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Development of a Safe and Scalable Oxidation Process for the Preparation of 6-Hydroxybuspirone: Application of In-Line Monitoring for Process Ruggedness and Product Quality

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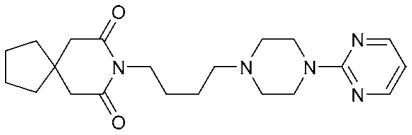
Abstract:

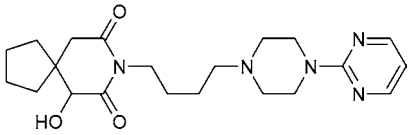
The development of a safe and scalable oxidation process for the hydroxylation of the azapirone psychotropic agent buspirone (1) to furnish 6-hydroxybuspirone (2) is described. A mechanistic understanding of how key process factors affected product quality led to the successful application of FTIR as a process analytical technology (PAT) tool. This enabled *real time* quality assurance and the development of an effective and efficient manufacturing process. The identification of impurities and the development of recrystallization methods to provide active pharmaceutical ingredients (API) with optimal purity will also be addressed.

Introduction

Buspirone (**1**), manufactured and marketed by Bristol-Myers Squibb as Buspar (hydrochloride salt of buspirone), is employed for the treatment of anxiety disorders and depression.[1] Studies show Buspar is extensively metabolized in the body to several compounds.[2] One such metabolite was identified as the hydroxylated derivative, (±)-6-hydroxybuspirone (**2**), which, like buspirone, demonstrates a strong affinity for the human 5-HT_{1A} receptor (Figure 1).[3]



Buspirone **1**



6-Hydroxybuspirone **2**

Figure 1.

One attractive strategy for the synthesis of 6-hydroxybuspirone involves a one-step conversion from buspirone, owing to its long-term availability as an inexpensive starting material. Several synthetic approaches to 6-hydroxybuspirone have been disclosed by our colleagues in Drug Discovery; however, these were not amendable to development because of reagent costs and purification challenges.[4]

Process research and development were therefore presented with the challenge to develop a safe, robust, and scalable process to enable the multikilogram production of **2** to support toxicology studies, formulation development, and clinical trials.

Results and Discussion

Initial Experimentation. One of the classical oxidation processes for the conversion of a ketone to the corresponding α-hydroxyketone was first published in 1962 by Barton et al..[5] It involves the formation of the enolate followed by oxidation employing oxygen. After isolation, the intermediate hydroperoxide is then reduced with zinc dust in acetic acid to furnish the desired alcohol. Later, in 1968, Gardner and co-workers[6] reported that the oxidation and reduction could be achieved in a one-pot process by performing the reaction in the presence of trialkyl phosphites.

Early experiments for the α-hydroxylation of **1** employed KHMDS in THF for enolate formation, followed by sparging with air in the presence of 1 equiv of triethyl phosphite at low temperature (−78 °C). Conversion, monitored by analytical HPLC, showed 74% **2**, 20% starting material **1**, and varying amounts of several impurities. The variation of the impurities formed throughout processing presented a formidable challenge during process optimization of this drug candidate. Purification using silica gel chromatography provided **2** in a moderate yield of 44%.

Process Optimization. Typically this reaction was run in THF at concentrations of 20 mL/g. This was the preferred solvent owing to the solubility of the starting material, product, and the intermediate enolate at low temperatures. The THF process also provided a cleaner reaction profile compared to other solvents. Research efforts therefore focused on three areas: phosphite stoichiometry, the workup and isolation protocol, and the control of enolate **3** formation.

Triethyl Phosphite Concentration. Product quality was shown to be dependent on the phosphite stoichiometry. In the absence of triethyl phosphite, a 1:1 mixture of starting

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(1) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton J. F. *J. Chem. Soc.* **1962**, 1578.
(2) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, 3294.
(3) New, J. S. *Med. Res. Rev.* **1990**, *10*, 283−326.
(4) Mayol, R. F.; et al. *Clin. Pharmacol. Ther*. **1985**, *37*, 210
(5) Mayol, R. F. U.S. Patent 2000/6150365.
(6) (a) Yevich, J. P.; Mayol, R. F.; Li, J.; Ruediger, E. H. US Patent 2003/0069251 A1. (b) Yevich, J. P.; Mayol, R. F.; Li, J.; Yocca, F. WO 03/009851 A1; (c) Yevich, J. P.; Mayol, R. F.; Li, J.; Yocca, F. U.S. Patent 2003/0022899 A1.

