An Efficient Synthesis of 2-(Methylaminomethyl)-4,5-Dialkyl-1H-Imidazoles.

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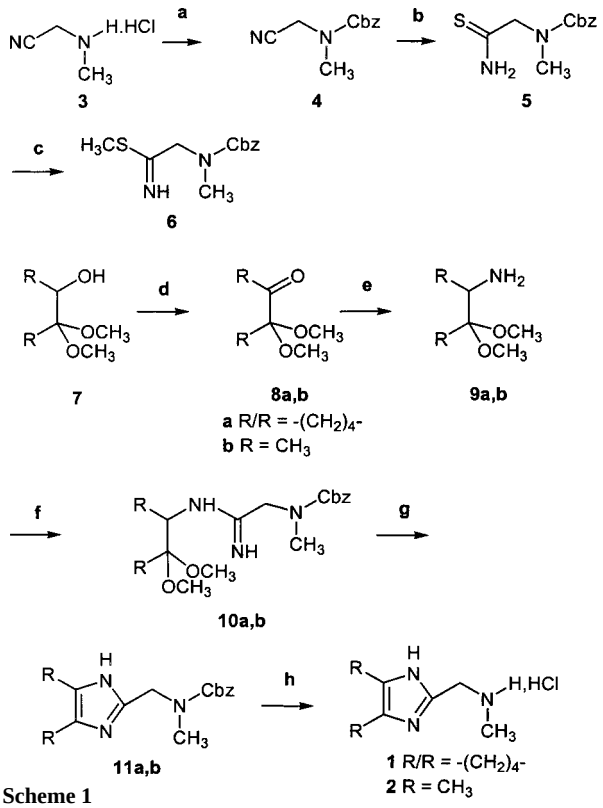
Received 3 June 1998

Abstract: A mild and convenient synthesis of 2-(methylaminomethyl)-4,5-dialkyl-1H-imidazoles is described. The procedure was used in the preparation of 2-(methylaminomethyl)-4,5,6,7-tetrahydro-1H-benzimidazole **1** and 2-(methylaminomethyl)-4,5-dimethyl-1H-imidazole **2**.

As part of a recent medicinal chemistry program, we required a general and efficient synthesis of 2-(alkylaminomethyl)-substituted imidazoles. The method we developed is exemplified in scheme 1 by the synthesis of 2-(methylaminomethyl)-4,5-dialkyl-1H-imidazoles, specifically 2-(methylaminomethyl)-4,5,6,7-tetrahydro-1H-benzimidazole **1** and 2-(methylaminomethyl)-4,5-dimethyl-1H-imidazole **2**.

Numerous syntheses of 2-(aminomethyl)- and 2-(alkylaminomethyl)-4,5-dialkyl-1H-imidazoles have been reported[2]. The methods we tried were not reliable for our examples, affording low yields and multiple products. An excellent method for the synthesis of imidazoles has been described by Hoff[3] in which an amidine is cyclized with an α-substituted-acetal. We have found this method to be equally applicable with an α-substituted ketal[4], leading to the desired 2-(alkylaminomethyl)-substituted imidazoles.

The syntheses of the imidazoles **1** and **2** are shown below in Scheme 1.



Scheme 1

a) CbzCl, DIEA, CH_2Cl_2, rt, 5h ; **b)** H_2S, Et_3N, DMF, rt, 16h ; **c)** CH_3I, acetone, rt, 3h ; **d)** TPAP, NMO, 4 Å sieves, CH_2Cl_2, rt, 16h; **e)** $NaBH_3CN$, NH_4OAc, MeOH, rt, 3h ; **f)** **6**, MeOH, 60°C, 3h ; **g)** HCl 6N, rt, 1h ; **h)** HCl(g), MeOH, 10%Pd/C, H_2, 50psi, 5h

