Organic Process Research & Development **2001**, *5*, 593–598

Discovery and Development of a Commercial Synthesis of Azafenidin

Rafael Shapiro,*,† Robert DiCosimo,‡ Susan M. Hennessey,† Barry Stieglitz,† Onorato Campopiano,† and George C. Chiang†

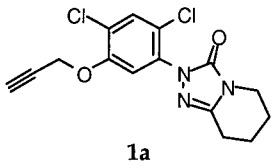
DuPont Agricutural Products and DuPont Central Research and Development, Wilmington, Delaware, 19898, U.S.A.

Abstract:

A commercial synthesis of the DuPont herbicide azafenidin is described. Discovery of a novel synthesis of the triazolinone ring system and a practical, environmentally benign process to 5-cyanovaleramide were critical breakthroughs in enabling azafenidin to be manufactured at an acceptable cost. The process began with the selective hydrolysis of DuPont's nylon intermediate, adiponitrile, to 5-cyanovaleramide. This was converted via Hofmann rearrangement and Pinner-type cyclization to afford the key amidine carboxylate intermediate containing both carbon atoms of the triazolinone ring. The preservation of all six carbon atoms of adiponitrile set up a 2 + 3 cyclocondensation with arylhydrazines, which replaced a costly 4 + 1 cyclocondensation of an amidrazone with phosgene or a phosgene surrogate used in the original route. This new triazolinone process was optimized to afford the commercial product in a highly efficient and economical fashion.

Introduction

Azafenidin (**1a**) is a new, selective preemergence herbicide which was first synthesized in the late 1970s at DuPont[1] and is currently being developed and commercialized in many worldwide specialty markets.

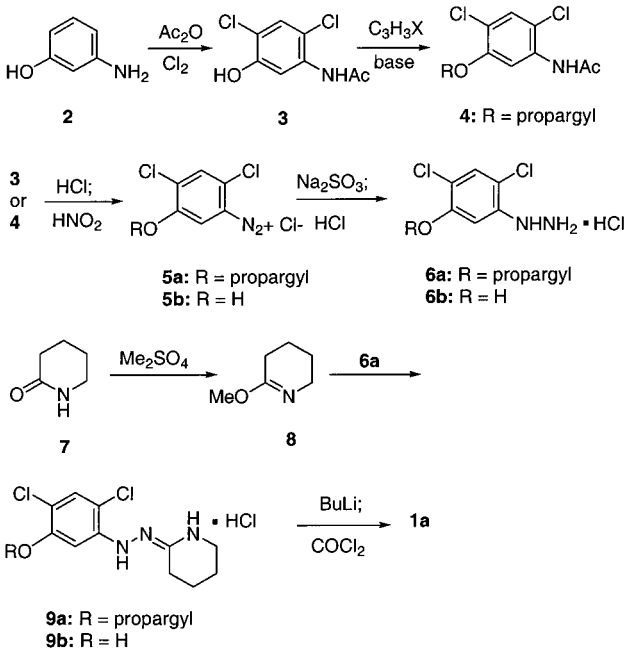


1a

Its good toxicological profile, low residual levels in edible commodities, favorable ecological profile, low mobility in soils, and relatively rapid soil degradation are among its most favorable attributes. However, its development presented process scientists with the considerable challenge of meeting the cost requirements of the specialty-herbicide marketplace.

The original laboratory synthesis is outlined in Scheme 1, wherein the arylhydrazine **6a** was prepared by the classical Fischer hydrazine synthesis and coupled with imino ether **8** to form amidrazone **9a**. Amidrazone **9a** was converted to its dilithio derivative and cyclized with phosgene to afford azafenidin.

Scheme 1



Upon scrutiny of this route by process chemists, several barriers to commercialization presented themselves. Of greatest concern was the use of expensive and hazardous reagents, namely butyllithium, phosgene, and propargyl bromide. Second, hydrolysis and diazotization of **4a** generated a relatively insoluble diazonium salt **5a**, which presented difficulties of productivity, mixing efficiency, and most of all, operational safety. Furthermore, δ-valerolactam **7** was not commercially available in sufficient quantity, and toll-manufacture would have been rather costly. In the course of trying to find a more economical route to δ-valerolactam, a serendipitous discovery led to the development of an entirely new process. This avoided the troublesome cyclization of **9a** and made the new route a viable one for manufacture of the herbicide.[2]

New Route Discovery

Addressing the most critical issue first, we sought a more suitable replacement for the *n*-butyllithium/phosgene system in the last step. Various simple, nonhazardous bases and carbonates were tried, but with only limited success: reactions were generally sluggish, leading under forced conditions to poor yields of triazolinone and many uncharacterized side products. Two "phosgene equivalents" which provided good

* To whom correspondence should be addressed. Current address: Bristol-Myers Squibb Pharmaceuticals Co. E-mail: rafael.shapiro@dupontpharma.com. Telephone: (302) 695-2463. Fax: (302) 695-4632.

