Organic Process Research & Development **2003**, *7*, 1043–1047

Safety vs Efficiency in the Development of a High-Energy Compound

Sally Gut Ruggeri,* David R. Bill, Dennis E. Bourassa, Michael J. Castaldi, Tim L. Houck, David H. Brown Ripin, Lulin Wei, and Neil Weston†

Pfizer Inc., Chemical Research and Development, Pfizer Global Research Division, Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

A scalable route to 5-(2-carboxy-pyridin-2-yloxy)-benz[1,2,5]-oxadiazole (3) is demonstrated. The synthesis was designed to minimize potential safety issues with a previously practiced route and, in particular, to avoid the handling of 5-hydroxybenzofurazan, which was found to decompose with a large energy release at relatively low temperatures. The new route builds the benzofurazan moiety onto a nicotinonitrile core to avoid high-energy intermediates with low onset temperatures of decomposition.

Introduction

During the early development of a medicinally active compound, the most important goal is the identification of an efficient, environmentally friendly route that is adequate to supply the demand for material. Usually, this requires defining the shortest possible route that utilizes inexpensive, readily available starting materials and reagents and that translates well to larger scale. In certain instances, however, other factors can override the focus on efficiency as defined by step count. Discussed below is a recent example from our laboratories in which a shorter synthesis was rejected in favor of a longer one due to safety considerations.

Initial Synthesis

Acid **3** (Scheme 1) needed to be prepared on multikilogram scale to support a developmental candidate. The initial route to **3** involved the coupling of 5-hydroxybenzofurazan (**1**) with an alkyl ester of 2-chloronicotinic acid. The coupling could be achieved either as a neat melt or in a high-boiling solvent such as dimethylformamide (DMF) in the presence of a base (Table 1, entries 1−2). The reaction was complete within a few hours under the melt conditions but required ≥11 days when run in solution. After the coupling, the ester was hydrolyzed to the acid under standard conditions. From a scale-up perspective, neither alternative for the initial reaction was attractive, since transfers of neat mixtures can be difficult, and tying up equipment for multiday reactions is an inefficient use of resources.

The benzofurazan moiety is not one that is commonly utilized in the pharmaceutical industry; therefore, we had relatively little experience with its properties at the outset of our investigation. Before beginning experimentation, we

Scheme 1

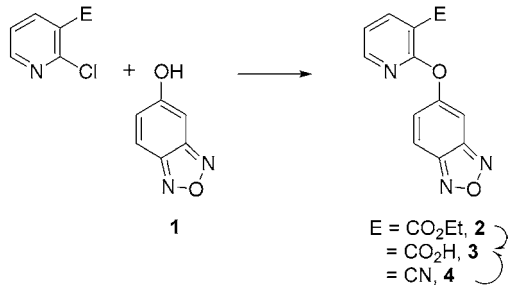


Table 1

entry	E	conditions	yield (%)
1	CO_2Et	170 °C, 4 h	85
2	CO_2Et	K_2CO_3, DMF, 90 °C, 11 d	40−45
3	CO_2H	CuI, KO^{t}Bu, pyridine, 120 °C	25
4	CN	KO^{t}Bu, DMAC, 55 °C	67

decided to collect as much information as possible regarding its physical properties. One of the first analyses we performed was differential scanning calorimetry (DSC) measurements to gauge the thermal stability of the intermediates and products containing it. We discovered that 5-hydroxybenzofurazan has a relatively low onset temperature of decomposition, with a large energy release (2664 J/g, onset @133 °C). The intermediates containing it have similar energy releases, but at higher onset temperatures (**2**: 1490 J/g, onset @237 °C; **3**: 1500 J/g, onset @194 °C). These data meant that the neat melt conditions would not be viable to operate from a safety perspective, since the reaction temperature would exceed the onset of decomposition, precluding effective engineering controls. We were also not comfortable utilizing the DMF procedure, since we felt that the reaction temperature was too close to the decomposition onset temperature and the solvent would not provide a boiling point barrier in the event of overheating.[1]

Development of a Safer Route

Our first attempt to improve the coupling was to survey a wide variety of solvents and bases, to see if the reaction would occur in a reasonable period of time and at a lower temperature. We were not able to identify any conditions that substantially improved the original DMF reaction, and

* Corresponding author. Telephone: (860) 441-5437. Fax: (860) 441-3630. E-mail: sally_gut@groton.pfizer.com.

