

# Novel Method for the Synthesis of Substituted Imidazothiazolones

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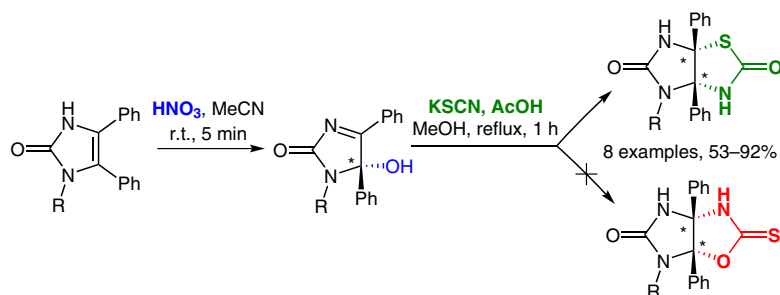
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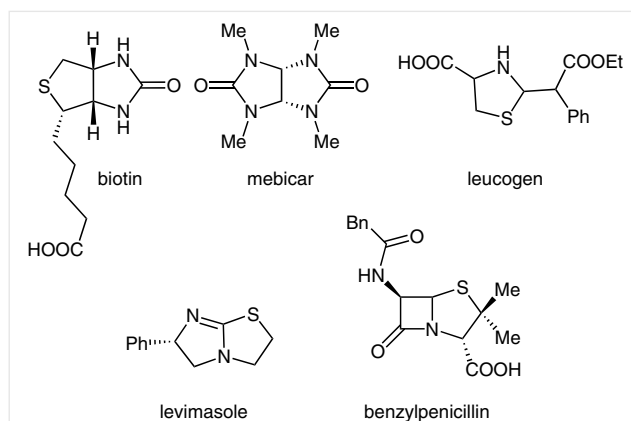
**Abstract** A general and highly selective method for the synthesis of 4-substituted 3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d][1,3]thiazole-2,5(3H)-diones has been developed through a new reaction of 1-substituted 5-hydroxy-4,5-diphenyl-1H-imidazol-2(5H)-ones with potassium thiocyanate in the presence of acetic acid in acetonitrile. Details of supramolecular organization in the crystalline imidazothiazolones, as revealed by X-ray diffraction, are highlighted.

**Key words** cyclocondensations, potassium thiocyanate, heterocycles, polycycles, imidazolones, imidazothiazoles

Imidazolidin-2-one and thiazole moieties are present in several heterocyclic molecules that exhibit various biological and pharmacological activities (Figure 1). For instance, biotin is found in all eukaryotic cells, where it acts as a co-factor for carboxylase enzymes such as acetyl-coenzyme A (CoA) carboxylase, pyruvate carboxylases, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylases.<sup>1</sup>

Mebicar {1,3,4,6-tetramethyltetrahydroimidazo[4,5-d]imidazole-2,5(1H,3H)-dione} is used as a tranquilizer.<sup>2</sup> Leucogen is used to vaccinate cats against feline leukemia virus.<sup>3</sup> Levimasole, an antihelminthic drug, is used as an immunomodulator in rheumatoid arthritis and as an adjuvant therapy in the treatment of colorectal cancer and head-and-neck cancer.<sup>4</sup> Penicillin and other penicillin-like  $\beta$ -lactams are among the most important antibiotics for both humans and animals.<sup>5</sup>

Therefore, the synthesis of heterocycles containing these two moieties in the same molecule is of both synthetic and practical interest. However, only few examples of

