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Umpolung cyclization reaction of *N*-cinnamoylthioureas in the presence of DBU†

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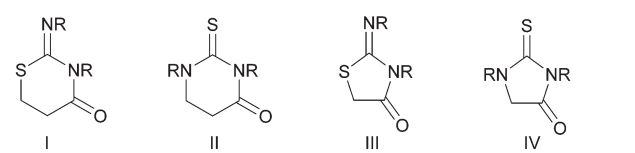
A novel regioselective cyclization reaction of *N*-cinnamoylthioureas leading to six- or five-membered heterocyclic compounds was developed. *N*-Cinnamoylthioureas in the presence of trifluoroacetic acid (TFA) underwent the well-established intramolecular cycloaddition reaction to give 2-imino-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-ones in good yields. On the other hand, the reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeded in an unprecedented "umpolung" cyclization fashion to afford five-membered 2-imino-1,3-thiazolidin-4-ones and/or 2-thioxoimidazolidine-4-ones. The reaction was considered to occur *via* a cycloadduct of DBU with the cinnamoyl moiety followed by intramolecular attack of the thiourea group.

Introduction

Heterocyclic compounds containing heteroatoms such as nitrogen and sulfur in the skeleton are present in many natural products and are widely used as medical pesticides and functional materials. For example, six-membered iminothiazinone (iminothiazinanone) (I, Scheme 1) is a substrate attracting attention as a novel therapeutic agent that stops or slows the progression of Parkinson's disease.[1] Thioxopyrimidinones (II) are utilized as anti-allergic and anti-cancer agents.[2] 2-Iminothiazolidin-4-ones (III) and their derivatives display a broad spectrum of biological activities[3] and exhibit pharmaceutical activities as a sphingosine-1-phosphate receptor agonist[4] and a preferential hCA inhibitor,[5] pronounced anticonvulsant activity[6] as a selective GSK-3β inhibitor,[7] and antiproliferative activity against cancer cell lines.[8] Thiohydantoin (2-thioxoimidazolidin-4-one) analogues (IV) display a range of biological activities, such as antimycobacterial,[9] antiviral,[10] NADPH oxidase inhibition[11] and antitumor properties.[12] Therefore, the development of efficient and practical methods for the synthesis of such heterocycles is an interesting research area in organic and pharmaceutical chemistry. All these heterocycles were usually provided by cyclization reactions of thioureas with acid derivatives, and suitable methods for each substituent were adopted.[13,14] If we can generate these heterocycles from the same starting materials by changing the reaction conditions or catalysts, this methodology will become a facile and useful synthetic process leading to diverse heterocycles.

We have developed a facile intramolecular cyclization of *N*-cinnamoylthioureas leading to six-membered heterocycles, iminothiazinone I, under acidic conditions. Furthermore, we found an unprecedented "umpolung" cyclization reaction leading to five-membered heterocycles, iminothiazolidinones III and thiohydantoins IV, by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst. The "umpolung" reaction has been proposed for acyl anion equivalents, and many fine examples using 1,3-thiazines,[15] thiazolium ions,[16] the benzoin reaction,[17] and ketimines[18] have been reported. Furthermore, the Morita–Baylis–Hillman reaction initiated with the conjugate addition of a Brønsted base to enones is also a representative "umpolung" reaction.[19] Recently, the reaction was applied to the intramolecular cyclization of alkyl-



Scheme 1 Various heterocyclic compounds with high pharmaceutical activities.

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imines using a Brønsted base.[20] These various types of "umpolung" reactions have expanded the range of organic syntheses. We have now discovered a novel example of an intramolecular "umpolung" cyclization leading to five-membered heterocycles.

Results and discussion

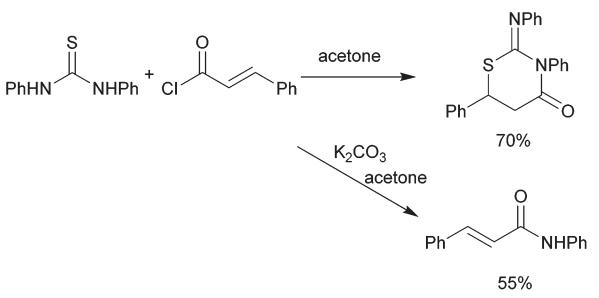
Previously, Britsun *et al.* reported that the reaction of *N*,*N*′-diphenylthiourea with cinnamoyl chloride in acetone without a base gave an iminothiazinone.[13] In the presence of potassium carbonate, however, cinnamanilide was the sole product (Scheme 2). In these reactions, the intermediacy of *N*-cinnamoylthiourea was suggested based on the decomposition to the anilide.

We synthesized a variety of *N*-cinnamoylthioureas **1a–j** and investigated their cyclizations under both acidic and basic conditions. *N*-Cinnamoylthioureas **1a–j** were easily produced by acylation of the corresponding thioureas using cinnamoyl chloride and triethylamine in the presence of molecular sieves (4 Å) (Scheme 3). When unsymmetrical thioureas were used, selective acylation took place on the nitrogen atoms of the anilide moieties leading to **1f–j** in moderate yields. In these cases, the formation of diacylated thioureas as by-products caused a decrease in the chemical yields.

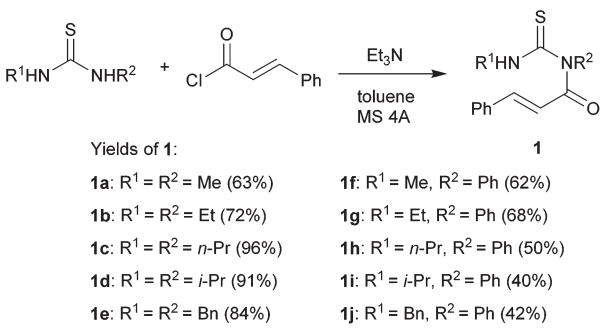
We first examined the intramolecular cycloaddition of **1** leading to iminothiazinones (I) or thioxopyrimidinones (II) under acidic conditions (Scheme 4). *N*-Cinnamoyl-*N*,*N*′-dimethylthiourea **1a** was dissolved in toluene and stirred at room temperature in the presence of trifluoroacetic acid. The starting materials disappeared after 0.5 h. An efficient and product-selective reaction was promoted, and the intramolecular cycloaddition product **2a** by C–S bond formation was obtained in 97% yield. Similar cycloadditions occurred in other substrates **1b–1j** leading to iminothiazinones **2b–2j** in good yields. In all cases, other isomers, such as thioxopyrimidinones **2′** formed by C–N bond formation, could not be observed under acidic conditions. The structures of the products were determined spectroscopically. Additionally, the structures of **2h**, **2i**, and **2j** were unequivocally established by single crystal X-ray structure analysis (Fig. S1–S3†).

In the crystallographic analysis of **2h**, the imide group adopts an almost planar conformation owing to the strong conjugation between the imino group and both the nitrogen and sulfur atoms, and the two phenyl rings are in an almost perpendicular conformation relative to the thiazinone ring (Fig. S1†). Bond lengths are also shown in the figure. The sulfur atom is conjugated with the imino group, thus this C–S bond is shorter than the other C–S bond. The alkyl substituent on the imino-nitrogen atom is placed in the *Z* configuration oriented toward the sulfur atom to avoid steric interaction with the phenyl ring on the nitrogen atom. Other iminothiazinones **2i** and **2j** adopted similar conformations to **2h** in the crystal lattice (Fig. S2 & S3†).

