Organic Process Research & Development

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Telescoped Flow Process for the Syntheses of *N*-Aryl Pyrazoles

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Supporting Information

ABSTRACT: *N*-Aryl pyrazoles were prepared from anilines in a three step telescoped approach. An aniline was diazotized to give the diazonium fluoroborate, followed by reduction with tin(II) chloride to give the corresponding hydrazine, which in turn reacted with a ketoenamine to give the *N*-aryl pyrazole. The deprotection of the methyl ether was accomplished with $PhBCl_2$ to give the final product. The continuous flow methodology was used to minimize accumulation of the highly energetic and potentially explosive diazonium salt and hydrazine intermediates to enable the safe scale-up of *N*-aryl pyrazoles. The heterogeneous reaction mixture was successfully handled in both lab scale and production scale. A continuous extraction was employed to remove organic impurities from the diazotization step, which eliminated the need for chromatography in the purification of the final *N*-aryl pyrazole.

INTRODUCTION

The pyrazole moiety has been shown as a key pharmacophore in many pharmaceutically active agents. Naturally occurring Pyrazofurin (**1**), a *C*-nucleoside isolated from *Streptomyces candidus* in 1969, possessed broad-spectrum antiviral activity.[1] Multiple blockbuster drugs celecoxib (**2**, Celebrex), rimonabant (**3**, Acomplia), sildenafil (**4**, Viagra) (Figure 1), and the recently approved lung cancer drug crizotinib (**5**, Xalkori) feature a pyrazole substructure.

A number of synthetic methods have been developed for the formation of pyrazoles.[2,3] Among them, the Knorr[4] cyclocondensation offers direct entry to the pyrazole via cyclocondensation of hydrazines with 1,3-dicarbonyl compounds or their surrogates (Scheme 1). The commercial availability of ketoenamines, RC(O)CH=CHNMe$_2$ (R = H, Me, Ph, OEt) and the accessibility of hydrazines make the Knorr reaction one of the most attractive methods for the preparation of pyrazoles. Importantly, when the nitrogen groups of hydrazines are electronically or sterically biased, reasonable regioselectivity can be achieved in the pyrazole formation.[5]

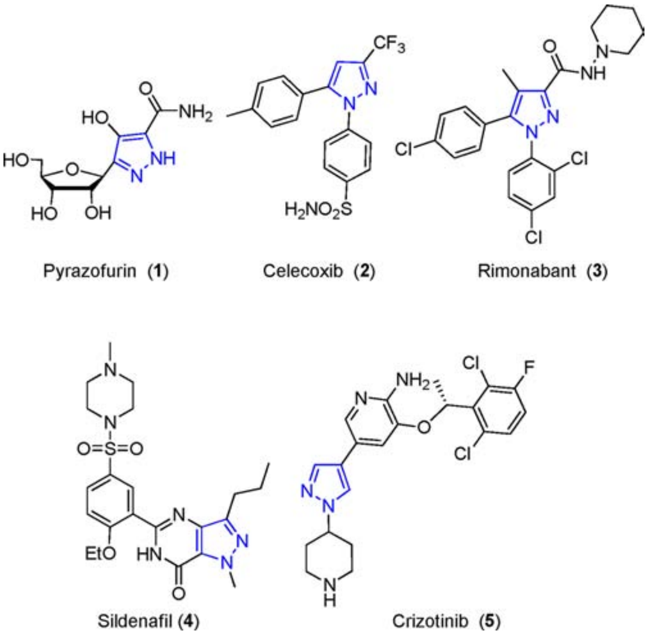
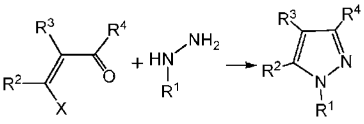

Pyrazofurin (**1**) Celecoxib (**2**) Rimonabant (**3**)
Sildenafil (**4**) Crizotinib (**5**)

Figure 1. Compounds with a pyrazole moiety.

