Novel Syntheses of 2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde: A Key Intermediate for the Synthesis of the Angiotensin II Antagonist Losartan

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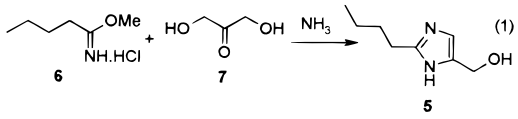
Reaction of glycine methyl ester (**19**) with imidate **18** under carefully optimized conditions allowed preparation of the rather unstable imidazolinone **11** in ca. 90% yield. Reaction of **11** with $POCl_3$/DMF followed by aqueous workup gave aldehyde **2**, a key intermediate for the synthesis of the angiotensin II antagonist Losartan, in ca. 55% yield. Structural identification of intermediates and byproducts formed during both the reaction to prepare **11** and the reaction of **11** with $POCl_3$/DMF allowed development of several closely related syntheses of aldehyde **2**.

Introduction

Merck's Losartan potassium (Cozaar, **1**) was the first angiotensin II antagonist to gain the approval of the regulatory authorities as a treatment for hypertension.[1] A key step in the published syntheses of **1** is the regioselective N-alkylation of 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde (**2**) using either 4-bromobenzyl bromide (**3**)[2] or 4-arylbenzyl bromide **4**[3] (Scheme 1); for this reason there has been considerable interest in the development of economically viable and technically feasible syntheses of aldehyde **2**. Most published syntheses of **2** make use of alcohol **5**, which can be prepared *via* reaction of imidate hydrochloride **6** with dihydroxyacetone (**7**) and ammonia (eq 1) at elevated temperature and pressure.[4,5] Alcohol **5** has been converted to **2** *via*



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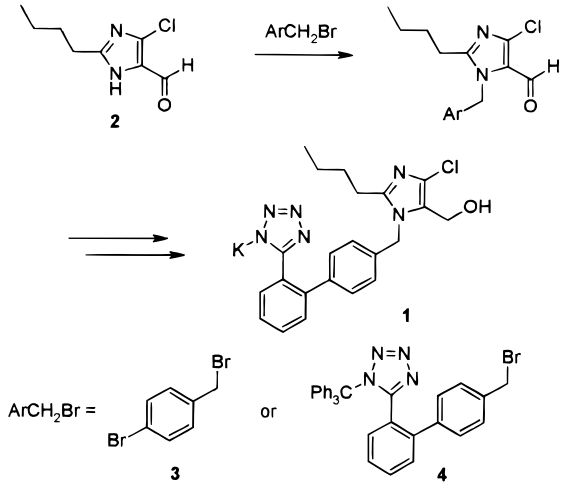
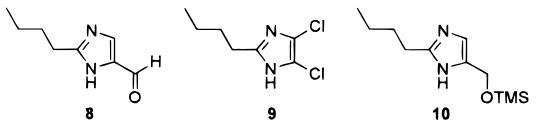
both chlorination−oxidation[5] and oxidation−chlorination[6] protocols, although one disadvantage common to both approaches appears to be formation of dichloroimidazole **9** as a byproduct of the chlorination of either alcohol **5**[5] or aldehyde **8**.[6] In addition to carrying out spectroscopic investigations into the mechanism of the reaction of **6** with **7** and ammonia, Merck scientists showed that the formation of **9** could be prevented by employment of **10**, the OTMS-protected derivative of **5**, as the substrate for chlorination.[5]

Scheme 1



2 1 3 4

The alternative approaches to aldehyde **2** described in this publication[7] are based on the proposition that the presence of the β-chloroenal moiety in **2** should allow its access *via* reaction of the previously unreported 2-butyl-2-imidazolin-5-one (**11**) with Vilsmeier reagents (eq 2).



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(1) *Scrip* **1994**, *1963*, 23.

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(6) Yamamoto, T.; Hibi, Y.; Ogawa, T. (Nippon Gohsei). US Patent 5,395,943, March 7, 1995.

(7) Preliminary communication. Griffiths, G. J. *Chimia* **1997**, *51*, 283.

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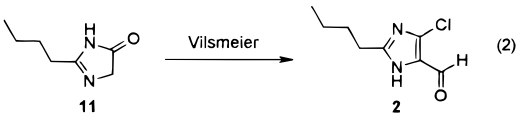
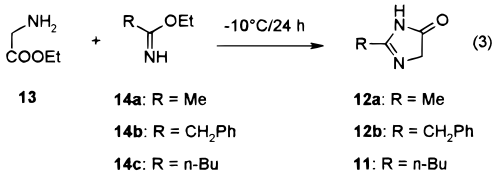
As described below, structural identification of interme-



diates and byproducts formed during both the reaction of **11** with Vilsmeier reagents and the reaction used to prepare **11** allowed development of several closely related syntheses of **2**.[8]