† Current address: AstraZeneca Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, UK.

(1) Additional safety testing was carried out on this step, including accelerating rate calorimetry (ARC) and vent-sizing experiments. The data from these experiments indicated that adequate engineering controls were not possible in the intended manufacturing equipment.

10.1021/op0341059 CCC: $25.00 © 2003 American Chemical Society
Published on Web 10/01/2003

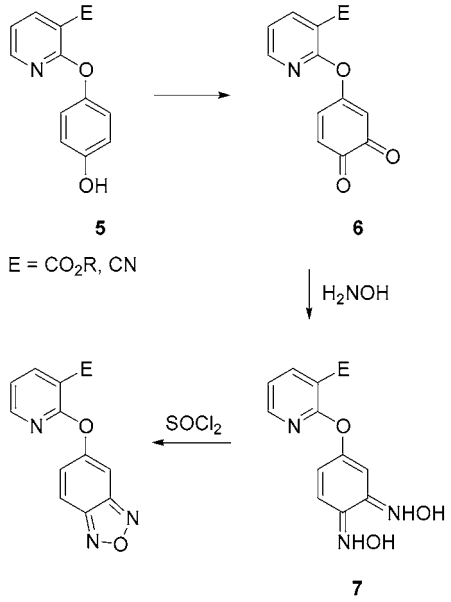
we began to look at alternate electrophilic coupling partners. The most direct route to acid **3** would utilize the Ullman coupling of **1** with 2-chloronicotinic acid (Table 1, entry 3). This coupling reaction did proceed to provide the desired product under a variety of conditions, although the best conditions still needed high reaction temperatures, and given the difficulty in removing the copper from the organic products, only a 25% yield was obtained after chromatography. In addition, the starting 5-hydroxybenzofurazan and product (acid **3**) were both found to decompose when exposed to copper(0), copper(1), and copper(2) salts under conditions similar to those for the coupling reaction. Due to the instability of the reagent and product to the reaction conditions, the yield of the product did not seem likely to improve, and we did not pursue this route further.

We next decided to investigate the nicotinonitrile analogue, reasoning that it should be a better electrophile than either the ester or acid. The switch to 2-chloronicotinonitrile proved to be very successful (Table 1, entry 4). The coupling with **1** occurred at reasonable temperatures and dilution conditions, and the desired product (**4**) was isolated on laboratory scale in 67% yield.

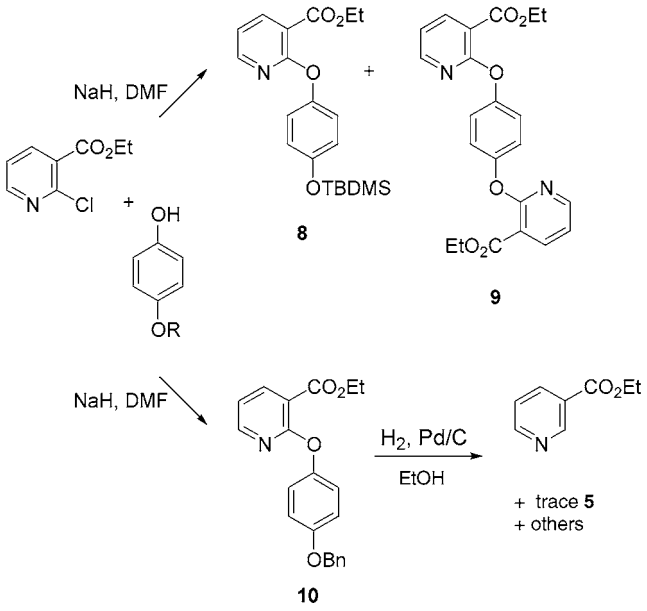
While the nitrile-based approach was feasible for scale-up, we were still not satisfied with it because of the need for shipping, storing, and reacting the 5-hydroxybenzofurazan. The trend we had observed in acquiring DSCs of the intermediates suggested that higher-molecular weight compounds containing the benzofurazan moiety would be expected to have an onset temperature of decomposition high enough to be able to operate within normal reaction ranges with a good safety margin. We wanted to avoid having low-molecular weight species with the relatively unstable functional group. Therefore, we undertook an investigation into building the benzofurazan onto the nicotinic core of the desired product.

