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Synthesis and Application of Imidazole Derivatives. Introduction of Carbogenic Substituents into the 5-Position of 1-Methyl-1*H*-imidazole

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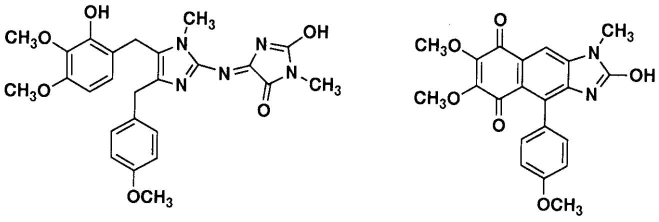
The 5-position of 1-methyl-2-phenylthio-1*H*-imidazole (12a) was lithiated by lithium 2,2,6,6-tetramethylpiperidide, and the produced carbanion was reacted with various electrophiles to give the corresponding 5-substituted derivatives in good yields. The reaction position was confirmed by ^{1}H-NMR spectroscopy and X-ray crystallography. The phenylthio group of the 5-substituted compounds could be easily removed by treatment with Raney-nickel.

Keywords lithiation; 1-methyl-1*H*-imidazole; X-ray crystallography; lithium 2,2,6,6-tetramethylpiperidide; 1-methyl-2-phenylthio-1*H*-imidazole; carbanion; electrophile; desulfurization

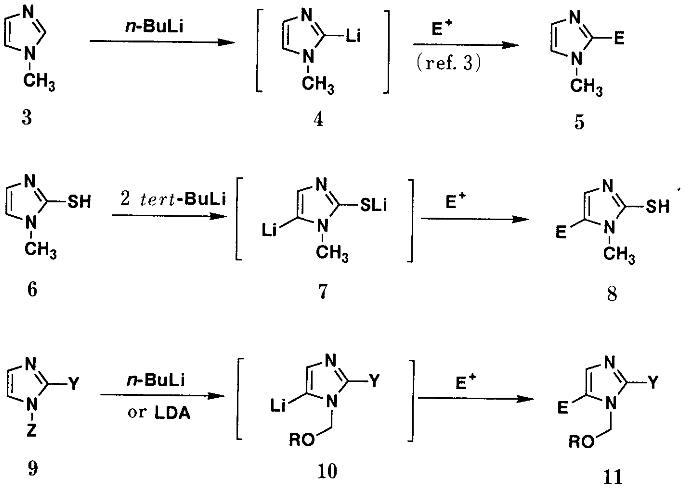
In the last ten years, we have been interested in the chemistry and the biological activities of 1*H*-imidazole, 1*H*-1,2,4-triazole and benzimidazole derivatives.[1] Recently, several imidazole-containing marine natural products of biological interest, such as pyronaamidine (**1**) and kealiiquinone (**2**), which are 1,2,4,5-fully substituted 1*H*-imidazole derivatives, have been isolated.[2]

We wished to develope a total synthesis of these natural products starting from 1-methyl-1*H*-imidazole (**3**), but the introduction of carbon substituents into the 4- and 5-positions of **3** has not been well established. Namely, introduction of a carbogenic substituent at the 2-position of a 1-alkyl-1*H*-imidazole such as **3** can be done through the corresponding 2-lithio-imidazole such as **4**, which is easily produced by treatment with *n*-butyllithium.[3] On the other hand, lithiation of the 5-position has recently been examined by several organic chemists and achieved by the introduction of an appropriate protecting group (-Y) into the most reactive 2-position and introduction of an alkoxymethyl or phenylsulfonyl group at the 1-position as a directing group for metallation at the 5-position.[4] But these methods seem to be unsuitable for synthesis of the natural products **1** and **2** because of the abnormal stability of the 1-protecting group (*e.g.*, 1-CH_2OCH_3) to acidic hydrolysis,[4] the general instability of the-SH group[4c] and the equivalence between C^4 and C^5 due to the tautomerism of the imidazole ring after removal of the 1-protecting group.



1 2

Chart 1



Z=SEM ; Y=PhS
Z=MOM ; Y=PhS
Z=EOM ; Y=PhS

E$^+$: electrophile
SEM : trimethylsilylethoxymethyl-
MOM : methoxymethyl-
EOM : ethoxymethyl-
LDA : lithium diisopropylamide

Chart 2

Lithiation of the 5- and 4-position of 1-methyl-2-aryl- and alkylthio-1*H*-imidazoles such as **12a** and **12b**, which do not have a directing group at the 1-position, has not been reported. This paper deals with protection of the 2-position of 1-methyl-1*H*-imidazole (**3**) by arylthio and alkylthio groups, and with effective introduction of a carbon substituent at the 5-position under mild conditions through 5-lithiation of 1-methyl-2-aryl- and alkylthio-1*H*-imidazoles (**12**), which have no directing group at the 1-position.

