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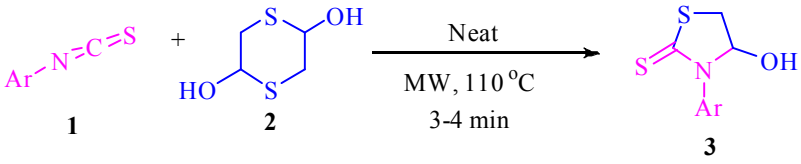

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A facile synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones through novel domino reactions of aryl isothiocyanates and 1,4-dithiane-2,5-diol under solvent- and catalyst-free microwave irradiation is reported.This highly atom efficient reaction presumably proceeds *via* 2-mercaptoacetaldehyde generation/thia-Michael addition/regioselective hemiaminalization domino sequence. This reaction also proceeds in good yields with aryl isocyanates affording 3-phenylthiazol-2(3*H*)-ones.

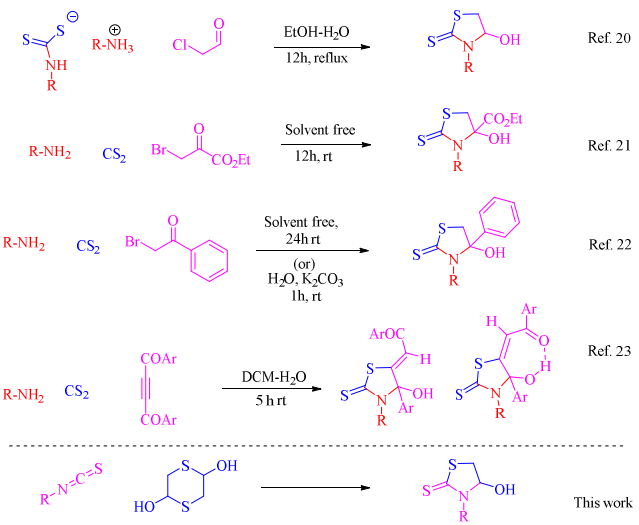
Introduction

In recent years, synthetic organic chemists have made tremendous efforts to design environmentally benign protocols for the assembly of biologically and medicinally active compounds. In particular, solvent- and catalyst-free methodologies[1] play a crucial role in pharmaceutical industries. These protocols significantly reduce the use of organic solvents and minimize waste generation.

Microwave irradiation has emerged as an important facet of green chemistry and one of the most powerful synthetic tools in the field of drug discovery and new methodology development research. Compared to conventional heating, microwave heating has better homogeneity, shorter reaction time, enhanced reaction rate, higher yield and improved purity rendering this process greener.[2]

Domino reactions[3] constitute another important synthetic tool in drug discovery programmes especially in the synthesis of heterocycles and total synthesis of natural products.[4] These reactions allow the generation of combinatorial libraries of high levels of structural diversity and complexity by two or more bond forming reactions under the same reaction conditions without adding additional reagents and catalysts. These reactions are endowed with (a) operational simplicity, (b) easy automation, (c) resource effectiveness, (e) atom economy and (f) minimal waste generation bringing them under the purview of green chemistry.

Drug-like small heterocycles are amongst the most ubiquitous pharmacophores[5] and hence have attracted great interest in chemical and medical communities. Rhodanine and its derivatives, known from the beginning of 20th century, constitute one of the most privileged scaffolds that possess a wide range of medicinal activities[6] likeantiviral,[7] antimicrobial,[8] antimalarial,[9] anticancer[10] and inhibitory activities such as HIV-1,[11] HIV-1 gp41,[12] JSP-1,[13] IKKβ,[14] PRL-3,[15] and cholesterol esterase.[16] The 3-phenylthiazole-2(3*H*)-thiones act as COX-2 inhibitors,[17] tyrosinaseinhibitors[18] and combretastatin analogs.[19]



Scheme 1. Some strategies for the synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones

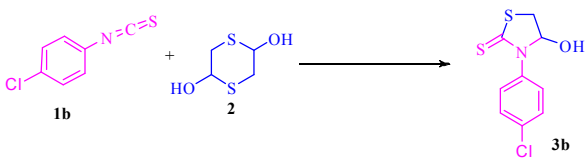
The previously reported methods for the construction of 4-hydroxy-3-arylthiazolidine-2-thione (Scheme 1) include i) [*N*-4-methylphenyl]ammonium dithiocarbamate and chloro-acetaldehyde in ethanol-water mixture,[20] ii) reaction between primary amines, carbon disulphide and ethyl bromopyruvate in solvent-free condition,[21] iii) reaction between amines, carbon disulphide and α-bromoketone in solvent-free condition[22a] as well as in the presence of K_2CO_3 in water[22b] and iv) reaction between aliphatic amines, carbon disulphide and acetylenic esters under neutral condition in water/DCM mixture.[23]