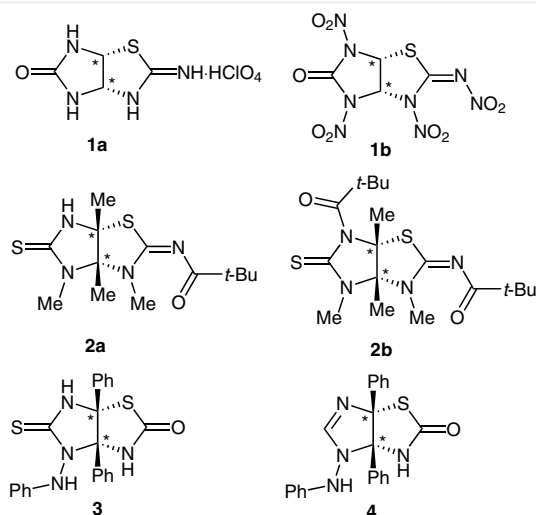


**Figure 1** Representative examples of drugs containing imidazolidin-2-one or thiazole moieties

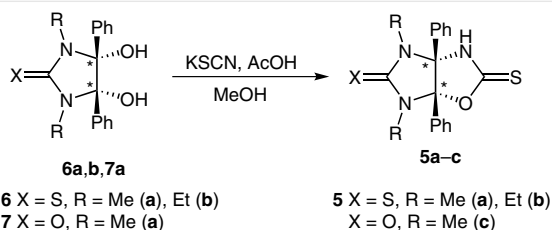
substituted 2H-imidazo[4,5-d]thiazoles **1–4** (Figure 2) have been reported,<sup>6</sup> as no general approach to their synthesis has been developed.

Here, we propose a novel highly selective method for the synthesis of 4-substituted 3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d][1,3]thiazole-2,5(3H)-dione (imidazothiazolones) through condensation of 1-substituted 5-hydroxy-4,5-diphenyl-1,5-dihydro-2H-imidazol-2-ones (imidazolones) with potassium thiocyanate in the presence of acetic acid in methanol.

Our motivation for choosing these reactions arose from our recent synthesis of imidazoxazoles **5a–c** by simple reactions of (4S\*,5R\*)-1,3-dialkyl-4,5-dihydroxy-4,5-diphenylimidazolidin-2-(thi)ones (**6a,b** and **7a**) with potassium thiocyanate and acetic acid (Scheme 1).<sup>7</sup> The mechanism of the formation of compounds **5a–c** was reported in our previous communication.<sup>7</sup>



**Figure 2** Some heterocycles containing the imidazolidine and thiazole moieties



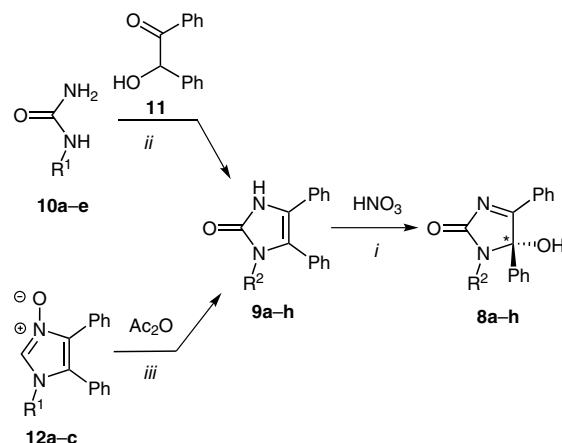
**Scheme 1** Synthesis of the known imidazoxazole derivatives **5a–c**. Reagents and conditions: KSCN, AcOH, MeOH, reflux, 1 h.

Imidazolones **8a–h** were prepared from the corresponding imidazolinones **9a–h** in 72–90% yield by treatment with nitric acid in acetonitrile (Table 1). Note that the melting points and NMR spectra of compounds **8a** and **8e** are markedly different from those reported earlier by Mobinikhaledi and Amiri.<sup>8</sup> The structure and homogeneity of the compound **8a** were confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, elemental analysis, and X-ray diffraction (Figure 3). We can therefore confirm that compounds other than **8a** and **8e** were obtained by Mobinikhaledi and Amiri.<sup>8</sup>

Imidazolinones **9a–e** were prepared by using a simple approach, starting from ureas **10a–e** and benzoin (2-hydroxy-1,2-diphenylethanone; **11**) (Table 1, entries 1–5).<sup>9</sup> Compounds **9f–h** were prepared from the corresponding imidazole oxides **12a–c** (entries 6–8).<sup>10</sup>

