Organic Process Research & Development **2001**, *5*, 581−586

Large-Scale Synthesis of a Pyrrolo[2,3-*d*]pyrimidine via Dakin−West Reaction and Dimroth Rearrangement

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Abstract:

Pyrrolo[2,3-*d*]pyrimidines have been widely investigated as pharmaceutically active compounds. In this article, we present a short and efficient synthesis of 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine starting from cheap alanine and malononitrile. To the best of our knowledge, the first application of a Dakin−West reaction on plant scale is demonstrated by elaboration of a modified procedure avoiding uncontrolled release of carbon dioxide. Pyrimidine ring formation is achieved in a simple one-pot reaction which is followed by an equally simple isomerization. The whole synthesis requires neither chromatographies nor extractions, no waste treatment and no special equipment, resulting in a remarkably ecological as well as economical process.

Introduction

Derivatives of pyrrolo[2,3-*d*]pyrimidines have been extensively investigated as inhibitors of epidermal growth factor receptor (EGF-R) protein tyrosine kinase, and their potential as a treatment for proliferative diseases involving mitogenic signaling from the EGF-R has been recognized.[1] Optimization of selectivity and the biological profile of such pyrrolopyrimidine derivatives by variation of the substitution pattern, carried out at our research department, led to compound CGP 59326 (**1**) (Figure 1) being promoted to development status as an antitumor agent. To support further biological profiling as well as to supply drug substance for initial clinical trails, large amounts in the 100-kg range of this heterocyclic compound had to be synthesized.

Research Synthesis. The existing research synthesis (Scheme 1) was relatively straightforward and, with some optimization, was regarded as suitable for scale-up in this early development phase. However, for the following main reasons, we aimed at the elaboration of an improved, alternative synthesis to be applied already for the first GMP-campaign in the pilot plant despite significant time constraints:

(1) The use of a benzyl-protecting group for the pyrrole amine functionality was mandatory for the outlined synthetic strategy; however, deprotection turned out to be technically unfavorable because it required a large excess of aluminum trichloride which subsequently had to be quenched and disposed of.

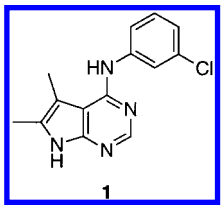

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Figure 1.

(2) The pyrimidine cyclisation step in boiling formic acid raised safety concerns and resulted in dark coloration of the product which made cumbersome purification procedures necessary.

(3) The hydroxy- as well as the chloropyrimidine intermediates had extremely poor solubility that resulted in dilute reactions and a large excess of phosphorus oxychloride being used for the chlorination step.

Development Synthesis Strategy. Pyrrolo[2,3-*d*]pyrimidine derivatives and their synthesis are very abundant in the literature.[2] In general, it is favorable to synthesize the pyrrole ring first and to subsequently build up the pyrimidine ring even though the opposite strategy has been applied as well.[3] For the synthesis of **1**, we came to the conclusion that 2-amino-3-cyano-4,5-dimethylpyrrole **3** was the intermediate of choice. Its simple synthesis from 3-amino-2-butanone and malonodinitrile has already been described more than 30 years ago[4] and it is sufficiently stable towards air oxidation to allow for normal handling in a production facility. From this pyrrole we intended to modify the pyrimidine ring formation in such a way that no protection was needed and that formic acid was eliminated. For a successful application of this synthesis concept (Scheme 2), we therefore needed to find solutions to the following two key issues:

(1) the preparation of 3-amino-2-butanone derivative **2** and

(2) an alternative procedure for the formation of the pyrimidine ring

Results and Discussion

Pyrrole Synthesis. Since 3-amino-2-butanone is not a stable compound, literature suggests that it may be used in its stable, *N*-acetylated form **2** for pyrrole condensation.[5]

(1) (a) Traxler, P.; Bold, G.; Lang, M.; Frei, J. PCT Int. Appl. WO 9807726, 1998. (b) Traxler, P.; Bold, G.; Brill, W.; Frei, J. PCT Int. Appl. WO 9702266, 1997. (c) Traxler, P.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N *J. Pharm. Belg*. **1997**, *52*(2), 88. (d) Traxler, P. *Expert Opin. Ther. Pat.* **1997**, *7*(6), 571 and references therein.

