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Synthesis of Thiazolidine-2-thiones via One-Pot A³-coupling / Carbon Disulfide Incorporation Process

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Abstract: A copper-catalyzed two-step one-pot procedure for the synthesis of thiazolidine-2-thiones was developed. The process involves three-component coupling of an alkyne, an aldehyde, and an amine (A³-coupling) followed by trapping of the resulting propargylamine with carbon disulfide and subsequent cyclization.

Introduction

Five-membered heterocycles containing nitrogen and sulfur atoms such as rhodanines, 4-thiazolidinones, and 2,4-thiazolidinediones proved to be promising scaffolds for identifying potential antibacterial, antiviral, antidiabetic and anticancer agents.^[1] Chiral oxazolidinethiones and thiazolidinethiones, sulfur-containing modifications of the well-known Evans oxazolidinones, have found broad application as highly selective and efficient chiral auxiliaries.^[2] Therefore, the development of novel synthetic approaches towards this class of heterocycles continues to be well-justified.

Propargylic compounds such as propargylic alcohols and propargylamines have recently emerged as useful building blocks and intermediates in heterocyclic chemistry.^[3] This can be partially attributed to the recent progress in the development of efficient catalytic methods for their synthesis. Most notable transformations include transition metal-catalyzed additions of terminal alkynes to imines and closely related three-component coupling of alkynes, aldehydes, and amines (A³-coupling) allowing to access various types of propargylamines.^[4]

With respect to the synthesis of heterocycles, a lot of work has been done on the addition of secondary propargylamines^[5] to various heteroallenes and subsequent transition metal-catalyzed or electrophile-mediated cyclizations. For example, propargylguanidines originated from propargylamines and carbodiimides could be selectively converted into either

imidazolidin-2-imines^[6] or pyrimidin-2-imines^[7] by choosing the appropriate catalytic system. Propargylureas accessed from propargylamines and isocyanates are even more versatile and could be efficiently transformed into imidazol-2-ones,^[8] imidazolidin-2-ones,^[9] pyrimidin-2-ones^[10] and oxazolidin-2-imines^[11] in a chemo- and regioselective manner. Analogously, isothiocyanate-derived propargylthiureas have been utilized to prepare imidazol-2-thiones^[12] and thiazolidin-2-imines.^[13] Carbon dioxide (CO₂) can also be incorporated into heterocycles by reacting with propargylamines **1**^[14] or propargylalcohols **2**^[15] through a large number of synthetic protocols (Scheme 1a, left part). In contrast, a very few examples are described for its sulfur analogue carbon disulfide (CS₂, Scheme 1a, right part).^[16,17] In this paper, we present a general approach towards thiazolidine-2-thiones **5** via a copper-catalyzed three-component coupling of a primary amine, an aldehyde and an alkyne (A³-coupling) followed by the incorporation of CS₂ (Scheme 1b).^[18,19]

Scheme 1. Incorporation of carbon dioxide (CO₂) and carbon disulfide (CS₂) into heterocycles by reacting with propargylic compounds.

Results and Discussion

Despite that the first A³-coupling step is a well studied transformation, some adjustments were required to combine it with the second CS₂ incorporation step to develop a two-step one-pot process for the generation of thiazolidine-2-thiones **5**. We have selected *p*-methoxybenzyl amine (**7a**), butyraldehyde (**8a**) and phenyl acetylene (**9a**) as model substrates for the optimization studies (Table 1). The first trial was conducted using an excess of **8a** and **9a**, 10 mol% of CuBr as catalyst and toluene as solvent. After carrying out the A³-coupling step at 100°C for 3 h, 2 equiv of CS₂ were added and the reaction was

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heated at 50°C for 2 h, allowing to obtain the desired thiazolidine-2-thione **5a** in 25 % NMR yield (Table 1, entry 1). Increasing amounts of CuBr catalyst and CS₂ up to 15 mol% and 3 equiv respectively led to an improved yield of 47 % (Table 1, entry 2), while no further amplification was achieved by increasing the excess of CS₂ up to 4 equiv (Table 1, entry 3). Varying the **7a:8a:9a** ratio led to a decreased yield of **5a** (Table 1, entries 4 and 5). On the other hand, some improvement was made by elevating the reaction temperature in the CS₂ incorporation step to 100°C (Table 1, entry 6). A slight increase in the reaction time for both steps of the process also proved to

be beneficial (Table 1, entries 7 and 8) allowing to obtain **5a** in up to 56 % isolated yield (Table 1, entry 8). At the same time, the use of prolonged reaction times of 7 h and 16 h in the A³-coupling step led to diminished yields of **5a** (Table 1, entries 9 and 10). Utilizing other copper salts as a catalyst (Table 1, entries 11-13) or switching to other solvents (Table 1, entries 14-16) failed to upgrade the reaction outcome. Besides, the yield of **5a** could not be improved by the addition of organic base during the second step of the process (Table 1, entry 17).

