The Sodium/Ammonia Reduction of 5-Ethoxycarbonyl-4-methylimidazole: A Key Intermediate in the Synthesis of Cimetidine

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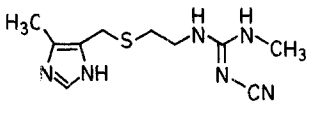
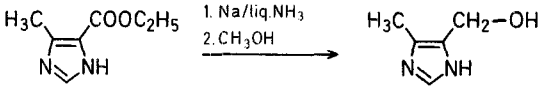
Cimetidine (**1**) is a histamine hydrogen-receptor antagonist used in the treatment of gastric ulcers. 4-Methyl-5-hydroxymethylimidazole (**3**) is a potential intermediate for the synthesis of cimetidine (**1**). We describe here a commercially practicable method to prepare the key intermediate **3**.



1

4-Methyl-5-hydroxymethylimidazole hydrochloride (**3** · HCl) has been prepared by the lithium aluminum hydride reduction of the corresponding ester in 42% yield[1], by an electrochemical reduction of the ester[2] or the corresponding acid[3] and by hydroxymethylation[4] of 4-methylimidazole. We have now discovered that **2** can be reduced to **3** using sodium in liquid ammonia. This is the first example of the selective reduction of a heterocyclic ester to the corresponding alcohol using these conditions[5,6].

We initially observed that 5-ethoxycarbonyl-4-methylimidazole (**2**) could be reduced to **3** using Bouveault-Blanc conditions but the yields were relatively low. Sodium dissolution in alcohol became very slow as the concentration of alkoxide increased and attempts to drive the reaction to completion by heating the solution resulted in rapid decomposition of the desired product and low yields of **3**.

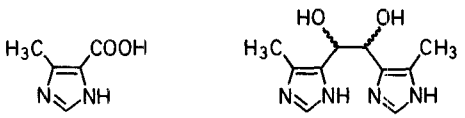


2 **3**

These observations led us to evaluate the reduction of **2** in liquid ammonia where sodium is very soluble at low temperatures; we were cognizant of the predicted complexities in this system[7–18]. We found that yields of 85% of **3** can be readily achieved. Possible side reactions such as Birch reduction and overreduction[19–23], which have been reported in similar cases, were never observed with any of the reaction conditions explored. Certain specified conditions must be followed however to minimize other competing reactions.

A major competing side reaction is the formation of the corresponding acid **4**[24], which is obtained on work up. This reaction, favored by low alkali metal concentration and stable leaving radicals, has been reported to have some synthetic utility[25]. We found that the acid **4** was formed in 25% or more yield when sodium was added to the ester **2** in ammonia. To maximize the yield of **3**, it is necessary to add the ester **2** to a preformed solution of sodium in ammonia so that the ester **2** always encounters a high sodium concentration. Even using this preferred procedure, we observed that the content of the acid ranged as high as 10%. Saponification of the ester **2** by ammonia contaminated with water was ruled out by showing that added aliquots of water did not affect the production of acid **4**. The problem was shown to be localized depletion of the sodium concentrations (sometimes visible by a brief localized decolorization of the solution) which was readily controlled (usually < 2%) by efficient agitation and the addition of the ester in small (~ 1/20) portions.

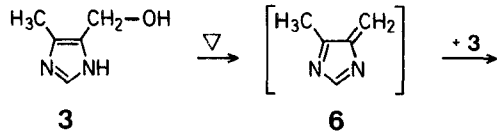
In the reduction of some esters, radical coupling becomes a major pathway, especially when good proton sources are absent[18]. In the case of **2** too, coupled products were observed. The major coupled products are the diols **5**[27] present in an approximately 1 : 1 ratio of the *meso* and *dl* pair. With no added proton source, these products were formed to the extent of 5–6% as measured by H.P.L.C. against the purified compounds as standards. Addition of one equivalent of *t*-butanol reduced the diol formation to ~ 3%; addition of 3 equivalents of *t*-butanol reduced diol formation even more.



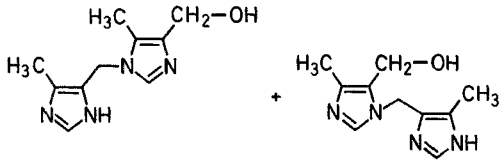
4 **5**

Experimentally, the sodium/ammonia reduction of **2** is eminently practical[5]. The product **3** is stable in the solution for at least 3 h. Despite the high water solubility of **3**, and its low solubility in organic solvents, except the lower alcohols, separation of **3** from the concomitantly formed inorganic salts was readily accomplished by removing the ammonia and leaching the residue with isopropanol. Concentration, acidification, and dilution with acetone or acetone/ether precipitated **3** as its hydrochloride salt; the latter generally contained 0.5–3% inorganic salts, primarily ammonium chloride. While the reduction could be done equally well using lithium in ammonia, the greater solubility of lithium chloride in isopropanol compared to sodium chloride gave rise to a less pure product due to contamination by lithium salts.

Two other products, sometimes detected in low yield (< 1 %), were the isomeric imidazoles **7** and **8** probably formed via **6**[28,29]. Their formation can be essentially prevented by using mild work-up conditions. Synthesis and structural assignments of **7** and **8** have been reported[30,31].