These synthetic methods, however, suffer from one or more disadvantages like limited diversity, polymeric nature of precursor (chloroacetaldehyde), need for excess amount of one of the reactent, long reaction time, toxic solvents, moderate yields, mixture of products, need for chromatographic separation and laborious workup. Therefore, from the perspective of green chemistry, evolution of new eco-friendly synthetic protocols is highly desirable. Consequently, we describe in this manuscript our findings on the synthesis of a library of 4-hydroxy-3-arylthiazolidine-2-thiones through two-component solvent- and catalyst-free microwave irradiation as a continuation of our interest in the construction of biologically relevant heterocycles employing tandem/domino/sequential processes and green transformations.[24] It is to be noted that 1,4-dithiane-2,5-diol has been used as the sulfur source instead of the conventional carbon disulfide.

Results and Discussion

We started our investigation on the reaction between 1-chloro-4-isothiocyanatobenzene **1b** and 1,4-dithiane-2,5-diol **2** (0.5 mmol) in the presence of a catalytic amount of TEA (25mol%) in ethanol under reflux condition.

Table 1. Optimization of reaction conditions for the synthesis **3b**.

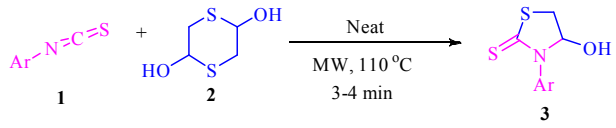


Entry	Base (25 mol %)	Solvent	Conditions[a]	Yield of 3b[b] (%)
1	TEA	EtOH	Thermal, 3h, reflux	82
2	TEA	EtOH	MW, 3min	85
3	TEA	MeOH	MW, 3min	78
4	TEA	DMF	MW, 4min	71
5	TEA	CH_3CN	MW, 4min	63
6	TEA	THF	MW, 3min	34
7	TEA	Water	MW, 4min	56
8	TEA	-	MW, 3min	86
9	DIPEA	-	MW, 3min	81
10	DBU	-	MW, 3min	69
11	DABCO	-	MW, 3min	62
12	K_2CO_3	-	MW, 3min	57
13	KF/Al_2O_3	-	MW, 3min	78
14	-	-	MW, 3min	88
15	-[c]	-	MW, 3min 110 °C	90
16	-[c]	-	MW, 3min 120 °C	89

[a]All microwave reactions performed at 120 W, 100 °C and 1 bar pressure; [b]Isolated yield after purification; [c]These microwave reactions performed at 120 W and 1 bar pressure.

This reaction proceeded smoothly furnishing 82% yield (entry 1) of 3-(4-chlorophenyl)-4-hydroxythiazolidine-2-thione **3b**. Then we investigated the reaction of an equimolar mixture of the reactants under microwave irradiation which gave a slightly enhanced 85% yield of **3b** (entry 2) compared to that obtained under reflux condition. Then reaction was examined in several solvents *viz.* EtOH, MeOH, DMF, CH_3CN, THF and water (entries 3-7) as well as under solvent-free (entry 8) condition with microwave irradiation at 100°C. The results showed that the reaction under solvent-free condition is as good as that in EtOH affording **3b** in 86% yield. We then investigated the reaction in the presence of several bases like DIPEA, DBU, DABCO, K_2CO_3 and KF/Al_2O_3 (entries 9-13) which led to no further improvement in the yield of the product. Interestingly, in the absence of any base (entry 14), this reaction afforded an excellent yield, 88% of **3b**. The reaction of an equimolar mixture of the reactants upon irradiation with microwaves at 110°C for 3 min led to 90% yield of **3b**, while the same reaction at 120°C for 3 min. resulted in 89% yield (entries 15-16). The data listed in Table 1 show that the solvent- and catalyst-free microwave irradiation at 110°C is optimal reaction condition for the synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones. With these optimized reaction conditions, we explored the scope of the reaction employing a series of arylisothiocyanates bearing different substituents in the aryl ring. It is found that the arylisothiocyanates having highly electron-withdrawing/electron-releasing groups such as 4-NO_2, 4-CF_3 and 4-NMe_2 in the aryl ring as well as aliphatic isothiocyanates failed to afford the product.