Table 1. Optimization of the reaction conditions^[a]

Entry	7a:8a:9a ratio	Cu catalyst	Solvent	Time1 [h]	Temp [°C]	Time2 [h]	x	Yield [%] ^[b]
1	1:1.25:2	CuBr (10 mol%)	toluene	3	50	2	2	25 (19) ^[c]
2	1:1.25:2	CuBr (15 mol%)	toluene	3	50	2	3	47
3	1:1.25:2	CuBr (15 mol%)	toluene	3	50	2	4	45
4	1:1.25:2.5	CuBr (15 mol%)	toluene	3	50	2	3	36
5	1.25:1:2	CuBr (15 mol%)	toluene	3	50	2	3	40
6	1:1.25:2	CuBr (15 mol%)	toluene	3	100	2	3	53
7	1:1.25:2	CuBr (15 mol%)	toluene	3	100	3	3	54
8	1:1.25:2	CuBr (15 mol%)	toluene	5	100	3	3	62 (56)^[c]
9	1:1.25:2	CuBr (15 mol%)	toluene	7	100	3	3	55
10	1:1.25:2	CuBr (15 mol%)	toluene	16	100	3	3	32
11	1:1.25:2	CuCl (15 mol%)	toluene	5	100	3	3	47
12	1:1.25:2	CuI (15 mol%)	toluene	5	100	3	3	38
13	1:1.25:2	CuBr ₂ (15 mol%)	toluene	5	100	3	3	44
14	1:1.25:2	CuBr (15 mol%)	dioxane	5	100	3	3	53
15	1:1.25:2	CuBr (15 mol%)	MeCN	5	100	3	3	37
16	1:1.25:2	CuBr (15 mol%)	EtOH	5	100	3	3	19
17 ^[d]	1:1.25:2	CuBr (15 mol%)	toluene	5	100	3	3	43

[a] The reactions were run on 0.8 mmol scale in 1 mL of solvent under argon atmosphere in a sealed screw-cap vials. [b] Yields were determined by ¹H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [c] Isolated yield is given in parentheses. [d] 0.5 equiv of Et₃N were used as an additive in the second step.

Figure 1. X-ray crystallographic structure of **5a**, showing thermal displacement ellipsoids at the 50% probability level.

The structure of (Z)-5-benzylidene-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione **5a**, a product of the model reaction of **7a**, **8a** and **9a** was ascertained by X-ray crystallographic analysis (Figure 1).^[20]

With these results at hand, we decided to evaluate the scope of our process (Table 2). Testing various primary amines **7a-g** in a combination with butyraldehyde (**8a**) and phenyl acetylene (**9a**) we were able to obtain thiazolidine-2-thiones **5a-g** in yields ranging from 37% to 70% (Table 2, entries 1-7). Exploring the aldehyde component, we have found that the yield of the

Table 2. Scope of the process^[a]

Entry	Amine 7 , R ¹	Aldehyde 8 , R ²	Alkyne 9 , R ³	Product 5	Yield [%] ^[b]
1	7a , PMB	8a , Pr	9a , Ph	5a	56
2	7b , Bn	8a , Pr	9a , Ph	5b	45
3	7c , 4-FC ₆ H ₄ CH ₂	8a , Pr	9a , Ph	5c	54
4	7d , 4-ClC ₆ H ₄ CH ₂	8a , Pr	9a , Ph	5d	37
5	7e , PhCH ₂ CH ₂	8a , Pr	9a , Ph	5e	67
6	7f , MeOCH ₂ CH ₂	8a , Pr	9a , Ph	5f	49
7	7g , Pentyl	8a , Pr	9a , Ph	5g	70
8	7a , PMB	8b , Bu	9a , Ph	5h	55
9	7a , PMB	8c , <i>i</i> Bu	9a , Ph	5i	44
10	7a , PMB	8d , Bn	9a , Ph	5j	39
11	7a , PMB	8e , CH ₂ =CH(CH ₂) ₇ CH ₂	9a , Ph	5k	26
12	7a , PMB	8f , Ph	9a , Ph	5l	24
13	7a , PMB	8a , Pr	9b , 4-MeC ₆ H ₄	5m	60
14	7a , PMB	8a , Pr	9c , 4-EtC ₆ H ₄	5n	66
15	7a , PMB	8a , Pr	9d , 4-PentylC ₆ H ₄	5o	59
16	7a , PMB	8a , Pr	9e , 4- <i>t</i> BuC ₆ H ₄	5p	52
17	7a , PMB	8a , Pr	9f , 3-MeC ₆ H ₄	5q	61
18	7a , PMB	8a , Pr	9g , 4-MeOC ₆ H ₄	5r	57
19	7a , PMB	8a , Pr	9h , 4-FC ₆ H ₄	5s	54
20	7a , PMB	8a , Pr	9i , 3-ClC ₆ H ₄	5t	61
21	7a , PMB	8a , Pr	9j , 4-CF ₃ C ₆ H ₄	5u	31
22	7a , PMB	8a , Pr	9k , Thiophen-3-yl	5v	73
23	7a , PMB	8a , Pr	9l , CyCH ₂	5w	33

