Synthesis of 2-Substituted 1-Hydroxyimidazoles through Directed Lithiation

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Benzylation of 3-hydroxyimidazole 1-oxide gave 3-(benzyloxy)imidazole 1-oxide, which was deoxygenated with phosphorous trichloride to produce 1-(benzyloxy)imidazole. 1-(Benzyloxy)imidazole was deprotonated selectively at C-2 by *n*-butyllithium. The anion formed was reacted with electrophiles to give 1-(benzyloxy)imidazoles with carbon, halogen, silicon, or sulfur substituents at the 2-position. Subsequent debenzylation afforded 2-substituted 1-hydroxyimidazoles which in turn could be deoxygenated to give 2-substituted imidazoles.

Introduction

1-Hydroxyimidazoles[1−4] are useful intermediates for the preparation of pharmaceuticals and agricultural chemicals. They are usually obtained by condensation of monooximes of 1,2-diketones with ammonia and an aldehyde[5−10] or with an aldimine.[11] 1-Hydroxyimidazoles have also been prepared by reaction of α-hydroxylamino oximes with triethyl orthoformate followed by dehydration[12] or by reaction of olefins and nitrosyl hydrogen sulfate in the presence of aliphatic nitriles.[13−16] 1-Hydroxyimidazoles have been obtained by selective reduction of 3-hydroxyimidazole 1-oxide.[9,17] prepared by cyclization of a 1,2-diketone, an aldehyde, and hydroxylamine. Finally, 1-hydroxyimidazole (**5a**) was synthesized by N-oxidation of imidazole with peroxyphthalic acid[18] or 3-chloroperbenzoic acid.[19]

All of these reactions produce unsubstituted or alkyl- or aryl-substituted 1-hydroxyimidazoles. Only a few 1-hydroxyimidazoles with functional substituents have been reported.[20−25] The methods used are frequently effective but not general. No examples of introduction of functional substituents *after* the cyclization seem to have been reported.

In order to get more general access to 1-hydroxyimidazoles with an array of different substituents, a highly selective method for the introduction of a variety of substituents in 1-hydroxyimidazole (**5a**) *after* the imidazole ring has been formed has now been developed. The method is based on deprotonation followed by reaction with an electrophile.

Results and Discussion

The starting material in the present approach was 1-(benzyloxy)imidazole (**3**), which can be prepared in several ways. The known methods were optimized but could not compete with a new method described below.

The first method for the preparation of 1-(benzyloxy)-imidazole (**3**) is oxidation of imidazole with 3-chloroperbenzoic acid followed by O-benzylation without isolating the intermediate 1-hydroxyimidazole (**5a**).[19] The overall yield was optimized to 14% (see the Experimental Section), but the method is hampered by two tedious continuous extractions during workup in order to remove 3-chlorobenzoic acid and unchanged imidazole.

The second method for the preparation of 1-(benzyloxy)imidazole (**3**) was based on O-benzylation of 1-hydroxyimidazole (**5a**) prepared in fair yield by partial hydrogenolysis of 3-hydroxyimidazole 1-oxide (**1**), in its turn obtained in 80% yield from glyoxal, formaldehyde, and hydroxylamine.[17] The sequence was optimized to give 1-(benzyloxy)imidazole (**3**) in 50−55% overall yield.

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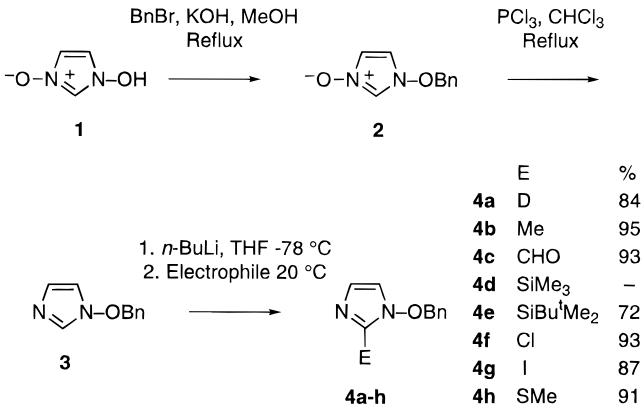
Scheme 1



	E	%
4a	D	84
4b	Me	95
4c	CHO	93
4d	$SiMe_3$	–
4e	$SiBu^tMe_2$	72
4f	Cl	93
4g	I	87
4h	SMe	91

The drawbacks of this method are the long reaction time for the hydrogenolysis (about 1 week); contamination by imidazole (about 15%, which had to be removed by continuous extraction prior to benzylation); and the difficulties in performing the hydrogenolysis on a large scale.

