Organic Process Research & Development **2004**, *8,* 62−71

The Synthesis of the High-Potency Sweetener, NC-00637. Part 2: Preparation of the Pyridine Moiety

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Abstract:
The pyridine moiety within the high-potency sweetener, NC-00637 (1), 5-amino-2-cyanopyridine (4), was prepared from 2-hydroxy-5-nitropyridine (10). The sequence involved the conversion of the hydroxy group to bromide followed by substitution with cyanide to give 2-cyano-5-nitropyridine (8). Reduction of the nitro group proved to be troublesome when catalytic hydrogenation was used. Iron with an acid gave a reproducible reaction that could be used at scale.

Introduction

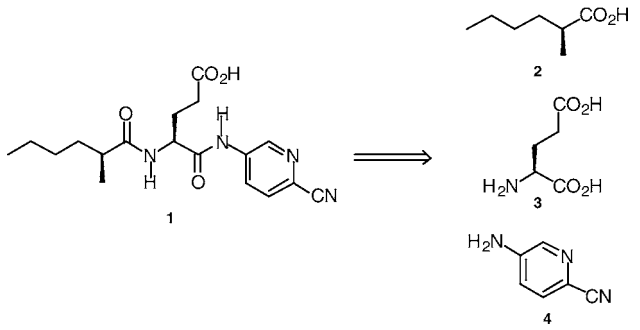
In relation to our studies on the synthesis of the new sweetener candidate, NC-00637 (**1**), we have already described the preparation of the aliphatic moiety, 2-methylhexanoic acid (**2**).[1] Our synthetic strategy for **1** (Scheme 1) required the use of three building blocks of which the acid **2** was one. The other two components were L-glutamic acid (**3**) and 5-amino-2-cyanopyridine (**4**), which was given the trivial acronym CAP. In another contribution we describe the strategy for the selective protection of the glutamate part and the coupling of the components to for the final compound **1**.[2]

The amine **4** is a poor nucleophile; this property complicated the coupling reactions.[2] However, as described below, the lack of basicity also allowed for some leeway in the purification and separation methods; the pyridine nitrogen is not basic—in our hands, the dihydrochloride salt could not be prepared.

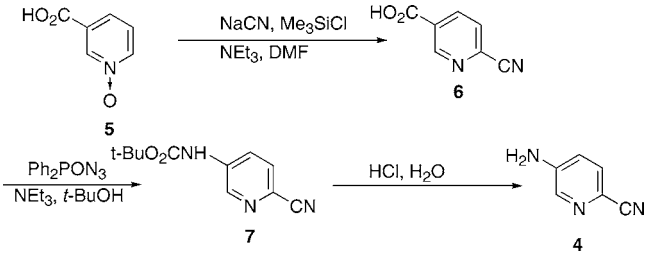
When work commenced on the large-scale synthesis of NC-00637, the final component in the coupling sequence, the pyridinylamine **4**, was not commercially available but was known in the literature from a photochemical substitution of a 2-halopyridine by cyanide.[3] In addition, this portion of the molecule, although deceptively simple in structure, was the most expensive to produce. This work describes the methods investigated to make the amine **4**.

At the outset of this work, initial material was obtained by the method outlined in Scheme 2.[4] It had already been noted by the NutraSweet discovery group that this approach was difficult to scale up. Many of the steps provided material

Scheme 1



Scheme 2



that was difficult to purify, and some of the reagents, in particular phosphorus azide, were perceived as potential hazards for very large-scale work. In addition, the cost was extremely high, with little hope for significant reductions with larger volumes. The literature does comment that Curtius rearrangements with 5-substituted pyridines can be problematic.[5]

The *N*-oxide **5** is commercially available and readily prepared from nicotinic acid. The reaction with trimethylsilyl cyanide, which was formed in situ, provided **6** as the major product, but a significant amount of the regioisomer was also formed. These two isomers were difficult to separate. The subsequent Curtius rearrangement gave a variable yield of **7**. *tert*-Butyl alcohol was found to be the best alcohol to trap the intermediate isocyanate, and on the up-side, this was the simplest carbamate to hydrolyze without concomitant hydrolysis of the nitrile unit.

Considerable effort was expended looking for alternative routes to the amine **4**. Nearly all of these resulted in failure. In many cases, the failure was due to the unique array of functional groups. The problem was compounded by the lack

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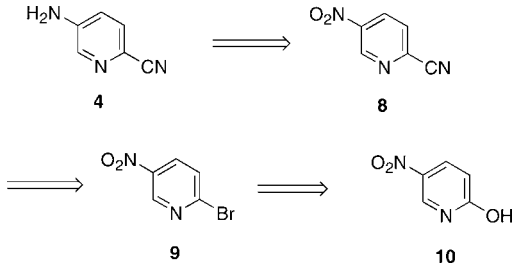
(1) Ager, D. J.; Babler, S.; Froen, D. E.; Laneman, S. A.; Pantaleone, D. P.; Ptakash, I.; Zhi, B. *Org. Proc. Research. Dev.* **2003**, *7*, 369.
(2) See following paper: Ager, D. J.; Babler, S.; Erickson, R. A.; Froen, D. E.; Kittleson, J.; Pantaleone, D. P.; Prakash, I.; Zhi, B. *Org. Proc. Research. Dev.* **2004**, *8*, 72−85.
(3) Frolov, A. N.; El'tsov, A. V.; Kul'bitskaya, O. V. *Khimia Geterotsiklicheskikh Soedinenii* **1974**, *12*, 1645; *Chem. Abs.* **1975**, *75*, 169701.
(4) Nofre, C.; Tinti, J. C. Eur. Pat. 511087; U.S. Patent 5,272,272, 1993. See also; Nofre, C.; Tinti, J. C. U.S. Patent 5,430,182, 1995; U.S. Patent 5,374,733, 1994; U.S. Patent 5,310,908, 1994; and U.S. Patent 5,196,540, 1993.
(5) Saikachi, H.; Kitagawa, T. *Chem. Pharm. Bull.* **1978**, *26*, 1054; see also: Finch, N. U.S. Patent 4,273,779, 1981.

Published on Web 12/04/2003
10.1021/op034110c CCC: $27.50 © 2004 American Chemical Society

Scheme 3

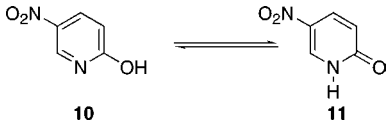


of suitable starting pyridines. Others have also had need to access **4** for pharmacological studies.[6] One approach has been to react ammonia with 5-halo-2-cyanopyridines to effect a substitution,[7] which is related to our final method in that a substitution reaction is involved. However, all of these preparations were laboratory-scale syntheses.