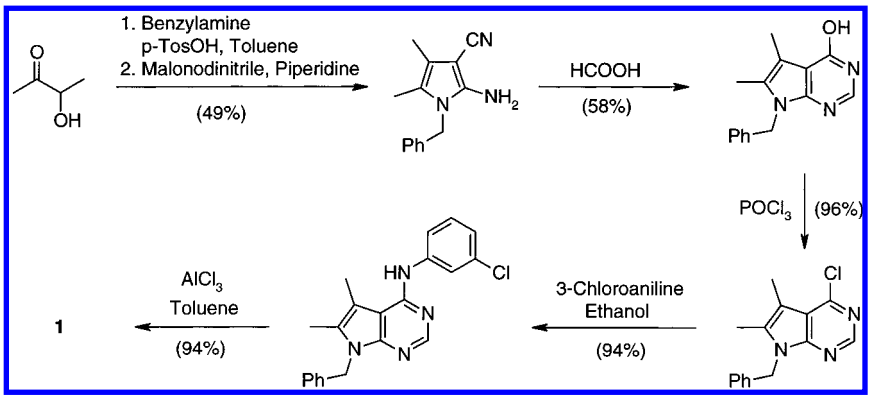
(2) For reviews, see for example: (a) Melik, R. G.; Khachatryan, V. E.; Gapoyan, A. S. *Russ. Chem. Rev.* **1985**, *54* (3), 262. (b) Amarnath, V.; Madhav, R. *Synthesis* **1974**, *12*, 837. (c) Roth, H. J.; Eger, K. *Arch Pharm. (Weinheim, Ger.)* **1975**, *308*, 252.

(3) See, for example: (a) Sakamoto, T.; Satoh, Ch.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1993**, *41*, 1 (1), 81. (b) Itoh, T.; Fujii, I.; Tomii, Y.; Nishimura, H.; Ogura, H.; Mizuno, Y. *Heterocycles* **1986**, *25* (4), 927.

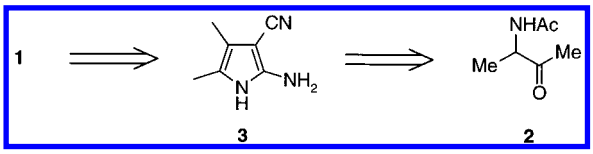
(4) Gewald, K. *Z. Chem.* **1961**, *1*, 349.

10.1021/op010041v CCC: $20.00
Published on Web 10/12/2001

Scheme 1



Scheme 2



However, **2** is not a commercially available compound. α-Acylaminoketones of this type are easily accessible from the corresponding amino acids and anhydrides, a reaction that was initially described by Dakin and West in 1928[6] and therefore is known as the Dakin−West reaction. Although the Dakin−West reaction is by no means of general use to any type of amino acid,[7] its application to alanine to form the desired aminoketone **2** is well documented.[8] Since (racemic) alanine is very cheap, this seemed to be an attractive approach to the synthesis of pyrrole **3**. However, there is one major drawback to the Dakin−West reaction regarding its scale-up to plant scale: it is accompanied by an almost sudden and uncontrolled formation of one equivalent of carbon dioxide, which is absolutely prohibitive on technical scale. Our initial attempts to control formation of carbon dioxide by the variation of reaction parameters such as addition of components and control of temperature all failed and in addition never produced yields which were at least comparable to the standard protocol. Thus, we decided to look more closely at the reaction mechanism.

