SYNTHESIS OF 4-HYDROXY-1-METHYLBENZIMIDAZOLE AND 7-HYDROXY-1-METHYLBENZIMIDAZOLE

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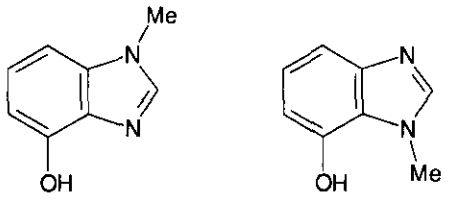
Abstract- 4-Hydroxy-1-methylbenzimidazole (**1**) was synthesised *via* condensation of 2-amino-3-nitrophenol (**3**) with trimethyl orthoformate, reduction of the resulting 4-nitrobenzoxazole (**4**) to amine (**5**), reaction with hydroxymethylbenzotriazole to form benzotriazolyl adduct (**6**), reduction to give 4-methylaminobenzoxazole (**7**), and finally base catalyzed rearrangement. The synthesis of 7-hydroxy-1-methylbenzimidazole (**2**) was accomplished by reduction of **4** with sodium borohydride to form 3-nitro-2-methylaminophenol (**8**), followed by hydrogenation to give amino derivative (**9**) and condensation with trimethyl orthoformate.

Many examples of *C*-hydroxybenzimidazoles have been described including those displaying potent herbicidal activity[1] and enzyme, such as 5-lipoxygenase, inhibition.[2] Previous synthetic approaches have been somewhat laborious. Thus, 5- and 6-hydroxy-1-methylbenzimidazoles, required for an investigation of vitamin B_{12} activity,[3] were made in 5% and 26% overall yields respectively by successive: i) preparation of the *N*-tosylate of either 3-nitro-4-aminophenol ethyl ether (for 5-hydroxy-1-methylbenzimidazole) or 4-nitro-3-aminophenol methyl ether (for 6-hydroxy-1-methylbenzimidazole); ii) methylation of the *N*-tosylate with dimethyl sulfate; iii)

hydrolysis to give the free base; iv) reduction of the nitro group with tin/hydrochloric acid; v) cyclization with formic acid and finally vi) dealkylation with 6 M hydrochloric acid. *N*-Methylbenzimidazoles have been most commonly prepared by methylation of the benzimidazole ring.[4,5] Eschweiler-Clark conditions have been used to regioselectively methylate and simultaneously cyclize 2-amino-4-nitroaniline to give 1-methyl-6-nitrobenzimidazole.[6]

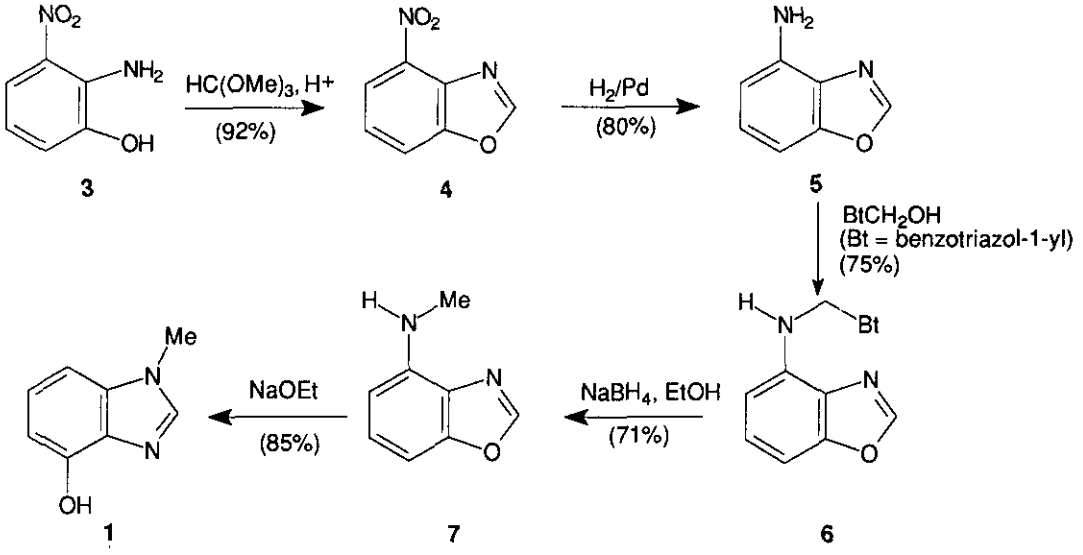
The methods described here for the synthesis 4- and 7-hydroxy-1-methylbenzimidazoles (**1**) and (**2**) take advantage of intermediate benzoxazoles; because of the proximity of the hydroxy group to the benzimidazole ring, the final products can be obtained isomerically pure in good overall yields. The present study represents an extension of our work on 4-amino-7-hydroxybenzimidazole.[7]