[a] All reactions were run using CuBr (17 mg, 0.12 mmol), amine **7** (0.8 mmol), aldehyde **8** (1 mmol), acetylene **9** (1.6 mmol) and CS₂ (183 mg, 2.4 mmol) in toluene (1 mL) under argon atmosphere in a sealed screw-cap vials. [b] Isolated yields.

Scheme 2. Tentative reaction pathway and control experiments.

thiazolidine-2-thione **5** gradually drops as a result of increasing bulk or the side-chain elongation. Thus, valeraldehyde **8d** furnished thiazolidine-2-thione **5h** in 55% yield (Table 2, entry 8). Branched isovaleraldehyde **8c** (Table 2, entry 9) and 2-phenylacetaldehyde **8d** (Table 2, entry 10) delivered **5i** and **5j** in 44% and 39%, respectively (Table 2, entries 9 and 10). Undec-10-enal **8e** and aromatic benzaldehyde **8f** were found to be the least efficient (Table 2, entries 11 and 12). For the terminal alkyne part, we first examined various aromatic acetylenes **9b-j** bearing a range of sterically and electronically different substituents on the phenyl ring (Table 2, entries 13-21). These reactions furnished thiazolidine-2-thiones **5m-t** with consistently good yields of 54% to 66% with an exception of thiazolidine-2-thione **5u** derived from electron-deficient 1-ethynyl-4-(trifluoromethyl)benzene (**9j**). Heteroaromatic 3-ethynylthiophene (**9k**) also worked well yielding thiazolidine-2-thione **5v** in 73% (Table 2, entry 22). Finally, we investigated the reaction of aliphatic prop-2-ynylcyclohexane (**9l**) that afforded product **5w** in 33% yield (Table 2, entry 23).

A tentative reaction pathway is shown in Scheme 2. The first step of the process constitutes the standard copper(I)-catalyzed A³-coupling. Copper activates the triple bond of the alkyne **9** to form the π -complex **B** while primary amine **7** and aldehyde **8** condense generating imine **A**. Next, the copper acetylide **C**,

obtained by the deprotonation of **B**, reacts with imine **A** resulting in the formation of the propargylamine **1** and the regeneration of the copper catalyst. In the second step of the process propargylamine **1** reacts with CS₂ to give the adduct **D** that further cyclizes into the final thiazolidine-2-thione **5**. We have found that the incorporation of CS₂ can be accomplished in the absence of the copper(I)-catalyst, if the overall process is conducted in a stepwise manner. Furthermore, the control experiments clearly demonstrate that the presence of copper(I)-catalyst has no influence on the reaction of propargylamine **1** with CS₂. On the other hand, the efficiency of the one-pot procedure is significantly higher compared to the stepwise approach.

Conclusions

In conclusion, we have established a general process for the synthesis of thiazolidine-2-thiones starting from readily available primary amines, aldehydes, terminal alkynes and carbon disulfide. The developed one-pot procedure involving a copper-catalyzed A³-coupling followed by carbon disulfide incorporation is fast and operationally simple. The scope of the process was

examined with respect to all variable components allowing to attain a set of title compounds in fair yields.

Experimental Section

^1H and ^{13}C NMR spectra were recorded with 400 and 100 MHz respectively using BrukerAvance instrument. The ^1H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. Melting points were recorded on a Reichert Thermovar apparatus. HRMS ESI spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 $\mu\text{L}/\text{min}$ and spectra were obtained in positive ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

General procedure for the synthesis of thiazolidine-2-thiones 5 (Table 2)

Copper (I) bromide catalyst (17 mg, 0.12 mmol) was placed in a screw cap vial followed by addition of dry toluene (1 mL), amine **7** (0.8 mmol), aldehyde **8** (1 mmol), and acetylene **9** (1.6 mmol). The resulting mixture was flushed with nitrogen, sealed and stirred at 100 °C for 5 h. Then carbon disulfide (183 mg, 2.4 mmol) was added and the mixture was stirred at 100 °C for 3 h. The resulting mixture was diluted with DCM, concentrated with silica and subjected to column chromatography on silicagel with heptane-EtOAc (1→5%) as eluent to give the desired thiazolidine-2-thione **5**. Products **5f**, **h**, **i**, **o**, **r**, **s**, **u**, **v** were additionally washed with pentane after column chromatography.

