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Thiocarbonyl fluoride generated *in situ* from difluorocarbene for cyclization of vicinal X-H substituted amines (X = N, O or S)

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ABSTRACT

Difluorocarbene has served as a versatile intermediate in organic synthesis. The transformation of difluorocarbene into thiocarbonyl fluoride, which was discovered by us previously, can be developed as a synthetic tool for the cyclization of vicinal X-H substituted amines to provide various five-membered heterocycles. However, aryl amines are required to be used and difluoromethylation of the N—H bond or a newly generated S-H bond cannot be suppressed. Herein we describe the use of thiocarbonyl fluoride generated *in situ* as a thiocarbonyl source for the cyclization of vicinal X-H substituted alkyl amines (*X* = N, O, S) to provide imidazolidine-2-thiones, oxazolidine-2-thiones and thiazolidine-2-thiones. The use of alkyl amines constructs different heterocycles with those obtained from aryl amines. The free N—H bond remains intact without being difluoromethylated.

1. Introduction

As a singlet carbene, difluorocarbene is stabilized by the electron-donating effect of the fluorine lone pairs and destabilized by the electron-withdrawing nature of the fluorine element [1]. The stabilizing and destabilizing effects of the fluorine atoms make difluorocarbene a moderately electrophilic species, which has served as a versatile intermediate in organic synthesis [2]. Difluorocarbene usually acts as a CF_2 source for various transformations [2], such as difluoromethylation of X-H bonds [3] and transition-metal-catalyzed difluorocarbene transfer [2e,4], leading to various -CF_2- molecules (Scheme 1, eq 1, path a). Recently, extensive studies have shown that difluorocarbene can also act as a C_1 source of various nonfluorinated groups, such as carbonyl [5], cyanide [6] and isocyanide [7] groups (eq 1, path b).

$Ph_3P^+CF_2CO_2^-$ (PDFA), which was proposed as an intermediate by Burton in 1967 [8] and was successfully synthesized by us in 2013 [9], has proved to be an efficient difluorocarbene reagent. The use of PDFA by us [2b,6,10] and other groups [11] allowed for new discoveries in difluorocarbene chemistry. We first found that difluorocarbene can be captured by a suitable oxygen [10d], sulfur [10a,b,c] or nitrogen [6b] source to *in situ* generate carbonyl fluoride (CF_2═*O*), thiocarbonyl fluoride (CF_2═*S*), or cyanide anion (CN^-), respectively (Scheme 1, eq 1, path c). The *in situ* generation of these reactive intermediates was develop as synthetic tools to permit some challenging transformations, such as ^{18}O-trifluoromethoxylation [10d], ^{18}F-trifluoromethylthiolation [10a,10b] and cyanodifluoromethylation [6b]. Especially, the formation of thiocarbonyl fluoride received our substantial interest. Although thiocarbonyl fluoride is an important chemical feedstock, its synthetic utility remains largely unexplored due to its high toxicity and low availability. Its preparation usually requires the use of hazardous reagents (such as thiophosgene) and/or a high reaction temperature (500 °C) [12], and its storage and transportation require special safety precautions because it is highly toxic and is a gas at room temperature (bp = −54 °C) [12a]. The *in situ* generation and the immediate transformations of thiocarbonyl fluoride can avoid the storage and transportation, and more importantly, mild reaction conditions may make experimental studies possible [13]. The thiocarbonyl-fluoride formation from difluorocarbene has been applied to ^{18}F-trifluoromethylthiolation [10a,10b] and the synthesis of various heterocycles [10c,14]. Thiocarbonyl fluoride, generated *in situ*, can act as a thiocarbonyl source to react with vicinal X-H substituted amines (*X* = O, S or N) to form five-membered cycles, reported by us (Scheme 1, eq 2, path d) [10c] and

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the group of Weng (eq 2, path d) [14b]. However, both of the X-H and amino groups are required to be attached to aromatic rings. Furthermore, difluoromethylation of the N—H or a newly generated S-H group with difluorocarbene cannot be suppressed due to the high nucleophilicity of these two groups and the good electrophilicity of difluorocarbene, giving HCF_2-S or HCF_2-N products. In Weng's case, the X-H group vicinal to the amino group has to be a hydroxyl group (eq 2, path e). In contrast, we found that alkyl X-H substituted amines would react with thiocarbonyl fluoride to provide five-membered heterocycles with the N—H group remaining intact, and the X-H group can be NH, OH and SH groups, demonstrating a wide substrate scope (Scheme 1, eq 3). Preliminary results are described in this work.