There are not many approaches to furazans described in the literature[2] that are amenable to large-scale synthesis. The method that appeared to be most benign from a safety and handling perspective utilizes the cyclodehydration of a bis-(oxime).[3] The potential application of this methodology to the system of interest in shown in Scheme 2. The requisite bis(oxime) (**7**) might be accessible via an ortho quinone precursor (**6**), which in turn might arise from a phenol derivative (**5**). We began to investigate this approach by considering ways to access **5**, which would require the coupling of a monoprotected dihydroquinone with 2-chloronicotinic esters or nitriles (Scheme 3). The initial choices for protecting groups were *tert*-butyldimethylsilyl (TBDMS) and benzyl, which would be relatively easily removed in a subsequent reaction. During reaction of the TBDMS-protected dihydroquinone, partial desilylation was observed, leading to a bis-arylation species (**9**) as a major byproduct. The benzyl analogue reacted uneventfully to give **10**. However, subsequent attempts to remove the protecting group resulted in competitive reductive cleavage of the 2-aryloxy substituent, and in some cases ethyl nicotinate was

Scheme 2



Scheme 3

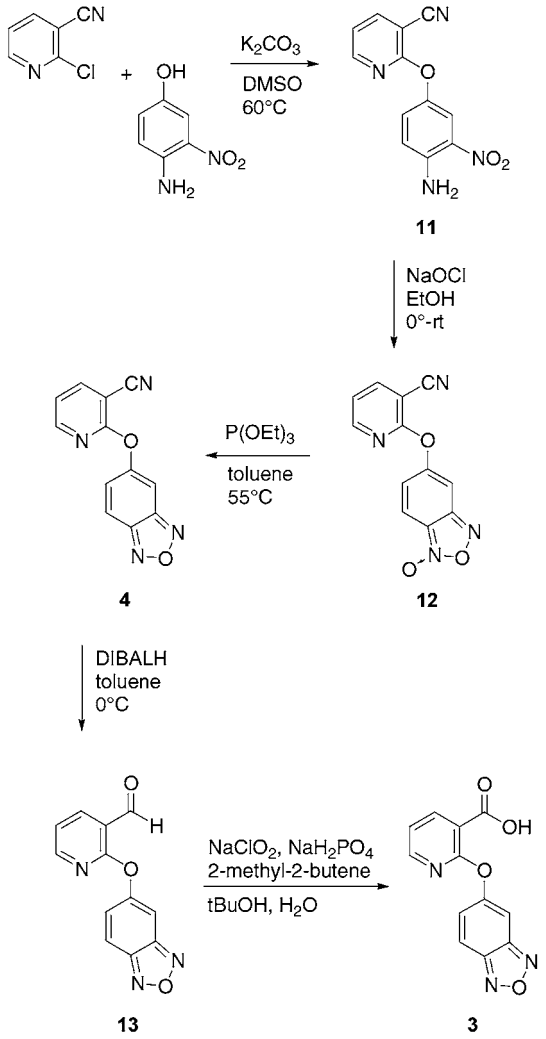


the major product. Since the chemistry in this route appeared to be less robust than hoped for, we decided to investigate other approaches.

Another approach that has been successful in the literature is the cyclization of ortho-nitro anilines.[4] We had initially avoided this approach since it generates the *N*-oxide of the desired benzofurazan (benzofuroxan) as an intermediate (Scheme 4), and there was concern that it would have worse thermal stability properties than the parent.[5] Another question was how regioselective the addition of the requisite aminophenol would be, and thus whether the amine would require a protecting group. We were pleased to find that 4-amino-3-nitrophenol couples with 2-chloronicotinonitrile very

(2) For a general review, see Boulton, A. J.; Ghosh, P. B. *Adv. Heterocycl. Chem.* **1969**, *10*, 1.
(3) Pollet, P.; Gelin, S. *Synthesis* **1979**, 977.
(4) Mallory, F. B. *Organic Syntheses*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, p 74.
(5) Some benzofuroxans have been defined as explosive. See: Gaughran, R. J.; Picard, J. P.; Kaufman, J. V. R. *J. Am. Chem. Soc.* **1954**, *76*, 2333.

