A Rapid and Efficient Synthesis of 2-Butyl-5-Chloro-3*H*-Imidazole-4-Carboxaldehyde

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Received 22 December 2003; revised 7 January 2004

Abstract: A rapid, efficient, cost effective procedure has been developed for the synthesis of 2-butyl-5-chloro-3*H*-imidazole-4-carboxaldehyde. Preparation of methyl pentanimidate was accomplished in just 12 hours, followed by a sequence of reactions without isolation and purification of the formed intermediates. The final compound was purified by simple acid-base treatment to get a product with 99.9% HPLC purity.

Key words: imidazole, imidates, Vilsmeier reagents, nitrile, tetrazole

Introduction

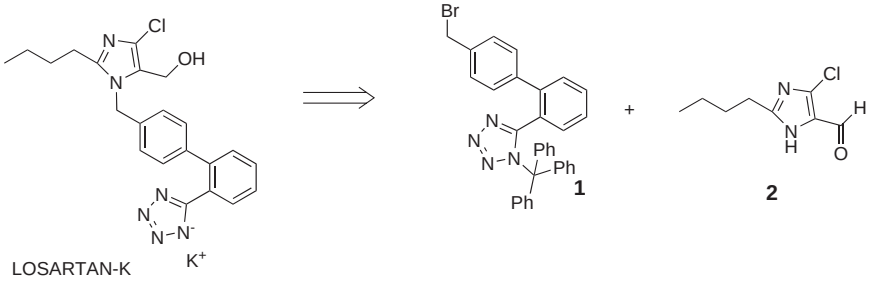
Losartan-K, popularly known as Cozaar, was the first non-peptide angiotensin II receptor antagonist to get approval for the treatment of hypertension.[1,2] Due to its high market value over the world,[3] cost effective synthesis of its intermediates viz, 4-bromomethyl-2,2-biphenyltetrazole **1** and 2-butyl-5-chloro-3*H*-imidazole-4-carboxaldehyde (**2**) attracted the attention of several laboratories.[2,4–8] Having developed an efficient process[9,10] for the intermediate **1**, we have now focused our interest on developing a novel procedure for the most important intermediate **2** in the synthesis of Losartan-K (Scheme 1).

The literature methods[4,7] developed for the preparation of **2** make use of 2-butyl 4-hydroxymethyl imidazole prepared via the reaction of pentanimidate hydrochloride, dihydroxy acetone and ammonia at high temperature and pressure.[11] The alcohol thus formed was then converted to **2** by oxidation-chlorination[12] or chlorination-oxidation[5] methods. This procedure is not commercially viable because of the use of high temperature and pressure and also due to the formation of dichloroimidazole as byproduct. Although later methods[12] employed trimethylsilyl (TMS) protected alcohol, the procedure is not suitable for commercial exploitation because of the added cost of TMS in the process. The alternate approach described by Griffith et.al,[13,14] involve the preparation, isolation and distillation of methyl pentanimidate, its condensation with glycine and then cyclization-chlorination-formylation using Vilsmeier reagents. In the above procedure, preparation of methyl pentanimidate in dibutyl ether itself takes six days for completion of the reaction, followed by work up procedures at several stages to isolate and purify the intermediates.

In our attempts to prepare Losartan-K, we[15] have targeted a fast and industrially viable process for the preparation of **2**. We herein report an improved and practical procedure for the preparation of 2-butyl-5-chloro-3*H*-imidazole-4-carboxaldehyde (**2**) (Scheme 2), wherein methyl pentanimidate was made in just 12 hours without any solvent, followed by a sequence of reactions without isolation and purification of the formed intermediates. The final compound **2** was purified by simple acid-base treatment followed by recrystallization (99.9% HPLC purity).