1-Methyl-2-phenylthio-1*H*-imidazole (**12a**) was prepared in 89.2% yield by lithiation of **3** with *n*-butyllithium followed by treatment with diphenyldisulfide, and the 2-*tert*-butylthio analogue (**12b**) was similarly prepared. Lithiation of **12a** under various reaction conditions was examined by comparing yields of **14a** produced by treatment of the

TABLE I. Lithiation Conditions for the Conversion of **12a** to **14a**

Run	Lithiation reagent	Solvent	Yield (%)[a]
1	*n*-BuLi	THF	Complex mixture
2	*sec*-BuLi	THF	14.1
3	LDA	THF	41.6
4	LDA	DME/THF	62.4
5	LTMP	THF	65.1
6	LTMP	TMEDA/THF	68.8
7	LTMP	DME/THF	74.3

a) Isolated yield. TMEDA: *N*,*N*,*N'*,*N'*-tetramethylethylenediamine.

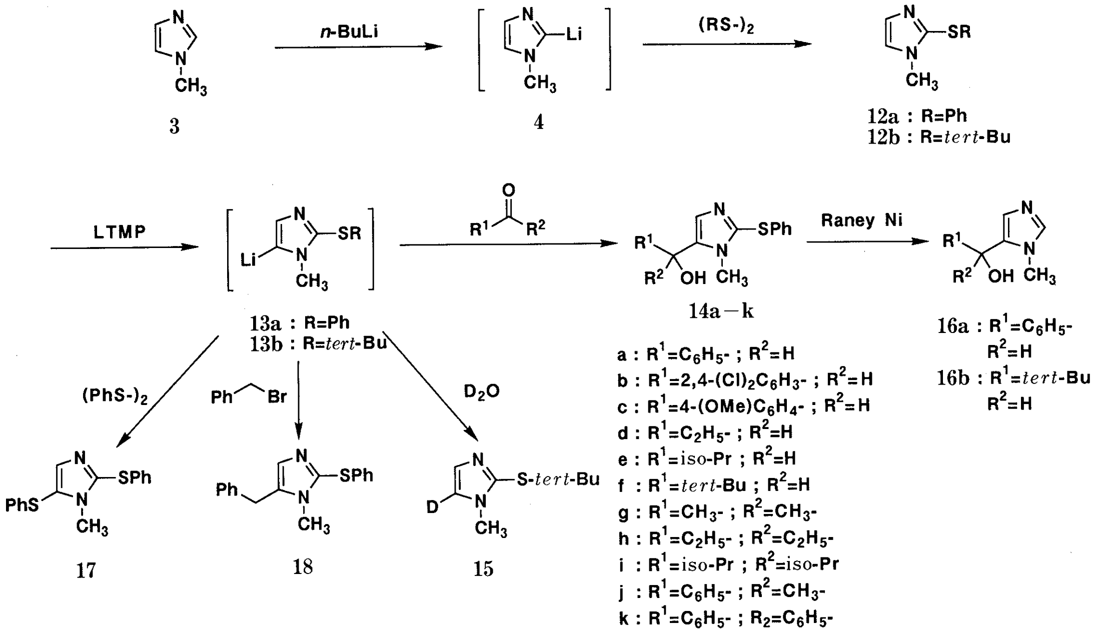


Chart 3

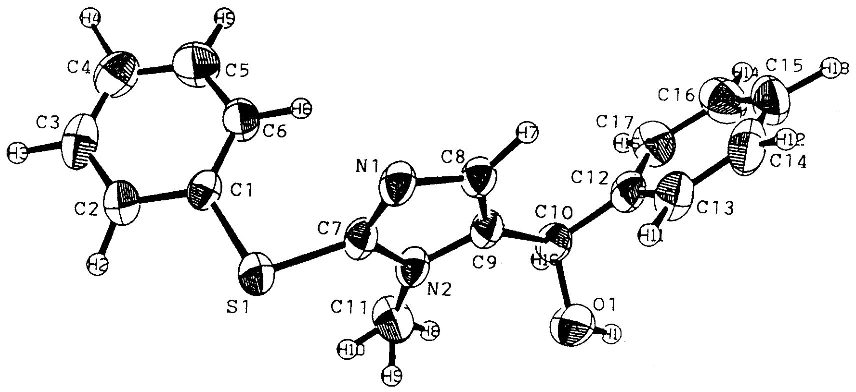


Fig. 1. An ORTEP Drawing of **14a**

intermediate **13a** with benzaldehyde. The results are summarized in Table I. Lithiation of **12a** by *n*- or *sec*-butyllithium (runs 1 and 2) gave a complex mixtures, probably due to accompanying cleavage of the sulfide function, but in the latter case the desired product (**14a**) was also isolated in 14.1% yield. Metallation of **12a** with lithium diisopropylamide (LDA; run 3 and 4) proceeded with little complication, but a considerable amount of the starting material (**12a**) was recovered. The best yield (74.3%) was obtained in run 7, in which lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used in a mixture of 1,2-dimethoxyethane (DME) and tetrahydofuran (THF). Hereafter, the condition of run 7 were used for lithiation of the 5-position of **12**.