In a new approach, 3-hydroxyimidazole 1-oxide (**1**) was first benzylated to give 3-(benzyloxy)imidazole 1-oxide (**2**). The *N*-oxide **2** without isolation was then deoxygenated using phosphorous trichloride to give 1-(benzyloxy)-imidazole (**3**) in 69% overall yield. This method provides a quick and simple procedure suitable for large-scale preparation of 1-(benzyloxy)imidazole (**3**). This method is also the best route to 1-hydroxyimidazole (**5a**) since 1-(benzyloxy)imidazole (**3**) could be converted almost quantitatively into 1-hydroxyimidazole (**5a**) by hydrogenolysis under mild conditions.

The benzyloxy group displays ortho-directing capabilities in metalation reactions with lithium bases, as was demonstrated recently in the pyrazole[26] and the 1,2,3-triazole series.[27]

1-(Benzyloxy)imidazole (**3**) was lithiated by treatment with *n*-butyllithium at −78 °C. Quenching by addition of methanol-*O*-*d* showed that metalation takes place selectively at the 2-position and is complete in less than 5 min. The position of the deuteration was established by ^{1}H-NMR and ^{13}C-NMR spectroscopy. The carbon signals of 1-(benzyloxy)imidazole (**3**) were assigned by the characteristic C−H coupling constants. The proton signals were then assigned by means of C−H correlated spectra (see the Experimental Section).

The metalation can be followed by addition of different electrophiles. In this way a series of carbon, silicon, halogen, and sulfur substituents could be introduced selectively at the 2-position to give the products **4a**−**h** in high yields (Scheme 1).

All products **4a**−**h** were stable except the 2-trimethylsilyl compound **4d** which could not be isolated since it underwent quantitative hydrolysis during the aqueous workup producing 1-(benzyloxy)imidazole (**3**). The formation of the trimethylsilyl compound **4d**, expected to be unstable,[28−30] was proven by the fact that it could be further deprotonated *in situ* at C-5.[31]

The (benzyloxy)imidazoles **4** could be debenzylated by palladium-catalyzed hydrogenolysis under mild conditions to give the corresponding 2-substituted 1-hydroxyimidazoles **5b** and **5c**. Under these conditions 1-(benzyloxy)-2-chloroimidazole (**4f**) also lost its halogen atom to give 1-hydroxyimidazole (**5a**) as the hydrochloride. However, selective debenzylation of 1-(benzyloxy)-2-chloroimidazole (**4f**) to 1-hydroxy-2-chloroimidazole hydrochloride (**5c**·HCl) could be effected with concd hydrochloric acid (Scheme 2).

Several methods have been devised for the reductive removal of the *N*-hydroxy group of 1-hydroxyimidazoles. Such dehydroxylation has been effected by palladium-catalyzed hydrogenolysis at room temperature for extended reaction times[24,32] or by using titanium trichloride,[15] sodium borohydride,[9] sodium bis(2-methoxyethoxy) aluminum dihydride (Red-Al, Aldrich),[14] or zinc in formic acid.[33] Therefore, the present method for introduction of substituents in 1-hydroxyimidazole also provides access to the corresponding substituted imidazoles. As an example, 1-hydroxyimidazole (**5a**) was reduced by hydrogen in the presence of palladium to give imidazole (**6a**) in 89% yield. Under these conditions 1-hydroxy-2-chloroimidazole (**5c**) lost the halogen. However, reduction with titanium trichloride proceeded selectively, producing 2-chloroimidazole (**6b**) in quantitative yield. The present approach to the preparation of 2-chloroimidazole (**6b**) gives higher yields than previous methods.[34,35]

In conclusion, a new method which seems superior to previous ones for the preparation of 1-(benzyloxy)imidazole (**3**) has been developed. The benzyloxy group is an excellent ortho-directing group in lithiation reactions which give access to 2-substituted 1-(benzyloxy)imidazoles (**4a**−**h**). Debenzylation and deoxygenation could be performed in separate steps under mild conditions compatible with sensitive substituents giving rise to 2-substituted 1-hydroxyimidazoles and imidazoles.