Scheme 4



smoothly under mild conditions (K_2CO_3, DMSO, 60 °C). There was no evidence of competitive reaction with the electron-deficient amine. The product was easily isolated by filtration of the reaction mixture after precipitation with water, affording nitrile **11** in 77% yield.

The oxidative cyclization of nitroamine **11** to benzofuroxan **12** proved to be remarkably facile. The cyclization occurs very rapidly with bleach and can be monitored by the loss of color in the starting mixture. Any exotherm can be controlled by the rate of addition of bleach to a solution of the starting material in ethanol. The product was insoluble in the reaction mixture and was isolated by a simple filtration, resulting in a quantitative yield of benzofuroxan **12**. Testing of **12** showed that it has a large energy of decomposition (Table 2, entry 3), but at a high onset relative to the reaction temperature, providing a large enough safety window to comfortably handle the potential thermal hazard.

Reduction of benzofuroxan **12** to the desired benzofurazan **4** was run, according to literature precedent,[6] by treating **12** with a trialkyl phosphite at 55 °C. Although we had hoped to avoid any heating of the benzofuroxan, the reduction was sluggish at lower temperatures, and we reasoned that the solvent (toluene) would provide an adequate barrier in the case of inadvertent overheating. On laboratory scale, the product was isolated by displacement of the toluene with *N*,*N*-dimethylacetamide (DMAC) and precipitation with water. The desired nitrile **4** was isolated in 99% yield after drying under vacuum.

(6) Baldwin, J. J.; Claremon, D. A.; Elliott, J. M. Ponticello, G. S.; Remy, D. C.; Selnick, H. G. U.S. Patent 5,032,604, 1991.

Table 2

entry	compound	DSC results (ΔH)
1	4-amino-3-nitrophenol	2212 J/g, onset @157 °C
2	**11**	1658 J/g, onset @237 °C
3	**12**	2191 J/g, onset @154 °C
4	**4**	1872 J/g, onset @250 °C
5	**13**	1539 J/g, onset @216 °C
6	**3**	1500 J/g, onset @194 °C

Having reached our goal of identifying a safe, scalable synthesis of **4**, we turned our attention to hydrolysis of the nitrile. Unfortunately, under the more forcing conditions required for nitrile vs ester hydrolysis, the aromatic phenol that had just been installed was cleaved competitively. However, a standard two-step protocol of reduction to the aldehyde followed by oxidation to the acid was successful. Nitrile **4** could be reduced with DIBALH in 97% yield, and the intermediate aldehyde **13** oxidized with sodium chlorite to obtain acid **3** in 94% yield.

Table 2 shows the DSC results obtained for the nitro starting material and the intermediates. As projected from the results first observed in the nicotinic ester series, the higher-molecular weight species have an improved safety margin with regard to decomposition onset. While all the energy releases are large, they occur at a high onset temperature relative to the reaction temperature, or the reaction solvent of higher boiling point provides an adequate barrier to reaching the decomposition temperature.

All of the steps described above were performed on multikilogram scale after extensive safety testing (including reaction calorimetry, accelerating rate calorimetry (ARC) testing, and impact sensitivity testing) indicated that the reactions could be conducted safely in the intended manufacturing equipment. The reactions proceeded smoothly and cleanly and well within a reasonable safety window. In particular, the first three steps of the process worked extremely well. They were carried out on a 25-kg scale and delivered the desired intermediate **4** in 75% overall yield. The isolated wet cakes of **11** and **12** were used without further drying or purification for processing ease and speed.

The workup of the DIBALH reduction was somewhat problematic during scale-up. Precipitation of an oily substance was observed, which necessitated the addition of solid supports to remove it so that clogging of equipment would not occur. Additionally, high volumes of toluene and 1 M HCl were required to work up the reaction. This resulted in a much lower recovery of **12** than had been observed on smaller scale. Further refinement of the workup procedure would undoubtedly improve the recovery.