Scheme 1. Knorr Cyclocondensation



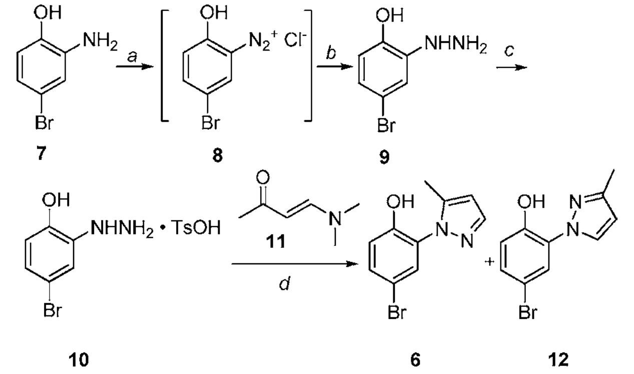
We adopted such an approach in the synthesis of *N*-aryl pyrazole **6**, a key intermediate for an ongoing research program (Scheme 2). The synthesis started with diazotization of 2-amino-4-bromophenol (**7**), followed by reduction of the diazonium salt **8** to give the hydrazine **9**. The isolation of **9** was complicated by the presence of tin oxides in the reaction mixture. After cumbersome extractive workup, crude **9** was isolated and purified by forming the tosylate salt (**10**). Subsequently, **10** was reacted with ketoenamine **11** to give the aryl pyrazole **6**. The regioisomer **12** (8−10% by HPLC) was formed as a byproduct and was removed by silica gel chromatography. While the synthesis was relatively straightforward on small scale, the involvement of energetic intermediates (diazonium **8** and hydrazine **9**) with low differential scanning calorimetry (DSC) onset temperatures[6] presented potential safety hazards for scale-up. Thus, we turned our attention to developing a continuous flow process to address the safety concerns in scale-up. Continuous flow technology offers many

Special Issue: Safety of Chemical Processes 12

Received: July 31, 2012
Published: August 23, 2012

dx.doi.org/10.1021/op300209p | *Org. Process Res. Dev.* 2012, 16, 2031−2035

Scheme 2. Original Synthesis of *N*-Aryl Pyrazole 6



[a](a) $NaNO_2$, aq HCl, 0 °C. (b) $SnCl_2$, EtOH, AcOH, 0 °C to RT; then extractive workup. (c) $TsOH·H_2O$. (d) AcOH, RT.

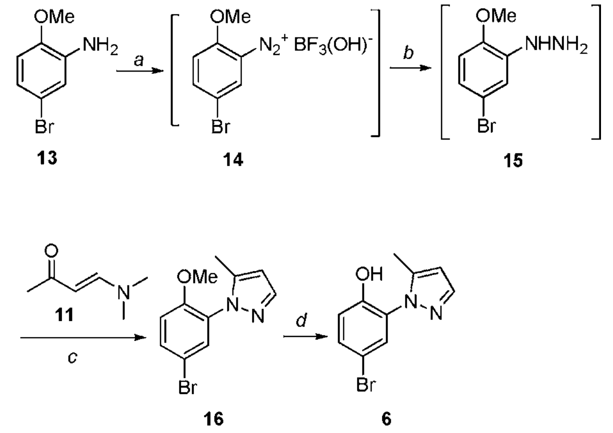
advantages over batch methods, including precise control of stoichiometry, reaction time, and temperature; high reproducibility; and often better reaction yields.[7] The much higher surface area to volume ratio under flow conditions renders highly efficient heat transfer. When coupled with the much smaller volume in the reaction train, safety hazards in handling exothermic reactions associated with explosive intermediates are minimized.[8]