2. Results and discussion

Although we have shown that low-polarity solvents favor for the generation of difluorocarbene [3b,15], only low yields were obtained for the cyclization in cyclohexane or toluene (entries 1, 2). Various reaction solvents were then screened, and it was found that the solvent significantly affected the yield (entries 1–9). The desired conversion may be completely suppressed without using a suitable solvent. To our delight, 1,2-dimethoxyethane (DME) as a solvent gave an excellent yield (entry 6). The examination of the temperature effect revealed that 80 °C was favorable for the reaction (entry 6 vs entries 10–13). The loading of PDFA had to be in slight excess (1.5 equiv), otherwise the yield would be decreased dramatically (entry 6 vs entries 14, 15). The molar ratios of **1a**:PDFA:S was further screened, but no increase in the yield was observed (entries 16–19).

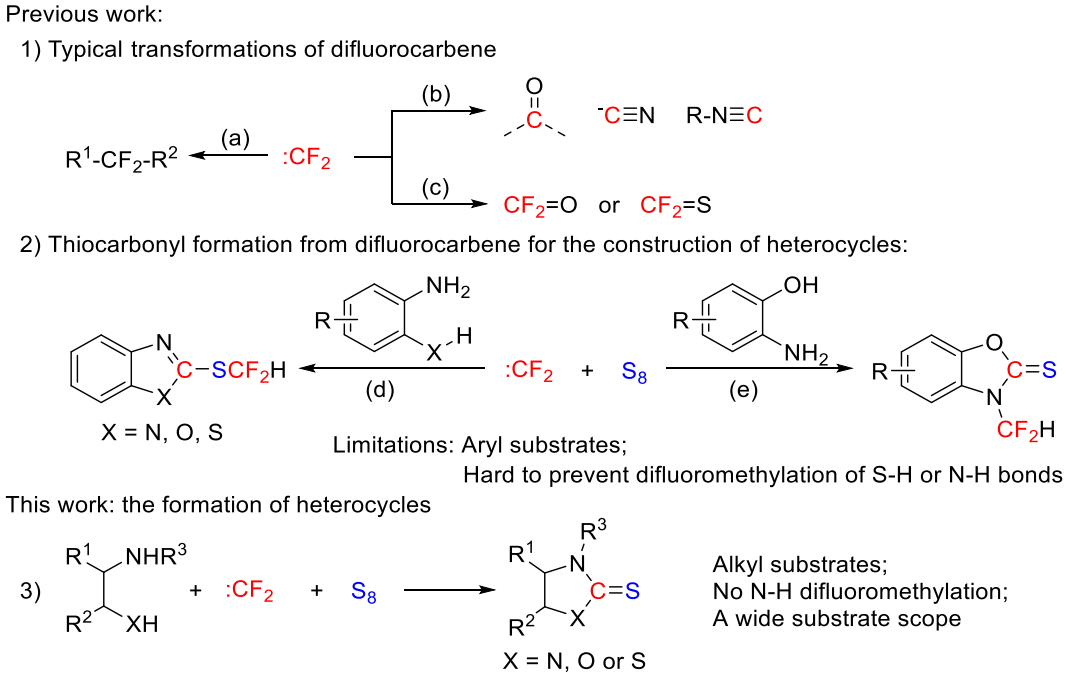
With the optimal reaction conditions in hand (Table 1, entry 6), we then investigated the substrate scope of the *in situ* generation of thiocarbonyl fluoride and the subsequent cyclization of vicinal X-H substituted amines. As shown in Scheme 2, all reaction proceeded rapidly and moderate to high yield were obtained within 10 min. The process could be extended to a wide range of vicinal diamines to provide various imidazolidine-2-thione (**2a-i**). Both primary (**2a-2f**) and secondary (**2 g-2i**) amines are reactive under these conditions. To our surprise, aryl diamine can also be converted into the desired thiourea (**2j**), as sharp contrast to our previous observations that aryl diamines would be transformed into HCF_2S-substituted imidazoles (Scheme 1, eq 2, path d) [10c]. The aryl group would be a driving force for the tautomerism of the cyclic thiourea unit to form a imidazole ring due to a conjugation effect, generating a new S-H group, which would then undergo difluoromethylation with difluorocarbene to deliver a HCF_2S-substituted imidazole. The significant difference should be ascribed to the loading of the difluorocarbene reagent, PDFA. The thiourea unit remained intact due to the less loading in this work. Besides diamines, vicinal hydroxyl amines also show good reactivity. Various oxazolidine-2-thiones were obtained in moderate yields (**2k-2n**). A hydrochloride form (RNH_3^+ Cl^-) can also be used as a substrate (**2o**). However, this salt is not soluble in the reaction solvent and the nucleophilicity of the amino group is decreased compared with the free amino group. Therefore, the desired product was produced in a low yield (**2o**).

