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ARTICLE TYPE

DMAP-Promoted domino annulation of β-ketothioamides with internal alkynes: A highly regioselective access to functionalized 1,3-thiazolidin-4-ones at room temperature

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DMAP-mediated rapid and efficient one-pot regioselective access to functionalized 1,3-thiazolidin-4-ones *via* annulation of β-ketothioamides with internal alkynes has been achieved under mild reaction conditions. The merit of this straightforward domino protocol is highlighted by its operational simplicity, short reaction time, tolerance of a large variety of functional groups, and efficiency of producing two new bonds (C−S and C−N) and one thiazolidine ring.

Introduction

In recent years, the development of new domino strategies[1] that provide synthetic efficiency and atom economy has been an important goal of synthetic chemistry, and continues to be a great challenge. 1,3-Thiazolidin-4-ones are an important group of heterocyclic compounds that appear in a plethora of natural products as well as in various pharmaceutical compounds.[2] They are not only synthetically important scaffolds but also possess a wide range of promising biological activities such as anti-inflammatory,[3a] antimicrobial,[3b,c] anti-tubercular,[3d] anti-HIV[3e,f] and anti-viral.[3g] Some derivatives proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentrations with minimal cytotoxicity, thereby acting as non-nucleoside HIV-1 RT inhibitors (NNRTIs).[3h] Furthermore, thiazolidine based compounds were found to be a prominent heat shock protein 70 (Hsp 70) inhibitor[4a] and cyclooxygenase (COX-2) inhibitor.[4b,c] Moreover, some thiazolidin-4-one derivatives are also used for the synthesis of highly efficient dyes sensitized solar cells.[5] The utility of 1,3-thiazolidin-4-ones as synthons for various applications has given impetus to these studies.

In general, 1,3-thiazolidin-4-ones have been prepared by the condensation of aldehyde, amine (or Schiff's base) with mercaptoacetic acid.[6] Bolognese et al.[7a] employing microwave technique and Lingampalle and co-workers[7b] utilizing ionic liquid synthesized thazoilidin-4-one derivatives. Borisevich et al.[8a] synthesized 1,3-thiazolidin-4-ones using thioamide and alkyne or maleic anhydride. The use of Baker's yeast,[8b] and Bi $(SCH_2COOH)_3$,[8c] as a catalyst have also been reported for the preparation of 1,3-thiazolidin-4-ones. Although the aforesaid methods enriched approaches to thiazolidin-4-one derivatives, most of them suffer from one or more limitations, such as poor yield, harsh reaction conditions, limited functional group tolerability, highly toxic reagents and tedious work-up procedure. Therefore, the exploration of more general, efficient, rapid, and viable routes for the construction of functionalized 1,3-thiazolidin-4-one scaffolds, particularly those with wide general applicability to achieve more flexible substitution patterns from readily available precursors is quite desirable.

In continuation of our ongoing research for the development of new methodologies for various heterocyclic systems by exploiting reactions of β-oxodithioesters,[9] herein, we report the first example of highly regioselective synthesis of functionalized 1,3-thiazolidin-4-ones via cascade annulation of β-ketothioamides with internal alkynes promoted by DMAP at room temperature (Scheme 1).

Results and Discussion

A rapidly increasing recognition of the rich and fascinating chemistry of β-oxodithioesters for the synthesis of various important heterocycles has been brought out recently by our group.[9] β-Ketothioamides (KTAs) as polyfunctional scaffolds bearing several reactive sites with general structure **1** (Fig. 1), are shown to exhibit intriguing multinucleophilic reactivities and have proven to be important building blocks in the construction of various heterocyclic systems.[10] In recent years, extensive work in this area has been done on the reactivities of the nucleophilic sites (N & C, O & S, and C & S atoms) of KTAs with dielectrophilic groups. However, the coupling reaction by means of N and S nucleophilic sites of KTAs with internal alkynes promoted by DMAP to form highly substituted 1,3-thiazolidin-4-ones has not been disclosed to date.

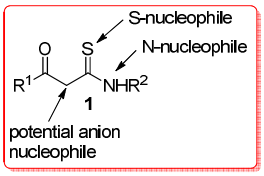
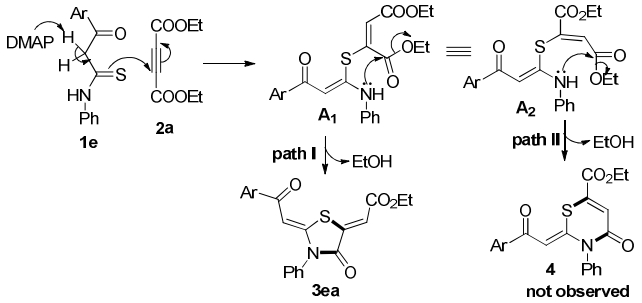


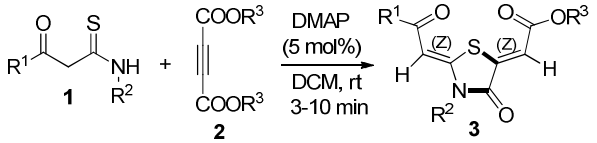
Fig. 1 Reactivity profile of β-ketothioamide.