One method we investigated took advantage of the availability of nicotinamide. The introduction of the cyano group could be achieved through the *N*-oxide in a manner analgous to that illustrated in Scheme 2. Our focus, therefore, was on the conversions of the carboxylic acid group to an amine. Rather than perform a Curtius rearrangement, we looked at a Hoffman degradation with a variety of reagents. In an alcoholic solvent, such as ethanol, the use of chlorine or bleach led to reaction at the nitrile moiety. The Hoffman degradation could be achieved in ~70% yield by reaction of the amide with chlorine in acetonitrile; other solvents gave inferior yields. The *N*-chloro compound then underwent the degradation by the addition of potassium carbonate. Good conversions could only be achieved if the *N*-chloro compound was isolated and this was considered to be a major safety issue for large-scale work and this approach was dropped.

One method that did provide some promise is outlined in a retrosynthetic sense in Scheme 3. It was thought that the amine could be obtained by reduction of the nitro compound **8** even though this would mean reduction in the presence of the nitrile group. As pyridines are susceptible to nucleophilic additions at the 2-position, a substitution reaction aided by the para nitro group seemed feasible. Although Aldrich does list 2-bromo-5-nitropyridine (**9)** in their catalogue, it is very expensive (ca. $5/g). Thus, as the hydroxy compound **10** is available in bulk, this was considered as our starting material. In some listings the hydroxy compound **10** is given as the tautomeric pyridinone **11** (vide infra). Although other halogen derivatives might be considered as alternatives, as the discussion below indicates, the bromo compound **8** provided the cleanest methodology in the following cyanide displacement reaction.

Scheme 4



Bromination Step

From the literature, access to a 2-halopyridine can be accomplished in a number of ways, including: a diazotization reaction from the appropriate amine,[8] a related reaction of the amino compound with a brominating agent, substitution of a pyridinium salt,[9,10] use of an *N*-pyridyl palladium complex,[11] or bromination of a pyridine either directly[12] or through the *N*-oxide.[13] Conversion of a 2-hydroxypyridine to the corresponding 2-bromo derivative has been accomplished with a dehydrating agent, such as phosphorus pentoxide, and a bromide source[14] or NBS in the presence of triphenylphosphine.[15] These methods all have a disadvantage be it a low yield, obnoxious reagent, harsh conditions, a multistep sequence to access the substrate, or combinations thereof. To us, the best approach seemed to be a displacement reaction on either 2-amino- or 2-hydroxy-5-nitropyridine. As the starting material for the preparation of 2-hydroxy-5-nitropyridine (**10**) is 2-amino-5-nitropyridine by a Sandmeyer reaction with water acting as the nucleophile, the literature report for the direct conversion of 2-amino-5-nitropyridine (**8**) to 2-bromo-5-nitropyridine (**9**) looked encouraging.[8] In our hands, copious amounts of bromine and nitrogen oxides were evolved during the reaction. Removal of these noxious byproducts was not simple, and this approach was dropped.

A variety of methods were tried for the conversion of the hydroxy compound **10** to the bromide **9**. In most cases, the yields were low or the reaction failed completely. For example, use of phosphorus tribromide in a variety of solvents resulted in failure. 2-Hydroxy-5-nitropyridine (**10**) can exist as the 2-pyridone tautomer **11** (Scheme 4).[16] NMR and IR spectroscopic evidence[17] suggests that the hydroxy compound is the major contributor in a variety of solvents. In nonpolar solvents intermolecular hydrogen-bonding can also be discerned. The presence of the tautomer, as well as the hydrogen-bonding, could be the reason the conversion to the desired bromo compound was very sluggish. This was in line with other workers' observations.[16]

Phosphorus pentabromide did perform the desired reaction, but only at higher temperatures (Scheme 5). When

(6) Suh, W. G.; Oh, U. T.; Kim, H. D.; Lee, J. W.; Park, H. G.; Park, O. H.; Lee, Y. S.; Park, Y. H.; Joo, Y. H.; Choi, J. K.; Lim, K. M.; Kim, S. Y.; Kim, J. K.; Koh, H. J.; Moh, J. H.; Jeong, Y. S.; Yi, J. B.; Oh, Y. I. World Patent Appl. 0216318, 2002; Yamauchi, K.; Chugenji, M.; Matsuno, S.; Eda, M.; Nakamura, N.; Yamauchi, K. Jpn. Pat. Appl. 08175995; *Chem. Abs.* **1996**, *125*, 221590; Yamaguchi, K.; Matsuno, S.; Imada, M.; Nakamura, N. Jpn. Pat. Appl. 08175993; *Chem. Abs.* **1996**, *125*, 221589; Takemoto, T.; Ed, M.; Hihara, M.; Okada, T.; Sakashita, H.; Eiraku, M.; Fukaya, C.; Nakamura, N.; Sugiura, M.; Matzno, S.; Goda, M.; Uchida, Y. Eur. Pat. 503627.
(7) Ueno, T.; Kimura, Y.; Kasuga, Y. Jpn. Pat. Appl. 2001302639; *Chem. Abs.* **2001**, *135*, 331348
(8) Boyer, J. H.; McCane, D. I.; McCarville, W. J.; Tweedie, A. T. *J. Am. Chem. Soc.* **1953**, *75*, 5298.
(9) Oae, S.; Shinhama, K.; Kim, Y. H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1065; Kondo, S.; Nakanishi, M.; Tsuda, K. *J. Heterocycl. Chem.* **1984**, *21*, 1243.
(10) Katritzky, A. R.; Gruntz, U.; Ikizler, A. A.; Kenny, D. H.; Leddy, B. P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 436.
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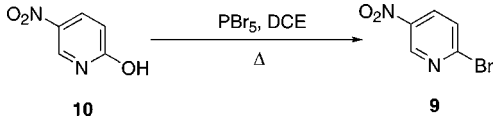
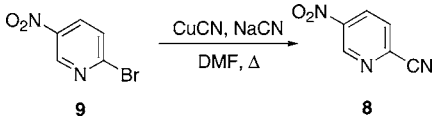
(14) Kato, Y.; Okada, S.; Tomimoto, K.; Mase, T. *Tetrahedron Lett*. **2001**, *42*, 4849.
(15) Sugimoto, O.; Mori, M.; Tanji, K.-I. *Tetrahedron Lett*. **1999**, *40*, 7477.
(16) Katritzky, A. R.; Pozharskii, A. F. In *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Oxford, 2000,; pp 45−46.
(17) See the Aldrich Catalogue.