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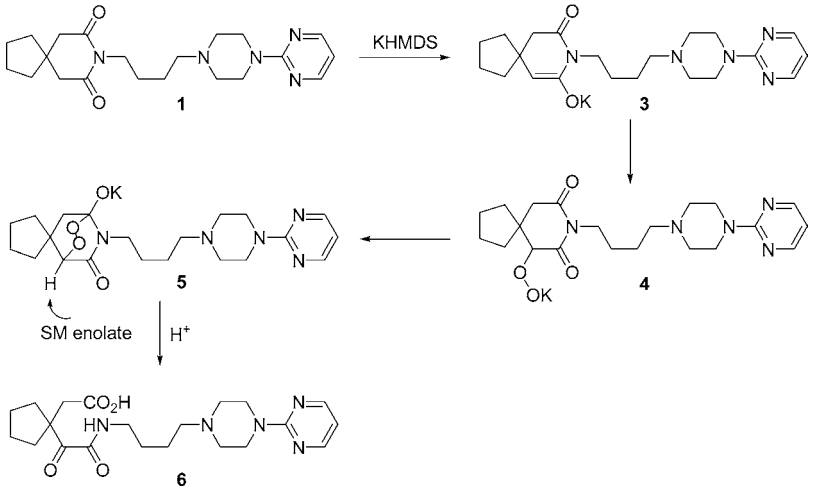
Scheme 1. **Impurity formation in the absence of triethyl phosphate**



material **1** and the corresponding keto acid **6** was observed presumably through the pathway shown in Scheme 1.

Early laboratory experiments for the oxidation of **1** to **2** therefore employed 1.1 equiv of triethyl phosphite resulting in improved conversion, but the product was still contaminated with a number of unidentified impurities. A systematic study of the phosphite stoichiometry revealed that a charge of triethyl phosphite greater than 3.0 equiv provided reactions with significantly cleaner profiles but that further increase of the level of phosphite led to higher losses of product during the isolation. The decision was therefore made to perform this reaction with 3.5 equiv of triethyl phosphite to balance purity and product loss.

One additional concern with regard to safety was the formation of presumably unstable hydroperoxide **4** as an intermediate in this process. The presence of an excess of the reductant, triethyl phosphite, should ensure that the concentration of **4** did not build up throughout the course of the reaction. In situ testing for peroxides throughout the oxidation process with peroxide test strips indicated low levels at or below 1 mg/L suggesting the peroxide intermediate **4** is immediately consumed by the phosphite.

Evolution of the Isolation. The initial procedure for the workup and isolation of **2** involved neutralization, phase separation, back-extraction with ethyl acetate, brine washes, and isolation by precipitation with heptanes. This expedient process provided good product recovery; however, most impurities coprecipitated leading to an inferior quality product. We subsequently found that an exchange of the THF reaction solvent with ethyl acetate after neutralization, followed by slow addition of heptanes and seeding to effect crystallization, gave crystalline material with improved purity. The drawbacks to this crystallization procedure were high mother liquor losses, on the order of 15 mol %, and a tendency for the product to oil before crystallization. A more robust protocol was developed based on earlier experiences learned while developing a process for the HCl salt of **2**. The mixture was quenched, neutralized by the addition of aqueous HCl, and diluted with MTBE. This provided several advantages to the previous workups. The addition of MTBE afforded better phase separations during the back-extractions and aqueous washes, and the low boiling point of MTBE enabled a facile exchange of the MTBE/THF organic layer to isopropyl alcohol until the IPA/THF ratio was >25:1 and KF < 1.0% by GC and Karl−Fisher titration, respectively. Upon cooling and seeding, **2** crystallized reliably from the mixture. The mother liquor losses during this isolation were generally lower (6−8 mol %) than those by other direct crystallization techniques and provided product with an improved purity profile.