† DuPont Agricutural Products.

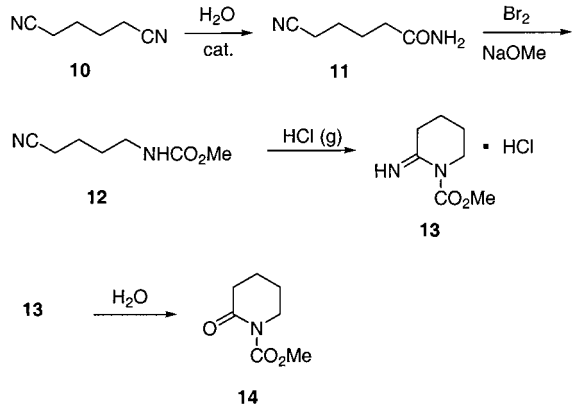
‡ DuPont Central Research and Development.

(1) Wolf, A. D. U.S. Patent 4,139,364, 1979; Wolf, A. D. U.S. Patent 4,213,773, 1980.

(2) Shapiro, R. U.S. Patent 5,705,639, 1998.

10.1021/op9901994 CCC: $20.00
Published on Web 10/23/2001

Scheme 2

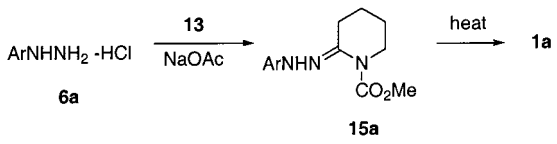


yields of **1a** were eventually found: 1,1′-carbonyldiimidazole and benzenesulfonyl isocyanate. Either of these was a significant improvement, but recovery of the coproduct, imidazole or benzenesulfonamide, would have been required for either method to be economical. This additional processing would not have been a simple matter.

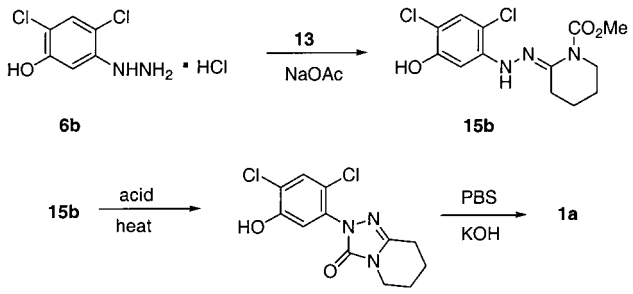
At the same time, we found that propargyl benzenesulfonate (PBS) was preferable as a propargylating agent for phenols than either the volatile chloride or the shock-sensitive bromide. Its stability was confirmed by differential-scanning calorimetry (DSC) and accelerated reaction calorimetry (ARC). Furthermore, it is prepared quite easily by the reaction of propargyl alcohol with benzenesulfonyl chloride in aqueous caustic, and the crude organic layer can be used as such after phase separation.[3] High yields of propargyl ether, **4a**, were obtained by reacting **3** with PBS and aqueous KOH/K_2CO_3 in toluene and 5 mol % of tetraethylammonium bromide as a phase-transfer catalyst. Dichloroacetamidophenol **3** was prepared in 65% yield by a modification of a literature procedure,[4] whereby *m*-aminophenol was treated with 1 equiv of acetic anhydride, followed by 2 equiv of chlorine. The propargyl ether was hydrolyzed with 18% aqueous HCl in methanol, directly diazotized after removal of methanol, reduced with sulfite, and hydrolyzed with aqueous HCl to afford **6a** in 82% yield over three steps. The propargylation step could be omitted to afford **6b**, the alternative hydrazine component in the process (see below). We then began to address the important issue of the piperidine portion of the azafendin molecule (Scheme 2).