Another change that was made during the scale-up was the omission of a chlorine radical scavenger in the final oxidation. On laboratory scale, 2-methyl-2-butene had been

used, but its low flash point (−45 °C) precluded its use on scale. Other scavengers were considered, but they either had similarly low flash points or would be difficult to purge during isolation of the product. In the end, it was decided to equip the reactor with sequential caustic/sodium bisulfite scrubbers to trap any chlorine generated during the oxidation. The sodium chlorite solution was added to the reaction slowly via narrow-bore tubing to control the rate of chlorine generation. After extensive testing of *tert*-butyl alcohol vapor and chlorine mixtures, it was concluded that dilution of the off-gas mixture with nitrogen would eliminate the chances for vapor phase combustion of the mixture. A strong nitrogen purge was placed on the reactor for the duration as a safety precaution. The oxidation proceeded very smoothly and produced the desired acid **3** in 89% yield and 99.7% purity.

Conclusions

A safer, scalable synthesis of 5-(2-carboxy-pyridin-2-yloxy)-benz[1,2,5]oxadiazole (**3**) has been demonstrated. The synthesis sacrifices efficiency in terms of step count to address safety concerns with handling 5-hydroxybenzofurazan, which was found to be a high-energy compound with a low onset temperature of decomposition. All the steps of the new route were demonstrated at pilot-plant scale with no safety issues.

Experimental Section

General. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by TLC or HPLC. In examples where the crude product was carried on directly, a small sample was dried, if necessary, to collect analytical data. HPLC analyses were performed using either a Zorbax SB-CN 4.6 mm × 150 mm column or a Symmetry C-8 3.9 mm × 150 mm column, and a mobile phase consisting of acetonitrile and either 0.5% perchloric acid or 0.2% phosphoric acid. Mass spectral data was collected on a Hewlett-Packard GC/MS instrument (HP5890 GC, HP5972 MS), HP-1 column (12.5 m × 0.2 m × 0.33 μm film thickness). Proton and carbon NMR spectroscopies were performed on a Bruker-Spectrospin Avance 400 MHz instrument. Karl Fischer measurements were obtained on a Mettler Toledo DL38 Volumetric Karl Fischer apparatus. DSC testing used a Mettler Toledo DSC 821e instrument. Each experiment (typical sample size 5−15 mg) was carried out from 25 to 400 °C @ 4 °C/min using a high-pressure gold plated test pan.

4-(2-Cyano-pyridin-2-yloxy)-2-nitro-phenylamine (11). A clean, nitrogen-purged vessel was charged with 53 gal of DMSO, 2-chloro-3-cyanopyridine (25.0 kg, 180 mol), 4-amino-3-nitrophenol (29.2 kg, 189 mol) and powdered potassium carbonate[7] (49.9 kg, 361 mol). The mixture was heated to 55−60 °C for 4 h and then cooled to 35−45 °C. Water (132 gal) was added, and the resulting slurry was granulated at 20−25 °C for 30 min. The solids were isolated by filtration and rinsed with water (66 gal). The product was carried forward into the next step without further purification or drying. The purity of the solids was 99.0% by HPLC. MS *m*/*z* (M^+) 256; ^{1}H NMR (DMSO) δ 8.40 (dd, J = 7.6, 1.9 Hz, 1H), 8.37 (dd, J = 5.0, 1.9 Hz, 1H), 7.83 (d, J = 2.7 Hz, 1H), 7.52 (s, 2H), 7.38 (dd, J = 9.1, 2.7 Hz, 1H), 7.30 (dd, J = 7.6, 5.0 Hz, 1H), 7.09 (d, J = 9.1 Hz, 1H); ^{13}C NMR (DMSO) δ 163.05, 151.70, 144.59, 144.49, 140.72, 131.25, 129.11, 120.28, 118.98, 117.32, 115.03, 96.42.

