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Copper(II)-Catalyzed [3+2] Annulation of Thioamides with AIBN: Facile Access to Highly Functionalized Thiazolidin-4-ones

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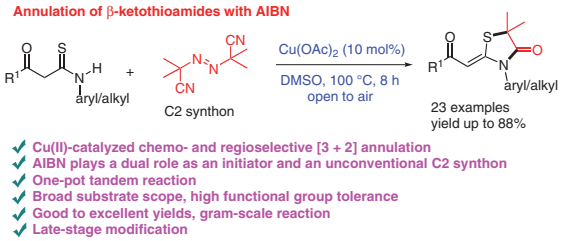

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Abstract An efficient and versatile copper-catalyzed intermolecular radical [3+2] annulation of thioamides with azobisisobutyronitrile (AIBN) is described. This two-component copper(II)-catalyzed transformation is achieved in one pot via cascade formation of C–S/C–N bonds through cyclization of an in situ generated *N*,*S*-acetal intermediate derived from a β-ketothioamide. This operationally simple method allows direct access to synthetically demanding thiazolidin-4-ones in good to excellent yields containing diverse functional groups of different electronic and steric nature. The readily available reaction partners, the avoidance of expensive/toxic reagents and a gram-scale synthesis are additional attributes of this strategy. AIBN plays a dual role as a radical initiator and an unusual source of a two-carbon coupling partner. Notably, the products possess *Z* stereochemistry with regard to the exocyclic C=C double bond at position 2 of the thiazolidine ring.

Key words β-ketothioamides, AIBN, domino annulation, one-pot reaction, 1,3-thiazolidin-4-ones

N,S-Heterocycles represent a class of significant building blocks that exist widely in natural products, agrochemicals, and pharmaceuticals. Amongst them, thiazolines and their derivatives are basic structural motifs embedded in a large number of bioactive natural products, pharmaceuticals and functional materials.[1] Furthermore, the utility of 1,3-thiazolidin-4-ones as important synthetic targets, both in academic laboratories and in the pharmaceutical industry, as value-added compounds has become prevalent.[2] Many substituted thiazolidines show wide-ranging pharmacological properties such as antihistaminic,[3a] anticancer,[3b] selective COX-2 inhibition[3c] and anti-HIV[3d] activity (Figure 1). In recent years, amongst five-membered nitrogen and sulfur heterocyclic compounds, 1,3-thiazoldin-4-ones have been extensively studied and show significant potential as therapeutic agents against various diseases. Considering these applications, many approaches for the synthesis of 4-thiazolidinones have been established.[4,5] Recently, Jagodziński et al.[6a] and our group[6b,c] synthesized thiazolidin-4-ones via reactions of β-ketothioamides with different coupling partners in a step-economic manner (Scheme 1). However, these methodologies were unable to tolerate moieties containing sensitive functional groups on the thioamides to produce thiazolidinones with high flexibility. Therefore, owing to their importance in medicinal and pharmaceutical chemistry as well as in materials science, there is a need to develop new and efficient methodologies for the synthesis of substituted thiazolidinone derivatives, especially examples possessing a carbonyl functionality.

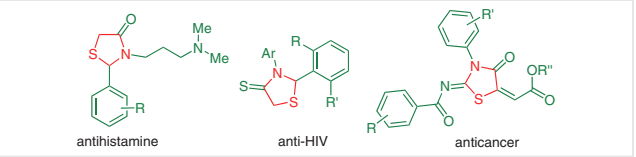
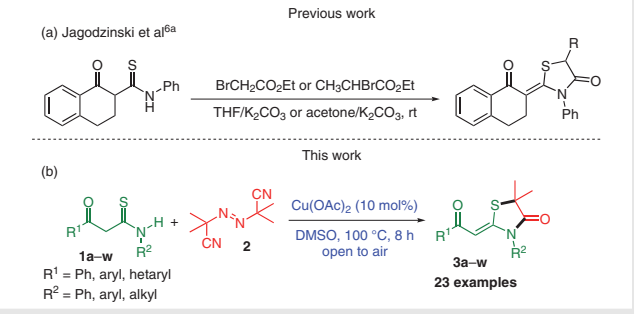


Figure 1 Biologically active 1,3-thiazolidinones



Scheme 1 Methods for the synthesis of 1,3-thiazolidinones

Azobisisobutyronitrile (AIBN) has been widely used as a radical initiator in a myriad of chemical transformations by extruding a molecule of N_2 to form the 2-cyanoprop-2-yl

