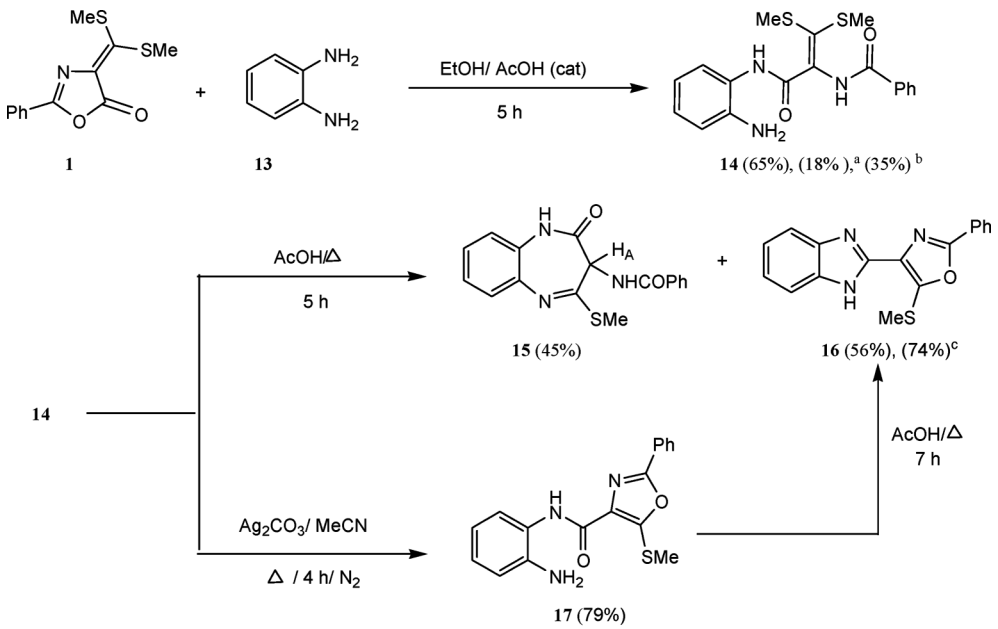
Chart 1

formed from **4i** through a similar mechanistic pathway (Schemes 3 and 4).

To further explore the versatility of **1** for the synthesis of novel heterocycles, we investigated the reaction of diamines such as *o*-phenylenediamine and ethylenediamine with **1** and the results are summarized in Schemes 5–7. Thus, the ketene dithioacetal **1** was reacted with *o*-phenylenediamine **13** (1 equiv.) in various solvents like benzene, xylene and ethanol. The product isolated in varying yields on prolonged refluxing was characterized as the open-chain 1 : 1 adduct **14** formed by nucleophile ring opening of **1** by one of the amino groups of *o*-phenylenediamine (Scheme 5). The product



Scheme 4



a, Yield of **14** in refluxing xylene (2.5 h). b, yield of **14** in refluxing benzene (72 h). c, yield of **16** from **17.**

Scheme 5

14 was obtained in increased yield (65%) within shorter time (5 h) when **1** was reacted with **13** in refluxing ethanol in the presence of a trace of acetic acid (Scheme 5). Reaction of *o*-phenylenediamine with 2 equivalents of **1** also yielded the open-chain anilide **14** (62%) as the only product under these conditions without any trace of bisadduct formed by ring opening of **1** by the second amino group of **14**. When the open-chain anilide **14** was subjected to further transformation in refluxing acetic acid (5 h), work-up of the reaction mixture yielded two products which were characterized as the substituted 3*H*-1,5-benzodiazepinone **15** (45%) and 2-(5-methylthio-2-phenyl-4-oxazolyl)-1*H*-benzimidazole **16** (56%) on the basis of their spectral and analytical data (Scheme 5). Intramolecular cyclization of **14** in the presence of silver carbonate in refluxing acetonitrile[13] furnished the *N*-(2-aminophenyl)-5-(methylthio)-2-phenyloxazol-4-carboxamide **17** in 79% yield as observed in our earlier studies (Scheme 5).[13] Thermal cyclization of **17** in refluxing glacial acetic acid also afforded the 2-(5-methylthio-2-phenyl-4-oxazolyl)benzimidazole **16** in 74% yield (Scheme 5). A probable mechanism for the formation of products **15–16** from the anilide adduct **14** is depicted in Scheme 6. Thus, intramolecular 1,4-conjugate addition of the amino group in **14** to the α-amidoketenedithioacetal moiety and subsequent elimination of methylmercaptan yields the 1,5-benzodiazepinone **15** (route a), which exists exclusively in the tautomeric form **15** with no trace of **15A** as evidenced by the presence of a one proton signal at δ 5.1 (d, 1H, J = 6 Hz) for H_A in its ^{1}H NMR spectrum (Scheme 6).[17] On the other hand, sequential intramolecular dehydrative cyclization of **14** followed by elimination of methylmercaptan through intermediates **19** and **20** yields 2-(5-methylthio-2-phenyl-4-oxazolyl)benzimidazole **16** as the other major product (route b, Scheme 6).