While exploring alternative routes to δ-valerolactam or derivatives, we found that an attractive strategy was to partially hydrolyze inexpensive adiponitrile (ADN, **10**) and convert the resulting 5-cyanovaleramide (**11**) to *N*-cyanobutylcarbamate, **12**, using a methanolic variant of the Hofmann rearrangement. During the course of cyclization studies, we discovered that **12** reacted cleanly in aprotic solvents with anhydrous HCl to form the novel imidate derivative **13**. Subsequent hydrolysis afforded **14**, the *N*-methoxycarbonyl derivative of **7**. According to a Schering patent,[5] **14** had been condensed with arylhydrazines related

Scheme 3



Scheme 4



to our substrate to form analogues of **1a**, albeit in low yield. We were unable to produce significant quantities of **1a** by this method, however.

Returning to intermediate **13**, we discovered that under anhydrous conditions, in the presence of 1 equiv of a weak base such as pyridine or sodium acetate, it could be condensed with **6a** to form amidrazone carboxylate **15a** in excellent yield (Scheme 3). Heating this material in xylene at reflux afforded azafenidin along with many uncharacterized byproducts. Upon further experimentation, it was found that the cyclization of **15a** is catalyzed by a weak acid, for example, acetic acid, thus allowing the reaction to be conducted at significantly lower temperatures and shorter reaction times, affording a purer product and upwards of 10% higher yields. We speculate that the acid catalyst functions by causing **15a** (assumed to be of the *E*-configuration) to isomerize to the *Z*-isomer which can then rapidly close to form methanol and the triazolone.

The discovery of this new process proved to be even more critical than was realized at the time. We had expected our supplier to provide commercial quantities of the arylhydrazine **6a**, but due to the aforementioned diazotization problems, we were required instead to use phenolic hydrazine **6b**, which was much more amenable to large-scale manufacture. The original process would not have been compatible with the phenolic substrate, but now **6b**, obtained in 70% overall yield from **3** by the Fischer hydrazine synthesis described above, could be condensed with the iminopiperidine salt **13** to afford an 85% isolated yield of **15b**. This was cyclized to **1b** which was not isolated but was directly propargylated with PBS to afford **1a**, in 93% yield from **15b** (Scheme 4).

Process Optimization

Nitrile Hydration. The first step in the process was the selective hydration of ADN to 5-cyanovaleramide (**11**). Of the several chemical methods available in the literature,[6] none was as attractive for kilogram-scale synthesis as an unpublished method discovered in our Nylon department several years previously.[7] This involved the use of manganese dioxide with a stoichiometric amount of water in neat ADN.

(3) Reppe, W. *Liebig's Ann. Chem.* **1955**, *596*, 1.
(4) Jacobs, W. A.; Heidelberger, M.; Rolf, I. P. *J. Am. Chem. Soc.* **1919**, *41*, 458.
(5) Blume, F.; Franke, W.; Arndt, F.; Rees, R. U.S. Patent 4,859,230, 1989.

The reaction was run to 25% conversion and 80% selectivity to **11**; polar byproducts such as adipamide were left in the spent MnO_2 cake after dilution with toluene and filtration. Cooling the hot toluene filtrate precipitated anhydrous 5-cyanovaleramide in a high state of purity; recovery and recycle of unreacted ADN was achieved by concentration of the mother liquor. Although this was an expeditious way to obtain pilot-plant quantities of quality **11**, the consequences of disposing of or recycling large quantities of manganese dioxide provided incentive to find a "greener" process, and thus enzyme-catalysis was investigated.

Aliphatic nitriles are readily hydrolyzed to the corresponding amides by the nitrile hydratase (EC 4.2.1.84) of a variety of bacteria and fungi.[8] In the present case, we required sufficient regioselectivity to minimize adipamide formation; the absence of amidase activity that could result in carboxylic acid formation was also important. A variety of microbes were evaluated, and *Rhodococcus erythropolis* A4[9] was initially selected for process development.

R. erythropolis A4 cells were immobilized in calcium alginate beads prior to use. Hydrolysis reactions were run at 5 °C, as the stability of the enzyme decreased markedly above this temperature. Batch reactions in 20 mM sodium butyrate/5 mM $CaCl_2$ buffer were begun as a three-phase mixture of ADN and a suspension of catalyst beads in 20 mM sodium butyrate/5 mM $CaCl_2$ (pH 7.0) to produce 0.75 M 5-cyanovaleramide. Extending the reaction time once conversion was nearly complete caused very slow conversion of **11** to adipamide. Catalyst recycle was accomplished simply by removing 90% of the solution phase, followed by the addition of ADN and buffer to the heel. Sixty consecutive batch reactions converted a total of 2400 lb of adiponitrile to afford a 9.0 wt % solution of **11** in 93% yield, with a catalyst productivity (kg/kg) of greater than 1000/1. Isolation of **11** consisted of distillation of water, dissolution in boiling methanol, and filtration of insoluble adipamide and salts. The resulting methanolic solution was suitable for use in the subsequent step.

