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Synthesis of Thiazolidine-2-thiones via One-Pot A^3-coupling / Carbon Disulfide Incorporation Process

Anton A. Nechaev,[a] Anatoly A. Peshkov,[a] Kristof Van Hecke,[b] Vsevolod A. Peshkov,*[c] Erik V. Van der Eycken*[a]

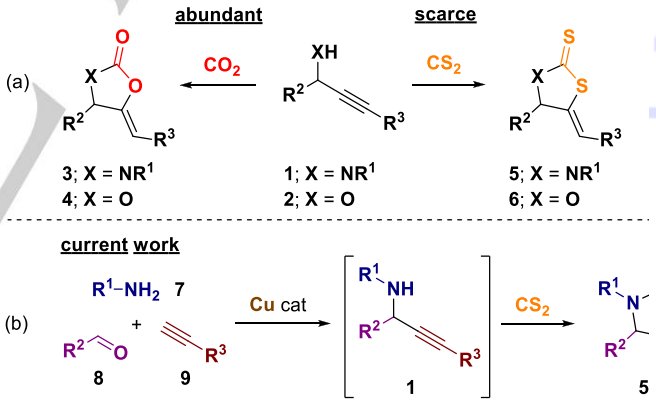
Abstract: A copper-catalyzed two-step one-pot procedure for the synthesis of thiazolidine-2-thiones was developed. The process involves three-component coupling of an alkyne, an aldehyde, and an amine (A^3-coupling) followed by trapping of the resulting propargylamine with carbon disulfide and subsequent 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 (A^3-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 propargylthioureas have been utilized to prepare imidazol-2-thiones[12] and thiazolidin-2-imines.[13] Carbon dioxide (CO_2) 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 (CS_2, 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 (A^3-coupling) followed by the incorporation of CS_2 (Scheme 1b).[18,19]



Scheme 1. Incorporation of carbon dioxide (CO_2) and carbon disulfide (CS_2) into heterocycles by reacting with propargylic compounds.

Results and Discussion

Despite that the first A^3-coupling step is a well studied transformation, some adjustments were required to combine it with the second CS_2 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 A^3-coupling step at 100°C for 3 h, 2 equiv of CS_2 were added and the reaction was

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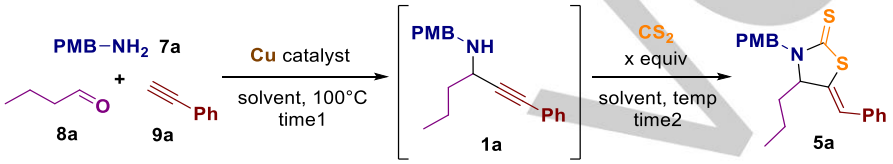
heated at 50°C for 2 h, allowing to obtain the desired thiazolidine-2-thione **5a** in 25 % NMR yield (Table 1, entry 1). Increasing amounts of CuBr catalyst and CS_2 up to 15 mol% and 3 equiv respectively led to an improved yield of 47 % (Table 1, entry 2), while no further amplification was achieved by increasing the excess of CS_2 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 CS_2 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 A^3-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 ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [c] Isolated yield is given in parentheses. [d] 0.5 equiv of Et_3N were used as an additive in the second step.

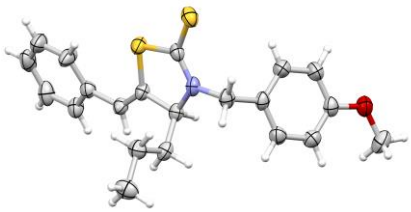
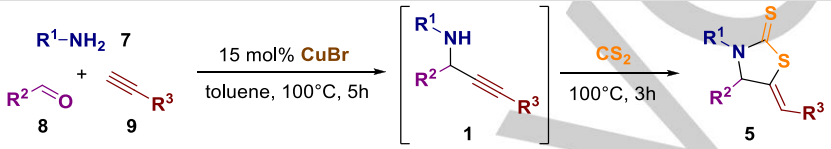


Figure 1. X-ray crystallographic structure of **5a**, showing thermal displacement ellipsoids at the 50% probability level.