Scheme 5



10 9

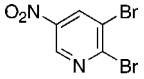
Scheme 6



9 8

dichloromethane or chloroform was used as the solvent, very little reaction was observed. However, in 1,2-dichloroethane (DCE) at reflux, the reaction proceeded smoothly. In addition to chlorinated solvents, ethereal solvents such methyl *tert*-butyl ether could be used to accomplish the reaction. However, the workup was not as simple because phase separations became problematic. The use of aromatic hydrocarbon solvents, such as toluene, also provided product, but halogenation of the solvent was a competing reaction. Thus, our efforts concentrated around the use of 1,2-dichloroethane as solvent. It should also be noted that phosphorus oxybromide does allow conversion of 2-hydroxy-5-nitropyridine to 2-bromo-5-nitropyridine, but in our hands, the amount of phosphorus pentabromide could not be reduced below an equimolar amount without a significant loss in yield.

Once the reagent and reaction conditions were defined, optimisation work was necessary to remove a byproduct formed in the reaction. This compound was 2,3-dibromo-5-nitropyridine (**12**). Fortunately, this byproduct is very soluble in hexane and could be removed either by crystallisation (the dibromo compound **12** remaining in the mother liquors) or by hot hexane washes of the solid. The crude orange solid was recrystallised from hexane. The yield was about 60%. The use of a sodium thiosulphate wash was quickly dismissed as the orange colour of the product from this procedure was not due to bromine. A further change in the workup procedure was to use hot solvents so that volumes could be minimised and product did not crystallise out during handling and isolation. To ease isolation, ethyl acetate was used in place of 1,2-dichloroethane for the extractions. Again, as the dibromide **12** is more soluble in nonpolar solvents, a mixed-solvent precipitation allowed isolation of the desired monobromide **9**, the undesired dibromo byproduct remaining in solution. In the modified procedure, evaporation to dryness was no longer a step. As the temperature of the extractions could be controlled in the pilot plant, this method was used for scale-up and then transferred to an external toll manufacturer and used on a multikilogram scale.



12

Cyanide Displacement

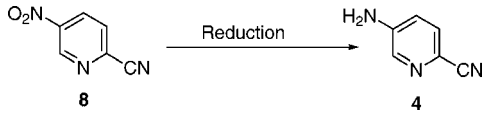
This specific reaction (Scheme 6) is known from the literature.[3] However, the reaction workup for this cyanide nucleophilic displacement is somewhat unusual as it employs ethylenediamine followed by sodium cyanide.[3] An alternative procedure from 2-chloro-5-nitropyridine is also known with *N*-methylpyrrolidone as solvent,[6] but in our hands the isolation of the product was always cumbersome and low yielding. Our first few reactions with copper cyanide on the bromide **9** provided very low yields of the required 2-cyano product **8**. The use of sodium cyanide−copper cyanide complex increased the yield, but still not to an acceptable level. Our thoughts turned to the unusual workup procedure in the literature. When the reaction was followed by TLC, complex mixtures could often be seen; the reaction mixture went black. However, when HPLC was used, the reaction mixture showed a very clean conversion of the bromide to the cyanide. Our conclusion, therefore, was that the desired product was being destroyed during the workup stage. The use of a wide variety of conditions showed that this was indeed the case. The reaction mixture itself is very basic, and when added to water hydrolysis of the cyano group to the amide and, on occasion, even the carboxylic acid can occur. To avoid this hydrolysis, acid workup conditions had to be employed. However, we chose to use a buffer as this alleviated any possibility for the evolution of hydrogen cyanide (a potential safety problem). With the buffer conditions, as described in the Experimental Section, we did not detect any hydrogen cyanide evolution.

The initial isolation conditions were changed to provide a method for the removal of DMF. The product is low melting, and crystallisation often proved troublesome when this polar solvent was present as an impurity. As the cyano compound **8** is not very soluble in hexane, multiple recycles had to be employed to circumvent the use of an extremely large amount of solvent. In addition this method of purification was complicated by the melting point of the product being below the boiling point of hexane—problems with oils sometimes occurred. The solution to this oiling problem turned out to be isolation of solid **8** from water itself, the DMF being soluble in water, while the product is not.

When the crude product **8** was isolated from water, toluene was used as the solvent for the recrystallisation with hexane as the antisolvent. This procedure provided less-coloured material. The procedure was transferred to a toll manufacturer for scale-up with a slight variation with regard to the workup procedure. The reaction mixture was diluted with isopropyl acetate so that higher temperatures could be employed during the separation process than when ethyl acetate was used. In addition, the phase separations were cleaner with isopropyl acetate. The buffer was then added. In this way, the product remained in the organic phase and did not have to be extracted or separated from the inorganic salts. Charcoal treatment was used to remove the colour.

The substitution reaction is clearly a candidate for the use of phase transfer catalysts either between solid and solution phases or liquid/liquid phases. Although a wide variety of conditions were tried, most resulted in no reaction. One of the key parameters seemed to be the use of high temperature to bring about the reaction.

Scheme 7



8 **4**

Reduction Step

This step (Scheme 7) was the most problematic to scale up due to competing side reactions. Indeed at larger scales, unwanted reactions often become the major pathway, and the amount of amine **4** formed was very low. Isolation of the desired amine from these complex reaction mixtures was not a trivial task as the 2-cyano-5-aminopyridine (**4**) is such a weak base.

The first method used a hydrogenation with palladium on charcoal in THF. As the scale was relatively small, 10% palladium on charcoal was used at a large molar ratio of catalyst-to-substrate ratio. The cost of scaling up this reaction directly was prohibitive. It was found that methanol gave a better conversion and that the amount of catalyst could be significantly reduced. However, even at a few gram scale, the reaction showed that it was capricious, and the amount of catalyst again had to be increased to ensure conversion. In some cases, even when identical conditions, including the same lots of solvents, reactants, and reagents were used, one reaction would proceed without problems while another would stall. As this step was key to the whole synthetic strategy for this part of the molecule, a complete study of reducing agents was undertaken. Hydrogenation of the HCl salt of 2-cyano-5-nitropyridine was also attempted, but this invariably gave a mixture of products.

One of the criteria of the screening process was that the reaction was repeatable. This was often achieved by the use of large amounts of catalyst. One method that provided some hope was the use of a transfer hydrogenation with ammonium formate as the hydrogen source (see Experimental Section, Procedure 3). However, this still required high catalyst loadings to ensure reproducibility.

As the reaction was stalling in some cases, it was felt that a lower catalyst usage in methanol was the path to take. To show that this was feasible, a recycle study was performed at laboratory scale in methanol (procedure 4). We did find that the catalyst could be recycled through the reduction as long as some fresh catalyst was also added. Thus, when hydrogen uptake slowed, the reaction mixture could be filtered and either fresh catalyst added to the liquors and hydrogenation continued, or fresh catalyst added to the filtered material and this reused—the addition of extra catalyst directly to the reaction mixture was never satisfactory. The material produced had a light- to dark-brown colour even after recrystallisation. This colour was probably due to small amounts of azo-type compounds being present. One pilot-plant run was performed, and not only did the reaction stall, but the formation of byproducts also become significant. Clearly, this was not the reduction path to take without a complete study of the reaction mechanism and conditions.