Finally, we also studied the nucleophilic ring opening of **1** with ethylenediamine **21** as shown in Scheme 7. Thus, treatment of **21** with either one or two equivalents of **1** in ethanol at room temperature provided only the bis-adduct **22** formed by attack of the more basic two amino groups on two molecules of **1** (Scheme 7). Intramolecular cyclodehydration of **22** in the presence of anhydrous sodium acetate in refluxing acetic acid afforded the ethylene bridge tethered bis-imidazolone **23** in 55% yield. Similarly, 2-phenyl-5-(methylthio)-bisoxazol-4-carboxamide **24** was obtained in high yield by intramolecular 5-*endo* cyclization of the bisamide adduct **22** in the presence of silver carbonate (Scheme 7).

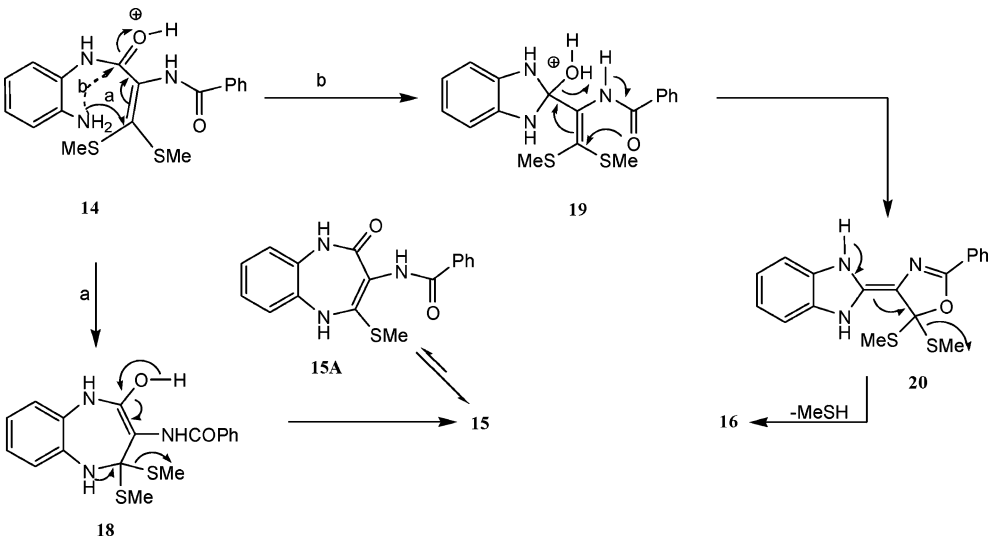
Conclusion

In summary, we have further demonstrated in the present paper the synthetic versatility of 4-bis(methylthio)methylene-2-phenyloxazol-5-one (**1**) for preparation of a variety of novel heterocyclic compounds. The protocols involve nucleophilic ring opening of **1** with various primary aliphatic/aromatic amines or diamines and subsequent transformations of the resulting amide adducts to either 4-bis(methylthio)methylene-2-phenyl-1-alkyl/arylimidazol-5(4*H*)-one **5** (*via* cyclodehydration) or to other novel heterocycles under appropriate conditions involving mechanistically interesting rearrangements. It should be noted that 2-substituted 4-bis(methylthio)methyleneimidazol-5-ones are virtually unexplored in the literature, except for one report,[18] and further work to examine their synthetic applications as well as their potential biological activity are in progress.