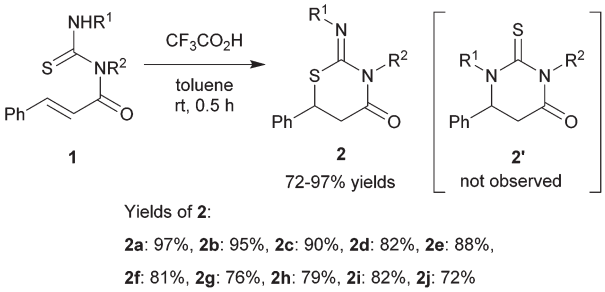
Next, we examined the reaction of **1a–j** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 5). When the reaction was run in toluene at room temperature in the presence of DBU and molecular sieves (4 Å), unprecedented "umpolung" reaction products were obtained. When **1a** was reacted at rt for 0.5 h until the starting material disappeared,



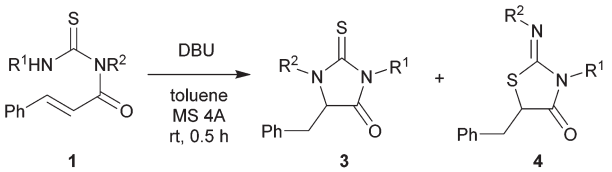
Scheme 2 Reaction of *N*,*N*′-diphenylthiourea with cinnamoyl chloride.



Scheme 3 Synthesis of various *N*-cinnamoylthioureas **1a–1j**.



Scheme 4 Cyclization of *N*-cinnamoylthioureas **1a–1j** under acidic conditions. A dried toluene (2.0 mL) solution of **1** (0.400 mmol) and TFA (4.00 mmol) was stirred at room temperature for 0.5 hours.



Scheme 5 "Umpolung" cyclization reaction of **1a–j** in the presence of DBU.

Table 1 Cyclization reaction of **1a–j** in the presence of DBU and molecular sieves[a]

Entry	Urea **1**	R^1	R^2	Yield of **3** (%)	Yield of **4** (%)
1	**1a**	Me	Me	81	0
2	**1b**	Et	Et	75	0
3	**1c**	*n*-Pr	*n*-Pr	70	0
4	**1d**	*i*-Pr	*i*-Pr	77	8
5	**1e**	Bn	Bn	51	0
6	**1f**	Me	Ph	10	65
7	**1g**	Et	Ph	3	71
8	**1h**	*n*-Pr	Ph	6	57
9	**1i**	i-Pr	Ph	3	32[b]
10	**1j**	Bn	Ph	11	66

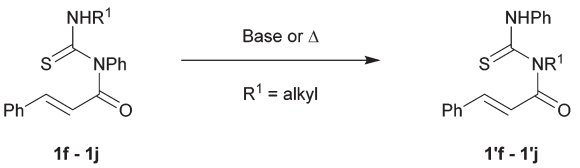
[a] A dried toluene (8.0 mL) solution of **1** (1.20 mmol) and DBU (0.600 mmol) was stirred at room temperature for 0.5 hours in the presence of molecular sieves (4 Å, 1.5 g). [b] Cinnamanilide was obtained in 50% yield.

five-membered thiohydantoin **3a** was obtained in 81% yield (Table 1, entry 1). Cyclization of other *N*-acylthioureas **1b–1e** also proceeded efficiently and gave the corresponding thiohydantoins **3b–3e** (entries 2–5). In the case of the reaction of **1d**, a small amount of **4d** was also produced in 8% yield (entry 4).

When asymmetrically substituted *N*-alkyl-*N*′-cinnamoyl-*N*′-phenylthioureas **1f–1j** were used for the reaction, the major products changed and iminothiazolidinones **4f–4j** were obtained, accompanied by a small amount of **3** (entries 6–10).

The structures of all these materials were determined spectroscopically. Additionally, the structures of **3i**, **3j** and **4g** were unequivocally established by single crystal X-ray analysis (Fig. S4–S6†). Both thiohydantoins and iminothiazolidinones adopted planar conformations. The substituent on the imino-nitrogen atom of **4g** was inclined toward the sulfur atom owing to the steric interaction as in the cases of iminothiazinones **2**.

As can be seen from the molecular structures, three unique phenomena were promoted in this cyclization using DBU. The first is that the rearrangement of the cinnamoyl group occurred before the cyclization reaction in the case of the phenylthioureas (Scheme 6). Although it cannot be distinguished in the case of **1a–e**, it is clear that the cinnamoyl group rearranged from the nitrogen atom substituted R^2 (Ph) group to the other nitrogen atom substituted by the alkyl group in the cases of **1f–j**, whereas the rearrangement did not take place in the cyclization under acidic conditions as shown in Scheme 4. Rearrangement of the acyl group for *N*-acylthioureas is well-known for arylthioureas under thermal or basic conditions.[21] Under basic conditions, it seems that **1′** is more stable than **1**, because the deprotonated amidate anion from **1′** can delocalize through the aryl group, whereas the anion cannot conjugate with the alkyl group. This fast rearrangement occurred before cyclization to form **3** and **4** in the case of **1f–1j**.



1f - 1j 1'f - 1'j

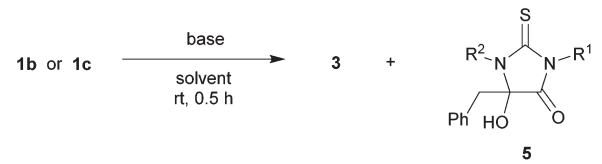
Scheme 6 Rearrangement of *N*-cinnamoylthioureas **1f–1j** under basic conditions.

In the case of the reaction using **1i**, cinnamanilide was obtained by decomposition of **1i** before acyl transformation. The steric hindrance of the isopropyl group prevented effective transformation of the cinnamoyl group (Table 1, entry 9).

The second phenomenon is the reaction mechanism. The α-position of the cinnamoyl group reacted with the nitrogen or sulfur atom of the thiourea group. Michael additions typically occur at the β-position of α,β-unsaturated groups, and six-membered heterocycles **2** or **2′** should be formed as in the case of the reaction under acidic conditions.

Next we examined the reaction by changing bases and the effect of molecular sieves (Scheme 7 and Table 2). Other bases such as triethylamine, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), or 1,4-diazabicyclo[2.2.2]octane (DABCO) were inert in this cyclization (Table 2, entries 1–3). On the other hand, the use of 1,8-diazabicyclo[4.3.0]nona-7-ene (DBN) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) also worked as in the case of the reaction with DBU (Table 2, entries 4 and 5). This "umpolung" cyclization reaction is peculiar for DBU, DBN and TBD.

The conjugate addition of DBU to enones is supported by the well-known reaction mechanism for the Morita–Baylis–Hillman reaction.[19] Furthermore, the addition of DBU to coumarins, tetrazines and hydroxyalkynoates leading to cycliza-



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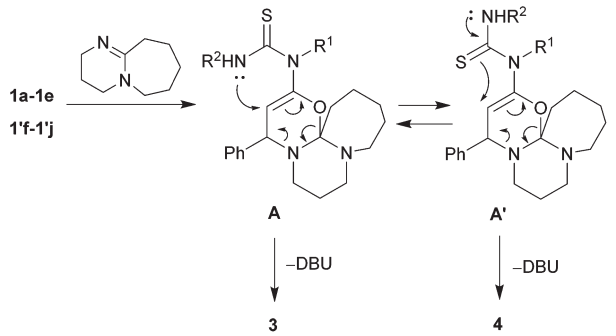
Scheme 7 Cyclization reaction of **1b** and **1c** in the presence of a variety of bases with or without molecular sieves.

Table 2 Cyclization reaction of **1b** and **1c** in the presence of a variety of bases with or without molecular sieves[a]

Entry	Urea **1**	Solvent	Base	Yield of **3** (%)	Yield of **5** (%)
1[b,c]	**1b**	Toluene	Et_3N	0	0
2[b,d]	**1b**	Toluene	DMAP	0	0
3[b,e]	**1b**	Toluene	DABCO	0	0
4[b,f]	**1b**	Toluene	DBN	74	0
5[b,g]	**1b**	Toluene	TBD	46	0
6[c,h]	**1b**	Toluene	DBU	21	10
7[c,h]	**1b**	CH_2Cl_2	DBU	10	61
8[c,h]	**1b**	THF	DBU	0	87
9[c,h]	**1c**	Toluene	DBU	59	12

[a] Each solvent (8.0 mL) containing **1** (1.20 mmol) and a base (0.600 mmol) was stirred with or without molecular sieves (4 Å, 1.5 g) at room temperature for 0.5 h. [b] The reaction was conducted with molecular sieves. [c] Et_3N was used as a base. [d] DMAP was used as a base. [e] DABCO was used as a base. [f] DBN was used as a base. [g] TBD was used as a base. [h] The reaction was conducted without molecular sieves in the presence of DBU (1.50 mmol).