(Z)-5-benzylidene-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione (5a).

Yield: 165 mg (56%); yellow solid; mp 98–101 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.39–7.31 (m, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.25–7.19 (m, 3H), 6.88 (d, J = 8.6 Hz, 2H), 6.32 (d, J = 1.2 Hz, 1H), 5.93 (d, J = 14.8 Hz, 1H), 4.79–4.73 (m, 1H), 4.15 (d, J = 14.8 Hz, 1H), 3.79 (s, 3H), 2.10–1.98 (m, 1H), 1.79–1.67 (m, 1H), 1.52–1.29 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.3, 159.7, 135.4, 132.7, 129.7, 128.8, 128.1, 127.6, 126.9, 119.7, 114.5, 72.4, 55.5, 49.1, 36.5, 16.0, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{21}\text{H}_{24}\text{NOS}_2^+$ calcd. 370.1294, found 370.1325.

(Z)-3-benzyl-5-benzylidene-4-propylthiazolidine-2-thione (5b).

Yield: 122 mg (45%); yellow solid; mp 95–97 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.41–7.30 (m, 7H), 7.28–7.21 (m, 3H), 6.34 (d, J = 1.0 Hz, 1H), 6.01 (d, J = 15.0 Hz, 1H), 4.81–4.76 (m, 1H), 4.24 (d, J = 15.0 Hz, 1H), 2.11–1.99 (m, 1H), 1.80–1.69 (m, 1H), 1.55–1.29 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.7, 135.4, 134.9, 132.6, 129.1, 128.9, 128.4, 128.3, 128.1, 127.6, 119.8, 72.5, 49.6, 36.5, 16.0, 14.0.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{20}\text{H}_{22}\text{NS}_2^+$ calcd. 340.1188, found 340.1189.

(Z)-5-benzylidene-3-(4-fluorobenzyl)-4-propylthiazolidine-2-thione (5c).

Yield: 156 mg (54%); yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 7.40–7.30 (m, 4H), 7.27–7.19 (m, 3H), 7.09–7.01 (m, 2H), 6.35 (d, J = 1.2 Hz, 1H), 5.91 (d, J = 15.0 Hz, 1H), 4.80–4.73 (m, 1H), 4.24 (d, J = 15.0 Hz, 1H), 2.09–1.96 (m, 1H), 1.81–1.69 (m, 1H), 1.53–1.28 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.8, 162.7 (d, J = 247.3 Hz), 135.3, 132.3, 130.8 (d, J = 3.3 Hz), 130.0 (d, J = 8.2 Hz), 128.9, 128.1, 127.6, 120.0, 116.1 (d, J = 21.6 Hz), 72.5, 48.8, 36.5, 16.0, 14.0.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{20}\text{H}_{21}\text{FNS}_2^+$ calcd. 358.1094, found 358.110.

(Z)-5-benzylidene-3-(4-chlorobenzyl)-4-propylthiazolidine-2-thione (5d).

Yield: 110 mg (37%); brownish oil.

^1H NMR (400 MHz, CDCl_3): δ 7.40–7.32 (m, 4H), 7.32–7.20 (m, 5H), 6.35 (d, J = 1.0 Hz, 1H), 5.94 (d, J = 15.1 Hz, 1H), 4.78–4.72 (m, 1H), 4.22 (d, J = 15.1 Hz, 1H), 2.08–1.96 (m, 1H), 1.80–1.69 (m, 1H), 1.54–1.26 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 194.0, 135.3, 134.4, 133.5, 132.3, 129.6, 129.4, 128.9, 128.1, 127.7, 120.1, 72.5, 48.9, 36.5, 16.1, 14.0.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{20}\text{H}_{21}\text{ClNS}_2^+$ calcd. 374.0798, found 374.0805.

(Z)-5-benzylidene-3-phenethyl-4-propylthiazolidine-2-thione (5e).