The reactions of *β*-ketothioamides **1** with internal alkynes **2** might occur in two directions, as shown in Scheme 1. The nucleophilic attack of thiocarbonyl sulfur of **1e** on internal alkyne **2a** generates intermediate $\mathbf{A_1}$. Intermediate $\mathbf{A_1}$ could probably undergo intramolecular N-cyclization *via* its two possible rotamers $\mathbf{A_1}$ and $\mathbf{A_2}$ through two pathways to furnish 2,3,5-trisubstituted thiazolidin-4-one **3ea** and 1,3-thiazine-4-one-6-carboxylate **4**, respectively (Scheme 1, pathways I and II). When the equimolar amount of **1e** and **2a** was stirred in 5 mL of DCM at room temperature only one product isomer was obtained. However, the common characterization involving IR, ^{1}H and ^{13}C NMR, and HRMS analyses could not sufficiently identify the structure of the product as **3ea** or **4**. Fortunately, we obtained a single crystal of the product **3ea**, and the X-ray diffraction analysis of **3ea** (Fig. 2) revealed that the obtained product was a thiazolidin-4-one derivative making the protocol highly regioselective.



Scheme 1 Regioselectivity of the reaction.

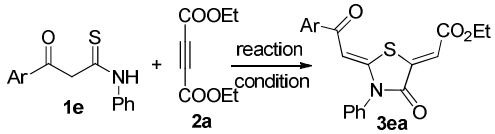
In this paper, we report a facile and efficient one-pot highly regioselective synthesis of 2,3,5-trisubstituted thiazolidin-4-ones **3** via cascade annulation of *β*-ketothioamides **1** with doubly activated internal alkynes **2** mediated by 4-dimethylaminopyridine (DMAP) at room temperature (Scheme 2). DMAP is a frequently used least expensive and less toxic organic Lewis base, which finds widespread application in a number of chemical reactions.[11] Our literature survey at this stage revealed that there is no report on the use of DMAP as a catalyst in the synthesis of 1,3-thiazolidin-4-ones from *β*-ketothioamides. Our main strategy in this work is to develop a new methodology which is easy, fast and cleaner than conventional reactions.



Scheme 2 Synthesis of 2,3,5-trisubstituted thiazolidin-4-ones.

Encouraged by the above result, we focussed on exploring the optimal reaction conditions for the synthesis of thiazolidin-4-one derivatives **3**. *β*-Ketothioamide **1e** and internal alkyne **2a** were selected as the test substrates to optimize the reaction conditions. The various attempts are summarized in Table 1. Initially, the equimolar amount of **1e** and **2a** in EtOH (5 mL) or DCM (5 mL) was stirred at room temperature without any catalyst, the target compound **3ea** was obtained in 12% and 22% yields respectively, and most of the **1e** remained unconsumed (Table 1, entries 1 and 2). Next, different organic bases such as DMAP, DABCO, DBU, DBN, pyridine and Et_3N were employed as the catalyst. Delightedly, 5 mol% of DMAP gave the desired product **3ea** in 92% yield within 3 min in DCM at room temperature (Table 1, entry 3). Other organic bases also promoted the reaction towards the formation of desired compound **3ea** but their catalytic efficiency was inferior to that of DMAP (Table 1, entries 4-8). With DMAP Lewis base as a good catalyst in hand, next we intended to optimize its loading, and it was found that the use of 5 mol% of DMAP provided the best result (Table 1, entry 3). Increasing the DMAP loading did not give the significant change (Table 1, entry 9). Reducing the DMAP loading to 3 mol% reduced the yield and prolonged the reaction time significantly (Table 1, entry 10). Further, use of other polar protic and aprotic solvents such as EtOH, MeOH and CH_3CN could not improve the results (Table 1, entries 11-13). The use of H_2O as the solvent shut down the reaction because of its poor ability to dissolve the substrates (Table 1, entry 14). Next, to have the green conditions, the above optimized reaction was performed under solvent-free conditions, which gave the desired product **3ea** in 56% yield after 35 min. (Table 1, entry 15). Obviously, screening of the solvents revealed that DCM turned out to be an appropriate solvent, as it not only resulted in a shorter reaction time but also provided a higher yield than the other examined solvents. Consequently, optimal conditions were identified as equimolar amounts of **1e** and **2a,** 5 mol% of DMAP in DCM (5 mL) at room temperature.

Table 1 Optimization of the reaction conditions[a]



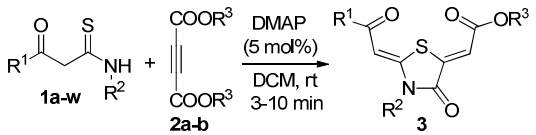
Entry	Catalyst (mol%)	Solvent (5 ml)	Time	Yield[b] (%)
1	none	EtOH	10 h	12[c]
2	none	DCM	10 h	22[c]
3	DMAP (5)	DCM	3 min	92
4	DABCO (5)	DCM	3 min	58
5	DBU (5)	DCM	3 min	53
6	DBN (5)	DCM	3 min	55
7	Pyridine (5)	DCM	8 min	72
8	Et_3N (5)	DCM	3 min	78
9	DMAP (10)	DCM	3 min	92
10	DMAP (3)	DCM	7 min	84
11	DMAP (5)	EtOH	3 min	74
12	DMAP (5)	MeOH	3 min	68
13	DMAP (5)	CH_3CN	3 min	76
14	DMAP (5)	H_2O	3 h	NR[d]
15	DMAP (5)	none	35 min	56

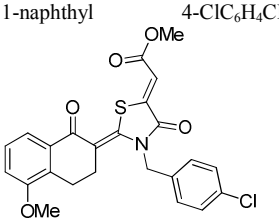
[a] Reaction conditions: The mixture of **1e** (1 mmol), **2a** (1 mmol) and solvent (5 mL) was stirred at room temperature. [b] Isolated pure yields. [c] **1e** remained unconsumed, [d] No reaction.