The nitrile hydratase of *R. erythropolis* A4 is unusual in that it requires a light-activation step,[10] and the microbial enzyme so activated will rapidly lose activity if stored in the absence of light prior to use. The requirement of light activation of the cells during harvesting from fermentation broth added additional cost to catalyst manufacture. With more extensive screening we identified a more desirable catalyst. *Pseudomonas chlororaphis* B23 had been first isolated and characterized by H. Yamada and co-workers[11] and was later used in immobilized form by the Nitto Chemical Industry Co. (now merged with Mitsubihi Rayon Co.) for the manufacture of acrylamide from acrylonitrile.[12] This highly selective monohydration method now did not require an activation step and furthermore proved to be superior in both enzyme stability and productivity to *R. erythropolis* A4.

The first commercial-scale production of **11** using the *P. chlororaphis* B23/alginate beads converted a total of 12.7 Mt of ADN in 58 consecutive 400-gal batch reactions with catalyst recycle. Using the same procedures and conditions as previously defined, now it was possible to produce a final product concentration of 1.5 M (19 wt %) in the aqueous buffer, increasing the reaction time from 3.5 to 5.5 h. At 97% conversion of ADN, 13.6 Mt (93%) of 5-cyanovaleramide was obtained, now with a productivity (kg/kg) of 3150/1.

Hofmann Rearrangement and Pinner Cyclization. Scale-up of the Hofmann rearrangement of **11** presented the challenge of safely generating and reacting large quantities of the high-energy *N*-bromoamide salt. The best methods we could find in the literature for generating high yields of methyl carbamates from amides in methanol involved the use either of very low temperature[13] or rapid decomposition.[14] We found an improved and more practical procedure was to form the sodium salt of the *N*-bromoamide by adding exactly 1 equiv of bromine to a solution of **12** in methanol containing slightly more than 2 equiv of sodium methoxide at 0−5 °C. Accelerated-rate calorimetry (ARC) tests of methanol solutions thus generated showed that in case cooling was lost the intermediate would be stable for ca. 24 h before an uncontrollable reaction would occur. The safest way to conduct the exothermic decomposition to **11** was thus to feed the cold solution of the intermediate to boiling methanol, whereby yields of 92−94% could be consistently achieved on a large scale.

The intramolecular Pinner-type reaction of **11** was originally conducted in diethyl ether to provide crystalline **13**; replacing this hazardous solvent with a more suitable one such as toluene resulted in the precipitation of **13** as an oil which trapped HCl, making the material hygroscopic and difficult to carry into the subsequent step. To induce

(6) (a) Berther, C. *Chem. Ber*. **1959**, *92*, 2616 [basic ion-exchange resin]; (b) Wiley: R. H.; Morgan, H. S., Jr. *J. Org. Chem.* **1950**, *15*, 800 [basic hydrogen peroxide]; (c) Zil'berman, E. N.; Kulikova, A. E. *J. Gen. Chem. USSR* **1959**, *29*, 1671 [HCl gas/ether]; (d) Witzel, T.; Fuchs, E.; Merger, F. U.S. Patent 5,347,033, 1994 [Cu catalyst].

(7) Sieja, J. Personal communication.

(8) (a) Holland, H. L. *Curr. Opin. Chem. Biol.* **1998**, *2*, 77. (b) Sugai, T.; Yamazaki, T.; Yokoyama, M.; Ohta, H. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1419. (c) Meth-Cohn, O.; Wang, M.-X. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3197. (d) Hoenicke-Schmidt, P.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.*, **1990**, 648. (e) Blakey, A. J.; Williams, E.; O'Reilly, C. *FEMS Microbiol. Lett.* **1995**, *129*, 57. (f) Crosby, J.; Moilliet, J.; Parrat, J. S.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1679. (g) DeRaadt, A.; Klempier, N.; Faber, K. T.; Griengl, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 137. (h) Yokoyama, M.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1081. (i) Cohen, M. A.; Sawden, J.; Turner, N. J. *Tetrahedron Lett.* **1990**, *31*, 7223.