Identifying and Minimizing Impurities. Identification of process impurities and a mechanistic understanding of their origin often lead to improved process conditions and a quality product. Impurities associated with this process are shown in Figure 2. Two major impurities common to this transformation were the starting material **1** and the over-oxidized product 6,10-dihydroxybuspirone **8**. Excess base produced impurity **8** in a 10:1 ratio of isomers favoring the *trans*-diol. Experimentally, we observed that the amount of excess base correlated well with the amount of diol **8** produced (i.e., 5% excess base resulted in 5% diol production). On the other hand, an undercharge of the base gave an incomplete reaction leading to product contamination with **1**. Since the amount of base is critical to both yield and quality, we titrated the base in triplicate and measured water in all the THF solutions to ensure an accurate charge.

The isolation procedure incorporated a rugged crystallization of the product directly from the process stream. Occasionally, however, batches were produced where the levels of these known impurities (Figure 2) were greater than those observed in the qualifying toxicology batch. The process therefore required a recrystallization to ensure that API of the desired purity could be reliably obtained. Determination of the solubility of these impurities in various solvents using automated instrumentation enabled a rapid development of rework procedures (Figure 3).

After screening several solvents, anisole appeared to provide the greatest difference in solubility between product **2** and the major impurities starting material **1** and diol **8**. To purge the diol impurity **8**, a reverse crystallization was developed wherein the material was dissolved in anisole at 90 °C, cooled to ambient temperature, and seeded with 0.25 wt % diol seeds to crystallize **8**. After removal of **8** by filtration, the anisole was concentrated to half its initial

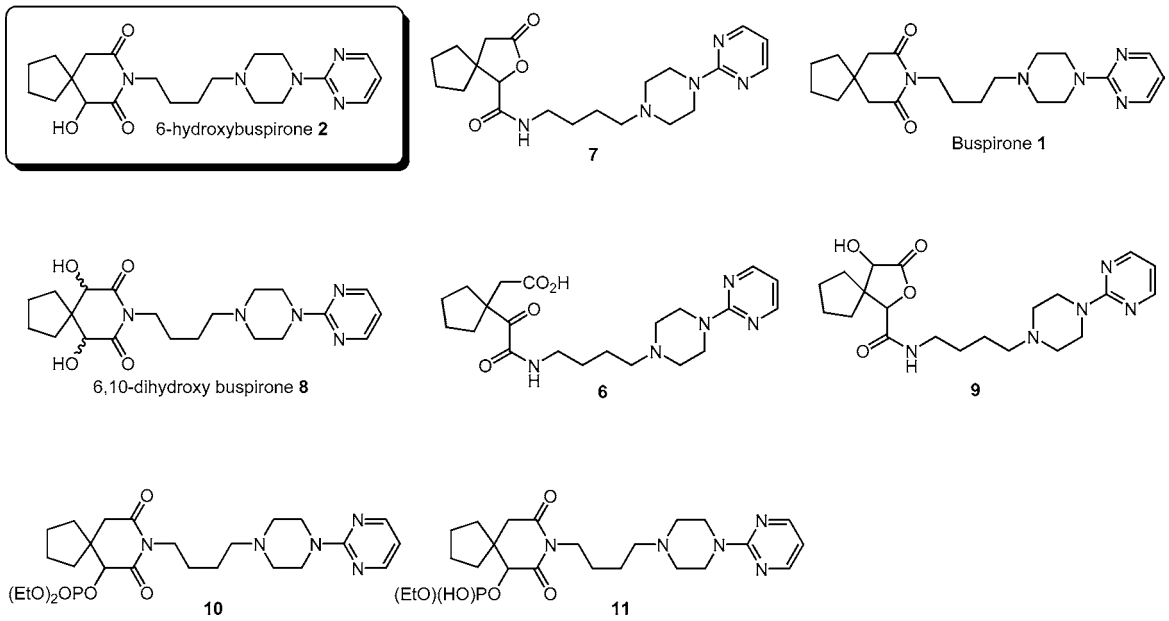


Figure 2. **Structures of impurities identified in the oxidation of buspirone (1).**