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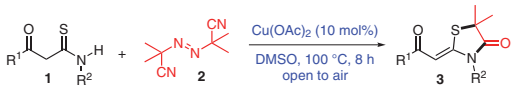
radical. This radical species is relatively stable and usually reacts with bonds that are weaker than most C–H bonds.[7] Thus, hydrogen-atom abstraction from the solvent or reactant is generally not a complicating factor. Recently, AIBN was reported to initiate aerobic oxidation reactions by taking advantage of peroxy radicals.[8] Another advantage of AIBN is that it is easily handled and does not experience induced decomposition; that is, the kinetics of its reaction are first order, regardless of the solvent or initiator concentration.[9]

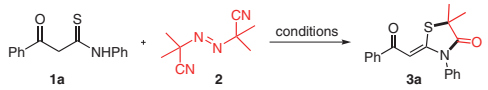
The success of any annulation strategy relies on the judicious choice of starting materials. Simple and unique examples of such starting materials are β-ketothioamides that are well-documented as intriguing synthons for the synthesis of valuable heterocyclic scaffolds.[10] Their chameleonic nature (both nucleophilic and electrophilic) allows for diverse reactivities, for example, they can participate in various cascade annulation reactions. Indeed, they can act as nucleophiles by attacking electrophiles and as electrophiles being intercepted by different nucleophiles. Site-selectivity in β-ketothioamide derivatizations has been achieved by leveraging several factors.[11] Against this background, and based on our experience in the chemistry of β-ketothioamides,[10] it was envisioned that the annulation of β-ketothioamides with AIBN would provide access to interesting and potentially useful heterocyclic frameworks. To the best of our knowledge, the copper-catalyzed [3+2] intermolecular cascade annulation of β-ketothioamides with AIBN by a radical cyclization process was unknown until this work. To this end, we herein disclose the $Cu(OAc)_2$-catalyzed annulative coupling of β-ketothioamides **1** with AIBN (**2**) for the synthesis of highly functionalized thiazolidinones **3** (Scheme 2).



Scheme 2 Synthesis of thiazolidinones via cyclization of β-ketothioamides

To verify the feasibility of the hypothesized reaction, we began our investigation by employing 3-oxo-*N*,3-diphenylpropanethioamide (**1a**) as a model substrate and AIBN (**2**) as a coupling partner, and the results are summarized in Table 1. The reaction of **1a** and **2** at 100 °C in DMSO under open air for 24 hours did not proceed at all, and the starting materials remained completely unconsumed (entry 1). Next, we carried out the above model reaction in the presence of 10 mol% of $Cu(OAc)_2$ at room temperature under open air for 24 hours, but unfortunately the attempt again failed (entry 2). Subsequently, we performed the model reaction of **1a** and **2** in the presence of 10 mol% of $Cu(OAc)_2$ at 50 °C for 24 hours. To our delight, the desired thiazolidinone **3a** was obtained in 42% yield (entry 3). Encouraged by this preliminary result, we systematically evaluated various parameters to optimize the reaction conditions. Consequently, the temperature of the reaction was selected initially; the above test reaction was performed at 80 °C, which enabled the formation of the desired product **3a** in 63% yield within 12 hours (entry 4). Further increasing the temperature to 100 °C improved the yield to 78% within 10 hours (entry 5). Next, to improve the efficiency of the reaction, we screened higher equivalents of AIBN, and it was found that 3.0 equivalents of AIBN at 100 °C furnished the desired product **3a** in 88% yield within 8 hours (entries 6–8). Decreasing or increasing the loading of $Cu(OAc)_2$ did not

Table 1 Optimization of the Reaction Conditions for the Synthesis of **3a**[a]



Entry	AIBN (equiv)	Solvent	Cat. (mol%)	Temp (°C)	Time (h)	Yield (%)[b]
1	1	DMSO	none	100	24	NR[c]
2	1	DMSO	$Cu(OAc)_2$ (10)	rt	24	NR[c]
3	1	DMSO	$Cu(OAc)_2$ (10)	50	24	42
4	1	DMSO	$Cu(OAc)_2$ (10)	80	12	63
5	1	DMSO	$Cu(OAc)_2$ (10)	100	10	78
6	2	DMSO	$Cu(OAc)_2$ (10)	100	8	83
7	**3**	**DMSO**	**$Cu(OAc)_2$ (10)**	**100**	**8**	**88**
8	4	DMSO	$Cu(OAc)_2$ (10)	100	8	88
9	3	DMSO	$Cu(OAc)_2$ (5)	100	8	72
10	3	DMSO	$Cu(OAc)_2$ (15)	100	8	87
11	3	MeCN	$Cu(OAc)_2$ (10)	100	8	58
12	3	DMF	$Cu(OAc)_2$ (10)	100	8	76
13	3	DCE	$Cu(OAc)_2$ (10)	100	8	54
14	3	EtOH	$Cu(OAc)_2$ (10)	100	8	35
15	3	MeOH	$Cu(OAc)_2$ (10)	100	8	40
16	3	dioxane	$Cu(OAc)_2$ (10)	100	8	70
17	3	toluene	$Cu(OAc)_2$ (10)	100	8	50
18	3	DMSO	CuCl (10)	100	8	78
19	3	DMSO	CuI (10)	100	8	75
20	3	DMSO	CuBr (10)	100	8	72
21	3	DMSO	$CuCl_2$ (10)	100	8	82
22	3	DMSO	$CuBr_2$ (10)	100	8	80
23	3	DMSO	$NiCl_2$ (10)	100	8	66
24	3	DMSO	$CoCl_2$ (10)	100	8	trace
25	3	DMSO	$FeCl_2$ (10)	100	8	60