RESULTS AND DISCUSSION

1. Adapting the Batch Chemistry to Continuous Flow. As an industrial process of vast importance, the diazotization of aromatic amines has been well studied.[9] A continuous diazotization of anilines was reported in 1965 from the dye industry.[10] More recently, there have been several reports on generating diazonium salts as reactive intermediates using flow technology.[11] In the design of a continuous flow process for the synthesis of **6**, our objectives were to avoid the accumulation and isolation of both energetic intermediates **8** and **9**. We envisioned that appropriate reaction conditions in a telescoped process would satisfy these objectives. Thus, we set to enable reaction conditions for each transformation and explore telescoping opportunities. As expected, the diazotization of aniline **7** worked well under either aqueous ($NaNO_2$, aqueous HCl) or nonaqueous (*t*-BuONO, $BF_3·THF$)[12] conditions. Though it was highly desirable to eliminate $SnCl_2$ from the synthesis, our efforts to find alternative reducing agents to replace $SnCl_2$ were fruitless.[13] When crude diazonium **8** was carried to the $SnCl_2$ reduction, it failed to convert cleanly due to the presence of a number of impurities generated from the diazotization. This profile led to low overall yields when the hydrazine reaction mixture was subjected to the pyrazole formation. The use of $SnCl_2$ also complicated the workup and isolation, as a large amount of tin oxide byproduct gave a milky mixture. Tin oxides are only soluble in either highly acidic or basic aqueous media that were not suitable for the isolation of zwitterionic **9** or **6**. With that in mind, we turned to the methyl ether protected aniline **13** (less expensive than **7**) as the starting material. It offered a cleaner reduction step and resulted in a much more convenient isolation of hydrazine **15** or pyrazole **16**, as high pH conditions that solubilized tin oxides could be applied during the workup (Scheme 3).

To streamline the process, we next examined if ketoenamine **11** was stable in $SnCl_2$ (1 equiv)/EtOH, and we were pleased to observe no appreciable degradation at 20 °C. Since the reaction rates for the diazonium reduction and the cyclocondensation steps occurred within minutes, neither energetic intermediates **14** and **15** would be accumulated in a telescoped process.

Scheme 3. New Synthesis of *N*-Aryl Pyrazole 6



[a](a) *t*-BuONO, $BF_3·THF$ in 2-MeTHF; RT. (b) $SnCl_2$, 2-MeTHF/water, 0 °C. (c) 0−20 °C. (d) $PhBCl_2$, toluene, 95 °C, 3 h; recrystallization in iPrOH/water.

2. First Generation Flow Design. Since the diazonium intermediate **14** was observed to react further with the aniline starting material to give azo coupling byproduct, we wanted to avoid back mixing in a flow reactor. Thus, a plug flow design was selected (Figure 2) instead of a continuous stirred tank reactor (CSTR). Aniline **13** was combined with $BF_3·THF$ in THF as one feed stream. The resulting solution was evaluated for its stability, and it revealed no concerns for prolonged storage (24 h). *tert*-Butyl nitrite in THF was introduced as a separate stream. The two streams were pumped into a T-mixer followed by a PTFE coil to achieve a 10 min residence time for the diazotization reaction. The coil was submerged in a sonication[14] bath to allow the diazonium salt formed in the coil to move smoothly out of the PTFE coil without clogging. Crystallization of diazonium fluoroborate salt (**14**) in the reaction mixture resulted in a systemic pressure of 30−45 psi. It was noted that **14**, as a light and fluffy solid, was well suspended in THF. The effluent was directly added to a receiving flask containing $SnCl_2$ and ketoenamine **11** in ethanol. This design worked successfully for up to at least 100 g scale. After an extractive workup, pyrazole **16** was isolated by chromatography and underwent methyl ether deprotection using $PhBCl_2$[15] to give the desired product **6** in 35−40% overall yield.

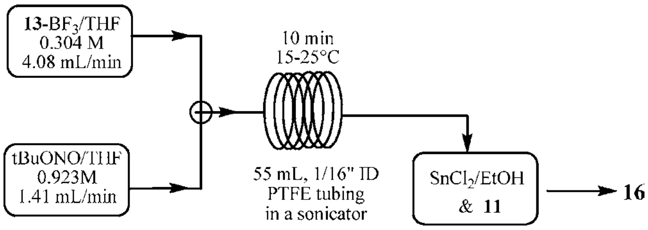


Figure 2. First generation flow setup for a three-step telescoped reaction to form pyrazole **16**.