Experimental Section

General Methods. All reactions involving air-sensitive reagents were performed under nitrogen using syringe−septum cap techniques. All glassware was flame-dried prior to use. Flash chromatography[36] was performed using silica gel (Merck 60, 70−230 mesh). Melting points are uncorrected. All new compounds were colorless, unless otherwise stated. NMR spectra were recorded on a 200 MHz instrument.[19] **Hydroxy- and alkoxyimidazoles were never distilled in amounts exceeding 100 mg since violent decomposition of imidazole 1-oxides has been reported taking place at ca. 150 °C.**[37]

Materials. All solvents and reagents were obtained from Fluka or Aldrich and used without further purification with the following exceptions: Tetrahydrofuran was distilled from Na/benzophenone under nitrogen prior to use. *n*-Butyllithium was titrated prior to use.[38] DMF was sequentially dried with and stored over 3 Å molecular sieves.[39]

1-(Benzyloxy)imidazole (3). Method a. A solution of imidazole (17 g) dissolved in ethyl acetate (3.4 L) was added to a solution of 55% 3-chloroperbenzoic acid (92.5 g) in ethyl

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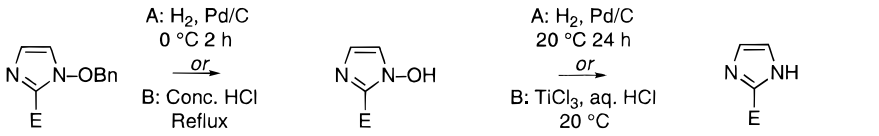
Scheme 2



	E
3	H
4c	CHO
4f	Cl

	Method	E	%
5a	A	H	96
5b	A	CHO	97
5a, HCl	A	H	99
5a, HCl	B	H	98
5c, HCl	B	Cl	89

	Method	E	%
6a	A	H	89
6b	B	Cl	100

acetate (1 L).[40] Stirring for 3 d, removal of the ethyl acetate, addition of water (250 mL), filtration, and extraction of the residue with water (5 × 50 mL) gave a combined aqueous solution which was evaporated to ca. 150 mL. 3-Chlorobenzoic acid and some imidazole were then removed by continuous extraction with diethyl ether for 2 d. The pH of the aqueous solution was then adjusted to 10 by addition of trisodium phosphate (16.4 g), and unchanged starting material was removed by continuous extraction with diethyl ether for 2 d. To the aqueous solution was added 33% aqueous sodium hydroxide (30 g). Evaporation to dryness, drying at 0.1 mmHg at 100 °C for 3 h, dissolution in DMF (68 mL) in a nitrogen atmosphere, cooling to 0 °C, addition of benzyl bromide (9.54 mL) during 10 min, stirring at room temperature for 18 h, addition of saturated aqueous sodium hydrogen carbonate (35 mL) and water (170 mL), extraction with dichloromethane (3 × 100 mL), drying ($MgSO_4$), removal of the dichloromethane, and flash chromatography (heptane−ethyl acetate, 2:1 → 0:1) gave 6.28 g (14%) of 1-(benzyloxy)imidazole (**3**) as a yellow oil (reported[25] bp 150 °C/0.05 mmHg). δ_H ($CDCl_3$): 7.26−7.39 (6H, m, Ph and H-2), 6.92 (1H, t, J = 1.25 Hz, H-5), 6.87 (t, J = 1.25 Hz, H-4), 5.08 (2H, s, CH_2). δ_C ($CDCl_3$):[41] 133.3 (s, C-1′), 131.4 (ddd, $J_{C-2,H-2}$ = 213.2 Hz, $J_{C-2,H-5}$ = 9.0 Hz, and $J_{C-2,H-4}$ = 5.6 Hz, C-2), 129.3 (dt, C-3′), 129.3 (dt, C-4′), 128.6 (ddd, C-2′), 125.2 (ddd, $J_{C-4,H-4}$ = 192.6 Hz, $J_{C-4,H-5}$ = 11.4 Hz, and $J_{C-4,H-2}$ = 8.8 Hz, C-4), 115.3 (ddd, $J_{C-5,H-5}$ = 194.0 Hz, $J_{C-5,H-4}$ = 16.1 Hz, and $J_{C-5,H-2}$ = 3.0 Hz, C-5), 82.3 (t, CH_2). The heteroaromatic proton signals were separated in C_6D_6 (δ (C_6D_6): 7.37 (t, J = 1.2 Hz, H-2), 7.10 (t, J = 1.2 Hz, H-5), 6.69 (t, J = 1.2 Hz, H-4). The proton signals were assigned by CH correlated spectra.

