Facile Conversion of Amino Acids into 1-Alkyl Imidazole-2-thiones, and Their Oxidative Desulfurization to Imidazoles with Benzoyl Peroxide

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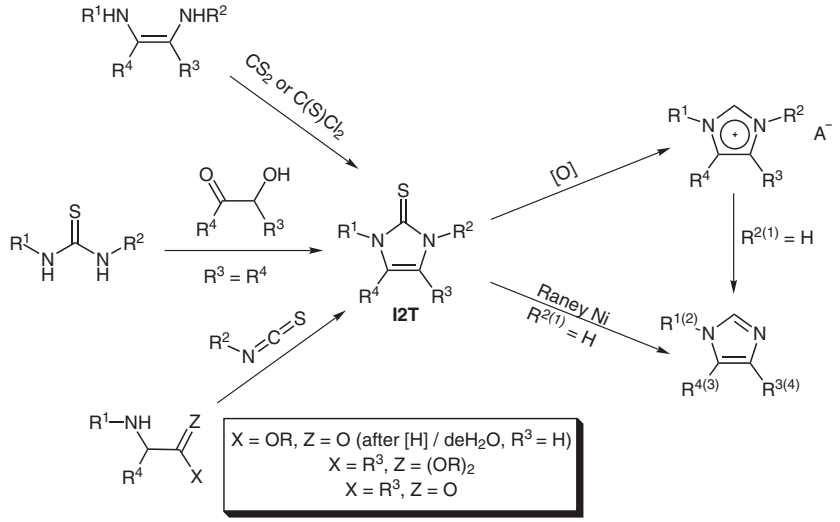
Abstract: Glycine was acylated with isothiocyanates and condensed to 3-alkyl 2-thiohydantoins, which were reduced with a mixture of sodium borohydride and lithium chloride and dehydrated to 1-alkyl imidazole-2-thiones. These were oxidatively desulfurized to imidazoles with benzoyl peroxide. No chromatography was required for model compounds. The methods developed were used to elaborate tyrosine to 1,4-di(*p*-methoxybenzyl)imidazole, a common intermediate in the syntheses of three imidazoles from the sponge *Leucetta*.

Key words: desulfurization, heterocycles, imidazoles, natural products, oxidation

Imidazole-2-thiones (**I2T**s, Scheme 1)[1,2] undergo oxidative desulfurization with acidic hydrogen peroxide,[3–8] MCPBA,[9] dimethyldioxirane,[10] iron(III) chloride,[11] and nitric acid.[12–14] Oxidation of 1,3-dialkyl **I2T**s by these methods delivers 1,3-dialkylimidazolium salts, whereas 1-alkyl **I2T**s yield neutral imidazoles after work-up. Reductive desulfurization of 1-alkyl **I2T**s to neutral imidazoles is typically accomplished with Raney nickel.[3,15]

The **I2T** reagent is classically prepared by acylation of an α-amino ketone or a 2-amino acetal with a thiocyanate, followed by cyclization of the intermediate.[3,4,16–18] This entry to an **I2T** and oxidative desulfurization of it (with nitric acid) dates back at least to Marckwald's 1892 report.[19] Alternative **I2T** syntheses include condensation of thioureas with α-hydroxycarbonyls,[20] and metal hydride reduction of an α-thioureido ester[21] or a 2-thiohydantoin (**2TH**)[22] followed by dehydration of the intermediate.

The classical preparation of 2-thiohydantoins (**2TH**s) is identical in concept to that of **I2T**s; acylation of an α-amino ester or acid with a thiocyanate is followed by cyclization of the intermediate.[22–28] This reaction also traces back at least as far as Marckwald and co-workers.[29] More recently it became famous as the basis of the Edman degradation, wherein the unmasked N-terminus of a peptide is acylated with a thiocyanate; cyclization at the resultant α-thioureido amide terminus expels a **2TH** and a peptide shortened by one amino acid residue.[30] Recent examples of alternative **2TH** syntheses include the reaction of α-isothiocyanato esters with amines followed by cycliza-