It is well-known that the proton nuclear magnetic resonance (^{1}H-NMR) signal of the C-5 proton of 1-methyl-1*H*-imidazole (**3**) generally appears upfield from that of the 4-position.[5] Unfortunately, the signal of the 4-proton in the ^{1}H-NMR spectrum of **14a** overlapped with those of the phenyl rings, so the lithiation and substitution at the 5-position could not be confirmed in this case. Fortunately, the ^{1}H-NMR signals of the 4- and 5-position protons in **12b** were distinct. Thus, **12b** was lithiated under similar reaction conditions to those of run 7, then the reaction mixture was treated with deuterium oxide to give 2-*tert*-butylthio-5-deuterio-1-methyl-1*H*-imidazole (**15**).

Incorporation of deuterium into **15** was estimated 63.6% on the basis of its ^{1}H-NMR spectrum, and the signal area of only the 5-proton was markedly decreased compared with those of other protons. Therefore, the lithiation of the 5-position of **12a** and **12b** can be estimated on the basis of these data. However, the above-mentioned assignment regarding C-4 and C-5 protons[5] seems to be ambiguous because the assignment was based on the very similar chemical shifts reported in the case of compound **3** (C^4-H at 7.03 ppm; C^5-H at 6.87 ppm).[5] So we decided to conduct X-ray crystallography of **14a**, and the structure **14a** was finally confirmed as shown in Fig. 1.

Various nucleophiles such as aldehydes, ketones, benzyl bromide and diphenyl disulfide were treated with a solution of 5-lithio-1-methyl-2-phenylthio-1*H*-imidazole (**13a**) to give the corresponding 5-substituted products in good to moderate yields, and the results are summarized in the experimental section.

The 2-phenylthio group of **14a** and **14f** was easily removed

TABLE II. Positional Parameters for **14a**

Atom	x	y	z
S(1)	0.77062 (9)	0.12524 (8)	0.68499 (6)
O(1)	0.9331 (2)	0.1852 (2)	1.1084 (2)
N(1)	0.6508 (2)	0.2650 (2)	0.7934 (2)
N(2)	0.8577 (2)	0.2075 (2)	0.8833 (2)
C(1)	0.8073 (3)	0.2457 (3)	0.6111 (2)
C(2)	0.8339 (4)	0.2090 (4)	0.5236 (3)
C(3)	0.8581 (4)	0.2982 (5)	0.4605 (3)
C(4)	0.8568 (4)	0.4202 (4)	0.4828 (3)
C(5)	0.8331 (4)	0.4543 (4)	0.5701 (3)
C(6)	0.8074 (4)	0.3684 (4)	0.6344 (3)
C(7)	0.7574 (3)	0.2049 (3)	0.7911 (2)
C(8)	0.6851 (3)	0.3092 (3)	0.8917 (2)
C(9)	0.8114 (3)	0.2741 (3)	0.9487 (2)
C(10)	0.8980 (3)	0.3005 (3)	1.0579 (2)
C(11)	0.9891 (3)	0.1509 (4)	0.9072 (3)
C(12)	0.8302 (3)	0.3832 (3)	1.1141 (2)
C(13)	0.7110 (4)	0.3504 (4)	1.1268 (3)
C(14)	0.6544 (5)	0.4280 (5)	1.1806 (3)
C(15)	0.7171 (5)	0.5347 (5)	1.2235 (3)
C(16)	0.8353 (5)	0.5662 (4)	1.2125 (3)
C(17)	0.8911 (4)	0.4916 (4)	1.1569 (3)
H(1)	1.014 (5)	0.215 (4)	1.172 (4)
H(2)	0.833 (4)	0.127 (4)	0.511 (3)
H(3)	0.873 (3)	0.272 (3)	0.399 (3)
H(4)	0.872 (3)	0.481 (4)	0.437 (3)
H(5)	0.840 (3)	0.532 (3)	0.587 (3)
H(6)	0.793 (3)	0.395 (3)	0.692 (3)
H(7)	0.627 (3)	0.354 (2)	0.911 (2)
H(8)	1.0092	0.1322	0.8482
H(9)	0.9923	0.0752	0.9460
H(10)	1.0569	0.2043	0.9509
H(11)	0.664 (3)	0.274 (3)	1.095 (2)
H(12)	0.574 (4)	0.403 (4)	1.191 (3)
H(13)	0.685 (4)	0.585 (3)	1.260 (3)
H(14)	0.888 (3)	0.642 (3)	1.240 (2)
H(15)	0.974 (3)	0.513 (3)	1.145 (2)
H(16)	0.994 (3)	0.335 (2)	1.063 (2)