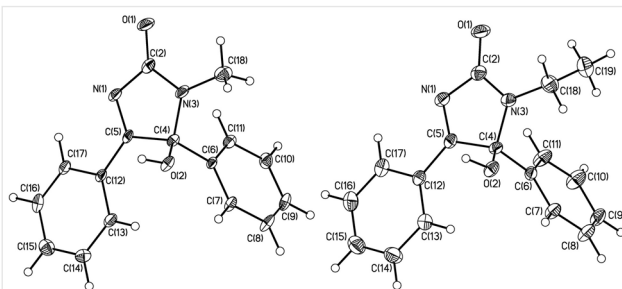
5-Hydroxy-1-methyl-4,5-diphenyl-1,5-dihydro-2H-imidazol-2-one (**8a**) was used as a model compound to develop a procedure for the synthesis of imidazothiazole **13a**. Under the conditions used for the formation of imidazoxazoles **5a–c**,<sup>7</sup> condensation of potassium thiocyanate with imidazolone **8a** in the presence of acetic acid gave the imidazothiazole **13a** in 35% yield (Table 2, entry 1). Methyl

**Table 1** Synthesis of 1-Substituted Imidazolones **8a–h**<sup>a</sup>



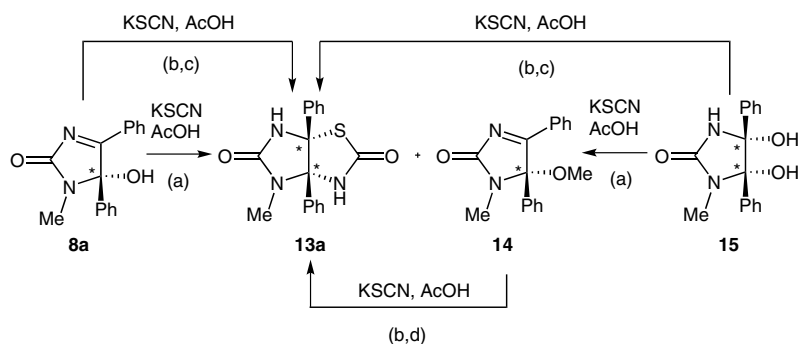
Entry	R <sup>1</sup> (compound <b>10</b> or <b>12</b> )	R <sup>2</sup> (compound <b>8</b> or <b>9</b> )	Yield (%) of <b>8</b>
1	Me ( <b>10a</b> )	Me ( <b>8a, 9a</b> )	88
2	Et ( <b>10b</b> )	Et ( <b>8b, 9b</b> )	81
3	Pr ( <b>10c</b> )	Pr ( <b>8c, 9c</b> )	83
4	Bu ( <b>10d</b> )	Bu ( <b>8d, 9d</b> )	80
5	Bn ( <b>10e</b> )	Bn ( <b>8e, 9e</b> )	90
6	(CH <sub>2</sub> ) <sub>2</sub> OH ( <b>12a</b> )	(CH <sub>2</sub> ) <sub>2</sub> OAc ( <b>8f, 9f</b> )	87
7	(CH <sub>2</sub> ) <sub>3</sub> OH ( <b>12b</b> )	(CH <sub>2</sub> ) <sub>3</sub> OAc ( <b>8g, 9g</b> )	72
8	(CH <sub>2</sub> ) <sub>4</sub> OH ( <b>12c</b> )	(CH <sub>2</sub> ) <sub>4</sub> OAc ( <b>8h, 9h</b> )	90

<sup>a</sup> Reaction conditions: (i) HNO<sub>3</sub>, MeCN, r.t., 5 min; (ii) **11**, ethylene glycol, 165 °C, 1 h; (iii) Ac<sub>2</sub>O, CHCl<sub>3</sub>, r.t., 24 h.



**Figure 3** General view of compounds **8a** (left) and **8b** (right); nonhydrogen atoms are shown as thermal ellipsoids at the 50% probability level

ether **14**<sup>11</sup> proved to be the second and major product of this reaction (entry 1); complete conversion of imidazolone **8a** into imidazothiazole **13a** occurred only after five hours (entry 2). An attempt to synthesize imidazothiazole **13a** from 4,5-dihydroxy-1-methyl-4,5-diphenylimidazolidin-2-one (**15**)<sup>11</sup> and potassium thiocyanate under the same conditions (AcOH, MeOH, reflux, 1 h) resulted in the formation of imidazothiazole **13a** and methyl ether **14** in 15% and 80% yields, respectively (entry 3). However, conversion of the compound **15** into imidazothiazole **13a** was complete after