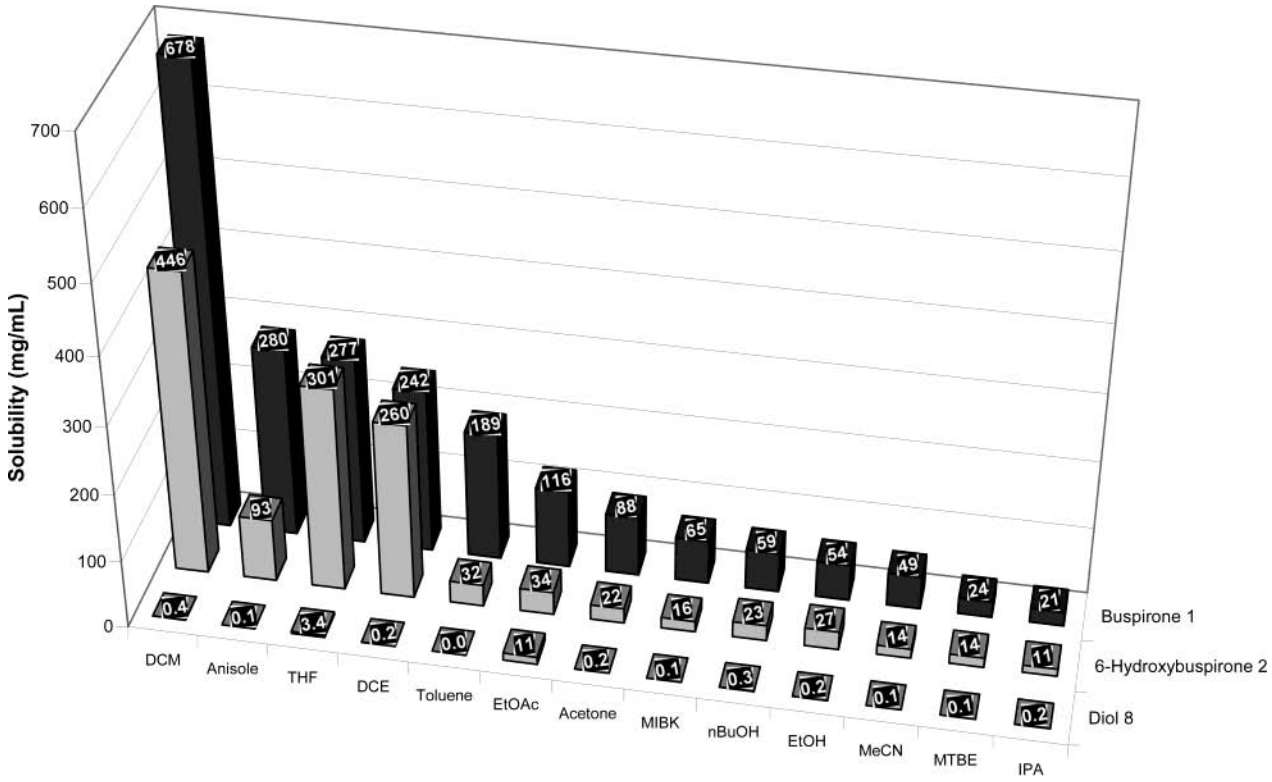


Figure 3. **Solubility measurements of 2 and key process impurities.**

volume and heptane was charged slowly to crystallize the product **2** with excellent purity. A recrystallization protocol from isopropyl alcohol was also developed that could purge up to 4% starting material **1**, thus providing a lower limit to the amount of base charged. It became apparent that a slight undercharge of the base was the preferred route as the removal of the diol impurity **8** was time-consuming and both labor- and equipment-intensive. Consequently, tight control of the base titer and water content proved crucial to the success of this reaction to avoid undercharging or overcharging the base (a typical base charge was 0.95−0.97 equiv).