3-Hydroxyimidazole 1-Oxide (1).[17] A stirred mixture of 40% aqueous glyoxal (7.6 mL), 37% aqueous formaldehyde (6.0 mL), and methanol (15 mL) was cooled to 0 °C, and a solution of hydroxylammonium chloride (9.26 g) in water (11.2 mL) was added, followed by addition of concd hydrochloric acid (1.33 mL) over 1 min. The resulting solution was stirred for 24 h at 20 °C and then, cooled to 0 °C, and the pH was adjusted to 4.1 (pH meter) with 33% aqueous sodium hydroxide while the temperature was kept below 20 °C. This caused precipitation. After the mixture was stirred for 1 h at 0 °C, the precipitate was filtered off, washed with water (10 mL, 0 °C), methanol (10 mL, 0 °C), and ether (20 mL), and dried to yield 5.35 g (80%) of 3-hydroxyimidazole 1-oxide (**1**), mp 178−180 °C. Recrystallization from water did not raise the melting point (reported[17] mp 178−180 °C).

1-(Benzyloxy)imidazole (3). Method b. To 3-hydroxyimidazole 1-oxide (**1**) (5.0 g, 50 mmol) dissolved in 4 M hydrochloric acid (35 mL) was added 10% palladium on carbon (0.26 g), and the mixture was hydrogenated at 95 °C and 1 atm until 1.5 L of hydrogen had been consumed (65−145 h). Filtration, removal of the solvents, and coevaporation twice with toluene gave 6.4 g of a 15:80:5 mixture of imidazole, 1-hydroxyimidazole (**5a**), and unchanged starting material (**1**) (^{1}H-NMR).[44] To this mixture was added trisodium phosphate (1.0 g, 2.6 mmol) and 33% aqueous sodium hydroxide (ca. 7 mL) until the pH was adjusted to 10. The solution was extracted with diethyl ether overnight in order to remove imidazole. The absence of imidazole in the aqueous solution should be confirmed by ^{1}H-NMR. The water was removed at 40 °C and 0.1 mmHg. The residue was then coevaporated with toluene (3 × 20 mL) and dried at 0.1 mmHg over P_2O_5 until constant weight.

Under nitrogen the residue was dissolved in dry dimethylformamide (20 mL). At 0 °C a 55% suspension of sodium hydride in mineral oil (50 mmol) and benzyl bromide (6.54 mL, 55 mmol) were added. After the mixture was stirred at 20 °C for 16 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added with caution. Dilution with water (50 mL), extraction with diethyl ether (5 × 100 mL), drying ($MgSO_4$), removal of diethyl ether, removal of DMF by drying at 0.01 mmHg overnight, and flash chromatography (heptane−ethyl acetate, 2:1 → 0:1) gave 4.35−4.8 g (50−55%) of 1-(benzyloxy)-imidazole (**3**), R_f 0.45 (ethyl acetate−acetic acid, 1:0.01), identical with the material above.