TABLE III. Intramolecular Distances

Atom	Atom	Distance	Atom	Atom	Distance
S1	C1	1.782 (3)	C8	C9	1.362 (4)
S1	C7	1.751 (3)	C8	H7	0.89 (3)
O1	C10	1.421 (4)	C9	C10	1.511 (4)
O1	H1	1.06 (5)	C10	C12	1.517 (4)
N1	C7	1.316 (4)	C10	H16	1.06 (3)
N1	C8	1.372 (4)	C11	H8	0.93
N2	C7	1.361 (3)	C11	H9	0.98
N2	C9	1.372 (4)	C11	H10	0.96
N2	C11	1.457 (4)	C12	C13	1.382 (5)
C1	C2	1.391 (4)	C12	C17	1.377 (5)
C1	C6	1.370 (5)	C13	C14	1.388 (5)
C2	C3	1.384 (5)	C13	H11	0.99 (3)
C2	H2	0.90 (4)	C14	C15	1.368 (6)
C3	C4	1.360 (6)	C14	H12	0.96 (4)
C3	H3	0.96 (3)	C15	C16	1.358 (6)
C4	C5	1.366 (6)	C15	H13	0.89 (4)
C4	H4	0.97 (4)	C16	C17	1.381 (5)
C5	C6	1.378 (5)	C16	H14	0.99 (3)
C5	H5	0.87 (4)	C17	H15	0.98 (3)
C6	H6	0.91 (3)			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

in moderate yields by the use of excess Raney-nickel (W-2) in refluxing ethanol to give the corresponding 1-methyl-5-substituted compounds (**16a** and **16b**, respectively).

TABLE IV. Torsion or Conformation Angles

(1)	(2)	(3)	(4)	Angle	(1)	(2)	(3)	(4)	Angle
S1	C1	C2	C3	177.6 (3)	C2	C3	C4	C5	1.0 (6)
S1	C1	C6	C5	−178.0 (3)	C3	C2	C1	C6	−1.0 (5)
S1	C7	N1	C8	178.5 (2)	C3	C4	C5	C6	−1.6 (7)
S1	C7	N2	C9	−178.0 (2)	C6	C1	S1	C7	−6.2 (3)
S1	C7	N2	C11	2.4 (5)	C7	N1	C8	C9	−0.8 (4)
O1	C10	C9	N2	−61.3 (4)	C7	N2	C9	C8	−0.5 (3)
O1	C10	C9	C8	122.3 (4)	C7	N2	C9	C10	−177.8 (3)
O1	C10	C12	C13	−61.6 (4)	C8	C9	N2	C11	179.1 (3)
O1	C10	C12	C17	116.0 (3)	C8	C9	C10	C12	−0.5 (5)
N1	C7	S1	C1	81.4 (3)	C9	C10	C12	C13	59.1 (4)
N1	C7	N2	C9	0.0 (4)	C9	C10	C12	C17	−123.4 (3)
N1	C7	N2	C11	−179.6 (3)	C10	C9	N2	C11	1.8 (5)
N1	C8	C9	N2	0.9 (4)	C10	C12	C13	C14	178.7 (3)
N1	C8	C9	C10	177.7 (3)	C10	C12	C17	C16	−177.0 (3)
N2	C7	S1	C1	−100.8 (3)	C12	C13	C14	C15	−1.9 (6)
N2	C7	N1	C8	0.5 (4)	C12	C17	C16	C15	−1.6 (6)
N2	C9	C10	C12	175.8 (3)	C13	C12	C17	C16	0.6 (5)
C1	C2	C3	C4	0.3 (6)	C13	C14	C15	C16	0.9 (6)
C1	C6	C5	C4	0.8 (6)	C14	C13	C12	C17	1.1 (5)
C2	C1	S1	C7	175.3 (3)	C14	C15	C16	C17	0.8 (6)
C2	C1	C6	C5	0.5 (6)					

The sign is positive if, when looking from atom 2 to atom 3, a clockwise motion of atom 1 would superimpose it on atom 4.

Thus, we have found a new and generally applicable procedure for introduction of an appropriate carbogenic substituent into the 5-position of 1-methyl-1*H*-imidazole (**3**) and for preparation of 1-methyl-5-substituted imidazoles such as **16a** and **16b**. Now we are trying to examine the introduction of appropriate carbogenic substituents into the 4-position of **14a**, **17** and their analogues. In particular, the 5-substituent of **14a** seems to be a convenient directing group for lithiation of the 4-position.

