Organic Process Research & Development **2007**, *11*, 693–698

Process Development for ABT-472, a Benzimidazole PARP Inhibitor

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Abstract:

A nine-step convergent process was developed for the synthesis of ABT-472, a benzimidazole PARP inhibitor. The identity and origin of several impurities were determined, and the process was modified to reduce or eliminate these impurities. A number of safety and control issues were investigated. The original synthesis was shortened to 9 steps and streamlined while maintaining a convergent strategy. A stable salt was selected, and control of the API solid form was established. The process was successfully scaled up to provide 8.5 kg of final product of >99% purity in 33% yield over 9 steps.

Introduction

Poly((ADP)-ribose) polymerases (PARPs) have been recognized as cellular signaling enzymes capable of catalyzing the transfer of ADP-ribose units from NAD+ to a number of acceptor proteins. PARP-1, the most characterized of these polymerases, is critical to the cellular response to DNA injury.[1] Selective binding of PARP-1 to sites of both single and double strand DNA damage ultimately results in the repair of the break. ABT-472 (**11**), an inhibitor of PARP-1, has been advanced for clinical evaluation as a potentiator of DNA damaging radio- and chemotherapy agents.[2] In order to obtain *in vivo* efficacy of ABT-472, an efficient, scalable synthetic route is needed. In this paper we report on the development of a route to ABT-472.

Results and Discussion

Our synthesis (Scheme 1) of ABT-472 commenced with the preparation of anhydride **2** from commercially available 3-nitrophthalic acid (**1**). As reported,[3] dehydration with neat acetic anhydride at 100−120 °C cleanly yielded the desired anhydride. Reaction calorimetry showed the dehydration to be mildly exothermic (−4.1 kcal/mol), however accelerating rate calorimetry (ARC)[4] indicated the potential for an extremely exothermic decomposition when the mixture was heated to greater than 100 °C in the presence of metals.[5] To safely control the reaction, the reaction mixture was diluted with isopropyl acetate, raising the initiation point to >140 °C, well above the boiling point of isopropyl acetate (85−91 °C). The maximum rate of heat evolution $((dT/dt)_{max})$ was reduced from 74 °C/min prior to dilution with isopropyl acetate to less than 1 °C/min after dilution. The latter experiment was run in the presence of stainless steel.

Slow addition of the anhydride **2** to an excess of ammonium hydroxide yielded a 90:8:2 mixture of ammonium salts of carboxamide **12**,[6] regioisomer **13**,[7,8] and phthalic acid **1** (Scheme 2).[9,10] Adjusting the pH of the reaction mixture to not more than 2 with aqueous hydrochloric acid caused free acid **14** to precipitate in 80% yield along with approximately 4% of the phthalic acid **1**. However, acid **14** was found to rapidly undergo isomerization and hydrolysis to diacid **1** upon standing in acidic media even at 0 °C.

To circumvent the instability of **14** in the presence of acid, we focused on isolation of the potassium salt **3** (Scheme 2). The potassium salt had the favorable properties of being a crystalline, nonhygroscopic solid that could be used directly in the subsequent Hofmann rearrangement, and **3** could be easily recovered by crystallization from isopropanol.[11] Addition of KOH to the crude reaction mixture followed by solvent exchange into isopropanol gave an 86% isolated yield of **3** with 99.8% purity.

The Hofmann rearrangement (Scheme 3) has usually been accomplished by addition of an amide to a solution of freshly prepared potassium hypobromite followed by heating,[12] although direct addition of bromine to an aqueous KOH solution of the amide has been preferred to avoid concerns regarding stability of the hypobromite.[13] Calorimetry during the direct addition procedure showed an exotherm of −140

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(1) *Curr. Med. Chem.* **2003**, *10*, 321.

(2) Lubisch, W.; Kock, M.; Hoger, T.; Schult, S.; Grandel, R.; Muller, R. *Preparation of benzimidazolecarboxamides as poly(ADP-ribose)polymerase inhibitors*. PCT Int. Appl. (2000), WO 2000032579 A1 20000608.

(3) *Organic Synthesis, Collective Volume 1*; Wiley: New York, 1932; p 402.

(4) Hoppe, T. *Chem. Eng. Prog.* **1992**, *88*, 70.

(5) (a) Tests were carried out in the presence of 316 stainless steel and titanium. (b) Explosions with nitric acid/acetic anhydride mixtures have been reported (Eaborn, C. *J. Organomet. Chem*. **1978**, *144*, 271. Andreozzi, R.; Marotta, R.; Sanchirico, R. *J. Haz. Matls.* **2002**, *90*, 111. Chervin, S.; Bodman, G. T.; Barnhart, R. W. *J. Haz. Matls.* **2006**, *130*, 48); however we are unaware of any examples of hazardous decompositions of aromatic nitro compounds in the presence of acetic anhydride. The mechanism of destabilization by metals is not known.