Imidazolidine-2-thiones [16] and oxazolidine-2-thiones [17] are heterocycles which show biological activities, and they have also found widespread applications in organic synthesis [18]. Therefore, determined efforts have been directed towards their synthesis [19]. The commonly used strategy usually requires the installation of an isothiocyanate (-NCS) or a thiourea group into substrates. In our protocol, the reactive thiocarbonyl fluoride is generated *in situ* under mild conditions and can effectively act as a C = S source for cyclization. All starting materials and reagents are cheap and widely available.

On the basis of our previous studies [10a,b,c] and the above results, we propose the plausible reaction mechanism as shown in Scheme 3. $Ph_3P^+CF_2CO_2^-$ would readily generate difluorocarbene under heating conditions, and difluorocarbene is rapidly captured by elemental sulfur to produce thiocarbonyl fluoride [10b,10c]. Thiocarbonyl fluoride is a highly electrophilic species and would be attacked by the amino group to give intermediate **A** or isothiocyanate **B**. The subsequent intramolecular nucleophilic attack provides the final product.

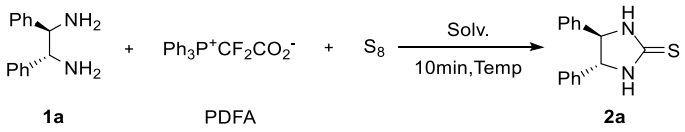
3. Conclusions

In summary, we have described the use of thiocarbonyl fluoride, generated *in situ* from difluorocarbene, as a thiocarbonyl source for the cyclization of vicinal X-H substituted amines (*X* = N, O or S) to provide imidazolidine-2-thiones, oxazolidine-2-thiones and thiazolidine-2-thiones. Although sequential steps are involved in the transformation,



Scheme 1. Transformations of difluorocarbene.

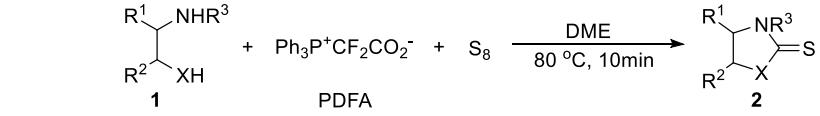
Table 1
The optimization of reaction conditions.