3. Second Generation Flow Design. While the first generation flow design allowed the successful scale up to meet the initial demands, isolation of the final product still required silica gel chromatography. As the program progressed, larger quantities of **6** were demanded, and it became evident a more robust synthesis was needed. Since most impurities[16] from the three-step sequence were generated in the diazotization step, and an excess of *tert*-butyl nitrite was found to give rise to high levels of impurities in the reduction, we envisioned an opportunity to introduce a continuous extraction to allow the separation of the water-soluble diazonium salt **13** from the organic-soluble impurities. This idea was demonstrated by isolating a small amount of purified **13** and carrying it forward to **16** with high purity and good yield, leading to the second generation flow design (Figure 3). The flow setup used two Fluid Metering Inc. (FMI) pumps (with the mechanism of valveless rotating and reciprocating piston metering) to introduce the feed streams. A stainless steel T-union was used as a mixer, which was joined by PTFE tubing to provide the required residence time. Considering the upper pressure limit of the pumps recommended by the manufacture is 100 psi, we used an automatic pressure shut-down device and set the trigger point at 100 psi. The effluent (out of the PTFE tubing) from the diazotization reaction was mixed with a water stream using a two staged continuous stirred tank reactor (CSTR); the resulting biphasic mixture then entered a glass standpipe decanter (Figure 4) for phase separation. The organic layer was continuously removed as a waste stream, while the aqueous phase was directed into a reaction vessel containing $SnCl_2$.

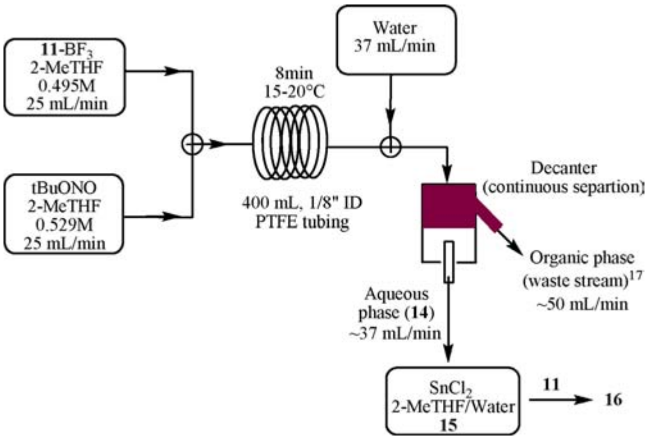


Figure 3. Second generation flow setup for a three-step telescoped reaction to form pyrazole **14**..

Some modifications of the chemistry were required to enable this new design. In order to facilitate the continuous extraction, the diazotization solvent was changed to 2-MeTHF to accelerate separation from the aqueous layer. We also realized that the residence time could be reduced from 10 to 8 min. Second, the $SnCl_2$ pot receiver was held at 0−5 °C during the reduction to provide a better purity profile, and ethanol was eliminated for more streamlined workup and isolation. Third, with water introduced to the system, the aqueous hydrazine intermediate presented a low hazard in thermal stability testing and it was deemed safe to accumulate hydrazine **15** in a solvent mixture of water/2-MeTHF. Ketoenamine **11** was added after the flow run was complete and then warmed to 20 °C for a cleaner reaction. Using this protocol, we executed two runs (800−1000 g) and obtained 51−55% overall yield of **6**. With flow rates of 25 mL/min for both the BF_3−aniline adduct and *tert*-butyl nitrite feed stream solutions, a back pressure of ∼30 psi was observed due to the diazonium solids present in the PTFE tubing. A picture of the 400 mL reaction coil used in the production run is shown in Figure 5. After approximately 3 min of residence time, diazonium salt started to crystallize from the reaction mixture. The solids were light and fluffy and moved through the coil smoothly. Liquid segments were noted as the solid segregated in mother liquor from the crystallization. The FMI pumps were able to handle the slurry formed in the 400 mL PTFE tubing ($^1/_8$″ i.d., $^1/_4$″ o.d., rated to handle 320 psi of pressure @ 23 °C) in a continuous ∼8 h operation. It is plausible that the pulsating effect generated from the FMI pumps might have helped in moving the slurry. A process hazard analysis (PHA) was conducted, and the following was recommended and followed: (1) All tubing and fittings used should be rated for much higher pressure at the operating temperature. The whole system was tested to ensure it could withstand up to 250 psi pressure with no leaks detected. (2) Each run should be closely monitored despite the implementation of an automatic shut down device at 100 psi. (3) In the