The protection of the commercially available N-methylamino acetonitrile hydrochloride **3**[5] with benzylchloroformate gave a quantitative yield of **4**, which was converted to the thioamide **5**[6] in 70% yield by reaction with H_2S in the presence of excess Et_3N in DMF at room temperature. Treatment of **5** with methyl iodide in acetone afforded the S-methyl thioimidate **6** which was obtained as a crystalline product in 89% yield[7]. Compound **8a** was prepared in 77% yield from commercially available α-hydroxyketal **7**[5] by catalytic oxidation with TPAP/NMO[8] in CH_2Cl_2. Subsequent reductive amination of **8a** by $NaBH_3CN$ and excess NH_4OAc in methanol at pH 6 gave the α-amino ketal **9a** in 70% yield[9]. The S-methyl thioimidate **6** was then stirred in methanol with 50% excess of the α-amino ketal **9a** at 60°C for 3 hours to give the amidine **10a**. Compound **10a** was then reacted without purification with 6N HCl to give an intermediate which spontaneously cyclized to give the 2,4,5- trisubstituted imidazole **11a** in an overall yield of 51% (based on **6**)[10] after purification by flash chromatography. Removal of the benzylcarbamate by catalytic hydrogenolysis afforded the 2-(methylaminomethyl)-4,5-disubstituted-1H-imidazole **1** in 79% yield.

Analogously, the dimethylimidazole **2**[10,11] was prepared from commercially available 3,3- dimethoxy-2-butanone in an overall yield of 35% (based on **6**) after flash chromatography.

In summary, we have demonstrated a convenient and mild synthesis of highly substituted imidazole derivatives. The method is exemplified by the preparation of the tetrahydrobenzimidazole and the dimethyl imidazole derivatives **1** and **2.** We believe that this route can be applied to a wide range of substituted imidazoles using for example thioamides derived from amino acids, and a wide range of α-hydroxy ketones.

Acknowledgments : The author would like to thank Dr D. Yamashita and Dr W. Bondinell for their help and guidance during the writing of this manuscript.

References and notes

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(5) All comercially available compounds were bought from Aldrich Chemical Company, Inc.

(6) Thioamide **5** has been synthesized by Culbertson, T. P.; Domagala, J. M.; Peterson, P.; Bongers, S.; Nichols, J. *J. Heterocyclic Chem.* **1987**, 24, 1509-1520 using pyridine as the solvent.

(7) ^{1}H NMR(400MHz) in $CDCl_3$ of **6 :** δ=7.3-7.5 (m, 5H, Ph), δ=5.20 (s, 2H, C**H$_2$**-Ph), δ=4.85 (s, 2H, C**H$_2$**-N), δ=3.05 (s, 3H, N-C**H$_3$**), δ=2.90 (s, 3H, S-C**H3**)

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(10) ^{1}H NMR(400MHz) in CD_3OD of **11a**: δ=7.3-7.5 (m, 5H, Ph), δ=5.15 (s, 2H, C**H$_2$**-Ph), δ=4.4 (s, 2H, C**H$_2$**-N), δ=3.05 (s, 3H, C**H$_3$**), δ=2.55 (m, 4H, -C**H$_2$**-imid.), δ=1.75 (m, 4H, CH_2-(C**H$_2$**)$_2$-CH_2).
^{1}H NMR(400MHz) in CD_3OD of **11b**: δ=7.3-7.5 (m, 5H, Ph), δ=5.15 (s, 2H, C**H$_2$**-Ph), δ=4.35 (s, 2H, C**H$_2$**-N), δ=2.95 (s, 3H, C**H$_3$**), δ=2.1 (s, 6H, 2C**H$_3$** of the imid.).

(11) **Typical procedure for the formation of 11a,b** : A solution of 2-amino-3,3-dimethoxy butane **9b** (1.05g, 7.89mmol) and N-(carbobenzyloxy)-N-(methyl)aminomethyl-S-methyl thioacetimidate **6** (2.0g, 5.26mmol) in methanol (30 ml) was heated at 60^{o}C for 2h, and then concentrated to give a yellow oil. The crude material was then dissolved in 6N HCl (30 ml) and stirred at room temperature 1h. The solution was basified to pH 12 with aqueous NaOH and then extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated to give a brown oil. Purification by flash chromatography (silica gel, 4% MeOH/CH_2Cl_2) gave N-(carbobenzyloxy)-N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methylamine **11b** as a clear oil (0.590g, 41%). MS (ES) m/e 274.0 $[M+H]^+$.