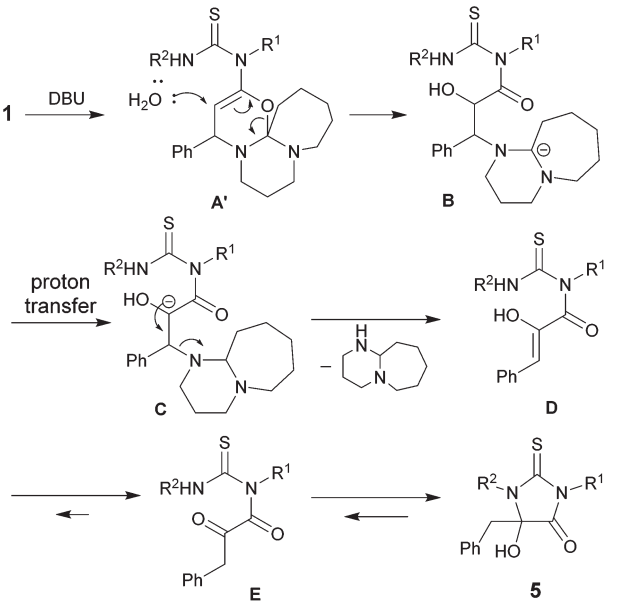


Scheme 8 Mechanism for the formation of five-membered heterocycles **3** and **4** in the presence of DBU.

tion products has also been reported.[22] While the cycloaddition of DBU with cinnamic acid derivatives is not unprecedented, a mechanism involving an intermediacy of a DBU adduct is advocated to explain this mysterious phenomenon (Scheme 8). The DBU undergoes cycloaddition to the enone group to form intermediate **A** or **A′**. Attack of the nitrogen atom affords **3**, and reaction with the sulfur atom gives **4**. The difference is reasonably understood in terms of the electron density of the sulfur atoms due to the substituents on the nitrogen atom, regardless of the alkyl or aryl group. Cleavage of the C–O bond followed by the elimination of DBU from the strained fused molecule aids in the addition of the sulfur or the nitrogen atom of the thiourea group. Unfortunately, no reaction intermediates were detected when the reaction was monitored by NMR spectroscopy.

The third phenomenon is that the apparent product selectivity depends on the substituents. *N*,*N*′-Dialkyl derivatives (**1a–1e**) selectively gave thiohydantoins that were formed by N–C bond formation between the nitrogen atom and the α-position of the cinnamoyl group. On the other hand, unsymmetrical derivatives (**1f–1j**) formed S–C bonds leading to iminothiazolidinones (**4f–4j**) as major products. This difference is reasonable in terms of the electron density of the sulfur atoms. In **1a–1e**, the electron-donating properties of the alkyl group make the electron density of the nitrogen atoms high. On the other hand, in *N*-phenyl derivatives **1f′–1j′**, lone pair electrons conjugated with the phenyl group lower the nucleophilicity of the nitrogen atoms compared to those of **1a–1e**, resulting in S–C bond formation.

We also examined the reaction with DBU without molecular sieves (Table 2, entries 6–9). When **1b** was stirred with an excess amount of DBU in toluene, the yield of **3b** decreased and unexpected **5b** was formed (Scheme 7 and Table 2, entry 6). The amount of water included in the solvent determined the reaction pathways. The use of CH_2Cl_2 increased the yield of **5b** to 61% (entry 7). The reaction in THF predominantly gave **5b** in 87% yield (entry 8). The unexpected oxygenated chemical structure of **5c**, obtained as a minor product from the reaction of **1c** in toluene without molecular sieves (entry 9), was determined by single crystal X-ray structure analysis (Fig. S7†).



Scheme 9 Plausible mechanism for the formation of **5** in the presence of DBU in a water-containing solvent.

The same intermediate **A** (**A′**) can be proposed for the formation of **5** as shown in Scheme 9. Addition of water gives the ring-opened product **B**, which is followed by proton transfer leading to **C**. Elimination of hydrogenated DBU gives **D**, which is transformed to α-oxoamide derivative **E**. Finally, intermolecular attack of the nitrogen atom leads to aminal compound **5**. In this reaction, DBU functions as a dehydrogenating reagent, which is known to occur in some cases.[23]

Conclusions

We provided a facile synthetic methodology for five- and six-membered heterocycles from easily available *N*-acylthioureas under acidic or basic conditions. All derivatives of these heterocycles are well known for various high pharmaceutical activities. The reaction in the presence of trifluoroacetic acid gives six-membered 2-imino-1,3-thiazin-4-ones in good yields regardless of the substituents on the nitrogen atoms. On the other hand, the reaction of *N*-acylthioureas with DBU promoted unprecedented "umpolung" reaction pathways leading to five-membered thiohydantoins from *N*-cinnamoyl-*N*,*N*′-dialkylthioureas and 2-imino-1,3-thiazolidin-4-ones from *N*-alkyl-*N*′-cinnamoyl-*N*′-phenylthioureas. A novel reaction mechanism involving the cycloaddition of DBU with the cinnamoyl group was proposed. Furthermore, the reaction in the presence of DBU in a water-containing solvent gave oxygenated 5-hydroxythiohydantoin derivatives, in which the same DBU adduct was proposed as an intermediate in the mechanistic pathway. Formation of this adduct was followed by the attack of a water molecule and the elimination of reduced DBU. Although unique heterocycles were obtained, the reaction mechanisms are unprecedented and are yet to be confirmed. However, in

the reaction in the presence of a base, it is undeniable that the reaction proceeds at a position that cannot be predicted in the usual electronic state. We are continuing to explore the reaction mechanism and the generality of the reaction.

Experimental section

General information

NMR spectra were recorded in $CDCl_3$ solutions on Bruker 300 and 400 spectrometers for ^{1}H- and ^{13}C-NMR. Chemical shifts are reported in parts per million (ppm) relative to TMS as an internal standard. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. High-resolution mass spectra (HRMS) were performed on an Orbitrap ThermoFisher Exactive ion trap mass spectrometer. X-ray single crystallographic analysis was conducted using a SMART APEX II (Bruker AXS) and APEX II ULTRA (Bruker AXS). Commercially available reagents and solvents were used without further purification.

Synthesis of *N*-cinnamoyl-*N*,*N*′-dimethylthiourea (1a). *N*,*N*′-Dimethylthiourea (0.890 g, 8.56 mmol) and triethylamine (1.30 g, 12.9 mmol) were added to a THF (20.0 mL) solution containing cinnamoyl chloride (1.70 g, 10.2 mmol) and molecular sieves (4 Å, 1.50 g) and the reaction mixture was stirred at room temperature for 3 hours. After the disappearance of *N*,*N*′-dimethylthiourea was confirmed by TLC, the solvent was removed under reduced pressure, and the residual mixture was dissolved in ethyl acetate and extracted with an acid and base. After removing the solvent again under reduced pressure, the obtained residue was separated by silica gel column chromatography using a mixed solvent of ethyl acetate–hexane (1 : 4) to afford *N*-cinnamoyl-*N*,*N*′-dimethylthiourea (**1a**) (0.880 g, 3.76 mmol, 44%). The obtained crystals were recrystallized from a mixed solvent of chloroform and hexane. The other cinnamoylthioureas (**1b–1j**) were synthesized in the same manner.

***N*-Cinnamoyl-*N*,*N*′-dimethylthiourea (1a).**[24] Yield: 63%; colorless needles; m.p. 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 3.22 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 6.93 (d, J = 15.3 Hz, 1H), 7.38–7.45 (m, 3H), 7.54–7.59 (m, 2H), 7.76 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.4, 38.6, 118.9, 128.3, 129.0, 130.9, 134.2, 146.3, 170.3, 185.3; IR (cm^{-1}, KBr) 3127 (N–H), 1648 (C═O).