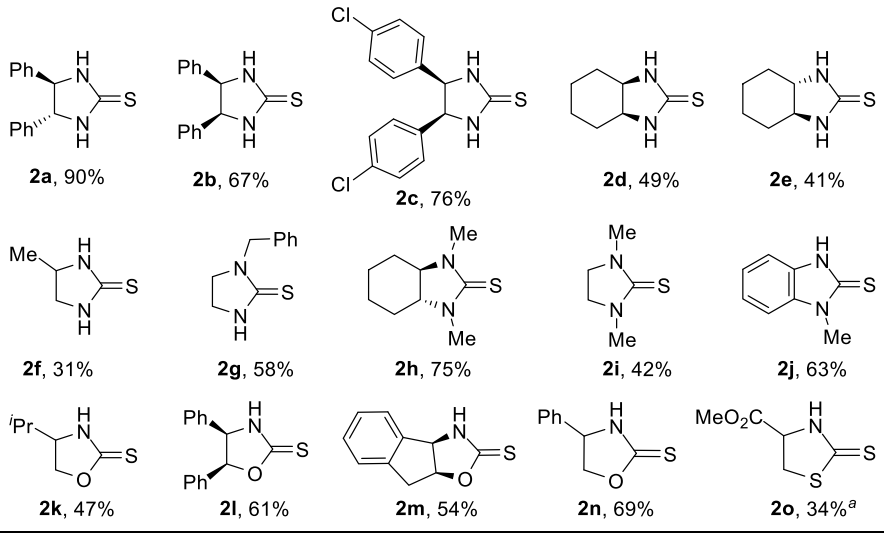
1a PDFA 2a

Entry	Solv.	Ratio[a]	Temp (°C)	Yield (%)[b]
1	Cyclohexane	1:1.5:0.375	80	24
2	Toluene	1:1.5:0.375	80	38
3	$ClCH_2CH_2Cl$	1:1.5:0.375	80	67
4	Dioxane	1:1.5:0.375	80	36
5	THF	1:1.5:0.375	80	52
6	DME	1:1.5:0.375	80	91
7	CH_3CN	1:1.5:0.375	80	31
8	DMSO	1:1.5:0.375	80	N.D.
9	DMF	1:1.5:0.375	80	35
10	DME	1:1.5:0.375	60	57
11	DME	1:1.5:0.375	70	69
12	DME	1:1.5:0.375	90	74
13	DME	1:1.5:0.375	120	63
14	DME	1:1:0.375	80	42
15	DME	1:1.25:0.375	80	62
16	DME	1:2:0.375	80	71
17	DME	1:1.5:0.125	80	29
18	DME	1:1.5:0.25	80	65
19	DME	1:1.5:0.5	80	56

Reaction conditions: substrate **1a** (0.2 mmol), PDFA and sulfur powder S_8 in DME (2 mL) at the indicated temperature for 10 min under an Ar atmosphere.
[a] Molar ratio of **1a**:PDFA:S_8.
[b] The yields were determined by ^1H NMR spectroscopy using as PhOMe an internal standard.



1 PDFA 2



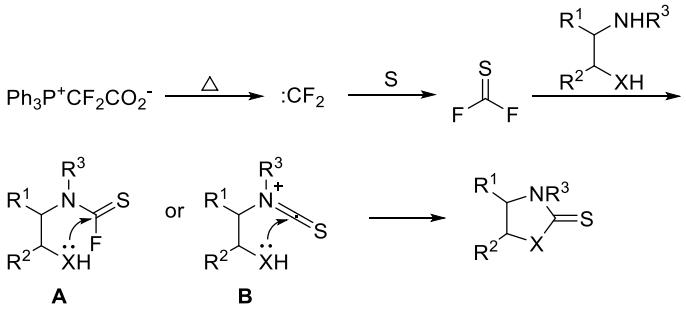
Scheme 2. Substrate scope investigations. Reaction conditions: substrate **1** (0.5 mmol), $Ph_3P^+CF_2CO_2^-$ (0.75 mmol) and sulfur powder S_8 (0.1875 mmol) in DME (5 mL) at 80 °C for 10 min under an Ar atmosphere. Isolated yields are shown. The relative configurations of products are the same as those of substrates. [a]A hydrochloride form (RNH_3^+ Cl^-) was used as a substrate.

a short reaction time (10 min) could give the desired products in moderate to high yields. The N—H bond in products remains intact despite its high nucleophilicity and the good electrophilicity of difluorocarbene. The facile synthetic protocol may find utility in the synthesis of biologically active heterocycles.

4. Experimental section

4.1. General remark

^1H, ^{13}C and ^{19}F NMR spectra were detected on a 500 MHz, 400 MHz or 300 MHz NMR spectrometer. Data for ^1H NMR, ^{13}C NMR and ^{19}F



Scheme 3. The proposed reaction mechanism.

NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (br = broad, *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *q* = quartet, coupling constant(s) in Hz). Mass spectra were obtained on GC–MS or ESI. High resolution mass data were recorded on a high-resolution mass spectrometer in the ESI mode. Unless noted, the substrates were bought from commercial suppliers and used without further purification.

4.2. General procedure for the reactions

Into a 20 mL sealed tube were added substrate **1a** (0.5 mmol, 106.1 mg, 1.0 equiv.), PDFA (0.75 mmol, 267.2 mg, 1.5 equiv.), S_8 (0.1875 mmol, 48.1 mg, 3 equiv.) and DME (5 mL) under an Ar atmosphere. The tube was sealed and the reaction mixture was stirred at 80 °C for 10 min. After the mixture was cooled to room temperature, the solvent was removed by concentration under vacuum and the residue was subjected to flash column chromatography with petroleum ether /ethyl acetate (10:1 ~ 4:1) as the eluent to afford product **2a** as a white solid (115.3 mg, 90 % yield).