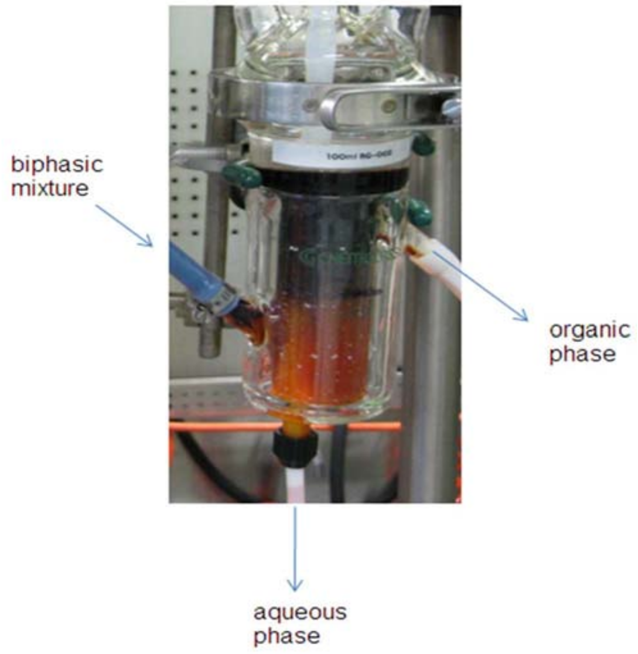


Figure 4. Continuous extraction in the second generation flow design.

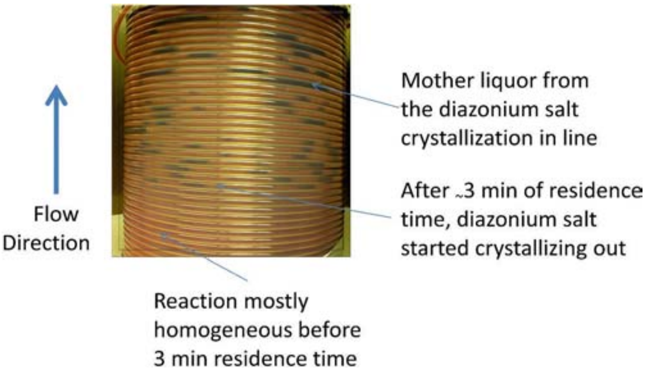


Figure 5. Diazonium fluoroborate salt crystallization in the reaction coil ($^1/_8$″ i.d., PTFE, 400 mL).

event of pressure buildup due to solid agglomeration, the coil containing the diazonium intermediate was to be flushed with water immediately and kept from exposure to air. Fortunately we did not run into a need to use the contingency plan in the kilogram scale flow run.

It is noteworthy that the continuous separation worked extremely well for this chemistry. The standpipe decanter vessel (100 mL) could accommodate flow rates of 120 mL/min per stream with facile layer separation. The emulsion zone between the phases was less than $^1/_2''$ during the course of both flow runs (Figure 4).

With crude **16** in hand, we sought an efficient workup and isolation method. Upon complete conversion of the hydrazine **15** to the pyrazole **16**, the aqueous phase was removed, and the organic phase was washed with 6 N aqueous NaOH. The mixture was filtered, and the filtrate was concentrated and treated with silica gel. This method effectively reduced the residual tin level to less than 10 ppm. The crude product was then subjected to demethylation using $PhBCl_2$ in toluene. Finally, a crystallization method was developed to remove the regioisomer **12** using a mixture of isopropanol and water.

■ CONCLUSION

We have described a flow process allowing the safe handling of the energetic intermediates. The maximum amount of diazonium **14** present in the system was 99 mmol (29.6 g, assuming 100% conversion) for the scale up using 400 mL coil. For comparison, a batch reaction of 1.0 kg scale would generate 4.9 mol of diazonium salt **14**. Under the worst case scenario of decomposition of all diazonium salt in the reaction system, approximately 2.2 L of nitrogen (under 1 atm pressure) would be generated in the continuous production scale. Whereas the batch reaction would generate 110 L of nitrogen upon decomposition.