Finally, we did find that the side reactions were determined to be a function of copper carried over from the previous step—higher copper content ensured higher amounts of side reactions. The recycle studies were in alignment with these findings as it was found that the copper tended to be absorbed onto the catalyst support. Thus, removal of this material before the addition of fresh catalyst removed the problematic trace metal contamination. From trace metal analysis we also found that different samples of the nitrile **8** contained variations in copper content even when taken from the same lot. As we had advanced with the dissolving metal reduction at this stage, which was also cheaper in terms of reagents, we decided to concentrate on this approach rather than the purification of the nitro compound **8**.

A number of byproducts were isolated from the metal-catalysed reduction. The majority of byproducts were coupled, that is they contained two pyridine rings. In some cases, as with the symmetrical hydrazine and azo compounds, prolonged reduction did give the desired monomeric amine, but reactions from the product amine and the cyano group of another molecule ensured a dead-end pathway from our perspective. As time was a critical parameter, coupled with the chemistry that had to precede this reduction step, an alternative method was sought. The presence of the nitrile limits the choice of reagents somewhat as this functional group can also be reduced. Other methods that have been used for this reaction, such as the use of sulphur-based systems, were not considered as the potential byproducts would not be compatible with a food additive.[18]

Dissolving Metal Reduction

The use of dissolving metal reductions has been used effectively for the reduction of aryl nitro compounds to the corresponding amine.[19] Metals (tin, zinc, and iron) in the presence of acids (hydrochloric, sulphuric, or acetic acid) and in a variety of solvents (THF, water, EtOAc, and combinations thereof), were tried for this reduction. All combinations worked to some extent. The correct combination was determined with three criteria in mind: ease of reaction/workup, yield, and cost. Zinc and tin were too expensive for large-scale reactions. Hydrochloric and sulphuric acids resulted in messy workup conditions for all the metals used. The metal of choice was iron. With the metal selected, the acids were again varied (acetic, hydrochloric, formic, trifluoroacetic, sulphuric acid) to determine their impact on the reaction. The best acid was acetic acid. Solvents were also varied (EtOAc, THF, *i*-PrOAc, *n*-BuOAc) to determine their contribution to the reaction. The best solvent was ethyl acetate. Concentrations and the order of addition of the reagents were thoroughly investigated. The reaction was a liquid/solid two-phase reaction. After the reaction was complete, some of the amine **4** that was produced was trapped in the iron salts. Isolation was complicated by long filtration times as the solids were very fine. Numerous methods to recover the trapped amine were tried. A biphasic slurry of iron salts, ethyl acetate, and either acid or base was investigated for the isolation of the desired

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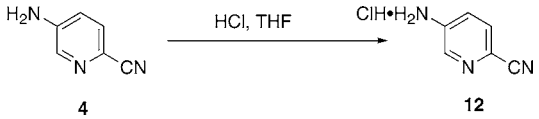
(19) See March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; pp 1103−1117.

Scheme 8



4 **12**

material. Solutions of various molarities of hydrochloric acid, sodium bicarbonate, sodium hydroxide, and sodium hydrosulphite were also investigated. All of the reactants freed the product from the iron. However, only the sodium hydrosulphite produced an iron salt that was filterable. The other reagents produced iron salts that were unmanageable and/or unfilterable. In many cases, a bright red sticky "mud" was produced. This reaction was successfully scaled up as described in Procedure 5 using the bisulphite method. The toll manufacturer also found that replacement of ethyl acetate by *n*-butyl acetate had some benefits for a faster filtration, but this is questionable as the final product was not of high purity.[2] The main impurities in these large batches were inorganic salts as determined by titration.

Formation of the Hydrochloride Salt

The coupling process to NC-00637 (**1**) required the hydrochloride salt **12**.[2] As already mentioned, the amine is not very basic. In aqueous media, an equilibrium exists between the salt and free base. An organic solvent had to be used where the salt was insoluble as this was required to drive the reaction in the desired direction. THF was found to be the solvent of choice (Scheme 8). This reaction was uneventful during scale-up; the original procedure was not significantly modified.

In addition, it was found that any inorganic material carried through from the dissolving metal reduction that was seen on occasion at larger scales from our toll supplier could simply be removed by filtration prior to the addition of the hydrogen chloride. It should be noted that no conditions could be found to form a bis-salt with the common strong inorganic or organic acids.

The hydrochloride salt could also be used as a purification process for the amine **4**. Treatment of the hydrochloride salt with an aqueous base in a biphasic mixture with ethyl acetate resulted in the free amine **4** in the organic layer. The addition of hexane while hot resulted in crystallisation of high-quality **4**.

Summary

Synthesis of 2-cyano-5-aminopyridine (**4**) was achieved by a three-step process that consisted of conversion of 2-hydroxy-5-nitropyridine (**10**) to the bromide (**9**) by use of phosphorus pentabromide. Nucleophilic displacement with sodium cyanide in the presence of copper cyanide lead to the nitrile (**8**). Reduction of the nitro group proved problematic, but the use of a dissolving metal reduction with iron in acetic acid gave a workable solution.

Experimental Section

The melting points are uncorrected. IR spectra (Nujol) were recorded on a Nicolet FT-IR spectrometer. ^{1}H NMR spectra were recorded on a GE 300 spectrometer in $CDCl_3$ using TMS as internal standard.

Laboratory hydrogenations were performed in mechanically stirred Parr reactors with external heating. In some cases, Fischer−Porter bottles fitted with appropriate inlet and outlet tubes and valves were used for screenings; external heat was applied through an oil bath, and stirring was magnetic. The systems included pressure sensors that were computer monitored to allow for the reactions to be followed by hydrogen uptake.

Analytical Methods

Unless otherwise noted, the method used to determine purity and follow reactions was HPLC: Analysis was performed with a Supelco LC-18, 25 cm × 4.6 mm i.d., 5 μm using a gradient elusion. Solvent A was 0.02 M heptanesulphonic acid, sodium salt in 1% aqueous triethylamine adjusted to pH 2.2, while solvent B was 95:5 (vol/vol) acetonitrile/water. The flow rate was 2 mL/min. The gradient was 92:8 solvent A:B for 15 min, then 50:50 solvent A:B for 10 min, and then returning to 92:8 for a further 10 min. Detection was at 254 nm with an injection volume of 25 μL. Retention times were 2-hydroxy-5-nitropyridine (3.0 min), 2-cyano-5-(hydroxyamino) pyridine (3.5 min), 2-cyano-5-aminopyridine (4.0 min), 2-cyano-5-nitropyridine (8.0 min), 2-bromo-5-nitropyridine (12.0 min), and 2,3-dibromo-5-nitropyridine (18.0 min). Sample preparation for injection was, for a liquid, to weigh about 250 mg of the sample into 5 mL of a 1:1 mixture (by volume) of solvents A and B that was then made up to 25 mL. For solid samples, 20 mg of sample was treated as for liquid samples.