1 **2**

Preparation of 4-hydroxy-1-methylbenzimidazole (1)

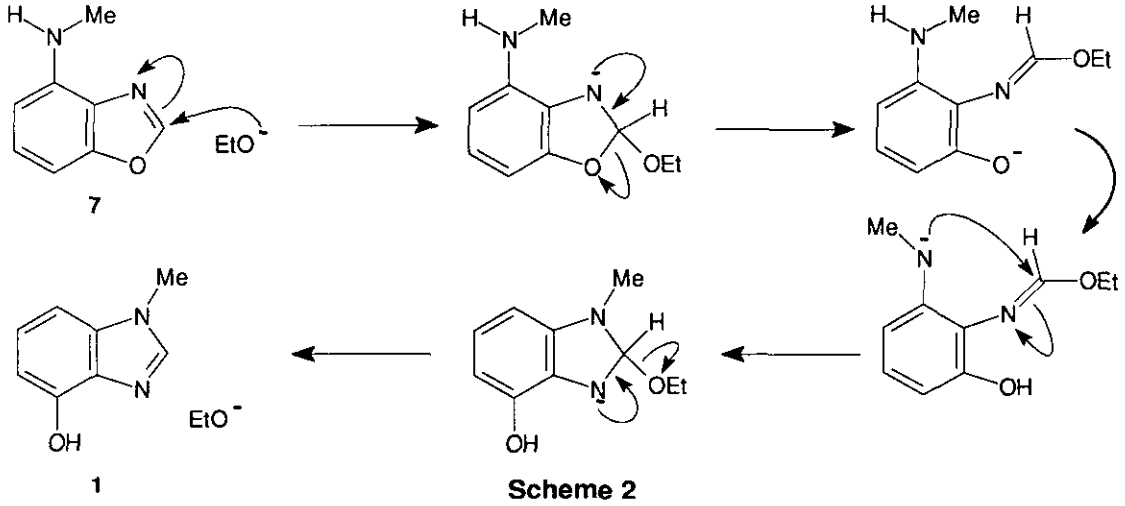
Preparation of **1** was accomplished in 33% overall yield in accordance with Scheme 1.



3 **4** **5** **6** **7** **1**

Scheme 1

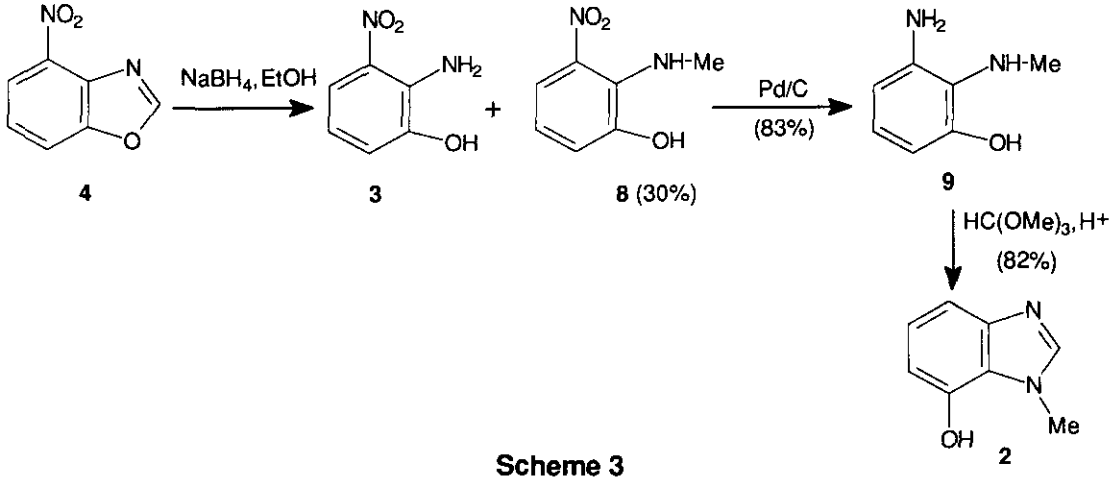
Benzoxazole (**4**) was prepared by modification of an earlier procedure for the synthesis of benzimidazole derivatives.[7] Thus, treatment of 2-nitro-3-aminophenol (**3**) with trimethyl orthoformate in the presence of an acid catalyst furnished 4-nitrobenzoxazole (**4**) in quantitative yield. Hydrogenation of **4** by modification of a literature method[8] produced the amine (**5**). The benzotriazolyl adduct (**6**) was prepared and reduced as previously reported by our group.[9,10] Reduction of **6** led to formation of both the expected 4-methylaminobenzoxazole (**7**) and a small amount of the target benzimidazole (**1**), suggesting that **7** slowly rearranged under the basic reduction conditions. Indeed, treatment of **7** with a saturated solution of sodium ethoxide furnished **1** exclusively. A suggested mechanism appears in Scheme 2 (cf ref [11]).



