An Efficient Synthesis of Chlorinated Imidazoles Through *tert*-Butyldimethylsilyloxy Derivatives

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The protection of 2-substituted imidazole-5-methanol derivatives by *tert*-BDMS allowed the chlorination of the heterocycle in position 4 with good yield whereas direct chlorination on the imidazole alcohol was unsuccessful.

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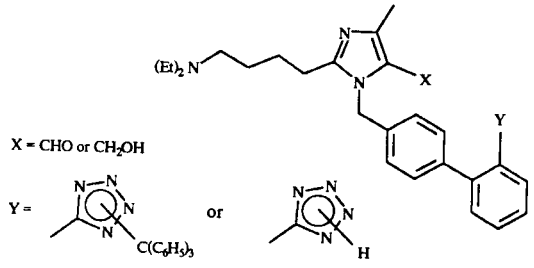
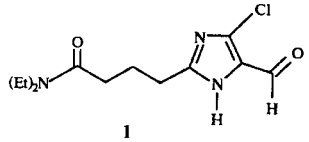
As part of our research on non peptidic AII antagonists, we needed to prepare compounds of the type:



An obvious precursor of these molecules was the aldehyde **1**, regioselective alkylation of which in position 1 [1,2], followed by lithium aluminium hydride reduction of the amide should lead to the desired products.



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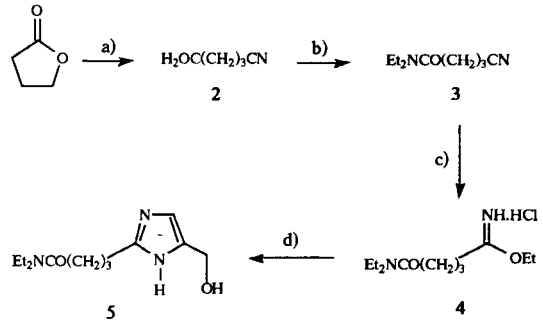
We report here a synthesis of **1** based on the pioneering work of Schunack [3] and then successfully examplified by Dupont de Nemours with Losartan [4]. The synthetic pathway is summarized in Scheme I.

Scheme I

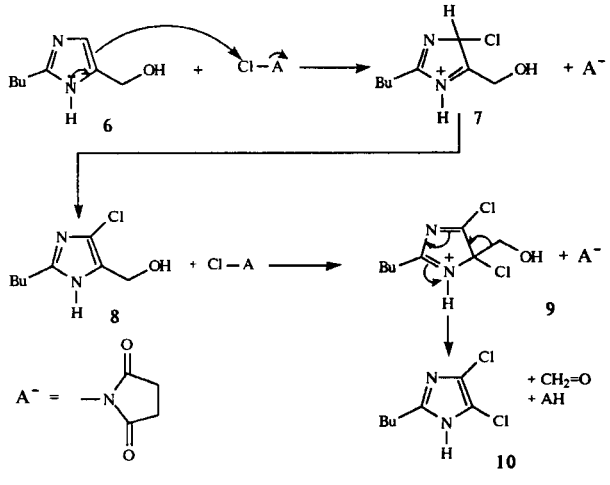


Reaction conditions: a) KCN/Δ, b) $HN(Et)_2$, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, HCl, dimethylaminopyridine, 12 hours, c) EtOH/HCl, d) dihydroxyacetone, NH_3, 45°C.

Reacting potassium cyanide with γ-butyrolactone afforded the nitrile acid **2** [5], which on coupling with diethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and *N,N*-dimethylaminopyridine led to the amide **3** in 60% yield. Formation of the imidazole **5** was accomplished in 50% yield by reacting the imidate **4** with dihydroxyacetone and ammonia. The next step was the chlorination of the imidazole ring. The classical electrophilic reaction with *N*-chlorosuccinimide (NCS) [6] was unsuccessful.

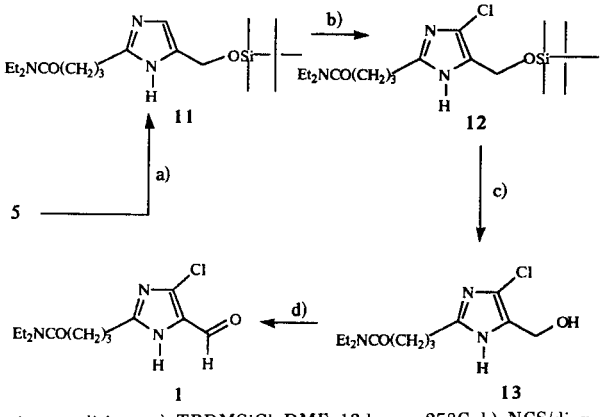
The chlorination problem has been solved by protecting the alcohol function of **5** with the *tert*-butyldimethylsilyl group (TBDMS) in order to avoid side reactions such as retrohydroxymethylation. The latter reaction was studied in a related series [7] and was shown to occur most likely by the mechanism described in Scheme II, involving an intermediate imidazolinium ion which can rearomatise to **8**. Further reaction of **8** with NCS gave the dichloro intermediate **9** which was able to undergo a retrohydroxymethylation thus accounting for the formation of the 4,5-dichloroimidazole **10** as a side-product (30%).