**Table 2** Optimization of Reaction Conditions for the Synthesis of Imidazothiazole **13a**

Entry	Reactant	Conditions	Yield (%) of <b>13a</b>
1	<b>8a</b>	(a) MeOH, reflux, 1 h	35 <sup>a</sup>
2	<b>8a</b>	(b) MeOH, reflux, 5 h	85
3	<b>15</b>	(a) MeOH, reflux, 1 h	15 <sup>b</sup>
4	<b>15</b>	(b) MeOH, reflux, 5 h	87
5	<b>14</b>	(b) MeOH, reflux, 5 h	89
6	<b>8a</b>	(c) MeCN, reflux, 1 h	92
7	<b>15</b>	(c) MeCN, reflux, 1 h	92
8	<b>14</b>	(d) MeCN, reflux, 2 h	90

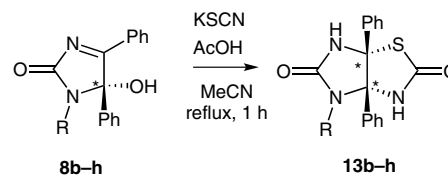
<sup>a</sup> A 60% yield of **14** was also obtained.<sup>b</sup> An 80% yield of **14** was also obtained.

five hours (entry 4); this can be explained by the initial formation of methyl ether **14** as a first stage in the reaction of imidazolone **8a** or imidazolidinone **15** with potassium thiocyanate in the presence of acetic acid in methanol; ether **14** then reacts with further potassium thiocyanate in the presence of acetic acid to give imidazothiazole **13a**. This hypothesis was confirmed by preparing imidazothiazole **13a** in 89% yield by condensation of methyl ether **14** with potassium thiocyanate in the presence of acetic acid under the same conditions (entry 5).

To optimize the procedure for the synthesis of imidazothiazole **13a**, acetonitrile was chosen as a solvent instead of methanol. The duration of the reactions of the compounds **8a** and **15** with potassium thiocyanate in the presence of acetic acid was reduced from five hours to one hour, and the yield of imidazothiazole **13a** increased from 85–87% to 92% (Table 2; compare entries 2 and 4 with entries 6 and 7). The reactivity of methyl ether **14** under similar conditions was lower; the reactions of the compound **14** in acetonitrile took two hours (entry 8). Our experiments showed that the similar results were obtained using the imidazolone **8a** and dihydroxyimidazolidinone **15**.

With the optimized conditions in hand, we examined reactions of various imidazolones **8b–h** with potassium thiocyanate in the presence of acetic acid in acetonitrile (Table 3, entries 1–7).<sup>12</sup> A detailed investigation of these condensations confirmed that we have developed a new

and highly selective method for the preparation of previously inaccessible imidazothiazoles **13b–h** in 53–88% yields.

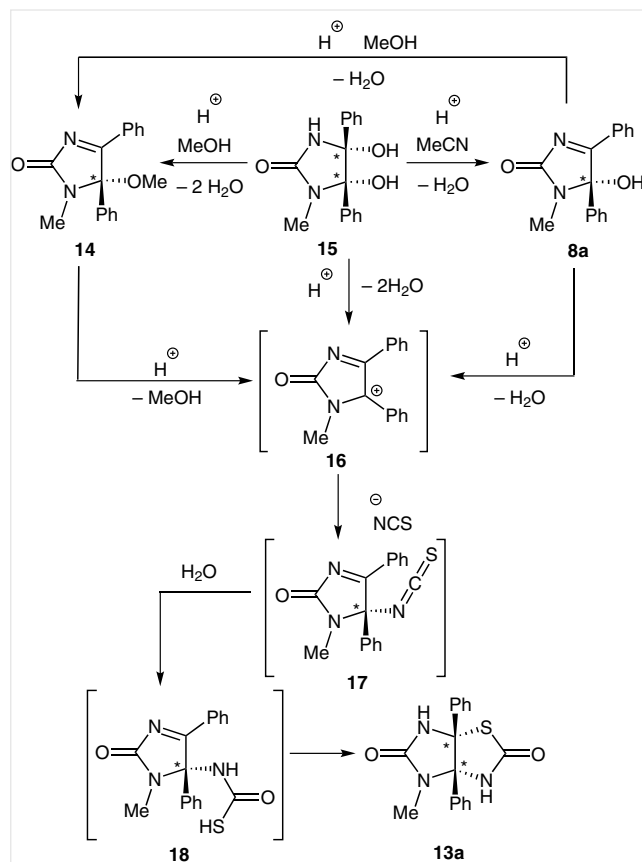
**Table 3** Synthesis of Imidazothiazoles **13b–h**<sup>a</sup>