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), catalyst, solvent (3 mL), 100 °C, air (unless otherwise stated).
[b] Yield of isolated product.
[c] NR = No reaction.

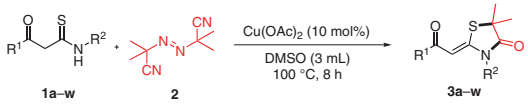
provide better results (entries 9 and 10). Different solvents such as MeCN, DMF, DCE, EtOH, MeOH, 1,4-dioxane and toluene were subsequently tested to identify the optimum solvent (entries 11–17); however, none of these were observed to be more efficient than DMSO. To evaluate the efficacy of other copper catalysts in this domino annulation, we screened several copper salts including CuCl, CuI, CuBr, $CuCl_2$ and $CuBr_2$ (entries 18–22). Interestingly, all these copper salts catalyzed this [3+2] annulation reaction but in lower yields than $Cu(OAc)_2$. Finally, we investigated $NiCl_2$, $CoCl_2$ and $FeCl_2$ as alternative metal catalysts, but these could not provide better results (entries 23–25). Thus, it has been found that the use of 10 mol% of $Cu(OAc)_2$ in DMSO at 100 °C represent optimum conditions for the cyclization of thioamides (entry 7).

With optimized conditions in hand, we next investigated the scope and functional group tolerance of this intermolecular [3+2] annulation by varying the substituents on the thioamides. A wide range of thioamides containing different substituents on the phenyl rings were well tolerated (Table 2). Substrates with phenyl rings possessing electron-donating (*ortho*-, *meta*- and *para*-Me, *meta*-MeO, 3,4-$OCH_2OC_6H_3$), halogen (4-Cl, 3-Br), and electron-withdrawing (*ortho*- and *para*-F_3C) substituents all reacted smoothly, giving the corresponding thiazolidinones **3a–k** in good to excellent yields. When using a heterocyclic moiety instead of a phenyl ring, such as 2-furyl, 2-thienyl, and 3-pyridyl, the corresponding thiazolidinones **3l–n** were generated in good yields. Furthermore, when thioamides bearing sterically hindered polycyclic and conjugated moieties such as 2-naphthyl and 4-biphenyl as R^1 were subjected to the standard reaction conditions, the expected products **3o** and **3p** were obtained in yields of 68% and 55%, respectively. To extend the substrate scope further, a few alicyclic and aliphatic thioamides prepared from alicyclic/aliphatic ketones (R^1 = cyclopropyl, cyclohexyl and *iso*-butyl) were also tested, but unfortunately the reactions with these thioamides led to very complex TLC patterns without the formation of the desired cyclized products. Thus, the negative outcomes with alicyclic/aliphatic thioamides under the optimized conditions limited the scope of our protocol to some extent.

We subsequently extended our studies towards the synthesis of *N*-aryl- and *N*-alkyl-substituted thiazolidinones. Our investigations revealed that the reactions of *N*-aryl/alkyl-substituted β-ketothioamides with AIBN under the standard conditions afforded the desired products **3q–w** in good yields.

Next, we scaled up the annulation reaction to evaluate its potential synthetic utility for practical applications. On a 4 mmol scale, the reaction of **1a** and **2** smoothly afforded the desired thiazolidinone **3a** in 85% yield (Scheme 3). In addition, we conducted two control experiments to explore the reaction mechanism (Scheme 4). Specifically, we found that the presence of a radical scavenger such as BHT (2,6-di-*tert*-butyl-4-methylphenol) prevented the reaction, suggesting that a radical process was involved (eq. 1). However, an N,N-disubstituted thioamide failed to react, indicating that the presence of a N–H bond was also crucial for the reaction to proceed (eq. 2). Performing the reaction under an O_2 atmosphere led to a slight improvement of the efficiency, whereas only a trace amount of the desired product was detected when the reaction was undertaken under a N_2 atmosphere, which demonstrates the importance of O_2 as an oxidant (eq. 3).