5-(2-Cyano-pyridin-2-yloxy)-benz[1,2,5]oxadiazole-1-oxide (12). A nitrogen-purged vessel was charged with 2B ethanol (122 gal), potassium hydroxide (11.1 kg, 198 mol), and the wet cake of **11** generated in the previous step. Clorox bleach (110 gal) was added at a rate that kept the reaction temperature below 35 °C. The solids were granulated for 1 h, filtered, and washed with water (110 gal). The product was carried forward into the next step without further purification or drying. MS *m*/*z* (M^+) 254; ^{1}H NMR (DMSO) 8.50 (dd, J = 7.7, 1.9 Hz, 1H), 8.45 (dd, J = 5.0, 1.9 Hz, 1H), 7.74 (bs, 2H), 7.42 (dd, J = 7.7, 5.0 Hz, 1H), 7.38 (bs, 1H); ^{13}C NMR (DMSO) δ 161.83, 151.80, 144.92, 142.50, 120.02, 114.71, 97.20 (7 of 12 carbons observed).

5-(2-Cyano-pyridin-2-yloxy)-benz[1,2,5]oxadiazole (4). A clean, nitrogen-purged vessel was charged with THF (86 gal), the wet cake of **12**, and triethyl phosphite (65.8 kg, 396 mol). The mixture was heated at 55−60 °C for 3 h and then cooled to 50−55 °C, and water (402 gal) prewarmed to 50 °C was added to the reaction. The reaction was cooled to 20−25 °C, and the solids were granulated for 7 h. The product was isolated by filtration and washed with water (151 gal). The solids were dried under vacuum at 50−55 °C until a KF of <0.5% was obtained, yielding 32.15 kg (75%) of the desired product. The purity of the material recovered was 94.9% by HPLC. MS *m*/*z* (M^+) 238; ^{1}H NMR (DMSO) δ 8.51 (dd, J = 7.6, 1.9 Hz, 1H), 8.45 (dd, J = 5.0, 1.9 Hz, 1H), 8.17 (dd, J = 9.7, 0.7 Hz, 1H), 8.01 (dd, J = 2.0, 0.7 Hz, 1H), 7.61 (dd, J = 9.7, 2.0 Hz, 1H), 7.43 (dd, J = 7.6, 5.0 Hz, 1H); ^{13}C NMR (DMSO) 161.93, 154.81, 151.85, 149.34, 147.43, 144.94, 130.78, 120.00, 117.59, 114.74, 105.35, 97.17.

5-(2-Formyl-pyridin-2-yloxy)-benz[1,2,5]oxadiazole (13). *Pilot-Plant Scale*. A clean, nitrogen-purged vessel was charged with **4 (**31.9 kg, 134 mol) and toluene (139 gal). The mixture was cooled to 0−5 °C, and a 1.5 M solution of DIBALH in toluene (113 kg, 200 mol) was added at a rate to maintain the internal temperature <5 °C. The reaction was stirred at 0−5 °C for 1 h. Upon reaction completion, a slurry of Celite (16 kg) in toluene (17 gal) was added followed by an aqueous HCl addition (51 L of concentrated HCl dissolved in 156 gal of water), maintaining the internal temperature at <10 °C during both additions. The slurry was warmed to 20−25 °C, stirred for 30 min, and then filtered over Celite. The solids were washed with a 1:1 mixture of water:toluene (20 gal). After separation of the layers of the filtrate, the aqueous layer was extracted a second time with toluene (54 gal). Silica gel (32 kg) was charged to the

(7) In a pilot run, the reaction was run with granular potassium carbonate, and the reaction took 20 h instead of less than 4.

combined toluene solutions, and the slurry was stirred for 60 min then filtered. The toluene filtrates were concentrated under vacuum to a low volume. The silica solids were charged to a vessel containing ethyl acetate (110 gal), stirred for 100 min, and filtered. The filtrate was added to the concentrated toluene mixture, and the combined organic layers were concentrated under vacuum to the lowest stirrable volume. Isopropyl ether (42 gal) was added at 30−40 °C. The resulting slurry was cooled to 10−20 °C and granulated for 10 h. The solids were isolated by filtration, washed with isopropyl ether (10 gal), and then dried under vacuum at 30−40 °C, giving 13.95 kg (43%) of aldehyde **13**. A second crop was obtained by further concentration of the mother liquors and isolated as before, giving an additional 1.25 kg (4%, 47% overall yield). The purity of the first crop was 98.7%, and that of the second crop was 99.5% by HPLC.

