Synthesis of Thiohydantoins by Phosphine-Catalyzed Reaction of Thioureas with Arylpropiolates

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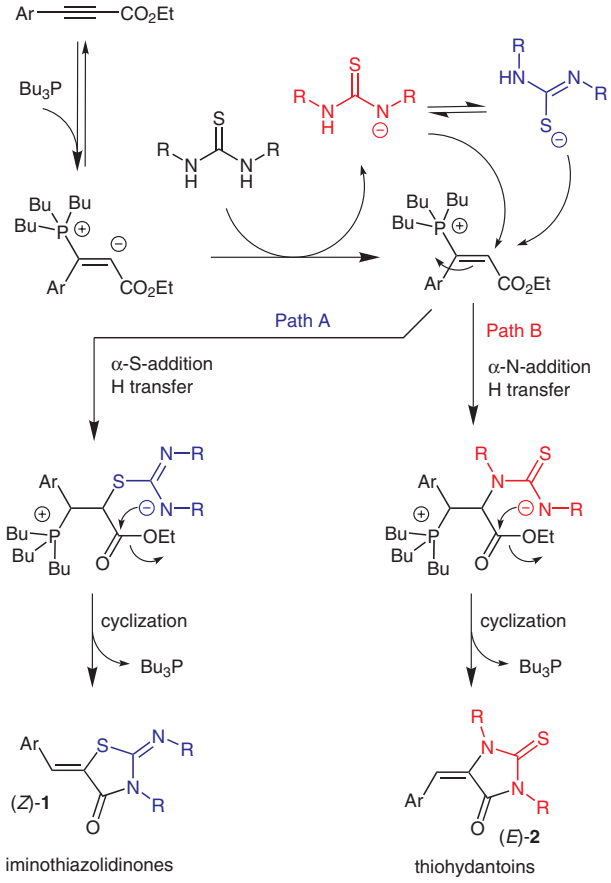
Abstract: A simple and efficient method for constructing thiohydantoin heterocycles using a phosphine-catalyzed tandem umpolung addition and intramolecular cyclization of thioureas on arylpropiolates is described.

Key words: thioureas, alkynes, catalysis, phosphines

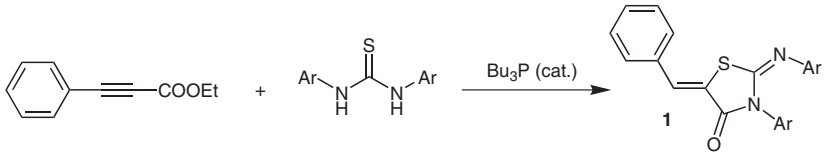
Small heterocyclic molecules are one of the predominant types of building block in medicinal chemistry.[1] New methods allowing simple and straightforward preparation of substituted heterocycles are powerful tools for exploring chemical diversity around a pharmacophoric core and therefore need to be developed. Among the 'drug-like' heterocycles, hydantoins and thiohydanthoins have been widely used for constructing products with pharmaceutical applications. Their reported biological activities (anticancer, anticonvulsant, antimuscarinic, antiulcer, antiarrythmic and schistosomicidal)[2] are largely influenced by the different constituents that are attached to the heterocyclic part. For this reason, there is a lot of interest in developing new strategies for the straightforward synthesis of substituted hydantoins and thiohydantoins.

In continuation of our efforts directed toward the synthesis of heterocyclic compounds using organocatalyzed reactions,[3] we describe herein an efficient and practical one-pot preparation of 5-arylidene-2-thiohydantoins **2**. These heterocyclic molecules are known to display interesting biological activities in the areas of antimycobacterial,[4] antiviral[5] and anticonvulsant indications.[6] The classical method for their synthesis needs two steps and involves the preparation of the thiohydantoin moiety followed by a Knoevenagel condensation with aldehydes.[7]

In a recent work,[3b] we have described a Bu_3P-catalyzed tandem umpolung addition and intramolecular cyclization of bifunctional pronucleophiles on arylpropiolates leading to sulfur heterocycles. Among the tested pronucleophiles, aryl or cyclic thioureas were found to react with arylpropiolates through an α-S-addition reaction and subsequent N-cyclization leading to (*Z*)-2-iminothiazolidin-4-ones derivatives **1** (Scheme 1, path A in Scheme 2).



Scheme 2 Proposed routes to heterocycles **1** and **2**



Scheme 1 Bu_3P catalyzed reaction of aromatic thioureas with arylpropiolates

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We envisioned that, depending on the nature of the thiourea, another reactivity profile might be observed. Indeed, thioureas displaying low level of SH tautomeric form (e.g., alkylthioureas) should undergo α-N- rather than α-S-addition on arylpropiolates under Bu_3P catalysis (Scheme 2, path B). The resulting umpolung α-N-adduct might then undergo N-cyclization resulting in the formation of thiohydantoin **2**.