Yield: 190 mg (67%); orange solid; mp 56–58 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.43–7.19 (m, 10H), 6.29 (d, J = 1.5 Hz, 1H), 4.62–4.47 (m, 2H), 3.48 (ddd, J = 13.5, 8.7, 7.3 Hz, 1H), 3.23–3.07 (m, 1H), 3.04–2.90 (m, 1H), 2.06–1.89 (m, 1H), 1.80–1.65 (m, 1H), 1.52–1.24 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 192.5, 138.2, 135.4, 133.0, 128.92, 128.86, 128.1, 127.6, 127.0, 119.8, 74.8, 48.5, 36.9, 32.8, 16.3, 14.0.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{21}\text{H}_{24}\text{NS}_2^+$ calcd. 354.1345, found 354.1342.

(Z)-5-benzylidene-3-(2-methoxyethyl)-4-propylthiazolidine-2-thione (5f).

Yield: 121 mg (49%); pale yellow solid; mp 63–65 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.42–7.33 (m, 2H), 7.30–7.21 (m, 3H), 6.43 (d, J = 1.6 Hz, 1H), 5.22–5.12 (m, 1H), 4.57 (ddd, J = 14.2, 4.0, 3.3 Hz, 1H), 3.77 (ddd, J = 10.2, 8.9, 3.2 Hz, 1H), 3.62 (dt, J = 10.2, 4.1, 3.5 Hz, 1H), 3.51 (ddd, J = 14.2, 8.9, 3.5 Hz, 1H), 3.35 (s, 3H), 2.18–2.01 (m, 1H), 1.86–1.70 (m, 1H), 1.55–1.22 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 192.9, 135.6, 133.3, 128.9, 128.1, 127.5, 119.6, 75.5, 70.3, 59.2, 46.5, 36.7, 16.2, 14.1.

HRMS (ESI, [M+H]⁺) for C₁₆H₂₂NOS₂⁺ calcd. 308.1137, found 308.1151.

(Z)-5-benzylidene-3-pentyl-4-propylthiazolidine-2-thione (5g).

Yield: 178 mg (70%); brownish oil.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.33 (m, 2H), 7.29-7.21 (m, 3H), 6.43 (d, *J* = 1.5 Hz, 1H), 4.99-4.92 (m, 1H), 4.39 (ddd, *J* = 13.7, 9.6, 6.6 Hz, 1H), 3.25 (ddd, *J* = 13.7, 9.2, 5.2 Hz, 1H), 2.09-1.96 (m, 1H), 1.85-1.61 (m, 3H), 1.55-1.27 (m, 6H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 192.2, 135.5, 133.1, 128.8, 128.1, 127.5, 119.6, 73.7, 46.6, 36.9, 29.0, 26.4, 22.4, 16.1, 14.04, 14.01.

HRMS (ESI, [M+H]⁺) for C₁₈H₂₆NS₂⁺ calcd. 320.1501, found 320.1505.

(Z)-5-benzylidene-4-butyl-3-(4-methoxybenzyl)thiazolidine-2-thione (5h).

Yield: 170 mg (55%); orange-red solid; mp 85–88 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.33 (m, 2H), 7.31-7.20 (m, 5H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.33 (d, *J* = 1.4 Hz, 1H), 5.95 (d, *J* = 14.8 Hz, 1H), 4.80-4.74 (m, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.81 (s, 3H), 2.13-2.01 (m, 1H), 1.81-1.69 (m, 1H), 1.49-1.21 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 193.4, 159.7, 135.5, 132.7, 129.8, 128.9, 128.1, 127.6, 126.9, 119.7, 114.5, 72.4, 55.5, 49.1, 34.1, 24.6, 22.7, 14.1.

HRMS (ESI, [M+H]⁺) for C₂₂H₂₆NOS₂⁺ calcd. 384.1450, found 384.1447.

(Z)-5-benzylidene-4-isobutyl-3-(4-methoxybenzyl)thiazolidine-2-thione (5i).

Yield: 136 mg (44%); brownish oil.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.32 (m, 2H), 7.30-7.18 (m, 5H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.32 (s, 1H), 5.98 (d, *J* = 14.8 Hz, 1H), 4.72-4.65 (m, 1H), 4.12 (d, *J* = 14.8 Hz, 1H), 3.81 (s, 3H), 1.97-1.79 (m, 2H), 1.65 (ddd, *J* = 13.4, 8.5, 3.1 Hz, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 193.1, 159.8, 135.3, 132.9, 129.8, 128.8, 128.2, 127.7, 127.0, 120.7, 114.5, 71.4, 55.5, 49.2, 42.1, 23.8, 23.6, 22.6.

HRMS (ESI, [M+H]⁺) for C₂₂H₂₆NOS₂⁺ calcd. 384.1450, found 384.1446.

(Z)-4-benzyl-5-benzylidene-3-(4-methoxybenzyl)thiazolidine-2-thione (5j).