Scheme 2

Preparation of 7-hydroxy-1-methylbenzimidazole (2)

Preparation of **2** was accomplished in 19% overall yield in accordance with Scheme 3.

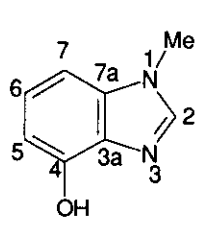


Scheme 3

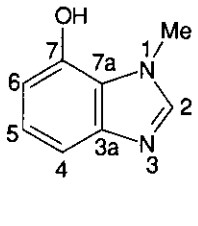
Reduction of **4** with sodium borohydride in ethanol led to the expected 3-nitro-2-methylaminophenol **(8)** (30%) along with a significant quantity of 2-amino-3-nitrophenol **(3)** as a result of alcoholysis under the strongly basic conditions. Hydrogenation[8] of **8** produced amine **(9)** in good yield (83%). Compounds **(8)** and **(9)** were found to be unstable and the formation of side products was significant. Cyclization of **9** with trimethyl orthoformate, followed by column chromatography gave the desired derivative **(2)** in addition to side products resulting from the decomposition of **9**.

^{1}H and ^{13}C nmr

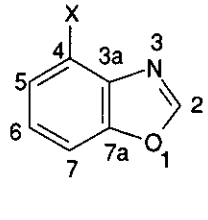
The nmr assignments of the benzoxazoles and benzimidazoles synthesized appear in Tables 1 and 2. Fully coupled ^{13}C nmr spectra of **1, 2** and **7** were recorded. The assignments of the remaining compounds were made by analogy.



1



2



4 - 7

Table 1: ^{1}H Nmr spectroscopy of benzimidazoles **(1)** and **(2)** and 4-substituted benzoxazoles **(4-7)**

cmpd	X (4-7)	H2	H5	H6	H7	X (4-7)	NMe (1,2)
1		7.89	6.84	7.24	6.91		3.82
		(s, 1H)	(d, 1H, 8.0)	(t, 1H, 8.0)	(d, 1H, 8.1)		
2		7.90	6.91	6.59	7.05‡		4.02
		(s, 1H)	(d, 1H, 8.0)	(t, 1H, 7.8)	(d, 1H 8.1)		
4	NO_2	8.38	8.27	7.60	7.98	-	
		(s, 1H)	(d, 1H, 8.1)	(t, 1H, 8.1)	(d, 1H, 8.1)		
5	NH_2	7.96	6.59	7.15	6.94	4.36(NH_2)	
		(s, 1H)	(d, 1H, 8.0)	(t, 1H, 8.0)	(d, 1H, 8.0)	(br s, 1H)	
6§	$NHCH_2Bt$	7.98	6.93	7.21	7.00	6.35(CH_2)	
		(s, 1H)	(d, 1H, 8.0)	(t, 1H, 8.0)	(d, 1H, 8.0)	(d, 2H, 6.0)	
7	NHMe	7.94	6.46	7.23	6.88	2.96(Me)	
		(s, 1H)	(t, 1H, 8.0)	(t, 1H, 8.0)	(d, 1H, 8.1)	(s, 3H)	

§ Complete nmr in experimental.
‡ H4 signal.

Table 2: ^{13}C Nmr spectroscopy of benzimidazoles (**1**) and (**2**) and 4-substituted benzoxazoles (**4-7**)

cmpd	X (4-7)	C2	C3a	C4	C5	C6	C7	C7a	X (4-7)	NMe (1,2)
1*§		140.5	134.8	147.7	99.0	121.8	105.1	131.3		29.2
2*§		144.0	145.5	108.1	122.5	110.1	124.2	146.0		33.6
4	NO_2	155.4	151.7	141.2	125.4	117.3	121.2	134.8	-	
5	NH_2	150.4	139.4	128.4	100.4	126.4	108.8	151.1	-	
6*§	$NHCH_2Bt$	152.2	138.7	128.0	100.6	127.6	106.0	150.7	57.2(CH_2)	
7§	NHMe	150.0	141.1	127.7	99.0	126.8	103.4	150.7	30.1(Me)	

* DMSO-d_6 solvent.
§ *Complete nmr in experimental.*

EXPERIMENTAL

General

Melting points are uncorrected. All nmr spectra were performed using a Varian VXR-300 spectrometer operating at 300 MHz in deuterochloroform as solvent unless otherwise stated. TMS was used as the internal reference. The symbol (#) indicates interchangeable resonances. Column chromatography was carried out on Merck Keiselgel 60 (5386) silica gel.