Scheme 1 Major routes to and from **I2T**s

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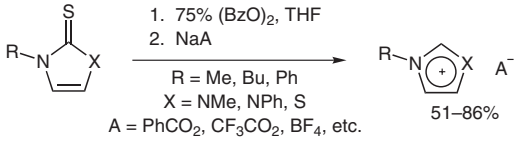
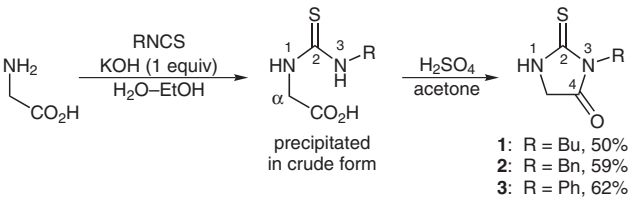
tion,[28,31,32] condensation of thioureas with 1,2-diones attended by alkyl group transfer under microwave irradiation,[28] and thionation of α-amino amides.[33]

We recently described[34] one-pot air- and water-insensitive syntheses of two 1,3-dialkyl **I2T**s from amino esters (Scheme 2, path A) alongside syntheses through **2TH**s, which were accessed in three cases by the thermal cyclization of intermediate α-thioureido esters (path B, X = alkyl), and in one case by the acid-catalyzed cyclization of an α-thioureido acid (path B, X = H).[22,23] We also utilized Markwalder and co-workers' DIBAL-H reduction of α-thioureido esters[21] in a one-pot reaction from ethyl *N*-butylglycinate (path C). The 1,3-dialkyl **I2T**s thus prepared, along with certain 3-alkyl thiazole-2-thiones, were oxidatively desulfurized to the corresponding salts with benzoyl peroxide (Equation 1),[34] and we expected the reaction could be applied to the synthesis of neutral imidazoles from 1-alkyl **I2T**s. Intriguingly, this sequence (amino ester or acid → **2TH** → **I2T** → imidazole) is apparently not well known (if at all) even though the newest elementary step is almost 40 years old.



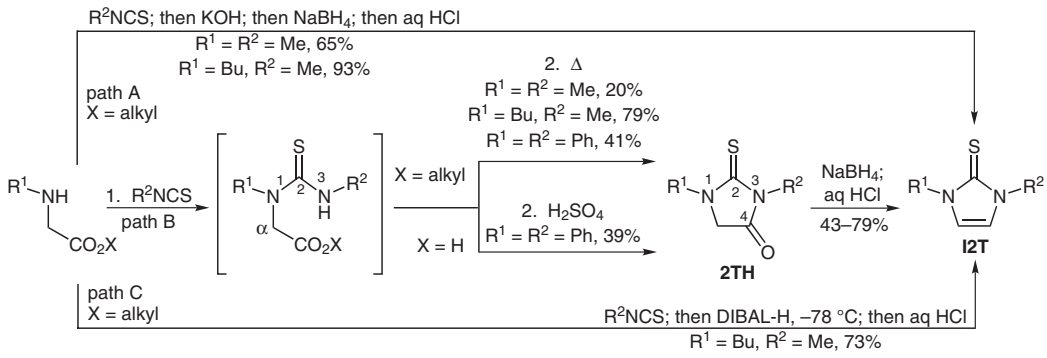
Equation 1 Syntheses of azolium salts from azole-2-thiones, including **I2T**s prepared according to Scheme 2[34]

All the 1,3-dialkyl **I2T** syntheses in Scheme 2 seemed reasonable for preparation of the 1-alkyl **I2T**s necessary for neutral imidazole syntheses, but, in practice, only one was suitable. Intermediate α-thioureido esters prepared by the acylation of ethyl glycinate with isothiocyanates could not be converted into **2TH**s under the influence of heat or sodium ethoxide (i.e., Scheme 2, paths A and B, R^1 = H, X = Et) or sulfuric acid (which we did not previously evaluate for the cyclization of α-thioureido esters). Note that the α-thioureido esters we had previously converted into **2TH**s were the 1,3-dialkyl varieties, whereas those that did not carry through were 3-alkyl. We also failed to recover **I2T** products when the crude α-thioureido esters from the reactions of ethyl glycinate and isothiocyanates were freed of protic impurities by a standard work-up and dried under vacuum overnight, then treated with DIBAL-H followed by acid (i.e., Scheme 2, path C, R^1 = H, X = Et).[21] The **2TH**s were only secured by acylating free glycinate with isothiocyanates and cyclizing the intermediate α-thioureido acids with sulfuric acid (Scheme 3).[22,23] The reactions proceeded in moderate yields because of competitive S-acylation,[35,36] but the method was suitable for a multigram preparation, and chromatography was not necessary. Isolation of **2TH**s **1**–**3** required only removal of acetone, inundation with aqueous sodium bicarbonate, and filtration; we presume the expected 2-thioamidine by-products were removed with the mother liquor.



