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Preparation of a Key Intermediate for the Angiotensin II Antagonist Losartan via Vilsmeier Chloroformylation

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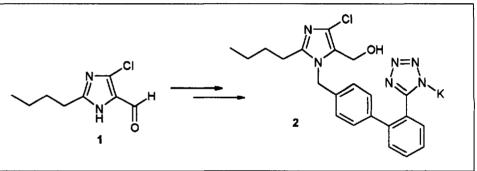
Abstract. A novel preparation of 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde (1), a key intermediate for the synthesis of the angiotensin II antagonist Losartan potassium, via Vilsmeier chloroformylation of imidazolinone **3** is described.

2-Butyl-5-chloro-3H-imidazole-4carbaldehyde (1) is a key intermediate (*Scheme 1*) in the published syntheses [1] of *Merck*'s antihypertensive Losartan potassium (*Cozaar*[®]) (2), the first angiotensin II antagonist to reach the market.

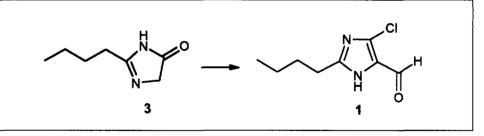
Several synthetic approaches to aldehyde **1** have been published, that most commonly used appears to be the dihydroxyacetone-based route originally described in a patent from *Takeda* [2] and further investigated by *Merck* [3]. The presence of the β -chloroenal moiety in **1** suggested the possibility of an alternative synthesis via Vilsmeier chloroformylation of imidazolinone **3** (*Scheme 2*).

Literature reports on the synthesis of 2alkylimidazolinones analogous to 3 are scarce; one publication by Jacquier and coworkers [4] described the preparation of 2-methylimidazolinone 4 in 64% yield by reaction (24 $h/-10^{\circ}$) of glycine ethyl ester with imidate 5 in the absence of solvent (Scheme 3). Several possible syntheses of 3 were investigated; the best was found to be a considerably improved variation of the Jacquier approach, namely reaction of glycine methyl ester (liberated by neutralisation of its hydrochloride using NaOH in methanol) with imidate 6(prepared from valeronitrile) in methanol/ water at 25° (Scheme 4). The formation of

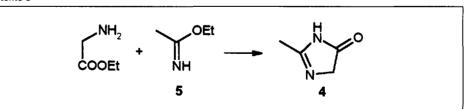
Scheme 1







Scheme 3



the principle by-products 7 and 8 could be almost completely suppressed by careful optimisation of the reaction parameters (in particular the pH), thus allowing isolation of highly pure 3 in *ca.* 90% yield.

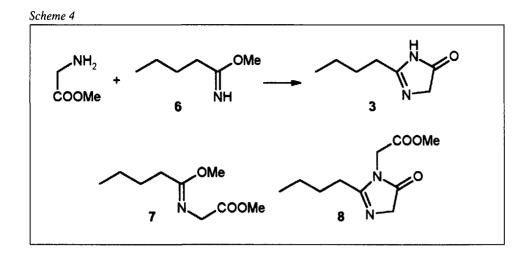
The Vilsmeier chloroformylation of carbonyl compounds has been carried out

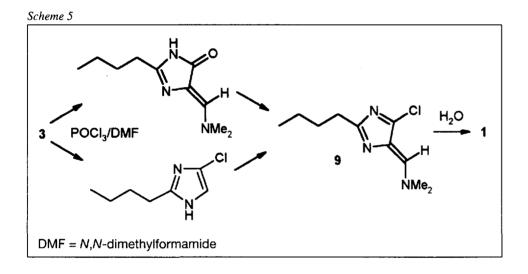
using many permutations of amide (e.g. DMF, N-methylformanilide), acid chloride (e.g. $SOCl_2$, $POCl_3$, $COCl_2$), and solvent [5]. After extensive experimentation, a procedure was developed in which $POCl_3$ (ca. 2.8 equiv.) was added to a suspension of **3** (1 equiv.) in toluene or chlorobenzene

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at $0-20^{\circ}$. The mixture was heated to *ca*. 80° before addition of DMF (*ca*. 2.8 equiv.) and further heating for 2–3 h at 100°. Quenching in water, neutralisation with aqueous NaOH, extraction with toluene and crystallisation gave aldehyde 1 of good purity in *ca*. 55% isolated yield based on 3. Subsequent recrystallisation from ethyl acetate gave 1 of excellent purity.

Mechanistic investigations indicated that conversion of 3 to 9, the precursor of 1, was proceeding by both formylationchlorination and chlorination-formylation (*Scheme 5*), though the former pathway was shown to be by far the dominant one.

For scaleup purposes a procedure without isolation of the relatively unstable 3was developed. Thus, reaction of glycine methyl ester with imidate 6 in toluene/ methanol/water followed by distillative removal of methanol and water gave a suspension of 3 in toluene which could be used directly for the *Vilsmeier* reaction.

In summary, this communication describes a novel and efficient synthesis of aldehyde 1 [6] which can be carried out without isolation and purification of intermediates.

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- [1] a) D.J. Carini, J.V. Duncia, P.E. Aldrich, A.T. Chiu, A.L. Johnson, M.E. Pierce, W.A. Price, J.B. Santella, III, G.J. Wells, R.R. Wexler, P.C. Wong, S.-E. Yoo, P.B. Timmermans, J. Med. Chem. 1991, 34, 2525; b) R.D. Larsen, A.O. King, C.Y. Chen, E.G. Corley, B.S. Foster, F.E. Roberts, C. Yang, D.R. Liebermann, R.A. Reamer, D.M. Tschaen, T.R. Verhoeven, P.J. Reider, Y.S. Lo, L.T. Rossano, A.S. Brookes, D. Meloni, J.R. Moore, J.F. Arnett, J. Org. Chem. 1994, 59, 6391.
- [2] JP 8298270, 18.6.1982 (Takeda Chemical Industries Ltd.) (Chem. Abstr. 1983, 98, 4543).
- [3] Y.-J. Shi, L.F. Frey, D.M. Tschaen, T.R. Verhoeven, Synth. Commun. 1993, 23, 2623.
- [4] R. Jacquier, J.-M. Lacombe, G. Maury, Bull. Soc. Chim. Fr. 1971, 1040.
- [5] C.M. Marson, Tetrahedron 1992, 18, 3659.
- [6] a) Eur. Pat. Application 579212, 19.1.1994
 (*LonzaAG*); b) Eur. Pat. Applications 614890, 614891, 614892, 14.9.1994 (*Lonza AG*).