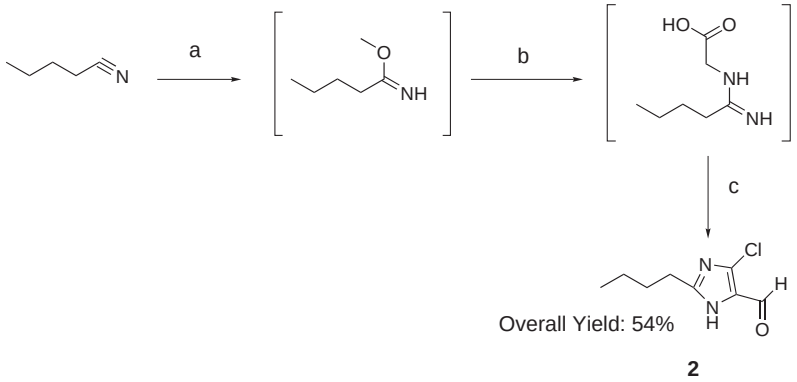
Results & Discussion

Pentanimidate hydrochloride is generally prepared[4,14] by passing HCl gas through a solution of valeronitrile and MeOH in Et_2O–dibutyl ether at –15 °C to 0 °C and maintaining the reaction mixture at 4 °C for six days. Our repeated attempts on this reaction made us realize that ether



Scheme 1

SYNTHESIS 2004, No. 4, pp 0506–0508
Advanced online publication: 09.02.2004
DOI: 10.1055/s-2004-815961; Art ID: Z18103SS



Scheme 2 (a) i. MeOH, HCl (g), 12 h, 20 °C, ii. Toluene, KOH (6 M); (b) Glycine, MeOH–H_2O, 15 h, 40 °C; (c) $POCl_3$, DMF, 100 °C, 3 h.

solvent was not necessary and that a moderate rise in temperature would result in faster product formation. Thus, HCl gas was passed through a solution of valeronitrile and MeOH at –10 °C to 5 °C and then the vessel was sealed tightly and stirred at 20 °C for 12 hours to get a cloudy white mass. After evaporating the solvents under vacuum, toluene was added to the salt obtained and the solution was neutralized with aqueous KOH solution. The toluene solution of the free base was directly added to the glycine suspension in MeOH–H_2O without any further treatment. After 15 hours, a small amount of the above reaction mixture was evaporated to dryness and analyzed by ^{1}H NMR spectroscopy in D_2O. The crude reaction mixture showed singlets at δ = 3.87 and δ = 3.55 for methylene protons of $NHCH_2C{=}O$ unit of (pentanimidoyalamino)acetic acid and glycine, respectively, in the ratio of 7:3 revealing that 70% of the (pentanimidoyalamino) acetic acid was formed. The butyl signals appeared as a triplet at δ = 2.53; two multiplets at δ = 1.53 and at δ = 1.70 and a triplet at δ = 0.91 in the ratio of 7:7:7:10 respectively, were consistent with the product formed (Scheme 2).

The crude reaction mixture was completely evaporated under vacuum and the resultant mass was dried by repeated evaporation with toluene. This was subjected to the modified Vilsmeier reaction by treating with $POCl_3$ at –5 °C followed by addition of DMF at a temperature below 75 °C. The reddish brown solution was heated to 100 °C and maintained at 100 °C for 3 hours. After cooling, the reaction mixture was poured into ice, neutralized to pH 6.0, extracted with toluene and concentrated to get an impure solid material. We devised an efficient method to isolate the product from the impurities by exploiting the acid-base nature of the imidazole formed. The toluene extract having the product in solution was treated with 10% aqueous KOH and the aqueous portion was carefully acidified with acetic acid to precipitate a solid that was recrystallized in toluene–cyclohexane solvent mixture to give a pale yellow solid in 99.9% HPLC purity. The purity of the product is much superior to the product prepared by Griffith's procedure (96.9%).[14] The product was characterized ^{13}C and ^{1}H NMR and mass spectral analysis and is in agreement with literature data.[14]

Conclusions

The above report describes a rapid, practical and commercially viable process for the preparation of 2-butyl-5-chloro-3*H*-Imidazole-4-carboxaldhyde. The procedure is attractive and speedy as it avoids the isolation and purification of the intermediates at the various stages. The reaction conditions are optimized to minimize impurity formation and to prepare the product in good yields and in highest purity.

