# 1-(Methyldithiocarbonyl)imidazole as Thiocarbonyl Transfer Reagent: A Facile One-Pot Three-Component Synthesis of 3,5- and 1,3,5-Substituted-2-Thiohydantoins

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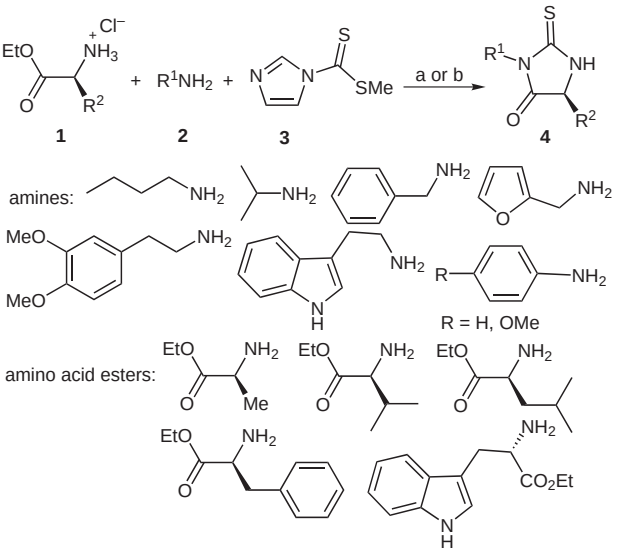
*Received 7 September 2006*

**Abstract:** An efficient three-component one-pot synthesis of 3,5- and 1,3,5-substituted 2-thiohydantoins employing easily accessible amino acid esters, primary amines and 1-(methyldithiocarbonyl)imidazole as thiocarbonyl transfer reagent has been reported.

**Key words:** thiohydantoins, multicomponent reactions, fused thiohydantoins, imidazole dithioate, amino acids

Hydantoins and their 2-thio analogues represent an important class of heterocycles displaying a broad range of biological (anticonvulsant, antiarrythmic, antimuscarine, antineuralgic, anticancer) activities.[1] Derivatives of 2-thiohydantoins also play an important role in organic synthesis, especially as starting materials for the preparation of synthetic intermediates with wide range of applications as therapeutics[2] as well as fungicides and herbicides.[3] They have also been used widely for the sequence analysis of polypeptides and proteins (Edman degradation).[4] These compounds are usually prepared by reaction of amino acids or amino acid esters with an isothiocyanate.[5] A few of the 2-thiohydantoins have been synthesized by reaction of amino acids with dithiocarbamate esters.[6] We have recently[7] reported synthetic application of 1-(methyldithiocarbonyl)imidazole as a useful thiocarbonyl transfer reagent[8] for the synthesis of symmetrical and unsymmetrical mono-, di- and trisubstituted thioureas and dithiocarbamates under mild and simple non-hazardous reaction conditions. In the present communication, we wish to report further application of this reagent for the efficient synthesis of a broad range of 3,5- and 1,3,5-substituted-2-thiohydantoins by its reaction with amino acid esters and amines in a three-component one-pot process.

