Syntheses and pK_a determination of 1-(*o*-hydroxyphenyl)imidazole carboxylic esters

James P. Collman,* Zhong Wang, Min Zhong and Li Zeng

Department of Chemistry, Stanford University, Stanford, California 94305-5080, USA

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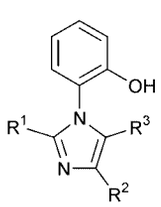
All three isomers of 1-(*o*-hydroxyphenyl)imidazole carboxylic esters (**1**–**3**) have been synthesized regioselectively *via* their methyl ether precursors. Methyl 1-(*o*-methoxyphenyl)imidazole-2-carboxylate (**6**) and the corresponding 1,4-isomer (**11**) were synthesized *via* Cu-catalyzed coupling of 2-iodoanisole with imidazole followed by methoxycarbonylation, and by direct coupling of 2-iodoanisole with methyl imidazole-4-carboxylate (**7**), respectively. The 1,5-isomer (**15**) was prepared by annulation of an *N*-aryl glycine ester derivative (**13**). The boron tribromide mediated cleavage of methyl ethers gave the hydroxyphenyl compounds (**1**–**3**) in good to excellent yields. These compounds can serve as building blocks for synthesizing a new generation of active-site model compounds of cytochrome *c* oxidase (C*c*O). The pK_a values have been determined by spectrophotometric measurements in order to provide a basis for the understanding of the proton transfer processes in C*c*O.

Introduction

Cytochrome *c* oxidase (C*c*O) is a key enzyme in aerobic organisms. It catalyzes the $4e^-$, $4H^+$ reduction of O_2, the pivotal final step in respiratory chains.[1,2] Cytochrome *c* oxidase contains four redox active metal sites. These consist of two a-type hemes (a and a_3) and two copper sites (Cu_A and Cu_B). Recently, a tyrosine-histidine (Tyr-His) crosslink forming a hydroxyphenyl–imidazole covalent bond was characterized at the active sites of both bacterial[3] and mammalian[4] forms of C*c*O by protein X-ray analyses. This post-translational modification was found to be critical for maintaining the tertiary structure of C*c*O, and the phenol-functionalized imidazole that forms part of the Cu_B binding site is speculated to participate in the proton and electron transfer steps during the catalytic O_2 reduction.[3,5–8] In order to decipher the key role of the crosslinked Tyr in the function of C*c*O, we became interested in preparing *N*-hydroxyphenyl-functionalized imidazole esters **1**–**3** as building blocks

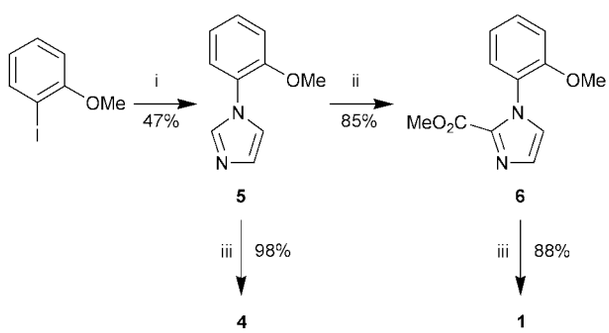


1 $R^1 = CO_2Me$, $R^2 = R^3 = H$
2 $R^1 = R^3 = H$, $R^2 = CO_2Me$
3 $R^1 = R^2 = H$, $R^3 = CO_2Et$
4 $R^1 = R^2 = R^3 = H$

for the synthesis of a new generation of model compounds that incorporate a Tyr-His like structure. Herein we report regioselective syntheses of these three isomers as well as measurements of their pK_a values, which may supply important information for understanding the biological proton transfer processes.