(6) Ritzeler, O.; Stilz, H. U.; Neises, B.; Bock, W. J., Jr.; Walser, A.; Flynn, G. A. *Preparation of benzimidazolecarboxylic acid amino acid amides as IκB kinase inhibitors.* PCT Int. Appl. (2001), WO 2001000610 A1 20010104.

(7) Oku, A.; Matsui, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3338.

(8) The regioisomer **13** was identified by ^{13}C NMR analysis and LC/MS.

(9) Ratio is area % based on HPLC. Variances in ratio due to sampling errors of the heterogeneous mixture were often observed.

(10) Ammonia in THF, DME, MeOH, and IPA gave ratios of **12:13** ranging from 32:1 to 14:1.

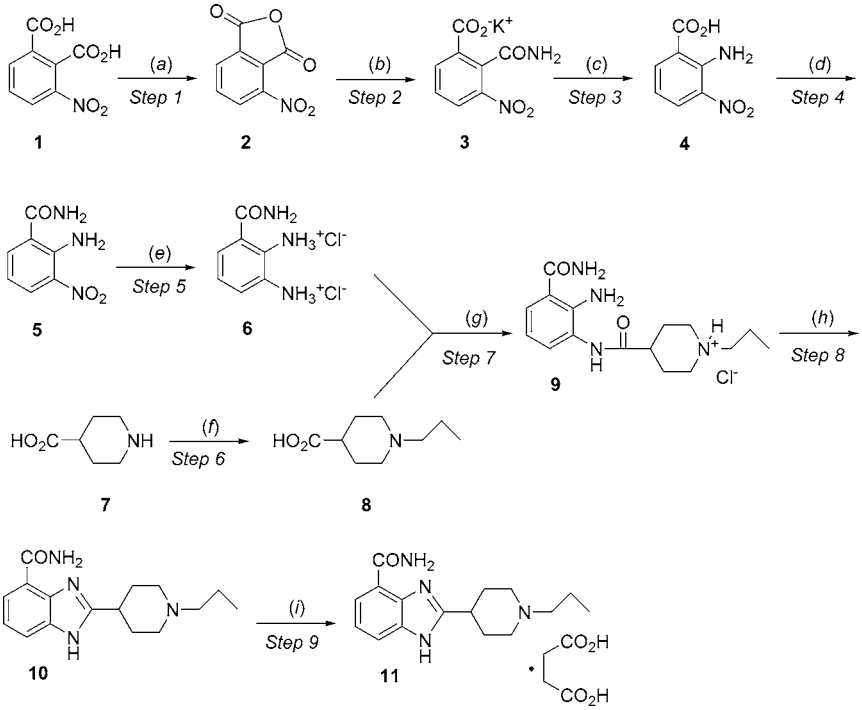
(11) Potassium salt **3** had a solubility of 15 mg/mL (reported as the free acid) in 22% water/IPA at 0 to 5 °C, while the potassium salt of the regioisomer **13** had a solubility of >20 mg/mL under the same conditions.

(12) Wallis, E. S.; Lane, J. F. Organic Reactions, Vol. 3; p 267.

(13) Beckwith, R. C.; Margerum, D. W. *Inorg. Chem*. **1997**, *36* (17), 3754.

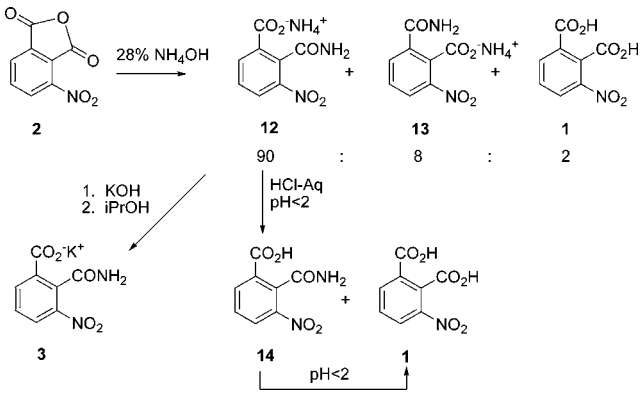
10.1021/op7000194 CCC: $37.00
Published on Web 05/15/2007

Scheme 1. **Scaled up route to ABT-472**[a]