Table 2. Substrate scope of the two-component reaction leading to **3**[a]



Entry	Ar	Comp	Time/min	Yield 3 %[b]
1	4-FC_6H_4	**3a**	4	88
2	4-ClC_6H_4	**3b**	4	90
3	4-BrC_6H_4	**3c**	4	92
4	C_6H_5	**3d**	3	96
5	4-MeC_6H_4	**3e**	3	94
6	4-EtC_6H_4	**3f**	3	93
7	4-$^{i}PrC_6H_4$	**3g**	3	95
8	4-$MeOC_6H_4$	**3h**	3	92
9	3-FC_6H_4	**3i**	3	93
10	3-BrC_6H_4	**3j**	4	91
11	3-MeC_6H_4	**3k**	4	92
12	3-$MeOC_6H_4$	**3l**	3	94
13	2-$MeOC_6H_4$	**3m**	3	96

[a]All microwave reactions performed at 120 W, 110 °C and 1 bar pressure; [b]Isolated yield after washing with cold ethanol.

The structures of 4-hydroxy-3-arylthiazolidine-2-thiones **3** were deduced from one- and two-dimensional NMR spectroscopic data as detailed for **3e** as a representative example (vide Supporting information). Finally, the structure of the product **3a** was confirmed unambiguously by a single crystal X-ray crystallographic study[25] (Figure 1).

This transformation is 100% atom-economic, as all atoms of the reactants are built-in into the structure of the product, when one mole of **1** and 0.5 mole of **2** are allowed to react. The synthetic efficiency of the reaction, as measured by the product of atom-economy and yield, is also quite high justifying this reaction as an

atom efficient reaction.

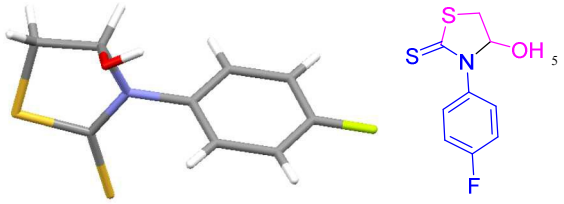
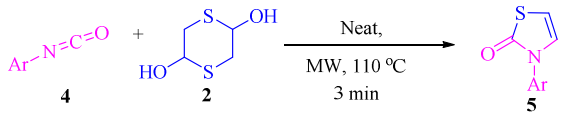


Figure 1. X-ray crystallographic structure for **3a**

We also performed the reaction of aryl isocyanates (1 mmol) **4** and 1,4-dithiane-2,5-diol (0.5 mmol) **2** under the same reaction conditions. This reaction furnished solely 3-phenylthiazol-2(3*H*)-one **5** in excellent yields, instead of the expected 4-hydroxy-3-phenylthiazolidin-2-one (**Table 3**). The accompanied easy dehydration in this case may be attributed to the acidity of the ring methylene hydrogens.

Table 3. Synthesis of 3-arylthiazol-2(3*H*)-ones **5**[a]

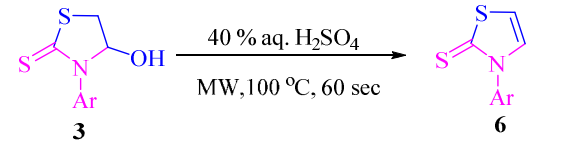


Entry	Ar	Comp	Time/min	Yield 5[b] %
1	C_6H_5	**5a**	3	95
2	4-ClC_6H_4	**5b**	3	94
3	4-$MeOC_6H_4$	**5c**	3	92

[a]All microwave reactions performed at 120 W, 110 °C and 1 bar pressure; [b]Isolated yield after washing with cold ethanol.

Further, we have also developed a rapid access to 3-arylthiazole-2(3*H*)-thione **6** in excellent yield from the reaction of **3** with 40% aq. H_2SO_4 (Table 4) under microwave irradiation in just 1 min – much quicker than the reported procedure.[26]