Results and discussion

The synthesis of **1** is straightforward. As shown in Scheme 1, reaction of commercially available 2-iodoanisole with sodium imidazolide salt at 150 °C in DMF in the presence of Cu powder gave the Ullmann coupling[9,10] product, **5**, in 47% yield. Methoxycarbonylation at the imidazole 2-position was achieved by a sequence of deprotonation with *n*-BuLi, quenching with chlorotrimethylsilane, and reaction with methyl chloroformate to afford the methyl ester **6**.[11] Treatment of **6** with BBr_3 in CH_2Cl_2 for 0.5 h at −78 °C and for another 1 h at 0 °C cleaved



Scheme 1 *Reagents and conditions*: i, sodium imidazolate, Cu powder, DMF, 150 °C, 4 h; ii, (a) *n*-BuLi, THF, −78 °C, 30 min, and then −20 °C, 40 min, (b) TMSCl, −78 °C, 1 h, (c) $ClCO_2Me$, −78 °C–rt, 12 h; iii, BBr_3, CH_2Cl_2, −78 °C, 0.5 h, then 0 °C, 1 h.

the aryl methyl ether to afford **1**. The overall yield is 35%. Compound **4** was prepared from **5** in nearly quantitative yield (98%) by direct demethylation with BBr_3.

Our original plan to synthesize **2** was by a diazotization–hydrolysis[12] transformation of the aniline derivative **9** as the key step (Scheme 2). Highly regioselective preparation of **9** can be achieved by aromatic nucleophilic substitution of 1-fluoro-2-nitrobenzene with methyl imidazole-4-carboxylate (**7**) and subsequent reduction of the nitro group with $SnCl_2$–HCl. However, in the attempted diazotization reaction of **9** with $NaNO_2$ followed by heating, no desired compound **2** was formed; only the reduction product **10** was obtained.

Compound **2** was then prepared according to Scheme 3. 2-Iodoanisole and **7** were directly coupled in DMF using 5 mol% Cu(I) triflate as the catalyst and 1 eq. Cs_2CO_3 as the base. The reaction mixture was heated at 100 °C for 8 h in the presence of 4 Å molecular sieves to ensure strictly anhydrous conditions; compound **11** was obtained in 40% isolated yield, while the regioisomer, 1-(*o*-methoxyphenyl)imidazole-5-carboxylate, was not formed.† Higher temperatures or trace amounts of

† A common problem with nucleophilic substitution by a 1*H*-4(5)-substituted imidazole is that the two tautomeric forms of the imidazole give rise to two possible regioisomers. It is significant that the present reaction affords exclusively the 1,4-substitution product. Besides steric factors, the high regioselectivity may stem from the electron-withdrawing ester group in **7** which favors anion formation at the N-1 position.

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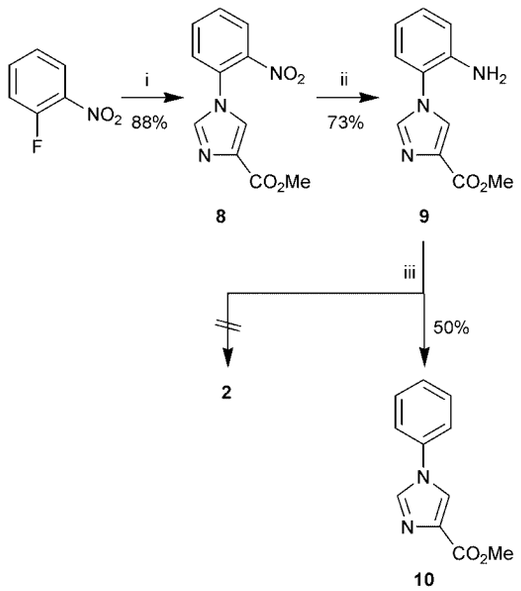
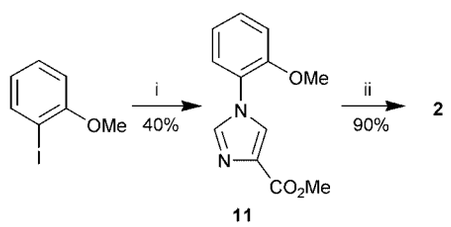