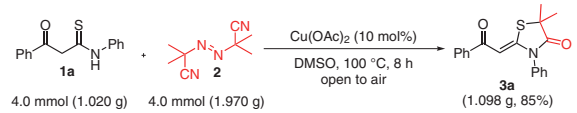
Table 2 Scope of β-Ketothioamides in Accessing Diverse Thiazolidin-4-ones[a]



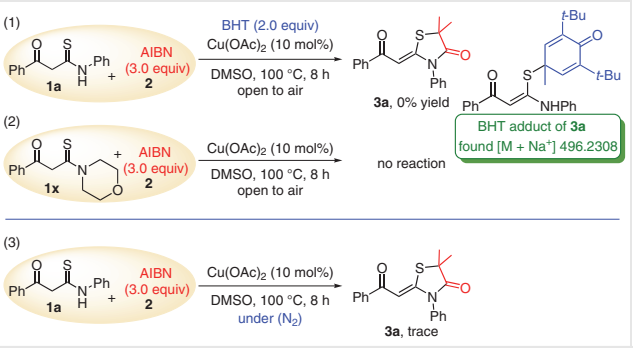
1a–w 2 3a–w

Product **3**	R^1	R^2	Yield (%)
3a	Ph	Ph	88
3b	2-MeC_6H_4	Ph	69
3c	3-MeC_6H_4	Ph	83
3d	4-MeC_6H_4	Ph	68
3e	3-$MeOC_6H_4$	Ph	85
3f	3,4-$OCH_2OC_6H_3$	Ph	75
3g	3,4,5-$(MeO)_3C_6H_2$	Ph	83
3h	3-BrC_6H_4	Ph	70
3i	4-ClC_6H_4	Ph	75
3j	2-$F_3CC_6H_4$	Ph	71
3k	4-$F_3CC_6H_4$	Ph	76
3l	2-furyl	Ph	69
3m	2-thienyl	Ph	65
3n	3-pyridyl	Ph	72
3o	1-naphthyl	Ph	68
3p	4-biphenyl	Ph	55
3q	Ph	4-MeC_6H_4	70
3r	Ph	4-$MeOC_6H_4$	71
3s	4-$MeOC_6H_4$	4-MeC_6H_4	88
3t	Ph	3-ClC_6H_4	72
3u	Ph	Me	73
3v	Ph	Et	69
3w	Ph	Bu	78

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), DMSO (3 mL), 100 °C, air.

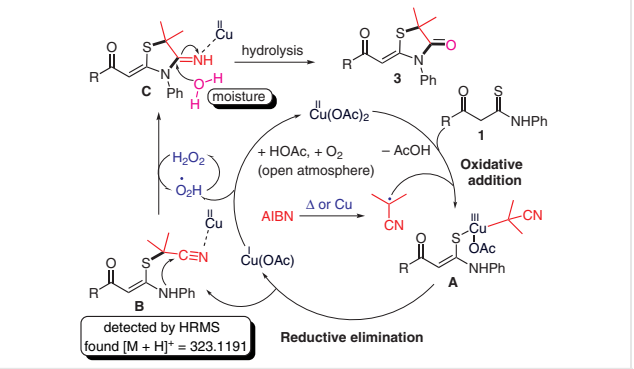


Scheme 3 Large-scale synthesis of compound **3a**



Scheme 4 Investigation of the mechanism via control experiments

On the basis of these control experiments and spectroscopic analyses, we have proposed a tentative mechanism for the newly developed annulation protocol, although a detailed pathway awaits further investigation (Scheme 5). The actual catalytically active copper species is expected to be high-valent Cu(III),[12] which undergoes reductive elimination to form intermediate **B** whilst generating Cu(I). This is followed by oxidation to give Cu(II) via the coaction of O_2 and AcOH, thereby completing the catalytic cycle. Subsequently, intramolecular cyclization of intermediate **B**, assisted by Cu(II), delivers intermediate C, which upon hydrolysis gives the desired product **3**.



Scheme 5 Proposed reaction mechanism

In summary, an operationally simple and efficient copper-catalyzed [3+2] annulation of thioamides with AIBN has been developed, providing rapid access to a series of 3-arylthiazolidin-4-ones. This strategy demonstrates a unique cyclization mode involving *N*,*S*-acetal intermediate **B**. The advantages of this procedure such as high-step economy, facile operation, and the utilization of environmentally friendly oxygen as the sole oxidant make this method practical and attractive. A successful gram-scale experiment indicated that this environmentally friendly method has potential industrial applications. Although a reasonable mechanism is proposed, further exploration of the mechanistic details are underway in our laboratory.