Table 4. Synthesis of 3-arylthiazole-2(3*H*)-thiones **6**

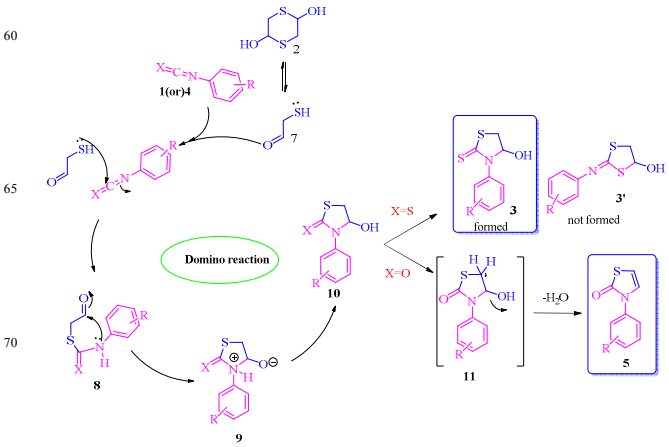


Entry	Ar	Comp.	Yield 6 %[a]
1	C_6H_5	**6a**	98
2	4-FC_6H_4	**6b**	96
3	4-EtC_6H_4	**6c**	94
4	3-FC_6H_4	**6d**	95
5	2-$MeOC_6H_4$	**6e**	97

[a]All microwave reactions performed at 120 W, 110 °C and 1 bar pressure.

The structures of 3-arylthiazole-2(3*H*)-thione **5** and 4-hydroxy-3-arylthiazolidin-2-one **6** have been deduced from their NMR spectroscopic data and ESI mass spectra as detailed for **5** and **6** (vide Supporting information).

The tentative mechanism for this transformation is outlined in Scheme 2. The first step presumably proceeds through the initial formation of 2-mercaptoacetaldehyde **7** from 1,4-dithiane-2,5-diol **2** which undergoes thia-Michael addition to arylisothiocyanate/aryl isocyanate **1/4** leading to the formation of intermediate **8**. Then this intermediate undergoes regioselective hemiaminalization affording product **3**. In this case, another possible regioisomer **3´** was not obtained even in traces. When X= O in **10**, subsequent elimination of water led to the product **5.**



Scheme 2. Probable domino sequence leading to the formation of **3** and **5**

Conclusion

In summary, we have developed an operationally facile, expedient, carbon disulfide free eco-friendly domino reaction for the synthesis of 4-hydroxy-3-thiazolidine-2-thiones, 3-arylthiazol-2(3*H*)-one and 3-arylthiazole-2(3*H*)-thiones in good to excellent yields from simple and inexpensive starting materials which involve a C-S and a C-N bond formation in a one pot operation with excellent atom economy. This present protocol may be useful for organic and medicinal applications.

Experimental Section

General information

Melting points were measured in open capillary tubes and are uncorrected. The microwave assisted reactions have been carried out in a Biotage Initiator instrument. The ^{1}H-NMR, ^{13}C-NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHN analyzer. Mass spectra were recorded in LCQ Fleet mass spectrometer, Thermo Fisher Instruments Limited, US. Electrospray ionisation mass spectrometry (ESI-MS) analysis was performed in the positive

ion mode on a liquid chromatographyion trap.

General procedure for the synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones, 3a-m: A vial containing a mixture of arylisothiocyanate (1 mmol) 1 and 1,4-dithiane-2,5-diol (0.5 mmol) 2 was placed in a microwave synthesizer. The vial was subjected to microwave irradiation programmed at 110°C, 120 W and 1 bar pressure. After 3-4 min of irradiation, the mixture was cooled to room temperature. Then the crude reaction mixture was triturated with cold ethanol to give pure products.

3-(4-Fluorophenyl)-4-hydroxythiazolidine-2-thione 3a: Isolated as off white solid. Yield: 88%; mp = 166-167 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 3.20 (d, J = 12.0 Hz, 1H), 3.89 (dd, J = 6.3, 12.0 Hz, 1H), 5.87 (t, J = 7.05 Hz, 1H), 7.28-7.35 (m, 2H), 7.38–7.43 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_c: 36.3, 91.9, 115.4(d, $^2J_{C,\,F}$ = 22.6 Hz), 130.0 (d, $^3J_{C,\,F}$ = 8.8 Hz), 135.1, 160.9 (d, $^1J_{C,\,F}$ = 243.3 Hz), 196.9; Anal. Calcd for $C_9H_8FNOS_2$; C, 47.15; H, 3.52; N, 6.11 %. Found: C, 47.10; H, 3.56; N, 6.19 %. ESI-MS: m/z. Calcd: 229.00; Found: 230.00 (M+1).