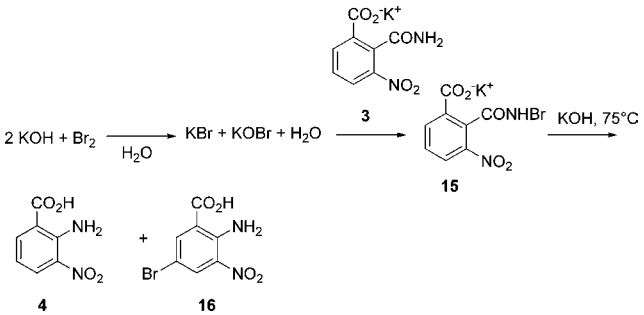


[a] Reagents and conditions: (*a*) Ac_2O, *i*-PAc, 80 °C; (*b*) 28% NH_4OH, KOH, *i*-PrOH; (*c*) (i) KOH, Br_2, 0° to 70 °C; (ii) Concd HCl; (*d*) (i) $SOCl_2$, DME, 50 °C; (ii) NH_4OH; (*e*) (i) Raney Ni, H_2, EtOAc/EtOH; (ii) HCl/EtOAc; (*f*) EtCHO, EtOH, Pd−C, H_2; (*g*) CDI, NMP, THF; (*h*) (i) AcOH, H_2O; (ii) NaOH; (*i*) Succinic Acid, IPA, i-PAc.

Scheme 2. **Ammonolysis of 3-nitrophthalic anhydride**



Scheme 3. **Step 3 reaction and byproducts**



kJ/mol, consistent with the calculated exotherm for formation of the *N*-bromoamide **15**.[14] Further heating to 75 °C gave a single thermal event corresponding to −761 kJ/mol. Analysis during the heating by both *in situ* IR and NMR suggested the individual steps of the rearrangement sequence could not be separated, and thus the heating was carried out slowly to control the temperature rise.[15]

The only major impurity identified after the rearrangement was the brominated arene **16**. Formation of **16** proved sensitive to the potassium hydroxide stoichiometry. With 5 equiv of base, the reaction yielded a 0.1:0.3:99.5 ratio of **3:16:4**, whereas with 3 equiv of base the ratio was 5.0:11.3:83.7. Presumably an excess of base reduces the concentration of protonated *N*-bromo amide **15** during the reaction.[16]

The reaction mixture was held at >60 °C to ensure destruction of residual potassium hypobromite as well as bromate and bromite byproducts, since acid quenching prior to complete decomposition of the oxidants also resulted in brominated impurity **16**.[17] Quenching with aqueous HCl after 1 h at 75 °C decomposed the intermediates and precipitated the desired nitroaniline **4** in 89% yield and >99% purity. The carboxylic acid in **4** was converted to the corresponding acid chloride[18] with thionyl chloride in DME, followed by an ammonium hydroxide quench to form amide **5** in 85−93% yield.

(14) Calculated exotherms were obtained from ChemDraw software (Cambridge-Soft Corporation, 100 Cambridge Park Drive, Cambridge, MA 02140, www.cambridgesoft.com). The exotherms also comparable to previously measured exotherms for *N*-bromination of amides. See: Amato, J. S.; Bagner, C.; Cvetovich, R. J.; Gomolka, S.; Hartner, F. W.; Reimer, R. *J. Org. Chem.* **1998**, *63*, 9533.

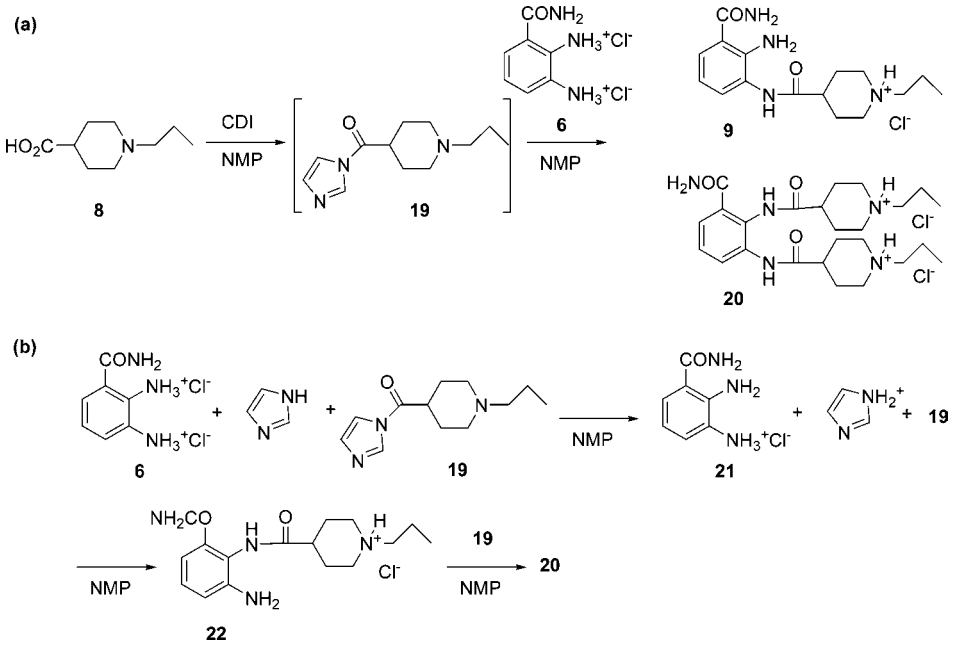
(15) (a) Denny, W. A.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1990**, *33*, 814. (b) Nagasaka, T.; Koseki, Y. *J. Org. Chem.* **1998**, *63*, 6797.