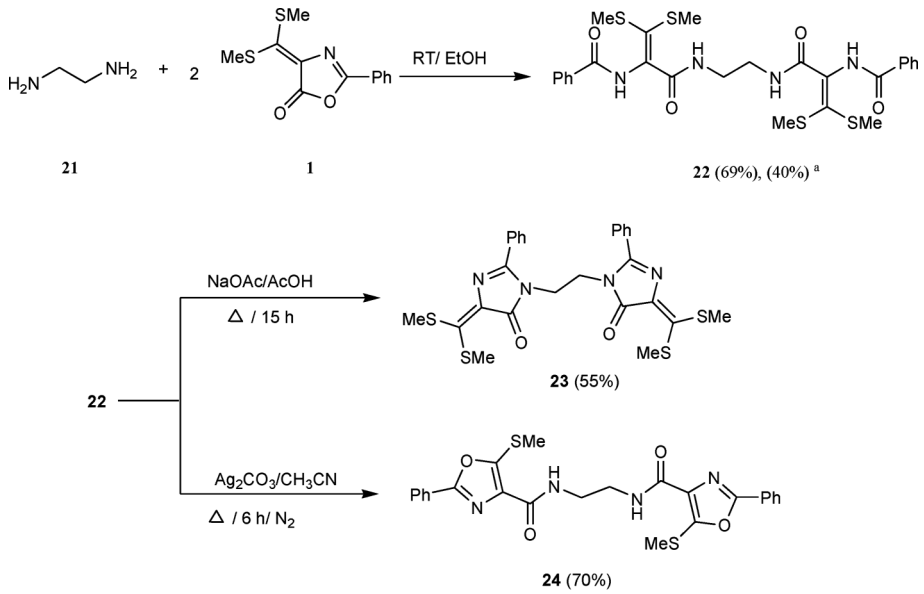
Experimental

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer and Jeol JNM Lambda and Jeol ECX-500 MHz (100 MHz, 400 MHz and 500 MHz) spectrometers with $CDCl_3$or DMSO-d_6 as solvent. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6 in ^{1}H, δ 77.0 for $CDCl_3$ and δ 40.45 for DMSO-d_6 in ^{13}C). Coupling constants (J) are reported in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet). MALDI (matrix assisted laser desorption ionisation) mass spectra were recorded on a Bruker Daltonics Ultrafelx II TOF/TOF. HRMS (ESI) were recorded on Waters Micromass Q-TOF Premier Mass Spectrometer. Infrared spectra were recorded with Bruker IFS 66 v/S and Perkin Elmer 1320 spectrometers. Melting points were



Scheme 6



a, yield of **22** with one equiv of **1**

Scheme 7

recorded using Mel-Temp apparatus (capillary method) and are uncorrected. Thin layer chromatography (TLC) analyses were performed on aluminium backed plates with a 0.2 mm layer of Kieselgel 60 F_{254} (Merck) and were visualized by UV (254 nm) and iodine indicator where appropriate. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and used without further purification. Acetonitrile was dried over P_2O_5 and stored over 4 Å molecular sieves. THF was distilled over sodium benzophenoneketyl. Silica gel (100–200 mesh) was used for column chromatography.

4-(Bis(methylthio)methylene)-2-phenyloxazol-5(4*H*)-one (**1**) was prepared according to the procedure reported in our previous paper.[13]

Synthesis of open chain amides 4a–l

Typical procedure. A solution of **1** (200 mg, 0.75 mmol) and the corresponding aliphatic amine (0.75 mmol) in absolute ethanol (10 ml) or dry THF (10 ml) was stirred at room temperature for 3–7 h (monitored by TLC), the solvent was evaporated under vacuum and the residue was triturated with diethyl ether to give a colorless solid, which was purified by crystallizing with ethyl acetate.