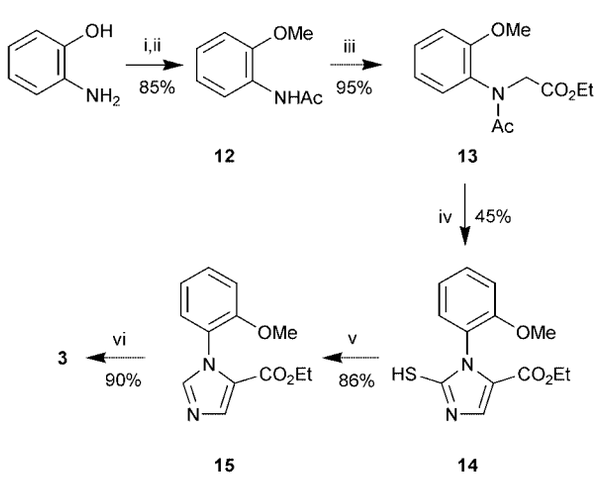
Scheme 2 *Reagents and conditions*: i, **7**, K_2CO_3, CH_3CN, reflux, 12 h; ii, $SnCl_2$–HCl, CH_2Cl_2, rt, 4 h; iii, $NaNO_2$–HCl, H_2O, 0 °C, 30 min, and then 50 °C, 1 h.



Scheme 3 *Reagents and conditions*: i, **7**, Cs_2CO_3, CuOTf (cat.), DMF, 100 °C, 8 h; ii, BBr_3, CH_2Cl_2, −78 °C, 0.5 h, then 0 °C, 1 h.

water in the solvent resulted in hydrolysis of the ester group and subsequent decarboxylation which significantly decreased the yield. With **11** in hand, demethylation was effected by BBr_3 to give **2** in 90% yield.

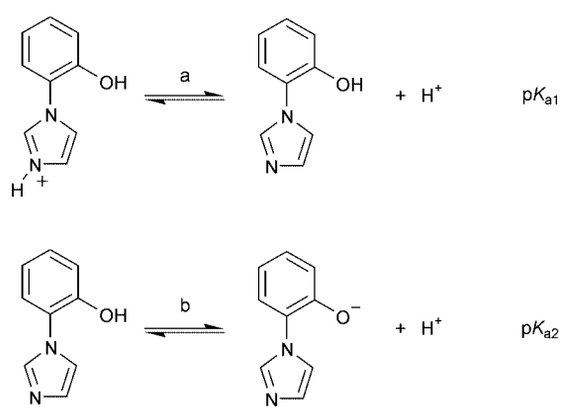
Due to steric hindrance factors, a 1,5-disubstitution pattern is more difficult to introduce into a preformed imidazole ring than the corresponding 1,4-disubstitution;[13,14] therefore the 1,5-isomer **3** was prepared *via* imidazole ring cyclization as shown in Scheme 4. From 2-aminophenol, the amino and hydroxy groups were first protected as the acetamide and



Scheme 4 *Reagents and conditions*: i, $(CH_3CO)_2O$, Et_3N, THF, 0 °C, 4 h; ii, CH_3I, K_2CO_3, CH_3CN, 40 °C, 6 h; iii, (a) NaH, THF, rt, 1 h, (b) $BrCH_2CO_2Et$, rt, 24 h; iv, (a) HCO_2Et, EtOK, 15 °C, 1 h, (b) KSCN, HCl, 50–70 °C, 2 h; v, HNO_3–$NaNO_2$, H_2O, 10 min; vi, BBr_3, CH_2Cl_2, −78 °C, 0.5 h, then 0 °C, 1 h.

methyl ether respectively to give **12**,[15,16] which was treated with NaH and reacted readily with ethyl bromoacetate to afford the *N*-aryl glycine ester **13**. Compound **13** was then annulated to furnish the imidazole ester following a literature procedure:[17] formylation with HCO_2Et–EtOK in benzene followed by cycloaddition with HSCN gave a mercaptoimidazole ester intermediate **14**, which was oxidized by HNO_3–$NaNO_2$ to yield **15**. In the final step, BBr_3 mediated demethylation furnished **3**. The overall yield was 28%.

In C*c*O, it is speculated that the covalently modified Tyr (Tyr-244 in bovine heart C*c*O;[3] Tyr-280 in *Paracoccus denitrificans* C*c*O[4]) phenol has a lower pK_a value than that of an unmodified Tyr residue. Thus, it substantially dissociates at physiological pH to give a phenolate anion, which may act as an electron donor in the catalytic mechanism of O_2 reduction. In order to verify this speculation, we were prompted to study the acidity and redox properties of the synthesized imidazolylphenol derivatives **1**–**3**, as well as of the parent compound **4**, by UV spectrophotometric methods.[18,19] The measurements were conducted at 25 °C in aqueous solutions, keeping a constant ionic strength of 0.01 M ($NaClO_4$). With each compound (**1**–**4**), a series of eight UV spectra were recorded while the pH was gradually increased from 2.0 to 9.0. For compound **4**, the main absorption band shifts from 267 to 296 nm on going from pH 5 to pH 9.‡ Two well distinguished steps can be observed, which have been correlated to the two dissociation events: between pH 5 and 7, the absorption maximum changes from 267 to 277 nm, accompanied by a slight increase in intensity ($\varepsilon_{max\ 267\ nm} = 4.3 \times 10^4$ dm^2 mol^{-1}; $\varepsilon_{max\ 277\ nm} = 4.5 \times 10^4$ dm^2 mol^{-1}). This corresponds to dissociation of the imidazolium species (Scheme 5, a). Between pH 7