(9) (a) Bernet, N.; Arnaud, A.; Galzy, P. *Biocatalysis* **1990**, *3*, 259. (b) Ingvorsen, K.; Godtfredsen, S. E.; Tsuchiya, R. T. *Ciba Found. Symp.* **1988**, *140* (*Cyanide Compd. Biol.*), 16. (c) Andresen, O.; Godtfredsen, S. E. 178106 B1, 1993.

(10) (a) Nagamune, T.; Kurata, H.; Hirata, M.; Honda, J.; Hirata, A.; Endo, I. *Photochem. Photobiol.* **1990**, *51*, 87. (b) Honda, J.; Kandori, H.; Okada, T.; Nagamune, T.; Shichida, Y.; Sasabe, H.; Endo, I. *Biochemistry* **1994**, *33*, 3577.

(11) (a) Nagasawa, T.; Nanba, H.; Ryuno, K.; Takeuchi, K.; Yamada, H. *Eur. J. Biochem.* **1987**, *162*, 691. (b) Yamada, H.; Ryuno, K.; Nagasawa, T.; Enomoto, K.; Watanabe, I. *Agric. Biol. Chem.* **1986**, *50*, 2859. (c) Asano, Y.; Yasuda, T.; Tani, Y.; Yamada, H. *Agric. Biol. Chem.* **1982**, *46*, 1183.

(12) (a) Ashina, Y.; Suto, M. *Bioprocess Technol.* **1993**, *16*, 91. (b) Kobayashi, M.; Nagasawa, T.; Yamada, H. *Trends Biotechnol.* **1992**, *10*, 402. (c) Nagasawa, T.; Ryuno, K.; Yamada, H. *Experientia* **1989**, *45*, 1066. (d) Ryuno, K.; Nagasawa, T.; Yamada, H. *Agric. Biol. Chem.* **1988**, *52*, 1813.

(13) Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290.

(14) Murr, B. L.; Lester, C. T. *J. Am. Chem. Soc.* **1955**, *77*, 1684.

crystallization, it was necessary to vacuum-purge the excess HCl (ca. 2 equivalents were required for complete conversion) and add an oxygenated solvent such as THF or acetone. The solids could then be filtered and washed to afford pure material.

Hydrazine Coupling and Triazolone Cyclization. Couplings of **13** with hydrazine hydrochloride salts were optimally performed in acetonitrile or alcohol solvents in the presence of 1.5−2 equiv of anhydrous sodium acetate to maintain an effective pH of 4−5; more basic conditions generally led to greater proportions of ring-opened products. Attempts to carry the crude reaction mass into the next (cyclization) step were unsuccessful; therefore, product isolation by dilution with water and filtration and drying was required. Optimum yields of 85−88% were obtained by this procedure.

Several acids and solvents were tested for the cyclization reaction. The preferred catalyst was tetrabutylammonium hydrogen sulfate in most cases; acetone was chosen as solvent for the preparation of **1b**, since that was the preferred solvent for the final propargylation step. This requires the use of scrupulously anhydrous acetone, since, in the presence of acid, any water present causes hydrolysis of **15b**, generating **14** and the acetone hydrazone of **6b**. The highly colored impurities unavoidably generated during the acid-catalyzed cyclization are easily eliminated due to the low solubility of **1b**, which is an added advantage to this approach.

The propargylation of **1b** to afford azafenidin was optimally carried out using acetone as solvent and potasssium hydroxide as base, since this combination provided high solubility of the phenoxide. The effective pH was kept at 11−12 to maximize the rate of coupling relative to hydrolytic decomposition of PBS. In addition to the many aforementioned advantages of the ultimate process, PBS usage was minimized by alkylating the phenol at the final step rather than earlier in the process.

Experimental Section

General. Unless otherwise indicated, all solvents used were commercial-grade and used without further purification. All reactions were conducted under nitrogen. Reaction yields (referred to herein as "a.i. yields") were determined by HPLC wt % analysis versus an analytical standard. Activated manganese (IV) oxide was purchased in bulk from Chemetals Corp., Baltimore, MD. Sodium alginate (Protonal LF 10/60) was obtained from Pronova Biopolymers. *P. chloraphis* B23 cell suspensions obtained from Mitsubishi Rayon Co. were stored at −80 °C. 2,4-Dichloro-5-acetamidophenol (**3**) was prepared by a modification of a literature procedure. Details of the biotransformation have been published elsewhere.[15]