2-Bromo-5-nitropyridine (9). *First Procedure.* A three-neck, 3-L flask was equipped with a mechanical stirrer, a thermometer, nitrogen, a condenser, and an addition funnel. Phosphorus tribromide (260.3 g, 90.3 mL, 0.961 mol) was dissolved in 1,2-dichloroethane (DCE) (150 mL), and the flask was cooled with an ice bath to about 5 °C. Bromine (153.7 g, 49.5 mL, 0.961 mol) was dissolved in DCE (270 mL) and then added dropwise to the PBr_3 with good mechanical stirring. A yellow precipitate of PBr_5 formed instantly. The addition time was about 45 min. The reaction mixture was a heavy, bright-yellow slurry of PBr_5 in DCE. The reaction was stirred for a further 30 min at 5−10 °C, and then the 2-hydroxy-5-nitropyridine (**10**) (122.49 g, 0.874 mol) was added as a solid. The ice bath was removed, and the dark-orange heterogeneous reaction mixture was heated to reflux. The reaction was heated under reflux for 3.5 h. There is a small evolution of bromine during this period. The slurry slowly dissolved, and then a fine solid dropped. The reaction was monitored by TLC or HPLC. When reaction was complete, it was cooled to 10 °C with an ice bath. Sodium hydroxide (1 N, 250 mL) was added dropwise with good stirring (this is very exothermic!). A precipitate formed that was not soluble in either the organic or aqueous phase. The slurry was filtered and washed with DCE (100 mL). The combined filtrates were separated. The organic phase was the top layer. The aqueous phase was extracted with DCE (2 × 250 mL). The combined organic phases were washed with 1 M sodium thiosulphate (100 mL), dried

(Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange solid that was recrystallised from hexane—some of the solid did not dissolve and had to be filtered off while hot. Repeating this recrystallisation using the mother liquors can increase the yield. It was sometimes necessary to repeat the recrystallisation to remove a faster-running impurity. Yield was about 60%. Mp 139−141 °C (lit.[17] mp 139−141 °C). Spectra were identical to an Aldrich sample.[17]

Second Procedure. In a four-necked 1-L flask equipped with a reflux condenser, stirrer, pressure equalising dropping funnel, and thermometer was placed of 1,2-dichloroethane (200 mL). Phosphorus tribromide (90 g; 31.25 mL) was added to this solvent and the solution cooled to 5 °C by an external ice bath. Bromine (50 g; 16.1 mL) was then added to the solution washing in with DCE (8 mL). The mixture was stirred while keeping cool, for about 15 min when no bromine vapors were visible above the liquid. 2-Hydroxy-5-nitropyridine (**10**) (40 g) was added as the solid. The mixture was heated under reflux for 2 h, then cooled to 10 °C, at which time the cold bath was removed. A sodium hydroxide solution [previously prepared by dilution of a 50% solution (120 g) with water (370 mL)] was slowly added to the mixture ensuring that the internal temperature did not exceed 50 °C through control of the addition rate. This addition is extremely exothermic. At the end of the addition, the pH was slightly basic. For the next series of steps, the mixture had to be kept at 50 °C so that product did not crystallise out. Ethyl acetate (133 mL) was added to the mixture and after stirring for 15 min, the aqueous layer (bottom) was separated. The organic layer was washed with water (60 mL) (still at 50 °C), and then concentrated to half volume with the help of vacuum. The residual solution was heated to 60 °C and heptane (470 mL) added. The mixture was then concentrated to half volume again by atmospheric distillation. Upon cooling, the product was isolated by filtration, washing the cake with heptane (72 mL), and air-drying. Yield was about 40 g (70%) or better.

2-Cyano-5-nitropyridine (8). *First Method.* A 2-L 4-neck, round-bottom flask was equipped with a condenser, thermometer, nitrogen inlet, pressure equalizing dropping funnel, and a mechanical stirrer. Sodium cyanide (28.92 g) and copper cyanide (79.36 g) were added to DMF (750 mL) at room temperature with stirring. The mixture was heated to 150 °C. 2-Bromo-5-nitropyridine (**9**) (120.0 g) was dissolved in DMF (250 mL) with warming to 50 °C and this temperature of the solution was maintained throughout the addition. The solution of **8** was added over 5 min to the reaction mixture. The reaction turned orange then black. The reaction mixture was heated under reflux for 1.5−2 h. The reaction was monitored by HPLC. An extended reaction time lead to degradation, but not at a significant rate. The mixture was then cooled to about 100 °C over 0.5 h. The reaction mixture was poured into aqueous 1 M potassium phosphate (monobasic) solution (2 L). A precipitate formed. The mixture was stirred for 0.25 h, and then filtered. The solid was washed with more aqueous buffer (500 mL), then EtOAc (3 × 500 mL). This washing had to be thorough to remove the product from the solid. All of these washings were combined. The organic phase was separated, and the aqueous phase extracted with EtOAc (3 × 400 mL). The combined organic extracts were washed with water (500 mL), and concentrated under reduced pressure (40°/15 mmHg then 70°/15 mmHg) to give an orange-brown oil. This oil was diluted with water (1 L) and stirred for 10 min. The black solid was purified by recrystallisation from hexane. This was done by use of 2 L of hexane and recycling the mother liquors. The product was still soluble in cold hexane, and the efficiency of this method could be increased by cooling the suspension to ice temperature prior to filtration. Four or five cycles were usually necessary to obtain all of the product. An alternative, use of a continuous extraction apparatus (the solid melts below the boiling point of hexane) provided a less labour intensive solution. The slightly yellow solid was recrystallised from hexane, if required, to give the product **8** (65−70%): mp 51−52 °C; IR ν_{max}(KBr) 2250, 1600, 1355 cm^{-1}; NMR: δ ($CDCl_3$) 9.56 (1H, d, J 4 Hz), 8.78 (1H, dd, J 4 and 8 Hz), and 8.12 (1H, d, J 8 Hz); $^{13}C(CDCl_3)$ 146.2, 145.2, 138.1, 132.8, 129.2, and 115.8.

Improved Workup Procedure. The reaction and initial isolation with ethyl acetate are as described above to give the oil. The oil was then diluted with toluene (1 L) and heated to 50 °C. Heptane (1 L) was then added and, if solid was still present, the mixture was filtered hot. To avoid crystallisation, the mixture was heated to 70° prior to the filtration during which, the temperature was not allowed to fall below 45 °C. The mixture was cooled to ambient temperature, and, if no solid was apparent, the mixture was seeded. Heptane (4 L) was then added over 0.5 h with good agitation. After stirring for a few minutes, the product was filtered and the cake washed with heptane (1 L).