Entry	R	Yield (%)
1	Et	74
2	Pr	88
3	Bu	80
4	Bn	85
5	(CH <sub>2</sub> ) <sub>2</sub> OAc	53
6	(CH <sub>2</sub> ) <sub>3</sub> OAc	57
7	(CH <sub>2</sub> ) <sub>4</sub> OAc	79

<sup>a</sup> Reagents and conditions: MeCN, reflux, 1 h.

We propose the following mechanism for the formation of imidazothiazole **13a** (Scheme 2). The first step in the reaction of imidazolone **8a**, **14**, or **15** with potassium thiocya-

nate in the presence of acetic acid is the formation of a cation **16**, which reacts with a thiocyanate anion as an N-nucleophile to give adduct **17**. Hydrolysis of the isothiocyanate fragment gives adduct **18**, which undergoes intramolecular cyclization to form imidazothiazole **13a**. Dehydration of the compound **15** might proceed directly, with the formation of the cation **16**, or via the intermediate **8a** or **14**, depending on the nature of the solvent.

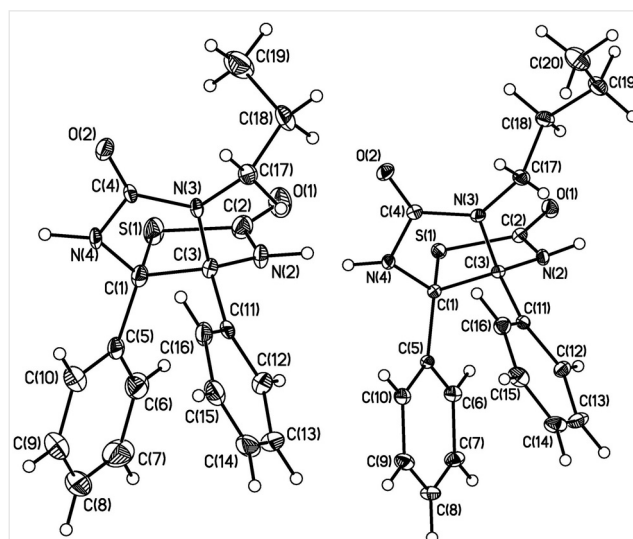


**Scheme 2** Proposed mechanisms for the formation of imidazothiazole **13a**

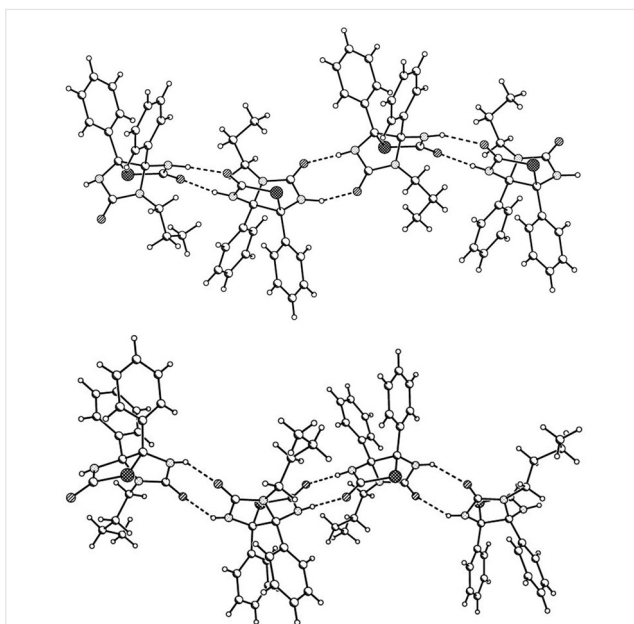
The structures of imidazolones **8a–h** and imidazothiazoles **13a–h** were confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, and by X-ray diffraction studies on compounds **8a,b** and **13c,d** (Figures 3 and 4). The X-ray diffraction results (CCDC 1011396–1011397 and 1011495–1011496; Table S1; see Supporting Information) showed that compounds **8a** and **8b** (Figure 3) are isostructural and that they crystallize in a noncentrosymmetric space group ( $P-42_1c$ ); their molecular geometries and supramolecular patterns are very similar. In both cases, the imidazolone ring is planar within 0.01 Å. The angle between its mean plane and that of the phenyl substituent at the atom C(5) is 9.4(1)–11.9(1)°, and the torsion angle C(6)C(4)C(5)C(12) characterizing the mutual disposition of the two phenyl substituents is 63.4(3)–68.70(18)°. In the crystals, the imidazolone mol-