4.3. Characterization data of products

***trans*-4,5-Diphenylimidazolidine-2-thione (2a)** [10c] as a white solid (115.3 mg, 90 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 6H), 7.29 – 7.26 (m, 4H), 6.46 (s, 2H), 4.82 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.63 (s), 139.01 (s), 129.19 (s), 128.88 (s), 126.42 (s), 70.21 (s); HR-MS (ESI) calcd. for $C_{15}H_{14}N_2S$ $[M+H]^+$: 255.0950, found: 255.0946.

***cis*-4,5-Diphenylimidazolidine-2-thione (2b)** [19b] as a white solid (85.4 mg, 67 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 2H), 7.09 – 6.99 (m, 6H), 6.93 – 6.85 (m, 4H), 5.30 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.26 (s), 137.21 (s), 127.59 (s), 127.18 (s), 64.58 (s); GC–MS (EI) calcd. for $C_{15}H_{14}N_2S$ $[M]^+$:254.1, found: 254.1.

***cis*-4,5-Bis(4-chlorophenyl)imidazolidine-2-thione (2c)** [20] as a white solid (122.8 mg, 76 % yield).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 2H), 7.18 (d, J = 8.1 Hz, 4H), 6.92 (d, J = 8.1 Hz, 4H), 5.34 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.29 (s), 136.19 (s), 131.78 (s), 128.94 (s), 127.73 (s), 63.61 (s); MS (ESI) calcd. for $C_{15}H_{12}Cl_2N_2S$ $[M+H]^+$: 323.0, found: 323.0.

***cis*-Octahydro-2H-benzo [*d*] imidazole-2-thione (2d)** [21] as a yellow solid (35.2 mg, 49 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 2H), 3.89 – 3.84 (m, 2H), 1.72 – 1.62 (m, 4H), 1.58 – 1.49 (m, 2H), 1.34 – 1.26 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.30 (s), 55.17 (s), 26.13 (s), 19.01 (s); GC–MS (EI) calcd. for $C_7H_{12}N_2S$ $[M]^+$: 156.1, found:156.1.

***trans*-Octahydro-2H-benzo [*d*] imidazole-2-thione (2e)** [19a] as a white solid (31.9 mg, 41 % yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 6.64 (s, 2H), 3.31 – 3.27 (m, 2H), 2.07 – 2.02 (m, 2H), 1.83 – 1.79 (m, 2H), 1.54 – 1.43 (m, 2H), 1.35 – 1.28 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.42 (s), 64.87 (s), 29.05 (s), 23.91 (s); GC–MS (EI) calcd. for $C_7H_{12}N_2S$ $[M]^+$: 156.1, found: 156.1.

4-Methylimidazolidine-2-thione (2f) [22] as a white solid (17.8 mg, 31 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (br, 1H), 6.72 (br, 1H), 4.20 – 4.07 (m, 1H), 3.81 (t, J = 9.5 Hz, 1H), 3.33 – 3.22 (m, 1H), 1.29 (d, J = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.06 (s), 53.20 (s), 52.02 (s), 20.83 (s); MS (ESI) calcd. for $C_4H_8N_2S$ $[M+H]^+$: 117.0, found: 117.0.

1-Benzylimidazolidine-2-thione (2 g) [23] as a white solid (55.6 mg, 58 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 6.35 (br, 1H), 4.81 (s, 2H), 3.56 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.69 (s), 136.16 (s), 128.81 (s), 128.22 (s), 127.90 (s), 50.92 (s), 48.03 (s), 41.37 (s); GC–MS (EI) calcd. for $C_{10}H_{12}N_2S$ $[M]^+$: 192.1, found: 192.1.

***trans*-1,3-Dimethyloctahydro-2H-benzo [*d*] imidazole-2-thione (2 h)** as a white solid (68.6 mg, 75 % yield). M.P.: 82.1–82.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 6H), 2.77 – 2.69 (m, 2H), 2.15 – 2.08 (m, 2H), 1.94 – 1.87 (m, 2H), 1.40 – 1.32 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.87 (s), 66.45 (s), 32.77 (s), 28.24 (s), 24.28 (s); IR (neat) ν 2938, 2856, 1469, 1428, 1387, 1375, 1333, 1311, 1261, 1239, 1204, 1132, 1120, 1080, 1063, 1049, 1013, 917, 825 cm^{-1}; HR-MS (FI) calcd. for $C_9H_{16}N_2S$ $[M]^+$: 184.1031, found: 184.1029.