***N*-(3-(3,4-Dimethoxyphenethylamino)-1,1-bis(methylthio)-3-oxoprop-1-en-2-yl)benzamide (4h).** White solid, yield: 255 mg (76%), mp 154–155 °C. R_f 0.35 (MeOH/DCM: 0.2/9.8). ν_{max} (KBr)/cm^{-1} 1258, 1509, 1629, 1652, 3191, 3348. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, SCH_3), 2.33(3H, s, SCH_3), 2.92 (2H, t, J = 8 Hz, CH_2), 3.74 (2H, t, J = 8 Hz, NCH_2), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.18 (1H, br s, NH), 6.79 (1H, d, J = 8 Hz, ArH), 6.82 (1H, dd, J_1 = 8 Hz, J_2 = 2 Hz, ArH), 6.85 (d, J = 1.6 Hz, ArH), 7.45–7.57 (3H, m, ArH), 7.85 (2H, d, J = 8 Hz, ArH), 8.38 (1H, s, NH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 16.3, 17.7, 34.7, 41.1, 55.9, 56.0, 111.4, 112.2, 120.8, 124.3, 127.5, 128.8, 131.6, 132.4, 133.0, 136.6, 147.6, 149.0, 164.0, 164.2. MS (MALDI/TOF): m/z calcd for $C_{22}H_{26}N_2O_4S_2$ [M + Na]$^+$ 469.1232; found 469.1801.

***N*-(3-(2-(2-Benzamido-3,3-bis(methylthio)acrylamido)ethylamino)-1,1-bis(methylthio)-3-oxoprop-1-en-2-yl)benzamide (22).** The bis adduct **22** was prepared as described above for **4a–i** by using two equivalents of ketene dithioacetal **1** (200 mg, 0.75 mmol) and one equivalent of ethylenediamine (0.024 ml, 0.37 mmol). White solid, yield: 150 mg (69%), mp 202–203 °C. R_f 0.3 (MeOH/DCM: 0.5/9.5). ν_{max} (KBr)/cm^{-1} 1284, 1513, 1649, 3300, 3334. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.31 (6H, s, 2 × SCH_3), 2.36 (6H, s, 2 × SCH_3), 3.69–3.71 (4H, m, CH_2–CH_2), 7.32–7.36 (4H, m, ArH) 7.39 (2H, br s, 2 × NH), 7.46–7.49 (2H, m, ArH), 7.60–7.63(4H, d, J = 8.4 Hz, ArH), 8.31(2H, br s, 2 × NH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 16.4, 17.9, 37.9, 123.2, 127.2, 128.5, 132.3, 132.7, 137.1, 164.1, 164.2. MS (MALDI/TOF): m/z calcd for $C_{26}H_{30}N_4O_4S_4$ [M + Na]$^+$ 613.1047; found 613.2230.

Synthesis of anilides 4j–l and 14

A solution of ketene dithioacetal **1** (200 mg, 0.75 mmol) and the corresponding aromatic amine (0.75 mmol) in absolute ethanol (10 ml) in the presence of a catalytic amount of acetic acid (0.05 ml) was refluxed for 4–5 h with constant stirring (monitored by TLC) and the reaction mixture was worked up as described above for **4a–i**.

***N*-(1-(2-Aminophenylcarbamoyl)-2,2-bis-(methylthio)vinyl)-benzamide (14).** Pale yellow solid, yield: 185 mg (65%), mp 164–165 °C. R_f 0.4 (MeOH/DCM: 2/8). ν_{max} (KBr)/cm^{-1} 1475, 1511, 1628, 1666, 3312, 3361, 3406. ^{1}HNMR δ_H (400 MHz, DMSO-d_6) 2.36 (3H, s, SCH_3), 2.38 (3H, s, SCH_3), 5.08 (2H, br s, NH_2), 6.53 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, ArH), 6.67 (1H, d, J = 8 Hz, ArH), 6.95 (2H, dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, ArH), 7.08 (1H, d, J = 7.6 Hz, ArH), 7.51–7.63 (3H, m, ArH), 7.95 (2H, d, J = 8.4 Hz, ArH), 9.5 (1H, br s, NH), 9.77 (1H, br s, NH).

^{13}CNMR δ_C (400 MHz, DMSO-d_6) 16.1, 16.7, 115.0, 115.5, 122.2, 126.7, 126.9, 127.5, 127.7, 128.5, 132.1, 133.0, 135.5, 144.2, 163.0, 164.6. MS (MALDI/TOF): *m/z* calcd for $C_{19}H_{20}N_2O_3S_2$ [M + Na]$^+$ 411.0813; found 411.0513.