Commercially available solvents and reagents were used as received. The β-ketothioamides **1** were synthesized by reported procedures.[11] Dimethyl sulfoxide (DMSO) was purchased from Merck. $Cu(OAc)_2$ was purchased from Sigma-Aldrich. All reactions were carried out using a single-neck round-bottomed (25 mL) borosilicate flask. The reactions were monitored by analytical thin-layer chromatography (TLC) using Merck precoated aluminum sheets, and samples were visualized by employing a UV lamp. Flash column chromatography was performed on Merck silica gel (230–400 mesh). Melting points were determined with a Buchi B-540 melting points apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL 500 FT-NMR spectrometer operating at 500 MHz and 125 MHz, respectively. Chemical shifts (δ) for ^1H and $^{13}C\{^1H\}$ NMR spectra are given in parts per million (ppm) using the residual solvent peaks as references relative to tetramethylsilane as an internal standard. Coupling constants (*J*) are reported in Hz. High-resolution mass spectrometry was performed in EI or ESI mode on Sciex X500R QTOF instruments. Compound names were generated using ChemDraw (ChemDraw 12.0) software.

Thiazolidin-4-ones 3; General Procedure

To a 25 mL oven-dried, single-neck round-bottom flask were added β-ketothioamide **1** (0.5 mmol, 1.0 equiv), azobisisobutyronitrile (AIBN) (**2**) (0.5 mmol, 3.0 equiv), $Cu(OAc)_2$ (10 mol%) and DMSO (3 mL). The reaction mixture was allowed to stir in an oil bath at 100 °C for 8 h under an open atmosphere. After completion of the reaction (monitored by TLC), it was quenched with water (10 mL). The mixture was then extracted with ethyl acetate (15 mL) and water (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude residue thus obtained was purified by silica gel column chromatography (using an increasing percentage of ethyl acetate in hexane) to give the pure product **3**. After evaporation of the solvent, the isolated product was dried under vacuum.

(*Z*)-5,5-Dimethyl-2-(2-oxo-2-phenylethylidene)-3-phenylthiazolidin-4-one (3a)

Yield: 142 mg (88%); yellow solid; mp 177 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.61–7.53 (m, 3 H, H_{Ar}), 7.45 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.36 (t, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.30 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 6.31 (s, 1 H, CH), 1.74 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 178.5, 159.7, 138.5, 135.4, 132.2, 130.3, 129.9, 128.5, 128.0, 127.5, 97.1, 48.9, 28.1.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{17}NO_2SNa$: 346.0872; found: 346.0837.

(*Z*)-5,5-Dimethyl-2-[2-oxo-2-(*o*-tolyl)ethylidene]-3-phenylthiazolidin-4-one (3b)

Yield: 116 mg (69%); yellow solid; mp 130 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.45 (m, 3 H, H_{Ar}), 7.26 (s, 1 H, H_{Ar}), 7.25–7.22 (m, 3 H, H_{Ar}), 7.15–7.09 (m, 2 H, H_{Ar}), 5.98 (s, 1 H, CH), 2.41 (s, 3 H, CH_3), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.9, 178.4, 158.7, 139.9, 137.0, 135.3, 131.4, 130.4, 130.2, 129.8, 127.9, 127.7, 125.6, 100.6, 48.9, 28.1, 20.6.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{20}NO_2S$: 338.1209; found: 338.1209.

(*Z*)-5,5-Dimethyl-2-[2-oxo-2-(*m*-tolyl)ethylidene]-3-phenylthiazolidin-4-one (3c)

Yield: 139 mg (83%); yellow solid; mp 126 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.51 (m, 4 H, H_{Ar}), 7.43 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.29 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.24–7.20 (m, 2 H, H_{Ar}), 6.28 (s, 1 H, CH), 2.32 (s, 3 H, CH_3), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.0, 178.5, 159.5, 138.6, 138.3, 135.5, 132.9, 130.2, 129.8, 128.3, 128.2, 128.0, 124.6, 97.3, 48.9, 28.1, 21.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}NO_2S$: 338.1209; found: 338.1211.

(*Z*)-5,5-Dimethyl-2-[2-oxo-2-(*p*-tolyl)ethylidene]-3-phenylthiazolidin-4-one (3d)

Yield: 114 mg (68%); orange solid; mp 135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.52 (m, 5 H, H_{Ar}), 7.30–7.28 (m, 2 H, H_{Ar}), 7.15 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.29 (s, 1 H, CH), 2.35 (s, 3 H, CH_3), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.6, 178.5, 159.3, 142.8, 136.0, 135.5, 130.2, 129.8, 129.2, 128.1, 127.7, 97.1, 48.9, 28.1, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}NO_2S$: 338.1209; found: 338.1212.