Second Method. DMF (60 mL) was placed in a four-neck flask equipped with a stirrer, thermometer, reflux condenser, and pressure equalising dropping funnel. Sodium cyanide (2.5 g) and copper cyanide (6.53 g) were then added, and the mixture was heated to 150 °C under nitrogen. In a separate flask, 2-bromo-5-nitro-pyridine (10.0 g) was dissolved in DMF (25 mL) by heating to about 80 °C. Once the cyanide salts had dissolved and the internal temperature of the DMF was 150 °C, the bromide solution was added in one portion. The reaction mixture was kept at 150 °C for 2 h. The mixture was allowed to cool to about 100 °C, and then isopropyl acetate (167 mL) was added. This was followed by 0.25 M potassium phosphate (monobasic) buffer (167 mL). The mixture was stirred for 0.5 h, and then the brown solid was filtered off. The solid was washed with isopropyl acetate (10 mL). The combined liquids were separated. Charcoal (1.0 g) was added to the organic solution and stirred for 0.5 h. The charcoal was filtered off and washed with isopropyl acetate (10 mL), and the charcoal treatment was repeated. Water (∼50 mL) was added to the filtrate, and the mixture was evaporated at 40 °C under vacuum until all of the organic solvent had been removed. Upon cooling, the product solidifies from the water. The product was filtered, washed with a small portion of water, and then air-dried. Yield was about 70%.

5-Amino-2-cyanopyridine (4). Catalytic Reduction Method. *Procedure 1.* The nitro compound **8** (0.51 g), 10% palladium on charcoal (0.39 g), and THF (50 mL) were placed in a Parr bottle. The mixture was placed under hydrogen (50 psi) at room temperature and shaken for 2 h. TLC showed that the reduction was complete. The mixture was filtered through a Celite pad. The solid was washed with ethyl acetate (10 mL). The combined washings were evaporated down to give the aminopyridine **4**: mp 149−151 °C; IR νmax ($CDCl_3$) 3420, 2222, 1583 cm^{-1}; ^1H NMR (d_6-DMSO) δ 8.00 (1H, d, J 2.6 Hz), 7.57 (1H, d, J 8.6 Hz), 6.95 (1H, dd, J 2.6 and 8.6 Hz), and 6.42 (2H, s). ^{13}C NMR 148.3, 137.7, 129.9, 119.2, 118.3, 117.5.

Procedure 2. The nitro compound **8** (0.5 g) was dissolved in MeOH (25 mL). 10% Palladium on charcoal (0.017 g) and MeOH (5 mL) were placed in a Fisher-Porter vessel under a nitrogen atmosphere. The nitro solution was added to the vessel. The mixture was placed under hydrogen (45 psi) and stirred at room temperature for 2 h. HPLC (or TLC) showed complete consumption of the starting material. The mixture was filtered and evaporated to give the aminopyridine **4**.

Procedure 3. 2-Cyano-5-nitropyridine (**8**) (13.29 g), 10% palladium on charcoal (13.29 g), and methanol (535 mL) were placed in a 1-L flask. Ammonium formate (26.42 g) was added and the mixture heated under reflux for 4 h. The reaction can be followed by TLC or HPLC. The mixture was filtered, then evaporated to provide a brown solid, which was recrystallised from ethyl acetate (200 mL) and hexane (500 mL). The yield of this step was about 75%.

Procedure 4. To a solution of 2-cyano-5-nitropyridine (**8**) (3.0 g) in methanol (150 mL) under nitrogen was added 0.45 g of 10% Pd−C or 4% Pd−C wet catalyst. The mixture was shaken under hydrogen using a 1-L Parr shaker-type reactor. The initial hydrogen pressure was 30 psi and after about 6 h, the hydrogen absorption stopped at the final pressure of 6 psi. After filtration, the methanol was evaporated and the residue was dissolved in ethyl acetate (150 mL). This solution was passed through a short silica gel column and washed with ethyl acetate. The solvent was removed to give a brown solid as product. The catalyst recovered was dried under vacuum and added to 225 mg of fresh Pd/C (10%). This catalyst was used to treat another 3.00 g of 2-cyano-5-nitropyridine in the same way as above. This process was repeated five times. The yield of this reaction is about 70−75%.

Procedure 5. In a 5-L round-bottom flask equipped with a mechanical stirrer, thermometer, reflux condenser, and dropping funnel was placed the nitro compound **8** (150 g) and iron powder (150 g). Ethyl acetate (1500 mL) was added, and gentle heating was started. Acetic acid (625 mL) was added dropwise at such a rate that no sharp rise in temperature occurred. The mixture was heated to reflux. After 2 h, a sample for analysis was taken to ensure that the reduction is complete. If the reaction was not complete, it was continued at reflux and could take up to an additional 2−4 h. When the reaction was complete, the mixture was cooled to 70 °C and then filtered, rinsing the solid with ethyl acetate (250 mL). The washes were combined with the original filtrate. The solids were dried under a nitrogen stream. The liquid and solid parts were treated separately.

The filtrate was placed in the 5-L round-bottom flask and cooled with an ice bath. Sodium hydroxide solution (10 N) was added until the pH was about 8.5. The reaction was very exothermic, and the temperature was kept below 40° by controlling the addition rate. Once the addition was complete, the mixture was stirred for an additional 15 min or until the internal temperature was below 20 °C. The layers were separated. The aqueous layer was extracted with ethyl acetate (375 mL). The organic layers were combined.

Water (DI, 1500 mL) was placed in a 5-L flask. Sodium bisulphite (435 g) was added and the mixture stirred to dissolve all the solids. Once a solution had been formed, ethyl acetate (1500 mL) was added. The solids from the original reaction filtration were then added, and the mixture was stirred at ambient temperature for 15 min. The mixture was filtered, washing the solid with ethyl acetate (125 mL). The layers of the filtrate were separated. The aqueous layer was extracted with ethyl acetate (375 mL). The combined ethyl extracts from this solid extraction were placed in a flask that was cooled in an ice bath. Sodium hydroxide solution (10 N) was added until the pH was about 8.5. The reaction is very exothermic and the temperature was kept below 40° by control of the addition rate. Once the addition was complete, the mixture was stirred for an additional 15 min or until the internal temperature was below 20 °C. The layers were separated. The aqueous layer was extracted with ethyl acetate (375 mL). The organic layers were combined.

The organic extracts from the filtrate and solid treatment were then combined and washed with brine (375 mL). The volume of the solution was then reduced to ∼1 L under vacuum. The vacuum was then released and the mixture heated to 60 °C. An equal volume of hexane was added, and the mixture was cooled to ambient temperature. A further 2 volumes of hexane were then added to the slurry. After stirring for an additional 2 h, the product was isolated by filtration, washing with a small amount of hexane and drying in vacuo at ambient temperature.