Scheme 5 Dissociation equilibria of **4**.

and 9, the absorption maximum shifts more dramatically from 277 to 296 nm with a large increase in extinction coefficient ($\varepsilon_{max\ 296\ nm} = 7.5 \times 10^4$ dm^2 mol^{-1}), corresponding to transformation of the neutral phenol to the phenolate (Scheme 5, b). In this pH range, a distinct isosbestic point is found at 282 nm. By fitting the relative extinction coefficients at different pH and wavelengths, pK_{a1} and pK_{a2} of **4** can be determined to be 6.12 and 7.86, respectively. Note that the pK_a for phenol group dissociation, pK_{a2} (7.86), is much lower than that of Tyr (pK_a = 9.21[20]). This supports the hypothesis that a significant portion of the crosslinked Tyr in natural C*c*O is in deprotonated form (*ca.* 22% at pH 7.3), which very possibly serves as an electron donor. The pK_a values of compounds **1**–**3** were analyzed similarly (Table 1). As shown in Table 1, the phenol groups of esters **1**–**3** are more acidic than that of **4**; this suggests that they can be deprotonated more readily and may operate as effective electron donors at even lower pH values.

‡ No significant spectral changes were observed in the pH range 2–5.

Table 1 pK_a values of **1**–**4** determined at 25 °C in 0.01 M $NaClO_4$ solution

Compound	**1**	**2**	**3**	**4**
pK_{a1}	4.05	4.25	4.30	6.12
pK_{a2}	6.58	6.80	6.89	7.86

In conclusion, we have developed regioselective methods for synthesizing all three isomers of 1-(*o*-hydroxyphenyl)-imidazole carboxylic esters and determined their pK_a values using spectrophotometry. These compounds can serve not only as building blocks for biomimetic syntheses, but are also potential precursors to bioactive (imidazol-1-yl)phenoxy compounds.[21] The application of these compounds to the synthesis of new active-site analogues of cytochrome *c* oxidase and the studies of their redox interactions with metal ions will be reported in due course.

Experimental

General

All reagents were used as supplied commercially unless otherwise noted. Anhydrous THF was distilled from sodium under N_2 before use. CH_2Cl_2 was distilled under N_2 from P_2O_5. DMF was dried with 4 Å molecular sieves and distilled under vacuum. 2-Acetamidoanisole (**12**) was prepared from 2-aminophenol according to literature procedures.[15,16] Melting points were determined on MEL-TEMP and are uncorrected. UV-VIS spectra were measured on a Hewlett-Packard 8452A Diode Array spectrophotometer. IR spectra were recorded on a Mattson Infinity 60AR spectrometer. ^{1}H NMR spectra were recorded on a Varian XL-400 instrument using $CDCl_3$ as the solvent unless otherwise noted. The pH values were measured by a Precision pH meter. Routine mass spectra were measured by the Mass Spectrometry Facility, University of California, San Francisco.

1-(*o*-Methoxyphenyl)imidazole (5)