To test the feasibility of this reaction, dialkylthioureas were reacted with ethyl phenylpropiolate in the presence of Bu_3P. To our delight, the reaction was found to work in the desired pathway and afforded the thiohydantoin heterocycle in moderate yield at room temperature (Table 1, entries 1 and 2). Yields might be improved by elevating the temperature (Table 1, entry 3) and by adding slowly the activated alkyne in the solution, the optimum dosage rate being 0.33 equivalent per hour (Table 1, entry 4). The reaction seems however to be limited to nonhindered thioureas: replacing dimethylthiourea by diethylthiourea dropped the yield from 76% to 47%, only 15% of desired product were observed with dibutylthiourea and no reaction at all occurred with diisopropylthiourea (Table 1, entries 4–7). No side product resulting from α-S-addition or noncyclized α-N-adducts was observed; in the case of unsuccessful reactions the starting alkyne was mostly recovered unchanged. These observations demonstrated the chemoselectivity of the reaction toward α-N- over α-S-addition when dialkylthioureas are used and let suppose that this α-N-addition is the limiting step of the process and do not tolerate bulky groups near the nitrogen atom.

In contrast to the formation of iminothiazolidinones **1**, the phosphine elimination step generates pure *E*-isomers of products **2** as the most thermodynamic stable isomers (Scheme 2). The structure of compound **2a** was unambiguously assigned by comparison to published NMR data and further proven by X-ray crystallography (Figure 1).[8]

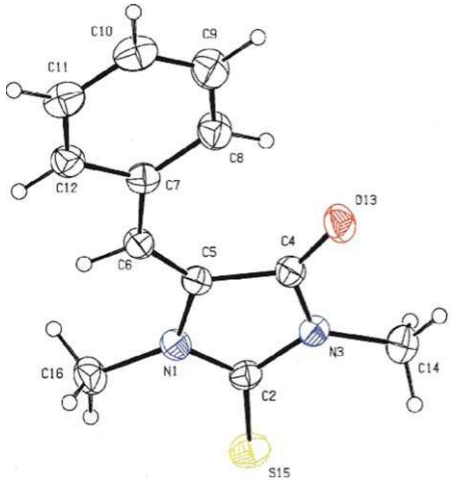


Figure 1 ORTEP diagram showing the crystal structure of compound **2a** with atomic numbering scheme for non-H atoms only

We thus used this reaction to prepare a range of 5-arylidene-2-thiohydantoins **3** and **4** by employing a panel of dissymmetric thioureas as starting materials. Taking into account the dramatic steric effect on the efficiency of the α-N-addition step, we planned to carry out the synthesis of thiohydantoins by employing dissymmetric thioureas that bear only one bulky moiety. Such substrates should undergo α-N-addition specifically with the less hindered nitrogen atom and therefore should generate only one regioisomer.

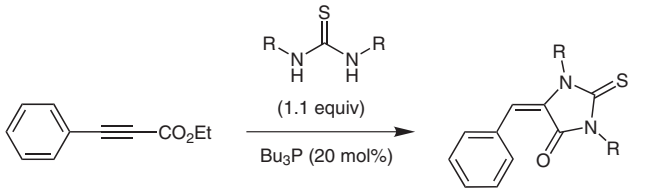
This assumption was confirmed by the results obtained with 15 thiourea substrates that were reacted with ethyl phenylpropiolate in the optimized conditions (Table 2). As expected, only one regioisomer, **3**, was obtained when dialkylthioureas bearing one methyl group on one side and a more bulky group on the other were used (Table 2, entries 1–5), although some exceptions were observed (Table 2, entries 6–8).

The reaction might also be successfully used with arylalkylthioureas. For these substrates again, no trace of product resulting from α-S-addition was observed. The nitrogen atom bearing aryl group participates well to the α-N-addition step and, depending on the size of the alkyl group, this participation can be exclusive (Table 2, entries 13, 14).

All the products were fully characterized and their structure established by NOESY experiments as well as by comparison to published ^1H and ^{13}C NMR data.[7]

The presented methodology appeared to be applicable for a variety of thiourea substrates affording a straightforward route to 5-arylidene-2-thiohydantoins, although mixture of regioisomers might be obtained for thioureas presenting no sufficient dissymmetry. There is indeed a competition in the α-N-addition step between the two nitrogen atoms of the thiourea reagent. The reactivity of the NH groups of the thiourea is influenced by steric hindrance,