1-(Methyldithiocarbonyl)imidazole (**3**) was prepared according to our earlier reported procedure[7] by treatment of imidazole with carbon disulfide in the presence of sodium hydride as base followed by alkylation with methyl iodide. In a typical experiment,[9] when equimolar quantities of alanine ethyl ester hydrochloride, benzylamine and 1-(methyldithiocarbonyl)imidazole were refluxed in ethanol (7–8 h) in the presence of triethylamine, the corresponding (*S*)-3-benzyl-5-methyl-2-thiohydantoin (**4a**) was obtained in 87% yield, whereas the use of corresponding free alanine, benzylamine and 1-(methyldithiocarbonyl)imidazole resulted in the formation of only 1,3-dibenzylthiourea and no trace of thiohydantoin **4a** was obtained. The reaction was equally facile in the presence of $K_2CO_3$ as base in acetonitrile yielding **4a** in comparable yield (85%). The versatility of the protocol was further demonstrated by the preparation of a library of 20 distinct thiohydantoins with two points of diversity starting from various primary amines and amino acid esters as shown in Scheme 1 and Figure 1. In general, yields of the thiohydantoins were excellent, ranging between 87–97%. The reaction scope of this methodology was further elaborated by preparation of nine thiohydantoins **7a**–**i** with a three-point diversity backbone from N-substituted amino acid esters by using three amino acid esters ($R^2$ = benzyl, isopropyl, methyl), three aldehydes ($R^3$ = 4-methoxyphenyl, 2-furyl and 2-thienyl) and four amines [$R^1$ = benzyl, *n*-butyl, 2-furylmethyl, 3-(indolyl)ethyl; Scheme 2]. Various N-substituted amino acid esters **6** were prepared by reductive N-alkylation with various aldehydes in the presence of sodium triacetoxyborohydride.[5b] When equimolar quantities of N-substituted amino acid ester **6a** ($R^2$ = $PhCH_2$, $R^3$ = 4-$MeOC_6H_4$), 2-furfurylamine and 1-(methyldithiocarbonyl)imidazole (**3**) were reacted in refluxing ethanol in the presence of triethylamine under the




**Scheme 1** Synthesis of 3,5-substituted 2-thiohydantoins **4**. *Reagents and conditions*: a) $Et_3N$, EtOH, Δ, 7–8 h; b) $K_2CO_3$, MeCN, Δ, 7–8 h.

***SYNLETT*** 2007, No. 2, pp 0251–0254
Advanced online publication: 24.01.2007
DOI: 10.1055/s-2007-967987; Art ID: D26406ST

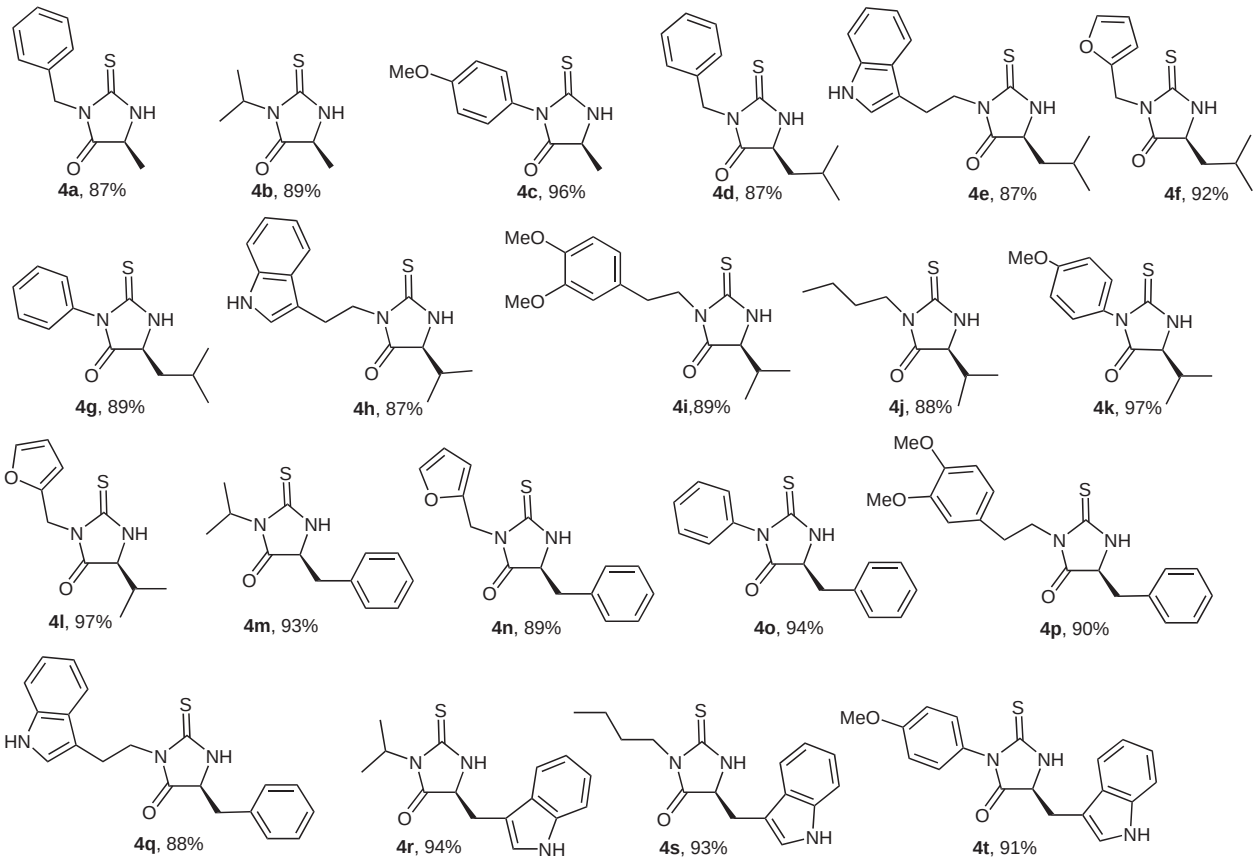
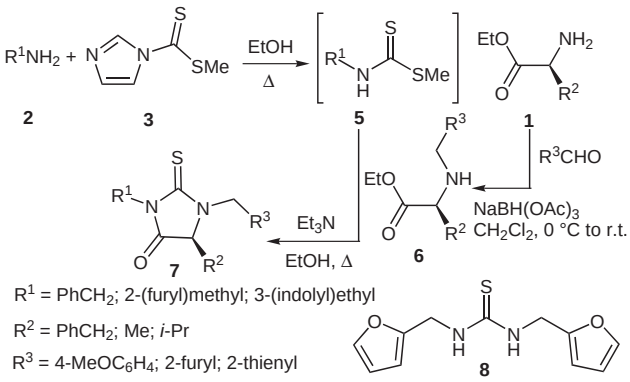