To a suspension of the sodium imidazolate salt (1.80 g, 20.0 mmol) in anhydrous DMF (4 mL) were added 2-iodoanisole (4.68 g, 20.0 mmol) and copper powder (0.126 g, 2.0 mmol). The reaction mixture was stirred at 150 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (15 mL) and water (5 mL), stirred for 1 h, and filtered. The organic layer was separated, washed with water, dried over anhydrous K_2CO_3, and evaporated to dryness under vacuum. The residue was purified by column chromatography on silica gel (eluent: methanol–CH_2Cl_2 = 5 : 95 v/v) to give **5** as a white solid (1.64 g, 47%). Mp 52–54 °C. ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1H), 7.34 (td, J = 7.7, 1.6 Hz, 1H), 7.27 (dd, J = 7.7, 1.6 Hz, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 7.08–6.98 (m, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 152.46, 137.71, 128.82, 128.76, 126.41, 125.41, 120.89, 120.16, 112.23, 55.69. IR (KBr) 3015, 1254, 1050, 755 cm^{-1}. MS (*m*/*z*) 174 (M^+), 159, 143, 107 (100), 65, 43. HRMS: calcd for $C_{10}H_{10}N_2O$ (M^+): 174.0793; found: 174.0790.

Methyl 1-(*o*-methoxyphenyl)imidazole-2-carboxylate (6)

To a solution of **5** (870 mg, 5.0 mmol) in dry THF at −78 °C under N_2 was added dropwise 2.5 M *n*-butyllithium in hexane (2.10 mL, 5.25 mmol). The reaction mixture was stirred for 30 min and then allowed to warm to −20 °C over 40 min. The mixture was cooled to −78 °C again and chlorotrimethylsilane (570 mg, 5.25 mmol) was added dropwise. After stirring for another hour, methyl chloroformate (496 mg, 5.25 mmol) was added *via* a syringe; the cold bath was then removed and the reaction was allowed to warm to room temperature and stirred for 12 h. Water was added to quench the reaction and the THF was removed on a rotary evaporator. The resulting slurry was extracted with CH_2Cl_2 (40 mL). The organic layer was separated, washed with water (10 mL × 2) and dried ($MgSO_4$). After removal of the drying agent and evaporation of solvents, the crude product was subjected to column chromatography on silica gel (eluent: ether–hexane = 1 : 3 v/v) to give the ester **6** (987 mg, 85%). Mp 104–106 °C. ^{1}H NMR ($CDCl_3$) δ 7.42 (td, J = 7.9, 1.6 Hz, 1H), 7.27 (s, 1H), 7.23 (dd, J = 5.5, 1.6 Hz, 1H), 7.09 (s, 1H), 7.04–6.99 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.64, 154.05, 137.50, 130.27, 129.65, 127.19, 127.04, 126.16, 120.42, 111.72, 55.62, 52.08. IR (KBr) 3012, 1718, 1110 cm^{-1}. EIMS (*m*/*z*) 232 (M^+), 201, 173 (100), 144, 92, 77, 68, 59. HRMS: calcd for $C_{12}H_{12}N_2O_3$ (M^+): 232.0847; found: 232.0850.

Methyl 1-(*o*-hydroxyphenyl)imidazole-2-carboxylate (1)

A typical procedure for the demethylation of the methyl aryl ethers is given as follows. To a solution of **6** (232 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (2 mL) was added BBr_3 (377 mg, 1.5 mmol) at −78 °C under N_2. The mixture was stirred at −78 °C for 0.5 h and at 0 °C for 1 h. The excess of BBr_3 was quenched by adding one drop of MeOH and the resulting mixture was concentrated. The residue was subjected to column chromatography on silica gel (eluent: methanol–CH_2Cl_2 = 5 : 95 v/v) to give **1** (192 mg, 88%). Mp 217–219 °C. ^{1}H NMR (CD_3OD) δ 7.26 (s, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.06 (s, 1H), 7.00–6.94 (m, 2H), 3.73 (s, 3H). ^{13}C NMR (CD_3OD) δ 160.57, 154.11, 131.90, 131.17, 124.25, 124.21, 122.97, 121.58, 115.44, 115.21, 51.25. IR (KBr) 3362, 3008, 1720, 1204, 1110, 736 cm^{-1}. EIMS (*m*/*z*) 218 (M^+), 203, 187, 145, 113, 92, 57 (100). HRMS: calcd for $C_{11}H_{10}N_2O_3$ (M^+): 218.0691; found: 218.0695.