Table 1 Optimization of the Reaction



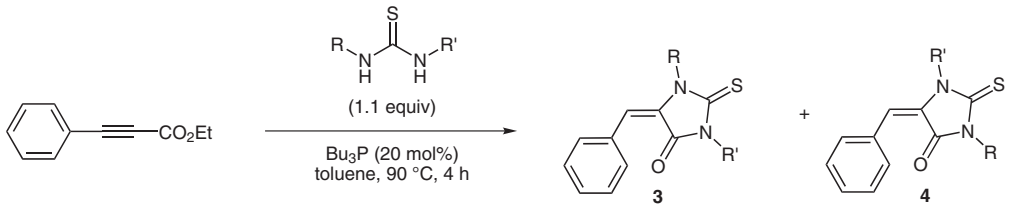
Entry	R	Conditions	Alkyne dosage rate	Product	Yield[a] (%)
1	Me	*i*-PrOH, 25 °C, 4 h	–	**2a**	48
2	Me	toluene, 25 °C, 4 h	–	**2a**	46
3	Me	toluene, 90 °C, 4 h	–	**2a**	56
4	Me	toluene, 90 °C, 4 h	0.33 equiv/h	**2a**	76
5	Et	toluene, 90 °C, 4 h	0.33 equiv/h	**2b**	47
6	Bu	toluene, 90 °C, 4 h	0.33 equiv/h	**2c**	15
7	*i*-Pr	toluene, 90 °C, 4 h	0.33 equiv/h	**2d**	n.d.

[a] Isolated yield.

nucleophilicity, and pK_a. Attempts to improve the chemoselectivity of the reaction by changing the experimental conditions such as replacing toluene by *i*-PrOH or decreasing the temperature were unsuccessful.

Although the procedure showed some limitations (poor yields with hindered thioureas, mixture of regioisomers for certain substrates), it presents many practical advantages over previous reported methods. Besides the fact that the reaction is trivial to run and uses readily available substrates,[9] product recovery is particularly easy. After evaporation of the crude reaction mixture, the thiohydantoins were precipitated in *i*-PrOH and were obtained as pure *E*-isomer after simple filtration and washing. This reaction is therefore well adapted to the preparation of libraries of these biologically active compounds.

Table 2 Phosphate-Catalyzed Reaction of Thioureas with Arylpropiolates Leading to Thiohydantoin Derivatives[a]



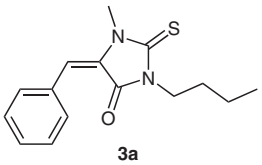
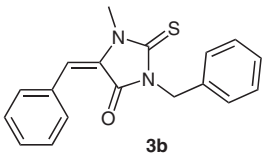
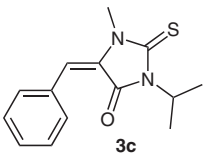
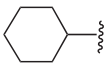
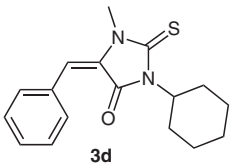
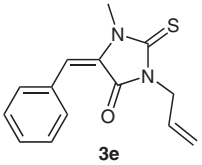
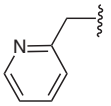
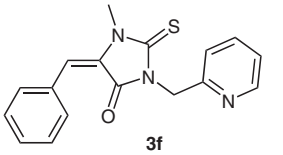
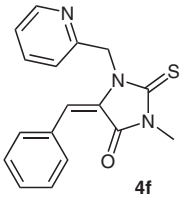
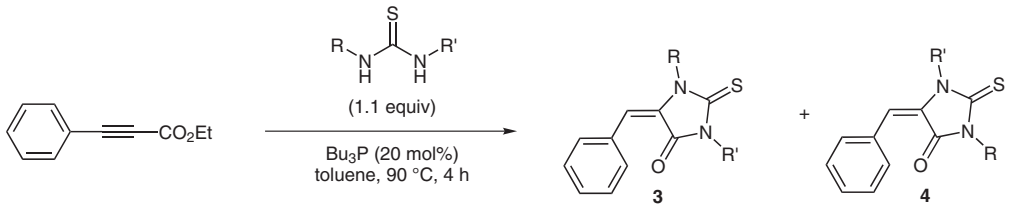
Entry	R	R′	Product(s)	Ratio[b] **3/4**	Yield (%)[c]
1	Me	Bu	 **3a**	100:0	53
2	Me	Bn	 **3b**	100:0	73
3	Me	*i*-Pr	 **3c**	100:0	45
4	Me		 **3d**	100:0	68
5	Me		 **3e**	100:0	53
6	Me		 **3f** +  **4f**	80:20	65

Table 2 Phosphate-Catalyzed Reaction of Thioureas with Arylpropiolates Leading to Thiohydantoin Derivatives[a] (continued)