**Figure 1** Synthesis of substituted 2-thiohydantoins **4a**–**t** with two points of diversity

earlier-described conditions, the desired 1,3,5-trisubstituted 2-thiohydantoin **7a** was obtained only in 57% yield along with the formation of thiourea **8** in 32% yield. On the other hand, prior generation of dithiocarbamate **5a** [$R^1$ = 2-(furyl)methyl] by reaction of 2-furfurylamine and **3** followed by sequential addition of N-substituted amino acid ester **6a** in the presence of triethylamine as base in refluxing ethanol afforded the corresponding (*S*)-5-benzyl-3-(2-furfuryl)-1-(4-methoxybenzyl)-2-thiohydantoin (**7a**) in 84% yield (Figure 2).[10] These observations can be explained in terms of higher reactivity of primary amines towards **3** in comparison to N-substituted amino acid esters **6** yielding dithiocarbamate **5** as initial sole intermediate. Reaction of **5a** with N-substituted amino acid ester **6a** affords the thiohydantoin **7a** whereas its reaction with remaining primary amine (furfuryl amine) in the reaction mixture furnishes the thiourea **8** as the side product. These reaction conditions were subsequently followed for the synthesis of trisubstituted thiohydantoins **7b**–**i** in a two-step one-pot process (Scheme 2, Figure 2).

Finally, we have also explored the cyclization of L-proline ester hydrochloride **9** to fused thiohydantoin derivatives **10** (Scheme 3). When the L-proline ester hydrochloride **9**, benzylamine and 1-(methyldithiocarbonyl)imidazole (**3**) were refluxed together in methanol in the presence of triethylamine, the only product isolated was dibenzylthiourea formed in 89% yield along with the trace amount of **10a** (3%). However, prior generation of dithiocarbamate




**Scheme 2** Synthesis of 1,3,5-trisubstituted 2-thiohydantoins **7**

**5b** ($R^1$ = benzyl) by reaction of benzylamine with **3** in refluxing methanol followed by addition of L-proline ester hydrochloride and triethylamine furnished the fused thiohydantoin **10a** in 92% yield (Scheme 3). The other N-substituted fused thiohydantoins **10b**–**c** were also obtained in good yields following a similar sequential three-component one-pot procedure (Scheme 3).