1-(*o*-Hydroxyphenyl)imidazole (4)

This compound was prepared from **5** with the same procedure as **1** except that the eluent for column chromatography was changed to methanol–CH_2Cl_2 = 10 : 90 (v/v). Yield 98%. Mp 233.5–235 °C (lit.,[22] 233–234 °C). ^{1}H NMR for **4**·HCl (CD_3OD) δ 8.96 (s, 1H), 7.68 (s, 1H), 7.51 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 8.0 Hz, 1H). ^{13}C NMR for **4**·HCl (CD_3OD) δ 154.61, 140.11, 140.00, 134.79, 129.16, 126.60, 124.21, 123.82, 120.57. IR (KBr) 3550, 3024, 748 cm^{-1}. EIMS (*m*/*z*) 160 (M^+), 133 (100), 120, 104, 78, 65, 57. HRMS: calcd for $C_9H_8N_2O$ (M^+): 160.064; found: 160.064.

Methyl 1-(*o*-nitrophenyl)imidazole-4-carboxylate (8)

A mixture of 1-fluoro-2-nitrobenzene (1.55 g, 11.0 mmol), methyl imidazole-4-carboxylate (**7**) (1.26 g, 10.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) in acetonitrile (30 mL) was heated at reflux for 12 h. After the reaction mixture was cooled to room temperature, it was filtered and the solid was washed with ethyl acetate (10 mL × 2). The combined organic solution was dried over anhydrous $MgSO_4$ and evaporated to dryness to give a pale yellow solid. Recrystallization from petroleum ether–ethyl acetate yielded the pure product **8** as a white solid (2.17 g, 88%). Mp 172–174 °C. ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 162.72, 138.01, 134.78, 134.19, 130.64, 129.65, 128.89, 126.12, 125.81, 121.70, 51.90. IR (KBr) 3025, 1718, 1540, 1122, 756 cm^{-1}. EIMS: 248 (M^+ + H), 230, 216, 160, 134, 105 (100), 78. HRMS: calcd for $C_{11}H_{10}N_3O_4$ (M^+ + H): 248.0671; found: 248.0657.

Methyl 1-(*o*-aminophenyl)imidazole-4-carboxylate (9)

To a solution of **8** (1.24 g, 5.0 mmol) in CH_2Cl_2 (15 mL) was added a solution of $SnCl_2$·$2H_2O$ (3.60 g, 16.0 mmol) in 3 M HCl (10 mL). The mixture was stirred at room temperature for

4 h. K_2CO_3 (*ca.* 1 g) was slowly added to the reaction mixture until the evolution of CO_2 ceased. The mixture was then filtered and the solid was washed subsequently with CH_2Cl_2 (15 mL × 2) and water (15 mL × 2). The aqueous layer of the filtrate was separated and extracted with ethyl acetate (15 mL × 3). The organic phases were combined and dried over $MgSO_4$. Evaporation of the solvents gave compound **9** as a white solid (0.79 g, 73%). Mp 98–100 °C. ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 1.2 Hz, 1H), 7.66 (d, J = 1.2 Hz, 1H), 7.24 (td, J = 8.0, 1.4 Hz, 1H), 7.08 (dd, J = 8.0, 1.4 Hz, 1H), 6.84 (dd, J = 8.0, 1.4 Hz, 1H), 6.80 (td, J = 8.0, 1.4 Hz, 1H), 3.89 (s, 3H), 3.66 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 163.06, 141.66, 138.48, 130.45, 126.90, 126.12, 122.16, 121.71, 118.70, 116.70, 51.80. IR (KBr) 3440, 3378, 3017, 1725, 1092, 740 cm^{-1}. EIMS (*m*/*z*) 217 (M^+), 186, 158 (100), 132, 119, 92, 77, 65. HRMS: calcd for $C_{11}H_{11}N_3O_2$ (M^+): 217.0851; found: 217.0850.

Methyl 1-phenylimidazole-4-carboxylate (10)

The diazotization reaction of **9** followed a literature procedure.[3] The reduction product, methyl 1-phenylimidazole-4-carboxylate (**10**) was obtained in 50% yield. Mp 89–90 °C. ^{1}H NMR (CD_3OD) δ 8.17 (d, J = 1.4 Hz, 1H), 8.12 (d, J = 1.4 Hz, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 3.76 (s, 3H). IR (KBr) 3005, 1720, 1125, 764 cm^{-1}. EIMS (*m*/*z*) 202 (M^+), 171 (100), 144, 116, 104, 89, 77. HRMS: calcd for $C_{11}H_{10}N_2O_2$ (M^+): 202.0742; found: 202.0750.