1-(Benzyloxy)imidazole (3). Method c. 1-Hydroxyimidazole 3-oxide (**1**) (10.04 g, 100 mmol) and 85% potassium hydroxide (8.6 g, 130 mmol) was dissolved in methanol (100 mL). When the solution was clear, benzyl bromide (11.9 mL, 100 mmol) was added during 2 min, and the mixture was refluxed for 1 h. Filtration and extraction of the filter cake with MeOH (2 × 80 mL) and removal of the solvent gave a brown oil which was suspended in chloroform (100 mL). The suspension was cooled to 0 °C, and phosporous trichloride (62 mL, 7 equiv) was added at such a rate that the internal temperature was kept under 25 °C. The mixture was refluxed for 1.5 h and cooled. Solvents and excess PCl_3 were removed *in vacuo*. Treatment by addition of toluene (100 mL) and evaporation was repeated twice. Addition of water (250 mL) and Et_2O (200 mL), adjustment to pH 10 by addition of K_2CO_3 (ca. 75 g), separation of the organic layer, extraction of the aqueous solution with Et_2O (3 × 150 mL), drying of the combined organic phases ($MgSO_4$), filtration, evaporation, and flash chromatography (heptane−CH_2Cl_2−Pr^iOH, 1:1:0 → 1:1:5%) gave 12.0 g (69%) of 1-(benzyloxy)imidazole as a yellow oil which crystallized upon cooling. Mp 31−33 °C, R_f 0.26 (heptane−CH_2Cl_2−Pr^iOH, 1:1:5%), identical with the material above.

Lithiation−Standard Procedure. Under nitrogen, a solution of 1-(benzyloxy)imidazole (**3**) (174 mg, 1.0 mmol) in tetrahydrofuran (8 mL) was cooled to −78 °C. *n*-Butyllithium (1.68 M in hexanes, 0.71 mL, 1.2 mmol) was added with

(40) Imidazole and 3-chloroperbenzoic acid should not be mixed in the dry state because this may lead to a violent reaction.

(41) The carbon signals of 1-(benzyloxy)imidazole (**3**) were assigned assuming that $\delta_{C-2} > \delta_{C-4} > \delta_{C-5}$, as in other 1-substituted imidazoles.[42,43] The assignment was confirmed by the characteristic large one bond C−H coupling of C-2 and the distinct two and three C−H couplings of C-5 ($^2J_{C-5,H-4}$ = 16.1 and $^3J_{C-5,H-2}$ = 3.0 Hz) which are different from those of C-4 (both in the range 8.8−11.6 Hz).[42,43] The assignment of the ^{1}H- and ^{13}C-NMR signals of the 2-substituted 1-(benzyloxy)imidazoles (**6a**−**h**) was based on the NMR chemical shifts of 1-(benzyloxy)imidazole (**3**) and coupled ^{13}C-NMR spectra.

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(44) All starting material is consumed if the reaction time is increased, but the yield of **4** decreases due to its further reduction to imidazole.

stirring during 2 min. After the mixture was stirred for an additional 5 min, the electrophile was added. Stirring was continued at −78 °C for 1 h, and then the reaction mixture was allowed to warm to 20 °C in the course of 1 h. Stirring was continued at 20 °C for an additional 0.5 h. The mixture was worked up by addition of saturated aqueous sodium hydrogen carbonate (10 mL), extraction with dichloromethane (5 × 10 mL), drying ($MgSO_4$), filtration, and removal of the dichloromethane to give the crude product.

Preparation of 2-Substituted 1-(Benzyloxy)imidazoles. 1-(Benzyloxy)-2-[^{2}H]imidazole (4a). After addition of monodeuteriomethanol (CH_3OD, 0.20 mL), the mixture was worked up as above to give a crude product which was flash chromatographed (heptane−ethyl acetate, 2:1 → 0:1), affording 146 mg (84 %) of 1-(benzyloxy)-2-[^{2}H]imidazole (**4a**). The ^{1}H spectrum (in C_6D_6 solution) was identical with that of the starting material except that the signal from H-2 was absent and the signals from H-4 and H-5 each collapsed to doublets. The signal from C-2 appeared as a triplet (J_{CD} = 32.5 Hz).