Pilot Plant Campaign. The optimized process employed NaHMDS as the preferred base with triethyl phosphite as the reductant owing to a combination of cost, availability, and convenience. To obtain a clean reaction profile, the optimal triethyl phosphite charge and temperature were 3.5 equiv and −70 °C, respectively. In addition, lab experiments showed the rate of oxidation was significantly faster using pure oxygen instead of air. However, from a safety perspective this could not be readily scaled up owing to our decision to limit the level of oxygen in the headspace to less than 6%. To keep the headspace oxygen level low, we sparged

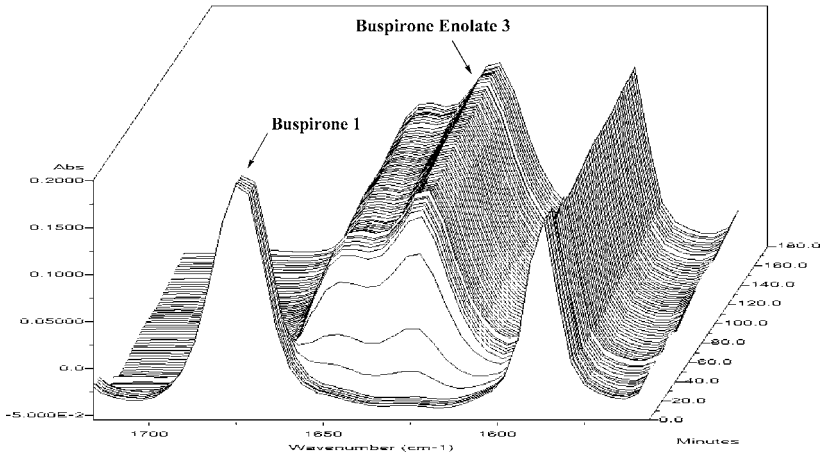


Figure 4.

the reaction with air and employed a 3:1 volumetric ratio of nitrogen to the air sparge. This effectively kept the oxygen level in the headspace at or below 5.5% which was monitored using an explosion proof oxygen monitor (N-TRON).[7] When the reaction was complete, the oxygen sparge was replaced with a nitrogen sparge until the off-gas was below 0.5% oxygen.

The first pilot-plant batch with a 10 kg input of **1** employed 0.95 equiv of 1 N NaHMDS in THF, providing 7.35 kg of **2** in 71% yield and >98 HPLC area percent (area %) purity. The next batch again employed 0.95 equiv of base (a different lot than the base used in the first batch) with a 12.46 kg input of **1** providing 8.96 kg of **2** in 69% yield. However, this material did not meet specifications for purity due to the formation of undesired side products, namely the 6,10-dihydroxybuspirone (**8**) (13 area %). This suggested an approximated additional 13% (1.08 equiv) of base had been charged. Among other issues that accounted for the discrepancy in the overcharge of base, it was theorized that the NaHMDS (1 N in THF, stored in a pressure bomb) had crystallized from the THF resulting in a nonhomogeneous solution, therefore providing a nonrepresentative sample for the titration. This would result in a lower apparent titer and an overcharge of the base. The rework from anisole purged the diol **8** affording material in excellent purity (>99 area %) in 70% recovery. This, however, demonstrated that the process did not possess suitable robustness. The initial optimized procedure (vida infra) relied on two corrections to estimate the amount of base needed to deprotonate **1**, namely adventitious water and base titer. Although this methodology was sufficient to produce several high-quality batches of **2**, there was the occasional failure as evidenced above, as excess base could easily be added, leading to the production of 6,10-dihydroxybuspirone (**8**). This impurity was difficult to purge and therefore best controlled with processing conditions. Additionally, it was observed in the laboratory that certain lots of triethyl phosphite accounted for lower conversions in the oxygenation reaction due to its air and moisture sensitivity. As a result, each lot of phosphite was use tested prior to running the process on scale.

In-Process Monitoring Using React-IR. Subsequent work in the laboratory focused on introducing *Process Analytical Technology* (PAT)[8] using an in-line monitoring tool to achieve process ruggedness and consistently ensure acceptable and reproducible product quality. Specifically, in situ FTIR was employed to monitor the deprotonation of **1**. This enabled a more precise determination of the endpoint for enolate formation. The FTIR profile for the deprotonation of **1** is shown in Figure 4. Signals at 1677 cm^{-1} and 1627 cm^{-1} correspond to the starting material **1** and the enolate **3**, respectively.