Hydrochloride Salt (12). Into a 5-L Erlenmeyer flask was charged the amine **4** (350 g) and dry THF (2800 mL). The contents were stirred until all solids had dissolved. If solid still remained after 1 h, the mixture was filtered. The flask was cooled in an ice bath and hydrogen chloride gas bubbled through until no more solid formation was apparent. The flask was kept in the cold bath for 2 h, and then the solid was isolated by filtration. The salt was washed with THF (2 × 100 mL) and then dried at ambient temperature in a vacuum oven. The yield was essentially quantative.

Large-Scale Runs. The sizes of these reactions were limited by the equipment available to us. In some cases, multiple runs of a particular step had to be run to obtain sufficient material to carry on. These reactions were later transferred to a toll manufacturer, but this resulted in quality issues.[2]

2-Bromo-5-nitropyridine (9). For these operations, sensors and alarms were present to detect bromine and HBr gases.

Ethylene dichloride (30.9 kg) was charged to a 30-gal reactor. Phosphorus tribromide (11.2 kg) was placed in a 5-gal transfer tank. Ethylene dichloride (1 kg) was placed in a 2-gal transfer tank. The 5-gal transfer tank was connected to the 30-gal reactor. The PBr_3 was added to the reactor. The 2-gal transfer tank was connected to the now empty 5-gal tank and the ethylene dichloride used to rinse the tanks and lines as it was added to the reactor. Ethylene dichloride (12.8 kg) was added to a 5-gal transfer tank followed by bromine (6.3 kg), and the contents of this tank were stirred for 15 min. The bromine solution was added to the PBr_3 solution. The 5-gal transfer tank and lines were rinsed with ethylene dichloride (1 kg) from a 2-gal transfer tank. After stirring for a few minutes the headspace was examined to ensure that there was no bromine vapour. 2-Hydroxy-5-nitropyridine (**10**) (5.0 kg) was added and the mixture heated under reflux for 2 h during which time the temperature increased from 84 to 88 °C. The mixture was then cooled to 10 °C. In a 5-gal transfer tank, 50% NaOH (816 g) was added to DI water (9.67 kg). This caustic solution was used to quench the reaction by slow addition at such a rate to ensure that the temperature of the liquid in the reactor did not exceed 50 °C. The mixture was then stirred at 25 °C for 30 min. NaOH (50%, 7.0 kg) was then slowly added so that no large exotherm occurred. The pH was checked to see if it was about 7. If not 50% NaOH was added in 3.5 kg portions (usually one extra addition sufficed). Once at pH 7, EtOAc (14.7 kg) was added and the mixture stirred for 15 min after which it was heated to 50 °C and held at this temperature for 30 min to dissolve any solids. While maintaining 50 °C, the phases were separated. The organic layer was transferred to a 100-gal reactor. The aqueous layer was adjusted so that its temperature was 25 °C and then extracted with EtOAc (5.1 kg). This extract was washed with water (6.4 kg) and then added to the original organic solution. (Note: During these extractions and washings each layer was verified whether it was organic or aqueous as large density changes occurred and inversion often occurred.) The combined EtOAc solution was dried with Na_2SO_4 and then filtered into a 30-gal reactor. The solvent was then removed by distillation to about one-quarter volume; the boiling point rose from 78 to 88 °C. The mixture was cooled to 70 °C and heptane (20.2 kg) added. The mixture was stirred at this temperature for 30 min and then cooled to 0 °C. The product was collected on a Nutsche filter, washing with heptane (5 kg), and then dried under vacuum in an oven at 40 °C overnight. Yield was 5.0 kg (70%)

2-Cyano-5-nitropyridine (8). These reactions were run with alarms and sensors to detect the presence of HCN.

First Procedure. DMF (29.8 kg) was charged to a 30-gal stainless steel reactor. This was followed by NaCN (1.2 kg) and CuCN (3.3 kg). The mixture was heated to 150 °C with stirring. During this period, DMF (10.1 kg) was placed in a 5-gal glass reactor followed by 2-bromo-5-nitropyridine (5.0 kg). This mixture was then heated to 80 °C with stirring until the bromide had dissolved. Once both mixtures were at temperature, the bromide solution was added to the inorganic cyanides. The reactor and lines were rinsed with DMF (1 kg). The resultant solution was heated at 150 °C for 2 h.

In a 100-gal reactor monobasic potassium phosphate (11.3 kg) was dissolved in DI water (72 kg). The temperature was maintained at 20 °C. The cyanide reaction was quenched by transfer to the phosphate solution ensuring that the temperature of the DMF solution at no time went below 100 °C. The internal temperature of the 100-gal reactor was kept below 90°. The resultant mixture was stirred for 15 min and then filtered through a Rosenmund filter recycling the mother liquors until they became clear. The cake was then washed with a solution of potassium phosphate (2.8 kg) in DI water (18 kg) by use of the Rosenmund agitator for 1h. The reactor used for the quench was rinsed with EtOAc (80 kg), ensuring that all surfaces were washed. This wash was then held in the reactor. The Rosenmund agitator was stopped and the liquid removed under vacuum. EtOAc (19 kg) used as the rinse was charged to the Rosenmund, and this was stirred for 1 h and then removed under vacuum. The treatment of the solid with EtOAc was repeated in 19-kg lots until all the organic solvent had been used. The resultant combined filtrates were stirred for 30 min then allowed to separate. The aqueous phase was run off and then back-extracted twice with EtOAc (2×9 kg). The combined organic extracts were washed with water (21 kg). Charcoal (Darco, 1 kg) was added, and the mixture was stirred for 15 min and then filtered through a Nutsche. The filtrate was heated to boiling in a 100-gal reactor and the solvent removed until stirring could not be accomplished as the solution fell below the agitator level. The resultant solution was then transferred to a 30-gal reactor that contained toluene (2.9 kg) and heptane (7 kg). Distillation was then continued at atmospheric pressure until minimal volume was achieved; again that the liquid was below the agitator level. The reactor was then cooled to 20 °C and water (3.3 kg) added. The mixture was seeded with product (10 g) and stirred for 30 min. The product was collected on a Nutsche filter, washed with heptane (5 kg), and then dried under a stream of dry nitrogen at ambient temperature. The yield was 3.5 kg (63%).

Second Procedure. The actual reaction was performed in three separate lots that were combined for the final work up. This was because the 30-gal system could maintain the desired temperature while the 100-gal system could not.

DMF (14.3 kg) was charged to a 30-gal stainless steel reactor followed by NaCN (0.625 kg) and CuCN (1.63 kg). The mixture was heated to 150 °C with stirring. During this period, DMF (6.0 kg) was placed in a 5-gal glass reactor followed by 2-bromo-5-nitropyridine (2.5 kg). This mixture was then heated to 80 °C with stirring until the bromide had dissolved. Once both mixtures were at temperature, the bromide solution was added to the inorganic cyanides. The reactor and lines were rinsed with DMF (1 kg). The resultant solution was heated at 150 °C for 2 h and then cooled to cooled to 100 °C.