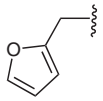
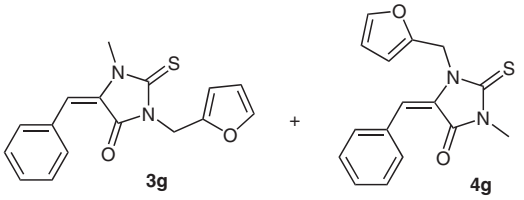
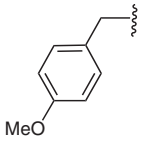
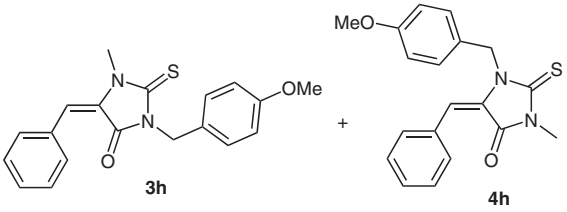
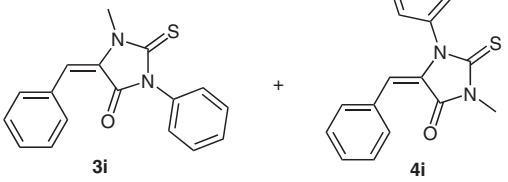
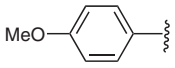
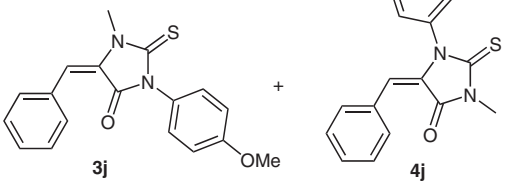
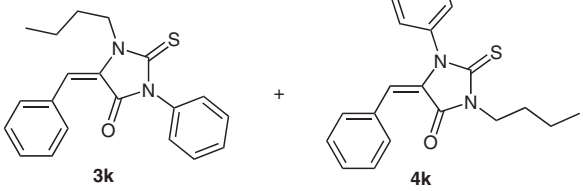
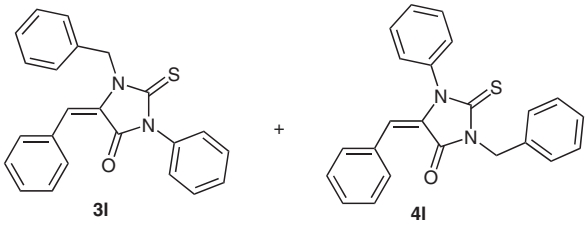
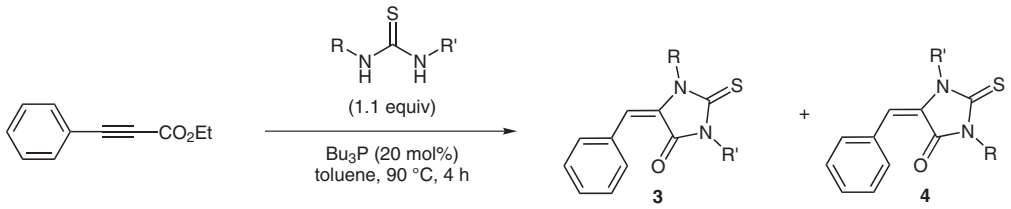
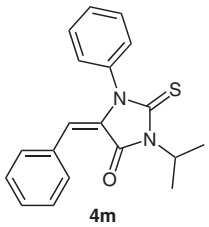
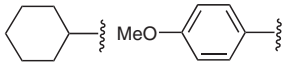
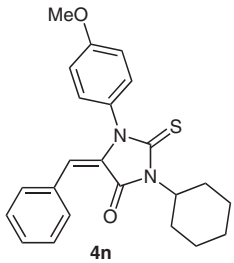
Entry	R	R′	Product(s)	Ratio[b] **3/4**	Yield (%)[c]
7	Me		 **3g** + **4g**	80:20	73
8	Me		 **3h** + **4h**	85:15	73
9	Me	Ph	 **3i** + **4i**	70:30	67
10	Me		 **3j** + **4j**	60:40	69
11	Bu	Ph	 **3k** + **4k**	25:75	40
12	Bn	Ph	 **3l** + **4l**	30:70	44

Table 2 Phosphate-Catalyzed Reaction of Thioureas with Arylpropiolates Leading to Thiohydantoin Derivatives[a] (continued)



Entry	R	R′	Product(s)	Ratio[b] **3/4**	Yield (%)[c]
13	*i*-Pr	Ph	 **4m**	0:100	39
14			 **4n**	0:100	51

[a] Alkyne (1 equiv) was added dropwise over 3 h (dosage rate = 0.33 equiv/h).
[b] Ratios were determined after precipitation.
[c] Total isolated yield.

In conclusion, we have developed a simple and practical method for the preparation of arylidenethiohydantoin heterocycles via Bu_3P-catalyzed tandem α-N-addition and intramolecular N-cyclization of thioureas on arylpropiolates. This strategy offers a new and straightforward way for constructing this type of heterocycles and, by its practical aspects, has potential application in combinatorial chemistry.

All reagents were used directly as obtained commercially unless otherwise noted. Melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. Flash chromatography was carried out on Merck silica gel (40–63 μm). IR spectra were obtained on a PerkinElmer system 2000 FT-IR spectrophotometer. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) were measured on a Bruker Avance 400 MHz spectrometer. Electrospray mass spectra were obtained using an ESI/TOF Mariner mass spectrometer.