General procedure for the synthesis of 4-bis(methylthio)methylene-1-alkyl/aryl-2-phenyl-imidazol-5-(4*H*)-ones 5a–b, 5d–l and 23 from 4a–b, 4d–l and 22

A suspension of the respective open-chain amide or anilide (0.45 mmol) and freshly fused anhydrous sodium acetate (150 mg, 1.8 mmol) in glacial acetic acid (10 ml) was heated under reflux with stirring for 10–15 h (monitored by TLC). The reaction mixture was poured into ice-cold water (20 ml) and neutralized with saturated $NaHCO_3$ solution (25 ml) and extracted with dichloromethane (3 × 50 ml). The organic layer was washed with water (2 × 50 ml) and saturated NaCl solution (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give crude residue which was purified by column chromatography over silica gel using hexane–ethyl acetate as eluent.

4-(Bis(methylthio)methylene)-1-ethyl-2-phenyl-1*H*-imidazol-5-(4*H*)-one (5a). Yellow solid, yield: 132 mg (70%), mp 86–88 °C. R_f 0.6 (EtOAc/hexane: 3/7). ν_{max} (KBr)/cm^{-1} 1444, 1492, 1547, 1665. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* = 7.0 Hz, CH_3), 2.61 (3H, s, SCH_3), 2.78 (3H, s, SCH_3), 3.77 (2H, q, *J* = 7.0 Hz, CH_2), 7.42–7.47 (3H, m, ArH), 7.64–7.66 (2H, m, ArH). ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.5, 18.2, 19.6, 36.8, 128.1, 128.7, 129.7, 130.6, 134.7, 155.0, 155.7, 164.7. MS (MALDI/TOF): *m/z* calcd for $C_{14}H_{16}N_2OS_2$ [M + H]$^+$ 293.0782; found 293.1055.

4-(Bis(methylthio)methylene)-1-(3,4-dimethoxyphenethyl)–2-phenyl-1*H*-imidazol-5-(4*H*)-one (5h). Yellow solid, yield: 110 mg (58%), mp 153–154 °C. R_f 0.2 (EtOAc/hexane: 2/8). ν_{max} (KBr)/cm^{-1} 1027, 1261, 1495, 1513, 1678. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.64 (3H, s, SCH_3), 2.79 (3H, s, SCH_3), 2.78 (2H, t, *J* = 4.8 Hz, CH_2), 3.74 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.98 (2H, t, *J* = 7.6 Hz, NCH_2), 6.46 (1H, d, *J* = 2 Hz, ArH), 6.50 (1H, dd, *J* = 8 Hz, *J* = 2 Hz, ArH), 6.67 (1H, d, *J* = 8 Hz, ArH), 7.39–7.48 (5H, m, ArH). ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 18.4, 19.7, 34.5, 43.4, 55.7, 56.0, 111.3, 111.9, 120.8, 128.2, 128.5, 130.0, 130.3, 130.4, 135.0, 147.8, 149.0, 155.3, 156.0, 165.0. MS (MALDI/TOF): *m/z* calcd for $C_{22}H_{24}N_2O_3S_2$ [M + H]$^+$ 429.1306; found 429.1461.

4-(Bis(methylthio)methylene)-1-(2-(1*H*-indol-3-yl)ethyl)-2-phenyl-1*H*-imidazol-5-(4*H*)-one (5i). Yellow solid, yield: 115 mg (61%), mp 113–114 °C. R_f 0.4 (EtOAc/hexane: 4/6). ν_{max} (KBr)/cm^{-1} 1107, 1443, 1489, 1562, 1657, 1671, 3322. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.65 (3H, s, SCH_3), 2.79 (3H, s, SCH_3), 3.04 (2H, t, *J* = 7.6 Hz, CH_2), 4.04 (2H, t, *J* = 7.6 Hz, NCH_2), 6.90 (1H, d, *J* = 2 Hz, ArH), 7.01 (1H, dd, J_1 = 8 Hz, J_2 = 1.2 Hz, ArH), 7.15 (1H, dd, J_1 = 8 Hz, J_2 = 1.2 Hz, ArH), 7.29–7.38 (4H, m, ArH), 7.41–7.49 (3H, m, ArH), 7.97 (1H, br s, NH). ^{13}C NMR δ_C (100 MHz $CDCl_3$) 18.4, 19.7, 24.8, 42.6, 111.0, 112.2, 118.6, 119.5, 122.1, 122.2, 127.2, 128.1, 128.6, 130.0, 130.3, 135.2, 136.2, 155.5, 155.7, 165.1. MS (MALDI/TOF): *m/z* calcd for $C_{22}H_{21}N_3OS_2$ [M + H]$^+$ 408.1204; found 408.1448.