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]

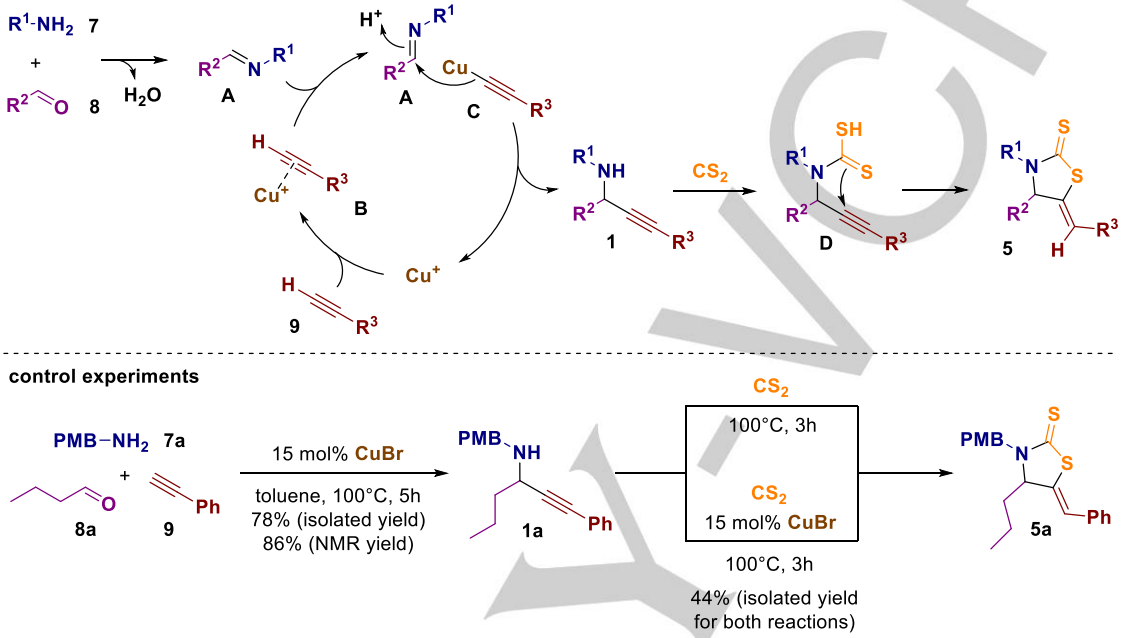
With these results at hand, we decided to evaluate the scope of our process (Table 2). Testing various primary amines **7a-g** in a combination with butyraldehyde (**8a**) and phenyl acetylene (**9a**) we were able to obtain thiazolidine-2-thiones **5a-g** in yields ranging from 37% to 70% (Table 2, 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-$FC_6H_4CH_2$	**8a**, Pr	**9a**, Ph	**5c**	54
4	**7d**, 4-$ClC_6H_4CH_2$	**8a**, Pr	**9a**, Ph	**5d**	37
5	**7e**, $PhCH_2CH_2$	**8a**, Pr	**9a**, Ph	**5e**	67
6	**7f**, $MeOCH_2CH_2$	**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*Bu	**9a**, Ph	**5i**	44
10	**7a**, PMB	**8d**, Bn	**9a**, Ph	**5j**	39
11	**7a**, PMB	**8e**, $CH_2=CH(CH_2)_7CH_2$	**9a**, Ph	**5k**	26
12	**7a**, PMB	**8f**, Ph	**9a**, Ph	**5l**	24
13	**7a**, PMB	**8a**, Pr	**9b**, 4-MeC_6H_4	**5m**	60
14	**7a**, PMB	**8a**, Pr	**9c**, 4-EtC_6H_4	**5n**	66
15	**7a**, PMB	**8a**, Pr	**9d**, 4-PentylC_6H_4	**5o**	59
16	**7a**, PMB	**8a**, Pr	**9e**, 4-*t*BuC_6H_4	**5p**	52
17	**7a**, PMB	**8a**, Pr	**9f**, 3-MeC_6H_4	**5q**	61
18	**7a**, PMB	**8a**, Pr	**9g**, 4-$MeOC_6H_4$	**5r**	57
19	**7a**, PMB	**8a**, Pr	**9h**, 4-FC_6H_4	**5s**	54
20	**7a**, PMB	**8a**, Pr	**9i**, 3-ClC_6H_4	**5t**	61
21	**7a**, PMB	**8a**, Pr	**9j**, 4-$CF_3C_6H_4$	**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 CS_2 (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 A^3-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 CS_2 to give the adduct **D** that further cyclizes into the final thiazolidine-2-thione **5**. We have found that the incorporation of CS_2 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 CS_2. 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 A^3-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