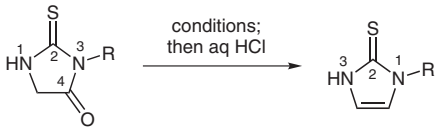
Scheme 3 Synthesis of 3-alkyl **I2T**s (yields are from glycine)

The conditions used to reduce and dehydrate 1,3-dialkyl **2TH**s were not applicable to the conversion of 3-alkyl **2TH**s **1**–**3** to 1-alkyl **I2T**s **4**–**6** (Table 1). Simple combination of **2** with 1.1 equivalents sodium borohydride in ethanol or glyme–ethanol (3:1) at room temperature gave an incomplete reaction, and the reagent was still not consumed when 2.2 equivalents of sodium borohydride were used. In TLC analyses of acidified reaction aliquots, the reagent and product spots were joined by a third spot less mobile than either of the others. If the reactions were left long enough at room temperature, both reagent and desired product were undetectable by TLC and only the least mobile of the three compounds remained. When this product was isolated, it could not be adequately characterized. However, its TLC characteristics are consistent with a 2-thioureido alcohol, the by-product we would expect from ring-chain tautomerism and overreduction as discussed by Scott and Henderson, who also reduced **2TH**s with borohydrides.[22] This overreduction was still observed at 0 °C, but suppressed at –15 to –5 °C. Application of lithium chloride[22,37,38] at this temperature forced the reaction to



Scheme 2 Syntheses of 1,3-dialkyl **I2T**s on the way to 1,3-dialkylimidazolium salts[34]

Table 1 Optimization of the Syntheses of **4–6**



1: R = Bu
2: R = Bn
3: R = Ph

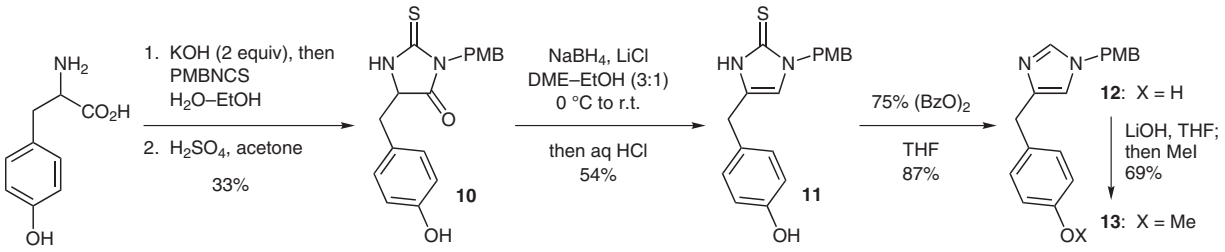
4: R = Bu
5: R = Bn
6: R = Ph

	Conditions					
R	$NaBH_4$ (equiv)	LiCl (equiv)	Solvent	Temp (°C)	Time (h)	Result[a]
Bn	1.1	0	EtOH or 3:1 DME–EtOH	r.t.	16	DNC; OR starts
Bn	2.2	0	EtOH or 3:1 DME–EtOH	r.t.	16	DNC; OR starts
Bn	2.2	0	EtOH or 3:1 DME–EtOH	0	16	DNC; OR starts
Bn	2.2	0	EtOH or 3:1 DME–EtOH	–15 to –5	16	DNC; no OR
Bn	2.2	0	EtOH or 3:1 DME–EtOH	–20 to –30	16	NR
Bn	1.1	1.1	3:1 DME–EtOH	r.t.	6	C; OR starts
Bn	1.1	1.1	3:1 DME–EtOH	0	8	DNC; no OR
Bn	2.2	2.2	3:1 DME–EtOH	0	6	C; OR starts
Bn	2.2	2.2	3:1 DME–EtOH	–15 to –5	6	C; no OR; 97%
Bu	2.2	2.2	3:1 DME–EtOH	–15 to –5	6	C; no OR; 88%
Ph	2.2	2.2	3:1 DME–EtOH	–25 to –15	6	C; no OR; 71%
Bu, Bn, or Ph	1.1	0	pyridine	r.t.	24	NR
Bu, Bn, or Ph	1.1	1.1	pyridine	r.t.	24	NR
Bu, Bn, or Ph	2.2	2.2	pyridine	r.t.	24	NR

[a] Abbreviations: DNC = does not complete; OR = overreduction; NR = no reaction; C = completes.