Experimental

All melting points are uncorrected. Infrared spectra (IR) were taken with a Shimadzu IR-410 spectrometer. ^{1}H-NMR spectra were obtained at 80 MHz on a Varian CFT-20 (80 MHz) or a Varian XL-300 (300 MHz) spectrometer, and the chemical shifts are given in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); quar (quartet); m (multiplet); br (broad). High-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 spectrometer. X-Ray crystallography was done with a Rigaku AFC5R diffractometer. In the work-up procedure, solvent was removed from the organic layer containing the desired product under reduced pressure by using a rotary evaporator. Anhydrous sodium sulfate was used as a drying agent. A Kugel-Rohr apparatus was used for the vacuum distillation of crude oils or low-melting-point products. Column chromatography was carried out by using Merck Kieselgel 60 (Art. 7734).

1-Methyl-2-phenylthio-1*H*-imidazole (12a) A solution of 1.6 M *n*-butyllithium in hexane (31.25 ml, 50 mmol) was added under an N_2 atmosphere at −78 °C to a solution of **3** (4.0 ml, 50 mmol) in THF (100 ml). The mixture was stirred for 15 min, then diphenyldisulfide (10.92 g, 50 mmol) was added, and the whole was stirred for 30 min. A 10% HCl solution (40 ml) was added. The aqueous layer was washed with ether (30 ml × 2), and the aqueous layer was basified with powdered K_2CO_3. The liberated free base was extracted with ethyl acetate (50 ml × 4), dried and evaporated to give an oily residue, which was purified by distillation *in vacuo*. bp 174 °C (0.15 mmHg). Yield, 8.47 g (89.2%). IR ($CHCl_3$); 1580, 1478, 1456 cm^{-1}. ^{1}H-NMR ($CDCl_3$; 300 MHz): 3.63 (s, 3H, $-NC\underline{H}_3$), 7.07 (d, 1H, C^5-H, $J=1.3$ Hz), 7.17 (d, 1H, C^4-H, $J=1.3$ Hz), 7.12—7.27 (m, 5H, Ar-H). Low-resolution MS (LRMS) m/z: 190 (M^+).

2-*tert*-Butylthio-1-methyl-1*H*-imidazole (12b) Compound **12b** was obtained by a similar procedure to that used for the synthesis of **12a** except for use of **12a** (0.80 ml, 10 mmol) and di-*tert*-butyldisulfide (1.93 ml, 10 mmol). bp 81 °C (0.07 mmHg). Yield, 703.8 mg (41.4%). IR ($CHCl_3$):

2935, 1451 cm^{-1}. ^{1}H-NMR (CDCl$_3$; 300 MHz): 1.36 (s, 9H, $-$SC(CH$_3$)$_3$), 3.74 (s, 3H, $-$NCH$_3$), 7.03 (d, 1H, C^5-H, J=1.3 Hz), 7.15 (d, 1H, C^4-H, J=1.3 Hz). HRMS m/z: Calcd for $C_8H_{14}N_2S$, 170.0880. Found, 170.0887 (M$^+$).

General Procedure for the Synthesis of 5-(1-Alkyl or aryl-1-hydroxymethyl)-1-methyl-2-phenylthio-1*H*-imidazole (14); Synthesis of 5-(1-Hydroxy-1-phenylmethyl)-1-methyl-2-phenylthio-1*H*-imidazole (14a) as an Example A THF solution (4 ml) of 2,2,6,6-tetramethylpiperidine (186 μl, 1.1 mmol) and DME (2 ml) was cooled to -78 °C, and a solution of 1.6 M *n*-butyllithium in hexane (0.625 ml, 1 mmol) was added under an N_2 atmosphere. The mixture was stirred for 15 min at -78 °C, then **12a** (166 μl, 1.0 mmol) was added dropwise, and the mixture was stirred for 1 h. Benzaldehyde (102 μl, 1 mmol) was added, and the reaction mixture was stirred overnight at room temperature. Water (5 ml) was added and the product was extracted with ethyl acetate (10 ml × 4). After removal of the solvent, the residue was recrystallized from ethyl acetate to give colorless prisms. mp 154.2—154.6 °C. Yield, 220 mg (74.3%). IR (KBr): 3113 cm^{-1} (OH). ^{1}H-NMR (DMSO-d_6; 300 MHz): 3.52 (s, 3H, $-$NCH$_3$), 5.83 (d, 1H, C$\underline{H}$(OH)Ar, J=4.9 Hz), 6.09 (d, 1H, $-$OH, J=5.3 Hz), 6.63 (s, 1H, C^4-H), 7.06—7.40 (m, 10H, Ar-H). *Anal.* Calcd for $C_{17}H_{16}N_2OS \cdot 1/4\,H_2O$: C, 67.86; H, 5.53; N, 9.31. Found: C, 68.05; H, 5.55; N, 9.05.

