Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Practical Synthesis of 2-Butyl-4(5)-chloro-5(4)-hydroxymethyl- 1H-imidazole

Yao-Jun Shi [a] , Lisa F. Frey [a] , David M. Tschaen [a] & Thomas R. Verhoeven [a]

[a] Department of Process Research, Merck Research Laboratory, P.O. Box 2000, Rahway, New Jersey, 07065

Published online: 24 Sep 2006.

To cite this article: Yao-Jun Shi , Lisa F. Frey , David M. Tschaen & Thomas R. Verhoeven (1993): A Practical Synthesis of 2-Butyl-4(5)-chloro-5(4)-hydroxymethyl-1H-imidazole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:18, 2623-2630

To link to this article: http://dx.doi.org/10.1080/00397919308012598

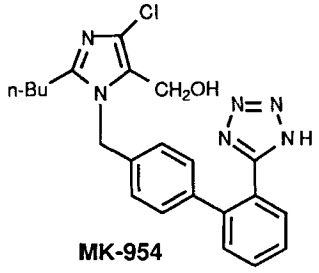
SYNTHETIC COMMUNICATIONS, 23(18), 2623-2630 (1993)

A PRACTICAL SYNTHESIS OF 2-BUTYL-4(5)-CHLORO-5(4)-HYDROXYMETHYL-1H-IMIDAZOLE

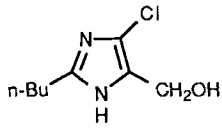
Yao-Jun Shi,* Lisa F. Frey, David M. Tschaen and Thomas R. Verhoeven

Department of Process Research
Merck Research Laboratory,
P.O. Box 2000, Rahway, New Jersey 07065

Abstract: A practical process for the synthesis of 2-butyl-4-hydroxymethyl imidazole (**4**) followed by chlorination to provide chloroimidazole **1** in an overall 71% yield has been developed.



MK-954

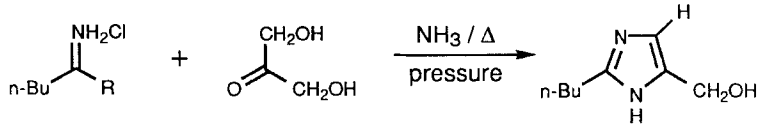


1

* To whom correspondence should be addressed.

As part of an on-going project for the preparation of the potent nonpeptide angiotensin II receptor antagonist (**MK-954**)[1], a practical synthesis of the titled compound **1** was required. Our approach involves the synthesis of imidazole **4** followed by the chlorination to give chloroimidazole **1**. There are several literature reports describing the synthesis of 2-butyl-4-hydroxymethyl imidazole (**4**).[2] (**Scheme I**) However, the existing methods are of limited utility because they require elevated reaction temperatures and extremely high pressures (420 psi).[2a]

Scheme I



2a, R = OEt
2b, R = OMe
2c, R = NH_2

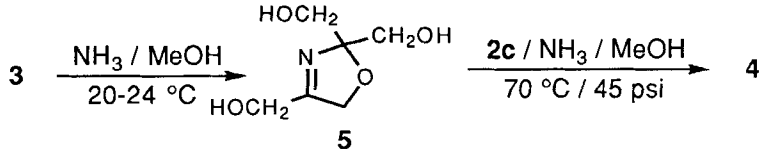
3

4

During the study of these reactions, we discovered that the reaction pressure can be significantly reduced if the proper co-solvent is chosen (e.g. diisopropyl ether, toluene and methanol). When methanol is used, a homogeneous solution is obtained and the reaction between valeroamidine hydrochloride (**2c**)[2c] and 1,3-dihydroxyacetone (**3**) in the presence of 10 equivalents of ammonia at 70 °C affords the product **4** in 79 % yield. Under these conditions the maximum reaction pressure observed is 45 psi which is a practical operating pressure. The significant reduction of pressure (400 psi to 45 psi) is a reflection of the greater solubility of NH_3 in methanol as compared with the absence of solvent (or the solubility in diisopropyl ether or toluene).