Yield: 130 mg (39%); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.17 (m, 8H), 7.10-7.04 (m, 4H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.02 (d, *J* = 14.9 Hz, 1H), 5.80 (s, 1H), 4.79 (ddd, *J* = 7.4, 4.4, 1.1 Hz, 1H), 4.23 (d, *J* = 14.9 Hz, 1H), 3.82 (s, 3H), 3.23 (dd, *J* = 13.6, 4.3 Hz, 1H), 3.08 (dd, *J* = 13.6, 7.5 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 193.6, 159.8, 135.2, 134.9, 131.3, 130.0, 129.8, 128.78, 128.77, 128.1, 127.7, 127.5, 126.9, 121.4, 114.6, 73.6, 55.5, 49.7, 40.3.

HRMS (ESI, [M+H]⁺) for C₂₅H₂₄NOS₂⁺ calcd. 418.1294, found 418.1281.

(Z)-5-benzylidene-4-(dec-9-enyl)-3-(4-methoxybenzyl)thiazolidine-2-thione (5k).

Yield: 97 mg (26%); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.32 (m, 2H), 7.31-7.19 (m, 5H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.32 (s, 1H), 5.92 (d, *J* = 14.8 Hz, 1H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.03-4.88 (m, 2H), 4.80-4.73 (m, 1H), 4.16 (d, *J* = 14.8 Hz, 1H), 3.80 (s, 3H), 2.11-1.96 (m, 3H), 1.82-1.64 (m, 1H), 1.48-1.20 (m, 12H).

¹³C NMR (100 MHz, CDCl₃): δ 193.3, 159.7, 139.2, 135.5, 132.7, 129.7, 128.8, 128.1, 127.6, 126.9, 119.7, 114.5, 114.3, 72.5, 55.4, 49.2, 34.3, 33.9, 29.6, 29.48, 29.46, 29.1, 29.0, 22.5.

HRMS (ESI, [M+H]⁺) for C₂₈H₃₆NOS₂⁺ calcd. 466.2233, found 466.2237.

(Z)-5-benzylidene-3-(4-methoxybenzyl)-4-phenylthiazolidine-2-thione (5l).

Yield: 77 mg (24%); yellow solid; mp 116–119 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.50-7.39 (m, 3H), 7.35-7.27 (m, 4H), 7.24-7.11 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.14 (d, *J* = 1.8 Hz, 1H), 5.95 (d, *J* = 14.5 Hz, 1H), 5.62 (d, *J* = 1.9 Hz, 1H), 3.82 (s, 3H), 3.68 (d, *J* = 14.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 193.2, 159.7, 138.5, 135.4, 132.8, 130.1, 129.7, 129.6, 128.8, 128.1, 127.6, 127.5, 126.7, 121.8, 114.4, 76.6, 55.5, 49.2.

HRMS (ESI, [M+H]⁺) for C₂₄H₂₂NOS₂⁺ calcd. 404.1137, found 404.1135.

(Z)-3-(4-methoxybenzyl)-5-(4-methylbenzylidene)-4-propylthiazolidine-2-thione (5m).

Yield: 185 mg (60%); yellow solid; mp 77–79 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.30 (d, *J* = 1.6 Hz, 1H), 5.94 (d, *J* = 14.8 Hz, 1H), 4.80-4.70 (m, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.81 (s, 3H), 2.34 (s, 3H), 2.12-1.95 (m, 1H), 1.81-1.65 (m, 1H), 1.56-1.25 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 193.4, 159.7, 137.5, 132.6, 131.3, 129.7, 129.5, 128.0, 126.9, 119.7, 114.5, 72.3, 55.4, 49.1, 36.5, 21.3, 16.0, 14.0.

HRMS (ESI, [M+H]⁺) for C₂₂H₂₆NOS₂⁺ calcd. 384.1450, found 384.1449.

(Z)-5-(4-ethylbenzylidene)-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione (5n).

Yield: 210 mg (66%); brownish oil.

¹H NMR (400 MHz, CDCl₃): δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 1.3 Hz, 1H), 5.95 (d, *J* = 14.8 Hz, 1H), 4.79-4.71 (m, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.81 (s, 3H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.10-1.97 (m, 1H), 1.78-1.66

(m, 1H), 1.53-1.27 (m, 2H), 1.23 (t, $J = 7.6$ Hz, 3H), 0.92 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.5, 159.7, 143.9, 132.9, 131.4, 129.7, 128.4, 128.1, 127.0, 119.7, 114.5, 72.3, 55.5, 49.1, 36.5, 28.7, 16.0, 15.6, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{23}\text{H}_{28}\text{NOS}_2^+$ calcd. 398.1607, found 398.1629.