***N*-Cinnamoyl-*N*,*N*′-diethylthiourea (1b).** Yield: 72%; colorless powder; m.p. 139–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.4 Hz, 3H), 1.44 (t, J = 6.9 Hz, 3H), 3.70 (qd, J = 7.4, 4.9 Hz, 2H), 4.54 (q, J = 7.0 Hz, 2H), 6.95 (d, J = 15.3 Hz, 1H), 7.41–7.44 (m, 3H), 7.54–7.58 (m, 2H), 7.79 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 15.1, 41.8, 44.5, 119.0, 128.2, 129.0, 130.7, 134.3, 146.4, 170.0, 183.5; IR (cm^{-1}, KBr) 3170 (NH), 1647 (C═O); HRMS (ESI-MS) m/z calcd for $C_{14}H_{18}N_2OS$ + Na 285.1032, found 285.1024.

***N*-Cinnamoyl-*N*,*N*′-dipropylthiourea (1c).** Yield: 91%; colorless powder; m.p. 119–120 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H), 1.73 (sex, J = 7.3 Hz, 2H), 1.87 (sext, J = 7.6 Hz, 2H), 3.64 (td, J = 7.3, 4.9 Hz, 2H), 4.37–4.42 (m, 2H), 6.91 (d, J = 15.2 Hz, 1H), 7.26–7.46 (m, 3H), 7.53–7.57 (m, 2H), 7.79 (d, J = 15.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0, 11.7, 21.3, 23.1, 48.9, 50.9, 119.0, 128.2, 129.0, 130.7, 134.3, 145.2, 146.3, 170.1, 183.9; IR (cm^{-1}, KBr) 3170 (NH), 1647 (C═O); HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + H 291.1526, found 291.1525.

***N*-Cinnamoyl-*N*,*N*′-diisopropylthiourea (1d).** Yield: 96%; colorless needles; m.p. 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J = 6.8 Hz, 6H), 1.40 (d, J = 6.8 Hz, 6H), 4.61 (sept, J = 6.8 Hz, 1H), 4.70–4.74 (m, 1H), 6.66 (d, J = 15.5 Hz, 1H), 7.26–7.30 (m, 5H), 7.54 (d, J = 15.5 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.8, 48.3, 48.4, 118.9, 127.8, 128.8, 129.8, 134.4, 142.7, 164.0, 182.5; IR (cm^{-1}, KBr) 3191 (NH), 1639 (C═O); HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + H 291.1526, found 291 1520.

***N*-Cinnamoyl-*N*,*N*′-dibenzylthiourea (1e).** Yield: 84%; colorless powder; m.p. 113–115 °C; ^{1}H NMR ($CDCl_3$) δ 4.93 (d, J = 4.9 Hz, 2H), 5.86 (s, 2H), 6.77 (d, J = 15.3 Hz, 1H), 7.23–7.45 (m, 15H), 7.69 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.6, 53.0, 119.4, 126.0, 127.4, 127.5, 127.8, 128.0, 128.2, 128.9, 128.9, 130.7, 134.2, 136.4, 137.4, 146.6, 170.7, 184.8; IR (cm^{-1}, KBr) 3207 (NH), 1644 (C═O); HRMS (ESI-MS) m/z calcd for $C_{24}H_{22}N_2OS$ + Na 409.1345, found 409.1340.

***N*-Cinnamoyl-*N*-phenyl-*N*′-methylthiourea (1f).**[24] Yield: 62%; yellow needles; m.p. 127–129 °C; ^{1}H NMR ($CDCl_3$) δ 3.26 (d, J = 4.8 Hz, 3H), 6.09 (d, J = 15.5 Hz, 1H), 7.20–7.37 (m, 8H), 7.48–7.52 (m, 3H), 7.70 (d, J = 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.1, 119.5, 128.2, 128.8, 129.0, 129.3, 130.2, 130.6, 134.1, 141.2, 145.4, 169.3, 185.2; IR (cm^{-1}, KBr) 3214 (NH), 1658 (C═O).

***N*-Cinnamoyl-*N*-phenyl-*N*′-ethylthiourea (1g).** Yield: 68%; yellow needles; m.p. 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.3 Hz, 3H), 3.74 (qd, J = 7.3, 4.9 Hz, 2H), 6.08 (d, J = 15.4 Hz, 1H), 7.20–7.36 (m, 8H), 7.47–7.55 (m, 3H), 7.69 (d, J = 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 41.6, 119.7, 128.3, 128.9, 129.0, 129.3, 130.3, 130.7, 134.1, 141.1, 145.3, 169.4, 183.9; IR (cm^{-1}, KBr) 3278 (NH), 1655 (C═O); HRMS (ESI-MS) m/z calcd for $C_{18}H_{18}N_2OS$ + Na 333.1032, found 333.1027.

***N*-Cinnamoyl-*N*-phenyl-*N*′-propylthiourea (1h).** Yield: 38%; yellow needles; m.p. 109–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7.3 Hz, 3H), 1.79 (sex, J = 7.3 Hz, 2H), 3.68 (td, J = 7.3, 4.9 Hz, 2H), 6.08 (d, J = 15.5 Hz, 1H), 7.20–7.37 (m, 8H), 7.48–7.55 (m, 3H), 7.70 (d, J = 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ11.7, 21.4, 48.6, 119.7, 128.3, 128.9, 129.0, 129.3, 130.3, 130.7, 134.1, 141.1, 145.4, 169.4, 184.0; IR (cm^{-1}, KBr) 3125 (NH), 1656 (C═O); HRMS (ESI-MS) m/z calcd for $C_{19}H_{20}N_2OS$ + Na 347.1189, found 347.1182.

***N*-Cinnamoyl-*N*-phenyl-*N*′-isopropylthiourea (1i).** Yield: 49%; yellow needles; m.p. 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J = 6.3 Hz, 6H), 4.50–4.66 (m, 1H), 6.07 (d, J = 15.4 Hz, 1H), 7.20–7.37 (m, 8H), 7.47–7.54 (m, 3H), 7.69 (d, J = 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 48.4, 119.8, 128.2, 128.8, 129.2, 130.3, 130.6, 134.1, 141.1, 145.3, 169.4, 182.6; IR (cm^{-1}, KBr) 3198 (NH), 1655 (C═O); HRMS (ESI-MS) m/z calcd for $C_{19}H_{20}N_2OS$ + Na 347.1189, found 347.1179.

***N*-Cinnamoyl-*N*-phenyl-*N*′-benzylthiourea (1j).** Yield: 42%; yellow needles; m.p. 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 4.91 (d, J =

4.8 Hz, 2H), 6.08 (d, J = 15.4 Hz, 1H), 7.18–7.76 (m, 15H), 7.68 (d, J = 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.0, 119.4, 127.8, 128.0, 128.3, 128.8, 129.0, 129.4, 130.2, 130.7, 134.0, 136.4, 141.1, 145.6, 169.4, 184.2; IR (cm^{-1}, KBr) 3200 (NH), 1655 (C═O); HRMS (ESI-MS) m/z calcd for $C_{23}H_{20}N_2OS$ + H 373.1369, found 373.1369.

Cyclization reaction of **1a–1j** in the presence of trifluoroacetic acid. *N*-Cinnamoyl-*N*,*N*′-dimethylthiourea (**1a**) (0.100 g, 0.427 mmol) and trifluoroacetic acid (0.450 g, 3.95 mmol) were dissolved in toluene (2.0 mL) and the mixture was stirred at room temperature for 0.5 hours under an argon atmosphere. After the disappearance of **1a** was confirmed by TLC, base extraction was carried out using aqueous sodium bicarbonate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using a mixed solvent of ethyl acetate–hexane (1 : 5) to afford *N*,*N*′-dimethyl-6-phenyl-2-iminotetrahydro-1,3-thiazin-4-one (**2a**) (0.097 g, 0.415 mmol, 97%). The obtained crystals were recrystallized from a mixed solvent of chloroform and hexane. Other 1,3-thiazin-4-ones (**2b–2j**) were synthesized in the same manner.