With the optimal conditions in hand (Table 1, entry 3), we commenced exploring the substrate scope and generality of this strategy. The results are summarized in Table 2. As can be seen, a wide range of twenty three *β*-ketothioamides **1a-w** derived from aromatic (containing both electron-donating and electron-withdrawing groups), heteroaromatic and aliphatic ketones were

well-tolerated, and in all cases the reactions proceeded smoothly to afford the corresponding thiazolidin-4-ones **3** in good to excellent yields. To assess the generality and applicability of this methodology, attempts to expand the scope of the reaction proved successful and a wide range of R^1 groups (aromatic, heteroaromatic, and aliphatic) and R^2 (aromatic and aliphatic) were incorporated, which provided a functional handle for further manipulation.

Table 2 Substrate scope for the synthesis of thiazolidin-4-ones[a]



Product	R^1	R^2	R^3	Time (min)	Yield[b] (%)
3aa	C_6H_5	C_6H_5	Et	3	85
3ba	4-BrC_6H_4	C_6H_5	Et	4	83
3ca	4-MeC_6H_4	C_6H_5	Et	3	84
3da	2-ClC_6H_4	C_6H_5	Et	3	82
3ea	3,4-OCH_2O-C_6H_3	C_6H_5	Et	3	92
3fa	4-Ph-C_6H_4	C_6H_5	Et	5	82
3ga	1-naphthyl	C_6H_5	Et	5	80
3ha	2-thienyl	C_6H_5	Et	3	90
3ia	2-furyl	C_6H_5	Et	3	88
3ja	*i*-propyl	C_6H_5	Et	4	78
3ka	*t*-butyl	C_6H_5	Et	4	75
3la	4-BrC_6H_4	Me	Et	3	85
3ma	4-MeC_6H_4	Me	Et	3	87
3na	3,4-OCH_2O-C_6H_3	Me	Et	4	88
3oa	2-thienyl	Me	Et	3	90
3mb	4-MeC_6H_4	Me	Me	3	86
3lb	4-BrC_6H_4	Me	Me	3	84
3nb	3,4-OCH_2O-C_6H_3	Me	Me	3	89
3ob	2-thienyl	Me	Me	3	92
3pb	4-OMeC_6H_4	*n*-butyl	Me	5	78
3qb	2-thienyl	*n*-butyl	Me	5	81
3ra	4-OMeC_6H_4	cyclopropyl	Et	5	78
3rb	4-OMeC_6H_4	cyclopropyl	Me	5	80
3sb	2-thienyl	cyclopropyl	Me	5	80
3tb	2-thienyl	cyclohexyl	Me	7	74
3ub	2-thienyl	$C_6H_5CH_2$	Me	8	78
3vb	1-naphthyl	4-Cl$C_6H_4CH_2$	Me	10	76
3wb				10	71

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), DCM (5 mL), stirring at rt; [b] isolated pure yields.

Even extremely electron-rich aromatic *β*-ketothioamides such as **1h**, **1i**, **1o** and **1q** proceeded smoothly affording the desired products in excellent yields (Table 2, **3ha**, **3ia**, **3oa** and **3qb**). However, *β*-ketothioamides (**1s-u)** bearing cyclopropyl, cyclohexyl and benzyl substituents as R^2 afforded comparatively lower yields (Table 2, **3sb**, **3tb** and **3ub**) than those bearing phenyl as R^2. In addition to incorporation of aryl, heteroaryl, and aliphatic substituents at R^1, extended aromatics are also viable for this protocol (Table 2, **3fa**, **3ga** and **3vb**). To amplify molecular diversity, we also used *β*-ketothioamide **1w** derived from 5-methoxytetralone, which was tolerated well and afforded the desired product in 71% yield (Table 2, **3wb**).

We also focused on employing internal alkynes bearing methyl and ethyl substituents (R^3) in this protocol, which were tolerated well to give the desired products in good yields. However, when some unsymmetrical electron-deficient alkynes such as 3-phenylpropiolate and acetyl phenyl acetylene were used under the optimized reaction conditions, reaction did not occur even after 24 h of stirring, thus limiting the scope of this protocol to some extent.

The structures of all of the newly synthesized thiazolidine-4-one derivatives **3** were identified by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra and unequivocally confirmed by the X-ray single crystal diffraction analysis of two representative compounds **3ea** and **3qb** (Fig. 2). From the crystallographic data for compounds **3ea** and **3qb**, a Z-stereochemistry was observed for the both exocyclic double bonds at 2- and 5-positions of thiazolidine ring.

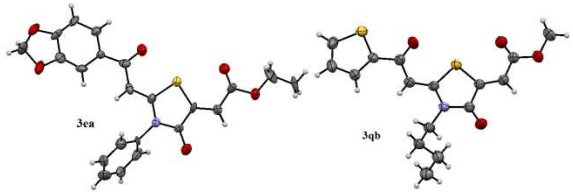
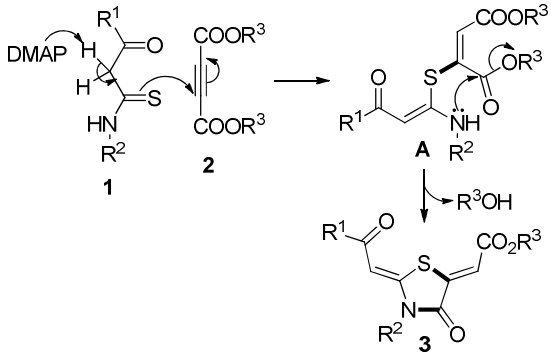


Fig. 2 ORTEP diagrams of **3ea** and **3qb**.