Even though the Dakin−West reaction can hardly be considered well-known, there is quite a lot of work published about it, including some very detailed mechanistic investigations particularly by Steglich.[9] It seems to be generally accepted that the mechanism involves dehydrative formation of an azlactone (oxazolinone) which is then C-acylated (in equilibria with O-acylation), undergoes ring-opening hydrolysis, and then decarboxylates to form the acylamino ketone (Scheme 3).[10] Most experimental procedures for Dakin−West reactions reported in the literature work more or less the same way: a mixture of amino acid, anhydride, and pyridine (typically in the very empirical ratio of about 1:6:11) is heated to reflux, at which time, a relatively sudden, strong evolution of carbon dioxide appears and fades again soon thereafter. Any experimenting with this procedure or conditions usually results in reduced or no yield of the desired aminoketone product. To the best of our knowledge, there never was a procedure reported that avoided this uncontrolled formation of carbon dioxide; as a matter of fact, we did not succeed in finding any published application of the Dakin−West reaction on a technical scale.[11]

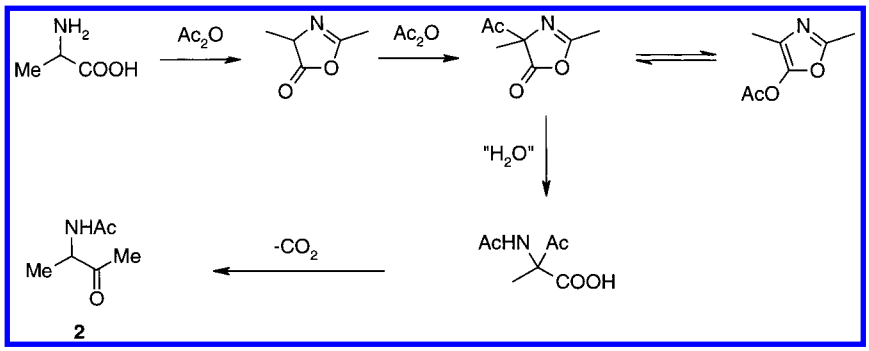
After some of our own investigations confirmed the mechanism outlined above, we concluded that the following kinetic interpretation would at least partly explain the peculiarities of the Dakin−West reaction: as we see in Scheme 3, ring-opening hydrolysis of acylated azlactone formally requires one equivalent of water. Because there certainly is no sufficient amount of water in a boiling reaction mixture of excess anhydride and pyridine, this "water-equivalent" has to come from the formation of acetic anhydride from acetic acid. Acetic acid itself is formed in the first two steps of the reaction sequence, namely N-acylation and azlactone condensation. Therefore its initial concentration in the reaction mixture is very low, and hence azlactone hydrolysis is very slow. Once the mixture is heated and N-acylation of alanine starts to pick up, acetic acid concentration increases rapidly and therefore azlactone hydrolysis is accelerated. The following decarboxylation is virtually spontaneous. This results in the reaction having a typical, self-accelerating kinetic, which is exactly what you **do not** want to have in a plant, particularly not if equivalent amounts of gas are formed during a reaction.

To test this hypothesis, we performed experiments where we added various amounts of acetic acid to the initial mixture of acetic anhydride and pyridine—an idea which surprisingly never has been investigated in the literature. The results were convincing: one equivalent of acetic acid made it possible to run the reaction in an addition-controlled mode with

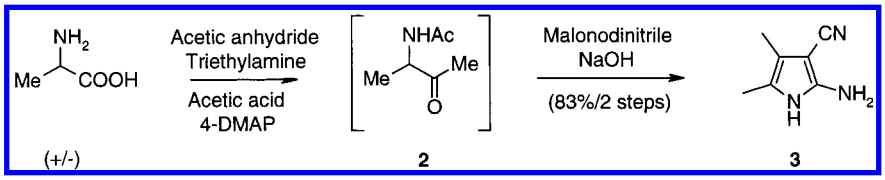
(5) (a) Shvedov, V. I.; Mezentseva, M. V.; Grinev, A. N. *Khim. Geterotsikl. Soedin.* **1975**, *9*, 1217. (b) Wamhoff, H.; Wehling, B. *Synthesis* **1976**, 51.
(6) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91 and 745.
(7) For a review on the Dakin−West reaction, see: Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 91.
(8) (a) Wiley: R. H.; Borum, O. H. *J. Am. Chem. Soc.* **1948**, *70*, 2005. (b) King, J. A.; McMillan, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2814.
(9) (a) Cleland, G. H.; Niemann, C. *J. Am. Chem. Soc.* **1949**, *71*, 841. (b) Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1968**, *13*, 1619, (c) Steglich, W.; Höfle, G. *Chem. Ber.* **1969**, *102*, 883. (d) Steglich, W.; Höfle, G. *Chem. Ber.* **1969**, *102*, 899. (e) Steglich, W.; Höfle, G.; Prox, A. *Chem. Ber.* **1972**, *105*, 1718. (f) Knorr, R. *Chem. Ber.* **1971**, *104*, 3633. (g) Allinger, N. L.; Wang, G. L.; Dewhurst, B. B. *J. Org. Chem.* **1974**, *39*, 9 (12), 1730.