(*Z*)-2-[2-(3-Methoxyphenyl)-2-oxoethylidene]-5,5-dimethyl-3-phenylthiazolidin-4-one (3e)

Yield: 150 mg (85%); yellow solid; mp 113 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.52 (m, 3 H, H_{Ar}), 7.34 (s, 1 H, H_{Ar}), 7.29 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.23 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.18 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.00 (dd, *J* = 8.0, 2.2 Hz, 1 H, H_{Ar}), 6.28 (s, 1 H, CH), 3.80 (s, 3 H, CH_3), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.5, 178.5, 159.8, 140.0, 135.4, 130.3, 129.9, 129.4, 128.0, 119.9, 118.5, 112.2, 97.2, 55.4, 48.9, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO_3SNa$: 376.0978; found: 376.0954.

(*Z*)-2-[2-(Benzo[*d*][1,3]dioxol-5-yl)-2-oxoethylidene]-5,5-dimethyl-3-phenylthiazolidin-4-one (3f)

Yield: 137 mg (75%); yellow solid; mp 142 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.56 (m, 3 H, H_{Ar}), 7.33–7.27 (m, 4 H, H_{Ar}), 6.77 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 6.25 (s, 1 H, CH), 6.02 (s, 2 H, CH_2), 1.76 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.1, 178.5, 159.2, 151.0, 148.0, 135.5, 133.3, 130.2, 129.9, 128.0, 123.2, 107.9, 107.8, 101.7, 96.8, 48.9, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}NO_4SNa$: 390.0770; found: 390.0740.

(*Z*)-5,5-Dimethyl-2-[2-oxo-2-(3,4,5-trimethoxyphenyl)ethylidene]-3-phenylthiazolidin-4-one (3g)

Yield: 171 mg (83%); pale yellow sticky solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.50 (m, 3 H, H_{Ar}), 7.30–7.29 (m, 2 H, H_{Ar}), 6.94 (s, 2 H, H_{Ar}), 6.21 (s, 1 H, CH), 3.84 (s, 3 H, CH_3), 3.79 (s, 6 H, CH_3), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.7, 178.4, 159.7, 153.0, 141.9, 135.4, 133.9, 130.1, 129.9, 128.0, 105.2, 96.9, 60.9, 56.2, 49.0, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_5SNa$: 436.1189; found: 436.1160.

(*Z*)-2-[2-(3-Bromophenyl)-2-oxoethylidene]-5,5-dimethyl-3-phenylthiazolidin-4-one (3h)

Yield: 140 mg (70%); yellow solid; mp 114 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 1 H, H_{Ar}), 7.62–7.56 (m, 5 H, H_{Ar}), 7.29 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.23 (t, *J* = 8.0 Hz, 1 H, H_{Ar}), 6.22 (s, 1 H, CH), 1.74 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.2, 178.5, 160.8, 140.4, 135.3, 135.0, 130.7, 130.4, 130.1, 128.0, 126.0, 122.9, 96.6, 49.0, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}BrNO_2S$: 402.0158; found: 402.0153.

(*Z*)-2-[2-(4-Chlorophenyl)-2-oxoethylidene]-5,5-dimethyl-3-phenylthiazolidin-4-one (3i)

Yield: 113 mg (75%); yellow solid; mp 142 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.54 (m, 5 H, H_{Ar}), 7.33–7.28 (m, 4 H, H_{Ar}), 6.24 (s, 1 H, CH), 1.74 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.4, 178.5, 160.4, 138.4, 136.8, 135.3, 130.3, 130.0, 129.0, 128.8, 128.0, 96.6, 49.0, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd $C_{19}H_{17}{}^{35}ClNO_2S$: 358.0663; found: 358.0669; *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}{}^{37}ClNO_2S$: 360.0639; found: 360.0652.

(*Z*)-5,5-Dimethyl-2-{2-oxo-2-[2-(trifluoromethyl)phenyl]ethylidene}-3-phenylthiazolidin-4-one (3j)

Yield: 138 mg (71%); yellow solid; mp 133 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.53–7.43 (m, 5 H, H_{Ar}), 7.35 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.25 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 5.86 (s, 1 H, CH), 1.74 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 178.4, 159.8, 140.7, 135.1, 131.8, 130.1, 129.8, 129.7, 128.1, 127.9, 127.2, 126.5 (q, $^2J_{C-F}$ = 4.7 Hz), 123.7 (q, $^1J_{C-F}$ = 272.1 Hz), 100.2, 49.2, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}F_3NO_2S$: 392.0927; found: 392.0921.