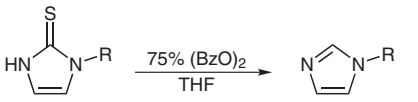
completion. Refinement of these conditions is reported in Table 1 for **2** only, but **1** gave identical results and **3** differed only by reducing and overreducing at lower temperatures. The **2TH**s were not freely soluble in glyme–ethanol (3:1), but disappeared over the course of the reaction. They were only appreciably soluble in pyridine. Since molecular borane, liberated during the desired reaction, could be contributing to overreduction, and because pyridine can scavenge borane,[39] we expected that a reaction in pyridine would be ideal. However, no reaction occurred, even with excess sodium borohydride and lithium chloride at room temperature. Presumably, the **2TH**s were chelated to or deprotonated by pyridine at N(1), and additional electron density at C(4) stifled the reduction.[22]

Desulfurization of the **I2T**s with benzoyl peroxide was straightforward and imidazoles **7–9** were obtained after simple work-up (Equation 2). To show the utility of this route, we prepared compound **13**, which was previously prepared by Ohta and co-workers in five synthetic steps and elaborated to three imidazole alkaloids (isonaamine A, and isonaamidines A and C) from the sponge *Leucetta*.[40] They commenced with lithiation of 1-SEM-2-phenylthioimidazole, which is made from imidazole in two synthetic steps, both of which require strictly anhydrous conditions.[41,42] We prepared *p*-methoxybenzyl isothiocyanate from *p*-methoxybenzylamine and thiophosgene on a large scale, based on the method of Threadgill and co-workers,[43] and added it to preformed tyrosine dianion (Scheme 4). Cyclization in sulfuric acid and acetone proceeded in low yield, but no chromatography was necessary and the reaction was amenable to the preparation of several grams of **10**. Compound **10** was less sensitive to the conditions of reduction than the model **2TH**s. Indeed, compound **10** was so sturdy that it was not entirely consumed after several days at room temperature with occasional replenishment of lithium and borohydride salts. Thus, the reduction of **10** was accomplished in moderate yield and chromatographic purification was necessary. The feature reaction proceeded smoothly and in high yield; like the model imidazoles, isolation of **12** required only a simple work-up. Starting from tyrosine required a methylation to deliver **13**. We decided not to acylate *O*-methyltyrosine and to complete the synthesis of **13** in four steps instead of five, because the commercial derivative is roughly 100 times as expensive as the parent compound.



Scheme 4 Synthesis of **13**

In deferring methylation, however, we concluded the synthesis of **13** in 69% yield after a chromatographic purification. It is noteworthy that Ohta and co-workers demethylated both aryl methyl ethers of **13** for their syntheses of isonaamine A and isonaamidine A.[40] Thus, a demethylation of **12** at the PMB ether would be an alternative formal synthesis of two of the three *Leucetta* imidazoles. However, our goal was to demonstrate the amino acid → **2TH** → **I2T** → imidazole sequence; as far as we can ascertain, these entries to **7**–**9** and **13** constitute the first examples.



4: R = Bu
5: R = Bn
6: R = Ph

7: R = Bu, 81%
8: R = Bn, 56%
9: R = Ph, 82%

Equation 2 Oxidative desulfurization of 1-alkyl **I2T**s to neutral imidazoles with benzoyl peroxide

This route relies on adapted precedents to deliver 3-alkyl **2TH**s and 1-alkyl **I2T**s.[22,23] The oxidative desulfurizations of 1-alkyl **I2T**s to imidazoles with benzoyl peroxide are new to this report. The syntheses presented highlight the operational simplicity of the net conversion because scrupulously dry glassware, reagents, or solvents were not required at any point, and chromatography following reactions characteristic of the sequence was only required following the incomplete reduction of **10** to **11**.

All reagents were used as received from commercial sources. Melting points were recorded on a MelTemp apparatus and are uncorrected. NMR spectra were recorded on a Varian Mercury 400 spectrometer with TMS as internal standard. Mass spectra were collected on a Hewlett-Packard 5970 (EI). IR spectra were taken in ATR mode on a BioRad Excalibur Series FTS 4000 fitted with a Specac Golden Gate Diamond accessory. High-resolution mass spectra were taken on a Bruker Daltonics 4.7T FTMS (EI).