(*Z*)-3-Methyl-2-(methylimino)-6-phenyl-1,3-thiazinan-4-one (2a).[24] Yield: 97%; colorless needles; m.p. 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 3.16 (s, 3H), 3.16–3.22 (m, 2H), 3.36 (s, 3H), 4.52 (dd, J = 10.7, 4.4 Hz, 1H), 7.32–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.0, 37.5, 40.6, 42.4, 127.3, 128.7, 129.1, 137.2, 151.0, 169.3; IR (cm^{-1}, KBr) 1673, 1606.

(*Z*)-3-Ethyl-2-(ethylimino)-6-phenyl-1,3-thiazinan-4-one (2b). Yield: 95%; colorless needles; m.p. 64–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 6.9 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 3.16 (t, J = 5.0 Hz, 2H), 3.27–3.45 (m, 2H), 4.02–4.19 (m, 2H), 4.47 (dd, J = 9.6, 5.1 Hz, 1H), 7.30–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.0, 15.8, 38.8, 40.6, 42.6, 45.3, 76.6, 77.0, 77.4, 127.3, 128.6, 129.1, 137.5, 147.0, 168.7; IR (cm^{-1}, KBr) 1680, 1591; HRMS (ESI-MS) m/z calcd for $C_{14}H_{18}N_2OS$ + H 263.1213, found 263.1208.

(*Z*)-6-Phenyl-3-propyl-2-(propylimino)-1,3-thiazinan-4-one (2c). Yield: 90%; colorless needles; m.p. 55–57 °C; ^{1}H NMR ($CDCl_3$) δ0.90 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H), 1.56–1.72 (m, 4H), 3.17 (t, J = 5.0 Hz, 2H), 3.25 (td, J = 6.8, 2.6 Hz, 2H), 3.95–4.10 (m, 2H), 4.48 (dd, J = 9.5, 5.3 Hz, 1H), 7.30–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.4, 12.0, 20.9, 24.0, 40.7, 42.7, 45.0, 52.4, 127.3, 128.6, 129.1, 137.5, 147.2, 168.9; IR (cm^{-1}, KBr) 1684, 1607; HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + H 291.1526, found 291.1521.

(*Z*)-3-Isopropyl-2-(isopropylimino)-6-phenyl-1,3-thiazinan-4-one (2d). Yield: 82%; colorless needles; m.p. 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 6.3 Hz, 6H), 1.40 (d, J = 6.8 Hz, 3H), 1.46 (d, J = 6.8 Hz, 3H), 3.10 (d, J = 7.5 Hz, 2H), 3.67 (sept, J = 6.3 Hz, 1H), 4.43–4.54 (m, 1H), 4.99 (sept, J = 6.8 Hz, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.6, 23.3, 23.3, 41.4, 43.8, 49.5, 51.8, 127.4, 128.4, 129.0, 137.7, 144.6, 169.6; IR (cm^{-1}, KBr) 1684, 1596; HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + H 291.1526, found 291.1520.

(*Z*)-3-Benzyl-2-(benzylimino)-6-phenyl-1,3-thiazinan-4-one (2e). Yield: 88%; colorless needles; m.p. 123–124 °C; ^{1}H NMR ($CDCl_3$) δ 3.20–3.31 (m, 2H), 4.46–4.59 (m, 3H), 5.38 (s, 2H), 7.20–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 40.7, 42.5, 46.0, 54.1, 126.6, 127.0, 127.3, 127.4, 128.2, 128.2, 128.5, 128.7, 129.1, 137.1, 137.9, 139.6, 148.7, 169.0; IR (cm^{-1}, KBr) 1678, 1617; HRMS (ESI-MS) m/z calcd for $C_{24}H_{22}N_2OS$ + H 387.1526, found 387.1525.

(*Z*)-2-(Methylimino)-3,6-diphenyl-1,3-thiazinan-4-one (2f).[24] Yield: 81%; colorless needles; m.p. 188–190 °C; ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.36–3.42 (m, 2H), 4.73 (dd, J = 9.3, 5.1 Hz, 1H), 7.14–7.17 (m, 2H), 7.34–7.48 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 38.0, 41.0, 43.0, 127.3, 128.0, 128.7, 128.8, 129.1, 129.2, 137.2, 138.6, 151.5, 169.1; IR (cm^{-1}, KBr) 1681, 1611.

(*Z*)-2-(Ethylimino)-3,6-diphenyl-1,3-thiazinan-4-one (2g). Yield: 76%; colorless needles; m.p. 168–169 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 3H), 3.28–3.39 (m, 4H), 4.71 (dd, J = 9.6, 5.1 Hz, 1H), 7.13–7.16 (m, 2H), 7.32–7.51 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 15.1, 41.1, 43.1, 45.6, 127.4, 127.7, 128.8, 128.9, 129.2, 137.4, 138.9, 148.8, 169.2; IR (cm^{-1}, KBr) 1685, 1604; HRMS (ESI-MS) m/z calcd for $C_{18}H_{18}N_2OS$ + H 311.1213, found 311.1205.

(*Z*)-3,6-Diphenyl-2-(propylimino)-1,3-thiazinan-4-one (2h). Yield: 79%; colorless needles; m.p. 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.1 Hz, 3H), 1.46 (sex, J = 7.1 Hz, 2H), 3.21 (t, J = 7.1 Hz, 2H), 3.30–3.44 (m, 2H), 4.70 (dd, J = 9.6, 4.8 Hz, 1H), 7.13–7.16 (m, 2H), 7.31–7.45 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 11.7, 23.5, 41.1, 43.1, 52.7, 127.3, 127.6, 128.7, 128.7, 128.8, 129.2, 137.3, 138.8, 148.6, 169.2; IR (cm^{-1}, KBr) 1685, 1600; HRMS (ESI-MS) m/z calcd for $C_{19}H_{20}N_2OS$ + H 325.1369, found 325.1363.

(*Z*)-2-(Isopropylimino)-3,6-diphenyl-1,3-thiazinan-4-one (2i). Yield: 82%; colorless needles; m.p. 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.2 Hz, 3H), 1.01 (d, J = 6.2 Hz, 3H), 3.28–3.43 (m, 2H), 3.64 (sept, J = 6.2 Hz, 1H), 4.69 (dd, J = 11.6, 6.2 Hz, 1H), 7.08–7.14 (m, 2H), 7.29–7.57 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 23.0, 41.1, 43.2, 51.8, 127.3, 127.8, 128.6, 128.7, 129.1, 137.4, 139.1, 146.3, 169.3; IR (cm^{-1}, KBr) 1686, 1600; HRMS (ESI-MS) m/z calcd for $C_{19}H_{20}N_2OS$ + H 325.1369, found 325.1363.

(*Z*)-2-(Benzylimino)-3,6-diphenyl-1,3-thiazinan-4-one (2j). Yield: 72%; colorless needles; m.p. 201–202 °C; ^{1}H NMR ($CDCl_3$) δ 3.34–3.48 (m, 2H), 4.51 (s, 2H), 4.75 (dd, J = 9.8, 4.7 Hz, 1H), 7.04–7.49 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 41.3, 43.0, 53.8, 126.4, 126.9, 127.4, 127.9, 128.1, 128.8, 129.0, 129.2, 137.1, 138.7, 139.5, 150.2, 169.2; IR (cm^{-1}, KBr) 1685, 1616; HRMS (ESI-MS) m/z calcd for $C_{23}H_{20}N_2OS$ + H 373.1369, found 373.1366.

Cyclization of **1a–j** in the presence of DBU. To a dried toluene (8.0 mL) solution of *N*-cinnamoyl-*N*,*N*′-dimethylthiourea (**1a**) (0.308 g, 1.32 mmol), DBU (0.100 g, 0.66 mmol) was added and the mixture was stirred at room temperature for 0.5 hours in the presence of molecular sieves (4 Å, 1.50 g). After acid extraction and removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using a mixed solvent of ethyl acetate–hexane (1 : 3) to give *N*,*N*′-dimethyl-5-benzyl-2-thiohydantoin (**3a**) (81% yield, 0.249 g, 1.07 mmol). Other 5-benzyl-2-thiohydantoins (**3b–3j**) and 5-benzyl-2-iminothiazolidin-4-ones (**4f–4j**) were synthesized by the same procedure.