Bu_3P-Catalyzed Construction of Thiohydantoins; Typical Procedure

A mixture of 1,3-disubstituted thiourea (5 mmol, 1.1 equiv) and Bu_3P (250 μL, 0.2 equiv) in anhyd toluene (5 mL) was heated at 90 °C under argon. Ethyl phenylpropiolate (5 mmol, 1 equiv) in anhyd toluene (5 mL) was added dropwise over 3 h (syringe pump, 0.33 equiv/h). After the addition, the mixture was heated for 1 h and then concentrated under reduced pressure. The residue was precipitated by the addition of EtOH, recovered by filtration, and washed with *i*-PrOH to afford the desired product as the pure *E*-isomer.

1,3-Dimethyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (2a)

Yellow solid; mp 140–142 °C.

IR (KBr): 3089, 2922, 1960, 1892, 1716, 1619, 1568, 1482, 1389, 1141, 1092, 1046, 752, 683, 566 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.45–7.35 (m, 3 H), 6.44 (s, 1 H), 3.57 (s, 3 H), 3.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 161.5, 131.9, 130.7, 129.9, 129, 128.3, 120.6, 30.5, 28.1.

MS (ESI): *m*/*z* = 233 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{12}H_{12}N_2OS$ + Na: 255.0568; found: 255.0564.

1,3-Diethyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (2b)

Yellow solid; mp 105 °C.

IR (KBr): 3092, 2981, 2934, 1958, 1902, 1766, 1717, 1617, 1572, 1470, 1388, 1313, 1268, 1184, 1136, 1111, 1068, 1020, 928, 883, 837, 753, 687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H), 7.45–7.35 (m, 3 H), 6.49 (s, 1 H), 4.21 (q, *J* = 6.8 Hz, 2 H), 3.99 (q, *J* = 6.8 Hz, 2 H), 1.40–1.20 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 161.5, 132, 130.7, 129.8, 128.3, 127.7, 119.9, 38.3, 36.8, 13, 12.0.

MS: *m*/*z* = 261 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{16}N_2OS$ + Na: 283.0881; found: 283.0870.

1,3-Dibutyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (2c)
The title compound was purified by flash chromatography (hexane–CH_2Cl_2, 7:3); yellow oil.

IR (film): 2959, 2933, 2872, 1727, 1656, 1622, 1573, 1402, 1293, 1220, 1084, 970, 753, 690, 569 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.45–7.35 (m, 3 H), 6.48 (s, 1 H), 4.14 (t, *J* = 7.6 Hz, 2 H), 3.92 (t, *J* = 7.6 Hz, 2 H), 1.85–1.65 (m, 4 H), 1.46 (m, 2 H), 1.37 (m, 2 H), 1.01 (t, *J* = 7.6 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 161.7, 132, 130.7, 129.7, 128.3, 128, 119.9, 43.2, 41.7, 29.8, 29, 20.06, 20.03, 13.8, 13.7.

MS (ESI): *m*/*z* = 339 $[M + Na]^+$.

3-Butyl-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3a)
Yellow solid; mp 117–119 °C.

IR (KBr): 3071, 2959, 2869, 1722, 1623, 1570, 1475, 1388, 1316, 1220, 1141, 1095, 926, 881, 832, 748, 685, 521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (m, 2 H), 7.45–7.35 (m, 3 H), 6.47 (s, 1 H), 3.93 (t, *J* = 7.6 Hz, 2 H), 3.61 (s, 3 H) 1.69 (m, 2 H), 1.37 (m, 2 H), 0.95 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 161.5, 131.9, 130.7, 129.8, 129.1, 128.3, 120.3, 41.8, 30.4, 29.8, 20.0, 13.7.

MS (ESI): *m*/*z* = 275 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{15}H_{18}N_2OS$ + Na: 297.1038; found: 297.1029.

3-Benzyl-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3b)
Yellow solid; mp 184–186 °C.

IR (KBr): 3065, 2942, 1710, 1616, 1570, 1473, 1431, 1413, 1377, 1327, 1221, 1087, 753, 706, 684, 516 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H), 7.51 (d, *J* = 6.8 Hz, 2 H), 7.45–7.25 (m, 6 H), 6.49 (s, 1 H), 5.14 (s, 2 H), 3.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 161.4, 135.8, 131.9, 130.7, 129.9, 129, 128.8, 128.4, 128.3, 127.8, 120.7, 45.1, 30.6.

MS (ESI): *m*/*z* = 309 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{18}H_{16}N_2OS$ + Na: 331.0881; found: 331.0883.

3-Isopropyl-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3c)
Yellow solid; mp 152–153 °C.