ecules are assembled with O–H...O hydrogen bonds [O...O 2.6706(16)–2.701(2) Å, OHO 164(1)–175(1)°] to form hydrogen-bonded tetramers around the  $-4$  axis.

The homogeneity of the compound **8a** was confirmed by powder X-ray diffraction (Table S1 and Figure S1, see Supporting Information). The structures of the imidazothiazoles **13a–h** were confirmed by X-ray diffraction studies on compounds **13c** and **13d** (Figure 4), which have similar molecular geometries and supramolecular organizations in their crystals. In both cases, the thiazole and imidazole moieties have an envelope conformation in which the deviation of atoms C(3) and C(1) is 0.35(1)–0.39(1) Å. The angle between the mean planes of the heterocycles and the torsion angle C(5)C(1)C(3)C(11) characterizing the mutual disposition of the phenyl substituents are within the narrow ranges 107.2(1)–109.7(1)° and 23.02(19)–30.27(19)°, respectively. Note that the imidazothiazole **13c** crystallizes with four independent molecules in an asymmetric part of the unit cell. If these molecules are overlapped, the heterocyclic moieties coincide nicely, but the alkyl chains do not; the relevant pseudo-torsion angle C(3)N(3)C(18)C(19) for one of these is 41.22(1)° versus 60.65(1)–61.68(1)° for the others. In crystals of **13c** and **13d**, similar hydrogen-bonded chains are formed through N–H...O hydrogen bonds [N...O 2.766(2)–3.009(2) Å, NHO 148(1)–178(1)°]; the corresponding features in **13c** involve all four of its independent molecules. In these chains (Figure 5), the imidazothiazole molecules are either related by an inversion center (**13d**) or arranged in a 'head-to-tail' mode (**13c**); in the latter case, the symmetry-equivalent species from the neighboring chains form dimers through weak C–H...O contacts, resulting in centrosymmetric crystal structures (space group  $P-1$ ).



**Figure 4** General view of compounds **13c** (left) and **13d** (right); non-hydrogen atoms are shown as thermal ellipsoids at the 50% probability level



**Figure 5** Hydrogen-bonded chains in crystals of **13c** (top) and **13d** (bottom)

In summary, we have developed a general method for the synthesis of 1-substituted 5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones through the reaction of 1-substituted 5-hydroxy-1*H*-imidazol-2(5*H*)-ones with potassium thiocyanate in the presence of acetic acid. The desired compounds were obtained in good to excellent yields from easily available starting materials. Further investigations on extending this approach to other imidazoline derivatives, as well as studies on their pharmacological applications, are currently in progress.

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## Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1560657>.