Scheme II



As expected, the action of NCS on the silylated compound **11** gave the target molecule **12** in 52% yield (Scheme III). Deprotection of the silyl group using *n*-tetrabutylammonium fluoride in THF afforded the primary alcohol **13** which was subsequently oxidized in the target molecule **1** using manganese dioxide in dichloromethane.

Scheme III



Reaction conditions: a) TBDMSiCl, DMF, 12 hours, 25°C, b) NCS/dioxane, 4 hours, 25°C, c) *n*-Bu_4NF, THF, 2 hours, 25°C, d) MnO_2, CH_2Cl_2, 12 hours, 25°C.

In conclusion, using TBDMS as a protecting group for an hydroxyl function on the imidazole ring during the chlorination step, we succeeded in synthesizing the highly functionalized imidazole **1** with an overall yield of 13% from **2**. It is noteworthy that the use of the less hindered trimethylsilyl chloride was much less satisfactory.

EXPERIMENTAL

Reactions are carried out under a nitrogen flow. All reagents and solvents were of commercial quality. Flash chromatography purification was realized with Merck Geduran SI 60 silica (0.040-0.063 mm). The ^1H nmr spectra were recorded on a Bruker AC 300 P spectrometer; the chemical shifts are given in δ units downfield from the internal standard tetramethylsilane; ir spectra were recorded on a Perkin Elmer 782 spectrometer. Elemental analyses were carried out with a Perkin Elmer 2400 C, H, N Elemental Analyser. Melting points were determined on a Kofler hot stage.

4-Cyano-*N,N*-diethylbutanamide **3**.

To a solution of 22.6 g (20 mmoles) of **2** in 500 ml of dichloromethane were added 40 g (20 mmoles) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride, 24.4 g (20 mmoles) of dimethylaminopyrine and 20 ml (20 mmoles) of diethylamine. Thereafter, the mixture was stirred at room temperature overnight and then poured into water. After extraction with ethyl acetate, the organic layers were washed twice with 1 *N* hydrochloric acid and then with water. The usual workup afforded 57 g (60%) of the cyanoamide **3** as a colorless liquid. An analytical sample was obtained after Kugelrohr distillation (bp 14 mm Hg, 170°); ir (sodium chloride): 2980-2940, 2240 (C=N), 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.12 (t, 3H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.2 Hz), 2.01 (quint, 2H, J = 6.8 Hz), 2.51 (m, 4H), 3.35 (m, 4H); ms: m/z (electronic impact) 168, 128, 100, 72, 58.

N,N-Diethyl-4-(5-hydroxymethylimidazol-2-yl)butanamide **5**. Synthesis of the Imidate **4**.

To a solution of 5 g (29.72 mmoles) of **3** in 7 ml (118 mmoles) of absolute ethanol, 4.3 g (118 mmoles) of hydrochloric acid gas was bubbled. This mixture was kept one day at 0° and then concentrated *in vacuo* to afford the crude imidate as an oil; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.00 (t, 3H, J = 7.4 Hz) 1.08 (t, 3H, J = 7.4 Hz), 1.34 (t, 3H, J = 7.0 Hz), 1.64 (quint, 2H, J = 7.2 Hz), 2.37 (t, 2H, J = 7.0 Hz), 2.64 (t, 1H, J = 7.4 Hz, 3.25 (quint, 4H, J = 7.4 Hz), 4.39 (q, 2H, J = 7.0 Hz), 11.02 (s, 1H), 11.92 (s, 1H).

Synthesis of **5**.

The crude imidate **4** was put into an autoclave cooled down to −40°, and 10.8 g (0.12 mole) of dihydroxyacetone was added. Liquid ammonia (400 ml) was then added carefully. The sealed bomb was heated up to 45° and then kept one night at this temperature. After degasing, methanol was added and the mixture was then put into a flask. Most of the solvent was evaporated after filtration of the salts. The residue was chromatographed (dichloromethane-methanol, 9:1, v/v) to afford 14.5 g (50%) of **5** as an oil. An analytical sample was obtained after several crystallizations, mp 79°; ir (potassium bromide): 3500-3300, 3200, 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13 (t, 3H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz), 1.98 (quint, 2H, J = 6.8 Hz), 2.39 (t, 2H, J = 6.8 Hz), 2.79 (t, 2H, J = 6.8 Hz), 3.32 (q, 2H, J = 7.0 Hz), 3.39 (q, 2H, J = 7.0 Hz), 4.60 (s, 2H), 6.85 (s, 1H).

Anal. Calcd. for $C_{12}H_{21}N_3O_2 \cdot 0.7H_2O$: C, 57.13; H, 8.96; N, 16.65. Found: C, 57.60; H, 8.54; N, 16.7.

N,N-Diethyl-4-[5-(*t*-butyldimethylsilyloxymethyl)imidazol-2-yl]-butanamide **11**.