3-(4-Chlorophenyl)-4-hydroxythiazolidine-2-thione 3b: Isolated as off white solid. Yield: 90%; mp = 153-154 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 3.20 (d, J = 11.7 Hz, 1H), 3.90 (dd, J = 6.6, 11.8 Hz, 1H), 5.90 (t, J = 6.0 Hz, 1H), 7.35–7.47 (m, 2H), 7.55 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_c: 36.8, 92.2, 128.9, 130.0, 132.5, 138.1, 197.3; Anal. Calcd for $C_9H_8ClNOS_2$: C, 43.99; H, 3.28; N, 5.70%. Found: C, 44.08; H, 3.23; N, 5.73 %. ESI-MS: m/z. Calcd: 244.97; Found: 246.05 (M+1).

3-(4-Bromophenyl)-4-hydroxythiazolidine-2-thione 3c: Isolated as off white solid. Yield: 92%; mp = 148-149 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.31 (dd, J = 1.5, 12.3 Hz, 1H), 3.63 (d, J = 9.3 Hz, 1H), 3.89 (dd, J = 6.0, 12.3 Hz, 1H), 5.79 (t, J = 5.7 Hz, 1H), 7.31-7.36 (m, 2H), 7.57-7.62 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$ + DMSO-d$_6$) δ_c: 36.5, 91.6, 121.1, 129.1, 131.4, 137.7, 197.4; Anal. Calcd for $C_9H_8BrNOS_2$; C, 37.25; H, 2.78; N, 4.83 %. Found: C, 37.32; H, 2.89; N, 4.88%. ESI-MS: m/z. Calcd: 288.92; Found: 287.94 (M-1), 289.91 (M+1).

4-Hydroxy-3-phenylthiazolidine-2-thione 3d: Isolated as off white solid. Yield: 96%; mp = 157-158 °C [168 °C][20]; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 3.20 (dd, J = 2.1, 12.0 Hz, 1H), 3.91 (dd, J = 6.3, 12.0 Hz, 1H), 5.88-5.93 (m, 1H) 7.32-7.41 (m, 3H), 7.45-7.56 (m, 2H);^{13}C NMR (75 MHz, DMSO-d^6) δ_c: 36.8, 92.4, 128.0, 128.1, 128.9, 139.3, 196.9; Anal. Calcd for $C_9H_9NOS_2$ C, 51.16; H, 4.29; N, 6.63 %. Found: C, 51.24; H, 4.33; N, 6.68%. ESI-MS: m/z. Calcd: 211.01; Found: 212.08 (M+1).

4-Hydroxy-3-(p-tolyl)thiazolidine-2-thione 3e: Isolated as white solid; Yield 94%; mp = 130-131 ºC [143-44 °C][20]; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 2.39 (s, 3H), 3.29 (dd, J = 12.3, 1.5 Hz, 1H), 3.63 (brs, 1H), 3.86 (dd, J = 12.1, 6.1 Hz, 1H), 5.78 (brs, 1H), 7.41-7.72 (m, 4H); ^{13}C NMR (75 MHz, CDCl3) δ_C: 20.8, 36.7, 92.4, 127.9, 129.4, 136.7, 137.5, 196.8; Anal. Calcd for $C_{10}H_{11}NOS_2$ C, 53.31; H, 4.92; N, 6.22 %. Found: C, 53.35; H, 4.99; N, 6.17 %. ESI-MS: m/z. Calcd: 225.03; Found: 226.03 (M+1).

3-(4-ethylphenyl)-4-hydroxythiazolidine-2-thione 3f: Isolated as white solid; Yield: 93%; mp = 148-149 °C; ^{1}H NMR (300 MHz, CDCl$_3$ + DMSO-d$_6$) δ_H: 1.25 (t, J = 7.6 Hz, 3H), 2. 68 (q, J = 7.5 Hz, 2H), 3.28 (d, J = 12.0 Hz, 1H), 3.81 (dd, J = 6.3, 12.0 Hz, 1H), 5.79 (t, J = 6.6 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$ + DMSO-d$_6$) δ_c: 15.5, 27.9, 36.7, 92.4, 127.9, 128.2, 136.9, 143.6, 196.8; Anal. Calcd for $C_{11}H_{13}NOS_2$; C, 55.20; H, 5.47; N, 5.85 %. Found: C, 55.14; H, 5.52; N, 5.76%. ESI-MS: m/z. Calcd: 239.04; Found: 239.99 (M+1).