Cyclization of **1b** in the presence of a variety of bases with molecular sieves. To a dried toluene (8.0 mL) solution of *N*-cinnamoyl-*N*,*N*′-diethylthiourea (**1b**) (0.300 g, 1.15 mmol), triethylamine (0.058 g, 0.573 mmol) was added and the mixture was stirred at room temperature for 0.5 hours under an argon atmosphere. After acid extraction and removal of the solvent under reduced pressure, the residue was analysed by NMR spectroscopy. When trimethylamine, DMAP, or DABCO was used as a base, starting materials were recovered. The use of DBN and TBD gave **3b** as summarized in Table 2.

5-Benzyl-1,3-dimethyl-2-thioxoimidazolidin-4-one (3a). Yield: 81%; colorless prisms; m.p. 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.16 (dd, J = 14.6, 5.4 Hz, 1H), 3.24 (s, 3H), 3.28 (dd, J = 14.6, 4.6 Hz, 1H), 4.22 (t, J = 4.9 Hz, 1H), 7.02–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.0, 33.0, 35.7, 64.9, 127.6, 128.7, 129.0, 133.9, 172.7, 183.1; IR (cm^{-1}, neat) 1744 (C═O); HRMS (ESI-MS) m/z calcd for $C_{12}H_{14}N_2OS$ + H 235.0900, found 235.0899.

5-Benzyl-1,3-diethyl-2-thioxoimidazolidin-4-one (3b). Yield: 75%; colorless prisms; m.p. 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 3.17 (dd, J = 14.6, 4.5 Hz, 1H), 3.25 (dd, J = 14.6, 4.5 Hz, 1H), 3.37 (sex, J = 7.2 Hz, 1H), 3.67 (q, J = 7.2 Hz, 1H), 3.67 (q, J = 7.2 Hz, 1H), 4.29 (t, J = 4.5 Hz, 1H), 4.47 (sex, J = 7.2 Hz, 1H), 7.08–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.9, 12.3, 34.8, 36.4, 39.5, 61.3, 127.5, 128.5, 129.2, 133.4, 172.6, 181.7; IR (cm^{-1}, KBr) 1737 (C═O); HRMS (ESI-MS) m/z calcd for $C_{14}H_{18}N_2OS$ + Na 285.1032, found 285.1030.

5-Benzyl-1,3-dipropyl-2-thioxoimidazolidin-4-one (3c). Yield: 70%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.69 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 1.21–1.38 (m, 2H), 1.57–1.75 (m, 2H), 3.12–3.30 (m, 3H), 3.50–3.65 (m, 2H), 4.28 (t, J = 4.5 Hz, 1H), 4.38 (ddd, J = 14.0, 9.3, 7.1 Hz, 1H), 7.08–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.0, 11.1, 20.1, 20.5, 34.8, 43.1, 46.3, 61.9, 127.5, 128.6, 129.2, 133.5, 172.8, 182.4; IR (cm^{-1}, neat) 1741 (C═O); HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + Na 313.1345, found 313.1338.

5-Benzyl-1,3-diisopropyl-2-thioxoimidazolidin-4-one (3d). Yield: 77%; colorless prisms; m.p. 73–74 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.54 (d, J = 6.6 Hz, 3H), 3.24 (d, J = 4.5 Hz, 2H), 4.22 (t, J = 4.5 Hz, 1H), 4.72 (sept, J = 6.8, 1H), 5.01 (sept, J = 6.8, 1H), 7.16–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.9, 19.1, 19.6, 21.7, 36.9, 47.5, 50.2, 60.2, 127.4, 128.4, 129.7, 133.6, 173.0, 183.3; IR (cm^{-1}, KBr) 1735 (C═O); HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + Na 313.1345, found 313.1335.

1,3,5-Tribenzyl-2-thioxoimidazolidin-4-one (3e). Yield: 51%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.12 (dd, J = 14.7, 4.6 Hz, 1H), 3.23 (dd, J = 14.7, 4.6 Hz, 1H), 4.12 (t, J = 4.6 Hz, 1H), 4.27 (d, J = 15.0 Hz, 1H), 4.88 (d, J = 14.7 Hz, 1H), 4.96 (d, J = 14.7 Hz, 1H), 5.96 (d, J = 15.0 Hz, 1H), 6.99–7.37 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 34.8, 45.2, 48.5, 61.2, 127.4, 127.5, 128.0, 128.2, 128.3, 128.8, 129.0, 129.2, 133.5, 134.7, 135.4, 172.6, 183.1; IR (cm^{-1}, neat) 1748 (C═O); HRMS (ESI-MS) m/z calcd for $C_{24}H_{22}N_2OS$ + Na 409.1345, found 409.1344.

5-Benzyl-3-methyl-1-phenyl-2-thioxoimidazolidin-4-one (3f). Yield: 10%; colorless prisms; m.p. 91–92 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (dd, J = 14.4, 5.2 Hz, 1H), 3.20 (s, 3H), 3.25 (dd, J = 14.6, 4.1 Hz, 1H), 4.89 (dd, J = 5.2, 4.1 Hz, 1H), 6.91–6.96 (m, 2H), 7.16–7.22 (m, 3H), 7.32–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.2, 53.1, 64.7, 126.2, 127.4, 127.7, 128.4, 129.1, 129.4, 133.5, 136.5, 172.2, 182.1; IR (cm^{-1}, KBr) 1750 (C═O); HRMS (ESI-MS) m/z calcd for $C_{17}H_{16}N_2OS$ + H 297.1056, found 297.1057.

5-Benzyl-3-ethyl-1-phenyl-2-thioxoimidazolidin-4-one (3g). Yield: 3%; colorless prisms; m.p. 81–83 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 3.04 (dd, J = 14.4, 4.9 Hz, 1H), 3.25 (dd, J = 14.4, 4.0 Hz, 1H), 3.76–3.90 (m, 2H), 4.86 (dd, J = 4.9, 4.0 Hz, 1H), 6.96–6.99 (m, 2H), 7.17–7.52 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 12.4, 35.0, 36.8, 64.4, 126.2, 127.5, 127.7, 128.4, 129.1, 129.6, 133.3, 136.6, 171.9, 181.5; IR (cm^{-1}, KBr) 1743 (C═O); HRMS (ESI-MS) m/z calcd for $C_{18}H_{18}N_2OS$ + Na 333.1032, found 333.1027.

5-Benzyl-1-phenyl-3-propyl-2-thioxoimidazolidin-4-one (3h). Yield: 6%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.77 (t, J = 10.1 Hz, 3H), 1.40–1.53 (m, 2H), 3.04 (dd, J = 14.4, 4.8 Hz, 1H), 3.25 (dd, J = 14.4, 4.0 Hz, 1H), 3.64–3.81 (m, 2H), 4.87 (dd, J = 4.8, 4.0 Hz, 1H), 6.95–6.98 (m, 2H), 7.20–7.52 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 11.1, 20.6, 34.9, 43.4, 64.4, 126.2, 127.5, 127.6, 128.4, 129.1, 129.7, 133.3, 136.6, 172.1, 182.0; IR (cm^{-1}, neat) 1743 (C═O); HRMS (ESI-MS) m/z calcd for $C_{19}H_{20}N_2OS$ + H 325.1369, found 325.1365.

5-Benzyl-3-isopropyl-1-phenyl-2-thioxoimidazolidin-4-one (3i). Yield: 3%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 7.0 Hz, 3H), 1.42 (d, J = 7.0 Hz, 3H), 3.00 (dd, J = 14.4, 4.8 Hz, 1H), 3.23 (dd, J = 14.4, 3.8 Hz, 1H), 4.77 (dd, J = 4.8, 3.8 Hz, 1H), 4.86 (sep, J = 7.0 Hz, 1H), 6.97–7.01 (m, 2H), 7.20–7.23 (m, 3H), 7.34–7.52 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.5, 18.9, 34.9, 48.2, 63.9, 126.4, 127.5, 127.7, 128.3, 129.1, 129.8, 133.4, 137.0, 172.2, 182.3; IR (cm^{-1}, neat) 1739 (C═O); HRMS (ESI-MS) m/z calcd for $C_{19}H_{20}N_2OS$ + H 325.1369, found 325.1369.

