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

Gareth J. Griffiths*

Abstract. A novel preparation of 2-butyl-5-chloro-3H-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-4-carbaldehyde (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 2-alkylimidazolinones 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/-100) 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 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. SOCl₂, POCl₃, COCl₂), and solvent [5]. After extensive experimentation, a procedure was developed in which POCl₃ (ca. 2.8 equiv.) was added to a suspension of 3 (1 equiv.) in toluene or chlorobenzene.
at 0–20°. 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 formylation-chlorination 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 3 was 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.