4,5-Dimethylimidazole: A Correction and Alternative Synthesis

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Fractional vacuum distillation of the product obtained from thermal condensation of acetoin with formamide is a formic acid complex of 4,5-dimethylimidazole, and not the expected free base. The ^1H and ^{13}C nmr spectra suggest that the product may be closer to a 1:1 hydrogen-bonded adduct than to a true salt. Commercial 4-hydroxymethyl-5-methylimidazole is converted quantitatively to the 4-chloromethyl derivative with thionyl chloride; hydrogenolysis of the latter compound provides 4,5-dimethylimidazole in an overall 80-90% yield, doubling the yield obtained by the classical method.

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During studies on oxidative functionalization of alkylimidazoles [1], we found that 4,5-dimethylimidazole, **1**, which had been prepared according to Brederick [2] from acetoin and formamide, consumed *ca.* one equivalent of Ce(IV) without undergoing *any* apparent chemical change. This puzzle was filed with other numerous mysteries in imidazole chemistry for later reinvestigation. More recently, we had occasion to use ^1H-nmr to follow the kinetics of halogenation of the same compound. The presence of an extraneous one-proton signal at low field (Table 1) led us to suspect that the material we, as well as Brederick and others [3], had assumed to be the free base was, in fact, the formic acid salt [4]. Our suspicion was confirmed by ^{13}C-nmr (Table 2) and by elemental analysis [5]; thus, our earlier observation of a readily oxidizable component was now explicable.

The salt was converted to the free base by several ether extractions of its solution in saturated aqueous sodium carbonate, drying of the combined extracts (magnesium sulfate), evaporation of solvent and drying of the crystalline residue under vacuum. This material gave ^1H and ^{13}C nmr spectra quite different from those of the salt, but the same mp [6]. The similarity in melting points suggests that dissociation of the salt occurs prior to its melting, a property consistent with the evidence for codistillation during the synthesis. Comparisons of the nmr spectra of the formate salt with those of the trifluoroacetate and the hydrochloride **4** also suggest that proton transfer to the ring nitrogen by formic acid is far from complete and that the species may be closer to a hydrogen-bonded complex. This view is supported by comparison of the nmr data measured in DMSO-d_6 and in deuteriochlo-

Table 1

^1H NMR Data for 4,5-Dimethylimidazole (300 MHz) [a]

	δ (DMSO-d_6)				δ (deuteriochloroform)			
Compound	CH_3's	H-2	HCO_2^-	NH^+	CH_3's	H-2	HCO_2^-	NH
1.	2.03	7.32			2.12	7.44		10.92 [b]
1. HCOOH	2.08	7.79	8.30	13.80 [c]	2.27	8.03	8.77	
1. CF_3COOH	2.15	8.56						
1. HCl	2.18	8.86						

[a] All signals are singlets unless otherwise indicated. [b] Broad s, 1H. [c] Broad s, 2H.

Table 2

^{13}C NMR Data for 4,5-Dimethylimidazole (300 MHz) [a]

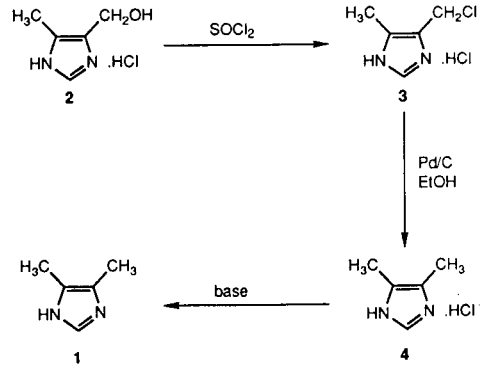
	δ (DMSO-d_6)				δ (deuteriochloroform)			
Compound	CH_3's	C-4,5	C-2	HCO_2^-	CH_3's	C-4,5	C-2	HCO_2^-
1	10.6	125.2	132.2		10.6	126.6	132.3	
1. HCOOH	9.9	125.5	132.0	164.2	9.2	125.5	130.3	168.8
1. CF_3COOH	8.8	124.4	131.7					
1. HCl	8.4	124.0	131.2					

[a] Signals for ring carbons were assigned by analysis of proton-coupled spectra.

roform: δ values for the formate complex are closer to those of the free base in the more polar solvent; furthermore, the ^{13}C signal at lowest field in DMSO-d_6 matches that for formic acid (166.3) rather than that for formate ion (171.3).

Following completion of these studies, we learned that Brederick's product had been previously recognized as the formate salt [8]. Evidently, the earlier report had not achieved wide notice and it seemed that a reemphasis and note of caution would be appropriate and useful. We have not reinvestigated the syntheses of the numerous other 4,5-dialkylimidazoles described by Brederick [2]; however, the boiling point ranges for these compounds suggest that they may also distill as complexes in combination with the formic acid released during the synthesis [9]. For many purposes, the presence of an equivalent of formic acid may be irrelevant; for our studies on oxidation, halogenation, *etc.*, such contamination is unacceptable and subsequent conversion to the free base becomes essential.

Recalculation of the literature yield (55%) of **1** [2] for the presence of one equivalent of formic acid provides an actual yield of 37%. Our efforts to increase or even match the literature yield have required collection of distillate over a wider boiling range than the 165-175° (10 mm) given, but with the risk of codistillation of side products. We have, therefore, examined alternative syntheses of **1**. The current availability and moderate cost of 4-hydroxymethyl-5-methylimidazole (**2**) led us to consider methods for the reductive removal of the hydroxyl function. Direct hydrogenolysis of the benzyl-like alcohol in a Parr apparatus, with or without additional acid, proved unsuccessful. A simple and quantitative conversion of **2** to 4-chloromethyl-5-methylimidazole hydrochloride (**3**) has recently been reported [10]. We have verified this conversion and find that catalytic hydrogenolysis of **3** (10% Pd/C in ethanol, 40 Psi, 25°) for 3-4 days provides a nearly quantitative yield of 4,5-dimethylimidazole hydrochloride (**4**) [11]. Conversion of **4** to **1** is performed as previously described for the formate salt, providing an overall yield of **1** from **2** of 80-90% [12]. We feel that the combination of greatly improved yield and the elimination of the need for careful fractional vacuum distillation provides a gratifying alternative to the classical synthesis of 4,5-dimethylimidazole.



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[4] The same low-field signal was observed by Bernarducci *et al.* [3a], and was attributed to the NH function. This assignment is readily excluded since the signal is not lost in the presence of perdeuteriomethanol.

[5] Mp 116-118° (ether); ms: (CI, NH_3), m/z 97 (M + 1). *Anal.* Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.75; H, 7.08; N, 19.72.

[6] Mp. 116-118° (lit mp 120° [7]); ms: (CI, NH_3), m/z 97 (M + 1). *Anal.* Calcd. for $C_5H_8N_2$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.41; H, 8.44; N, 29.06.

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[9] See E. Salwińska and J. Suwiński, *Pol. J. Chem.*, **53**, 2339 (1979).

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[11] The reduction of **2** to **4** with phosphorus and hydriodic acid at 160° has been described [7].

[12] An alternative synthesis which avoids the use of formamide provided a yield of 42%; A. Khalaj and M. Ghafari, *Tetrahedron Letters*, **27**, 5019 (1986).