1,3-Dimethylimidazolidine-2-thione (2i) [24] as a white solid (27.1 mg, 42 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 4H), 3.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.45 (s), 48.36 (s), 35.20 (s); GC–MS (EI) calcd. for $C_5H_{10}N_2S$ $[M]^+$: 130.1, found: 130.1.

1-Methyl-1,3-dihydro-2H-benzo [*d*] imidazole-2-thione (2j) [25] as a white solid (51.9 mg, 63 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (br, 1H), 7.28 – 7.15 (m, 4H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.03 (s), 132.27 (s), 129.50 (s), 122.42 (s), 121.86 (s), 109.23 (s), 108.05 (s), 29.50 (s); GC–MS (EI) calcd. for $C_8H_8N_2S$ $[M]^+$: 164.0, found: 164.0.

4-Isopropyloxazolidine-2-thione (2k) [19b] as a brown oil (34.2 mg, 47 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br, 1H), 4.69 (t, J = 9.1 Hz, 1H), 4.38 (dd, J = 9.0, 6.7 Hz, 1H), 3.89 – 3.82 (m, 1H), 1.88 – 1.79 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.59 (s), 72.53 (s), 61.48 (s), 31.19 (s), 17.03 (s), 16.87 (s); GC–MS (EI) calcd. for $C_6H_{11}NOS$ $[M]^+$: 145.1, found: 145.1

***cis*-4,5-Diphenyloxazolidine-2-thione (2l)** [26] as a white solid (75.5 mg, 61 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br, 1H), 7.18 – 7.02 (m, 6H), 6.98–6.88 (m, 4H), 6.16 (d, J = 8.7 Hz, 1H), 5.36 (d, J = 8.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.30 (s), 134.45 (s), 133.09 (s), 128.64 (s), 128.51 (s), 128.47 (s), 128.06 (s), 127.12 (s), 126.40 (s), 88.00 (s), 64.83 (s); GC–MS (EI) calcd. for $C_{15}H_{13}NOS$ $[M]^+$: 255.1, found: 255.1.

cis-3,3a,8,8a-Tetrahydro-2H-indeno [1,2-*d*] oxazole-2-thione (2 m) [27] as a white solid (50.7 mg, 54 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br, 1H), 7.28 – 7.13 (m, 4H), 5.65 – 5.58 (m, 1H), 5.32 (d, J = 7.6 Hz, 1H), 3.38 (d, J = 4.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.82 (s), 139.44 (s), 138.48 (s), 129.93 (s), 128.24 (s), 125.74 (s), 125.04 (s), 87.21 (s), 65.36 (s), 38.96 (s); GC–MS (EI) calcd. for $C_{10}H_9NOS$ $[M]^+$: 191.0, found: 191.0.

(*S*)−4-Phenyloxazolidine-2-thione (2n) [28] as a white solid (60.5 mg, 69 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br, 1H), 7.38 – 7.26 (m, 3H), 7.26 – 7.18 (m, 2H), 5.06 (dd, J = 9.3, 7.0 Hz, 1H), 4.91 (t, J = 9.1 Hz, 1H), 4.38 (dd, J = 8.9, 6.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.76 (s), 137.96 (s), 129.34 (s), 129.14 (s), 126.23 (s), 77.64 (s), 60.17 (s); GC–MS (EI) calcd. for C_9H_9NOS $[M]^+$: 179.0, found: 179.0.

Methyl-2-thioxothiazolidine-4-carboxylate (2o) [29] as a white solid (29.2 mg, 34 % yield). The used substrate is a hydrochloride form (RNH_3^+ Cl^-). ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.01 (br, 1H), 4.86 – 4.82 (m, 1H), 3.84 (s, 3H), 3.82 – 3.78 (m, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.49 (s), 169.04 (s), 63.82 (s), 53.56 (s), 35.62 (s); MS (ESI) calcd. for $C_5H_7NO_2S_2$ $[M+Na]^+$: 200.0, found $[M+Na]^+$: 200.2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data is included in the manuscript.

Acknowledgements

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2023.110212.

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