In the diazotization step, while the feed streams were homogeneous solutions in the flow operation, the product stream became a slurry after ∼3 min of residence time. The solid/liquid heterogeneous reaction mixture (5−7 wt % solids) was successfully handled at kilogram scale production scale (400 mL PTFE $^1/_8''$ i.d. coil) without sonication. The continuous extraction employing a simple stand pipe decanter effectively removed organic-soluble impurities from the diazonium salt (**14**), which also resulted in higher throughput in the three step telescoped process.

Despite the successful outcome of the flow runs demonstrated in the preparation of *N*-aryl pyrozole **6**, the robustness of the process on any scale larger than 1 kg of **13** and longer duration is yet to be tested. We plan to further investigate the flow design if the need arises for greater demand of the aryl pyrazole **6**. Additionally, process improvements on the product isolation and the demethylation step will also be necessary.

■ EXPERIMENTAL SECTION

PTFE tubing was purchased from Omegaflex (this flexible tubing offers good transparency for applications that require visual inspection; the $^1/_4''$ o.d., $^1/_8''$ i.d. tubing is designed to withstand 320 psi of pressure at 23 °C). LCMS was recorded with an HP-1100MSD using API-ES ionization mode. HPLC analyses were carried out in HP-1100 using a Water Atlantis T3 column (stable-bond C18) (3 μm, 3 mm ×75 mm) with acetonitrile:0.1% TFA aqueous buffer (95/5 to 5/95 in 8 min) as mobile phase (1.2 mL/min) and detection at 210 nm wavelength.

1-(5-Bromo-2-methoxyphenyl)-5-methyl-1*H*-pyrazole (16). Boron trifluoride−tetrahydrofuran complex (972 g, 6.95 mol) was added over 20 min to a solution of 5-bromo-2-methoxyaniline (1.00 kg, 4.95 mol) in 2-methyltetrahydrofuran (6 L), and the mixture was filtered through Celite. The filtrate was brought to a volume of 10 L with additional 2-methyltetrahydrofuran. In a separate container, *tert*-butyl nitrite (546 g, 5.29 mol) was dissolved in 2-methyltetrahydrofuran (9.0 L); the volume was then adjusted to 10 L by addition of 2-methyltetrahydrofuran. To effect diazotization (**CAUTION**: solid diazonium salts will form in the tubing; conduct this work only in a properly designed flow setup with the approval of process safety engineers), the two solutions were pumped by two Ismatec pumps (model C.P. 78020-50) equipped with FMI heads at 25 mL/min flow rate per stream into a T-mixer ($^1/_8''$ OD T-union) connected to a 400 mL PTFE coil ($^1/_8''$ ID; $^1/_4''$ OD). At a combined flow rate of 50 mL/min, the reaction mixture had a total residence time of 8 min in the coil. The pumps were started simultaneously, and the effluent exiting the reaction coil was sent to a two-stage continuous stirred-tank reactor (CSTR), where diazonium fluoroborate (**12**) was mixed with water (introduced continuously at a flow rate of 37 mL/min). The aqueous layer was continuously separated in a stand pipe decanter and sent to a jacketed 75 L reactor containing a mixture of tin(II) chloride dihydrate (2.82 kg, 14.9 mol), 2-methyltetrahydrofuran (10 L), and water (5 L) at 0 °C. After 2 h, the reduction was deemed complete, as determined by HPLC analysis. (3*E*)-4-(Dimethylamino)but-3-en-2-one (562 g, 4.97 mol) was charged, and the jacket temperature was adjusted to 20 °C. After 12 h, the layers were separated and the organic layer was washed with 1 N aqueous NaOH solution (3 × 20 L). The organic layer was concentrated (35 °C, 100 mbar) in a 20 L rotovap bulb containing silica gel (1.5 kg) until a free-flowing powder was obtained. The material was loaded onto a pad of silica gel (2.0 kg), and elution was carried out with 2-methyltetrahydrofuran (12 L). The eluent was concentrated *in vacuo* (45 °C, 60 mmHg) and was displaced with toluene and then was concentrated to give the crude product as a dark red oil (1.202 kg), as a mixture of the title product (**16**) and the regioisomeric pyrazole in a roughly 9:1 ratio (as assessed by ^{1}H NMR). Quantitative-NMR analysis indicated the crude product contained 56 wt % of **16** (677 g, 2.53 mol, 51% yield). HRMS: m/z $(M + H)^+$ calcd for $C_{11}H_{15}rN_2O$: 267.0133/269.0133; found: 267.01269/269.01038. ^{1}H NMR (400 MHz, d_6-DMSO): 7.66 (1H, dd, J = 8.8, 1.8 Hz), 7.55−7.45 (2H, m), 7.21 (1H, d, J = 8.8 Hz), 6.2 (1H, d, J = 0.8 Hz), 3.77 (3H, s), 2.08 (3H, s). ^{13}C NMR (400 MHz, d_6-DMSO) 153.49, 140.24, 139.71, 132.79, 131.18, 129.42, 114.67, 111.19, 105.48, 56.02, 10.79.