Results and Discussion

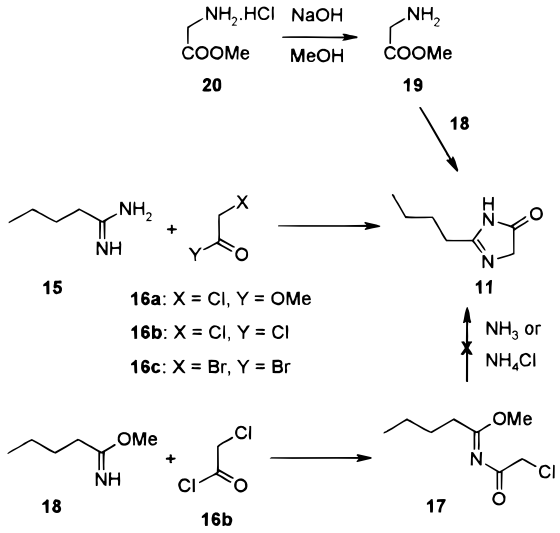
Synthesis and Reactivity of Imidazolinone 11. A survey of the literature revealed that the chemistry of imidazolinones of general structure **12** (R = alkyl) had received little attention. Jacquier and co-workers had, however, prepared imidazolinones **12a** and **12b** by allowing glycine ethyl ester (**13**) to react with imidates **14a** and **14b**, respectively, for 24 h at −10 °C in the absence of a solvent (eq **3**).[9] The same publication described



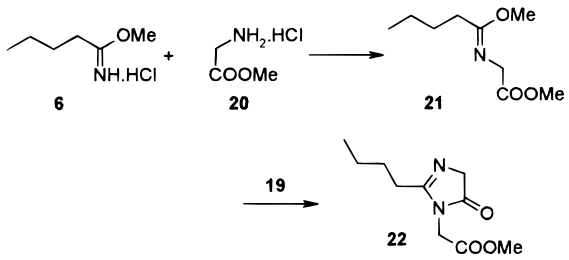
spectroscopic (^{1}H NMR, IR, UV) evidence which indicated that **12a** and **12b** existed predominantly in the 2-imidazolin-5-one tautomeric form. Initial small quantities of imidazolinone **11** were prepared by reaction of imidate **14c** with **13** under the conditions described by Jacquier, although the reaction suffered from poor reproducibility and gave **11** in at best *ca.* 40% yield. Among the alternative syntheses of **11** investigated (Scheme 2) was the reaction of amidine **15** with the chloro- and bromoacetic acid derivatives **16a**−**c** under widely ranging reaction conditions (variation of solvent, base, temperature, etc). Although **11** was among the main products formed under almost all the conditions tested, an efficient removal of the accompanying byproducts proved impossible. Also unsuccessful were attempts to prepare **11** by reaction of either ammonia or ammonium chloride with imidate **17**, which was obtained in high yield by reaction of imidate **18** with acid chloride **16b** in CH_2Cl_2 in the presence of Et_3N.

The lack of success achieved using the approaches described above led us to seek a more efficient variation of the Jacquier method to prepare **11**. After considerable experimentation, a method was developed which involved reaction of glycine methyl ester (**19**) (liberated by addition of hydrochloride **20** to a methanolic solution of NaOH) with imidate **18** (added either in pure form or as a

Scheme 2

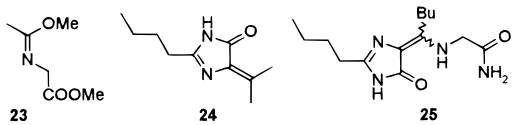


Scheme 3



solution in toluene) at ambient temperature in MeOH containing the suspended NaCl and the 1 equiv of water formed during the neutralization of **20** (Scheme 2). Careful workup gave **11** of relatively good purity in *ca.* 90% yield. Attempts to further purify the rather unstable **11** by recrystallization, sublimation, or chromatography on silica gel were unsuccessful. Crucial to the success of the reaction between **18** and **19** was the maintenance of mildly basic conditions which brought about almost complete suppression of formation of the principle byproducts **21** and **22**. A reference sample of **21** was prepared by reaction of **20** with imidate hydrochloride **6** under the conditions used by Meyers[10] for the preparation of **23**. Reaction of **21** with methyl ester **19** in MeOH at ambient temperature gave a reference sample of **22** (Scheme 3).

A key feature of the reactivity of **11** is the nucleophilicity of C(4) as evidenced by the facile formation of **24** on treatment of **11** with acetone and the partial conversion to a relatively insoluble dimer (shown spectroscopically to be a mixture of the (*E*) and (*Z*) forms of imidazolinone **25**) when solutions of **11** in CH_2Cl_2 or MeOH were concentrated, particularly under alkaline conditions.