In conclusion, we have developed an efficient three-component two-step one-pot synthesis of substituted thiohydantoins using 1-(methyldithiocarbonyl)imidazole as thiocarbonyl transfer agent. The product thiohydantoins contain two or three valuable substituents allowing for considerable molecular diversity. All the three building

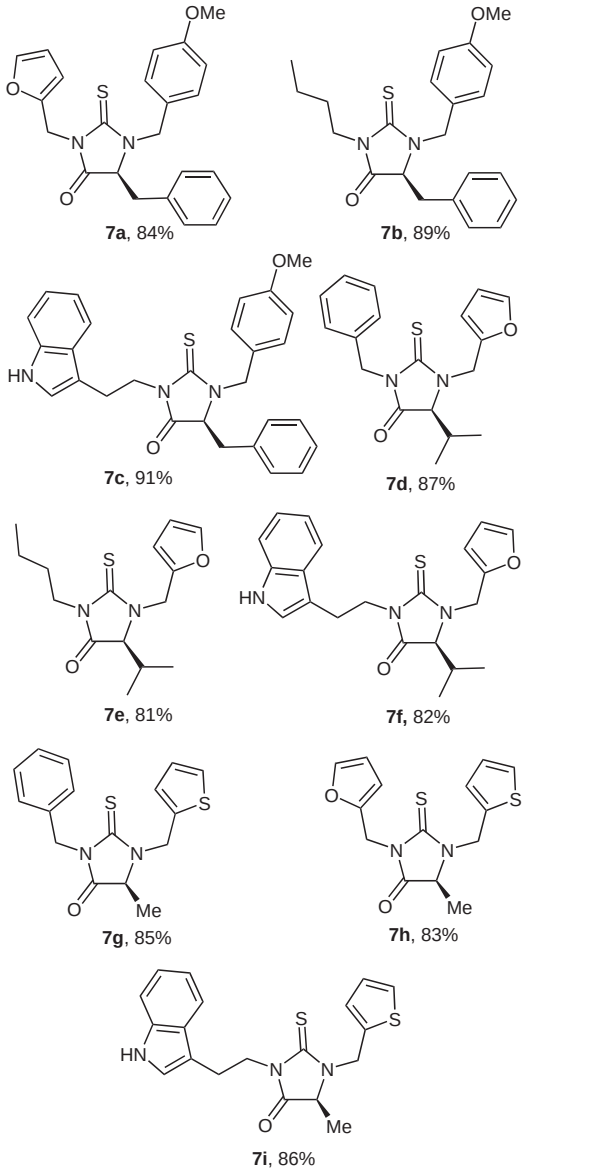
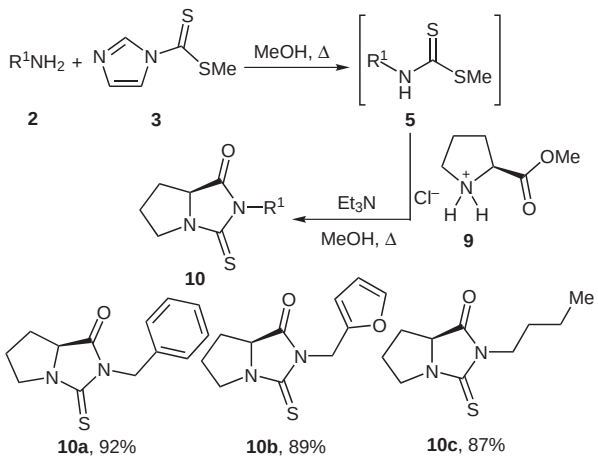



**Figure 2** Synthesis of 1,3,5-trisubstituted 2-thiohydantoins **7a**–**i** with three points of diversity




**Scheme 3** Synthesis of N-substituted fused 3-thiohydantoins **10**

blocks, i.e. amino acid esters, primary amines and 1-(methyldithiocarbonyl)imidazole are easily available, besides the method does not require the less readily available isothiocyanates, which are commonly employed in standard preparation of thiohydantoins.[5] We believe that dithiocarbamates such as **5** are masked isothiocyanate synthons and react with amines by elimination–addition mechanism.[8] The method is also amenable to solid-phase synthesis of thiohydantoins which is underway in our laboratory.