1-(Benzyloxy)-2-methylimidazole (4b). Methyl iodide (5 equiv) was added, and the mixture was stirred at −78 °C for 1 h. In order to destroy excess of methyl iodide, 33% dimethylamine in ethanol (5 mL) was added at −78 °C, and the mixture was worked up as above to give 179 mg (95%) of 1-(benzyloxy)-2-methylimidazole (**4b**) as a yellow oil. Ball−tube distillation at 150 °C/2 mmHg gave an analytical specimen. Anal. Found: C, 69.94; H, 6.39; N, 14.82. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. δ_H ($CDCl_3$): 7.26−7.41 (5H, m), 6.88 (1H, d, J = 1.5 Hz), 6.79 (1H, d, J = 1.5 Hz), 5.05 (2H, s), 2.13 (3H, s). δ_C ($CDCl_3$): 139.7, 133.0, 129.4, 129.2, 128.4, 123.3 ($J_{C-4,H-4}$ = 191.5 Hz and $J_{C-4,H-5}$ = 8.3 Hz, C-4), 114.4 ($J_{C-5,H-5}$ = 193.3 Hz and $J_{C-5,H-4}$ = 15.7 Hz, C-5), 81.0, 11.0.

1-(Benzyloxy)-2-formylimidazole (4c). After addition of dimethylformamide (0.38 mL, 4.8 equiv), the mixture was stirred as in the standard procedure. Then 2 M aqueous hydrochloric acid (5 mL) was added, and the mixture was stirred for 1 h. Addition of saturated aqueous $NaHCO_3$ to adjust the pH to 10 and extractive workup with dichloromethane as described above gave a residue which by flash chromatography (heptane−ethyl acetate, 4:1 → 0:1) afforded 188 mg (93%) of 1-(benzyloxy)-2-formylimidazole (**4c**). Mp: 57−58 °C (ethyl acetate−heptane). Anal. Found: C, 65.14; H, 5.06; N, 13.76. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. δ_H: 9.76 (1H, d, J = 0.8 Hz), 7.38 (5H, s), 7.07 (1H, d, J = 1.0 Hz), 6.99 (1H, t, J = 0.9 Hz), 5.23 (2H, s). δ_C ($CDCl_3$): 178.9 (J_{C-H} = 187.5 Hz, C=O), 138.5 ($J_{C-2,CHO}$ = 29.1 Hz, $J_{C-2,H-4}$ = 8.8 Hz, and $J_{C-2,H-5}$ = 5.6 Hz, C-2), 132.5, 129.8, 129.5, 128.6, 127.4 ($J_{C-4,H-4}$ = 195.5 Hz and $J_{C-4,H-5}$ = 8.4 Hz, C-4), 121.8 ($J_{C-5,H-5}$ = 195.3 Hz and $J_{C-5,H-4}$ = 16.3 Hz, C-5), 82.4.

1-(Benzyloxy)-2-(*tert*-butyldimethylsilyl)imidazole (4e). After addition of *tert*-butyldimethylchlorosilane (284 mg, 1.35 equiv) dissolved in tetrahydrofuran (1.8 mL), the mixture was stirred and worked up as described above to give a residue which upon flash chromatography (heptane−ethyl acetate−triethylamine, 2:1:0.075 → 0:1:0.025) gave 208 mg (72%) of 1-(benzyloxy)-2-(*tert*-butyldimethylsilyl)imidazole (**4e**) as an oil. δ_H ($CDCl_3$): 7.36−7.44 (5H, m), 7.07 (1H, d, J = 1.2 Hz), 6.96 (1H, d, J = 1.2 Hz), 5.11 (2H, s), 0.94 (9H, s), 0.39 (6H, s). δ_C ($CDCl_3$): 144.1, 133.7, 129.1, 128.9, 128.7, 126.9, 117.2, 82.2, 26.4, 17.4, −5.8. Attempted ball−tube distillation at 1 mmHg led to clean desilylation producing the starting material **3**.

1-(Benzyloxy)-2-chloroimidazole (4f). After addition of hexachloroethane (474 mg, 2.0 equiv) dissolved in tetrahydrofuran (1.9 mL), the mixture was stirred and worked up as in the standard procedure to give a residue which by flash chromatography (heptane−ethyl acetate, 2:1 → 0:1) gave 193 mg (93%) of 1-(benzyloxy)-2-chloroimidazole (**4f**), mp 51−52 °C. Recrystallization (ethyl acetate−heptane) raised the mp to 56 °C. Anal. Found: C, 57.70; H, 4.42; N, 13.40. Calcd for $C_{10}H_9N_2OCl$: C, 57.57; H, 4.35; N, 13.43). δ_H ($CDCl_3$): 7.35−7.43 (5H, m), 6.82 (1H, d J = 1.6 Hz), 6.76 (1H, d J = 1.6 Hz), 5.12 (2H, s). δ_C ($CDCl_3$): 132.6, 129.7, 129.6, 128.6, 127.1, 123.9 ($J_{C-4,H-4}$ = 196.3 Hz and $J_{C-4,H-5}$ = 8.1 Hz, C-4), 117.7 ($J_{C-5,H-5}$ = 196.7 Hz and $J_{C-5,H-4}$ = 15.2 Hz, C-5), 81.7.