Reaction of Imidazolinone 11 with $POCl_3$/DMF. Early reactions of imidazolinone **11** with $POCl_3$/DMF followed by aqueous hydrolysis gave black, tarry mixtures containing only small amounts of aldehyde **2**. Optimiza-

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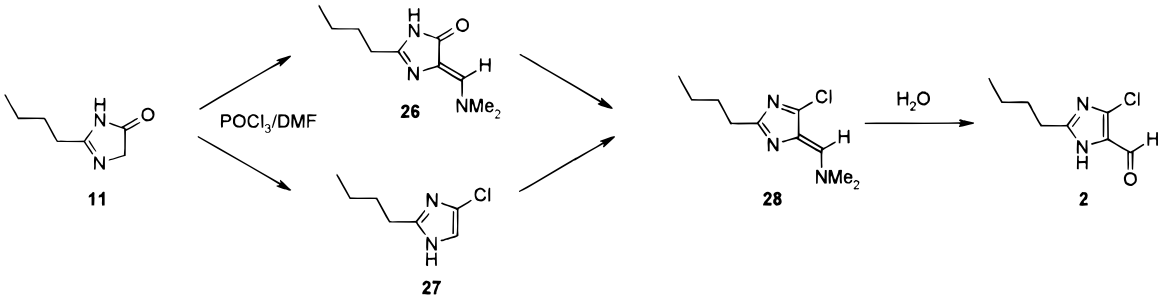
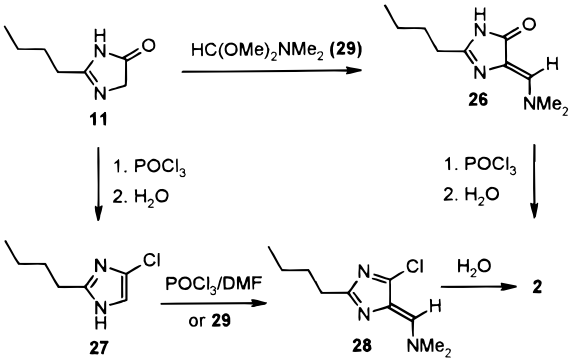
(10) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111.

Scheme 4

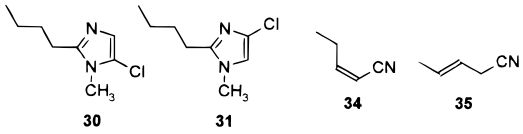


Scheme 5



tion of reaction parameters (in particular solvent, stoichiometry, temperature, and addition sequence) led to development of a procedure in which $POCl_3$ (ca. 2.8 equiv) was added to a suspension of **11** (1.0 equiv) in toluene at 0−20 °C. After heating to 80 °C and addition of DMF (ca. 2.8 equiv), the reaction mixture (which turned black during the addition of DMF) was heated for 2−3 h at 100 °C before quenching in water at 20−30 °C. Extractive workup followed by crystallization gave aldehyde **2** in ca. 55% yield based on **11**. Subsequent development of a "one-pot" procedure allowed preparation of **2** (HPLC purity > 98%) without isolation of **11** in 55% yield based on **19**. The two main byproducts in the mother liquors from crystallization of **2** were identified as imidazolinone **26** and chloroimidazole **27**; this suggested that the conversion of **11** to **2** might be proceeding *via* concurrent formylation−chlorination and chlorination−formylation sequences, both leading to the common intermediate **28** (Scheme 4). Two factors in particular indicated that formylation−chlorination was the dominant pathway: (1) Treatment of **11** with $POCl_3$/DMF at ca. 40 °C gave **26** as the major product; **27** was not formed under these conditions. (2) Formylation of **27** proceeded sluggishly and was incomplete even with a large excess of $POCl_3$/DMF under forcing conditions (T > 100 °C), whereas chlorination of **26** was relatively rapid under the same conditions (see below).

The proposed intermediate **28** could not be isolated from the Vilsmeier mixture; its preparation by an alternative method is described below. The identification of **26** and **27** suggested several alternatives for the preparation of aldehyde **2** from imidazolinone **11** as shown in Scheme 5. Thus treatment of imidazolinone **11** with acetal **29** in CH_2Cl_2 at room temperature gave **26** in 44% yield after recrystallization from EtOAc. The yield of **26** in solution appeared to be almost quantitative with the main losses occurring during workup and recrystallization, which were not optimized. Treatment of **26** with $POCl_3$ (4 equiv) for 1.5 h at 100 °C followed by distillative removal of excess $POCl_3$ and aqueous workup gave **2** (HPLC purity 95.5%) in 88% yield. Reaction of imidazolinone **11** with $POCl_3$ in chlorobenzene followed by aqueous workup gave chloromidazole **27** in ca. 30% yield. As mentioned above, the formylation of **27** with $POCl_3$/DMF could not be driven to completion; thus, reaction of **27** with $POCl_3$ (3 equiv) and DMF (3 equiv) in chlorobenzene for 4 h at 100 °C followed by aqueous hydrolysis gave a mixture of **2** and **27** (ratio ca. 2.5:1 by ^{1}H NMR). The course of the reaction of chloroimidazole **27** with the alternative formylating agent **29** was influenced by the addition of catalytic quantities of acid or base. Thus, reaction of **27** with **29** in chlorobenzene at reflux in the presence of CH_3SO_3H (5 wt %) gave **28** contaminated by almost equivalent amounts of the *N*-methylimidazoles **30** and **31** as measured by ^{1}H NMR. Repetition of the reaction in the presence of Et_3N (6 wt %) gave **28** containing only traces of **30** and **31**. Aqueous acidic hydrolysis of **28** gave aldehyde **2** (purity ca. 75% by ^{1}H NMR) in an unoptimized yield of ca. 65% based on **27**. The structures of the *N*-methylimidazoles **30** and **31** were confirmed by their preparation (as a mixture) by treatment of **27** with CH_3I in CH_2Cl_2. The use of **29** as a methylating agent is well documented;[11] one example of imidazole N-methylation using **29** was reported by Hosmane and coworkers.[12]