(10) This mechanism was originally proposed by Cleland and Niemann (see ref 9a); it only applies to the Dakin−West reaction of primary amino acids.
(11) For a typical lab-scale experiment in milligram or low-gram range, the amount of carbon dioxide evolved is certainly too small to be of any concern. Hence, there is no need for an alternative procedure to the Dakin−West reaction on lab scale.

Scheme 3



Scheme 4



carbon dioxide evolution being directly linked to alanine addition. As an extra benefit, acetic anhydride and pyridine excess could now be significantly reduced. This modified procedure was run successfully and with well-controlled carbon dioxide evolution on a 0.5 kmol scale in a 600-L reactor, whereby acetic anhydride, acetic acid, and pyridine were charged into the reactor and heated to ca. 120 °C, and alanine (45 kg) was then added as a slurry in pyridine over 2−3 h.

In a second step, we tried to improve the reaction by adapting the above-described findings to the modified Dakin−West procedure with triethylamine/DMAP introduced by Steglich in 1969.[12] This method requires much smaller amounts of anhydride and base and is therefore economically more advantageous. Indeed, the above-described modification of the classical Dakin−West reaction by the addition of acetic acid to the starting mixture worked equally well when applied to the triethylamine/DMAP procedure. Over 0.5 kmol alanine (50 kg) was successfully converted to acetylaminobutanone **2** in a 400-L reactor in over 90% yield with carbon dioxide evolution (∼11 000 L!), once again being in a virtually linear relationship to alanine addition. The crude product solution was concentrated by evaporation of acetic acid, acetic anhydride, and triethylamine. This concentrate was diluted with water and malonodinitrile, and the resulting solution was added to 30% sodium hydroxide, whereby pyrrole **3** was formed and precipitated in an extremely fast, exothermic, but fully addition-controlled reaction.[13] Crystalline pyrrole **3** was directly isolated by centrifugation, was washed with water, and was dried and did not require further purification.[14] Neither distillate nor mother liquor required any special treatment. This procedure for the synthesis of pyrrole **3** (Scheme 4) is very efficient, high-yielding (83−85% over two steps calculated from alanine) and requires only two standard reactors.

Pyrimidine Ring Synthesis. Numerous examples are reported in the literature, whereby 2-amino-3-cyano furans, pyrans, or other related derivatives are converted to pyrimidines particularly by formic acid, formamide, or mixtures thereof.[15] As outlined in the introduction of this contribution, we intended to avoid this type of conversion. Already back in 1964, Taylor and Hendess reported a procedure[16] where an unprotected amino-cyano-pyrrole was converted to an aminopyrrolopyrimidine derivative by trimethyl orthoformate and ammonia. However, in the more recent literature, this method is only used for thiophens,[17] pyrans,[18] pyrazines,[19] or other heterocycles lacking a free amino group,[20] and almost exclusively in combination with hydrazine as the amine component, indicating a somewhat limited scope of this method, particularly for unprotected pyrroles.