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- (12) **1-Substituted 5-Hydroxy-4,5-diphenyl-1,5-dihydro-2*H*-imidazol-2-ones 8a–h; General Procedure**  
63% aq HNO<sub>3</sub> (5 mL) was added dropwise to a suspension of the appropriate imidazolone **9a–h** (4 mmol) in MeCN (25 mL). The reaction was monitored by the dissolution of the precipitated **9a–h** and by the change in color of the solution. The mixture was then extracted with 1:1 CHCl<sub>3</sub>/H<sub>2</sub>O, the CHCl<sub>3</sub> layer was evaporated, and the product was washed with Et<sub>2</sub>O.  
**5-Hydroxy-1-methyl-4,5-diphenyl-1,5-dihydro-2*H*-imidazol-2-one (8a)**  
White powder; yield: 0.94 g (88%); mp 222–224 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 2.55 (s, 3 H, Me), 7.25–7.48 (m, 7 H, Ph), 7.52–7.56 (m, 1 H, Ph), 7.75 (s, 1 H, OH), 8.01–8.04 (m, 2 H, Ph). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 23.82 (Me), 92.61 [C(Ph)OH], 125.18, 128.75, 128.83, 129.05, 129.60, 133.35, 136.61 (Ph), 163.44 (C=O), 186.39 (C=N). MS: *m/z* (%) = 266 (6) [M<sup>+</sup>], 250 (61), 180 (13), 163 (56), 135 (53), 134 (56), 118 (100). Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.07; H, 5.34; N 10.47.  
**1-Ethyl-5-hydroxy-4,5-diphenyl-1,5-dihydro-2*H*-imidazol-2-one (8b)**  
White powder; yield: 0.91 g (81%); mp 214–216 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 0.88 (t, *J* = 7.1 Hz, 3 H, Me), 2.87–3.04 (m, 1 H, CH<sub>2</sub>), 3.13–3.30 (m, 1 H, CH<sub>2</sub>), 7.25–7.50 (m, 7 H, Ph), 7.53–7.57 (m, 1 H, Ph), 7.73 (s, 1 H, OH), 7.99–8.02 (m, 2 H, Ph). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ = 13.79 (Me), 33.58 (CH<sub>2</sub>), 92.81 [C(Ph)OH], 125.20, 128.75, 128.82, 128.97, 129.65, 133.32, 137.32 (Ph), 163.38 (C=O), 186.07 (C=N). MS: *m/z* (%) = 280 (13) [M<sup>+</sup>], 252 (3), 208 (4), 177 (50), 165 (8), 148 (75), 134 (35), 105 (75), 91 (7), 77 (100). Anal. Calcd for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.79; H, 5.78; N, 10.06.  
**4-Substituted 3a,6a-Diphenyltetrahydro-2*H*-imidazo[4,5-*d*][1,3]thiazole-2,5(3*H*)-diones 13a–h; General Procedure**  
AcOH (3.00 mL) was added to a solution of the appropriate imidazolone **8a–h** (4 mmol) and KSCN (0.44 g, 4.5 mmol) in MeCN (17 mL) at r.t., and the mixture was refluxed for 1 h. The

mixture was allowed to cool to r.t. and kept for 24 h to give a precipitate.

**(3aR\*,6aR\*)-4-Methyl-3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d][1,3]thiazole-2,5(3H)-dione (13a)**

White powder; yield: 1.20 g (92%); mp >300 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 2.64 (s, 3 H, Me), 6.85–6.98 (m, 2 H, Ph), 7.01–7.17 (m, 6 H, Ph), 7.18–7.28 (m, 2 H, Ph), 8.35 [s, 1 H, NH(NCO)], 9.72 [s, 1 H, NH(SCO)]. <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 25.73 (Me), 83.19, 87.52 [(Ph)–C–C–(Ph)], 126.93, 127.49, 127.57, 128.07, 128.18, 128.71 (Ph), 132.92, 137.51 [C(Ph)], 158.38 [(N)C=O], 171.91 [(S)C=O]. HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>S: 326.0958; found: 326.0958.

**(3aR\*,6aR\*)-4-Ethyl-3a,6a-diphenyltetrahydro-2H-imidazo[4,5-d][1,3]thiazole-2,5(3H)-dione (13b)**

White powder; yield: 1.22 g (74%); mp 235–237 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 1.12 (t, *J* = 7.0 Hz, 3 H, Me), 2.71–2.91 (m, 1 H, CH<sub>2</sub>), 3.31–3.50 (m, 1 H, CH<sub>2</sub>), 6.90–7.01 (m, 2 H, Ph), 7.02–7.19 (m, 6 H, Ph), 7.20–7.31 (m, 2 H, Ph), 8.20 [s, 1 H, NH(NCO)], 9.65 [s, 1 H, NH(SCO)]. <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 14.80 (Me), 35.15 (CH<sub>2</sub>), 83.81, 87.80 [(Ph)–C–C–(Ph)], 126.95, 127.47, 127.51, 127.84, 128.14, 128.65 (Ph), 133.87, 137.49 [C(Ph)], 158.42 [(N)C=O], 172.27 [(S)C=O]. HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub>S: 340.1114; found: 340.1110.