(Z)-3-(4-methoxybenzyl)-5-(4-pentylbenzylidene)-4-propylthiazolidine-2-thione (5o).

Yield: 208 mg (59%); yellow solid; mp 51–53 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, $J = 8.6$ Hz, 2H), 7.18 (d, $J = 8.3$ Hz, 2H), 7.14 (d, $J = 8.3$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.30 (d, $J = 1.4$ Hz, 1H), 5.95 (d, $J = 14.8$ Hz, 1H), 4.78-4.71 (m, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 2.63-2.52 (m, 2H), 2.10-1.97 (m, 1H), 1.78-1.66 (m, 1H), 1.66-1.23 (m, 8H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.89 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.5, 159.7, 142.7, 132.8, 131.4, 129.7, 128.9, 128.0, 127.0, 119.8, 114.5, 72.3, 55.5, 49.1, 36.5, 35.8, 31.6, 31.1, 22.7, 16.0, 14.2, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{26}\text{H}_{34}\text{NOS}_2^+$ calcd. 440.2076, found 440.2068.

(Z)-5-(4-tert-butylbenzylidene)-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione (5p).

Yield: 176 mg (52%); yellow solid; mp 45–46 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.39 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.30 (d, $J = 1.6$ Hz, 1H), 5.95 (d, $J = 14.8$ Hz, 1H), 4.79-4.70 (m, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 2.13-1.96 (m, 1H), 1.79-1.62 (m, 1H), 1.52-1.18 (m, 11H), 0.91 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.5, 159.7, 150.8, 132.6, 131.5, 129.7, 127.9, 127.0, 125.8, 119.6, 114.5, 72.4, 55.5, 49.1, 36.5, 34.8, 31.4, 16.0, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{25}\text{H}_{32}\text{NOS}_2^+$ calcd. 426.1920, found 426.1917.

(Z)-3-(4-methoxybenzyl)-5-(3-methylbenzylidene)-4-propylthiazolidine-2-thione (5q).

Yield: 186 mg (61%); brownish oil.

^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, $J = 8.6$ Hz, 2H), 7.26-7.21 (s, 1H), 7.09-6.99 (m, 3H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.30 (d, $J = 1.7$ Hz, 1H), 5.95 (d, $J = 14.8$ Hz, 1H), 4.79-4.71 (m, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 2.35 (s, 3H), 2.12-1.96 (m, 1H), 1.80-1.65 (m, 1H), 1.56-1.25 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.5, 159.7, 138.6, 135.4, 132.3, 129.7, 128.8, 128.7, 128.4, 126.9, 125.3, 119.9, 114.5, 72.3, 55.5, 49.1, 36.5, 21.6, 16.0, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{22}\text{H}_{26}\text{NOS}_2^+$ calcd. 384.1450, found 384.1451.

(Z)-3-(4-methoxybenzyl)-5-(4-methoxybenzylidene)-4-propylthiazolidine-2-thione (5r).

Yield: 183 mg (57%); yellow solid; mp 68–70 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.26 (d, $J = 1.6$ Hz, 1H), 5.95 (d, $J = 14.8$ Hz, 1H), 4.76-4.69 (m, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 2.10-1.95 (m, 1H), 1.79-1.64 (m, 1H), 1.53-1.25 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.5, 159.7, 159.0, 129.9, 129.7, 129.5, 128.2, 127.0, 119.4, 114.5, 114.3, 72.3, 55.49, 55.47, 49.1, 36.5, 16.1, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{22}\text{H}_{26}\text{NO}_2\text{S}_2^+$ calcd. 400.1399, found 400.1401.

(Z)-5-(4-fluorobenzylidene)-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione (5s).

Yield: 168 mg (54%); yellow solid; mp 104–106 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, $J = 8.6$ Hz, 2H), 7.24-7.15 (m, 2H), 7.09-7.01 (m, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.28 (d, $J = 1.2$ Hz, 1H), 5.94 (d, $J = 14.8$ Hz, 1H), 4.77-4.71 (m, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 2.11-1.96 (m, 1H), 1.79-1.66 (m, 1H), 1.53-1.27 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.0, 161.9 (d, $J = 248.8$ Hz), 159.8, 132.6 (d, $J = 2.2$ Hz), 131.7 (d, $J = 3.3$ Hz), 129.8 (d, $J = 8.1$ Hz), 129.7, 126.9, 118.6, 115.9 (d, $J = 21.7$ Hz), 114.5, 72.3, 55.5, 49.1, 36.4, 16.0, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{21}\text{H}_{23}\text{FNOS}_2^+$ calcd. 388.1200, found 388.1210.