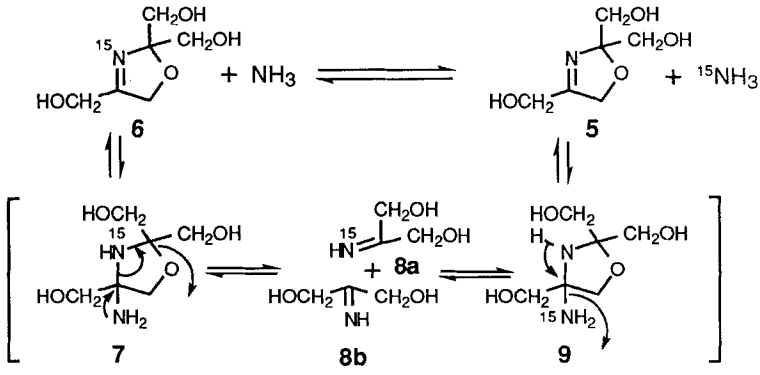
Although no additional NH_3 is needed for the construction of the imidazole ring during the reaction shown in **Scheme I**, our results indicate that a large excess (10 eq.) of ammonia is necessary. This led us to carefully examine the methanolic mixture of amidine hydrochloride **2c**, dihydroxyacetone **3**, and ammonia. Interestingly, we found that the 3-oxazoline **5** is formed at room temperature[3,4] but no imidazole **4** is observed. However, when the mixture is subjected to 70° C and 45 psi the imidazole **4** is generated (**Scheme II**).

Scheme II



In order to understand the function of 3-oxazoline **5** in the reaction, an ^{15}N labeling experiment was carried out with 3-oxazoline **6**[3] which was quantitatively synthesized from the reaction of $^{15}NH_3$ with 1,3-dihydroxyacetone (**3**) in methanol (in methanol 1,3-dihydroxyacetone (**3**) exists as a mixture of its monomers and dimers.). When the 3-oxazoline **6** is treated with NH_3 at 70 °C for 4.0 h in an autoclave the 3-oxazoline **5** is produced. ^{15}N and ^{13}C NMR analysis shows the presence of a scrambled mixture of **5** and **6** in a 1:4 ratio. This result indicates a possible dynamic equilibrium between **5** and **6** as shown in **Scheme III**.

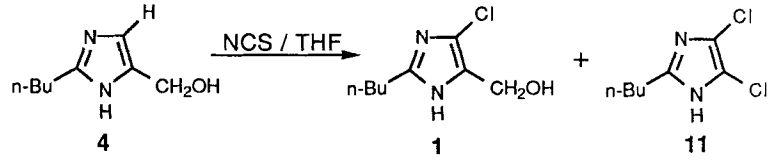
Scheme III



The NH_3 attack on **6** leads to the formation of **7** which ring-opens to form the unstable species **8a** and **8b**. The re-combination of **8a** and **8b** affords **9**, thus resulting in the label scrambling noted in the experiment. It is possible that a species such as **8**, instead of 1,3-dihydroxyacetone (**3**) or 3-oxazoline **5**, could be the reactive intermediate for the construction of the imidazole ring. These results are also consistent with the fact that a large excess of NH_3 (10 equivalents) is a mandatory element for successful reaction. Ammonia is necessary in order to drive the equilibrium from **6** to **8**.

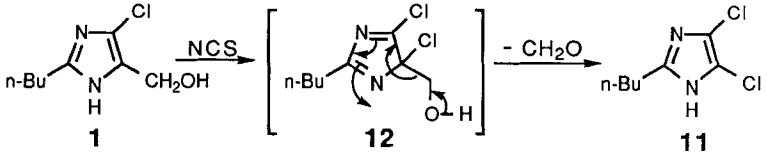
Direct chlorination of **4** following the literature procedure,[2b] produces chloroimidazole **1** in moderate yield (65%) along with 2-5% of recovered **4** and byproduct **11** (2-butyl-4,5-dichloroimidazole, 5-10%). (**Scheme IV**)

Scheme IV



Dichloroimidazole **11** can be independently synthesized from the reaction of chloroimidazole **1** with NCS, which indicates that there are competing reactions of NCS with chloroimidazole **1** and imidazole **4** during the chlorination reaction. A possible pathway for this reaction is presented in **Scheme V**.