14b: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (1.66 ml, 10 mmol) and 2,4-dichloro-benzaldehyde (1.75 g, 10 mmol). Purification by column chromatography (ethyl acetate : *n*-hexane = 5 : 1) and recrystallization from isopropyl ether–ether gave colorless needles, mp 188—189 °C. Yield was 2.08 g (56.9%). IR (KBr): 3064 cm^{-1} (OH). ^{1}H-NMR (DMSO-d_6; 300 MHz): 3.67 (s, 3H, $-$NCH$_3$), 5.95 (d, 1H, C$\underline{H}$(OH)Ar, J=4.0 Hz), 6.34 (d, 1H, $-$OH, J=5.5 Hz), 6.40 (s, 1H, C^4-H), 7.07—7.76 (m, 8H, Ar-H). *Anal.* Calcd for $C_{17}H_{14}Cl_2N_2OS$: C, 55.90; H, 3.86; N, 7.67. Found: C, 55.64; H, 3.88; N, 7.89.

14c: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (166 μl, 1 mmol) and *p*-anisaldehyde (122 μl, 1 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 20 : 1) and recrystallization from DMF–H$_2$O gave colorless needles, mp 145—147 °C. Yield. 165 mg (50.6%). IR (KBr): 3114 cm^{-1} (OH). ^{1}H-NMR (DMSO-d_6; 300 MHz): 3.51 (s, 3H, $-$NCH$_3$), 3.75 (s, 3H, $-$OCH$_3$), 5.76 (d, 1H, C$\underline{H}$(OH)Ar, J=3.0 Hz), 5.98 (d, 1H, $-$OH, J=4.9 Hz), 6.64 (s, 1H, C^4-H), 6.92—7.35 (m, 9H, Ar-H). *Anal.* Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.04; H, 5.60; N, 8.48.

14d: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (166 μl, 1 mmol) and propionaldehyde (72 μl, 1 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 20 : 1) and recrystallization from ethyl acetate–*n*-hexane gave colorless needles, mp 89—91 °C. Yield. 124 mg (50.0%) IR (KBr): 3065 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 1.03 (t, 3H, $-$CH$_2$C$\underline{H}_3$, J=7.4 Hz), 1.94 (m, 2H, $-$C$\underline{H}_2$CH$_3$), 2.12—2.87 (br, 1H, $-$OH), 3.66 (s, 3H, $-$NC$\underline{H}_3$), 4.54 (t, 1H, C$\underline{H}$(OH)Ar, J=6.4 Hz), 7.11 (s, 1H, C^4-H), 7.13—7.27 (m, 5H, Ar-H). *Anal.* Calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.44; H, 6.61; N, 11.06.

14e: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (166 μl, 1 mmol) and isobutylaldehyde (91 μl, 1 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 20 : 1) and recrystallization from ethyl acetate–*n*-hexane gave colorless needles, mp 89—91 °C. Yield, 146 mg (55.7%). IR (KBr): 3117 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 0.88 and 1.11 (each d, 6H, $-$CH (C$\underline{H}_3$)$_2$, J=6.7 Hz), 2.12 (m, 1H, $-$C$\underline{H}$(CH$_3$)$_2$), 2.66—2.76 (br, 1H, $-$OH), 3.64 (s, 3H, $-$NCH$_3$), 4.31 (d, 1H, C$\underline{H}$(OH)Ar, J=8.0 Hz), 7.03 (s, 1H, C^4-H), 7.09—7.23 (m, 5H, Ar-H). *Anal.* Calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91; N, 10.68. Found: C, 64.06; H, 7.08; N, 10.66.

14f: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (166 μl, 1 mmol) and pivalaldehyde (109 μl, 1 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 30 : 1) and recrystallization from ethyl acetate–*n*-hexane gave colorless needles, mp 88—89 °C. Yield, 175 mg (63.4%). IR (KBr): 3145 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 0.99 (s, 9H, $-$C(CH$_3$)$_3$), 1.97—2.63 (br, 1H, $-$OH), 3.59 (s, 3H, $-$NCH$_3$), 4.42 (s, 1H, C$\underline{H}$(OH)Ar), 7.06—7.27 (m, 6H, C^4-H, Ar-H). *Anal.* Calcd for $C_{15}H_{20}N_2OS$: C, 65.18; H, 7.29; N, 10.14. Found: C, 64.89; H, 7.40; N, 10.00.

14g: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (332 μl, 2 mmol) and acetone (0.73 ml, 10 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 20 : 1) and recrystallization from ethyl acetate–*n*-hexane gave colorless needles. mp 83—85 °C. Yield, 195 mg (39.3%). IR (CHCl$_3$): 3117 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 1.64 (s, 6H, $-$CH (OH) (C$\underline{H}_3$)$_2$), 2.45—2.53 (br, 1H, $-$OH), 3.82 (s, 3H, $-$NCH$_3$), 7.14 (s, 1H, C^4-H), 7.22—7.27 (m, 5H, Ar-H). *Anal.* Calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.85; H, 6.65; N, 11.30.