Methyl 1-(*o*-methoxyphenyl)imidazole-4-carboxylate (11)

A dry 100 mL Schlenk flask equipped with a reflux condenser was charged with 2-iodoanisole (1.40 g, 6.0 mmol), methyl imidazole-4-carboxylate (**7**) (0.63 g, 5.0 mmol), Cs_2CO_3 (1.48 g, 5.0 mmol), 4 Å molecular sieves (1 g) and anhydrous DMF (20 mL). The system was degassed by evacuation and refilling with N_2 several times. CuOTf (53 mg, 0.25 mmol) was then added to the mixture against a slow N_2 flow. The resulting mixture was heated to 100 °C and stirred for 8 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated *in vacuo* while controlling the temperature at 40–50 °C. The residue was subjected to preparative TLC on silica gel (eluent: CH_2Cl_2–hexane = 30 : 70 v/v saturated with ammonia) to give **11** (0.46 g, 40%). Mp 86–87 °C. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 1.4 Hz, 1H), 7.74 (d, J = 1.4 Hz, 1H), 7.39 (td, J = 7.6, 1.6 Hz, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.08–7.02 (m, 2H), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 163.31, 152.42, 138.41, 133.33, 129.83, 126.43, 125.37, 121.05, 115.04, 112.35, 55.82, 51.67. IR (KBr) 3010, 1722, 1245, 1110, 745 cm^{-1}. EIMS (*m*/*z*) 232 (M^+), 201, 174 (100), 147, 134, 77. HRMS: calcd for $C_{12}H_{12}N_2O_3$ (M^+): 232.0848; found 232.0855.

Methyl 1-(*o*-hydroxyphenyl)imidazole-4-carboxylate (2)

This compound was prepared from **11** using the same procedure as for **1**. Yield 90%. Mp 211–213 °C. ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 1.3 Hz, 1H), 7.70 (d, J = 1.3 Hz, 1H), 7.20 (td, J = 7.8, 1.5 Hz, 1H), 7.11 (dd, J = 7.8, 1.5 Hz, 1H), 6.98–6.92 (m, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.21, 150.91, 139.21, 135.34, 128.72, 127.67, 127.48, 121.85, 111.14, 110.50, 51.67. IR (KBr) 3550, 3010, 1718, 1195, 1110, 735 cm^{-1}. EIMS (*m*/*z*) 218 (M^+), 187, 165, 113, 92 (100), 77, 57. HRMS: calcd for $C_{11}H_{10}N_2O_3$ (M^+): 218.0691; found: 218.0685.

N-Acetyl-*N*-(*o*-methoxyphenyl)glycine ethyl ester (13)

A solution of 2-acetamidoanisole (**12**) (6.60 g, 40.0 mmol) in anhydrous THF (50 mL) was cooled to 0 °C with an ice–water bath. To this solution was added slowly 60% NaH in mineral oil (1.68 g, 42.0 mmol) with constant stirring. After addition of NaH, the mixture was stirred for another 1 h at rt, and ethyl bromoacetate (7.02 g, 42.0 mmol) was added. The resulting mixture was stirred for 24 h at rt. Most of the THF was evaporated on a rotary evaporator. Ether (400 mL) was added to the residue, and the mixture was washed with brine (40 mL × 2). The organic layer was separated and dried over $MgSO_4$. After removal of the solvents, the residue was subjected to column chromatography on silica gel (eluent: ethyl acetate–hexane = 15 : 85 v/v) to give **13** as an oil (9.54 g, 95%). ^{1}H NMR ($CDCl_3$) δ 7.40 (dd, J = 8.1, 1.5 Hz, 1H), 7.29 (td, J = 8.1, 1.5 Hz, 1H), 6.95–6.89 (m, 2H), 4.93 (d, J = 17.4 Hz, 1H), 4.18–4.06 (m, 2H), 3.80 (s, 3H), 3.59 (d, J = 17.4 Hz, 1H), 1.81 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.48, 169.53, 154.64, 131.27, 130.26, 129.62, 120.88, 111.68, 60.95, 55.42, 49.66, 21.45, 14.07. IR (neat) 3010, 2980, 1742, 1650, 1175, 750 cm^{-1}. EIMS (*m*/*z*) 251 (M^+), 209, 136 (100), 120, 77. HRMS: calcd for $C_{13}H_{17}NO_4$ (M^+): 251.1158; found: 251.1153.