On the basis of the above experimental results together with the related reports, a plausible reaction scenario for this one-pot cycloaddition reaction is outlined in Scheme 3. The first step in the mechanism is believed to be the abstraction of the acidic proton of methylene of *β*-ketothioamide **1** by DMAP followed by nucleophilic attack of thiocarbonyl sulfur atom to the *sp*-hybridized carbon of **2** (thia-Michael type addition)**,** to generate an open-chain intermediate *α*-oxoketene-N,S-acetal **A**. The intermediate N,S-acetal **A** undergoes intramolecular N-cyclization with the extrusion of R^3OH to give the thiazolidin-4-one **3**. This operationally simple and two-component cascade annulation concomitantly created two new bonds (C–S and C–N) leading to thiazolidine ring.



Scheme 3 Plausible mechanism for the formation of thiazolidin-4-ones **3**.

Conclusion

We have successfully developed a straightforward, mild and efficient highly regioselective cascade annulation to synthesize densely functionalized thiazolidine-4-one derivatives utilizing KTAs and internal alkynes in DCM at room temperature

promoted by DMAP within 3-10 min. The procedure can be considered as an ideal means for the synthesis of thiazolidine-4-ones because of the following features: (1) the simplicity of execution and rapid production of thiazolidine-4-ones by cascade annulation, which minimizes the generation of waste; (2) no need for the use of any transition-metal catalyst or other additives; (3) high yields with flexible substitution patterns; (4) formation of two new bonds (S-C and N-C) and one ring in a single operation; (5) high atom-economy and an ecologically benign process in which only one molecule of either ethanol or methanol is lost. Further studies to expand the scope of KTAs as versatile building blocks are in progress and will be reported in due course.

Experimental Section

General Experimental

All the commercially available reagents were purchased from Merck, Aldrich and Fluka, and were used as received. All ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 300 FT-NMR spectrometer. Chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on PerkinElmer Spectrum Version 10.03.05 FT-IR spectrophotometer. Mass spectra were recorded on Agilent Q-TOF and Waters-Q-Tof Premier-HAB213 instrument. X-ray diffraction was measured on Xcalibur Oxford CCD Diffractometer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F_{254}) using UV light for visualization. Melting points were determined with Büchi B-540 melting point apparatus and are uncorrected.

General procedure for the synthesis of thiazolidin-4-ones (3aa–wb)

To a mixture of β-ketothioamide (1.0 mmol) and dialkyl acetylenedicarboxylate (1.0 mmol) in dichloromethane (5 mL) was added DMAP (5 mol%), and the reaction mixture was stirred for the stipulated period of time (Table 2) at room temperature. After completion of the reaction (monitored by TLC), water (20 mL) was added to the reaction mixture followed by extraction with dichloromethane (2 × 10 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and then evaporated in vacuo. The crude residue thus obtained was purified by column chromatography over silica gel using increasing percentage of ethyl acetate in hexane as eluent to afford pure thiazolidin-4-ones.

3aa: Yellow solid; m. p. 210-212 °C; IR (KBr, cm^{-1}): ν 2923, 2852, 1724, 1617, 1516, 1348, 1313, 1210, 1023; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 7.2 Hz, 2H); 7.63 - 7.58 (m, 3H); 7.49-7.33 (m, 5H); 6.97 (s, 1H); 6.45 (s, 1H); 4.36 (q, J = 7.2 Hz, 2H); 1.39 (t, J = 7.2 Hz, 3H) ; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 188.9, 165.8, 165.0, 156.0, 142.3, 138.1, 134.7, 132.8, 130.5, 128.7, 128.1, 127.9, 119.1, 99.3, 61.9, 14.5; HRMS [ESI] calcd for $C_{21}H_{17}NO_4S$ (M + H)$^+$: 380.0957, found: 380.0952.

3ba: Yellow solid; m. p. 248-250 °C; IR (KBr, cm^{-1}): ν 2985, 1708, 1684, 1564, 1526, 1418, 1310, 1190, 1027, 1004; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60-7.58 (m, 5H); 7.52 (d, J = 8.4 Hz, 2H); 7.33 (d, J = 6.3 Hz, 2H); 6.98 (s, 1H); 6.38 (s, 1H); 4.36 (q, J = 7.2 Hz, 2H); 1.38 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.5, 165.5, 164.7, 156.5, 141.8, 136.6, 134.3, 131.8, 130.3, 129.1, 127.8, 127.7, 119.2, 98.6, 61.7, 14.2; HRMS [ESI] calcd for $C_{21}H_{16}BrNO_4S$ (M + H)$^+$ / [(M + 2) + H]$^+$: 458.0062 / 460.0041, found: 458.0068 / 460.0024.

3ca: Yellow solid; m. p. 215-217 °C; IR (KBr, cm^{-1}): ν 2982, 1720, 1701, 1607, 1543, 1495, 1350, 1314, 1217, 1185, 1030; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.64-7.62 (m, 5H); 7.33 (d, J = 6.9 Hz, 2H); 7.18 (d, J = 8.1 Hz, 2H); 6.96 (s, 1H); 6.44 (s, 1H); 4.36 (q, J = 7.2 Hz, 2H); 2.36 (s, 3H); 1.38 (t, J = 7.2 Hz, 3H) . ^{13}C-NMR (75 MHz, $CDCl_3$): δ 188.3, 165.5, 164.7, 155.3, 143.3, 142.2, 135.4, 134.5, 130.2, 130.0, 129.2, 127.8, 118.6, 99.2, 61.6, 21.5, 14.2; HRMS [ESI] calcd for $C_{22}H_{19}NO_4S$ (M + H)$^+$: 394.1113, found: 394.1114.