2-Thiohydantoins 1–3; General Procedure

Based on the procedure of Johnson and Buchanan,[23] glycine (6.54 g, 87 mmol to make **1**; 5.46 g, 73 mmol to make **2**; 5.86 g, 78 mmol to make **3**) was dissolved in 1 equiv of 50% aq KOH (9.78 g, 87 mmol to make **1**; 8.16 g, 73 mmol to make **2**; 8.76 g, 78 mmol to make **3**), the soln was diluted with EtOH (1.2 mL per 1 g of 50% aq KOH), cooled to 0 °C, then treated dropwise with 1 equiv of the appropriate isothiocyanate (10.03 g, 87 mmol *n*-butyl to make **1**; 10.85 g, 73 mmol benzyl to make **2**; 10.55 g, 78 mmol phenyl to make **3**) in a volume of EtOH roughly equal to the supplied mass of 50% aq KOH. The mixture was stirred 3 h, then acidified with 1 M HCl (200 mL each). The crude α-thioureido acid was collected by suction filtration, and the filtrate was cooled to 0 °C and refiltered. The combined isolates were taken up in as little acetone as feasible (250 mL to make **1** and **2**, 300 mL to make **3**), dried ($MgSO_4$), gravity-filtered, treated with 96–98% H_2SO_4 (5 mL each), and followed to completion by TLC (eluent: Et_2O), where the α-thioureido acid appeared as a streak from the origin. When the product (R_f specified below) was the only mobile component in TLC (3 d to make **1** and **3**, 6 d to make **2**), the reaction was stripped of acetone, carefully neutralized with sat. aq $NaHCO_3$ (250 mL each), and suction-filtered.

3-Butyl-2-thiohydantoin (1)

After two crystallizations from *n*-C_7H_{16}–toluene (2:1), where **1** was harvested by simple decantation of the mother liquor, and one more crystallization from toluene followed by suction filtration, **1** (7.49 g, 50%) was recovered as colorless crystals; R_f = 0.78 (Et_2O); mp 106.5–109 °C (Lit.[28] mp 109.8–110.7 °C).

IR (ATR): 3262, 2960, 2926, 2873, 2857, 1708, 1506 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.15 (s, 1 H), 4.12 (s, 2 H), 3.64 (t, *J* = 8 Hz, 2 H), 1.52 (quint, *J* = 8 Hz, 2 H), 1.27 (sext, *J* = 8 Hz, 2 H), 0.89 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.3, 172.5, 48.2, 39.6, 29.2, 19.3, 13.4.

HRMS (EI): *m*/*z* calcd for $C_7H_{12}N_2OS$ [M^+]: 172.06703; found: 172.0666.

3-Benzyl-2-thiohydantoin (2)

Crystallization from EtOAc, which required a hot gravity filtration, afforded **2** (8.86 g, 59%) as large amber crystals; R_f = 0.78 (Et_2O); mp 176–177 °C (Lit.[26] mp 154–156 °C).

IR (ATR): 3268, 2904, 1709, 1507 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.31 (s, 1 H), 7.32 – 7.24 (m, 5 H), 4.87 (s, 2 H), 4.20 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.1, 172.5, 136.3, 128.2, 127.4, 127.1, 48.4, 43.2.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2OS$ [M^+]: 206.05138; found: 206.0509.

3-Phenyl-2-thiohydantoin (3)

Crystallization from nitromethane, which required a hot gravity filtration, afforded **3** (9.37 g, 62%) as bright yellow crystals; R_f = 0.62 (Et_2O); mp 248–252 °C (dec.) (Lit.[28] mp 258.3–259.7 °C; Lit.[44] mp 243 °C).

IR (ATR): 3140, 3000, 2953, 2913, 1758, 1516 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.40 (s, 1 H), 7.48 (t, *J* = 8 Hz, 2 H), 7.41 (t, *J* = 8 Hz, 1 H), 7.27 (d, *J* = 8 Hz, 2 H), 4.28 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.2, 172.0, 133.3, 128.7, 128.5, 128.4, 49.0.

HRMS (EI): *m*/*z* calcd for $C_9H_8N_2OS$ [M$^+$]: 192.03573; found: 192.0353.