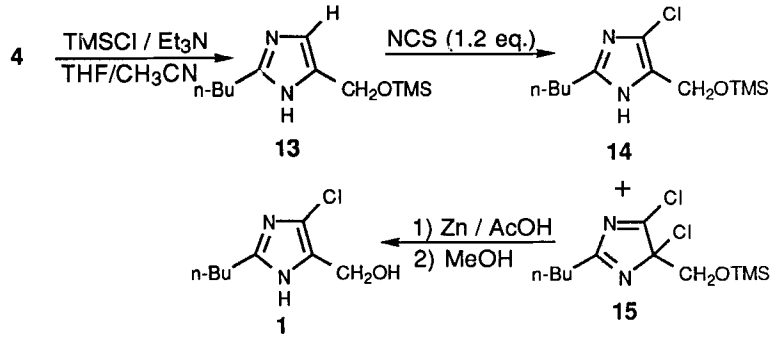
Scheme V



To overcome this obstacle we have found that carbon-bond cleavage and the elimination of HCHO from the intermediate **12** (**Scheme V**) can be suppressed by protection of the hydroxyl group in imidazole **4**. As shown in **Scheme VI**, when the hydroxyl group of **4** is protected as the TMS ether[5] prior to reaction with NCS, a mixture of **14** and **15** is generated. When this crude mixture is treated with zinc dust and acetic acid[6] followed by deprotection with methanol, the desired product **1** is produced in 90 % overall yield. This represents a 25% yield improvement over previously described methods for chlorination of **4**. In addition, this reaction sequence insures complete consumption of the starting material **4** while eliminating the formation of the dichloroimidazole **11**.

In summary, the imidazole **4** is synthesized from readily available amidine hydrochloride **2c** by a practical procedure in 79 % yield. The through-process of silylation, chlorination, reduction and desilylation of **4** affords the desired product **1** in 90 % overall yield.

Scheme VI



Experimental

2-Butyl-4-Hydroxymethyl Imidazole (4):

A methanol solution of valeroamidine hydrochloride (**2c**) (75.86 ml, 1.40M, 106 mmol, which was synthesized from the reaction of methyl valeroimidate with NH_3 at - 5° C by a literature method[2a]) in an autoclave (300 cc) was cooled to 0 °C and ammonia gas added (18.0 g, 1.06 mol), maintaining the temperature in the range of 0 - 20 °C (observed pressure - 10 psi). A solution of 1,3-dihydroxyacetone (**3**) (prepared by mixing 11.45 g, 63.36 mmol, of DHA-dimer with 35 ml of CH_3OH at 40 °C for 0.25 h then cooling to 20 °C) was added at 20-25 °C. The mixture was maintained at 25 °C for 0.75 h, heated to 70 °C over 0.45 h (observed pressure - 45 psi), maintained at that temperature for 6.0 h then cooled to 20 °C.

The solvent was evaporated in vacuo and water (40 ml) added. Aqueous NaOH solution (50% wt, 7.5 ml, 127.5 mmol) was slowly added maintaining a temperature of 15-20° C. Crystallization was induced by introducing seed crystals after 1/3 of the NaOH solution had been added. The slurry was aged at 20° C (4.0 h) then at 0° C (1 h), filtered, washed with cold water (5 mL, 0 - 5° C) and cold acetone (8 mL, 0 - 5° C), then dried in vacuo at 40 °C to provide **4** (11.28 g, 69% isolated).

For **5**: a colorless oil; IR (neat) [OH] 3320 (s), [C=N] 1670 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) ∂ 4.75 (s, 2H), 4.41 (s, 2H), 3.67 (s, 2H), 3.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 176.3, 114.1, 76.9, 65.0, 60.5.

For **4**: m.p. 82.5 - 84.5° C (H_2O) (lit.[2d] m.p. 88.6 - 88.8° C); ^1H NMR (300 MHz, D_2O) ∂ 6.94 (s, 1H), 4.49 (s, 2H), 2.65 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.25 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) ppm 151.5, 136.9, 117.8, 56.8, 30.7, 27.9, 22.3, 13.8.

2-Butyl-4(5)-Hydroxymethyl-5(4)-Chloroimidazole (1):[2b]

Trimethylsilyl chloride (TMSCl) (15.2 mL, 120 mmol) was slowly added to a slurry of 2-butyl-4-hydroxymethyl imidazole (**4**) (15.4 g, 100 mmol) and Et_3N (18.8 mL, 135 mmol) in a mixed solvent of THF (100 mL) and CH_3CN (125 mL) maintaining the temperature below 0 °C, and was stirred for 2 h. The NCS (16.02 g, 120 mmol) was added in portions at -5 - 0° C and after 0.75 h, the mixture filtered at 0° C and washed with THF (50 mL). To the filtrate was added acetic acid (22.9 mL, 400 mmol) followed by zinc dust (3.93 g, 60 mmol) at -5 - 0° C and the mixture was aged for 1.5 h at that temperature. Methanol (100 mL) was added and the mixture was allowed to warm to 20 °C over 2 h.