4-hydroxy-3-(4-isopropylphenyl)thiazolidine-2-thione 3g: Isolated as white solid; Yield: 95%; mp = 186-187 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 1.21 (d, J = 2.7 Hz, 3H), 1.23 (d, J = 3.3 Hz, 3H), 2,88-2.95 (m, 1H), 3.17 (d, J = 12.0 Hz, 1H), 3.88 (ddd, J = 3.2, 6.5, 11.9 Hz, 1H), 5.83 (m, 1H), 7.27-7.34 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_c: 23.8, 33.2, 36.7, 92.4, 126.8, 127.9, 136.9, 148.1, 196.8; Anal. Calcd for $C_{12}H_{15}NOS_2$; C, 56.88; H, 5.97; N, 5.53 %. Found:C, 56.98; H, 6.02; N, 5.60 %. ESI-MS: m/z. Calcd: 253.06; Found: 254.04 (M+1).

4-hydroxy-3-(4-methoxyphenyl)thiazolidine-2-thione 3h: Isolated as white solid; Yield: 92%; mp = 176-177 °C [162-63 °C][20]; ^{1}H NMR (300 MHz, CDCl$_3$ + DMSO-d$_6$) δ_H: 3.02 (m,1H), 3.54-3.59 (m, 4H), 4.45 (brs, 1H), 5.53 (brs, 1H), 6.71-6.79 (m, 2H), 7.07-7.17 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_c: 36.5, 55.4, 92.3, 114.1, 129.3, 131.9, 158.7, 196.9; Anal. Calcd for $C_{10}H_{11}NO_2S_2$; C, 49.77; H, 4.59; N, 5.80 %. Found: C, 49.69; H, 4.64; N, 5.89 %. ESI-MS: m/z. Calcd: 241.02; Found: 241.98 (M+1).

3-(3-fluorophenyl)-4-hydroxythiazolidine-2-thione 3i: Isolated as white solid; Yield: 93%; mp = 175-176 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 3.21 (dd, J = 7.2, 12.1 Hz, 1H), 3.89 (dd, J = 6.6, 12.0 Hz, 1H), 5.93-5.95 (m, 1H), 7.24-7.29 (m, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.48-7.55 (m, 1H);^{13}C NMR (75 MHz, DMSO-d$_6$) δ_c: 36.9, 92.3, 114.9 (d, $^2J_{C,\,F}$ =20.0 Hz), 115.3 (d, $^2J_{C,\,F}$ = 23.3 Hz), 124.4 (d, $^4J_{C,\,F}$ = 2.8 Hz), 130.5(d, $^3J_{C,\,F}$ = 8.9 Hz), 140.7(d, $^3J_{C,\,F}$ =10.2 Hz), 161.8 (d, $^1J_{C,\,F}$ = 242.8 Hz), 197.3; Anal. Calcd for $C_9H_8FNOS_2$: C, 47.15; H, 3.52; N, 6.11 %. Found: C, 47.18; H, 3.48; N, 6.17 %. ESI-MS: m/z. Calcd: 229.00; Found: 230.00 (M+1).

3-(3-bromophenyl)-4-hydroxythiazolidine-2-thione 3j: Isolated as white solid; Yield: 91%; mp =124-125 °C; ^{1}H NMR (300 MHz, CDCl$_3$ + DMSO-d$_6$) δ_H: 3.29-3.33 (m, 1H), 3.82 (d, J = 6.3, 12.0 Hz, 1H), 5.81 (t, J = 6.0 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), (7.35-7.40 (m, 1H), 7.50-7.53 (m, 1H), 7.63 (m, 1H);^{13}C NMR (75 MHz, DMSO-d$_6$) δ_c: 36.9, 92.3, 121.2, 127.5, 130.8, 130.9, 140.7, 197.4; Anal. Calcd for $C_9H_8BrNOS_2$; C, 37.25; H, 2.78; N, 4.83 %. Found: C, 37.18; H, 2.89; N, 4.87 %. ESI-MS: m/z. Calcd: 288.92; Found: 289.92 (M+1), 291.88 (M+2).

4-hydroxy-3-(m-tolyl)thiazolidine-2-thione 3k: Isolated as white solid; Yield: 92%; mp = 151-152 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) δ_H: 2.39 (s, 3H), 3.31 (dd, J = 1.5, 12.4 Hz, 1H), 3.53 (brs, 1H), 3.88 (dd, J = 6.0, 12.3 Hz, 1H), 5.81 (d, J = 5.7 Hz, 1H), 7.20-7.26 (m, 3H), 7.34-7.39 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 21.3, 37.2, 92.2, 124.7, 128.1, 129.3, 129.6, 138.6, 139.6, 198.1; Anal. Calcd for $C_{10}H_{11}NOS_2$; C, 53.31; H, 4.92; N, 6.22 %. Found: C, 53.40; H, 4.84; N, 6.28%. ESI-MS: m/z. Calcd: 225.03; Found: 226.01 (M+1).