Imidazole-2-thiones 4–6; General Procedure

A stock soln of 0.50 M LiCl/$NaBH_4$ in 3:1 DME–EtOH was prepared by vigorously stirring $NaBH_4$ (7.56 g, 200 mmol) into a fresh soln of LiCl (8.47 g, 200 mmol) in 3:1 DME–EtOH (300 mL). The soln was made up to 400 mL total with 3:1 DME–EtOH. NaCl formed as a fine precipitate[45] that was smoothly transferred in the necessary volume (128 mL, 64 mmol for **1**; 108 mL, 54 mmol for **2**; 116 mL, 58 mmol for **3**) for reduction of the appropriate **2TH** (5 g, 29 mmol **1**, 26 mmol **2**, 28 mmol **3**). The prepared soln was cooled to the temperature range specified in Table 1 before **2TH** was added in one portion. The reaction was followed by TLC analysis (eluent: Et_2O) of Et_2O extracts of acidified reaction aliquots. After 6 h, only **I2T** was visible. The reaction was quenched with concd HCl (50 mL), stirred 30 min, diluted with H_2O (50 mL), and washed with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with H_2O and brine (1 × 50 mL each), dried ($MgSO_4$), filtered, and concentrated to leave **4–6** as specified.

1-Butylimidazole-2-thione (4)

Yield: 4.35 g (97%); R_f = 0.44 (Et_2O); mp 80–81.5 °C (Lit.[17] mp 80–81 °C).

IR (ATR): 3092, 2954, 1571 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.13 (br s, 1 H), 6.74 (d, *J* = 1.6 Hz, 1 H), 6.71 (d, *J* = 1.6 Hz, 1 H), 4.01 (t, *J* = 8 Hz, 2 H), 1.76 (quint, *J* = 8 Hz, 2 H), 1.38 (sext, *J* = 8 Hz, 2 H), 0.95 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 117.7, 114.3, 46.6, 31.0, 19.6, 13.5.

MS (EI): *m*/*z* (%) = 156 (100, [M$^+$]), 127 (27, [M$^+$ – Et]), 123 (45, [M$^+$ – SH]), 114 (30, [M$^+$ – propene]), 100 (73, [M$^+$ – butene]).

HRMS (EI): *m*/*z* calcd for $C_7H_{12}N_2S$ [M$^+$]: 156.07212; found: 156.0718.

1-Benzylimidazole-2-thione (5)

Yield: 4.31 g (88%); R_f = 0.44 (Et_2O); mp 145–148 °C (Lit.[17] mp 145–146 °C).

IR (ATR): 3137, 3084, 3008, 2920, 1573 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.25 (br s, 1 H), 7.36–7.30 (br m, 5 H), 6.72 (d, *J* = 1.8 Hz, 1 H), 6.58 (d, *J* = 1.8 Hz, 1 H), 5.23 (s, 2 H) .

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 135.6, 128.8, 128.11, 128.10, 117.7, 114.7, 50.2.

MS (EI): *m*/*z* (%) = 190 (84, [M$^+$]), 157 (28, [M$^+$ – SH]), 91 (100, [Bn$^+$]).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2S$ [M$^+$]: 190.05647; found: 190.0559.

1-Phenylimidazole-2-thione (6)

Yield: 3.48 g (71%); R_f = 0.38 (Et_2O); mp 182–183 °C (Lit.[17] mp 179–180 °C; Lit.[18] mp 181 °C).

IR (ATR): 3071, 3005, 2894, 1574 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.45 (br s, 1 H), 7.59 (d, *J* = 8 Hz, 2 H), 7.50 (t, *J* = 8 Hz, 2 H), 7.42 (t, *J* = 8 Hz, 1 H), 6.86 (d, *J* = < 2 Hz, 1 H), 6.82 (d, *J* = < 2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 137.4, 129.1, 128.4, 125.9, 119.4, 115.1.

MS (EI): *m*/*z* (%) = 176 (69, [M$^+$]), 175 (100, [M$^+$ – H]), 77 (10, [Ph$^+$]).

HRMS (EI): *m*/*z* calcd for $C_9H_8N_2S$ [M$^+$]: 176.04082; found: 176.0404.

Oxidative Desulfurization of Imidazole-2-thiones to Imidazoles 7–9; General Procedure

Solid imidazole-2-thione (0.50 g, 3.2 mmol **4**, 2.6 mmol **5**, 2.8 mmol **6**) was added to a stirred slurry of 75% $(BzO)_2$ (5.17 g, 16 mmol for **4**; 4.24 g, 13 mmol for **5**; 4.58 g, 14 mmol for **6**) in THF (10 mL), which brought the reaction to spontaneous reflux. After cooling to r.t., the mixture was diluted with H_2O (20 mL) and Et_2O (20 mL). The aqueous layer was separated, and the organic layer was washed with H_2O (1 × 10 mL). The combined aqueous layers were washed with CH_2Cl_2 (3 × 10 mL), then treated with aq 6 M NaOH (2 mL), and stirred until $(BzO)_2$ was not detectable by TLC anymore (less than 1 h). The aqueous soln was washed with Et_2O (3 × 10 mL), the combined organic extracts were washed with H_2O and brine (1 × 10 mL each), dried ($MgSO_4$), filtered, and concentrated to leave **7–9** as specified below.