1-(Benzyloxy)-2-iodoimidazole (4g). After addition of iodine (567 mg, 2.2 equiv) and stirring as described in the standard procedure, $Na_2S_2O_3{\cdot}5H_2O$ (1 g) dissolved in 10 mL of water was added. Normal workup then gave 289 mg of a residue which upon flash chromatography (heptane−ethyl acetate, 2:1 → 0:1) afforded 260 mg (87%) of 1-(benzyloxy)-2-iodoimidazole (**4g**), mp 78−79 °C (from ethyl acetate−pentane). Anal. Found: C, 40.18; H, 2.60; N, 9.25. Calcd for $C_{10}H_9N_2OI$: C, 40.02; H, 3.02; N, 9.33. δ_H ($CDCl_3$): 7.41 (5H, s), 6.97 (1H, d, J = 1.4 Hz), 6.96 (1H, d, J = 1.4 Hz), 5.13 (2H, s). δ_C ($CDCl_3$): 132.7, 129.8, 129.6, 128.9 ($J_{C-4,H-4}$ = 197.5 Hz and $J_{C-4,H-5}$ = 8.3 Hz, C-4), 128.7, 119.7 ($J_{C-5,H-5}$ = 194.3 Hz and $J_{C-5,H-4}$ = 15.5 Hz, C-5), 83.5 ($J_{C-2,H-4}$ = 7.6 Hz and $J_{C-2,H-5}$ = 11.4 Hz, C-2), 82.1. The compound should be stored in a refrigerator since it turns yellow on standing at room temperature.

1-(Benzyloxy)-2-(methylthio)imidazole (4h). After addition of dimethyl disulfide (0.25 mL, 3 equiv), the mixture was stirred and worked up as in the standard procedure to give 215 mg of a residue which was flash chromatographed (heptane−ethyl acetate, 4:1 → 0:1) to give 199 mg (91%) of 1-(benzyloxy)-2-(methylthio)imidazole (**4h**) as an oil. Ball−tube distillation (135 °C, 0.2 mmHg) afforded a colorless sample. Anal. Found: C, 59.26; H, 5.02; N, 12.50. Calcd for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72. δ_H ($CDCl_3$): 7.40 (5H, s), 6.87 (2H, s), 5.11 (2H, s), 2.60 (3H, s). δ_C ($CDCl_3$): 138.3, 133.1, 129.6, 129.3, 128.6, 125.1, 117.4, 81.1, 14.7.

Debenzylation with Hydrogen/Palladium on Carbon. 1-Hydroxyimidazole (5a). 1-(Benzyloxy)imidazole (**3**) (1.34 g), 10% palladium on carbon (263 mg), and methanol (65 mL) were stirred under hydrogen at 1 bar and 0 °C for 1 h. Filtration through kieselguhr and removal of the solvent gave 624 mg (96%) of 1-hydroxyimidazole (**5a**), mp 91−92 °C (from methanol−ethyl acetate, reported[17] mp 93 °C). The signals from H-4 and H-5 collapsed in D_2O solution as a doublet ($J_{H-4,H-2}$ = $J_{H-5,H-2}$ = 1.9 Hz). Separate signals for H-4 and H-5 were observed in DMSO as broad singlets. The unambiguous assignment of the signals from H-4 and H-5 and from C-4 and C-5 will be discussed in a separate paper. δ_H (DMSO-d_6): 7.82 (1H, bs), 7.24 (1H, bs), 6.85 (1H, bs). δ_C (DMSO-d_6): 131.5 (ddd, J = 223.8, 4.7, and 4.4 Hz, C-2), 123.3 (ddd, J = 205.7, 12.2, and 4.6 Hz), 118.2 (ddd, J = 203.5, 10.7, and 6.5 Hz).