Lab Scale. A clean, dry round-bottomed flask was charged with **4** (3.57 g, 15 mmol) and toluene (60 mL). The mixture was cooled to 0 °C, and a 1.5 M solution of DIBALH in toluene (15 mL, 22.5 mmol) was added at a rate to keep the internal temperature <5 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C, and a solution of 1 N HCl was added at a rate to keep the temperature <10 °C. The resulting mixture was stirred at 0 °C for 30 min and extracted with isopropyl ether (IPE) three times. The IPE layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give 3.52 g of **13** which was used without further purification.

MS *m*/*z* (M^+) 241; ^{1}H NMR (DMSO) δ 10.41 (d, J = 0.8 Hz, 1H), 8.46 (dd, J = 5.0, 2.1 Hz, 1H), 8.33, (dd, J = 7.5, 2.1 Hz, 1H), 8.16 (dd, J = 9.5, 0.8 Hz, 1H), 7.94 (dd, J = 1.7, 0.8 Hz, 1H), 7.60 (dd, J = 9.5, 1.7 Hz, 1H), 7.43 (ddd, J = 7.5, 5.0, 0.8 Hz, 1H); ^{13}C NMR (DMSO) δ 188.62, 162.05, 155.58, 152.92, 149.40, 147.34, 139.06, 131.09, 120.72, 119.58, 117.36, 104.54.

(8) The overall system pressure was kept slightly below ambient pressure with partial vacuum pulled through the two in-line scrubbers containing an aqueous mixture of sodium hydroxide and sodium bisulfite to trap any chlorine formed.

5-(2-Carboxy-pyridin-2-yloxy)-benz[1,2,5]oxadiazole (3). A clean vessel was charged with water (20 gal), sodium hydrogen phosphate (25 kg, 183.5 mol), 5-(2-formyl-pyridin-2-yloxy)-benz[1,2,5]oxadiazole (15 kg, 62 mol), and *tert*-butyl alcohol (99 gal). The mixture was stirred for 1 h, and then a solution of sodium chlorite (34 kg, 379 mol) in water (40 gal) was added at a rate to keep the internal temperature <35 °C.[8] The reaction was quenched with a solution of sodium bisulfite (90 kg) in water (99 gal) at a rate to keep the temperature <25 °C. The *tert*-butyl alcohol was stripped at slightly below atmospheric temperature (to control the bisulfite fumes release) until the head temperature was 80 °C. After cooling to 20 °C, the solids were granulated for 5.5 h, filtered, and washed with water (10 gal). The wet cake was reslurried in water (30 gal) for 1 h at 80 °C. After cooling to 20−25 °C, the solids were slurried for 2 h, filtered, and washed with water (5 gal). The solids were dried in a vacuum oven at 45−55 °C until the KF was <0.5%, yielding 14.3 kg (89%) of the desired product. The purity by HPLC was 99.7%. MS *m*/*z* (M^+) 257; ^{1}H NMR (DMSO) δ 13.44 (s, 1H), 8.38−8.35 (m, 2H), 8.10 (dd, J = 9.5, 0.4 Hz, 1H), 7.68 (dd, J = 2.1, 0.4 Hz, 1H), 7.48 (dd, J = 9.5, 2.1 Hz, 1H), 7.37 (dd, J = 7.5, 5.0 Hz, 1H); ^{13}C NMR (DMSO) δ 165.23, 159.60, 156.48, 150.90, 149.52, 147.25, 142.28, 130.97, 120.46, 117.34, 116.75, 102.72.

Acknowledgment

We thank Jeff Adler, Joseph F. Bellavance, Thomas E. Brooks, Todd M. Carden, Jonathan S. Dykema, Ronald L. Foular, Jr., Thomas F. Limanni, Lawrence A. Lumbert, Dennis B. Mooney, Alden L. Peckham, and Walden J. Smolen for their assistance in successfully transferring the process to the pilot plant, and Matthew Jorgensen for analytical support. We thank Robert Chambers for useful discussions on the reactivity of the systems discussed.

Received for review July 28, 2003.

OP0341059