IR (KBr): 2987, 2974, 2933, 1724, 1621, 1474, 1415, 1396, 1351, 1247, 1122, 1082, 1059, 929, 833, 753, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (m, 2 H), 7.45–7.35 (m, 3 H), 6.47 (s, 1 H), 5.09 (sept, *J* = 7 Hz, 1 H), 3.61 (s, 3 H), 1.50 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 161.5, 131.9, 130.7, 129.7, 129.4, 128.3, 119.9, 48.1, 30.9, 19.1.

MS (ESI): *m*/*z* = 261 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{16}N_2OS$ + Na : 283.0881; found: 283.0889.

3-Cyclohexyl-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3d)
Yellow solid; mp 174–176 °C.

IR (KBr): 2923, 2857, 1721, 1621, 1571, 1473, 1414, 1394, 1361, 1228, 1181, 1146, 1097, 1080, 752, 688, 534 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (m, 2 H), 7.45–7.35 (m, 3 H), 6.46 (s, 1 H), 4.69 (m, 1 H), 3.61 (s, 3 H), 2.40–2.25 (m, 2 H), 1.90–1.60 (m, 5 H), 1.45–1.15 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 161.5, 131.9, 130.7, 129.7, 129.4, 128.3, 119.8, 55.9, 31.0, 28.6, 28.5, 25.9, 25.0.

MS (ESI): *m*/*z* = 301 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{17}H_{20}N_2OS$ + Na: 323.1194; found: 323.1201.

3-Allyl-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3e)
Yellow solid; mp 147–149 °C.

IR (KBr): 3092, 3067, 1723, 1621, 1474, 1412, 1378, 1227, 1178, 1093, 929, 887, 751, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H), 7.45–7.35 (m, 3 H), 6.49 (s, 1 H), 5.88 (m, 1 H), 5.35–5.2 (m, 2 H), 4.56 (d, *J* = 5.6 Hz, 2 H), 3.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 161.1, 131.9, 130.8, 130.7, 129.9, 129, 128.4, 120.7, 118.5, 43.9, 30.5.

MS (ESI): *m*/*z* = 259 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{14}N_2OS$ + Na: 281.0725; found: 281.0725.

1-Methyl-5-[(*E*)-1-phenylmethylidene]-3-pyridin-2-ylmethyl-2-thioxoimidazolidin-4-one (3f) and 3-Methyl-5-[(*E*)-1-phenylmethylidene]-1-pyridin-2-ylmethyl-2-thioxoimidazolidin-4-one (4f)
The title compounds were obtained by precipitation as a mixture (**3f/4f** = 80:20); yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 4.8 Hz, 0.25 H, **4f**), 8.54 (d, *J* = 4.8 Hz, 1 H, **3f**), 8.02 (m, 2 H, **3f**), 7.91 (m, 0.5 H, **3f**), 7.70–7.60 (m, 1.25 H, **3f** and **4f**), 7.45–7.1 (m, 6.25 H, **3f** and **4f**), 6.76 (s, 0.25 H, **4f**), 6.52 (s, 1 H, **3f**), 5.54 (s, 0.5 H, **4f**), 5.29 (s, 2 H, **3f**), 3.63 (s, 3 H, **3f**), 3.43 (s, 0.75 H, **4f**).

MS (ESI): *m*/*z* = 310 $[M + H]^+$ (**3f** and **4f**).

3-Furan-2-ylmethyl-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3g) and 1-Furan-2-ylmethyl-3-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4g)
The title compounds were obtained by precipitation as a mixture (**3g/4g** = 80:20); yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.95 (m, 2.5 H, **3g** and **4g**), 7.45–7.3 (m, 5 H, **3g** and **4g**), 6.83 (s, 0.25 H, **4g**), 6.50 (s, 1 H, **3g**), 6.45–6.4 (m, 1.25 H, **3g** and **4g**), 6.35 (dd, *J* = 3.2, 1.6 Hz, 0.25 H, **4g**), 6.31 (dd, *J* = 3.2, 1.6 Hz, 1 H, **3g**), 5.40 (s, 0.5 H, **4g**), 5.15 (s, 2 H, **3g**), 3.62 (s, 3 H, **3g**), 3.39 (s, 0.75 H, **4g**).

MS (ESI): *m*/*z* = 299 $[M + H]^+$ (**3g** and **4g**).