Unusual Byproducts from the Reaction of 11 with $POCl_3$/DMF. Preparative HPLC of crystallization mother liquors from the synthesis of **2** *via* reaction of **11** with $POCl_3$/DMF allowed isolation of milligram amounts of two additional byproducts which were identified spectroscopically as olefin **32** and dichloroimidazole **33**. Examples of analogous side-chain functionalization under Vilsmeier conditions could not be found in the literature. The valeronitrile used to syntheize imidazolinone **11** *via* imidate **18** (Scheme 2) had been prepared by catalytic hydrogenation of a mixture of nitriles **34** and **35**. The possibility that **32** and **33** arose from traces of **34** and/or **35** was excluded by careful analysis of the valeronitrile used and by experiments in which reaction of **11**, prepared from valeronitrile containing several percent of either **34** or **35**, with $POCl_3$/DMF did not give rise to

(11) Pindur, U. In Encyclopedia of Reagents for Organic Synthesis; Paquette, L. A., Ed.; Wiley and Sons: Chichester, England, 1995; pp 2075−2078.

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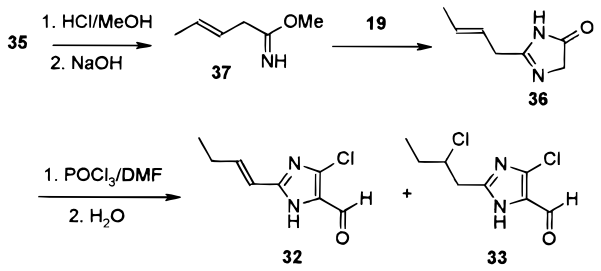
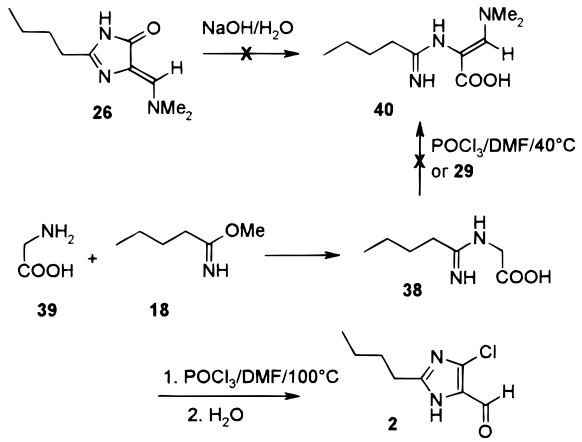
Scheme 6



Scheme 7



a significant increase in the extent of formation of either **32** or **33**. The details of the mechanism of formation of **32** and **33** during the reaction of **11** with $POCl_3$/DMF remain unclear, although it appears that the functionalization of the butyl side chain takes place at an early stage in the sequence of reactions leading from **11** to **2**; in particular, it was shown that chlorination of **26** (prepared as shown in Scheme 5) using either $POCl_3$ or $POCl_3$/DMF gave aldehyde **2** which contained significantly reduced levels of **32** and **33**. The extent of formation of **32** and **33** from the reaction of **11** with $POCl_3$/DMF could be reduced by using less DMF or by adding the DMF at lower temperature; however, these modifications were also accompanied by a significant reduction in the yields of **2**.

Several possibilities to prepare **32** and **33** were investigated; finally it was found that reaction of imidazolinone **36**, prepared from nitrile **35** via imidate **37**, with $POCl_3$/DMF (Scheme 6) gave a complex mixture from which relatively pure **32** and **33** could be isolated after several chromatographic purification steps.

Synthesis of Aldehyde 2 from Glycine. An additional byproduct formed during the preparation of imidazolinone **11** from **19** (Scheme 2) was identifed as amidine **38**. ^{1}H NMR and IR spectroscopy showed that some hydrolysis of methyl ester **19** to glycine (**39**) was taking place during liberation of **19** by addition of solid hydrochloride **20** to a solution of NaOH in MeOH; reaction of **39** with imidate **18** led to formation of **38**. After a small-scale experiment had shown that the reaction of **38** with $POCl_3$/DMF gave aldehyde **2**, it was decided that the "glycine route" (Scheme 7) to **2** should be investigated further. Reaction of **39** with imidate **18** in toluene/MeOH (containing a small amount of water to partially dissolve **39**) for 3−4 h at rt followed by filtration gave **38** as a stable white solid in 67% yield and with considerable losses in the filtrate. Repetition of the reaction with workup by addition of toluene followed by distillative removal of MeOH and water gave **38** in *ca.* 90% yield (as determined by ion chromatography) as a suspension in toluene. Treatment of this suspension with $POCl_3$/DMF under the conditions developed for conversion of **11** to **2** followed by aqueous workup and crystallization gave **2** in 55% yield based on **39**. Interestingly, samples of crude **2** formed by reaction of **38** with $POCl_3$/DMF contained no chloroimidazole **27** and also levels of **32** and **33** which were below the HPLC quantification limit. These observations suggested that conversion of amidine **38** to aldehyde **2** might not be proceeding *via* the expected cyclization of **38** to imidazolinone **11**. A likely alternative might be formylation of **38** to give **40** followed by cyclization of the latter to imidazolinone **26**; this possibility is supported by identification of **26** as one of the products of the reaction of **38** with $POCl_3$/DMF and by the earlier observation that reaction of **26** with $POCl_3$ or $POCl_3$/DMF gave **2** containing reduced levels of **32** and **33** compared with those formed during the reaction of **11** with $POCl_3$/DMF under similar conditions. Attempts to prepare the proposed intermediate **40** by reaction of **38** with either $POCl_3$/DMF at low temperature or with acetal **29** in MeOH were unsuccessful, as was an alternative approach *via* alkaline hydrolysis of imidazolinone **26** (Scheme 7).