4-Hydroxy-1-methylbenzimidazole (**1**): Benzoxazole (**7**) (1.3 g, 8.8 mmol) was stirred for two days in a saturated *sodium ethoxide solution* (50 ml) at room temperature. Water (25 ml) was added and the pH adjusted to approx 7 with 10% hydrochloric acid and the mixture extracted with chloroform (3 x 50 ml). The organic layer was dried (magnesium sulfate) and evaporated to dryness under reduced pressure. The solid was washed with ether to give a brown-green powder **1** (1.1 g, 85%), mp 220-222°C. Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.88; H, 5.47; N, 19.04. ^{13}C Nmr (δ, ppm): 29.2 (q, J=139.5 Hz, NMe), 99.0 (dd, J_1=164.0 Hz, J_2=8.4 Hz, C5), 105.1 (ddd, J_1=156.8 Hz, J_2=8.0 Hz, J_3=1.4 Hz, C7), 121.8 (d, J=158.6 Hz, C6), 131.3 (m, C3a), 134.8 (dq, J_1=~8 Hz, J_2=~3 Hz, C7a), 140.5 (dq, J_1=209.2 Hz, J_2=3.3 Hz, C2), 147.7 (d, J=6.0 Hz, C4).

7-Hydroxy-1-methylbenzimidazole (**2**): A mixture of **9** (1.38 g, 10 mmol), trimethyl orthoformate (0.98 g, 12 mmol) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) was heated at 120-130°C with stirring. Methanol was allowed to evaporate from the mixture. The solid was triturated with toluene and evaporated to dryness under reduced pressure. The solid residue was subjected to column chromatography (chloroform:methanol, 95:5) to give pure **2** (1.21 g, 82%) as a yellow-brown solid, mp 220-222°C. Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.14; H, 5.46; N, 18.94. ^{13}C Nmr (δ, ppm): 31.4 (q, J=140.0 Hz, Me), 108.6 (dm, J=150.9 Hz, C4), 105.6 (dd, J_1=161.2 Hz, J_2=7.6 Hz, C6), 120.2 (d, J=157.8, C5), 121.9, (m, C7), 142.2 (dq, J_1=203.6 Hz, J_2=3.4 Hz, C2), 143.2 (m, C3a), 144.0 (tm, J=~8 Hz, C7a).

4-Nitrobenzoxazole (**4**): To **3** (12.5 g, 81.1 mmol) was added trimethyl orthoformate (9.5 g, 89.6 mmol) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated to approx 100°C with stirring during which time a precipitate formed. The methanol generated was allowed to evaporate from the mixture. The resulting off-white solid was triturated with toluene and evaporated to dryness under reduced pressure. Recrystallization from ethanol gave needles of analytically pure **4** (12.30 g, 92%), mp 128°C. Anal. Calcd for $C_7H_4N_2O_3$: C, 51.23; H, 2.28; N 16.98. Found: C, 51.15; H, 2.46; N, 16.98.

4-Aminobenzoxazole (**5**): To **4** (6.57g, 40.1 mmol) suspended in methanol (100 ml) was added 10% palladium on activated carbon (0.7 g). The mixture was stirred in a reactor under a hydrogen atmosphere (500 psi) at room temperature for 40 min. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The resulting yellow black oil was dissolved in ether, filtered and evaporated to dryness under reduced pressure to give off-white crystals of **5** (4.39 g, 80%), mp 95°C. Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.55; N, 21.18. Found: C, 62.87; H, 4.51; N, 20.88.

