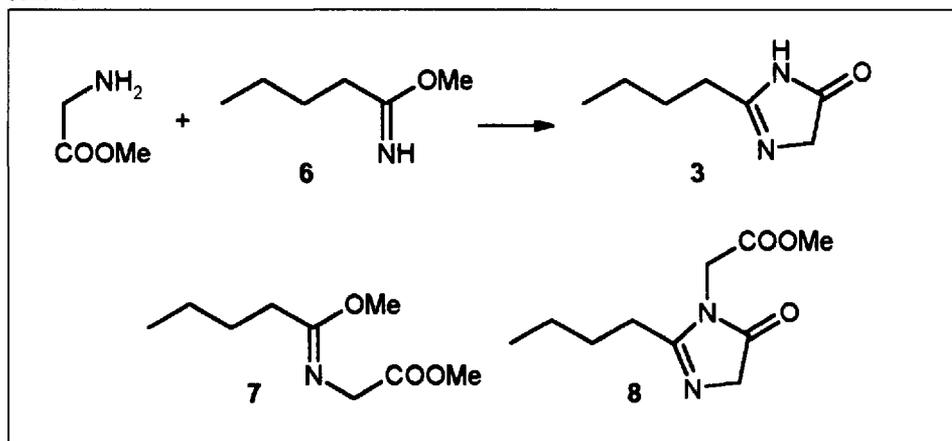
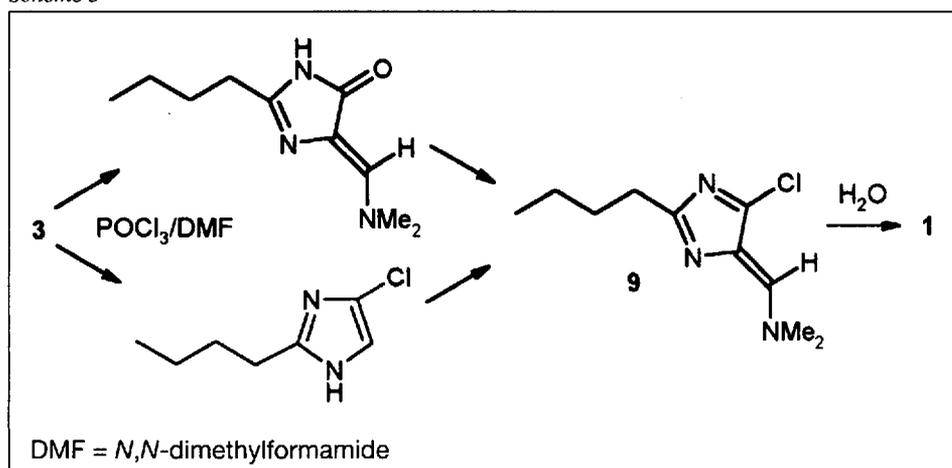




Scheme 4



Scheme 5



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.

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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 (*Lonza AG*); b) Eur. Pat. Applications 614890, 614891, 614892, 14.9.1994 (*Lonza AG*).