However, we reasoned that in principle, it should be possible to apply this type of pyrimidine ring formation to pyrroles under carefully optimized conditions which avoid side reactions at the pyrrole ring nitrogen. To explore this, we initially prepared iminoester **4a** (Figure 2) from pyrrole **3** and triethyl orthoformate. The crude iminoester was then treated with 3-chloroaniline. This sequence under various conditions at best produced moderate yields of 3-chlorophenyl-pyrrolopyrimidine **5** in rather unsatisfying quality. Therefore, the reaction sequence was changed: iminoester **4b** was formed from 3-chloroaniline and triethyl orthoformate under

(12) Steglich, W.; Höfle, G. *Angew. Chem.* **1969**, *81*(23), 1001.
(13) Safety remark: malonodinitrile decomposes autocatalytically at elevated temperatures with an adiabatic temperature rise in excess of 1000 °C! The initiation phase of the decomposition is shortened by bases. For these reasons, when performing this type of pyrrole condensation reactions on large scale, malonodinitrile should be the component being added to the sodium hydroxide solution rather than the opposite way to avoid a possible run-away reaction.
(14) Bulk substance was stored in barrels which were flushed with nitrogen to avoid pyrrole oxidation.
(15) See, for example: Pichler, H.; Folkers, G.; Roth, H. J.; Eger, K. *Liebigs Ann. Chem.* **1986**, *9*, 1485.
(16) Taylor, E. C.; Hendess, R. W. *J. Am. Chem. Soc.* **1964**, *86*, 951.
(17) See, for example: Shishoo, C. J.; Devani, M. B.; Ullas, G. V.; Ananthan, S.; Bhadti, V. S. J. *Heterocycl. Chem.* **1981**, *18*, 43.
(18) See, for example: Younes, M. I.; Metwally, S. A.; Atta, A. H. *Synthesis* **1990**, 704.
(19) See, for example: Taylor, E. C.; Hartke, K. S. *J. Am. Chem. Soc.* **1959**, *81*, 2456.
(20) See, for example: Birkett, P. R.; Chapleo, C. B.; MacKenzie, G. *Synthesis* **1991**, 152.

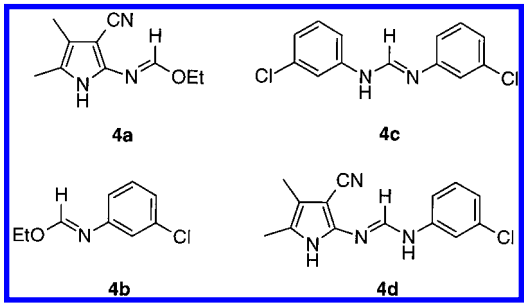


Figure 2.

acid catalysis[21] and isolated as a crude oil. Pyrrole **3** was then treated with iminoester **4b**. Lab experiments revealed that this procedure was definitely superior particularly after optimization of solvent, acid catalyst, and pH. The procedure was eventually run successfully in the pilot plant on 0.3 kmol scale. Pyrrole **3** was thereby dissolved in absolute ethanol, crude iminoester **4b** was added (slight excess), and the pH was adjusted to 8 by the addition of pyridinium tosylate solution in ethanol. After 24 h at room temperature, product **5** had precipitated from the reaction and was centrifuged, washed with ethanol, and dried.

Our lab experiments had made clear that the mechanism of this pyrimidine ring formation involves a series of ortho ester−iminoester−amidine equilibria between aniline, pyrrole-amine, and ortho ester. Since we never—not even in the above pilot campaign—observed a temperature rise during the reaction, we reasoned that precipitation of the product from the reaction mixture and not thermodynamic stability had to be the 'trap' which drives these equilibria to the product side.[22] Hence, it should be possible to run the reaction under kinetic control without preformation of an iminoester intermediate; this was potentially beneficial because any procedure involving heat in the presence of the pyrrole staring material unavoidably resulted in a more or less dark brown reaction mixture.