5-Cyanovaleramide (11): MnO_2 Method.[7] To 108 g (1.00 mol) of adiponitrile, 1 mL of water, 3 g of Celite, and 20 g of activated manganese dioxide, heated with efficient stirring to 125−130 °C, was added 6 mL of water, maintaining the inside temperature at 120−130 °C. After the addition was complete (about 1 h), the mixture was maintained at 130−135 °C with good stirring for 3 to 4 h longer. The condenser was allowed to remain warm to avoid plugging by ammonium carbonate. The mixture was allowed to cool to 60 °C and filtered. The filter cake was washed with three 80-mL portions of hot (55−60 °C) toluene, and the combined filtrate and washings were cooled under nitrogen to 0−5 °C and kept for 2 h. The product was filtered, washed several times with small portions of toluene, and suction-dried to afford 21 g (20−25% based on unrecovered adiponitrile) of **11**. The unreacted adiponitrile recovered by concentration of the filtrate in vacuo is of sufficient purity to be recycled to subsequent batches.

Methyl *N*-(4-Cyanobutyl) Carabamate (12). A solution of 88.6 g (0.410 mol) of 25 wt % sodium methoxide in methanol, 100 mL of methanol, and 25.2 g (0.200 mol) of 5-cyanovaleramide was cooled to 0−5 °C, and bromine (32.5 g, 0.203 mol) was added over 30 min. Meanwhile, a separate vessel was charged with 150 mL of methanol, and the methanol was brought to reflux. The cold slurry from the bromination reaction containing the N-bromoamide and sodium bromide was transferred by cannula over 20−30 min, maintaining the temperature of the heated mixture at 55−60 °C. The majority of the methanol (about 200 mL) was then distilled at atmospheric pressure, and 300 mL of toluene was added. The remaining methanol was then removed by azeotropic distillation with toluene at 60−65 °C. Sodium bromide was then removed by filtration to provide a ca. 18% toluene solution suitable for use in the subsequent step of the synthesis. The pure product may also be isolated by rotary evaporation to provide 29.4 g (94% crude yield) of **12** as a yellow or orange oil of 94−97% purity according to GC analysis. NMR ($CDCl_3$) δ 1.6 (m, 4H), 2.35 (t, 2H, $J = 6$ Hz), 3.18 (q, 2H, $J = 6$ Hz), 3.61 (s, 3H), 4.9 (br s, 1H). An analytical sample was obtained by short-path vacuum distillation, bp 140 °C/1 mm.

Methyl 2-Imino-1-piperidinecarboxylate Hydrochloride (13). A solution of 47 g (0.30 mol) of **12** in 300 mL of toluene was stirred with cooling in a bath maintained at 15−20 °C and HCl gas (33 g, 0.91 mol) was passed in during 2 h. A stream of nitrogen was passed vigorously through the well-stirred mixture with cooling at 10−15 °C for 1 h to purge excess HCl. Anhydrous THF (50 mL) was added to dissolve some slightly oily material, and the mixture was purged with nitrogen under reduced pressure for 30 min at 15−20 °C. The mixture was filtered, washed with two 20 mL portions of dry THF, and the cake was dried in vacuo at ambient temperature to provide 51.0 g (89%) of **13** as a white solid, mp 118−119 °C. ^{1}H NMR ($CDCl_3$) δ 1.7 (t, 2H, $J = 6$ Hz), 1.8 (t, 2H, $J = 6$ Hz), 3.15 (t, 2H, $J = 6$ Hz), 3.8 (t, 2H, $J = 6$ Hz), 3.82 (s, 3H), 10.2 (br s, 1H), 12.75 (br s, 1H).

***N*-(2,4-Dichloro-5-propargyloxyphenyl)acetamide (4a).** A solution of 38.0 g (0.577 mol) of 85% potassium hydroxide, 8.0 g (0.065 mol) of potassium carbonate, 6.0 g

(15) (a) DiCosimo, R.; Hann, E. C.; Eisenberg, A.; Fager, S. K.; Perkins, N. E.; Gallagher, F. G.; Cooper, S. M.; Gavagan, J. E.; Stieglitz, B.; Hennessey, S. M. Green Chemical Syntheses and Processes. *ACS Symp. Ser.* **2000**, *767*, 114. (b) Hann, E. C.; Eisenberg, A.; Fager, S. K.; Perkins, N. E.; Gallagher, F. G.; Cooper, S. M.; Gavagan, J. E.; Stieglitz, B.; Hennessey, S. M.; DiCosimo, R. *Bioorg. Med. Chem.* **1999**, *7*, 2239.