In a 30-gal reactor monobasic potassium phosphate (1.43 kg) was dissolved in DI water (42 kg). The temperature was maintained at 20 °C.

To the cyanide reaction was added *i*-PrOAc (36.3 kg) at such a rate that excess boiling did not occur. This mixture was then added to the phosphate solution that was then stirred for 30 min before being filtered through a Nutsche. The solid was rinsed with *i*-PrOAc (2 kg). The combined filtrates were then separated with the aqueous phase going to waste. The organic layer was then transferred to a 100-gal reactor and combined with those from two other reactions.

To these combined extracts was added charcoal (Darco, 0.75 kg) and the mixture stirred for 30 min. The charcoal was removed by a line filter, which together with the original reactor, were rinsed with *i*-PrOAc (5 kg). The charcoal treatment was repeated on the combined filtrates. Water (150 kg) was then added to the combined filtrates. The organic solvent was removed under vacuum keeping the jacket temperature below 40 °C. The mixture was then slowly cooled to 10 °C. The product was then collected on a Nutsche filter, washed with water (5 kg), and then dried under a stream of dry nitrogen at ambient temperature. Yield was ∼3.9 kg (71%).

5-Amino-2-cyanopyridine (4). This procedure was run by us and was reproducible. It was a trial to ensure that it could be run at the tollers, and as a consequence the reduction was run more dilute than in the lab experiments. The tollers then went back to the more concentrated reduction but then had problems removing the iron oxide which ended up in the product and had to be removed (see purification procedure).

EtOAc (108 kg) was charged to a 100-gal reactor followed by 2-cyano-5-nitropyridine (12.0 kg). The mixture was then stirred and iron powder (12.0 kg) added. The mixture was then heated to reflux (∼78 °C) and the jacket temperature set to 80 °C. Glacial acetic acid (53.4 kg) was added over 2 h. The addition rate was kept constant (0.593 kg/min). After approximately 5 min an exotherm was observed with the internal temperature rising to 85 °C. The jacket temperature was adjusted to 74−80° so that a gentle reflux was maintained. After the addition was complete, the jacket temperature was increased to 90° and reflux was maintained for 30 min. The mixture was analysed by HPLC, and heating under reflux was continued until the amount of the nitro compound was below 5% or if no change occurred within 1 h. The mixture was then cooled to 65 °C and filtered through a Nutsche. The reaction vessel, transfer lines, and cake were washed with EtOAc (12 kg). (Due to our equipment-size limitations the filter cake and the filtrate were handled separately. This was not done on larger scale as all were combined.)

Solid Treatment. The filter cake was charged to a mixture of sodium bisulphite (45 kg) in water (113 kg) and EtOAc (135 kg) that had been warmed to 70 °C in a 100-gal reactor and stirred at this temperature for 15 min before filtering through a Nutsche. The solid was rinsed with more EtOAc (20 kg). This filtrate was then separated. The aqueous phase was extracted with EtOAc (27 kg) that was combined with the organic layer from this solid treatment step. NaOH (10 N) was then added to this solution until the pH was 8.5 (∼14 kg). After stirring for 5 min the layers were allowed to separate. The aqueous layer was back-extracted with EtOAc (27 kg). These EtOAc solutions were then combined.

Liquid Treatment. The original filtrate was placed in a 100-gal reactor and cooled to 5−10 °C. NaOH solution (5N) was added until the pH was 8.5 (∼57 kg). After stirring for 10 min the layers were allowed to separate. The aqueous layer was separated and back-extracted with EtOAc (27 kg). This extract was combined with the EtOAc solution from the first separation in this filtrate workup sequence. The EtOAc was removed under vacuum with a jacket temperature of <45° until the weight was <75 kg. The EtOAc solution from the solid treatment was then added. This combined mixture was washed with saturated aqueous NaCl (30 kg). The EtOAc was then removed by vacuum distillation until the weight was <75 kg. The vacuum was then removed and the mixture heated to boiling. If any solids could be observed by visual means, EtOAc was added to complete solution. Hexane (63 kg) was then added, ensuring that excessive boiling did not occur. The mixture was held until solid formed when more hexane (129 kg) was added, and then the mixture was cooled to 15 °C. The solid was collected on a Nutsche, washed with hexane (39 kg), and dried at ambient temperature under a stream of dry nitrogen. Yield was 8.4 kg (88%).

Purification of Amine 4. As noted above impure samples were obtained from tollers (assays ranged from 78 to 98% on a wt/wt basis by HPLC and titration), and these were cleaned up as follows:

EtOAc (32 kg) was placed in a 30-gal reactor followed by the impure amine **4** (7.0 kg). The mixture was heated under reflux for 30 min and then filtered hot through a Nutsche. The procedure was repeated on the filter cake. Charcoal (Darco, 280 g) was added to the combined filtrates which was then heated under reflux for 30 min. The mixture was filtered hot through cartridge filters. The solution was concentrated to a third of its original volume by vacuum distillation and then cooled to ambient temperature. The solid was collected on a Nutsche and allowed to dry under a stream of dry nitrogen. A second crop was obtained from the filtrate by heating it to boiling and then setting the jacket temperature at 60 °C. Hexane (2× the weight of EtOAc present) was then added. The mixture was cooled to ambient temperature over 1 h and then filtered through a Nutsche, drying in a nitrogen stream. Both crops were within specifications (>98wt %/wt by HPLC and titration, and the solid was off-white to light-yellow in colour).

Preparation of Amine Hydrochloride 12. THF (96 kg) was charged to a glass-lined 100-gal reactor. The amine **4** (12.0 kg) was added and the mixture heated to boiling and then cooled to ambient temperature. The solution was then flitered through a sparkler Nutsche filter, returning the clear mother liquors to the reactor. The solution was cooled to 0 °C, and then HCl gas was bubbled through at 60 psig for 15 min. Nitrogen was then bubbled through the mixture for 15 min. The HCl addition was repeated twice more. After the

final addition, the mixture was stirred for 1 h at 0 °C. The solid was collected on a Nutsche. The reactor, line, and then cake were washed with THF (11 kg). The solid **12** was dried overnight at ambient temperature on the filter bed under a stream of dry nitrogen.

Acknowledgment

We acknowledge the contributions of Professor Alan Katritzky and his research group at the University of Florida. They spent considerable time and effort looking at alternative approaches for the synthesis of **4**, many of which have not been mentioned here. Dalpat Brahmbhatt is thanked for the development of the analytical method.

Received for review August 5, 2003.

OP034110C