4-hydroxy-3-(3-methoxyphenyl)thiazolidine-2-thione 3l: Isolated as white solid; Yield: 94%; mp = 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ_H: 3.27-3.31 (m, 1H), 3.78-3.84 (m, 4H), 5.81 (brs, 1H), 6.84 (brs, 1H), 6.90–6.94 (m, 1H), 7.00-7.02 (m, 2H), 7.34-7.39 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ_c: 36.8, 55.3, 92.4, 113.5, 113.8, 120.3, 129.6, 140.3, 159.5, 196.8; Anal. Calcd for $C_{10}H_{11}NO_2S_2$; C, 49.77; H, 4.59; N, 5.80 %. Found: C, 49.71; H, 4.64; N, 5.72 %. ESI-MS: m/z. Calcd: 241.02; Found: 242.06 (M+1).

4-hydroxy-3-(2-methoxyphenyl)thiazolidine-2-thione 3m: Isolated as white solid; Yield: 96%; mp = 79-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ_H: 3.22 (dd, J = 2.2, 12.1 Hz, 1H), 3.79 (s, 3H), 3.86 (dd, J = 6.7, 12.4 Hz, 1H), 5.75 (brs, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 36.3, 55.1, 90.0, 111.4, 120.0, 126.4, 129.2, 130.9, 196.9; Anal. Calcd for $C_{10}H_{11}NO_2S_2$; C, 49.77; H, 4.59; N, 5.80 %. Found: C, 49.73; H, 4.55; N, 5.89 %.

General procedure for the synthesis of 3-phenylthiazol-2(3*H*)-ones 5a-c: A vial containing a mixture of arylisocyanate (1 mmol) **4** and 1,4-dithiane-2,5-diol (0.5 mmol) **2** was placed in a Biotage microwave synthesizer. The vial was subjected to microwave irradiation programmed at 110 ^{o}C, 120 W and 1 bar pressure. After 3 min of irradiation, the mixture was cooled to room temperature. Then the crude reaction mixture was triturated with cold ethanol to give pure products **5a-c**.

3-phenylthiazol-2(3H)-one 5a: Isolated as off white. Yield: 95%; mp = 53-54°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.25 (d, J = 5.4 Hz, 1H), 6.82 (d, J = 5.4 Hz, 1H), 7.34-7.38 (m, 2H), 7.39-7.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 101.9, 124.3, 124.9, 127.6, 129.3, 136.7, 170.9; Anal. Calcd for C_9H_7NOS: C, 61.00; H, 3.98; N, 7.90 %. Found: C, 61.08; H, 3.91; N, 7.94 %.

3-(4-chlorophenyl)thiazol-2(3H)-one 5b: Isolated as off white solid. Yield: 94%; mp = 62-63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.26 (d, J = 5.4 Hz, 1H), 6.79 (d, J = 5.7 Hz, 1H), 7.38-7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 102.4, 124.4, 125.4, 129.4, 133.3, 135.2, 170.7; Anal. Calcd for C_9H_6ClNOS: C, 51.07; H, 2.86; N, 6.62 %. Found: C, 51.16; H, 2.92; N, 6.52 %.

3-(4-methoxyphenyl)thiazol-2(3H)-one 5c: Isolated as off white solid. Yield: 92%; mp = 55-56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.83 (s, 3H), 6.21 (d, J = 5.4 Hz, 1H), 6.76 (d, J = 5.4 Hz, 1H), 6.95-6.99 (m, 2H), 7.33-7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 55.4, 101.4, 114.5, 125.3, 125.8, 129.6, 158.8, 171.0; Anal. Calcd for $C_{10}H_9NO_2S$; C, 57.96; H, 4.38; N, 6.76 %. Found: C, 57.92; H, 4.45; N, 6.84 %. ESI-MS: m/z. Calcd: 207.04; Found: 208.03 (M+1).