3,5-Dibenzyl-1-phenyl-2-thioxoimidazolidin-4-one (3j). Yield: 11%; colorless powder; m.p. 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 3.04 (dd, J = 14.5, 5.1 Hz, 1H), 3.28 (dd, J = 14.5, 4.0 Hz, 1H), 4.92 (dd, J = 5.1, 4.0 Hz, 1H), 4.97 (d, J = 14.6 Hz, 1H), 5.04 (d, J = 14.6 Hz, 1H), 6.86–6.90 (m, 2H), 7.07–7.49 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 34.7, 45.1, 64.4, 126.2, 127.4, 127.5, 127.7, 128.3, 128.4, 128.5, 129.1, 129.6, 133.2, 135.3, 136.7, 172.0, 181.8; IR (cm^{-1}, KBr) 1741 (C═O); HRMS (ESI-MS) m/z calcd for $C_{23}H_{20}N_2OS$ + H 373.1369, found 373.1373.

(*Z*)-5-Benzyl-3-isopropyl-2-(isopropylimino)thiazolidin-4-one (4d). Yield: 8%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H), 1.34 (d, J = 7.0 Hz, 6H), 3.02 (dd, J = 13.9, 9.5 Hz, 1H), 3.32 (sept, J = 6.2 Hz, 1H), 3.47 (dd, J = 13.9, 3.6 Hz, 1H), 4.21 (dd, J = 9.5, 3.6 Hz, 1H), 4.66 (sept, J = 7.0, 1H), 7.22–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 18.7, 39.0, 47.7, 49.3, 120.8, 124.3, 127.2, 129.1, 129.4, 136.0, 148.4, 153.0, 173.8; IR (cm^{-1}, neat) 1714, 1637; HRMS (ESI-MS) m/z calcd for $C_{16}H_{22}N_2OS$ + H 291.1526, found 291.1522.

(*Z*)-5-Benzyl-2-(methylimino)-3-phenylthiazolidin-4-one (4f). Yield: 65%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.01 (dd, J = 14.1, 10.0 Hz, 1H), 3.28 (s, 3H), 3.57 (dd, J = 14.1, 3.7 Hz, 1H), 4.33 (dd, J = 10.0, 3.7 Hz, 1H), 6.88–6.91 (m, 2H), 7.08–7.33 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 29.5, 39.2, 50.3, 121.0, 124.5, 127.3, 128.6,

129.0, 129.1, 136.4, 148.0, 153.9, 173.8; IR (cm^{-1}, neat) 1720, 1620; HRMS (ESI-MS) *m*/*z* calcd for $C_{17}H_{16}N_2OS$ + H 297.1056, found 297.1055.

(*Z*)-5-Benzyl-2-(ethylimino)-3-phenylthiazolidin-4-one (4g). Yield: 71%; colorless prisms; m.p. 64–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 3.04 (dd, J = 14.1, 9.8 Hz, 1H), 3.51 (dd, J = 14.1, 3.7 Hz, 1H), 3.86 (q, J = 7.1 Hz, 1H), 3.86 (q, J = 7.1 Hz, 1H), 4.31 (dd, J = 9.8, 3.7 Hz, 1H), 6.85–6.94 (m, 2H), 7.05–7.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 12.5 38.1, 39.1, 50.0, 120.9, 124.4, 127.3, 128.5, 129.1, 129.2, 136.2, 148.2, 153.1, 173.5; IR (cm^{-1}, KBr) 1722, 1628; HRMS (ESI-MS) *m*/*z* calcd for $C_{18}H_{18}N_2OS$ + Na 333.1032, found 311.1020.

(*Z*)-5-Benzyl-3-phenyl-2-(propylimino)thiazolidin-4-one (4h). Yield: 57%; yellow oil; ^{1}H-NMR δ 0.92 (t, J = 7.4 Hz, 3H), 1.68 (sex, J = 7.4 Hz, 2H), 3.03 (dd, J = 14.0, 9.7 Hz, 1H), 3.75 (dd, J = 14.0, 3.7 Hz, 1H), 3.77 (t, J = 7.4 Hz, 2H), 4.31 (dd, J = 9.7, 3.7 Hz, 1H), 6.80–6.96 (m, 2H), 6.97–7.43 (m, 8H); ^{13}C-NMR δ 11.2, 20.5, 39.1, 50.0, 120.9, 124.4, 127.2, 128.5, 129.1, 129.2, 136.2, 148.2, 153.3, 173.8; IR (cm^{-1}, neat) 1718, 1641; HRMS (ESI-MS) *m*/*z* calcd for $C_{19}H_{20}N_2OS$ + H 325.1369, found 325.1364.

(*Z*)-5-Benzyl-2-(isopropylimino)-3-phenylthiazolidin-4-one (4i). Yield: 32%; yellow oil; ^{1}H-NMR δ 1.44 (d, J = 7.1 Hz, 6H), 3.07 (dd, J = 13.9, 9.0 Hz, 1H), 3.43 (dd, J = 13.9, 3.7 Hz, 1H), 4.23 (dd, J = 9.0, 3.7 Hz, 1H), 4.792 (sept, J = 7.1, 1H), 6.84–6.87 (m, 2H), 7.04–7.40 (m, 8H). ^{13}C-NMR δ 18.6, 18.7, 39.0, 47.7, 49.3, 120.8, 124.3, 127.2, 128.4, 129.1, 129.4, 136.0, 148.4, 153.0, 173.8; IR (cm^{-1}, neat) 1716, 1631; HRMS (ESI-MS) *m*/*z* calcd for $C_{19}H_{20}N_2OS$ + H 325.1369, found 325.1370.

(*Z*)-5-Benzyl-2-(benzylimino)-3-phenylthiazolidin-4-one (4j). Yield: 66%; colorless prisms; m.p. 81–82 °C; ^{1}H-NMR δ 3.02 (dd, J = 14.0, 9.7 Hz, 1H), 3.52 (dd, J = 14.0, 3.7 Hz, 1H), 4.34 (dd, J = 9.7, 3.7 Hz, 1H), 4.98 (s, 1H), 4.99 (s, 1H), 6.85–7.16 (m, 2H), 7.07–7.45 (m, 13H); ^{13}C-NMR δ 39.0, 46.1, 50.0, 120.9, 124.4, 127.2, 127.7, 128.4, 128.6, 128.8, 129.1, 135.8, 136.2, 148.0, 152.7, 173.6; IR (cm^{-1}, KBr) 1716, 1644; HRMS (ESI-MS) *m*/*z* calcd for $C_{23}H_{20}N_2OS$ + Na 395.1189, found 395.1189.

Cyclization of **1b–c** in the presence of DBU without molecular sieves. To a toluene (8.0 mL) solution of *N*-cinnamoyl-*N*,*N*′-diethylthiourea (**1b**) (0.314 g, 1.20 mmol), DBU (0.228 g, 1.50 mmol) was added and the mixture was stirred at room temperature for 0.5 hours under an argon atmosphere. After acid extraction and removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using a mixed solvent of ethyl acetate–hexane (1 : 3) to give *N*,*N*′-diethyl-5-benzyl-2-thiohydantoin (**3b**) (21% yield, 0.063 g, 0.24 mmol) and 5-benzyl-1,3-diethyl-5-hydroxy-2-thioxoimidazolidin-4-one (**5b**) (10% yield, 0.032 g, 0.115 mmol). Another 5-benzyl-5-hydroxy-1,3-diisopropyl-2-thioxoimidazolidin-4-one (**5c**) was synthesized by the same procedure.