Conclusion

Efficient "one-pot" procedures for the synthesis of aldehyde **2** by reaction of either the rather unstable imidazolinone **11** or amidine **38** with $POCl_3$/DMF have been developed and optimized; the two processes furnish **2** of comparable purity in almost identical overall yield. Two factors appear to favor the process involving amidine **38**, namely the greater stability of **38** compared to that of imidazolinone **11**, and the slight cost advantage (on a per mole basis) of glycine (**39**) over glycine methyl ester hydrochloride (**20**). Identification of byproducts formed during reaction of both **11** and **38** with $POCl_3$/DMF gave some information regarding the mechanisms involved.

Experimental Section

All reagents and solvents were used as obtained from commercial suppliers. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane for ^{1}H and ^{13}C. The multiplicity of the carbon signals were checked with DEPT experiments (s = C, d = CH, t = CH_2, q = CH_3). Infrared spectra (IR) were obtained using a Fourier transform spectrometer. Melting points are uncorrected. High resolution mass spectroscopy (HRMS) using electron impact ionisation was performed at Novartis Services AG, CH-4002 Basel.

Methyl Pentanimidate (18). A solution of valeronitrile (600 g, 7.2 mol) in MeOH (255 g, 7.9 mol) and Bu_2O (600 mL) was cooled to ca. −15 °C before passing in HCl gas (265 g, 7.25 mol) over 4.5 h at such a rate that the temperature could be maintained at ca. 0 °C. The mixture was stored for 6 days at ca. 4 °C, and the white precipitate was filtered, washed with ice-cold Et_2O, and dried under vacuum at room temperature to give hydrochloride **6** (795 g). A suspension of **6** (505.3 g, 3.33 mol) in Et_2O (1400 mL) was cooled to ca. −10 °C before addition of 6 M aqueous KOH (636 mL) with maintenance of the temperature at ca. −10 °C. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and evaporated at room temperature to give a solution of crude **18** (406 g, GC content

ca. 75 area %). Purification by distillation gave imidate **18** (190.8 g, GC content 98.7 area %, bp 34 °C/20 mbar). ^{1}H NMR ($CDCl_3$) δ 6.95 (1 H, s), 3.70 (3 H, s), 2.24 (2 H, m), 1.54 (2 H, m), 1.36 (2 H, m), 0.93 (3 H, t, J = 7.5 Hz); HRMS calcd for $C_6H_{12}NO$ ($M^+ - H$) 114.0919, found 114.0918.

2-Butyl-2-imidazolin-5-one (11). To a solution of NaOH (4.04 g, 101 mmol) in MeOH (32 mL) at 0 °C was added hydrochloride **20** (12.68 g, 101 mmol) in one portion whereupon the temperature sank to −11 °C. The white suspension was stirred for 15 min before addition of a solution of imidate **18** (11.74 g, 102 mmol) in toluene (18 mL). The mixture was stirred for 3 h at room temperature before adjustment of the pH from 9.9 to 7.0 by addition of a few drops of concd HCl. The mixture was filtered to remove NaCl, and the filtrate was concentrated at 20 °C and dried under vacuum before addition of CH_2Cl_2 (100 mL). The mixture was filtered to remove ca. 0.6 g of undissolved solid material (residual NaCl and traces of dimer **25**), and the filtrate was concentrated at 20 °C and dried under high vacuum to give **11** as a yellow solid (14.22 g, estimated purity by ^{1}H NMR 90−95%, 90−95% yield).

The analytical data from a small sample prepared in 30% yield by the method used by Jacquier[9] for the preparation of imidazolinones **12a** and **12b** were as follows: mp 79.5−80.5 °C ^{1}H NMR (DMSO-d_6) δ 10.8 (1 H, br s), 3.91 (2 H, s), 2.33 (2 H, m), 1.57 (2 H, m), 1.32 (2 H, m), 0.88 (3 H, t, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 183.4 (s), 164.9 (s), 58.5 (t), 29.3 (t), 27.1 (t), 21.6 (t), 13.5 (q); IR (KBr) 1737, 1619 cm^{-1}; Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N 19.98. Found: C, 58.4; H, 8.4; N, 20.0; HRMS calcd for $C_7H_{12}N_2O$ 140.0950, found 140.0948.