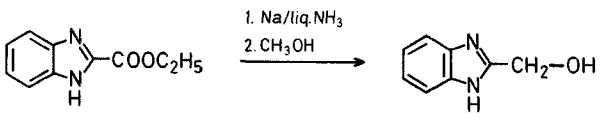
3 **6**



7 **8**

In summary, we have found the sodium/ammonia reduction of **2** to **3** can be readily achieved. Apart from the need to add the ester **2** to the sodium ammonia solution, the reaction is not especially sensitive to experimental conditions. The addition of one equivalent of *t*-butanol suppresses the already low level of undesirable coupling, however, this offers no real advantage in the synthesis of cimetidine because this diol is not carried through the sequence.

The high yield of the reduction of **2** to **3** suggested that this might be a generally useful reaction with applicability to other heterocyclic esters. These reaction conditions were applied to 2-ethoxycarbonylbenzimidazole **(9)** but the yield of benzimidazole-2-methanol **(10)** was lower than that of the reduction of **2** (48 % by H. P. L. C.). The reaction mixture was clearly more complicated although the major product was still the alcohol.



9 **10**

4-Methyl-5-hydroxymethylimidazole Hydrochloride (3 · HCl):
A 2 l three-necked flask equipped with an overhead stirrer (glass paddle) and a Dry Ice condenser is flushed with nitrogen and charged with liquid ammonia (~ 1000 ml) (a Dry Ice/acetone cooling bath aids this condensation and provides cooling during the reaction). Sodium (28.1 g, 1.22 mol) is introduced and stirred for about 10 min to complete dissolution. 5-Ethoxycarbonyl-4-methylimidazole (**2**; 41.7 g, 0.27 mol) is added in about 20 portions over 30 min. Methanol (~ 10 ml) is cautiously added dropwise to discharge the blue color followed by addition of a slight molar excess of ammonium chloride (66.0 g, 1.23 mol). Ammonia is removed under vacuum using a water bath (initially cold, later warm) leaving a solid residue. Isopropanol (1000 ml) is added and the solvent removed by distillation (50–55 °C) at reduced pressure to a volume of about 300 ml. Another portion of isopropanol (1000 ml) is then added and the mixture concentrated to about 500 ml at which point the pH of the distillate is about 7 (by wet pH paper). The solution is cooled to 40 °C and acidified with gaseous hydrogen chloride. The mixture is filtered and the filter cake washed with hot isopropanol (3 × 100 ml). the combined filtrate is concentrated to about 200 ml, resulting in extensive crystallization. The slurry is transferred with isopropanol (100 ml) into a solution of acetone/ether (800 ml + 300 ml) and allowed to stand overnight. The product is collected and dried at 50–60 °C in a vacuum oven; crude yield of **3** · HCl: 35.26 g. Assay by H.P.L.C. (μ Bondapak C-18 column eluted with 0.1 molar sodium dihydrogen phosphate solution adjusted to pH 4.2 with 85 % phosphoric acid, flow rate 0.9 ml/min, U. V. detection at 228 nm, R_T of **3** · HCl, 4.69 min; **5** · HCl, 3.52 min; **4** · HCl, 3.82 min, weight based compared to authentic samples) showed 5.3 % of coupled products **5** · HCl; 1.5 % carboxylic acid **4** · HCl and a 93.4 % assay for **3** · HCl.

Yield of **3** · HCl corrected for purity is 85 %; m.p. 245 °C (dec.) (Lit.[4], m.p. 240–242 °C, 239–240 °C). Two recrystallizations from isopropanol gives an analytically pure sample, m.p. 242–245 °C (dec.).

Benzimidazole-2-methanol (10):
A 250 ml three-necked flask equipped with an overhead stirrer (glass blade) is flushed with nitrogen and charged with liquid ammonia (100 ml) (a Dry Ice/acetone cooling bath aids this condensation and provides cooling during the reaction). Sodium (2.94 g, 0.128 mol) is introduced and stirred for 15 min to complete dissolution. 2-Ethoxycarbonylbenzimidazole (**9**; 5.13 g, 0.027 mol) is added portionwise over 30 min. Methanol is cautiously added dropwise to discharge the blue color followed by the addition of a slight molar excess of ammonium chloride (7.36 g, 0.137 mol). Ammonia is removed under vacuum using a water bath (initially cold, later warm) leaving a solid residue. Methanol (~ 50 ml) is added and vacuum reapplied to remove solvent. Isopropanol (150 ml) is then added and the mixture is heated at 75 °C for 0.5 h. The mixture is filtered hot and the filtrate evaporated to an orange oil which is analyzed by H.P.L.C. (weight based on authentic sample: C-18 μ-Bondapak 50/50, eluent: methanol/0.1 molar sodium dihydrogen phosphate solution adjusted to pH 4.2 with 85 % phosphoric acid, 1 ml/min, 228 nm) to contain 2.12 g (48 %) of the desired benzimidazole-2-methanol **(10)**. Preparative chromatography (prep 500, silica gel; 5 % methanol in chloroform) gives an analytically pure sample of benzimidazole-2-methanol **(10)**, m.p. 168–170 °C (Lit.[32], m.p. 171–172 °C.

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^{1}H-N.M.R. (D_2O): δ = 2.15(s, 3H); 2.22(s, 3H); 5.11(s, 2H); 5.15(s, 2H); 8.52(s, 1H); 8.55 ppm(s, 1H).
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