(*Z*)-5,5-Dimethyl-2-{2-oxo-2-[4-(trifluoromethyl)phenyl]ethylidene}-3-phenylthiazolidin-4-one (3k)

Yield: 148 mg (76%); yellow solid; mp 116 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.62–7.54 (m, 5 H, H_{Ar}), 7.29 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.27 (s, 1 H, CH), 1.75 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.5, 178.4, 161.2, 141.4, 135.3, 133.5, 130.3, 130.0, 128.0, 127.8, 125.6, 123.6 (q, $^1J_{C-F}$ = 272.1 Hz), 96.7, 49.1, 28.0.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{16}F_3NO_2SNa$: 414.0746; found: 414.0720.

(*Z*)-2-[2-(Furan-2-yl)-2-oxoethylidene]-5,5-dimethyl-3-phenylthiazolidin-4-one (3l)

Yield: 107 mg (69%); yellow solid; mp 141 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.52 (m, 3 H, H_{Ar}), 7.41 (s, 1 H, H_{Ar}), 7.28 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 6.02 (d, *J* = 3.0 Hz, 1 H, H_{Ar}), 6.43 (d, *J* = 4.0 Hz, 1 H, H_{Ar}), 6.20 (s, 1 H, CH), 1.72 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 177.7, 159.1, 153.7, 145.2, 135.3, 130.2, 129.8, 128.0, 115.2, 112.3, 96.8, 49.1, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_3S$: 314.0845; found: 314.0844.

(*Z*)-5,5-Dimethyl-2-[2-oxo-2-(thiophen-2-yl)ethylidene]-3-phenylthiazolidin-4-one (3m)

Yield: 106 mg (65%); yellow solid; mp 115 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.53 (m, 3 H, H_{Ar}), 7.50 (d, *J* = 5.0 Hz, 1 H, H_{Ar}), 7.34 (d, *J* = 4.0 Hz, 1 H, H_{Ar}), 7.29 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.20 (d, *J* = 4.75 Hz, 1 H, H_{Ar}), 6.14 (s, 1 H, CH), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.4, 178.4, 159.1, 145.8, 135.3, 132.5, 130.2, 129.9, 129.7, 128.1, 127.9, 97.1, 49.2, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{15}NO_2S_2Na$: 352.0436; found: 352.0419.

(*Z*)-5,5-Dimethyl-2-[2-oxo-2-(pyridin-3-yl)ethylidene]-3-phenylthiazolidin-4-one (3n)

Yield: 116 mg (72%); yellow solid; mp 164 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.84 (s, 1 H, H_{Ar}), 8.65 (d, *J* = 4.5 Hz, 1 H, H_{Ar}), 8.05 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.60–7.53 (m, 3 H, H_{Ar}), 7.34–7.27 (m, 3 H, H_{Ar}), 6.26 (s, 1 H, CH), 1.74 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.8, 178.4, 161.1, 152.5, 148.8, 135.2, 135.1, 133.8, 130.4, 130.1, 127.9, 123.6, 96.5, 49.1, 28.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1005; found: 325.1005.

(*Z*)-5,5-Dimethyl-2-[2-(naphthalen-2-yl)-2-oxoethylidene]-3-phenylthiazolidin-4-one (3o)

Yield: 126 mg (68%); yellow solid; mp 177 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, H_{Ar}), 7.86–7.81 (m, 4 H, H_{Ar}), 7.64–7.46 (m, 5 H, H_{Ar}), 7.34 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 6.47 (s, 1 H, CH), 1.76 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.6, 178.5, 159.7, 135.9, 135.5, 135.2, 132.6, 130.3, 129.9, 129.4, 128.4, 128.3, 128.1, 128.0, 127.8, 126.6, 124.0, 97.2, 48.9, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}NO_2S$: 374.1209; found: 374.1211.

(*Z*)-2-[2-([1,1′-Biphenyl]-4-yl)-2-oxoethylidene]-5,5-dimethyl-3-phenylthiazolidin-4-one (3p)

Yield: 109 mg (55%); brown solid; mp 164 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.62–7.54 (m, 7 H, H_{Ar}), 7.43 (t, *J* = 7.7 Hz, 2 H, H_{Ar}), 7.38–7.35 (m, 1 H, H_{Ar}), 7.32 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 6.35 (s, 1 H, CH), 1.75 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.3, 178.5, 159.7, 154.6, 144.9, 140.1, 137.3, 135.5, 130.3, 129.9, 129.0, 128.2, 128.1, 127.3, 127.2, 97.1, 49.0, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}NO_2S$: 400.1366; found: 400.1365.