5-Benzyl-1,3-diethyl-5-hydroxy-2-thioxoimidazolidin-4-one (5b). Yield: 87%; colorless prisms; m.p. 144–146 °C; ^{1}H-NMR δ 0.70 (t, J = 7.1 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H), 3.28 (q, J = 13.4 Hz, 2H), 3.51 (sex, J = 7.1, 1H), 3.65 (sex, J = 7.1, 2H), 4.21 (sex, J = 7.1, 1H), 4.41 (s, 1H), 7.01–7.06 (m, 2H), 7.21–7.24 (m, 3H); ^{13}C-NMR δ 12.2, 13.9, 35.9, 38.7, 40.9, 89.48, 127.8, 128.6, 129.6, 131.7, 173.4, 180.6; IR (cm^{-1}, KBr) 3283 (OH), 1719 (C=O); HRMS (ESI-MS) *m*/*z* calcd for $C_{14}H_{18}N_2O_2S$ + H 279.1162, found 279.1159.

5-Benzyl-5-hydroxy-1,3-diisopropyl-2-thioxoimidazolidin-4-one (5c). Yield: 59%; colorless prisms; m.p. 90–92 °C; ^{1}H-NMR δ 0.62 (t, J = 7.4 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H), 1.12 (sex, J = 7.5, 2H), 1.71–1.89 (m, 1H), 1.96–2.11 (m, 1H), 3.29 (q, J = 14.0 Hz, 2H), 3.33–3.59 (m, 3H), 4.09 (ddd, J = 13.6, 11.0, 5.0, 1H), 4.51 (s, 1H), 7.02–7.05 (m, 2H), 7.22–7.26 (m, 3H); 11.0, 11.5, 20.5, 21.7, 40.8, 42.7, 45.6, 89.3, 127.8, 128.6, 129.6, 131.7, 173.6, 181.3; IR (cm^{-1}, KBr) 3295 (OH), 1726 (C=O); HRMS (ESI-MS) *m*/*z* calcd for $C_{16}H_{22}N_2O_2S$ + H 307.1475, found 307.1472.

Single crystal X-ray structure analysis of 2h (CCDC 1859352†). Colorless prisms (0.20 × 0.10 × 0.05 mm^3), monoclinic space group $P2_1/c$, a = 12.8458(5) Å, b = 5.3427(2) Å, c = 24.6144(10) Å, β = 101.767(3)°, V = 1653.82(11) $Å^3$, Z = 4, λ (CuKα) = 1.54178 Å, ρ = 1.303 g cm^{-3}, μ (CuKα) = 1.776 mm^{-1}, 10 898 reflections measured (T = 173 K, 3.514° < θ < 68.341°), no. of independent data collected: 3012, no. of independent data used for refinement: 2264 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0495, wR_2 = 0.1324 [$I > 2s(I)$], R_1 = 0.0696, wR_2 = 0.1416 (all data), and GOF = 1.007, H-atom parameters constrained.

Single crystal X-ray structure analysis of 2i (CCDC 1859353†). Colorless prisms (0.20 × 0.05 × 0.05 mm^3), monoclinic space group $P2_1/c$, a = 13.0104(7) Å, b = 5.4301(3) Å, c = 24.2997(15) Å, β = 101.772(4)°, V = 1680.61(17) $Å^3$, Z = 4, λ (CuKα) = 1.54178 Å, ρ = 1.282 g cm^{-3}, μ (CuKα) = 1.747 mm^{-1}, 11 611 reflections measured (T = 173 K, 3.470° < θ < 68.239°), no. of independent data collected: 3051, no. of independent data used for refinement: 2600 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0468, wR_2 = 0.1307 [$I > 2s(I)$], R_1 = 0.0545, wR_2 = 0.1367 (all data), and GOF = 1.029, H-atom parameters constrained.

Single crystal X-ray structure analysis of 2j (CCDC 1859354†). Colorless prisms (0.50 × 0.20 × 0.10 mm^3), monoclinic space group $P2_1/c$, a = 13.613(2) Å, b = 5.3251(9) Å, c = 26.026(4) Å, β = 95.958(3)°, V = 1876.4(6) $Å^3$, Z = 4, λ (MoKα) = 0.71073 Å, ρ = 1.318 g cm^{-3}, μ (MoKα) = 0.188 mm^{-1}, 10 165 reflections measured (T = 173 K, 1.504° < θ < 27.502°), no. of independent data collected: 4244, no. of independent data used for refinement: 2649 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0521, wR_2 = 0.1235 [$I > 2s(I)$], R_1 = 0.0974, wR_2 = 0.1579 (all data), and GOF = 0.966, H-atom parameters constrained.

Single crystal X-ray structure analysis of 3i (CCDC 1859407†). Colorless prisms (0.30 × 0.20 × 0.10 mm^3), monoclinic space group $P2_1/c$, a = 12.4130(15) Å, b = 17.816(2) Å, c = 7.9085(10) Å, β = 106.841(2)°, V = 1674.0(4) $Å^3$, Z = 4, λ (MoKα) = 0.71073 Å, ρ = 1.287 g cm^{-3}, μ (MoKα) = 0.199 mm^{-1}, 9554 reflections measured (T = 173 K, 2.5558° < θ < 27.5219°), no. of independent data collected: 3838, no. of independent data used for refinement: 2379 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0512, wR_2 = 0.1170

[$I > 2s(I)$], R_1 = 0.0924, wR_2 = 0.1447 (all data), and GOF = 0.929, H-atom parameters constrained.

Single crystal X-ray structure analysis of 3j (CCDC 1859355†). Colorless prisms (0.50 × 0.50 × 0.10 mm^3), triclinic space group $P\bar{1}$, a = 8.887(2) Å, b = 9.348(2) Å, c = 12.182(3) Å, α = 80.025(3)°, β = 72.125(3)°, γ = 88.273(3)°, V = 948.3(4) Å^3, Z = 2, λ (MoKα) = 0.71073 Å, ρ = 1.304 g cm^{-3}, μ (MoKα) = 0.186 mm^{-1}, 5472 reflections measured (T = 173 K, 2.2128° < θ < 27.5491°), no. of independent data collected: 4141, no. of independent data used for refinement: 3585 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0365 wR_2 = 0.0914 [$I > 2s(I)$], R_1 = 0.0429, wR_2 = 0.0954 (all data), and GOF = 1.065, H-atom parameters constrained.

Single crystal X-ray structure analysis of 4g (CCDC 1859357†). Colorless prisms (0.50 × 0.50 × 0.10 mm^3), monoclinic space group $C2/c$, a = 34.665(4) Å, b = 6.9265(9) Å, c = 14.4146(18) Å, β = 113.1370(10)°, V = 3182.7(7) Å^3, Z = 8, λ (MoKα) = 0.71073 Å, ρ = 1.296 g cm^{-3}, μ (MoKα) = 0.207 mm^{-1}, 17 622 reflections measured (T = 173 K, 2.5558° < θ < 27.5219°), no. of independent data collected: 3651, no. of independent data used for refinement: 3146 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0310, wR_2 = 0.0789 [$I > 2s(I)$], R_1 = 0.0380, wR_2 = 0.0871 (all data), and GOF = 1.042, H-atom parameters constrained.

Single crystal X-ray structure analysis of 5c (CCDC 1859359†). Colorless prisms (0.40 × 0.30 × 0.10 mm^3), triclinic space group $P\bar{1}$, a = 8.7745(14) Å, b = 9.4352(16) Å, c = 20.409(3) Å, α = 93.504(2)°, β = 97.479(2)°, γ = 90.918(2)°, V = 1671.6(5) Å^3, Z = 4, λ (MoKα) = 0.71073 Å, ρ = 1.218 g cm^{-3}, μ (MoKα) = 0.200 mm^{-1}, 9602 reflections measured (T = 173 K, 2.1632° < θ < 23.5028°), no. of independent data collected: 7319, no. of independent data used for refinement: 4764 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0538, wR_2 = 0.1302 [$I > 2s(I)$], R_1 = 0.0851, wR_2 = 0.1602 (all data), and GOF = 0.999, H-atom parameters constrained.

Conflicts of interest

There are no conflicts to declare.

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