All the newly synthesized thiohydantoins are found to be optically active as evidenced by their optical rotation.[11] A study of the enantiomeric purity[12] of few thiohydantoins (**4a**,**f**,**g**, **7c**,**f**, **10a**) revealed that the reaction gives enantiomerically pure (>95% ee) thiohydantoins in some cases (**4g**, **7f**, **10a**), whereas racemization was observed in others (**4a**,**f**, **7c**), thus reducing the enantiomeric excess to 55–65%.

## Acknowledgment

We thank CSIR, New Delhi for financial support.

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(9) **General Procedure for the Preparation of 3,5-Substituted 2-Thiohydantoins 4.**
A solution of L-amino acid ethyl ester hydrochloride salt **1** (2.0 mmol), amine **2** (2.0 mmol), 1-(methyldithiocarbonyl)imidazole **3** (0.32 g, 2.0 mmol) and $Et_3N$ (0.58 mL, 4.2 mmol) in 15.0 mL of absolute EtOH was refluxed for 7–8 h (monitored by TLC). The reaction mixture was cooled to r.t. and concentrated under vacuo. The residue was dissolved in $CHCl_3$ (25 mL) and washed with $H_2O$ (2 × 20 mL), brine (20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure to afford the crude **4a**–**t**, which were purified by column chromatography over silica gel using hexane–EtOAc as eluent. All the newly synthesized thiohydantoins **4a**,**b**,**e**,**f**,**h**–**t**, **7a**–**i** and **10a**–**c** were characterized with the help of spectral and analytical data.

**(*S*)-3-Furan-2-ylmethyl-5-isobutyl-2-thioxo-imidazolidin-4-one (4f).**
Yield 92% (0.46 g); white solid; mp 132–133 °C; $R_f$ = 0.73 (5:1 hexane–EtOAc). IR (KBr): 3185, 3004, 2958, 1754, 1527, 1430, 1342, 1169, 738 cm$^{-1}$. $[a]_D^{25}$ –2.6 (*c* 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 2.44 Hz, 3 H), 0.93 (d, *J* = 2.44 Hz, 3 H), 1.52–1.59 (m, 1 H), 1.71–1.83 (m, 2 H), 4.12 (dd, *J* = 9.34, 2.72 Hz, 1 H), 4.93 (d, *J* = 15.12 Hz, 1 H), 4.98 (d, *J* = 15.12 Hz, 1 H, $CH_2$), 6.27 (dd, *J* = 3.16, 1.96 Hz, 1 H), 6.35 (dd, *J* = 3.40 Hz, 1 H), 7.30 (d, *J* = 0.72 Hz, 1 H), 8.20 (br s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 21.3, 22.9, 25.0, 37.4, 40.1, 57.9, 109.4, 110.3, 142.3, 148.5, 174.0, 182.9. MS-FAB: *m/z* (%) = 253 (100) [M + 1]. ESI-HRMS: *m/z* calcd for $C_{12}H_{16}N_2O_2SNa$: 275.0830 $[M + Na]^+$; found: 275.0838.