1-Hydroxyimidazole Hydrochloride (5a·HCl). Similarly, 1-(benzyloxy)-2-chloroimidazole (**4f**) (187 mg) in 2 h gave, after drying at 0.02 mmHg, 108 mg (99%) of 1-hydroxyimidazole hydrochloride (**5a**·HCl) as a hygroscopic crystal mass which was reprecipitated from methanol−ethyl acetate (reported[18] deliquescent crystals). δ_H (D_2O): 8.78 (1H, t, J = 1.8 Hz), 7.52 (1H, t, J = 1.8 Hz), 7.34 (1H, t, J = 1.8 Hz). δ_C ($CDCl_3$): 129.0, 122.8, 119.0.

1-Hydroxy-2-formylimidazole (5b). Similarly, 1-(benzyloxy)-2-formylimidazole (**4c**) (196 mg) in 1 h gave 106 mg (97%) of 1-hydroxy-2-formylimidazole (**5b**), which when recrystallized from ethyl acetate−heptane had mp 149 °C dec. Anal. Found: C, 42.59; H, 3.73; N, 24.27. Calcd for $C_4H_4N_2O_2$: 42.86; H, 3.60; N, 24.99. δ_H (DMSO-d_6): 9.70 (1H, s), 7.64 (1H, bs), 7.20 (1H, bs). δ_C (DMSO-d_6): 178.3, 138.6, 127.4, 123.1.

Debenzylation with Hydrochloric Acid. 1-Hydroxyimidazole Hydrochloride (5a·HCl). 1-(Benzyloxy)imidazole (**3**) (182 mg) and concd hydrochloric acid (5 mL) were refluxed for 2 h. Washing with dichloromethane (3 × 10 mL), back-extraction of the dichloromethane solutions with concd hydrochloric acid (10 mL), and evaporation of the combined aqueous solutions to dryness gave 124 mg (98%) of 1-hydroxyimidazole hydrochloride (**5a**·HCl), identical with the material described above.

1-Hydroxy-2-chloroimidazole Hydrochloride (5c·HCl). 1-(Benzyloxy)-2-chloroimidazole (**4f**) (283 mg) and concd hydrochloric acid (5 mL) were refluxed for 2 h. Washing with dichloromethane (3 × 10 mL), back-extraction of the dichloromethane solutions with concd hydrochloric acid (10 mL),

evaporation of the combined aqueous solutions to dryness, and coevaporation twice with 2 mL of toluene afforded 187 mg (89%) of 1-hydroxy-2-chloroimidazole hydrochloride (**5c**·HCl), mp 173 °C (from methanol−ethyl acetate). Anal. Found: C, 23.48; H, 2.40; N, 18.12. Calcd for $C_3H_4N_2OCl_2$: C, 23.25; H, 2.60; N, 18.08). δ_H (D_2O): 7.56 (1H, d, J = 2.45 Hz), 7.34 (1H, d, J = 2.45 Hz). δ_C (D_2O): 131.0, 120.6, 118.2.

Reduction of 1-Hydroxyimidazoles. Imidazole (6a). 1-Hydroxyimidazole (**5a**) (69 mg), 10% palladium on carbon (32 mg), and methanol (5 mL) were stirred under hydrogen at 1 bar and 20 °C for 24 h. Filtration through kieselguhr and removal of the solvent gave 50 mg (89%) of imidazole (**6a**), mp 88 °C (reported[45] mp 89−91 °C).

2-Chloroimidazole (6b). 1-Hydroxy-2-chloroimidazole hydrochloride (**5c**·HCl) (259 mg) was dissolved in methanol (10 mL), and a 15% solution of titanium trichloride in 20% aqueous HCl (2.9 mL) was added at 0 °C during 5 min. Stirring for 1 h, adjusting the pH to 10 with saturated aqueous sodium hydrogen carbonate, and continuous extraction with diethyl ether for 20 h gave 172 mg (100%) of 2-chloroimidazole (**6b**), mp 162−163 °C (reported[34] mp 164−165 °C). δ_H ($CDCl_3$): 7.03.

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