1-Butylimidazole (7)

Yield: 0.32 g (81%); colorless oil, which was authenticated with commercial 1-butylimidazole by ^{1}H and ^{13}C NMR spectra, and TLC (R_f = 0.10, Et_2O).

1-Benzylimidazole (8)

Yield: 0.23 g (56%); colorless crystals; mp 69.5–72 °C, which were authenticated with commercial 1-benzylimidazole (mp 68–70 °C) by mp, mixed mp, ^{1}H and ^{13}C NMR spectra, and TLC (R_f = 0.10, Et_2O).

1-Phenylimidazole (9)

Yield: 0.33 g (82%); colorless oil, which was authenticated with commercial 1-phenylimidazole by ^{1}H and ^{13}C NMR spectra, and TLC (R_f = 0.25, Et_2O).

3-(*p*-Methoxybenzyl)-5-(*p*-hydroxybenzyl)-2-thiohydantoin (10)

A mixture of tyrosine (8.14 g, 45 mmol) and 50% aq KOH (10.08 g, 90 mmol) was diluted with H_2O to a total volume of 50 mL and thoroughly dissolved before the addition of EtOH (150 mL). The soln was cooled to 0 °C, then treated dropwise with PMBNCS (8.05 g, 45 mmol, prepared based on a report from Threadgill and coworkers[43]) in EtOH (10 mL), stirred 3 h, treated with 1 M HCl (400 mL), stirred 1 h, and frozen at –30 °C overnight. The mixture was then allowed to reach r.t. again, and an aqueous layer separated from an orange solid. The aqueous layer was decanted and the orange solid was concentrated twice from acetone (200 mL each), redissolved in acetone (300 mL), dried ($MgSO_4$), filtered, and treated with 96–98% H_2SO_4 (10 mL). The cyclization required 3 d, whereupon acetone was removed in vacuo, the residue was treated with sat. aq $NaHCO_3$ (500 mL), and the mixture was washed with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with H_2O and brine (1 × 50 mL each), dried ($MgSO_4$), filtered, and evaporated to leave a dark-brown oil (19.98 g), which released crude **10** as yellow crystals upon standing. The dark supernatant was removed by pipette, and the separated material (6.54 g) was recrystallized from *i*-PrOH to deliver **10** (5.05 g, 33%); R_f = 0.78 (Et_2O); mp 163–165 °C.

IR (ATR): 3390, 3207, 3010, 2923, 2845, 1731, 1512 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.47 (s, 1 H, NH), 9.36 (s, 1 H, OH), 6.92 (d, *J* = 8 Hz, 2 H, ArH), 6.72 (d, *J* = 8 Hz, 2 H, ArH), 6.64–6.61 (m, 4 H, ArH), 4.62 (s, 2 H, NCH_2C$_6$H$_4$OMe), 4.59 (t, *J* = 4 Hz, 1 H, H-5), 3.70 (s, 3 H, OCH_3), 2.95 (d, *J* = 4 Hz, 2 H, CH_2C$_6$H$_4$OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 182.1, 173.7, 157.9, 156.2, 130.6, 127.7, 127.6, 124.2, 114.9, 113.3, 59.8, 54.8, 42.3, 34.5.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_3S$ [M$^+$]: 342.10381; found: 342.1031.

1-(*p*-Methoxybenzyl)-4-(*p*-hydroxybenzyl)imidazole-2-thione (11)

2-Thiohydantoin **10** (2.21 g, 6.5 mmol) was less sensitive to the conditions of reduction than the model compounds, and was added to a soln of $NaBH_4$ (0.54 g, 14 mmol) and LiCl (0.60 g, 14 mmol) in 3:1 DME–EtOH (30 mL) at 0 °C. The reaction was allowed to reach r.t. overnight. A TLC analysis showed incomplete consumption of **10**, but no overreduction. The reaction was stopped by the addition of concd HCl (10 mL). The mixture was stirred 30 min, diluted with H_2O (150 mL), and washed with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with H_2O and brine (1 × 20 mL each), dried ($MgSO_4$), filtered, plugged with 230–400 mesh silica gel (3 g), and concentrated. The silica gel plug was loaded on a silica gel column (230–400 mesh, 60 g) packed in EtOAc; elution with the same delivered **11** (1.14 g, 54%); R_f = 0.76 (EtOAc); mp 198–204 °C.