With this hypothesis in mind we initiated lab experiments which started with all three components, pyrrole **3**, 3-chloroaniline, and triethyl orthoformate and which varyied the ratios of staring materials and particularly the pH. In agreement with our hypothesis, we found that at slightly acidic pH the reaction proceeded relatively slowly but surprisingly cleanly. Our TLC- and NMR experiments confirmed that this formation of pyrrolopyrimidine **5** was distinct from the first procedure because only trace amounts of iminoester **4b** were detected in the reaction mixture. Instead, a new, major intermediate was found and upon isolation was identified as amidine **4c** which now seemed to be the species reactive towards the formation of the pyrimidine ring.[23] This interpretation was confirmed by preparative synthesis of amidine **4c** and conversion of pyrrole **3** to pyrrolopyrimidine **5** therewith. Further, the reaction could be accelerated by using excess aniline with respect to orthoacetate. To avoid the side reaction of intermediate amidine **4d** with a second pyrrole **3**, the procedure was changed from batch to semi-batch by adding pyrrole **3** over a few hours, therefore keeping the free pyrrole concentration in the reaction mixture low. As an additional benefit, this procedure allowed for the replacement of expensive pyridinium tosylate catalyst by acetic acid. This optimized and simplified process was run in the pilot plant on 0.45 kmol scale. Chloroaniline and triethyl orthoformate were dissolved in ethanol, and the pH of the solution was adjusted to ca. 5.5. Pyrrole **3** was then added over a few hours at 45−50 °C, precipitated pyrrolopyrimidine **5** was centrifuged off, washed, and dried as above. The yield in the pilot plant was over 80% (based on pyrrole **3**).

Chlorophenyl-pyrrolopyrimidine **5** now only needed to be converted to its isomer **1**. This isomerization, which is referred to as Dimroth rearrangement,[24] is not truly a rearrangement but rather a hydrolysis of the pyrimidine ring at the N3−C2 bond, subsequent rotation of 180° around the C9−C4 bond, and ring closure. For pyrrolopyrimidines, this type of isomerisation is very scarcely reported in the literature,[25] with only few more examples for other pyrimidine derivatives.[26] With that little precedence, the only thing which seemed obvious was that water would be required for the isomerisation to occur. First lab trails centered around the variation of catalyst (acid, base), cosolvent, and temperature. It turned out, that no catalyst at all was required and that reaction temperature was the most important parameter. A solvent mixture containing water, having the appropriate boiling point and a sufficient solubility for pyrrolopyrimidine **5** had to be elaborated. A mixture of ethylene glycol, ethanol, and water eventually turned out to be optimal; clean isomerization could be achieved in over 90% yield by simply refluxing for a few hours. Upon cooling, the product precipitates and can once again be isolated by filtration, washing and drying. This procedure was successfully run in the pilot plant in 0.3 kmol scale. (Scheme 5).

The drug substance free base was brought in its mesylate salt form by crystallisation from ethanol/water in the presence of methylsulfonic acid and final recrystallisation from acetone/water, which yielded a white powder with high purity (HPLC assay >99%) that met all internal specifications and was subsequently released for use in humans.

Conclusions

We have demonstrated the development of a very efficient synthesis of pyrrolopyrimidine **1** in only four simple steps from inexpensive starting materials such as racemic alanine,

(21) Glickman, A. S. U.S. Patent 2,684,976, 1954.

(22) This interpretation was later confirmed by applying the final, optimized procedure to different anilines: only those which gave pyrrolopyrimidines poorly soluble in ethanol and which were therefore precipitating from the reaction mixture could be prepared by this procedure.

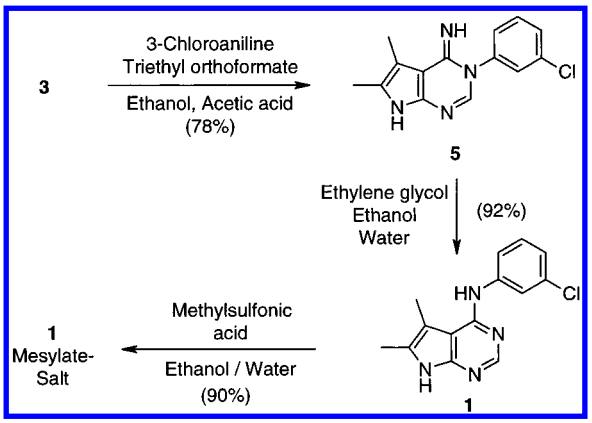
(23) NMR investigations on the synthesis of iminoester **4b** had shown earlier, that at lower temperature, amidine **4c** was the predominant product in the mixture, and only by heating above 120 °C and with excess orthoformate, could iminoester **4b** be obtained.

(24) For a review on Dimroth rearrangements, see for example: Wahren, M. *Z. Chem.* **1969**, *9*(7), 241.