(0.028 mol) of tetraethylammonium bromide, and 800 mL of water was stirred, and 132 g (0.596 mol) of **3** was added. The resulting clear solution was then heated to 65 °C, and 132 g (0.673 mol) of propargyl benzenesulfonate was added dropwise over 20 min with vigorous stirring. The temperature was raised to 75 °C and held for 1 h. The mixture was cooled to 35 °C, filtered, and washed with water. The product was then suction-dried to provide 145 g of **4a** as a tan solid, which had an assay of 98% (92% yield). ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.57 (t, 1H, J = 2.4 Hz), 4.78 (d, 2H, J = 2.4 Hz), 7.37 (s, 1H), 7.6 (br s, 1H), 8.36 (s, 1H).

(2,4-Dichloro-5-propargyloxy)phenylhydrazine Hydrochloride (6a). A mixture of 81.0 g (0.313 mol) of **4a**, 240 g (341 mL) of methanol, 90 mL of water, and 96 g (1.0 mol) of 37% HCl (aq) was heated to reflux (75 °C), whereupon it became a reddish-brown solution which was held for a total of 2 h at 75 °C. Water (420 mL) was added, and the solution was allowed to cool to 45 °C. The condenser was replaced by a distillation head with a 20-cm Vigreux column, and methanol was distilled at 130 mm. When the pot temperature reached 60 °C, the distillation was terminated, 600 mL of water was added, and the slurry was cooled to 0−5 °C. A solution of sodium nitrite (21.4 g, 0.31 mol) in 60 mL of water was added over 15 min, and the resulting slurry was stirred for an additional hour at 0−5 °C. Meanwhile, a 2-L three-necked flask equipped with an overhead stirrer, nitrogen inlet, thermometer, and pH probe was charged with 300 mL of water, 90 g (0.714 mol) of sodium sulfite, and 3.0 g (0.022 mol) of sodium dihydrogen phosphate monohydrate. The reducing medium was cooled to 0−5 °C, and the slurry of the diazonium salt was added over 5−15 min, during which time the pH fell from an initial value of 7.4 to 5.8−6.2. The pH was adjusted to pH 6.3, and the mixture was gradually warmed to 65 °C over 1 h and held at that temperature for an additional hour. The resulting disodium arylhydrazine disulfonate solution was clarified by filtration and concentrated to a volume of 790 mL (913 g) at reduced pressure. Meanwhile, a second flask was charged with 750 mL of 37% HCl, which was heated to 40 °C. The concentrated reduction solution was then added in portions over 20−30 min, keeping the acidic hydrolysis mixture at 45−50 °C. After the addition was complete, the mixture was stirred for an additional 60 min at 40−45 °C, cooled to 10−15 °C, and filtered. The light purple filter cake was washed with three 100-mL portions of ice−water to remove inorganic salts, and the product was suction-dried under nitrogen for 2 h. Final drying in the vacuum oven at 50 °C for 2 days provided 74.5 g of purplish-tan material having an assay of 92% (82% yield). ^{1}H NMR (DMSO-d_6) δ 3.7 (s, 1H), 4.9 (s, 2H), 7.3 (s, 1H), 7.5 (s, 1H), 8.2 (br s, 1H), 10.6 (br s).

(2,4-Dichloro-5-hydroxy)phenylhydrazine Hydrochloride (6b). This was prepared by a procedure similar to the one described above, except that the decomposition of the intermediate disulfonate salt was carried out by co-feeding the aqueous HCl and disulfonate to aqueous HCl containing seeds of the final product. The crude product was heavily contaminated with sulfate salts and was thus dissolved in methanol and assayed by HPLC before proceeding to the synthesis of **15b**.

Methyl 2-[(2,4-Dichloro-5-(propargyloxy)phenyl)-hydrazono]-1-piperidinecarboxylate (15a). To a suspension of 13.3 g (0.045 mol, assay 92%) of **6a** in 80 mL of acetonitrile was charged 12.3 g (0.150 mol) of anhydrous sodium acetate. The suspension was allowed to stir for 30 min at ambient temperature and was then cooled to 0−5 °C before charging 10.6 g (0.055 mol) of **13**. After 1 h, the mixture was poured onto ice−water, filtered, washed with water, suction-dried, and dried in the vacuum-oven at 50 °C for 3 h to provide 16.8 g of **15a** as a reddish solid. The crude product was purified by washing with 20−30 mL of cold 2-propanol and suction-dried to afford 16.0 g (95%) of pink material, HPLC assay = 96%, mp 137−138 °C. ^{1}H NMR ($CDCl_3$) δ1.74 (m, 2H), 1.82 (m, 2), 2.46 (t, 2H, J = 6 Hz), 2.52 (t, 1H, J = 2.4 Hz), 3.68 (t, 2H, J = 6 Hz), 3.73 (s, 3H), 4.75 (d, 2H, J = 2.4 Hz), 7.13 (s, 1H), 7.23 (s,1H), 7.26 (br s, 1H).