IR (ATR): 3128, 3069, 3013, 2964, 2924, 1511 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6): δ = 11.80 (s, 1 H, NH), 8.76 (s, 1 H, OH), 7.24 (d, *J* = 8 Hz, 2 H, ArH), 6.97 (d, *J* = 8 Hz, 2 H, ArH), 6.84 (d, *J* = 8 Hz, 2 H, ArH), 6.74 (d, *J* = 8 Hz, 2 H, ArH), 6.17 (s, 1 H, H-5), 5.06 (s, 2 H, NCH_2C$_6$H$_4$OMe), 3.77 (s, 3 H, OCH$_3$), 3.60 (s, 2 H, CH_2C$_6$H$_4$OH).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ = 160.5, 159.0, 155.9, 129.4, 129.3, 129.1, 128.3, 127.4, 115.3, 113.8, 113.6, 55.0, 49.1, 30.2.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_2S$ [M$^+$]: 326.10890; found: 326.1090.

1-(*p*-Methoxybenzyl)-4-(*p*-hydroxybenzyl)imidazole (12)

Solid **11** (1.0 g, 3.1 mmol) was added in one portion to a slurry of 75% $(BzO)_2$ (4.95 g, 15 mmol) in THF (5 mL). The reaction came to spontaneous reflux; after cooling back to r.t., the mixture was diluted with H_2O (20 mL) and Et_2O (20 mL). The aqueous layer was collected, and the organic layer was washed with H_2O (1 × 10 mL). The combined aqueous layers were washed with CH_2Cl_2 (3 × 5 mL), then treated with aq 6 M NaOH (5 mL) and stirred until no $(BzO)_2$ was visible by TLC (less than 1 h). The pH was lowered to 8 with sat. aq NH_4Cl (25 mL) before extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O and brine (1 × 20 mL each), dried ($MgSO_4$), filtered, and concentrated to leave **12** (0.79 g, 87%); mp 131–133 °C.

IR (ATR): 3106, 3034, 2996, 2903, 2829, 2787, 2669, 2580, 1609, 1509 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ = 7.44 (s, 1 H, ImH), 7.11 (d, *J* = 8 Hz, 2 H, ArH), 7.05 (d, *J* = 8 Hz, 2 H, ArH), 6.87 (d, *J* = 8 Hz, 2 H, ArH), 6.74 (d, *J* = 8 Hz, 2 H, ArH), 6.51 (s, 1 H, ImH), 4.95 (s, 2 H, NCH_2C$_6$H$_4$OMe), 4.47 (br s, 1 H, OH), 3.79 (s, 3 H, OCH$_3$), 3.77 (s, 2 H, CH_2C$_6$H$_4$OH).

^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD): δ = 159.7, 155.3, 142.9, 136.5, 131.0, 129.9, 129.2, 128.2, 116.4, 115.4, 114.5, 55.4, 50.6, 33.8.

MS (EI): *m*/*z* (%) = 294 (26, [M$^+$]), 121 (100, [*p*-MeOBn$^+$]).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_2$ [M$^+$]: 294.13683; found: 294.1367.

1,4-Di(*p*-methoxybenzyl)imidazole (13)

A soln of **12** (0.3053 g, 1.04 mmol) in THF (10 mL) was treated with LiOH·H_2O (0.0447 g, 1.07 mmol) and turned into a fine dispersion while stirring overnight. Addition of MeI (84 μL, 0.19 g, 1.35 mmol) gave a clear soln in 2 h, which was stirred another 4 h before the addition of H_2O (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic extracts were washed with H_2O and brine (1 × 20 mL each), dried ($MgSO_4$), filtered, and concentrated. After chromatography over 230–400 mesh silica gel (20 g) with a solvent gradient (EtOAc → 5:1 EtOAc–EtOH), the crude product (R_f = 0.40, 5:1 EtOAc–EtOH) still contained phenol **12**. The residue was redissolved in Et_2O (50 mL), washed with aq 3 M NaOH (3 × 25 mL), H_2O and brine (1 × 25 mL each), dried ($MgSO_4$), filtered, and concentrated to afford **13** (0.2200 g, 69%) with ^{1}H and ^{13}C NMR spectra matching those in the literature;[40] mp 83.5–86 °C (Lit.[40] mp 84–85 °C).

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