(25) Zaharan, M. A.; Pedersen, E. B.; Nielsen, C. *Monatsh. Chem.* **1995**, *126*(11), 1271.

(26) For example: (a) Brown, D. J.; Jacobsen, N. W. *J. Chem. Soc.* **1960**, 1978. (b) Taylor, E. C.; Loeffler, P. K. *J. Am. Chem. Soc.* **1960**, *82*, 3147. (c) Ohtsuka, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3909. (d) Antonov, D. M.; Belen'kii, L. I.; Dudinov, A. A.; Krayushkin, M. M. *Khim. Geterotsikl. Soedin.* **1994**, *4*, 450.

Scheme 5



malonodinitrile, chloroaniline, and triethyl orthoformate.[27] The procedure, which was successfully run on pilot plant scale, uses no special equipment. Intermediates **3**, **5**, and **1** (free base) are all crystallized directly from the reaction mixtures, whereas **2** is used in situ, making extractions or other cumbersome purification procedures unnecessary as well as minimizing the amount of waste produced. These factors all contribute to remarkably low costs for the drug substance. In addition, we—to the best of our knowledge—reported the first application of a Dakin−West reaction on technical scale with carbon dioxide evolution being controlled by addition of the amino acid thanks to a new, modified procedure.

Experimental Section

Experimental details are described only for the final process, which was successfully run in the pilot plant. Starting materials, solvents, and reagents were of technical grade. All reactions were carried out under inert atmosphere (N_2). NMR spectra where measured on a Varian Gemini 200 MHz spectrometer, chemical shifts are reported in ppm and referenced to the solvent lock signal. HPLC analyses were performed on a Nucleosil-C18 column (5 μm) with UV-detection using an aqueous sodium perchlorate buffer (solvent A)/acetonitrile (solvent B) gradient. HPLC assays are % w/w except where stated otherwise. Reference samples were prepared by additional chromatography and recrystallisation of compounds.

2-Amino-3-cyano-4,5-dimethylpyrrole (3). Acetic anhydride (338.5 g, 3.3 mol), acetic acid (45 g, 0.75 mol), triethylamine (379.5 g, 3.75 mol) and 4-(dimethylamino)-pyridine (1.83 g, 0.015 mol) were charged into a reaction vessel and heated to 50 °C. Racemic alanine (135 g, 1.5 mol) was added as a solid over 6 h thereby maintaining reaction tempeature at 45 to 55 °C. After completion of alanine addition, the reaction mixture was stirred at 50 °C for an additional 8 h. Acetic anhydride, triethylamine, and acetic acid were distilled off by vacuum distillation (10−15 mbar), gradually raising the jacket temperature to a maximum of 100 °C. The residue (GC assay > 95% acylaminoketone intermediate **2**) was cooled to room temperature and diluted with water (815 mL). Malonodinitrile (94.5 g, 1.425 mol) was added, and this mixture was slowly added to 500 g of aqueous sodium hydroxide solution (30%). The speed of addition was adjusted so that the reaction temperature did not exceed 60 °C. The resulting suspension was cooled to 0 °C, filtered, washed with water, and dried in vacum at 55 °C to yield 168 g (83% calculated from alanine) of pyrrole **3**: assay >96% (HPLC); mp (DSC) 172 °C (lit.[4] 163−165 °C); ^{1}H NMR(DMSO): 9.83 (s, 1H), 5.36 (s, 2H), 1.92 (s, 3H), 1.83 (s, 3H); MS (ESI$^+$) 136 (MH$^+$).