Methyl 2-[(2,4-Dichloro-5-hydroxyphenyl)-hydrazono]-1-piperidinecarboxylate (15b). A mixture of 18.5 g (0.226 mol) of anhydrous sodium acetate in 320 mL of methanol was cooled to −20 °C, 28.8 g (0.150 mol) of **13** was added, followed by 34.8 g (0.146 mol) of **6b** added over 20 min. The mixture was allowed to stir at −10 to 0 °C for 1 h, and then it was poured into 500 mL of a well-stirred mixture of water and ice. The product was filtered, washed with three 100-mL portions of water, and dried under reduced pressure to afford 44.6 g (92%) of **15b** as an orange solid, mp 158−159 °C. ^{1}H NMR (DMSO-d_6) δ 1.7 (m, 4H), 2.5 (t, 2H, J = 5.4 Hz), 3.57 (t, 2H, J = 5.4 Hz), 3.64 (s, 3H), 7.00 (s, 1H), 7.27 (s, 1H), 8.15 (br s, 1H), 10.3 (br s, 1H).

2-(2,4-Dichloro-5-hydroxyphenyl)-5,6,7,8-tetrhydro-1,2,4-triazolo[4,3-a]pyridin-3(2*H*)-one (1b). A slurry of 500 g of **15b** (1.46 mol) in 1 L of a 5% (v/v) solution of glacial acetic acid in dry ethyl acetate was heated at 65−70 °C for 4 h. Hexanes (500 mL) was added gradually, and the mixture was allowed to cool to ambient temperature. The dark red mixture was filtered, and the crystalline solid was slurry-washed with hexanes and then with cold 2-propanol. The product was suction-dried to yield 392 g of 98%-pure **1b** (89% yield) as a light brown solid, mp 218−219 °C. ^{1}H NMR (DMSO-d_6) δ 1.8 (m, 4H), 2.6 (t, 2H, J = 6 Hz), 3.50 (t, 2H, J = 6 Hz), 7.09 (s,1H), 7.60 (s, 1H), and 10.9 (br s, 1H).

Azafenidin (1a): Method A. A mixture of 10.0 g (25.3 mmol) of **15a**, 50 mL of toluene, and 0.50 g (8.3 mmol) of acetic acid was heated to reflux, and solvent was distilled over a 1-h period while a stream of nitrogen was slowly passed through the distillation apparatus. The solution was allowed to cool to 70 °C, and 50 mL of hexane was added gradually to precipitate the product. After the mixture was allowed to cool to ambient temperature, the crude product was filtered, washed with hexanes, and suction-dried to afford 8.0 g (94%) of pink azafenidin, mp 168−169 °C, ^{1}H NMR ($CDCl_3$) δ 1.9 (m, 4H), 2.55 (t, 1H, J = 2.4 Hz), 2,74 (t, 2H, J = 6 Hz), 3.67 (t, 2H, J = 6 Hz), 4.74 (d, 2H, J = 2.4 Hz), 7.13 (s, 1H), 7.50 (s, 1H).

Method B. To 150 g (0.490 mol) of **1b** in 300 mL of acetone were added 34.0 g (0.516 mol) of 85% KOH and 5 g (0.036 mol) of potassium carbonate in 30 mL of water. The mixture was heated to reflux (63 °C), and 110 g (0.57 mol) of propargyl benzenesulfonate was added dropwise over 30 min, maintaining the temperature at 60−65 °C. The resulting slurry was heated until the reaction was nearly complete, and then 120 mL of acetone was distilled. The reaction mixture was allowed to cool to ambient temperature, and 600 mL of cold water was added. The product was filtered, washed sequentially with water, cold 2-propanol, and hexanes. The product was dried in the vacuum oven at 50 °C overnight to provide 160 g of 96%-pure azafenidin (97.5% yield).

Acknowledgment

We thank Carl Reinbold, Don Farrell, Dave Suchanec, Sandra Griswold, Amy Eisenberg, and John Gavagan for invaluable technical assistance, and Edward Silveira, Wen Chang, Dan Robson, and Steven Platz for analytical support.

Received for review November 13, 1999.

OP9901994