(16) *N*-Bromoamides are known brominating agents, similar to NBS in the Wohl−Ziegler reaction. For example, see: Park, J. D.; Lycan, W. R.; Lacher, J. R. *J. Am. Chem. Soc.* **1954**, *76*, 1388.

(17) For example, see: Groweiss, A. *Org. Process Res. Dev.* **2000**, *4* (1), 30. Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett.* **1984**, 2045.

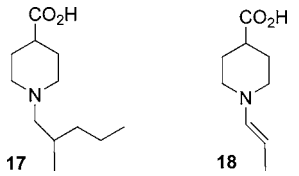
(18) (a) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G.; *et al. J. Med. Chem.* **1995**, *38*, 771. (b) Kukla, M. J.; Breslin, H. J.; Raeymaekers, A. H. M.; Van Gelder, J. L.; Janssen, P. A. *Preparation of antiviral tetrahydroimidazo-[1,4]benzodiazepin-2-thiones,* Eur. Pat. Appl. (1990), EP 384522 A1 19900829.

Scheme 4. **Coupling of the piperidine and diamine portions**



Initially the nitro group was reduced with palladium on carbon in THF/methanol, and the resulting diamine was isolated as the bis-hydrochloride salt **6**. A significant impurity (4−12%) tentatively identified as a dimeric hydrazine ($M + 1 = m/e$ 299 by APCI LC-MS) proved difficult to avoid or remove. Alternatively, Raney nickel in ethyl acetate/ethanol cleanly gave the diamine, which was not isolated but converted to the same bis-hydrochloride salt **6** in 86−90% yield and >99% purity with no hydrazinyl impurities observed.[19]

Piperidine acid **8** was prepared via reductive alkylation of isonipecotic acid **7** using Raney nickel, but varying amounts (2−20 mol %) of the *N*-2-methylpentyl impurity **17** were identified in the crude reaction mixtures. Similar aldehyde condensations via imines have been reported[20] and clearly were a problem in this reductive alkylation. In order to favor the desired reaction pathway, the catalyst loading was increased to 100 wt % Raney nickel and the propionaldehyde (1.2 equiv) was added in a controlled fashion over several hours to limit aldehyde concentration in the presence of enamine **18**. This technique yielded **8** in 89−93% isolated



yield and reduced the impurity **17** to undetectable levels. However, isolated product contained up to 1800 ppm levels of residual nickel. The nickel concentrations were found to correlate to the time between purging of the hydrogen and filtration of the catalyst, suggesting an instability of the catalyst matrix to the reaction mixture.

No comparable leaching effect was found with palladium on carbon. Thus, addition of propionaldehyde (1.5 equiv)[21] over 4.5 h to an ethanolic solution of acid **7** at ambient temperature and 40 psi hydrogen pressure yielded the desired acid **8** in 86−93% isolated yield, >98% purity, with less than 10 ppm of Pd.

The coupling of the piperidine acid **8** and the diamine **6** to form the amide **9** via the acylimidazole **19** (Scheme 4a) gave **9** in good yield by slowly adding **19** to a solution of **6**. A single-crystal X-ray confirmed the regiochemistry of the coupling (Figure 1). The main competing pathway was formation of the bis-amide **20**. Examination of the reaction course revealed that **20** was formed during the early part of the addition of acylimidazolide **19**. Presumably in the presence of substoichiometric amounts of base, the monohydrochloride salt **21** was selectively acylated at the 2-amino position. While this theory accounted for the observed product distributions, we have not been able to prepare or observe the 2-acyl intermediate **22** (Scheme 4b) or demonstrate its conversion to **20**. In order to avoid formation of this byproduct a solution of diamine dihydrochloride **6** was added to a solution of acylimidazole **19** and imidazole (from reaction of CDI with **8**), resulting in selective reaction at the more reactive 3-amino group to give **9** in 95% yield and 99.2% purity.[22]

The hydrochloride salt **9** was dissolved in water containing 2.5 equiv of acetic acid and refluxed until cyclization was complete. Isolation of the cyclized product as the free base

(19) (a) Hattori, K.; Yamamoto, H.; Mukoyoshi, K.; Kuroda, S. *Preparation of quinoxalinecarboxamides which have poly(adenosine 5′-diphospho-ribose)-polymerase inhibitory action*. PCT Int. Appl. (2003), WO 2003007959 A1 20030130. (b) Lubisch, W.; Kock, M.; Hoger, T. *Preparation of 2-phenylbenzimidazoles as poly(ADP-ribose) polymerase inhibitors*. PCT Int. Appl. (2000), 2000026192 A1 20000511.