Methyl (1-Methoxypentylideneamino)acetate (21). To a suspension of imidate hydrochloride **6** (106.2 g, 0.70 mol) in CH_2Cl_2 (1000 mL) at ca. 2 °C was added hydrochloride **20** (88.8 g, 0.71 mol) as a solid in three portions. The mixture was stirred at 6 h at ca. 0 °C and for 15 h at 22 °C before addition of a solution of triethylamine (71.2 g, 0.70 mol), whereupon the temperature rose to 28 °C. The mixture was stirred at 22 °C for 1 h before addition of pH 7 phosphate buffer (700 mL). The phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated at 20 °C/400 mbar to give a yellowish oil (111.3 g) which was distilled in vacuo to give **21** (56.6 g, 43.2%) as a colorless oil (99.1 GC area %, bp 49 °C/1 mbar). ^{1}H NMR ($CDCl_3$) δ 4.08 (2 H, s), 3.73 (3 H, s), 3.66 (3 H, s), 2.22 (2 H, m), 1.53 (2 H, m), 1.33 (2 H, m), 0.91 (3 H, t, J = 7.4 Hz); IR (neat) 1753, 1677 cm^{-1}; HRMS calcd for $C_9H_{17}NO_3$ 187.1208, found 187.1211.

Methyl (2-Butyl-5-oxo-2-imidazolin-l-yl)acetate (22). To a solution of NaOH (0.24 g, 6 mmol) in MeOH (11 mL) at 0 °C was added hydrochloride **20** (0.76 g, 6 mmol) in one portion. The white suspension was stirred for 15 min at 0 °C before addition of a solution of **21** (0.96 g, 5 mmol) in MeOH (5 mL). The mixture was stirred for 1 h at room temperature (GC analysis showed no **21**), concentrated under vacuum, and treated with CH_2Cl_2 (15 mL) and water (15 mL). The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and dried under high vacuum to give **22** as a viscous liquid (0.69 g, 97.5 GC area %) which later solidified. Attempts to carry out further purification of **22** led to decomposition, possibly due to a dimerization process analogous to that undergone by **11** (see above). ^{1}H NMR ($CDCl_3$) δ 4.26 (2 H, s), 4.15 (2 H, m), 3.78 (3H, s), 2.36 (2 H, m), 1.72 (2 H, m), 1.43 (2 H, m), 0.95 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 181.0 (s), 168.1 (s), 164.8 (s), 58.1 (t), 52.8 (q), 41.1 (t), 28.5 (t), 26.8 (t), 22.3 (t), 13.7 (q); HRMS calcd for $C_{10}H_{16}N_2O_3$ 212.1161, found 212.1162.

2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde (2). To a solution of NaOH (20.20 g, 0.50 mol) in MeOH (160 mL) at 0 °C was added hydrochloride **20** (63.42 g, 0.50 mol) in one portion whereupon the temperature sank to −10 °C. The white suspension was stirred for 15 min before addition of a solution of imidate **18** (57.6 g, 0.50 mol) in toluene (101 mL). The mixture was stirred for 3 h at room temperature before adjustment of the pH from 8.7 to 7.0 by addition of a few drops of concd H_2SO_4 and addition of toluene (500 mL). MeOH and water were removed by vacuum distillation, and the resulting orange suspension was cooled to 0 °C, treated with $POCl_3$ (214.7 g, 1.40 mol), stirred for 1 h at room temperature, and heated to 80 °C before addition of DMF (102.9 g, 1.40 mol) (T rose to 102 °C, HCl evolution). The black reaction mixture was heated for 2 h at 100 °C, cooled to 40 °C, and poured into water (350 mL) (exothermic reaction) with maintenance of the temperature at <30 °C. The reaction flask was washed with water (50 mL) and EtOAc (300 mL), and to the combined reaction mixture and wash liquors was added Celite (20.0 g). The mixture was stirred for 0.25 h at 25 °C before adjustment of the pH from −0.9 to +1.2 by addition of 30% NaOH (295.6 mL) and removal of the Celite by filtration. The layers were separated, and the organic phase was washed twice with water and evaporated to dryness at 65 °C. The residue was diluted with toluene (151 mL), and the mixture was heated to 60 °C and cooled slowly to −10 °C. The precipitate was filtered, washed with cold toluene, and dried to give **2** (51.9 g, HPLC content 98.6% based on comparison with a standard of known content, 54.8% yield based on **20**). ^{1}H NMR ($CDCl_3$) δ 12.44 (1 H, br s), 9.65 (1 H, s), 2.87 (2 H, t, J = 7.5 Hz), 1.79 (2 H, m), 1.39 (2 H, m), 0.93 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7 (d), 155.3 (s), 142.0 (s), 126.0 (s), 29.9 (t), 28.5 (t), 22.3 (t), 13.6 (q); IR (KBr) 1673, 1515 cm^{-1}; HRMS calcd for $C_8H_{11}ClN_2O$ 186.0560, found 186.0563.