14h: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (332 μl, 2 mmol) and 3-pentanone (202 μl, 2 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 50 : 1) and recrystallization from ethyl acetate–*n*-hexane gave colorless needles, mp 120—122 °C. Yield, 258 mg (54.0%). IR (CHCl$_3$): 3150 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 0.85 (t, 6H, $-$CH$_2$C$\underline{H}_3$, J=7.1 Hz), 1.88 (q, 4H, $-$C$\underline{H}_2$CH$_3$, J=7.1 Hz), 2.10 (s, 1H, $-$OH), 3.79 (s, 3H, $-$NCH$_3$), 6.97 (s, 1H, C^4-H), 7.08—7.27 (m, 5H, Ar-H). *Anal.* Calcd for $C_{15}H_{20}N_2OS$: C, 65.18; H, 7.29; N, 10.14. Found: C, 64.88; H, 7.31; N, 10.23.

14i: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (332 μl, 2 mmol) and 2,4-dimethyl-3-pentanone (354 μl, 2.5 mmol). Recrystallization from ethyl acetate gave colorless needles, mp 185—186 °C. Yield, 416 mg (68.9%). IR (CHCl$_3$): 3122 cm^{-1} (OH). ^{1}H-NMR (DMSO-d_6; 300 MHz): 0.77 and 0.81 (each d, 12H, $-$CH(C$\underline{H}_3$)$_2$, J=6.7 Hz), 2.31 (m, 2H, $-$C$\underline{H}$(CH$_3$)$_2$), 3.80 (s, 3H, $-$NCH$_3$), 4.61 (s, 1H, $-$OH), 6.88—7.33 (m, 6H, C^4-H, Ar-H). *Anal.* Calcd for $C_{17}H_{24}N_2OS$: C, 67.51; H, 7.33; N, 9.26. Found: C, 67.21; H, 7.58; N, 8.98.

14j: Obtained in a similar manner to that used for the synthesis of **14a** starting from **12a** (332 μl, 2 mmol) and acetophenone (233 μl, 2 mmol). Purification by column chromatography (CHCl$_3$: MeOH = 20 : 1) and recrystallization from ethyl acetate gave colorless needles, mp 164—166 °C. Yield, 432 mg (69.7%). IR (CHCl$_3$): 3048 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 1.92 (s, 3H, >C(OH)C$\underline{H}_3$), 3.05 (s, 1H, $-$OH), 3.23 (s, 3H, >NCH$_3$), 7.05—7.32 (m, 11H, C^4-H, Ar-H). *Anal.* Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.03. Found: C, 69.65; H, 5.79; N, 9.28.

14k: Obtained in a similar manner to that used for the synthesis of **14a**, starting from **12a** (332 μl, 2 mmol) and benzophenone (364 mg, 2 mmol). Recrystallization from ethyl acetate gave colorless needles, mp 168—169 °C. Yield, 676 mg (90.9%). IR (CHCl$_3$): 3050 cm^{-1} (OH). ^{1}H-NMR (CDCl$_3$; 300 MHz): 3.35 (s, 3H, $-$NCH$_3$), 3.67 (s, 1H, $-$OH), 6.43 (s, 1H, C^4-H), 7.10—7.32 (m, 15H, Ar-H). *Anal.* Calcd for $C_{23}H_{20}N_2OS$: C, 74.16; H, 5.41; N, 7.52. Found: C, 74.48; H, 5.45; N, 7.47.

1-Methyl-2,5-diphenylthio-1*H*-imidazole (17) This compound was obtained in almost the same manner as used for the synthesis of **14a**, starting from **12a** (1.66 ml, 10 mmol) and diphenyldisulfide (2.183 g, 10 mmol). The oily product was purified by column chromatography (AcOEt : *n*-hexane = 1 : 1). Yield, 2.706 g (90.8%). IR (CHCl$_3$): 1578, 1474 cm^{-1} (C$_6$H$_5$). ^{1}H-NMR (CDCl$_3$; 300 MHz): 3.49 (s, 3H, >NC$\underline{H}_3$), 7.02–7.28 (m, 10H, Ar-H), 7.54 (s, 1H, C^4-H). LRMS m/z: 298 (M$^+$). HRMS m/z: Calcd for $C_{16}H_{14}N_2S_2$, 298.0600. Found, 298.0599 (M$^+$).

5-Benzyl-1-methyl-2-phenylthio-1*H*-imidazole (18) This compound was obtained in almost the same manner as used for the synthesis of **14a**, starting from **12a** (166 μl, 10 mmol) and benzyl bromide (147 μl, 1.2 mmol). Purification by column chromatography (ethyl acetate : *n*-hexane = 1 : 1) and recrystallization from *n*-hexane gave colorless needles, mp 85—86 °C. Yield, 127 mg (45.4%). IR (CHCl$_3$): 2930, 1491 cm^{-1}. ^{1}H-NMR (CDCl$_3$; 80 MHz): 3.38 (s, 3H, $-$NCH$_3$), 3.95 (s, 2H, $-$C$\underline{H}_2$C$_6$H$_5$), 7.00 (s, 1H, C^4-H), 7.03—7.33 (m, 10H, Ar-H). *Anal.* Calcd for $C_{17}H_{16}N_2OS$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.77; H, 5.78; N, 9.80.