Incremental charges of base show a decrease of the SM **1** peak at 1677 cm^{-1} and a corresponding increase in the enolate **3** peak at 1627 cm^{-1} (Figure 5).

Other interesting observations were (i) deprotonation of the buspirone (**1**) was rapid and usually complete within 5 min after addition of the base, (ii) the enolate anion **3** was stable at or below −25 °C over a 12 h period (temperatures above −25 °C led to decomposition of the enolate [−15 °C, 3.6% decomposition of the enolate **6**; −5 °C, 7.6%; 5 °C, 18%; and 20 °C, 25%]), and (iii) addition of triethyl phosphite before addition of the base had no impact on the IR signal.

To ensure that excess base was not present, an improved process for the formation of enolate **3** was developed. Monitoring with FTIR, we charged the base until the signal for the starting material (1677 cm^{-1}) no longer declined. This indicated that we had achieved complete consumption of the starting material. A solution of starting material in THF was then charged back to the vessel in incremental amounts until the signal increased therefore indicating a slight excess of the starting material. Quantifying the signals while correcting for changes in concentration enabled a back charge to provide a 1−3% excess of starting material. *It is important to note that monitoring the deprotonation by FTIR allowed for variations in the base titer, water content, and phosphite quality*. This led to the successful production of sev-

(7) If the oxygen off-gas concentration had crept near 6%, the oxygen sparge would have been replaced with a nitrogen sparge and the combination of the two nitrogen streams would have quickly reduced the oxygen concentrations. It should also be noted that one can purchase custom filled cylinders containing 5% oxygen in nitrogen.

(8) FDA Draft Guidance for Industry; PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, August 2003.

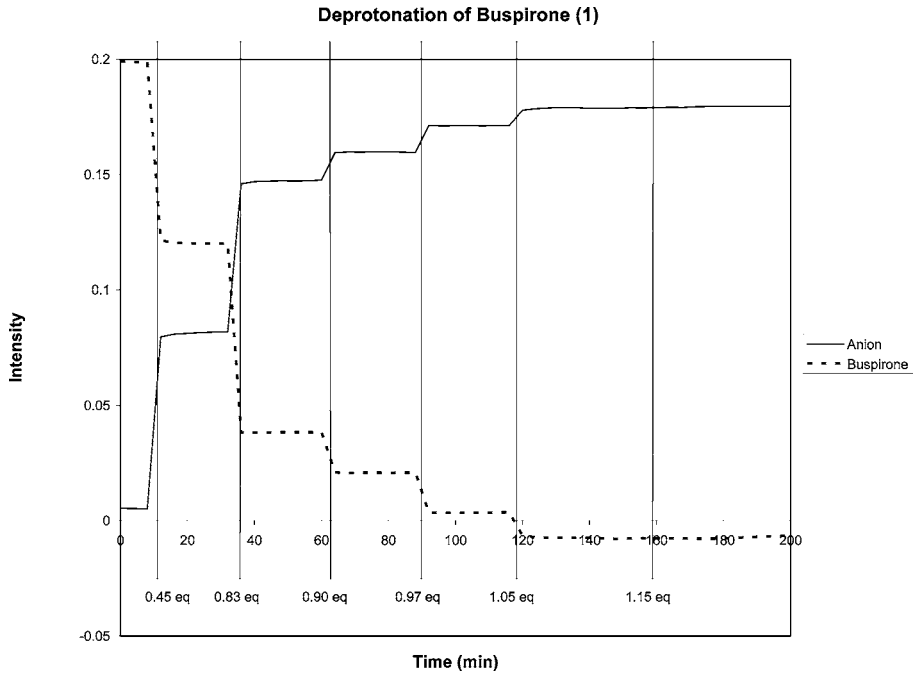


Figure 5.