(20) List, B., et. al. *J. Am. Chem Soc.* **2000**, *122* (10), 2395−2396. (b) Pollack, R. M.; Ritterstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 5064−5069.

(21) 1.5 equiv of propionaldehyde were necessary with Pd/C to allow for the competitive reduction of the propionaldehyde by the catalyst.

(22) When the diamine bis-hydrochloride **6** was deprotonated *in situ* with imidazole prior to addition of **19**, the desired amide **9** was formed with minimal formation (0.32%) of **20**.

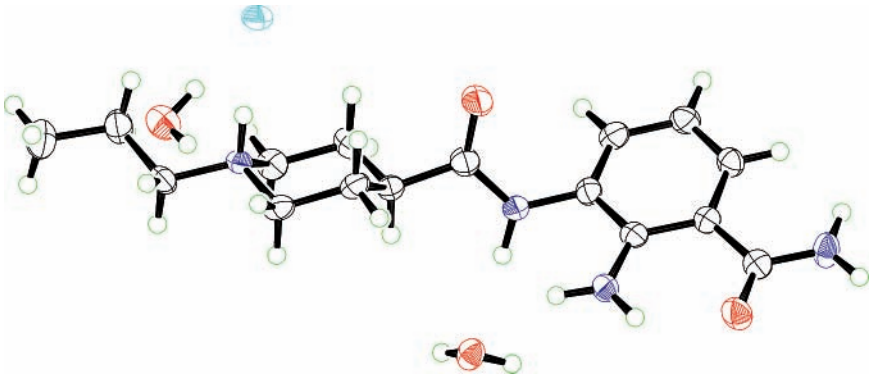


Figure 1. **ORTEP diagram of amide HCl salt 9 dihydrate.**

10 was accomplished in 86% yield and 96.2% purity by neutralization with sodium hydroxide.

Salt screening resulted in selection of the succinate salt **11**.[23] The salt was crystallized by addition of isopropyl acetate antisolvent to a methanol solution of the salt at 47 °C, resulting in a 79% yield of **11**.

Conclusions

ABT-472 was prepared in 32−35% overall yield in nine transformations. By evaluating the root cause of formation of impurities, the purity of the final product was controlled to >99.5%.

Experimental Section

3-Nitrophthalic Anhydride (2). A 100 L glass round-bottom flask was purged with nitrogen and charged with 25.0 kg of 3-nitrophthalic acid (**1**, 118.4 mol) and isopropyl acetate (21.7 kg). To the 100 L flask was charged acetic anhydride (25.4 kg, 249 mol, 2.1 equiv). The bath temperature was raised to 60 ± 5 °C, and the contents were stirred with the bath at 60 ± 5 °C until HPLC analysis showed not more than 2% starting material remaining. The slurry was transferred to a 30 gal glass-lined reactor with heptane (34.0 kg) used as a rinse and transferring agent, and the contents were cooled to 0 ± 5 °C. Once analysis of the supernatant showed less than 15 mg/mL of product, the material was filtered and the cake was washed with MTBE (78 kg) until analysis showed less than 1% acetic acid in the wash. The wet cake was dried at 55 ± 5 °C for 3 days until the loss by TGA was less than 1% for MTBE. Yield: 20.3 kg (86.0% assay adjusted yield).

2-(Aminocarbonyl)-3-nitrobenzoic Acid Potassium Salt (3). A nitrogen purged 115 L glass-lined reactor was charged with 28 wt % NH_4OH (65.6 kg, 525 mol). The reactor was cooled to 0 ± 5 °C, and 3-nitrophthalic anhydride (**2**) (38.4 kg, 200.9 mol) was charged over 2.5 h as a solid while maintaining the internal temperature below 15 °C. The internal temperature was adjusted to 20 ± 5 °C, and a solution of KOH (12.4 kg, 221.4 mol, 1.1 equiv) in water (19.4 kg) was added to the reaction mixture. The contents were distilled under vacuum with a jacket temperature of not more than 50 °C to reduce the volume to approximately 90 L. The internal temperature was adjusted to not more than 30 °C, and isopropanol (76 kg) was added to the mixture. The mixture was distilled under vacuum with a jacket temperature of not more than 50 °C to approximately 90 L. The internal temperature was again adjusted to not more than 30 °C and sampled to assay the isopropanol/water ratio. Isopropanol (76 kg) was added to the mixture to give a water/isopropanol ratio of not more than 0.22 (wt/wt), and the resulting slurry was mixed for not less than 1 h. The slurry was cooled to 0 °C and mixed for not less than 1 h until the supernatant was less than 20 mg/mL product. The batch was filtered, and the wet cake was washed with isopropanol (94 kg). The wet cake was purged with nitrogen for not less than 1 h and dried at 45 °C until the loss by TGA was not more than 5 wt % for isopropanol. Yield: 40.7 kg (86% assay adjusted yield).