4-(Bis(methylthio)methylene)-1-(3,4-dimethoxyphenyl)-2-phenyl-1*H*-imidazol-5-(4*H*)-one (5l). Yellow solid, yield: 124 mg (65%), mp 158–160 °C. R_f 0.3 (EtOAc/hexane: 4/6). ν_{max} (KBr)/cm^{-1} 1025, 1121, 1249, 1445, 1513, 1558, 1595, 1686. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.67 (3H, s, SCH_3), 2.91 (3H, s, SCH_3), 3.77 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.69 (2H, m, ArH), 6.85 (1H, d, *J* = 8.0 Hz, ArH), 7.29 (3H, m, ArH), 7.50 (2H, d, *J* = 7.5 Hz, ArH). ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 18.4, 20.1, 56.0, 110.8, 111.1, 119.9, 127.4, 128.2, 128.5, 128.7, 130.7, 133.0, 148.8, 149.3, 153.0, 157.8, 163.8. MS (MALDI/TOF): *m/z* calcd for $C_{20}H_{20}N_2O_3S_2$ [M + H]$^+$ 401.0994; found 401.1556.

4-(Bis(methylthio)methylene)-1-(2-(4-(bis(methylthio)methylene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)ethyl)-2-phenyl-1*H*-imidazol-5-(4*H*)-one (23). Yellow solid, yield: 103 mg (55%), mp 199–200 °C. R_f 0.6 (MeOH/DCM: 0.5/9.5). ν_{max} (KBr)/cm^{-1} 1461, 1666, 2854, 2922. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.59 (6H, s, 2 × SCH_3), 2.79 (6H, s, 2 × SCH_3), 4.02 (4H, s, CH_2–CH_2), 7.41–7.45 (6H, m, ArH), 7.51–7.53 (4H, m, ArH). ^{13}C NMR δ_C (100 MHz, $CDCl_3$). 18.2, 19.7, 40.3, 128.3, 128.7, 129.0, 130.6, 135.3, 154.2, 155.6, 164.7. MS (MALDI/TOF): *m/z* calcd for $C_{26}H_{26}N_4O_2S_4$ [M + H]$^+$ 555.1917; found 555.2283.

General procedure for $POCl_3$ induced cyclization of 4h and 4i

To a solution of **4h** or **4i** (0.47 mmol) in dry dioxane (10 ml), $POCl_3$ (0.16 ml, 1.82 mmol) was added drop-wise and the reaction mixture was refluxed for 3–6 h (monitored by TLC). It was then slowly poured over ice-cold water (20 ml), neutralized with saturated $NaHCO_3$ (25 ml), extracted with EtOAc (4 × 50 ml). The organic layer was washed with water (2 × 75 ml) and saturated NaCl solution (75 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give crude residue, which was purified by column chromatography over silica gel using hexane–ethyl acetate as eluent.

(*E*)-Methyl-2-benzamido-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanedithioate (7). Yellow solid, yield: 40 mg (22%), mp 123–124 °C. R_f 0.4 (EtOAc/hexane: 2/8). ν_{max} (KBr)/cm^{-1} 1027, 1261, 1454, 1516, 1641, 3423. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.66 (3H, s, SCH_3), 2.97 (2H, t, *J* = 6.8 Hz, CH_2), 3.80 (3H, s, OCH_3), 3.85 (2H, t, *J* = 6.8 Hz, NCH_2), 3.87 (3H, s, OCH_3), 6.76 (1H, br s, NH), 6.81 (2H, d, *J* = 1.2 Hz, ArH), 7.44 (3H, m, ArH), 7.95 (2H, m, ArH), 9.84 (1H, br s, NH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 16.5, 36.0, 45.1, 56.0, 111.7, 112.1, 120.8, 122.8, 126.1, 126.2, 128.7, 130.3, 130.4, 148.1, 149.2, 149.2, 159.6, 202.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{22}N_2O_3S_2$ [M + Na]$^+$ 437.0970; found 437.0964.