(*Z*)-2-Butyl-4-(dimethylaminomethylene)-2-imidazolin-5-one (26). To a solution of imidazolinone **11** (20.0 g, 143 mmol) in CH_2Cl_2 (300 mL) at 20 °C was added acetal **29** (27.72 g, purity ca. 92%, ca. 214 mmol) over 8 min whereupon the temperature rose to 27 °C. The clear red solution was stirred for 0.5 h, washed twice with water, dried ($MgSO_4$), filtered, and evaporated to dryness to give a brown solid (21.96 g). Recrystallization (with active charcoal treatment) from EtOAc gave **26** (12.32 g, 44%) as a pale brown solid, mp 115.5−117.5 °C; ^{1}H NMR ($CDCl_3$) δ 10.4 (1 H, br s), 7.07 (1 H, s), 3.55 (3 H, br s), 3.18 (3 H, br s), 2.50 (2 H, m), 1.66 (2 H, m), 1.40 (2 H, m), 0.93 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.6 (s), 150.7 (s), 141.3 (d), 115.1 (s), 46.2 (q), 39.5 (q), 29.5 (t), 28.9 (t), 22.4 (t), 13.8 (q); IR (KBr) 2929, 1683, 1605 cm^{-1}. Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.66; H, 8.77; N, 21.39.

2-Butyl-5-chloro-1*H*-imidazole (27). To a solution of $POCl_3$ (300 g, 1.92 mol) in chlorobenzene (70 mL) at 95 °C was added imidazolinone **11** (50.0 g, 0.36 mol) as a solid in one portion, whereupon the temperature rose to 103 °C. The red-black mixture was heated for 2 h at 100 °C and cooled to 80 °C before removal of $POCl_3$ and chlorobenzene (total 305.1 g) by vacuum distillation. The black, oily residue was added to a mixture of ice (500 g) and EtOAc (100 mL), and the pH was adjusted to 7 by addition of 30% NaOH (153 mL). The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated at 30 °C to give a residue (25.54 g) which was purified by chromatography on silica gel (elution with EtOAc/hexane 1:1) to give **27** (17.6 g, 31%), mp 62−64 °C; ^{1}H NMR ($CDCl_3$) δ 11.1 (1 H, br s), 6.85 (1 H, s), 2.72 (2 H, t, J = 7.5 Hz), 1.69 (2 H, m), 1.35 (2 H, m), 0.89 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 148.2 (s), 127.2 (s), 111.6 (d), 30.5 (t), 28.3 (t), 22.3 (t), 13.7 (q); IR (KBr) 1579, 1442 cm^{-1}. Anal. Calcd for $C_7H_{11}ClN_2$: C, 53.00; H, 6.99; N, 17.66. Found: C, 53.50; H, 7.00; N, 17.40.

(*E*)-Methyl Pent-3-enimidate (37). A solution of (*E*)-3-pentenenitrile (**35**) (90.1 g, purity ca. 90%, 1.0 mol) in MeOH (64.0 g, 2.0 mol) was cooled to 5 °C before bubbling in gaseous HCl (75.0 g, 2.06 mmol) over 2 h at such a rate that the temperature did not exceed 10 °C. The mixture was stirred for a further 2 h at ca. 7 °C before addition to a mixture of Et_2O (166 mL) and water (300 mL) at 8−16 °C; 30% NaOH (203.5 mL) was added simultaneously to maintain a pH of *ca.* 12. The phases were separated, and the organic layer was dried (MgSO4), filtered, and evaporated *in vacuo* to give an orange liquid containing **37** (70 GC area %). Attempted distillation through a 20 cm Vigreux column at ca. 300 mbar led to some decomposition but gave two fractions (total 43.4 g) containing

37 (70−76 GC area %) boiling at ca. 100 °C/300 mbar. ^{1}H NMR ($CDCl_3$) δ 7.0 (1 H, br s), 5.61 (1 H, m), 5.45 (1 H, m), 3.72 (3 H, s), 2.90 (2 H, m), 1.73 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 172.9 (s), 131.3 (d), 123.6 (d), 53.1 (q), 38.0 (t), 18.0 (q).