**(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethyl]-5-isopropyl-2-thioxoimidazolidin-4-one (4i).**
Yield 89% (0.57 g); colorless solid; mp 114–115 °C; $R_f$ = 0.76 (5:1 hexane–EtOAc). IR (KBr): 3188, 2949, 1747, 1515, 1441, 1350, 1269, 1152, 1028 cm$^{-1}$. $[\alpha]_D^{25}$ –5.4 (*c* 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.84 Hz, 3 H), 1.01 (d, *J* = 7.08 Hz, 3 H), 2.13–2.24 (m, 1 H), 2.90 (t, *J* = 8.08 Hz, 2 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 3.91 (dd, *J* = 4.04, 1.20 Hz, 1 H), 3.94–4.08 (m, 2 H), 6.76 (s, 1 H), 6.78 (dd, *J* = 4.40, 1.72 Hz, 2 H), 7.72 (br s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 16.1, 18.6, 30.6, 33.0, 42.1, 55.8, 64.4, 111.1, 112.0, 120.9, 130.1, 147.7, 148.7, 173.3, 184.1. MS-FAB: *m/z* (%) = 323 (100) [M + 1]. ESI-HRMS: *m/z* calcd for $C_{16}H_{22}N_2O_3SNa$: 345.1249 $[M + Na]^+$; found: 345.1215.

(10) **General Procedure for the Preparation of 1,3,5-Trisubstituted 2-Thiohydantoins 7 and N-Substituted Fused 3-Thiohydantoins 10.**
A solution of appropriate amine **2** (2.0 mmol) and 1-(methyldithiocarbonyl)imidazole (**3**, 0.32 g, 2.0 mmol) in 10 mL of absolute EtOH (or MeOH) was refluxed for 30 min. After the complete consumption of **3** (as shown by TLC), a mixture of appropriate N-substituted amino ester **6** (2.0 mmol) or L-proline methyl ester hydrochloride **9** (0.33 g, 2.0 mmol) and $Et_3N$ (0.58 mL, 4.2 mmol) in 5 mL absolute EtOH (or MeOH) was added and the reaction mixture was further refluxed for 6–7 h (monitored by TLC). It was then worked up and purified as described above to afford the products **7a**–**i** or **10a**–**c**.

**(*S*)-5-Benzyl-3-[2-(1*H*-indol-3-yl)ethyl]-1-(4-methoxybenzyl)-2-thioxoimidazolidin-4-one (7c).**
Yield 91% (0.85 g); yellow solid; mp 170–171 °C; $R_f$ = 0.56 (5:1 hexane–EtOAc). IR (KBr): 3404, 2927, 1750, 1473, 1350, 1263, 739 cm$^{-1}$. $[\alpha]_D^{25}$ –13.1 (*c* 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.69–2.83 (m, 2 H), 2.92 (dd, *J* = 14.52, 5.40 Hz, 1 H), 3.12 (dd, *J* = 14.54, 4.40 Hz, 1 H), 3.77 (s, 3 H), 3.92–3.98 (m, 2 H), 4.00 (t, *J* = 4.64 Hz, 1 H), 4.15 (d, *J* = 14.88 Hz, 1 H), 5.87 (d, *J* = 14.88 Hz, 1 H), 6.81 (d, *J* = 8.52 Hz, 2 H), 6.98 (d, *J* = 1.96 Hz, 1 H), 7.05 (d, *J* = 7.46 Hz, 2 H), 7.07 (dd, *J* = 5.60, 2.20 Hz, 2 H), 7.10 (t, *J* = 7.84 Hz, 1 H), 7.17 (t, *J* = 8.08 Hz, 1 H), 7.24 (t, *J* = 7.32 Hz, 3 H), 7.31 (d, *J* = 7.56 Hz, 1 H), 7.74 (d, *J* = 7.80 Hz, 1 H), 8.0 (br s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 22.9, 35.1, 42.3, 47.7, 55.2, 61.1, 111.0, 112.2, 114.2, 119.0, 119.4, 121.9, 122.1, 126.8, 127.4, 127.5, 128.6, 129.3, 129.6, 133.9, 136.0, 159.4, 172.7, 182.6. MS-FAB: *m/z* (%) = 470 (50) [M + 1], 121 (65). ESI-HRMS: *m/z* calcd for $C_{28}H_{27}N_3O_2SNa$: 492.1722 $[M + Na]^+$; found: 492.1762.