4-(Aminomethylene-1'-benzotriazolyl)benzoxazole (**6**): To a stirred solution of **5** (4.00 g, 30 mmol) in absolute ethanol (50 ml) was added hydroxymethylbenzotriazole (4.45 g, 30 mmol). The mixture was stirred overnight at room temperature. The precipitate was filtered, washed with ether and recrystallized from ethanol to give **6** as white needles (5.90 g, 75%), mp 155-156°C. Anal. Calcd for $C_{14}H_{11}N_5O$: C, 63.63; H, 3.81; N, 26.50. Found: C, 63.67; H, 4.16; N, 26.88. ^1H Nmr (δ, ppm): 5.92 (1H, br t, J=6.0 Hz, NH), 6.35 (2H, d, J=6.0 Hz, CH_2), 6.93 (1H, d, J=8.0 Hz, H5), 7.00 (1H, d, J=8.0 Hz, H7), 7.21 (1H, t, J=8.0 Hz, H6), 7.34 (1H, t, J=8.0 Hz, H6'), 7.44 (1H, t, J=8.0 Hz, H5'), 7.68 (1H, d, J=8.0 Hz, H7'), 8.04 (1H, t, J=8.0 Hz, H4'), 7.98, (1H, s, H2). ^{13}C Nmr (δ, ppm): 57.2 (CH_2), 100.6 (C5), 106.0 (C7), 111.7 (C6'), 119.4 (C5'), 124.4 (C7'), 126.8, (C4'), 127.6 (C6), 128.0 (C4), 132.6 (C7a'), 138.6 (C3a), 145.9 (C3a'), 150.7 (C7a), 152.2 (C2).

4-Methylaminobenzoxazole (**7**): To a stirred suspension of **6** (1 g, 3.7 mmol) in absolute ethanol (50 ml), under nitrogen, sodium borohydride (0.3 g, 9.3 mmol) was added, portionwise (0.1 g per portion) over six h until the starting material was consumed (tlc). The solution was diluted with water (25 ml), and the pH adjusted to approx 6 with 10% hydrochloric acid (to neutralize excess sodium borohydride), then readjusted to 9-10 with 10% sodium carbonate (to neutralize benzotriazole). The mixture was extracted with chloroform (3 x 20 ml), the organic layer dried (magnesium sulfate) and evaporated to dryness under reduced pressure. The resulting oil was dissolved in ether. The solid precipitate (**1**, 100 mg) was filtered and the filtrate evaporated to dryness under reduced pressure to give yellow needles of **7** (0.4 g, 71%), mp 75-76°C. Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.98; H, 5.52; N, 19.00. ^{13}C Nmr (δ, ppm): 30.14 (q, *J*=135.5 Hz, NMe), 99.0 (dm, *J*=160.3 Hz, C5), 103.4 (dd, J_1=157.6 Hz, J_2=6.5 Hz, C7), 126.8 (d, *J*=158.4 Hz, C6), 127.6 (m, C4), 142.1 (m, C3a), 150.0 (d, *J*=275.8 Hz, C2), 150.6 (dd, J_1=4.4 Hz, J_2=2.0 Hz, C7a).

2-Methylamino-3-nitrophenol (**8**): To a stirred solution of **4** (1.64 g, 10 mmol) in absolute ethanol (50 ml), sodium borohydride (0.32 g, 10 mmol) was slowly added, over three h until starting material was no longer detected (tlc). The solution was poured onto ice-cold water, slightly acidified with 20% acetic acid and extracted with chloroform (3 x 50 ml). The combined extracts were dried over sodium sulfate, evaporated to dryness under reduced pressure and subjected to column chromatography. Recrystallization from a mixture of ethanol and ether gave dark red grains of **8** (0.50 g, 30%), mp 123-124°C. Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.61; H, 4.71; N, 16.42. ^{1}H Nmr (δ, ppm): 3.18 (3H, s, Me), 6.51 (1H, dd, J_1=8.7 Hz, J_2=7.8 Hz, H5), 6.94 (1H, dd, J_1=7.8 Hz, J_2=1.2 Hz, H6), 7.53 (1H, dd, J_1=8.7 Hz, J_2=1.2 Hz, H4). ^{13}C Nmr (δ, ppm): 33.3 (Me), 114.4 (C2), 115.7 (C6), 116.6 (C5), 119.2 (C4), 137.9 (C3), 148.2 (C1).

3-Amino-2-methylaminophenol (**9**): A solution of **8** (1.68 g, 10 mmol) in ethanol (50 ml) and catalyst (10% Pd/C, 0.2 g) was hydrogenated (500 psi) at room temperature for 30 min. The reaction mixture was quickly filtered and the filtrate evaporated to dryness under reduced pressure to give **9** as an off-white solid (1.15 g, 83%), mp 132-134°C. ^{1}H Nmr (δ, ppm): 2.83 (3H, s, Me), 6.17 (1H, dd, J_1=8.1 Hz, J_2=1.5 Hz, H6), 6.35 (1H, dd, J_1=8.1 Hz, J_2=1.5 Hz, H4), 6.86 (1H, t, *J*=8.1 Hz, H5). ^{13}C Nmr (δ, ppm): 42.3 (Me), 104.2 (C6), 108.2 (C4), 124.0 (C2), 127.6 (C5), 144.9 (C3), 154.5 (C1).

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