3da: Yellow solid; m. p. 176-178 °C; IR (KBr, cm^{-1}): ν 3060, 1727, 1687, 1591, 1525, 1374, 1344, 1207, 1027; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.58 - 7.45 (m, 4H); 7.31-7.26 (m, 5H); 6.98 (s, 1H); 6.26 (s, 1H); 4.36 (q, J = 7.2 Hz, 2H); 1.38 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.9, 165.5, 164.6, 155.0, 141.9, 139.1, 134.2, 131.7, 131.1, 130.3, 130.1, 130.0, 129.8, 127.7, 126.9, 119.1, 103.3, 61.7, 14.2; HRMS [ESI] calcd for $C_{21}H_{16}ClNO_4S$ (M + H)$^+$: 414.0567, found: 414.0566.

3ea: Yellow solid; m. p. 280-282 °C; IR (KBr, cm^{-1}): ν 3075, 2922, 1720, 1697, 1604, 1535, 1493, 1437, 1359, 1254, 1206, 1187, 1094, 1036; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.62-7.60 (m, 2H); 7.34-7.29 (m, 5H); 6.96 (s, 1H); 6.76 (d, J = 8.1 Hz, 1H); 6.36 (s, 1H); 6.01 (s, 2H); 4.36 (q, J = 7.2 Hz, 2H); 1.38 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 186.7, 165.6, 164.7, 155.3, 151.4, 148.1, 142.2, 134.5, 132.7, 130.2, 130.0, 127.8, 123.6, 118.6, 107.8, 101.8, 99.0, 61.6, 14.2; HRMS [ESI] calcd for $C_{22}H_{17}NO_6S$ (M + H)$^+$: 424.0855, found: 424.0854.

3fa: Yellow solid; m. p. 220-222 °C; IR (KBr, cm^{-1}): ν 2924, 1713, 1633, 1605, 1559, 1537, 1495, 1352, 1214, 1186, 1051; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.81(d, J = 8.4 Hz, 2H); 7.62-7.56 (m, 7H); 7.46-7.34 (m, 5H); 6.98 (s, 1H); 6.49 (s, 1H); 4.37 (q, J = 7.2 Hz, 2H); 1.39 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 186.9, 164.5, 163.4, 154.6, 144.1, 141.4, 138.5, 135.6, 133.5, 129.2, 129.1, 127.9, 127.1, 126.9, 126.0, 117.1, 98.0, 60.5, 13.2; HRMS [ESI] calcd for $C_{27}H_{21}NO_4S$ (M + H)$^+$: 456.1270, found: 456.1264.

3ga: Yellow solid; m. p. 230-232 °C; IR (KBr, cm^{-1}): ν 3056, 2923, 1718, 1694, 1633, 1616, 1544, 1496, 1311, 1192, 1123, 1039; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H); 7.87-7.81(m, 4H); 7.65-7.49 (m, 5H); 7.38 (d, J = 7.2 Hz, 2H); 6.98 (s, 1H); 6.60 (s, 1H); 4.37 (q, J = 6.9 Hz, 2H); 1.39 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 188.5, 165.5, 164.8, 155.8, 142.1, 135.3, 134.5, 132.4, 130.3, 130.1, 129.4, 128.8, 128.4, 128.3, 127.9, 127.7, 126.6, 123.7, 118.9, 99.3, 61.6, 14.2; HRMS [ESI] calcd for $C_{25}H_{19}NO_4S$ (M + H)$^+$: 430.1113, found: 430.1113.

3ha: Yellow solid; m. p. 213-215 °C; IR (KBr, cm^{-1}): ν 3074, 2986, 1726, 1616, 1528, 1418, 1357, 1316, 1211, 1190; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60-7.56 (m, 4H); 7.40-7.32 (m, 3H); 7.03 (t, J = 4.2 Hz, 1H); 6.95 (s, 1H); 6.28 (s, 1H); 4.35 (q, J = 6.9

Hz, 2H); 1.38 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 181.1, 165.5, 164.6, 155.1, 145.2, 141.7, 134.3, 133.4, 130.5, 130.2, 130.1, 128.0, 127.8, 118.7, 99.2, 61.6, 14.2; HRMS [ESI] calcd for $C_{19}H_{15}NO_4S_2$ $(M + H)^+$: 386.0521, found: 386.0522.

3ia: Yellow solid; m. p. 216-218 °C; IR (KBr, cm^{-1}): ν 2986, 1727, 1693, 1632, 1572, 1533, 1474, 1376, 1313, 1230, 1187, 1053; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.62-7.59 (m, 3H); 7.46 (s, 1H); 7.32 (d, J = 7.2 Hz, 2H); 7.10 (d, J = 3.0 Hz, 1H); 6.96 (s, 1H); 6.48 (s, 1H); 6.35 (s, 1H); 4.36 (q, J = 7.2 Hz, 2H); 1.38 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 177.4, 165.5, 164.6, 155.1, 153.3, 145.7, 141.8, 134.3, 130.2, 130.0, 127.8, 118.8, 116.2, 112.5, 99.1, 61.6, 14.2; HRMS [ESI] calcd for $C_{19}H_{15}NO_5S$ $(M + H)^+$: 370.0749, found: 370.0748.