6,7-Dimethoxy-1-(5-methylthio-2-phenyl-4-thiazolyl)-3,4-dihydroisoquinoline (8). Yellow solid, yield: 99 mg (56%), mp 146–147 °C. R_f 0.3 (EtOAc/hexane: 2/8). ν_{max} (KBr)/cm^{-1} 1067, 1148, 1279, 1439, 1557. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.59 (3H, s, SCH_3), 2.75 (2H, t, *J* = 7.2 Hz, CH_2), 3.84 (3H, s, OCH_3), 3.92 (2H, t, *J* = 7.2 Hz, NCH_2), 3.94 (3H, s, OCH_3), 6.74 (1H, s, ArH), 7.39–7.44 (3H, m, ArH), 7.56 (1H, s, ArH), 7.91 (2H, d, *J* = 8 Hz, ArH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 21.00, 26.0, 47.3, 56.0, 56.1, 110.0, 112.1, 121.4, 126.0, 129.0, 129.8, 132.2, 133.6, 138.7, 147.1, 149.2, 150.9, 160.3, 163.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{20}N_2O_2S_2$ [M + H]$^+$ 397.1044; found 397.1046.

1-(5-Methylthio-2-phenyl-4-thiazolyl)-4,9-dihydro-3*H*-β-carboline (9). Yellow solid, yield: 110 mg (63%), mp 173–174 °C. R_f 0.45 (EtOAc/hexane:2/8). ν_{max} (KBr)/cm^{-1} 1103, 1233, 1407,

1511, 3128. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.66 (3H, s, SCH_3), 3.00 (2H, t, J = 8.0 Hz, CH_2), 4.20 (2H, t, J = 8.0 Hz, NCH_2), 7.14 (1H, dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, ArH), 7.29 (1H, dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, ArH), 7.46–7.55 (4H, m, ArH), 7.63 (1H, d, J = 8 Hz, ArH), 7.93 (2H, d, J = 8 Hz, ArH), 10.38 (1H, br s, NH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 19.4, 20.6, 48.6, 112.2, 116.8, 119.8, 119.9, 124.2, 125.4, 126.0, 128.2, 129.2, 130.1, 133.2, 136.2, 140.9, 145.5, 153.4, 162.5. HRMS (ESI): m/z calcd for $C_{21}H_{17}N_3S_2$ [M + H]$^+$ 376.0942; found 376.0943.

Rearrangement of 14 in refluxing glacial AcOH

A solution of **14** (200 mg, 0.52 mmol) in glacial acetic acid (10 ml) was refluxed for 5 h (monitored by TLC). The reaction mixture was poured in to ice-cold water (20 ml), neutralized with saturated $NaHCO_3$ solution (25 ml) and extracted with dichloromethane (3 × 50 ml). The organic layer was washed with water (2 × 50 ml) and saturated NaCl (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give viscous residue, which was purified by column chromatography over silica gel using hexane and ethyl acetate as eluent.

***N*-(4-Methylthio-2-oxo-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-benzamide (15).** White solid, yield: 78 mg (45%), mp 209–110 °C. R_f 0.3 (MeOH/DCM: 2/8). ν_{max} (KBr)/cm^{-1} 1586, 1654, 1689, 3264. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, SCH_3), 5.12 (1H, d, J = 6.4 Hz, (NCH (H_A in **15**), 7.03 (1H, d, J = 8 Hz, ArH), 7.20 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, ArH), 7.3 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, ArH), 7.43 (1H, d, J = 8 Hz, ArH), 7.48–7.59 (4H, m, 3 ArH and 1 NH), 7.83 (1H, br s, NH), 7.92 (2H, d, J = 7.2 Hz, ArH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 13.7, 57.0, 122.0, 126.0, 126.4, 126.7, 127.6, 127.8, 129.0, 132.4, 133.4, 140.0, 164.4, 165.7, 167.2. MS (MALDI/TOF): m/z calcd for $C_{17}H_{15}N_3O_2S$ [M + Na]$^+$ 348.0783; found 348.0245.