To a solution of 7 g (29.5 mmoles) of **5** in 70 ml of dimethylformamide was added 17 g (295 mmoles) of imidazole. A solution of 22 g (147 mmoles) of TBDMSiCl in 50 ml of dimethylformamide was then added dropwise into the mixture. After stirring overnight at room temperature, most of the solvent was evaporated. The mixture was washed with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The oily residue was purified by silica gel column chromatography eluting with ethyl acetate hexane (8:2, v/v) as eluent to give 9.5 g (90%) of **6** as an oil; ir (sodium chloride): 3200, 3160, 2980, 2940, 1650-1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.08 (s, 6H), 0.91 (s, 9H), 1.13 (t, 3H, J = 7.1 Hz), 1.17 (t, 3H, J = 7.1 Hz), 2.00 (quint, 2H, J = 6.9 Hz), 2.39 (t, 2H, J = 6.9 Hz), 2.82 (t, 2H, J = 6.9 Hz), 3.31 (q, 2H, J = 7.2 Hz), 3.36 (q, 2H, J = 7.2 Hz), 4.67 (s, 2H), 6.80 (s, 1H).

Anal. Calcd. for $C_{18}H_{35}N_3O_2Si$: C, 61.14; H, 9.98; N, 11.88. Found: C, 60.70; H, 9.56; N, 11.88.

N,N-Diethyl-4-[4-chloro-5-(*tert*-butyldimethylsilyloxymethyl)imidazol-2-yl]butanamide **12**.

To a solution of 13.7 g (38.7 mmoles) of **6** in 100 ml of dioxane, 5.2 g (40 mmoles) of *N*-chlorosuccinimide was added. The mixture was stirred 4 hours at room temperature. After evaporation of the solvent, water was added and the mixture was extracted with ethylacetate. After the classical workup the residue was chromatographed eluting with ethyl acetate-hexane (8:2, v/v) as eluent to afford 7.8 g (52%) of **7** as an oil; ir (sodium chloride): 3200, 2960, 2940, 1650-1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.087 (s, 6H), 0.89 (s, 9H), 1.13 (t, 3H, J = 7.3 Hz), 1.18 (t, 3H, J

= 7.3 Hz), 1.98 (quint, 2H, J = 6.8 Hz), 2.40 (t, 2H, J = 6.8 Hz), 2.76 (t, 2H, J = 6.8 Hz), 3.31 (q, 2H, J = 7.3 Hz), 3.39 (q, 2H, J = 7.3 Hz), 4.63 (s, 2H), 10.70 (s, 1H).

Anal. Calcd. for $C_{18}H_{34}ClN_3O_2Si$: C, 55.71; H, 8.83; N, 10.83. Found: C, 55.29; H, 8.41; N, 11.23.

N,N-Diethyl-4-(4-chloro-5-hydroxymethylimidazol-2-yl)butanamide **13**.

To a solution of 0.7 g (1.8 mmoles) of **7** in 7 ml of THF, was added dropwise a solution of 1 *M* tetrabutylammonium fluoride in 2 ml (2 mmoles) of THF. The mixture was stirred 2 hours at room temperature. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography eluting with ethyl acetate-hexane (9:1, v/v) as eluent to afford 0.25 g of **8** as a solid (50%), mp 162°; ir (potassium bromide): 3200, 3160, 2980, 2940, 1630 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.99 (t, 3H, J = 7.1 Hz), 1.06 (t, 3H, J = 7.1 Hz), 1.82 (t, 2H, J = 7.3 Hz), 2.30 (t, 2H, J = 7.3 Hz), 2.51 (m, 2H), 3.22 (m, 4H), 4.31 (d, 2H, J = 5.3 Hz), 5.10 (t, 1H, J = 5.3 Hz), 12.12 (s, 1H).

Anal. Calcd. for $C_{12}H_{20}ClN_3O_2$: C, 52.63; H, 7.36; N, 15.34. Found: C, 52.85; H, 7.17; N, 15.07.

N,N-Diethyl-4-(4-chloro-5-formylimidazol-2-yl)butanamide **1**.

To a solution of 0.26 g (0.95 mmole) of **8** in 7 ml of dichloromethane was added 0.36 g (47 mmoles) of manganese dioxide and the mixture was stirred at room temperature overnight. After filtration of manganese dioxide over Celite, the filtrate was evaporated and the residue was chromatographed eluting with ethyl acetate as eluent to give 0.24 g (90%) of **1** as an oil; ir (sodium chloride): 3150, 2980, 2940, 1670, 1620 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz), 2.06 (quint, 2H, J = 6.8 Hz), 2.44 (t, 2H, J = 6.7 Hz), 2.86 (t, 2H, J = 6.9 Hz), 3.32 (q, 2H, J = 7.1 Hz), 3.41 (q, 2H, J = 7.1 Hz), 9.67 (s, 1H).

Anal. Calcd. for $C_{12}H_{18}ClN_3O_2$: C, 53.03; H, 6.67; N, 15.46. Found: C, 53.07; H, 6.61; N, 15.16.

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