3ja: Yellow solid; m. p. 112-114 °C; IR (KBr, cm^{-1}): ν 2975, 2932, 1712, 1693, 1543, 1368, 1311, 1239, 1190, 1067, 1026; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59-7.54 (m, 2H); 7.28-7.25 (m, 3H); 6.92 (s, 1H); 5.74 (s, 1H); 4.33 (q, J = 7.2 Hz, 2H); 2.54-2.48 (m, 1H); 1.37 (t, J = 7.2 Hz, 3H); 1.04 (d, J = 6.6 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 202.8, 165.5, 153.6, 142.1, 134.4, 130.1, 129.9, 127.7, 118.3, 100.9, 61.5, 41.0, 18.3, 14.2; HRMS [ESI] calcd for $C_{18}H_{19}NO_4S$ $(M + H)^+$: 346.1113, found: 346.1115.

3ka: Yellow solid; m. p. 141-143 °C; IR (KBr, cm^{-1}): ν 3.65, 2965, 1715, 1694, 1529, 1373, 1318, 1222, 1193, 1082, 1024; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (brs, 3H); 7.28-7.26 (m, 2H); 6.92 (s, 1H); 5.93 (s, 1H); 4.34 (q, J = 3.6 Hz, 2H); 1.37 (t, J = 3.6 Hz, 3H); 1.05 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 204.3, 165.5, 164.7, 154.3, 142.2, 134.5, 130.1, 129.9, 127.7, 118.3, 98.5, 61.5, 43.0, 26.4, 14.2; HRMS [ESI] calcd for $C_{19}H_{21}NO_4S$ $(M + H)^+$: 360.1270, found: 360.1263.

3la: Yellow solid; m. p. 224-226 °C; IR (KBr, cm^{-1}): ν 3060, 1707, 1684, 1634, 1586, 1524, 1418, 1346, 1310, 1227, 1190, 1069; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 8.1 Hz, 2H); 7.60 (d, J = 8.1 Hz, 2H); 6.91 (s, 1H); 6.69 (s, 1H); 4.33 (q, J = 7.2 Hz, 2H); 3.43 (s, 3H); 1.37 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.3, 165.4, 164.9, 156.0, 141.9, 136.7, 131.9, 129.2, 127.7, 119.0, 96.6, 61.6, 30.1, 14.2; HRMS [ESI] calcd for $C_{16}H_{14}BrNO_4S$ $(M + H)^+/[(M + 2) + H]^+$: 395.9905/397.9885, found: 395.9909/397.9891.

3ma: Yellow solid; m. p. 186-188 °C; IR (KBr, cm^{-1}): ν 2984, 1706, 1688, 1637, 1606, 1531, 1419, 1343, 1309, 1233, 1180, 1059, 1027; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.5 Hz, 2H); 7.29 (2H merged with $CDCl_3$); 6.90 (s, 1H); 6.77 (s, 1H); 4.33 (q, J = 7.2 Hz, 2H); 3.43 (s, 3H); 2.47 (s, 3H); 1.37 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 188.2, 165.5, 165.0, 154.8, 143.5, 142.3, 135.5, 129.3, 127.8, 118.6, 97.2, 61.5, 30.1, 21.6, 14.2; HRMS [ESI] calcd for $C_{17}H_{17}NO_4S$ $(M + H)^+$: 332.0957, found: 332.0959.

3na: Yellow solid; m. p. 186-188 °C; IR (KBr, cm^{-1}): ν 3074, 2996, 1702, 1674, 1538, 1504, 1435, 1355, 1318, 1261, 1200, 1093, 1034; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.1 Hz, 1H); 7.47 (s, 1H); 6.90 (s, 1H); 6.86 (s, 1H); 6.69 (s, 1H); 6.06 (s, 2H); 4.33 (q, J = 6.9 Hz, 2H); 3.43 (s, 3H); 1.36 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 186.7, 165.5, 154.7, 151.5, 148.3, 142.3, 132.9, 126.2, 123.6, 118.5, 109.9, 107.8, 101.9, 101.7, 97.0, 61.5, 30.1, 14.2; HRMS [ESI] calcd for $C_{17}H_{15}NO_6S$ $(M + H)^+$: 362.0698, found: 362.0691.

3oa: Yellow solid; m. p. 182-184 °C; IR (KBr, cm^{-1}): ν 3115, 3099, 2983, 1699, 1614, 1537, 1425, 1360, 1317, 1242, 1195, 1028; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 3.6 Hz, 1H); 7.62 (d, J = 4.5 Hz, 1H); 7.12 (t, J = 4.2 Hz, 1H); 6.87 (s, 1H); 6.59 (s, 1H); 4.32 (q, J = 7.2 Hz, 2H); 3.41 (s, 3H); 1.36 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 180.9, 165.4, 164.8, 154.7, 145.2, 141.9, 133.2, 130.4, 128.1, 118.5, 97.4, 61.5, 30.0, 14.2; HRMS [ESI] calcd for $C_{14}H_{13}NO_4S_2$ $(M + H)^+$: 324.0364, found: 324.0364.

3mb: Yellow solid; m. p. 226-228 °C; IR (KBr, cm^{-1}): ν 2954, 1719, 1694, 1639, 1534, 1425, 1323, 1281, 1183, 1042, 1015; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.8 Hz, 2H); 7.26 (d, J = 6.9 Hz, 2H); 6.89 (s, 1H); 6.76 (s, 1H); 3.87 (s, 3H); 3.42 (s, 3H); 2.41 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 188.1, 165.9, 164.9, 154.6, 143.6, 142.6, 135.3, 129.3, 127.8, 117.9, 97.2, 52.3, 30.1, 21.6; HRMS [ESI] calcd for $C_{16}H_{15}NO_4S$ $(M + H)^+$: 318.0800, found: 318.0800.