4-Bromo-2-(5-methyl-1*H*-pyrazol-1-yl)phenol (6). A 20 L jacketed glass reactor was fitted with a recirculating scrubber charged with water (0.40 L), methanol (1.20 L), and ethanolamine (0.40 L). To the 20 L reactor were charged crude **16** (677 g active, 2.53 mol, 1.2 kg of total mass from above), and toluene (8.4 L) to afford a dark red solution that was stirred at 25 °C. Dichlorophenylborane (0.75 kg) was charged via a dropping funnel over 15 min while maintaining the temperature below 30 °C. The reaction mixture was heated to 95 °C for 3 h, then concentrated (60 °C, 60 mmHg) to ∼8 L, and then cooled to 20 °C. The mixture was quenched with 1 N aqueous NaOH solution (13.8 L). After the mixture was stirred for 30 min, the layers were separated and the toluene layer was extracted with additional 1 N aqueous NaOH solution (4.0 L). The aqueous layers were combined and were charged back to the 20 L reactor. The pH of the aqueous mixture was adjusted to 9.2 with concentrated HCl (0.65 L), resulting in a precipitation. The solids were collected by filtration in a Buchner funnel. The filter cake was charged back into the 20 L reactor and taken up in 2-propanol (6.72 L). The mixture was heated to 50 °C and stirred for 1 h and then cooled to 20 °C. Water (6.72 L) was slowly added over a 1 h period, and the resulting product slurry was stirred at 20 °C for 2 h. The product was filtered, rinsed with water (4.2 L), and dried (40 °C, 50 mmHg) for 24 h to give pure **6** (0.488 kg, 1.92 mol, 76% yield) as a white solid. HRMS: m/z $(M + H)^+$ calcd for $C_{10}H_{10}BrN_2O$: 252.9977/254.9977; found: 252.99726/254.99463. ^1H NMR (400 MHz, d_6-DMSO) 10.39 (1H, s), 7.50 (1H, s), 7.46 (1H, dd, J = 8.8, 2.3 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.01 (1H, d, 8.8 Hz), 6.18 (1H, s), 2.13 (3H, s). ^{13}C NMR (400 MHz, d_6-DMSO) 151.88, 140.21, 139.56, 132.43, 131.05, 128.35, 118.55, 109.33, 105.37, 10.92.

■ ASSOCIATED CONTENT

Supporting Information

Details of the DSC the results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Jim Hallissey, Brian Morgan, and Asaad Nematalla for Kilo Lab production support. We also thank Drs. Chris J. Helal, Russell J. Linderman, and Mr. Michael Fichtner for their valuable input in preparing the manuscript.

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(14) Process safety of aryl diazonium salts in PTFE tubing under sonication was not evaluated, as this approach was used for scale up.

(15) Demethylation using BCl_3 was not clean, probably due to fact that the methyl chloride formed was trapped under the reaction conditions.

(16) A dark brown mixture was noted invariably for the diazotization step. LCMS indicated the presence of dediazoniation, azo coupling, triazenes, and other polymeric substances. The continuous extraction also removed any excess *tert*-butyl nitrite from the diazotization step. These impurities along with the excess *tert*-butyl nitrite were removed as a waste stream in the continuous separation.