Ethyl 2-mercapto-1-(*o*-methoxyphenyl)imidazole-5-carboxylate (14)

In a dry Schlenk flask was placed a mixture of **13** (5.02 g, 20.0 mmol), ethyl formate (5.0 g, 67 mmol) and benzene (5 mL). The flask was cooled in an ice-bath and, with constant stirring, potassium ethoxide (1.77 g, 21.0 mmol) was added in small portions over 15 min. The reaction mixture was maintained below 15 °C, and stirred for another hour after all of the potassium ethoxide had been added. The mixture was then placed in a refrigerator to stand overnight, and then extracted with water. To the aqueous solution were added KSCN (2.04 g, 21.0 mmol) and 12 M HCl (3.8 mL). The mixture was heated with an oil bath at 50–70 °C for 2 h, and then allowed to stand overnight at room temperature. The mixture was extracted with ethyl acetate (15 mL × 3) and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvents, the residue was subjected to column chromatography on silica gel (eluent: ethyl acetate–hexane = 20 : 80 v/v) to give **14** (2.50 g, 45%). Mp 196 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ 12.45 (br s, 1H), 7.46 (s, 1H), 7.44 (td, J = 7.4, 1.5 Hz, 1H), 7.30 (dd, J = 7.4, 1.5 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 4.15–4.05 (m, 2H), 3.76 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 157.66, 154.87, 130.77, 129.43, 125.23, 122.52, 123.17, 121.72, 120.59, 111.97, 60.85, 55.82, 13.92. IR (KBr) 3015, 2065, 1722, 1250, 1124, 1040, 750 cm^{-1}. EIMS (*m*/*z*) 278 (M^+, 100), 245, 219, 189, 175, 77. HRMS: calcd for $C_{13}H_{14}N_2O_3S$ (M^+): 278.0725; found: 278.0730.

Ethyl 1-(*o*-methoxyphenyl)imidazole-5-carboxylate (15)

A solution of concentrated nitric acid (3.3 mL) and $NaNO_2$ (20 mg) in water (9.5 mL) was cooled to 0 °C in an ice-bath. To the solution was added **14** (2.36 g, 8.5 mmol) with continuous stirring. After all material had been added, the solution was stirred for another 10 min until the evolution of nitric oxide ceased. An excess of solid K_2CO_3 was added carefully with stirring. The mixture was extracted with ethyl acetate (15 mL × 3); the extract was dried ($MgSO_4$) and concentrated on a rotary evaporator. The residue was subjected to column chromatography on silica gel (eluent: ethyl acetate–hexane = 10 : 90 v/v) to give **15** (1.80 g, 86%). Mp 90–92 °C. ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 7.61 (s, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.05–6.88 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 159.19, 150.98, 131.87, 130.03, 125.65, 124.27, 122.62, 121.76, 115.33, 110.56, 61.88, 55.44, 13.43. IR (KBr) 3015, 1724, 1245, 1110, 740 cm^{-1}. EIMS (*m*/*z*) 246 (M^+), 245 ($M^+ - H$), 193, 176, 150, 136, 85, 64 (100). HRMS: calcd for $C_{13}H_{14}N_2O_3$ (M^+): 246.100; found: 246.100.

Ethyl 1-(*o*-hydroxyphenyl)imidazole-5-carboxylate (3)

This compound was prepared from **15** using the same procedure as for **1** except that ethanol was used to quench the reaction instead of methanol. Yield 90%. Mp 215–217 °C. ^{1}H

NMR (CD_3OD) δ 7.69 (s, 1H), 7.57 (s, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.83 (t, J = 7.2 Hz, 1H), 4.15 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CD_3OD) δ 156.20, 150.99, 138.95, 133.94, 131.99, 131.13, 129.06, 122.94, 121.75, 119.69, 61.03, 13.84. IR (KBr) 3545, 3012, 1722, 1200, 1110, 735 cm^{-1}. EIMS (*m*/*z*) 232 (M^+), 186 (100), 158, 132, 103, 81, 57. HRMS: calcd for $C_{12}H_{12}N_2O_3$ (M^+): 232.0848; found: 232.0844.

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