3lb: Yellow solid; m. p. 239-241 °C; IR (KBr, cm^{-1}): ν 2954, 1720, 1691, 1636, 1564, 1534, 1424, 1321, 1204, 1184, 1042, 1067; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J = 8.1 Hz, 2H); 7.62 (d, J = 8.4 Hz, 2H); 6.93 (s, 1H); 6.71 (s, 1H); 3.88 (s, 3H); 3.44 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 186.3, 164.8, 163.5, 154.3, 141.6, 135.6, 130.7, 128.4, 126.4, 116.5, 96.2, 51.3, 29.2; HRMS [ESI] calcd for $C_{15}H_{12}BrNO_4S$ $(M + H)^+/[(M+2)+H]^+$: 381.9749/383.9728, found: 381.9749/383.9729.

3nb: Yellow solid; m. p. 242-244 °C; IR (KBr, cm^{-1}): ν 2954, 1698, 1637, 1531, 1488, 1441, 1324, 1244, 1198, 1115, 1034; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.1 Hz, 1H); 7.46 (s, 1H); 6.90 (s, 1H); 6.87 (d, J = 8.4 Hz,1H); 6.69 (s, 1H); 6.05 (s, 2H); 3.87 (s, 3H); 3.42 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 186.7, 161.2, 158.4, 157.5, 154.6, 151.6, 142.6, 133.0, 126.9, 123.6, 118.0, 107.9, 101.9, 97.1, 52.4, 30.1; HRMS [ESI] calcd for $C_{16}H_{13}NO_6S$ $(M + H)^+$: 348.0542, found: 348.0537.

3ob: Yellow solid; m. p. 218-220 °C; IR (KBr, cm^{-1}): ν 2951, 1721, 1629, 1532, 1419, 1355, 1287, 1186, 1019; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 3.0 Hz, 1H); 7.62 (d, J = 3.9 Hz, 1H); 7.13 (t, J = 4.2 Hz, 1H); 6.87 (s, 1H); 6.59 (s, 1H); 3.86 (s, 3H); 3.42 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 180.9, 165.8, 164.9, 154.6, 145.3, 142.2, 133.1, 130.5, 128.1, 118.0, 97.5, 52.2, 30.1; HRMS [ESI] calcd for $C_{13}H_{11}NO_4S_2$ $(M + H)^+$: 310.0208, found: 310.0208.

3pb: Yellow solid; m. p. 160-162 °C; IR (KBr, cm^{-1}): ν 2957, 1705, 1600, 1531, 1324, 1262, 1199, 1167, 1021; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 2H); 6.97 (d, J = 8.1 Hz, 2H); 6.88 (s, 1H); 6.76 (s, 1H); 3.92 (t, J = 7.5 Hz, 2H); 3.88 (s, 3H); 3.87 (s, 3H); 1.75-1.65 (m, 2H); 1.47-1.39 (m, 2H); 1.00 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.2, 165.9,

165.0, 163.2, 153.7, 142.7, 131.0, 129.9, 117.7, 113.8, 96.9, 55.5, 52.3, 43.5, 29.0, 20.0, 13.6; HRMS [ESI] calcd for $C_{19}H_{17}NO_5S$ $(M + H)^+$ /$(M + Na)^+$: 376.1219/398.1038, found: 376.1205/398.1024.

3qb: Yellow solid; m. p. 160-162 °C; IR (KBr, cm^{-1}): ν 2939, 1698, 1626, 1534, 1368, 1326, 1205, 1064; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 3.3 Hz, 1H); 7.63 (d, J = 4.8 Hz, 1H); 7.14 (t, J = 4.2 Hz, 1H) 6.87 (s, 1H); 6.62 (s, 1H); 3.91 (t, J = 7.2 Hz, 2H); 3.86 (s, 3H); 1.74-1.69 (m, 2H); 1.47-1.39 (m, 2H); 1.00 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 180.9, 165.8, 164.9, 154.0, 145.3, 142.2, 133.2, 130.3, 128.1, 117.8, 97.3, 52.4, 43.5, 29.0, 20.0, 13.6; HRMS [ESI] calcd for $C_{16}H_{17}NO_4S_2$ $(M + H)^+$: 352.0677, found: 352.0677.

3ra: Yellow solid; m. p. 168-170 °C; IR (KBr, cm^{-1}): ν 2925, 1725, 1688, 1690, 1599, 1519, 1460, 1354, 1313, 1268, 1169, 1023; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 8.7 Hz, 2H); 7.19 (s, 1H); 6.97 (d, J = 8.7 Hz, 2H); 6.84 (s, 1H); 4.32 (q, J = 7.2 Hz, 2H); 3.88 (s, 3H); 2.78 – 2.77 (m, 1H); 1.36 (t, J = 7.2 Hz, 3H); 1.27 (d, J = 6.0 Hz, 2H); 1.04 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.3, 165.5, 165.3, 163.3, 154.7, 142.7, 131.1, 130.0, 129.9, 118.0, 113.8, 98.4, 61.4, 55.4, 25.6, 14.2, 7.5; HRMS [ESI] calcd for $C_{19}H_{19}NO_5S$ $(M + H)^+$: 374.1062, found: 374.1063.

3rb: Yellow solid; m. p. 228-230 °C; IR (KBr, cm^{-1}): ν 2927, 1714, 1693, 1594, 1533, 1428, 1357, 1324, 1223, 1195, 1165, 1027; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 8.4 Hz, 2H); 7.19 (s, 1H); 6.97 (d, J = 8.4 Hz, 2H); 6.85 (s, 1H); 3.88 (s, 3H); 3.86 (s, 3H); 2.77 (br, 1H); 1.27 (d, J = 6.6 Hz, 2H); 1.04 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.3, 165.9, 165.2, 163.3, 154.5, 143.0, 131.1, 130.0, 117.5, 113.8, 98.5, 55.5, 52.3, 25.6, 7.5; HRMS [ESI] calcd for $C_{18}H_{17}NO_5S$ $(M + H)^+$: 360.0906, found: 360.0903.