3-(3-Chlorophenyl)-5,6-dimethyl-4H-pyrrolo[2,3-*d*]pyrimidine-4-imine (5). Triethyl orthoformate (204.5 g, 1.35 mol), absolute ethanol (700 mL), and 3-chloroaniline (222 g, 1.72 mol) were charged into a reaction vessel, and the pH was adjusted to 5−5.5 by addition of acetic acid (6.65 g, 0.11 mol). The mixture was warmed to 50 °C and stirred for 1 h. Pyrrole **3** (166 g, 1.23 mol) was added as a solid over 6 h, maintaining temperature at 45−50 °C. After completion of the addition, the mixture was kept at 50 °C for additional 4 h and then for another 8 h at room temperature. Water (100 mL) was added, the mixture was cooled to 0 °C, and this temperature was maintained for 30 min. The resulting suspension was filtered, washed with ethanol/water (4:1), and dried in vacum at 50 °C to yield 261 g (78% calculated from pyrrole **3**) of pyrrolopyrimidine **5**: assay >98% (HPLC); mp >150 °C (change of crystal modification and dec); ^{1}H NMR (DMSO): 10.97 (s, 1H), 10.26 (s, 1H), 8.56 (s, 1H), 7.39−7.14 (m, 4H), 2.08 (s, 3H), 1.96 (s, 3H); MS (ESI$^+$) 273 (MH$^+$).

4-(3-Chlorophenylamino)-5,6-dimethyl-7H-pyrrolo-[2,3-*d*]pyrimidine (1) Free Base. A suspension of pyrrolopyrimidine **5** (300 g, 1.1 mol) in water (750 mL), absolute ethanol (750 mL), and ethylene glycol (1500 mL) was heated to 95 °C for 4 h. The mixture was cooled to room temperature within 90 min. After the temperature was maintained at room temperature for an additional hour, the suspension was filtered, washed with water, and dried under vacuum at 50 °C to yield 277 g (92% based on **5**) of pyrrolopyrimidine **1** (free base): assay >98% (HPLC); mp. 240−255 °C (change of crystal modification); ^{1}H NMR (DMSO): 11.53 (s, 1H), 8.21 (s, 1H), 8.15 (s, 1H), 7.95 (d, 1H), 7.71 (t, 1H), 7.33 (t, 1H), 7.03 (q, 1H), 2.41 (s, 3H), 2.28 (s, 3H); MS (ESI$^+$) 273 (MH$^+$).

4-(3-Chlorophenylamino)-5,6-dimethyl-7H-pyrrolo-[2,3-*d*]pyrimidine (1) Mesylate Salt. A mixture of free base **1** (30 g, 0.11 mol) in ethanol 97% (390 mL) and methylsulfonic acid (11.1 g, 0.115 mol) was heated to reflux for 45 min and then cooled to 0 °C within 3 h, whereby crystallisation occurred. The suspension was stirred at 0 °C for an additional 90 min and then filtered, washed with cold ethanol, and dried in vacum at 55 °C to yield 36.5 g (90%) of mesylate salt of **1**:assay >98% (HPLC) (analytical data see below).

4-(3-Chlorophenylamino)-5,6-dimethyl-7H-pyrrolo-[2,3-*d*]pyrimidine (1) Mesylate Salt; Final Drug Substance Recrystallisation. Mesylate salt **1** (30 g, 0.081 mol) was dissolved in acetone (204 mL) and water (36 mL) at reflux. The solution was filtered, and the filtrate was cooled to 30 °C within 3 h, seeding at 50 °C. The suspension was cooled

(27) Misun, M.; Fischer, R.; Mutz, M. PCT Int. Appl. WO 98/43973, 1998.

to 0 °C within 1 h, and acetone (500 mL) was added. The resulting suspension was filtered, washed with cold acetone, and dried in vacum at 55 °C to yield 26.4 g (88%) of pyrrolopyrimidine **1** mesylate salt: assay >99% (HPLC); sum of byproducts <0.5% area (HPLC); mp 215−222 °C; ^{1}H NMR (DMSO): 12.53 (s, 1H), 9.55 (s, 1H), 8.28 (s, 1H), 7.70 (s, 1H), 7.54−7.50 (m, 2H), 7.43−7.38 (m, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H); MS (ESI$^+$) 273 (MH^+).

Acknowledgment

The skillfull work of our technicians Ch. Kehrli, M. Haller, and L. Kohler is gratefully acknowledged. We thank Ch. Heuberger and his staff at the safety lab for thermodynamic investigations and M. Trüby and his team from the pilot plant for technical support with scale up.

Received for review May 18, 2001.
OP010041V