2-(5-Methylthio-2-phenyloxazol-4-yl)-1*H*-benzimidazole (16). White solid, yield: 92 mg (56%), mp 183–184 °C. R_f 0.5 (EtOAc/hexane: 4/6). ν_{max} (KBr)/cm^{-1} 1280, 1412, 3061. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.72 (3H, s, SCH_3), 7.26–7.31 (3H, m ArH), 7.50–7.52 (4H, m, ArH), 7.90 (1H, br s, NH), 8.11–8.13 (2H, m, ArH), 10.08 (1H, br s, NH).). ^{13}C NMR δ_C (400 MHz $CDCl_3$) 17.4, 110.7, 120.3, 122.5, 123.5, 126.6, 129.0, 131.1, 132.6, 133.1, 144.5, 144.7, 144.8, 162.4. MS (MALDI/TOF): m/z calcd for $C_{17}H_{13}N_3OS$ [M + H]$^+$ 307.0779; found 307.0842.

Silver carbonate-induced cyclization of 14 and 22: synthesis of *N*-(2-aminophenyl)-5-(methylthio)-2-phenyloxazol-4-carboxamide (17) and bisoxazolone (24)

A suspension of **14** (250 mg, 0.67 mmol) or the bis-adduct **22** (395 mg, 0.67 mmol) and Ag_2CO_3 (740 mg, 2.68 mmol) in 10 ml of acetonitrile was refluxed under nitrogen atmosphere with constant stirring for 4–5 h (monitored by TLC). Ag_2CO_3 was filtered off by sintered funnel and the filtrate was concentrated under reduced pressure to give crude residue, which was purified by column chromatography over silica gel using hexane and ethyl acetate as eluent.

***N*-(2-Aminophenyl)-5-(methylthio)-2-phenyloxazol-4-carboxamide (17).** White solid, yield: 138 mg (79%), mp 151–152 °C. R_f 0.5 (EtOAc/hexane:4/6). ν_{max} (KBr)/cm^{-1} 1505, 1556, 1660, 3219, 3333, 3427. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.71 (3H, s, SCH_3), 3.96 (2H, br s, NH_2), 6.82–6.86 (2H, m, ArH), 7.07 (1H, dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, ArH), 7.44 (1H, d, J = 8.0 Hz, ArH), 7.49–7.51 (3H, m, ArH), 8.02–8.04 (2H, m, ArH), 8.75 (1H, br s, NH). ^{13}C NMR δ_C (400 MHz, $CDCl_3$) 15.2, 118.0, 119.5, 124.0, 125.0, 126.3, 126.4, 127.0, 129.0, 131.0, 131.4, 140.5, 151.7, 159.3, 160.2.MS (MALDI/TOF): m/z calcd for $C_{17}H_{15}N_3O_2S$ [M + H]$^+$ 326.0973; found 325.9872 and [M +Na]$^+$ 348.0784; found 347.0891.

5-(Methylthio)-*N*-(2-(5-(methylthio)-2-phenyloxazole-4-carboxamido)ethyl)-2-phenyloxazole-4-carboxamide (24). White solid, yield: 141 mg (70%), mp 214–215 °C. R_f 0.4 (MeOH/DCM: 0.5/9.5). ν_{max} (KBr)/cm^{-1} 1247, 1569, 1646, 3291. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.66 (6H, 2 × SCH_3), 3.69–3.71 (4H, m, CH_2–CH_2), 7.36 (2H, br s, 2 × NH), 7.46 (6H, m, ArH), 7.99 (4H, m, ArH). ^{13}C NMR δ_C (400 MHz $CDCl_3$) 14.6, 15.2, 39.3, 126.2, 126.3, 126.5, 128.9, 129.0, 130.8, 131.7, 150.7, 160.3, 161.8. MS (MALDI/TOF): m/z calcd for $C_{24}H_{22}N_4O_4S_2$ [M + H]$^+$ 495.1160; found 495.1255.

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