3sb: Yellow solid; m. p. 232-234 °C; IR (KBr, cm^{-1}): ν 2955, 1700, 1622, 1598, 1517, 1421, 1361, 1315, 1225, 1190, 1066; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 2.7 Hz, 1H); 7.61 (d, J = 4.5 Hz, 1H); 7.13 (s, 1H); 7.03 (s, 1H); 6.83 (s, 1H); 3.85 (s, 3H); 2.75 (br, 1H); 1.25 (d, J = 5.4 Hz, 2H); 1.04 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 181.0, 165.8, 165.1, 154.9, 145.5, 142.5, 133.0, 130.4, 128.1, 117.7, 98.9, 52.3, 25.7, 7.4; HRMS [ESI] calcd for $C_{15}H_{13}NO_4S_2$ $(M + H)^+$: 336.0364, found: 336.0367.

3tb: Yellow solid; m. p. 207-209 °C; IR (KBr, cm^{-1}): ν 2928, 2852 1712, 1622, 1608, 1517, 1421, 1317, 1200, 1174, 1058; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H); 7.64 (d, J = 4.2 Hz, 1H); 7.17 (d, J = 4.2 Hz, 1H); 6.84 (s, 1H); 6.80 (s, 1H); 4.23 (br, 1H); 3.86 (s, 3H); 2.40-2.28 (m, 2H); 1.99-1.95 (m, 2H); 1.82-1.78 (m, 3H); 1.46-1.27 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 181.0, 166.0, 133.1, 130.2, 128.2, 126.6, 117.4, 97.8, 52.4, 28.6, 26.1, 25.1; HRMS [ESI] calcd for $C_{18}H_{19}NO_4S_2$ $(M + H)^+$: 378.0834, found: 378.0837.

3ub: Yellow solid; m. p. 212-214 °C; IR (KBr, cm^{-1}): ν 2985, 1726, 1616, 1528, 1418, 1357, 1316, 1210, 1189, 1031; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 4.5 Hz, 1H); 7.50 (d, J = 3.3 Hz, 1H); 7.38-7.30 (m, 5H); 7.09 (t, J = 4.2 Hz, 1H); 6.97 (s, 1H); 6.60 (s, 1H); 5.12 (s, 2H); 3.88 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 180.8, 165.8, 165.2, 153.2, 145.1, 142.0, 134.0, 133.4, 130.5, 129.2, 128.2, 126.9, 118.2, 98.9, 52.4, 47.3; HRMS [ESI] calcd for $C_{19}H_{15}NO_4S_2$ $(M + H)^+$ /$(M + Na)^+$: 386.0521/408.0340, found: 386.0510/408.0330.

3vb: Yellow solid; m. p. 170-172 °C; IR (KBr, cm^{-1}): ν 2946, 1717, 1694, 1614, 1572, 1533, 1324, 1202, 1114, 1092; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 8.1 Hz, 1H); 7.94 (d, J = 8.1 Hz, 1H); 7.86 (d, J = 7.8 Hz, 1H); 7.56-7.42 (m, 4H); 7.33 (d, J = 8.1 Hz, 2H); 7.17 (d, J = 8.1 Hz, 2H); 7.00 (s, 1H); 6.55 (s, 1H); 5.03 (s, 2H); 3.09 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 192.0, 165.9, 165.2, 153.0, 142.1, 137.4, 134.2, 133.7, 132.4, 132.1, 129.9, 129.3, 128.4, 128.3, 127.5, 126.8, 126.4, 125.3, 124.6, 118.7, 102.8, 52.2, 46.4; HRMS [ESI] calcd for $C_{25}H_{18}ClNO_4S$ $(M + H)^+$: 464.0723, found: 464.0727.

3wb: Yellow solid; m. p. 231-233 °C; IR (KBr, cm^{-1}): ν 2925, 1698, 1583, 1514, 1435, 1325, 1295, 1262, 1203, 1041; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.1 Hz, 1H); 7.34-7.24 (m, 3H); 7.07 (d, J = 8.1 Hz, 2H); 6.97 (d, J = 8.4 Hz, 1H); 6.86 (s, 1H); 5.28 (s, 2H); 3.86 (s, 3H); 3.81 (s, 3H); 2.93 (t, J = 6.0 Hz, 2H); 2.68-2.65 (m, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 186.4, 165.9, 165.1, 155.3, 145.7, 142.9, 134.3, 133.6, 131.6, 130.1, 128.1, 127.0, 126.6, 118.5, 114.8, 114.4, 111.0, 55.4, 51.2, 48.5, 25.3, 20.1; HRMS [ESI] calcd for $C_{24}H_{20}ClNO_5S$ $(M + H)^+$: 470.0829, found: 470.0812.

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† Electronic supplementary information (ESI) available: Starting materials **1** and **2** are defined and NMR (^{1}H & ^{13}C) spectra of all products. CCDC 972111 (**3ea**) and 961594 (**3qb**).

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DMAP-Promoted domino annulation of β-ketothioamides with internal alkynes: A highly regioselective access to functionalized 1,3-thiazolidin-4-ones at room temperature

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One-pot DMAP-mediated regioselective access to functionalized 1,3-thiazolidin-4-ones has been achieved via annulation of β-ketothioamides with internal alkynes under mild reaction conditions.