2-Amino-3-nitrobenzoic Acid (4). A 190 L glass-lined reactor was purged with nitrogen and charged with a solution of 13.0 kg of potassium hydroxide (232 mol, 5 equiv) in 110 kg of distilled water. The solution was cooled to 15 ± 5 °C, and **3** (11.0 kg, 46.5 mol) was then charged to the reactor. The resulting solution was cooled to 0 ± 5 °C, and bromine (7.4 kg, 46.4 mol, 1.0 equiv) was slowly added to the reactor using residual vacuum through Teflon tubing with a valve to control the addition rate. The internal temperature of the reaction was kept at not more than 5 °C during the addition. The mixture was kept at 0 ± 5 °C for not less than 30 min and sampled for analysis.[24] The reaction mixture was heated to 75 ± 5° C at a rate of approximately18 °C/h. Once at temperature, the mixture was heated for not less than 1 h. The reaction mixture was cooled to 50 °C, and concentrated hydrochloric acid (approximately 21.5 kg, 218 mol, 4.7 equiv) was slowly added to the reaction mixture to adjust the pH to less than 2.5 at a rate to control evolution of carbon dioxide. The resulting yellow slurry was cooled to 20 °C and mixed not less than 1 h. Once analysis of the supernatant showed not more than 2 mg/mL of product, the material was filtered. The filter cake was washed with water until the bromide/chloride content in the wash was not more than 0.1 mg/mL (>100 kg of water was required). The wet cake was

(23) *Handbook of Pharmaceutical Salts: Properties, Selection and Use, International Union of Pure and Applied Chemistry (IUPAC)*; Stahl, H. P., Wermuth, C. G., Eds.; Wiley-VCH: New York, 2002.

(24) A sample is heated to >60° C for not less than 5 min and then assayed using HPLC. The sample is considered to pass when less than 2 area % of **3** remains. Additional bromine could be added should the sample fail.

dried under vacuum at not more than 70 °C using a nitrogen bleed. The drying was considered complete when water determined by Karl Fischer titration was not more than 0.5% by weight. Yield: 7.6 kg (90% assay adjusted yield).

2-Amino-3-nitrobenzamide (5). A solution of **4** (6.0 kg, 32.9 mol) in DME (33 kg) was prepared and filtered into a 100 L glass round-bottom flask using DME (4 kg) as a rinse. The combined solution was sampled and checked for water content by Karl Fischer titration.[25] Thionyl chloride (5.2 kg, 43.7 mol, 1.33 equiv) was added to the solution while stirring; the reaction was mildly exothermic (ATR (Adiabatic Temperature Rise) = 7.7 °C). The reaction solution was then warmed to 50 ± 5 °C and stirred for not less than 12 h or until analysis showed the reaction was complete. The reaction was sampled, and an aliquot was reacted with 0.5 M ammonia in dioxane for 30 min prior to HPLC analysis. The reaction was considered complete if less than 1.0 PA% of starting material was detected. The reaction mixture was cooled to 25 ± 5 °C and slowly added to 28 wt % NH_4OH (42 kg, 715 mol, 22 equiv) in a 190 L glass-lined reactor, while the temperature was maintained at not more than 40 °C. *Safety Note: The reaction was strongly exothermic (ATR = 68 °C) and evolved a large volume of gas*. DME (2 kg) was used to rinse the flask. Orange solids precipitated out immediately. The mixture was warmed to 50 ± 5 °C and stirred for not less than 2 h. Water (47 kg) was added, and the mixture was warmed to 50 ± 5 °C and stirred for another 2 h. The slurry was cooled to 25 ± 5 °C and stirred for not less than 6 h or until the concentration of product in the supernatant was less than 1.0 mg/mL. The orange product was filtered and washed with water until the last wash had not more than 5 ppm of ammonium ion by IC analysis. A large variability was observed in the amount of water required over three runs: Run 1, 382 kg; Run 2, 181 kg; Run 3, 272 kg. The filter cake was washed with isopropyl alcohol (not less than 19 kg) to remove residual water, and then the wet cake was dried under vacuum at not more than 65 °C, for not less than 12 h. Drying was considered complete when the loss by TGA was less than 1.0% for isopropanol. Yield: 5.25−5.75 kg for three runs (85−93% assay adjusted yield).