Preparation of (*E*)-2-(But-1-en-1-yl)-5-chloroimidazole-4-carbaldehyde (32) and 5-Chloro-2-(2-chlorobutyl)imidazole-4-carbaldehyde (33) (without isolation of imidazolinone **36**). To a solution of NaOH (20.20 g, 0.50 mol) in MeOH (160 mL) at 0 °C was added hydrochloride **20** (63.42 g, 0.50 mol) in one portion whereupon the temperature sank to −10 °C. The white suspension was stirred for 15 min before addition of a solution of imidate **37** (129.5 g of a 43.7% (GC area %) solution in toluene, ca. 0.50 mol **37**). The mixture was stirred for 3 h at room temperature before adjustment of the pH from 9.0 to 7.0 by addition of a few drops of concd H_2SO_4 and addition of toluene (500 mL). MeOH and water were removed by vacuum distillation and the dark brown, sticky mixture was cooled to −2 °C, treated with $POCl_3$ (214.7 g, 1.40 mol), stirred for 1 h at room temperature, and heated to 80 °C before addition of DMF (102.9 g, 1.40 mol) (*T* rose to 100 °C, HCl evolution). The black reaction mixture was heated for 2 h at 100 °C, cooled to 40 °C, and poured into water (500 mL) (exothermic reaction) with maintenance of the temperature at <30 °C. The reaction flask was rinsed with water and EtOAc, and to the combined reaction mixture and wash liquors was added Celite (20.0 g). The pH of the mixture was adjusted from −0.5 to +1.0 by addition of 30% NaOH (240 mL), and the Celite was removed by filtration. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water (320 mL), dried ($MgSO_4$), filtered, and concentrated to give a dark brown liquid (16.1 g). Repeated chromatography on Kieselgel followed by recrystallization from n-hexane gave **32** (3.76 g) (estimated purity by ^{1}H NMR and HPLC ca. 95%) ^{1}H NMR ($CDCl_3$) δ 11.8 (1 H, br s), 9.63 (1 H, s), 7.04 (1 H, m), 6.36 (1 H, m), 2.32 (2 H, m), 1.12 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 177.3 (s), 149.8 (s), 144.3 (d), 142.4 (s), 116.0 (d), 26.1 (t), 12.6 (q); HRMS calcd for $C_8H_9ClN_2O$ 184.0403, found 184.0405. A sample of **33** (estimated purity by ^{1}H NMR and HPLC ca. 65%) was also obtained by repeated chromatography on Kieselgel. Attempts to purify **33** further by recrystallization were unsuccessful. ^{1}H NMR ($CDCl_3$) δ 11.8 (1 H, br s), 9.66 (1 H, s), 4.31 (1 H, m), 3.26 (2 H, m), 1.86 (2 H, m), 1.09 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7 (d), 150.1 (s), 141.1 (s), 126.2 (s), 61.8 (d), 37.7 (t), 31.3 (t), 10.9 (q); HRMS calcd for $C_8H_{10}Cl_2N_2O$ 220.0170, found 220.0178.

(Pentanimidoylamino)acetic Acid (38). The pH of a suspension of glycine (**39**) (37.54 g, 0.50 mol) in MeOH (160 mL) and water (9 mL) at 0 °C was adjusted to 9.5 by addition of 2 drops of 30% NaOH before addition of a solution of imidate **18** (57.6 g, 0.50 mol) in toluene (93 mL). The suspension was stirred overnight at room temperature, and the white precipitate was filtered, washed with toluene, and dried under vacuum to give **38** (52.91 g, 66.9%). mp 198.5−201 °C; ^{1}H NMR (DMSO-d_6) δ 8.8 (2 H, br s), 3.45 (2 H, s), 2.45 (2 H, m), 1.56 (2 H, m), 1.32 (2 H, m), 0.88 (3 H, t, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 167.1 (s), 166.2 (s), 46.6 (t), 31.6 (t), 28.7 (t), 21.2 (t), 13.4 (q); IR (KBr) 3354, 1626 cm^{-1}; Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.70; H, 9.10; N, 17.60; HRMS calcd for $C_6H_{11}N_2O_2$ ($M^+ - CH_3$) 143.0821, found 143.0818.

2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde (2) (preparation from **39** without isolation of **38**). The pH of a suspension of glycine (**39**) (38.1 g, 0.50 mol) in MeOH (160 mL) and water (9 mL) at 0 °C was adjusted from 8.0 to 9.5 by addition of 2 drops of 30% NaOH before addition of a solution of imidate **18** (57.6 g, 0.50 mol) in toluene (96 mL). The suspension was stirred overnight at room temperature, and the pH was adjusted from 10.1 to 7.0 by addition of a few drops of concd H_2SO_4 before addition of toluene (500 mL) and removal of ca. 500 g of solvent by vacuum distillation (GC analysis showed almost no residual methanol). The resulting suspension was cooled to 0 °C, treated with $POCl_3$ (219.0 g, 1.40 mol), and heated to 80 °C before addition of DMF (102.9 g, 1.40 mol) at such a rate that the temperature rose to 96 °C (HCl evolution). The dark brown reaction mixture was heated for 2 h at 100 °C, cooled to room temperature, and poured into water (350 mL) (exothermic reaction) with maintenance of the temperature at <30 °C. The reaction flask was rinsed with water and toluene, and to the combined reaction mixture and wash liquors was added Celite (20.0 g). The pH of the mixture was adjusted from −1.2 to +1.2 by addition of 30% NaOH (286.6 mL), and the Celite was filtered off and washed with water and toluene. The phases were separated, and the organic phase was washed twice with water. A portion (261.1 g) of the organic phase (total 530.2 g) was concentrated to 97.8 g, heated to 65 °C, and cooled to −10 °C. The precipitate was filtered, washed with toluene, and dried at 50 °C/30 mbar to give **2** (26.0 g, HPLC purity 96.9% based on comparison with a standard of known content, corresponding to a yield of 54.9% based on **39**).

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Supporting Information Available: Photocopies of ^{1}H NMR spectra for compounds **2**, **11**, **18**, **21**, **22**, **25**, **26**, **27**, **32**, **33**, and **38** and of ^{13}C NMR spectra of compounds **2**, **22**, **25**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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