3-(4-Methoxybenzyl)-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3h) and 1-(4-Methoxybenzyl)-3-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4h)
The title compounds were obtained by precipitation as a mixture (**3h/4h** = 85:15); yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H, **3h**), 7.88 (m, 0.4 H, **4h**), 7.49 (d, *J* = 8.8 Hz, 2 H, **3h**), 7.45–7.32 (m, 3.6 H, **3h** and **4h**), 7.26 (d, *J* = 8.8 Hz, 0.4 H, **4h**), 6.89 (d, *J* = 8.8 Hz, 0.4 H, **4h**), 6.83 (d, *J* = 8.8 Hz, 2 H, **3h**), 6.48 (s, 0.2 H, **4h**), 6.45 (s, 1 H, **3h**), 5.36 (s, 0.4 H, **4h**), 5.08 (s, 2 H, **3h**), 3.79 (s, 0.6 H, **4h**), 3.77 (s, 3 H, **3h**), 3.59 (s, 3 H, **3h**), 3.43 (s, 0.6 H, **4h**).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 177.8 (**4h**), 176.7 (**3h**), 161.6 (**4h**), 161.4 (**3h**), 159.2, 132.2 (**3h**), 132.1 (**4h**), 130.7, 130.1, 129.7, 129.1, 128.9, 128.3, 128.26, 128.23, 128.16, 128.1, 127.8, 126.9, 125.2, 121.1 (**4h**), 120.4 (**3h**), 114.2 (**4h**), 113.6 (**3h**), 55.2 (**4h**), 55.1 (**3h**), 46.5 (**4h**), 44.5 (**3h**), 30.5 (**3h**), 28.2 (**4h**).

MS (ESI): *m*/*z* = 339 $[M + H]^+$ (**3h** and **4h**).

1-Methyl-3-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3i) and 3-Methyl-1-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4i)

The title compounds were obtained by precipitation as a mixture (**3i/4i** = 70:30); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H, **3i**), 7.91 (m, 0.85 H, **4i**), 7.65–7.30 (m, 11.4 H, **3i** and **4i**), 6.59 (s, 1 H, **3i**), 6.20 (s, 0.4 H, **4i**), 3.72 (s, 3 H, **3i**), 3.48 (s, 1.25 H, **4i**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2 (**4i**), 176.6 (**3i**), 161.4 (**4i**), 161.2 (**3i**), 134.9, 133.2, 131.8, 130.9, 130.8, 130, 129.7, 129.25, 129.13, 129.06, 128.8, 128.41, 128.37, 128.32, 122.1 (**4i**), 121.1 (**3i**), 30.8 (**3i**), 28.2 (**4i**).

MS (ESI): *m*/*z* = 295 $[M + H]^+$ (**3i** and **4i**).

3-(4-Methoxyphenyl)-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3j) and 3-(4-Methoxyphenyl)-1-methyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4j)

The title compounds were obtained by precipitation as a mixture (**3j/4j** = 60:40); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 2 H, **3j**), 7.93 (m, 1.4 H, **4j**), 7.45–7.35 (m, 5.1 H, **3j** and **4j**), 7.27 (d, *J* = 8.8 Hz, 3.4 H, **3j** and **4j**), 7.09 (d, *J* = 8.8 Hz, 1.4 H, **4j**), 7.01 (d, *J* = 8.8 Hz, 2 H, **3j**), 6.57 (s, 1 H, **3j**), 6.21 (s, 0.7 H, **4j**), 3.89 (s, 2.1 H, **4j**), 3.84 (s, 3 H, **3j**), 3.70 (s, 3 H, **3j**), 3.46 (s, 2.1 H, **4j**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5 (**4j**), 177 (**3j**), 161.4 (**2-2j**), 161.39 (**3j**), 160.2 (**4j**), 159.8 (**3j**), 131.89, 131.86, 131, 130.9, 130.8, 130.3, 129.99, 129.98, 129.5, 128.9, 128.4, 128.3, 127.2, 125.7, 122.2 (**4j**), 121 (**3j**), 115.2 (**4j**), 114.4 (**3j**), 55.5 (**4j**), 55.4 (**3j**), 30.8 (**3j**), 28.2 (**4j**).

MS (ESI): *m*/*z* = 325 $[M + H]^+$ (**3j** and **4j**).

1-Butyl-3-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3k) and 3-Butyl-1-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4k)

The title compounds were obtained by precipitation as a mixture (**3k/4k** = 25:75); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 0.7 H, **3k**), 7.90 (m, 2 H, **4k**), 7.65–7.30 (m, 10.8 H, **3k** and **4k**), 6.59 (s, 0.35 H, **3k**), 6.17 (s, 1 H, **4k**), 4.22 (t, *J* = 7.6 Hz, 0.7 H, **3k**), 4.01 (t, *J* = 7.6 Hz, 2 H, **4k**), 1.85–1.70 (m, 2.7 H, **3k** and **4k**), 1.55–1.35 (m, 2.7 H, **3k** and **4k**), 1.03 (t, *J* = 7.6 Hz, 1.05 H, **3k**), 0.97 (t, *J* = 7.6 Hz, 3H, **4k**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9 (**4k**), 176.1 (**3k**), 161.3 (**3k** and **4k**), 134.9, 133.2, 131.8, 130.9, 130.8, 130, 129.9, 129.6, 129.3, 129.07, 129.01, 128.4, 128.31, 128.28, 127.8, 121.9 (**4k**), 120.7 (**3k**),43.6 (**3k**), 41.8 (**4k**), 29.7 (**4k**), 28.9 (**3k**), 20.13 (**4k**), 20.09 (**3k**), 13.8 (**3k**), 13.7 (**4k**).