2,3-Diaminobenzamide Bis-hydrochloride (6). A 550 L glass-lined pressure reactor was pressure checked and was purged with nitrogen. Raney Nickel (W. R. Grace 2800, 6.0 kg wet slurry) was charged to the reactor followed by water (0.3 kg) to rinse the catalyst into the reactor. Ethanol 2B (20.2 kg) was added to the reactor and mixed to disperse water. A slurry of **5** (16.0 kg, 88.3 mol) and ethyl acetate (161 kg) was transferred to the reactor, and additional ethyl acetate (200 kg) was used to rinse the substrate into the reactor. The reactor was pressure purged three times with hydrogen and pressurized to 40 psig with hydrogen. Agitation was increased to initiate the reaction. The reaction exotherm was allowed to increase to 40 °C and was held at this temperature (ATR = 52 °C) with cooling for 100 min, at which point hydrogen consumption ceased. The reaction was sampled and analyzed for completion. The sample passed when not more than 1.0 area % of starting material remained. The reactor was then pressure purged with nitrogen, and the contents were filtered through a bed of diatomaceous earth filter aid with backup filters. Ethyl acetate (60 kg) was charged to the reactor as a rinse and passed through the filters. Hydrogen chloride gas (8.4 kg, 230 mol) was added to the combined filtrates, while a reaction temperature of not more than 30 °C was maintained with cooling (ATR = 10 °C). The precipitated salt was mixed for 75 min, and a sample was taken to confirm that the pH was not more than 2. The slurry was filtered to collect a white solid, which was washed with ethyl acetate (152 kg). The wet cake was dried in a hastelloy dryer under vacuum for 16 h at 50 °C. Drying was considered complete when the loss by TGA was less than 1.0% for water. Yield: 19.08 kg (95.5% assay adjusted yield).

1-(1-Propyl)-piperidine-4-carboxylic Acid (8). A 180 L glass lined pressure reactor was pressure checked with nitrogen. Catalyst (5% palladium on carbon (50 wt % water wet, 3.0 kg, 10 wt % on dry basis), piperidine **7** (14.8 kg, 114.6 mol), and ethanol 2B (83 kg, 7 L/kg starting material) were charged to the reactor. A pressure canister was charged with propionaldehyde (12.0 kg, 206.6 mol, 1.8 equiv) and pressure purged with nitrogen before it was pressurized to 55 psi with nitrogen. The reactor was pressure purged three times with hydrogen and pressurized to 40 psi with hydrogen. Propionaldehyde from the pressure canister was added slowly to the reactor over 4.5 h, while a temperature of 25 ± 5 °C was maintained with cooling (ATR = 57 °C). The contents of the reactor were stirred a further 2 h under 40 psi hydrogen before sampling for completion. The reaction was held under hydrogen pressure until analysis showed less than 1.0 PA% starting material. An aliquot was derivatized with BSA (1 mL/10 mg **8**) and analyzed by GC. The reactor was then pressure purged with nitrogen, and the contents were filtered through a bed of filter aid with backup filters. Ethanol 2B (17 kg) was twice charged to the reactor and passed through the filters. The combined filtrates were concentrated under vacuum at not more than 50 °C internal temperature to approximately 73 L. Isopropyl acetate (105 kg) was added, and the mixture was again concentrated under vacuum at not more than 50 °C internal temperature to approximately 73 L. This was repeated for a total of 3 times. During the second distillation the product started to crystallize out and remained as a slurry for the remaining distillation. Isopropyl acetate (130 kg) was added, and the solution was stirred at 25 °C under nitrogen for approximately 7 h. A sample was checked for supernatant concentration of not more than 2.0 mg/mL. The product was filtered and washed with two portions of isopropyl acetate (35 kg, 38 kg). The wet cake was dried under vacuum at not more than 65 °C for not less than 12 h. A dryer sample was assayed for isopropyl acetate. Drying was considered complete when a sample showed less than 0.5% w/w isopropyl acetate. Yield: 17.8 kg (90% assay adjusted yield).

1-Methyl-piperidine-4-carboxylic Acid (2-Amino-3-carbamoyl-phenyl)-amide Hydrochloride (9). To a 100 L

(25) Water content of 0.02 to 0.04% w/w was determined for three runs (0.015 to 0.029 equiv of water). The thionyl chloride charge is adjusted to ensure that more than 1 equiv relative to the sum of substrate and water is added.