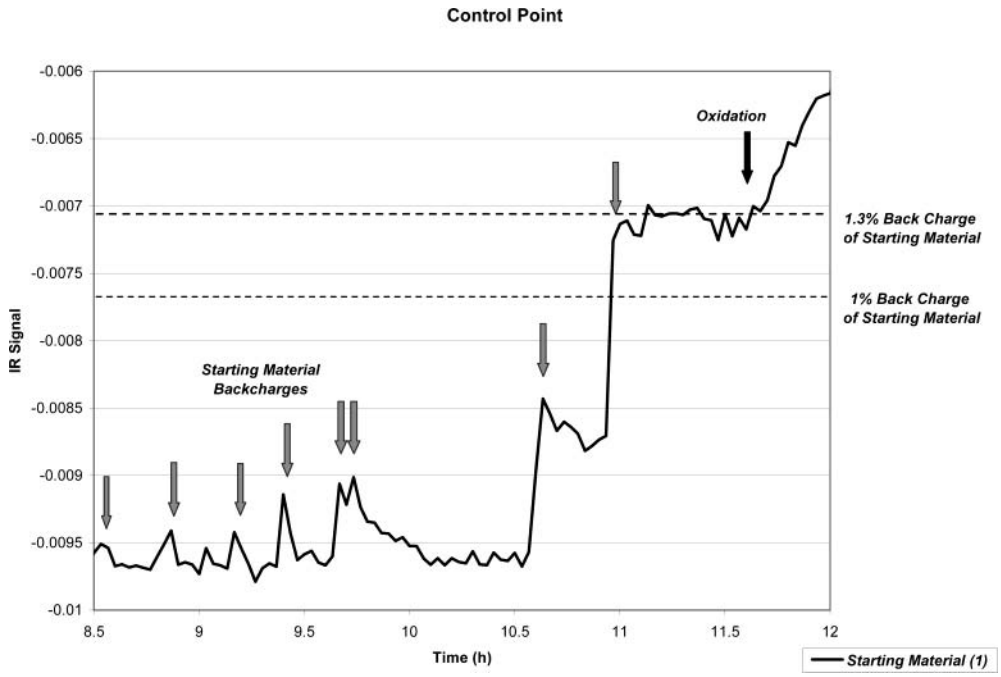


Figure 6. **IR signal of buspirone indicating the backcharges of the starting material to reach desired target of 1−3% excess buspirone.**

eral batches of **2** in the laboratory with low levels of diol impurity **8**.

This process was ultimately implemented in the pilot plant. Buspirone (**1**) (13.42 kg) was converted into **2** (8.96 kg) in 69% yield and >99 area %. For this plant run, we used the same lot of base that had caused problems in the previous batch (vida supra). NaHMDS (1.01 equiv of apparent titer of 1 M in THF) was charged, followed by a total back charge of 12 mol % **1**. This provided a stable, positive buspirone signal corresponding to a 1.3% excess of starting material by Process-IR (Figures 6 and 7). This generated API with low levels of starting material and diol. *Fortunately, despite the ambiguous base concentration, the employment of the FTIR to control the enolization endpoint provided lower levels of diol impurities and therefore exemplified its effectiveness as an in-process control for process optimization.*

Modified Workup Procedure: Understanding the Fate of the Triethyl Phosphite and Its Impact on Product Recovery. During the pilot plant campaign, losses of **2** to the mother liquor during the crystallization was about 10−15%. Experimentally, we have traced this rather high loss to the use of excess triethyl phosphite during the oxidation step. The excess triethyl phosphite (theoretical 2.5 equiv) remaining after the completion of the reaction hydrolyzes during the workup and crystallization protocol to diethyl