**(*S*)-1-Furan-2-ylmethyl-3-[2-(1*H*-indol-3-yl)ethyl]-5-isopropyl-2-thioxoimidazolidin-4-one (7f).**
Yield 82% (0.62 g); white solid; mp 143–144 °C; $R_f$ = 0.56 (5:1 hexane–EtOAc). IR (KBr): 3332, 1712, 1466, 1356, 1288, 1258, 1222, 1148, 1005, 747 cm$^{-1}$. $[a]_D^{25}$ –17.2 (*c* 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.84 Hz, 3 H), 1.14 (d, *J* = 7.08 Hz, 3 H), 2.34–2.41 (m, 1 H), 3.05–3.17 (m, 2 H), 3.77 (d, *J* = 3.40 Hz, 1 H), 4.09 (t, *J* = 8.32 Hz, 2 H), 4.42 (d, *J* = 15.60 Hz, 1 H), 5.67 (d, *J* = 15.60 Hz, 1 H), 6.34 (dd, *J* = 3.12, 1.96 Hz, 1 H), 6.37 (d, *J* = 3.16 Hz, 1 H), 7.07 (s, 1 H), 7.12 (dd, *J* = 7.08, 1.00 Hz, 1 H), 7.17 (dt, *J* = 7.94, 1.24 Hz, 1 H), 7.32 (d, *J* = 7.58 Hz, 1 H), 7.37 (d, *J* = 1.34 Hz, 1 H), 7.80 (d, *J* = 7.84 Hz, 1 H), 7.98 (br s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 15.6, 17.3, 23.5, 28.8, 41.1, 42.4, 65.8, 109.8, 110.6, 111.0, 112.2, 119.1, 119.4, 122.0, 122.2, 127.5, 136.1, 142.8, 148.5, 172.3, 182.7. MS-FAB: *m/z* (%) = 382 (100) [M + 1]. ESI-HRMS: *m/z* calcd for $C_{21}H_{23}N_3O_2SNa$: 404.1409 $[M + Na]^+$; found: 404.1436.

**(*S*)-2-Benzyl-3-thioxohexahydropyrrolo[1,2-*c*]imidazol-1-one (10a).**
Yield 92% (0.45 g); white solid; mp 80–81 °C; $R_f$ = 0.70 (5:1 hexane–EtOAc). IR (KBr): 3055, 2971, 2932, 1741, 1457, 1346, 1246, 1263, 1222, 1167, 962 cm$^{-1}$. $[a]_D^{25}$ –16.6 (*c* 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.55–1.63 (m, 1 H), 2.03–2.09 (m, 1 H), 2.11–2.22 (m, 2 H), 3.47 (ddd, *J* = 11.78, 8.68, 3.16 Hz, 1 H), 3.83–3.90 (m, 1 H), 4.09 (dd, *J* = 10.28, 6.84 Hz, 1 H), 4.83 (d, *J* = 14.64 Hz, 1 H), 4.93 (d, *J* = 14.64 Hz, 1 H), 7.15–7.24 (m, 3 H), 7.34–7.36 (m, 2 H). $^{13}$C NMR (100 MHz, CDCl3): δ = 26.6, 44.9, 48.2, 64.9, 127.7, 128.3, 128.5, 135.7, 173.3, 186.6. MS-FAB: *m/z* (%) = 247 (100) [M + 1]. ESI-HRMS: *m/z* calcd for $C_{13}H_{14}N_2OSNa$: 269.0724 $[M + Na]^+$; found: 269.0723.

(11) Optical rotation of **4o** $[\alpha]_D^{25}$ –46.7 (*c* 0.225, MeOH) was compared with the reported value $[\alpha]_D^{25}$ –40.5 (*c* 0.225, MeOH). See: Poupaert, J. H.; Cavalier, R.; Claesen, M. H.; Dumont, P. A. *J. Med. Chem.* **1975**, *18*, 1268.

(12) The optical purity was determined by chiral HPLC [Chiralcel OD column, hexane–2-PrOH, 9:1]; ee (%): **4a**, 64; **4f**, 58; **4g**, 95; **7c**, 58; **7f**, >99; **10a**, >99.