2-*tert*-Butylthio-5-deuterio-1-methyl-1*H*-imidazole (15) A THF solution (3 ml) of 2,2,6,6-tetramethylpiperidine (186 μl, 1.1 mmol) and DME (2 ml) was cooled to -78 °C, and 1.6 M *n*-butyllithium in hexane (0.625 ml, 1 mmol) was added under an N$_2$ atmosphere. The mixture was stirred for 15 min at -78 °C, then a THF solution (1 ml) of 2-*tert*-butylthio-1-methyl-1*H*-imidazole (**12b**, 170 mg, 1 mmol) was added dropwise, and the whole was stirred for 1 h. CH$_3$OD (0.4 ml) was added, and the mixture was stirred overnight at room temperature. Water (5 ml) was added and the product was extracted with ethyl acetate (10 ml × 3). After removal of the solvent, the residue was purified by column chromatography (AcOEt). ^{1}H-NMR (CDCl$_3$; 300 MHz): 1.36 (s, 9H, $-$SC(C$\underline{H}_3$)$_3$), 3.74 (s, 3H, $-$NCH$_3$), 7.03 (d, 0.35 H, C^5-H, J=1.3 Hz), 7.15 (s, 1H, C^4-H). The incorporation ratio of deuterium was estimated as 63.6% on the basis of the ^{1}H-NMR spectrum.

5-(1-Hydroxy-1-phenylmethyl)-1-methyl-1*H*-imidazole (16a) A suspension of 5-(1-hydroxy-1-phenylmethyl)-1-methyl-2-phenylthio-1*H*-imidazole (**14a**, 2.5 mmol, 740 mg) and Raney Ni (W-2, about 3.0 g) in EtOH was refluxed for 4 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to give a crystalline residue, which was recrystallized from ethyl acetate. mp 148.1—150.0 °C. Yield, 348 mg (74.0%). IR (CHCl$_3$): 2922, 1467 cm^{-1}. ^{1}H-NMR (CDCl$_3$; 300 MHz): 3.53 (s, 3H, $-$NCH$_3$), 4.07—4.13 (br, 1H, $-$OH), 5.86 (s, 1H, C$\underline{H}$(OH)Ar), 6.61 (s, 1H, C^4-$\underline{H}$), 7.27—7.38 (m, 6H, C^2–H, Ar-H). *Anal.* Calcd for

$C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.08; H, 6.42; N, 14.70.

5-(2,2-Dimethyl-1-hydroxypropyl)-1-methyl-1*H*-imidazole (16b) A suspension of 5-(2,2-dimethyl-1-hydroxypropyl)-1-methyl-2-phenylthio-1*H*-imidazole (**14f**, 5 mmol, 1.38 g) and Raney Ni (*ca.* 5g) in EtOH was refluxed for 5 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to give a residue, which was recrystallized from ethyl acetate. mp 150.2—152.4 °C. Yield, 635 mg (75.6%). IR (KBr): 3102, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$; 300 MHz): 1.00 (s, 9H, $-C(CH_3)_3$), 2.48—2.99 (br, 1H,-O$\underline{H}$), 3.63 (s, 3H, $-NCH_3$), 4.42 (s, 1H, C$\underline{H}$ (OH)), 6.94 (s, 1H, C^4-H), 7.29 (s, 1H, C^2-H). *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.96; H, 9.81; N, 16.36.

X-Ray Crystallography of 14a The crystal data of **14a** were collected on a Rigaku Denki AFC-5R diffractometer using MoK_α radiation at 23 °C. The intensities of all the reflections with 2θ values from 6.0° to 55.1° were measured by the ω–2θ scanning technique at a scan rate of 32.0°/min (in ω). In total, 3817 independent reflections were obtained.

Crystal Data for **14a**: $C_{17}H_{16}N_2OS$. $M_r=296.39$. Monoclinic (obtained by recrystallization from ethyl acetate). Lattice parameters: $a=10.620(3)$, $b=10.852$ (2), $c=13.845$ (1) Å; $\alpha=90.0$ (0), $\beta=109.60°$ (1), $\gamma=90.0$ (0), $V=1503.1$ Å^3 (5). $D_{\text{calc}}=1.244$ g/cm^3. $z=3$. Space group, $P2_1/n$ (♯14). Crystal dimensions (mm), 0.15 (W) × 0.10 (D) × 0.20 (H).

Structure Analysis and Refinement for **14a**: The structure was solved by a direct method using the TEXSAN crystallographic software, and refined by the full-matrix least-squares method. The final R-value was 5.2—4.7. An ORTEP drawing of the molecule, the atomic parameters, bond lengths and bond angles are given in Fig. 1, Tables II, III and IV, respectively.

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