General Procedure

In a three-necked 1 L round bottom flask equipped with stirrer, thermometer, and gas bubbler, a solution of valeronitrile (110 g, 1.32 mol) in MeOH (63 g, 1.95 mol) was taken and cooled to –10 °C under N_2. HCl gas (65 g, 2 mol) was bubbled below the surface of the liquid at such a rate that the reaction temperature was maintained below 5 °C. Stirring was continued at 20 °C for 12 h, to form thick white slurry, which was flushed with N_2 and dried under vacuum (10 mm) to get a thick white mass. Toluene (500 mL) was added to the reaction mixture, cooled to –10 °C and neutralized with 6 M KOH (250 mL) to pH 8 at such a rate that temperature of mixture was below 5 °C. The toluene layer was decanted and the aqueous layer was extracted with toluene (3 × 100 mL). The combined toluene layers of pentanimidate base was added dropwise, to a stirred mixture of glycine (100 g, 1.32 mol) in MeOH (300 mL) and water (50 mL) at 0 °C to –5 °C. The pH of the reaction mixture was brought to 8 by adding 2–3 drops of 6 M KOH and reaction was continued for 15 h at 40 °C. The reaction mixture was concentrated under vacuum and the suspension was dried by co-evaporation with toluene (5 × 100 mL). The pale yellow solid material suspended in toluene (150 mL), was cooled to –5 °C and $POCl_3$ (230 mL, 2.5 mol) was added drop wise within 20 min, DMF (137 mL, 1.76 mol) was added at such a rate that the temperature of reaction mixture was maintained below 75 °C. After complete addition, the contents of reaction mixture were held at 97–100 °C for 3 h. The reddish brown solution was cooled to r.t. and poured over crushed ice (1 kg) at 0 °C. Celite (100 g) was added with stirring and neutralized to pH 6.0 using 30% NaOH (500 mL). Celite was filtered and washed with toluene (100 mL). The combined toluene layer was separated and the product was extracted with 10% KOH (3 × 100 mL). The basic solution was cooled to 0 °C and acidified to pH 6.0 with acetic acid, to get a light brown colored solid, which was filtered. The crude product was taken in 1:5 mixture of toluene and cyclohexane (500 mL) and treated with charcoal at 80 °C, filtered and cooled to give pale yellow solid (132 g, 54% in overall yield); mp 93 °C (lit.[14] 92–95 °C), 99.9% HPLC purity. The ^{1}H NMR, ^{13}C NMR and mass spectra are in complete agreement with the literature values.[14]

References

(1) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Pierce, M. E.; Smith, R. D.; Wells, G. J.; Wang, P. C.; Wexier, P. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. *Drugs Fut.* **1991**, *16*, 305.
(2) 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. E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525; and references reported therein.
(3) *Scrip* **1994**, *1963*, 23.
(4) Takeda Chemical Industries Ltd., JP 5798270, **1982**; *Chem. Abstr.* **1983**, *98*, 4543a.
(5) Yamamoto, T.; Hibi, Y.; Ogawa, T. US Patent 5395943, **1995**.
(6) Elz, S.; Kramer, K.; Pertz, H. H.; Detert, H.; Laak, A. K.; Kuhne, R.; Schunack, W. *J. Med. Chem.* **2000**, *43*, 1073.
(7) Furukawa, Y.; Kishimoto, S.; Nishikawa, K. US Patent 4355040, **1982**.
(8) Basappa, M. P. S.; Mantelingu, K.; Swamy, S. N.; Rangappa, K. S. *Bioorg. Med. Chem.* **2003**, *11*, 4539.
(9) Pardhasaradhi, M.; Srinivas, K.; Snehalatha Nair, C. K. US patent 6326498, **2001**; *Chem. Abstr*. **2001**, *136*, 5996.
(10) Srinivas, K.; Snehalatha Nair, C. K.; Ramesh, S.; Pardhasaradhi, M. *Org. Prep. Proced. Int.* **2003**, *35*, 537.
(11) Dzurion, P.; Schunarck, W. *Arch. Phamazie* **1974**, *307*, 470.
(12) Shi, Y.-J.; Frey, L. F.; Tschaeu, D. M.; Verhoeven, T. R. *Synth. Commun.* **1993**, *23*, 2623.
(13) Griffiths, G. J. *Chimia* **1997**, *51*, 283.
(14) Griffiths, G. J.; Hauck, M. B.; Imwinkelried, R.; Kohr, J.; Roten, C.; Stucky, G. C. *J. Org. Chem.* **1999**, *64*, 8084.
(15) Pardhasaradhi, M.; Srinivas, K.; Snehalatha Nair, C. K.; Ramesh, S. Indian Patent NF132, **2002**.