MS (ESI): *m*/*z* = 337 $[M + H]^+$.

1-Benzyl-3-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (3l)

Precipitation gave a mixture of **3l/4l** (30:70). An analytically pure sample of **3l** was obtained by flash chromatography (hexane–CH_2Cl_2, 50:50); yellow solid; mp 186–187 °C.

IR (KBr): 3064, 3030, 1727, 1627, 1594, 1501, 1453, 1442, 1404, 1364, 1303, 1259, 1123, 1047, 1023, 931, 878, 840, 757, 737, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (m, 2 H), 7.60–7.30 (m, 13 H), 6.56 (s, 1 H), 5.54 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 161.3, 134.7, 133.3, 131.7, 130.9, 130, 129.2, 129.1, 129, 128.4, 128.3, 128, 127.5, 127, 122.1, 47.6.

MS (ESI): *m*/*z* = 371 $[M + H]^+$.

3-Benzyl-1-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4l)

Precipitation gave a mixture of **3l/4l** (30:70). A pure analytical sample of the title compound **4l** was obtained by flash chromatography (hexane–CH_2Cl_2, 50:50); yellow solid; mp 141–142 °C.

IR (KBr): 3059, 2360, 1726, 1622, 1593, 1497, 1452, 1423, 1397, 1378, 1303, 1282, 1147, 1061, 1027, 990, 929, 882, 759, 733, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (m, 2 H), 7.65–7.50 (m, 5 H), 7.45–7.30 (m, 8 H), 6.20 (s, 1 H), 5.25 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 161.2, 135.8, 134.9, 131.8, 130.85, 130.79, 130, 129.7, 129.3, 129.2, 128.5, 128.3, 127.9, 122.2, 45.2.

MS (ESI): *m*/*z* = 371 $[M + H]^+$.

3-Isopropyl-1-phenyl-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4m)

Yellow solid; mp 168–170 °C.

IR (KBr): 3049, 2976, 2937, 1723, 1625, 1593, 1571, 1497, 1452, 1396, 1337, 1151, 1088, 1069, 921, 851, 752, 686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (m, 2 H), 7.65–7.50 (m, 3 H), 7.45–7.30 (m, 5 H), 6.19 (s, 1 H), 5.21 (sept, *J* = 6.8 Hz, 1 H), 1.63 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177, 161.3, 135.2, 131.8, 131, 130.8, 129.9, 129.8, 129.6, 129.2, 128.2, 121.4, 58.2, 48.2, 19, 18.3.

MS (ESI): *m*/*z* = 323 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{19}H_{18}N_2OS$ + Na : 345.1038; found: 345.1049.

3-Cyclohexyl-1-(4-methoxyphenyl)-5-[(*E*)-1-phenylmethylidene]-2-thioxoimidazolidin-4-one (4n)

Yellow solid; mp 202–204 °C.

IR (KBr): 3072, 3014, 2918, 2850, 1719, 1625, 1585, 1511, 1462, 1446, 1396, 1320, 1247, 1147, 1047, 1023, 926, 885, 835, 756, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (m, 2 H), 7.40–7.30 (m, 3 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 6.17 (s, 1 H), 4.79 (m, 1 H), 3.89 (s, 3 H), 2.50–2.35 (m, 2 H), 1.95–1.80 (m, 4 H), 1.70 (m, 1 H), 1.45–1.20 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 161.4, 160.1, 131.9, 131.2, 130.8, 130.3, 129.7, 128.2, 127.7, 121.4, 115.2, 56, 55.5, 28.5, 26, 25.1.

MS (ESI): *m*/*z* = 393 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{23}H_{24}N_2O_2S$ + Na: 415.1456; found: 415.1467.

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(8) Crystal data of compound **2a**: $C_{12}H_{12}ON_2S$, M = 232; T = 293 (2) K, λ = 0.71073 Å; Crystal system = monoclinic; Space group: P 21/n; Unit cell dimensions: a = 12.036 Å, b = 8.065 Å, c = 12.966 Å, $\alpha = \gamma = 90.00°$, $\beta = 115.46°$; V = 1136.4 Å^3; Z = 4; D_{calc} = 1.358 g /cm^3; Absorption coefficient: 0.284 mm^{-1}; F(000) = 488; Crystal size: 0.25 × 0.25 × 0.10 mm; Reflections collected: 9597; Independent reflections: 2604 [R(int) = 0.0283]; Refinement method, full-matrix least-squares on F2; Goodness-of-fit on F2: 1.037; Final R indices [I > 2σ(I)] R1 = 0.0428, wR2 = 0.1052; R indices (all data) R1 = 0.0704, wR2 = 0.1204; Extinction coefficient: 0.033; Largest diff. peak and hole: 0.186 and –0.196e Å^{-3}.

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