The solvents were evaporated in vacuo after the filtration. Water (45 mL) was added followed by NaOH (50% wt, 13 mL). The resulting slurry was stirred at 40°C (1 h) and at 0°C (0.5 h). The product was filtered and re-slurried with H_2O (120 mL) at 40°C (1 h) and at 0°C (1 h). It was filtered and dried at 40° C to provide 14.84 g of **1** (79% isolated).

For **11**: m.p. 128.5 - 130.0° C (ether-hexane); ^1H NMR (300 MHz, $CDCl_3$) ∂ 2.72 (t, J = 7.9 Hz, 2H), 1.75 - 1.60 (m, 2H), 1.40 - 1.25 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 147.3, 116.9, 30.4, 28.5, 22.2, 13.7.

For **13**: ^1H NMR (300 MHz, $CDCl_3$) ∂ 4.40 (s, 2H), 2.45 (t, J = 7.2 Hz, 2H), 1.60 - 1.47 (m, 2H), 1.25 - 1.10 (m, 2H), 0.75 (t, J = 7.3 Hz, 3H).

For **14**: ^1H NMR (300 MHz, $CDCl_3$) ∂ 3.88 (d, J = 10.1 Hz, 1H), 3.76 (d, J = 10.1 Hz, 1H), 2.50 (t, J = 7.2 Hz, 2H), 1.60 - 1.45 (m, 2H), 1.25 - 1.10 (m, 2H), 0.72 (t, J = 7.3 Hz, 3H).

For **1**: m.p. 148.5 - 150.0° C (H_2O); ^1H NMR (300 MHz, DMSO-d_6) ∂ 5.11 (t, J = 5.0 Hz, 1H), 4.31 (d, J = 5.0 Hz, 2H), 3.35 (s, 1H), 2.54 (t, J = 7.5 Hz,

2H), 1.58 (m, 2H), 1.29 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) ppm 146.7, 124.0, 123.7, 51.9, 29.8, 27.3, 21.5, 13.5.

Acknowledgment: The authors express their gratitude to Mr. R.A. Reamer and Mrs. P. Simpson for their help with the structure elucidation of **5** and for performing both ^{13}C NMR and ^{15}N NMR studies on **6**.

References

1. Carini, D.J.; Duncia, J.V.; Aldrich, P.E.; Chiu, A.T.; Johnson, A.L.; Pierce, M.E.; Price, W.A.; Santella, J.B. III; Wells, G.J.; Wexler, R.R.; Wong, P.C.; Yoo, S. and Timmermans, P.B.M.W.M. *J. Med. Chem.*, **1991**, *34*, 2525, and references therein.

2. (a) Dzurion, P. and Schunack, W. *Archive Pharmaxie*, **1974**, *307*, 470; (b) Furukawa, Y.; Kishimoto, S. and Nishikawa, K. *U.S. Patent* , **1982**, 4, 355,040; (c) Matsumoto, I. *Japan Patent*, **1982**, 98,270; (d) Bovy, P.R. and Simmons, R.L., *J. Labelled Compd. Radiopharmaceuticals*, **1990**, *29*, 81; (e) Watson, S.P. *Synth. Commun.*, **1992**, *22*, 2971.

3. The 3-oxazoline **5** or **6** is synthesized by the reaction of 1,3-dihydroxyacetone (**3**) with NH_3 (or $^{15}NH_3$) in methanol at room temperature. When the reaction is completed the methanol is removed in vacuo, and the product is obtained as a colorless oil.

4. (a) Gaines, J.R. and Hansen, G.R., *J. Heterocycles*, **1963**, *1*, 96; (b) Pfoertner, K.-H.; Montavon, F. and Bernauer, K., *Helv. Chim. Acta*, **1985**, *68*, 600; (c) Weber, M.; Jakob, J. and Martens, J.; *J. Liebigs Ann. Chem.*, **1992**, *1*.

5. Greene, T.W. and Wuts, P.G.M. "*Protective Groups in Organic Synthesis*", John Wiley & Sons, New York, **1991**, 2nd Ed .

6. (a) Fieser, L.F. and Fieser, M. "*Organic Experiments*", Heath, D.C. and Co., Boston, **1964**, pp. 219; (b) Grieco, P.A. *J. Org. Chem.*, **1972**, *37*, 2363.

(Received in the USA 9 April 1993)