^{1}H and ^{13}C NMR spectra were recorded with 400 and 100 MHz respectively using BrukerAvance instrument. The ^{1}H 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 3μL/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 (1mL), 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,l,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.

^{1}H 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, $[M+H]^+$) for $C_{21}H_{24}NOS_2^+$ 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.

^{1}H 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, $[M+H]^+$) for $C_{20}H_{22}NS_2^+$ calcd. 340.1188, found 340.1189.

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

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

^{1}H 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, $[M+H]^+$) for $C_{20}H_{21}FNS_2^+$ calcd. 358.1094, found 358.110.

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

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

^{1}H 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, $[M+H]^+$) for $C_{20}H_{21}ClNS_2^+$ 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.

^{1}H 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, $[M+H]^+$) for $C_{21}H_{24}NS_2^+$ 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.

^{1}H 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 $C_{16}H_{22}NOS_2^+$ calcd. 308.1137, found 308.1151.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{26}NS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{26}NOS_2^+$ calcd. 384.1450, found 384.1447.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{26}NOS_2^+$ calcd. 384.1450, found 384.1446.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{24}NOS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{28}H_{36}NOS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{24}H_{22}NOS_2^+$ calcd. 404.1137, found 404.1135.

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

Yield: 185 mg (60%); yellow solid; mp77-79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.29 (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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{26}NOS_2^+$ calcd. 384.1450, found 384.1449.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (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, $[M+H]^+$) for $C_{23}H_{28}NOS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (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, $[M+H]^+$) for $C_{26}H_{34}NOS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.39 (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, $[M+H]^+$) for $C_{25}H_{32}NOS_2^+$ calcd. 426.1920, found 426.1917.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (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, $[M+H]^+$) for $C_{22}H_{26}NOS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (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, $[M+H]^+$) for $C_{22}H_{26}NO_2S_2^+$ 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.

^{1}H 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, $[M+H]^+$) for $C_{21}H_{23}FNOS_2^+$ calcd. 388.1200,found 388.1210.

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

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

^{1}H 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, $[M+H]^+$) for $C_{21}H_{23}ClNOS_2^+$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.61 (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, $[M+H]^+$) for $C_{22}H_{23}F_3NOS_2^+$ 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.

^{1}H 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, $[M+H]^+$) for $C_{19}H_{22}NOS_3^+$ calcd. 376.0858, found 376.0862.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): δ7.26 (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, $[M+H]^+$) for $C_{22}H_{32}NOS_2^+$ calcd. 390.1920, found 390.1917.

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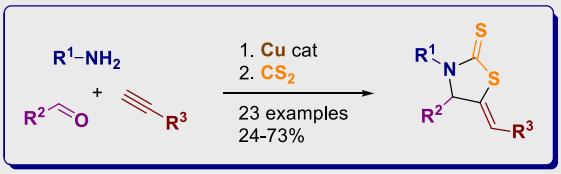
[20] CCDC 1502521 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

FULL PAPER



A copper-catalyzed two-step one-pot procedure involving A^3-coupling followed by carbon disulfide incorporation was developed to provide a diversity-oriented access to thiazolidine-2-thiones.

Multicomponent reactions

Anton A. Nechaev, Anatoly A. Peshkov, Kristof Van Hecke, Vsevolod A. Peshkov, Erik V. Van der Eycken**

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Synthesis of Thiazolidine-2-thiones via One-Pot A^3-coupling / Carbon Disulfide Incorporation Process