(*Z*)-5,5-Dimethyl-2-(2-oxo-2-phenylethylidene)-3-(*p*-tolyl)thiazolidin-4-one (3q)

Yield: 117 mg (70%); yellow solid; mp 163 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.46–7.43 (m, 1 H, H_{Ar}), 7.38–7.35 (m, 4 H, H_{Ar}), 7.17 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 6.32 (s, 1 H, CH), 2.46 (s, 3 H, CH_2), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 178.6, 159.9, 140.0, 138.6, 132.8, 132.1, 130.9, 128.5, 127.7, 127.6, 97.0, 48.9, 28.1, 21.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO_2S$: 360.1029; found: 360.1007.

(*Z*)-3-(4-Methoxyphenyl)-5,5-dimethyl-2-(2-oxo-2-phenylethylidene)thiazolidin-4-one (3r)

Yield: 125 mg (71%); brown solid; mp 156 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.45 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.36 (t, *J* = 7.7 Hz, 2 H, H_{Ar}), 7.20 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.07 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 6.32 (s, 1 H, CH), 3.88 (s, 3 H, CH_3), 1.72 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 178.7, 160.3, 160.1, 138.5, 132.1, 129.1, 128.7, 128.5, 127.8, 127.5, 115.4, 97.0, 55.6, 48.8, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO_3SNa$: 376.0978; found: 376.0977.

(*Z*)-2-[2-(4-Methoxyphenyl)-2-oxoethylidene]-5,5-dimethyl-3-(*p*-tolyl)thiazolidin-4-one (3s)

Yield: 161 mg (88%); yellow solid; mp 127 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.37 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.16 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.85 (d, *J* = 9.0 Hz, 2 H, H_{Ar}), 6.29 (s, 1 H, CH), 3.81 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 1.72 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.6, 178.6, 162.9, 159.0, 139.9, 132.9, 131.5, 130.9, 129.7, 127.8, 113.7, 96.9, 55.5, 48.8, 28.2, 21.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}NO_3S$: 368.1315; found: 368.1311.

(*Z*)-3-(3-Chlorophenyl)-5,5-dimethyl-2-(2-oxo-2-phenylethylidene)thiazolidin-4-one (3t)

Yield: 128 mg (72%); yellow solid; mp 142 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.53 (d, *J* = 4.5 Hz, 2 H, H_{Ar}), 7.47 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.38 (t, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.35 (s, 1 H, H_{Ar}), 7.26–7.20 (m, 1 H, H_{Ar}), 6.30 (s, 1 H, CH), 1.73 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 178.3, 159.1, 138.4, 136.4, 135.8, 132.3, 131.2, 130.3, 128.6, 127.6, 126.4, 97.1, 48.9, 28.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd $C_{19}H_{17}{}^{35}ClNO_2S$: 358.0663; found: 358.0668; *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}{}^{37}ClNO_2S$: 360.0639; found: 360.0649.

(*Z*)-3,5,5-Trimethyl-2-(2-oxo-2-phenylethylidene)thiazolidin-4-one (3u)

Yield: 95 mg (73%); yellow solid; mp 117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.52–7.43 (m, 3 H, H_{Ar}), 6.66 (s, 1 H, CH), 3.31 (s, 3 H, CH_3), 1.61 (s, 6 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.6, 178.7, 159.4, 138.7, 132.2, 128.6, 127.6, 95.1, 48.8, 30.5, 27.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_2S$: 262.0896; found: 262.0889.

(*Z*)-3-Ethyl-5,5-dimethyl-2-(2-oxo-2-phenylethylidene)thiazolidin-4-one (3v)

Yield: 94 mg (69%); yellow sticky solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.54–7.51 (m, 1 H, H_{Ar}), 7.46 (t, *J* = 7.5 Hz, 2 H, H_{Ar}), 6.68 (s, 1 H, CH), 3.87 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.61 (s, 6 H, CH_3), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 178.6, 158.6, 138.9, 132.1, 128.6, 127.6, 94.8, 48.6, 38.9, 27.8, 12.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}NO_2S$: 276.1053; found: 276.1057.

(*Z*)-3-Butyl-5,5-dimethyl-2-(2-oxo-2-phenylethylidene)thiazolidin-4-one (3w)

Yield: 118 mg (78%); brown sticky solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.52 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.48–7.45 (m, 2 H, H_{Ar}), 6.67 (s, 1 H, CH), 3.82 (t, *J* = 7.5 Hz, 2 H, CH_2), 1.69 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.61 (s, 6 H, CH_3), 1.44–1.36 (m, 2 H, CH_2), 0.99 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 179.0, 159.0, 138.9, 132.1, 128.7, 127.6, 95.0, 48.6, 43.7, 28.9, 27.9, 20.1, 13.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}NO_2S$: 304.1366; found: 304.1346.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1693-7535.

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