flask was charged carbonyldiimidazole (CDI) (7.7 kg, 47.5 mol) and anhydrous NMP (40 kg) under nitrogen. Dissolution was endothermic, and the mixture was warmed to 25 °C to dissolve solids. To a 110 L glass lined reactor was charged **8** (8.2 kg, 47.9 mol) and anhydrous NMP (9 kg), and the resulting slurry was stirred. The CDI solution was added to the slurry of **8** at a rate to control gas evolution. The reaction was slightly endothermic (ATR = −4 °C). When addition was complete, the flask was rinsed with anhydrous NMP (2 kg) and stirred 1 h at room temperature. After 1 h the reaction was sampled. A weighed aliquot was added to excess benzylamine in acetonitrile (sample/benzylamine/acetonitrile 1:1:2 v/v/v) and allowed to react for 30 min prior to HPLC analysis. Reaction was considered complete when the yield of benzylamine amide was >90%. The solution was heated to 50 °C. In a separate 100 L flask, **6** (8.9 kg, 39.7 mol) was dissolved in anhydrous NMP (49 kg) with heating to not more than 30 °C. The resulting solution of **6** was transferred to the solution of acylimidazole, and the temperature was allowed to rise through a mild exotherm (ATR = 22 °C). The reaction was stirred at 50 °C for 18−24 h until **6** was not more than 3 area % of the product peak by HPLC at 210 nm. Product precipitated during the course of the reaction. The contents of the reactor were cooled to room temperature and transferred to a 50 gal reactor using a rinse of NMP (5 kg). To the slurry was added 71 kg of THF to complete the precipitation. The mixture was stirred at room temperature until the concentration of product in the supernatant was not more than 2 mg/mL. The product was filtered. The filter cake was washed with agitation using 10% w/w water in *n*-butanol in portions until the wash liquors had not more than 10 mg/mL NMP. The product was dried under vacuum at not more than 50 °C until solvent levels were not more than 1% NMP and not more than 1% *n*-butanol. Yield: 11.8 kg (86% assay adjusted yield).

2-(1-Propyl-4-piperidinyl)-1*H*-benzimidazole-4-carboxamide (10). A solution of water (60 kg) and glacial acetic (5.4 kg) acid was prepared. To a reactor was charged **9** (11 kg, 32.2 mol), and the solid was dissolved in 55 kg of the acetic acid solution with heating under nitrogen. The solution was filtered into a 115 L glass lined reactor, and the remainder of the acetic acid solution was used as a rinse. The solution was heated to reflux for 4 h (reaction was endothermic), and a sample was taken. Reaction was continued until **9** was not more than 1 area % of the product by HPLC. The reaction was cooled to 20 °C, and the pH of the solution was adjusted to less than 12 by addition of 50% sodium hydroxide. Product precipitated during the addition. The reaction temperature was allowed to rise during the sodium hydroxide addition (ATR = 41 °C). The reaction was cooled to not more than 25 °C and stirred for 1 h. The slurry was checked for completion of precipitation with a supernatant concentration of not more than 1 mg/mL. The product was isolated in a filter dryer and washed with water until sodium in the wash liquors was not more than 20 μg/mL. The product was dried in the filter dryer under vacuum at 50 °C until the water content was not more than 3 wt % by Karl Fischer titration. Yield: 8.2 kg (86% assay adjusted yield).

2-(1-Propyl-4-piperidinyl)-1*H*-benzimidazole-4-carboxamide Succinate Salt (11). A solution of **10** (7.8 kg, 27.3 mol) and succinic acid (3.55 kg, 30.1 mol) in methanol (36 kg) was heated to 60 °C for 30 min. The solution was filtered into a 115 L glass lined reactor, and isopropyl acetate (10.8 kg) was added to the reactor. The solution was held at 50 °C for 30 min, and then the temperature was reduced to 47 °C.

Seed crystals of **11** (0.11 kg) were slurried in isopropyl acetate (1.0 kg) in a 4 L pressure canister and transferred to the reactor with a rinse of isopropyl acetate (0.5 kg). The reactor was held at 47 °C for 3 h, and isopropyl acetate (7.2 kg) was added to the reactor via a subsurface addition tube at 0.7 kg/min. The slurry was mixed for 1 h. Additional isopropyl acetate (7.2 kg) was added to the reactor in the same manner, and the slurry was mixed for 1 h. Isopropyl acetate (28.8 kg) was again added to the reactor in the same manner, and the slurry was held overnight at 47 °C. The slurry was cooled to 25 °C over 1 h and isolated in an agitated filter. The cake was washed with 1:2 w/w methanol−isopropyl acetate (60 kg) followed by isopropyl alcohol (84 kg). The wet cake was blown dry for 1 h in the filter and dried under vacuum at 50 °C overnight using a tray dryer. Drying was considered to be complete when the solid contained not more than 0.5 wt % of isopropanol and isopropyl acetate and not more than 0.3 wt % of methanol. The dried product was milled using a Fitzmill. Yield: 8.53 kg (premilling) (79% assay adjusted yield).

Acknowledgment

The authors thank Dr. Nancy Benz, Mr. Michael Moore, Ms. Christine Havrilla, and Dr. Thomas Gray of Abbott Laboratories for analytical method development and assistance. The authors also thank Shan Lin and Dr. Zhe Wang of Abbott Laboratories for the ARC data.

Supporting Information Available

X-ray crystal data for **9**. Optimization of stoichiometry for steps 2 and 3; optimization of reagent for step 3. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review January 26, 2007.

OP7000194