General procedure for the synthesis of 3-phenylthiazole-2(3*H*)-thiones 6a-e: A vial containing a mixture of 4-hydroxy-3-arylthiazolidine-2-thione **3** (1 mmol) and 40% aq. H_2SO_4 was placed in a Biotage microwave synthesizer. The vial was subjected to microwave irradiation programmed at 100^{o}C, 120 W and 1 bar pressure. The vial was cooled and the mixture poured into water. Then mixture was extracted with DCM; organic phases were collected and dried over Na_2SO_4. Removal of the solvent furnished pure 3-phenylthiazole-2(3*H*)-thiones **6a-e** as semisolids.

3-phenylthiazole-2(3H)-thione 6a: Isolated as off white solid. Yield: 98%; mp = 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.68 (d, J = 4.5 Hz, 1H), 7.13 (d, J = 4.5 Hz, 1H), 7.44–7.75 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 111.2, 126.4, 129.2, 129.4, 132.5, 138.5, 188.7; Anal. Calcd for $C_9H_7NS_2$; C, 55.93; H, 3.65; N, 7.25 %. Found: C, 56.01; H, 3.59; N, 7.28 %. ESI-MS: m/z. Calcd: 193.00; Found: 193.98 (M+1).

3-(4-fluorophenyl)thiazole-2(3H)-thione 6b: Isolated as off white solid. Yield: 96%; mp = 127-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.68 (d, J = 4.5 Hz, 1H), 7.11 (d, J = 4.8 Hz, 1H), 7.18-7.26 (m, 2H), 7.45-7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 111.3, 116.5 (d, $^2J_{C,F}$= 23.0 Hz), 128.5 (d, $^3J_{C,F}$ = 8.7 Hz), 132.4, 134.4, 162.4 (d, $^1J_{C,F}$ = 248.7 Hz), 188.9; Anal. Calcd for $C_9H_6FNS_2$; C, 51.17; H, 2.86; N, 6.63 %. Found: C, 51.12; H, 2.95; N, 6.67 %. ESI-MS: m/z. Calcd: 210.99; Found: 211.96 (M+1).

3-(4-ethylphenyl)thiazole-2(3H)-thione 6c: Isolated as viscous brown liquid. Yield: 94%; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.28 (t, J = 7.5 Hz, 3H), 2. 72 (q, J = 7.6 Hz, 2H), 6.66 (d, J = 4.5 Hz, 1H), 7.11 (d, J = 4.5, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.38-7.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 15.1, 28.4, 111.1, 126.1, 128.8, 132.7, 136.0, 145.4, 188.5; Anal. Calcd for $C_{11}H_{11}NS_2$; C, 59.69; H, 5.01; N, 6.33 %. Found: C, 59.79; H, 5.07; N, 6.26 %. ESI-MS: m/z. Calcd: 221.03; Found: 222.04 (M+1).

3-(3-fluorophenyl)thiazole-2(3H)-thione 6d: Isolated as off white solid. Yield: 95%; mp = 69-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.68 (d, J = 4.5 Hz, 1H), 7.12 (d, J = 4.5 Hz, 1H), 7.16-7.22 (m, 1H), 7.26-7.31 (m, 2H), 7.45-7.55 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 111.5, 114.4 (d, $^2J_{C,F}$ = 24.2 Hz), 116.3 (d, $^2J_{C,F}$ = 20.0 Hz), 122.2 (d, $^4J_{C,F}$ = 3.3 Hz), 130.7 (d, $^3J_{C,F}$ = 10.0 Hz), 132.1, 139.4 (d, $^3J_{C,F}$ = 7.5 Hz), 162.5 (d, $^1J_{C,F}$ = 247.5 Hz), 188.6; Anal. Calcd for $C_9H_6FNS_2$; C, 51.17; H, 2.86; N, 6.63 %. Found: C, 51.24; H, 2.97; N, 6.61 %. ESI-MS: m/z. Calcd: 210.99; Found: 211.96 (M+1).

3-(2-methoxyphenyl)thiazole-2(3H)-thione 6e: Isolated as off white solid. Yield: 97%; mp = 89-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.84 (s, 3H), 6.64 (d, J = 4.8 Hz, 1H), 7.02 (d, J = 4.8 Hz, 1H), 7.07-7.12 (m, 2H), 7.39-7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc: 55.8, 110.4, 112.6, 120.7, 126.9, 128.9, 130.9, 132.8, 154.0, 189.2; Anal. Calcd for $C_{10}H_9NOS_2$: C, 53.79; H,

4.06; N, 6.27 %. Found: C, 53.84; H, 4.03; N, 6.35 %. ESI-MS: m/z. Calcd: 223.01; Found: 223.95 (M+1).

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