(Z)-5-(3-chlorobenzylidene)-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione (5t).

Yield: 197 mg (61%); brownish oil.

^1H NMR (400 MHz, CDCl_3): δ 7.33-7.24 (m, 3H), 7.23-7.17 (m, 2H), 7.14-7.07 (m, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.25 (d, $J = 1.3$ Hz, 1H), 5.94 (d, $J = 14.8$ Hz, 1H), 4.79-4.72 (m, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 2.11-1.99 (m, 1H), 1.78-1.67 (m, 1H), 1.52-1.23 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 192.7, 159.8, 137.3, 134.91, 134.87, 130.1, 129.8, 128.1, 127.6, 126.8, 126.0, 118.2, 114.5, 72.4, 55.5, 49.2, 36.5, 16.0, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{21}\text{H}_{23}\text{ClNOS}_2^+$ calcd. 404.0904, found 404.0892.

(Z)-3-(4-methoxybenzyl)-4-propyl-5-(4-(trifluoromethyl)benzylidene)thiazolidine-2-thione (5u).

Yield: 110 mg (31%); yellow solid; mp 105–108 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.61 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 8.6$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.34 (d, $J = 0.8$ Hz, 1H), 5.95 (d, $J = 14.8$ Hz, 1H), 4.82-4.75 (m, 1H), 4.15 (d, $J = 14.8$ Hz,

1H), 3.81 (s, 3H), 2.14-2.01 (m, 1H), 1.81-1.69 (m, 1H), 1.53-1.27 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 192.4, 159.8, 138.9, 136.3, 129.8, 129.2 (q, $J = 32.7$ Hz), 128.2, 126.7, 125.8 (q, $J = 3.8$ Hz), 124.1 (q, $J = 271.9$ Hz), 118.1, 114.6, 72.6, 55.5, 49.2, 36.5, 16.0, 14.0.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{22}\text{H}_{23}\text{F}_3\text{NOS}_2^+$ calcd. 438.1168, found 438.1177.

(Z)-3-(4-methoxybenzyl)-4-propyl-5-(thiophen-3-ylmethylene)thiazolidine-2-thione (5v).

Yield: 219 mg (73%); brownish solid; mp 90–91 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.34-7.30 (m, 1H), 7.28 (d, $J = 8.6$ Hz, 2H), 7.16-7.13 (m, 1H), 7.09-7.05 (m, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.35 (d, $J = 1.4$ Hz, 1H), 5.95 (d, $J = 14.8$ Hz, 1H), 4.75-4.70 (m, 1H), 4.13 (d, $J = 14.8$ Hz, 1H), 3.81 (s, 3H), 2.09-1.98 (m, 1H), 1.77-1.64 (m, 1H), 1.52-1.24 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.0, 159.7, 137.0, 131.8, 129.7, 127.4, 126.9, 126.3, 123.3, 114.5, 114.0, 71.8, 55.5, 49.2, 36.4, 16.0, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{19}\text{H}_{22}\text{NOS}_3^+$ calcd. 376.0858, found 376.0862.

(Z)-5-(2-cyclohexylethylidene)-3-(4-methoxybenzyl)-4-propylthiazolidine-2-thione (5w).

Yield: 102 mg (33%); brownish oil.

^1H NMR (400 MHz, CDCl_3): δ 7.26 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.90 (d, $J = 14.8$ Hz, 1H), 5.35 (td, $J = 7.4, 1.6$ Hz, 1H), 4.57-4.50 (m, 1H), 4.08 (d, $J = 14.8$ Hz, 1H), 3.80 (s, 3H), 1.99-1.76 (m, 3H), 1.74-1.54 (m, 6H), 1.46-1.04 (m, 6H), 0.97-0.83 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.8, 159.6, 132.6, 129.7, 127.1, 119.6, 114.4, 70.0, 55.5, 49.2, 39.2, 38.1, 35.9, 33.2, 33.1, 26.5, 26.3, 16.1, 14.1.

HRMS (ESI, $[\text{M}+\text{H}]^+$) for $\text{C}_{22}\text{H}_{32}\text{NOS}_2^+$ calcd. 390.1920, found 390.1917.

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FULL PAPER

A copper-catalyzed two-step one-pot procedure involving A³-coupling followed by carbon disulfide incorporation was developed to provide a diversity-oriented access to thiazolidine-2-thiones.

Multicomponent reactions

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Synthesis of Thiazolidine-2-thiones via One-Pot A³-coupling / Carbon Disulfide Incorporation Process