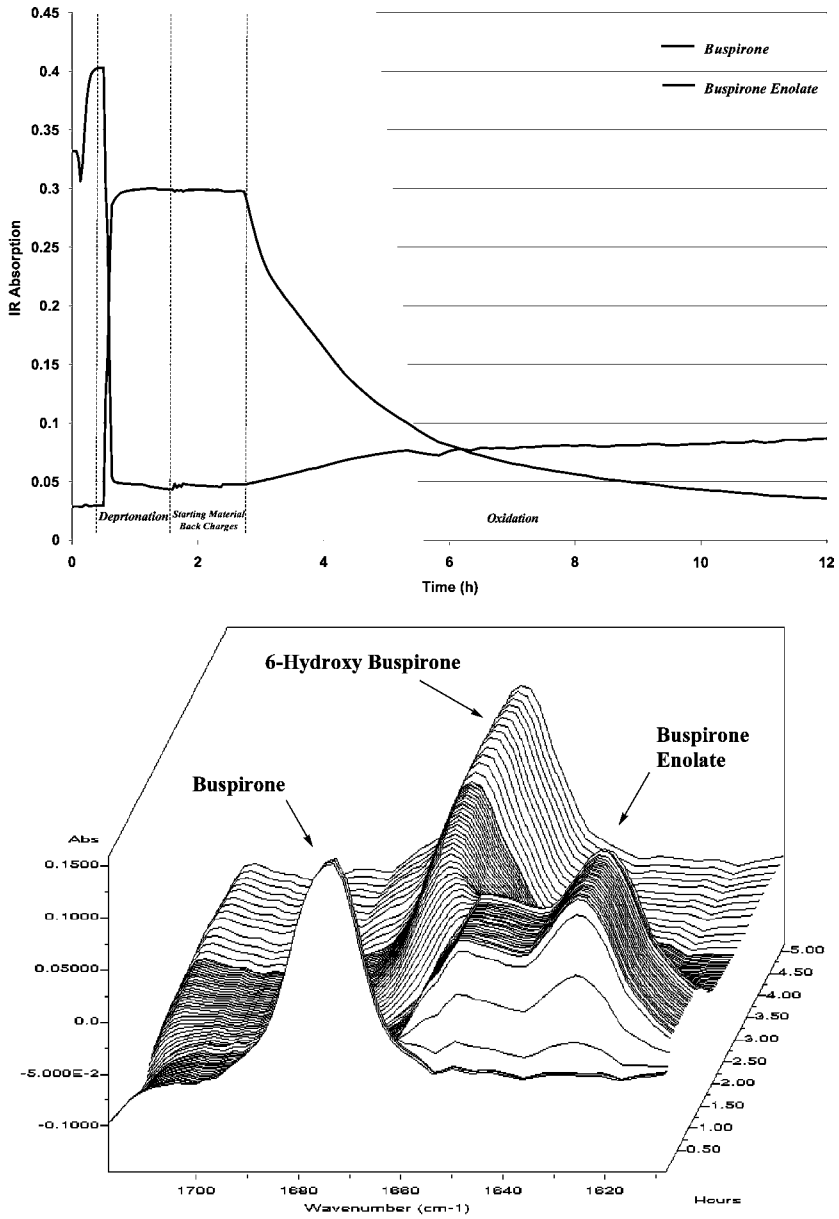


Figure 7. **IR data for the oxidation process.**

phosphite [$(EtO)_2P(OH)$], and we have determined that **2** has a very high solubility in both diethyl phosphite and diethyl phosphite/IPA mixtures. The amount of diethyl phosphite present in the crude reaction mixture corresponds to approximately 1 mL/g of **2**.

To overcome these high losses to the mother liquor, an alternative workup and isolation protocol was developed. When the oxidation is complete, the reaction mixture is treated with acid to lower the pH to approximately 2.0, whereupon the mixture is heated to hydrolyze the residual triethyl phosphite to phosphorous acid and monoethyl phosphorous acid. Subsequent neutralization with base, followed by aqueous extraction, removes the phosphorous acids. Solvent exchange of tetrahydrofuran with 2-propanol at reduced pressure followed by crystallization afforded **2** in yields of 70% with excellent purity (>99 area %). Using this new protocol, the losses to the mother liquor returned to their initial values observed in the laboratory of 6−8%.

Conclusions

In summary, we have demonstrated a practical and safe method for the aerobic oxidation of azapirones. The process is suitable for implementation on pilot plant scales. Optimization of the process conditions and workup provided cleaner reaction profiles and lower losses to the waste streams, respectively. Further process control afforded by the use of the in-line FTIR monitoring tool ultimately ensured product quality and prevented the need for batch reprocessing.

Experimental Section

General. NaHMDS (1 N) and HCl (1 N) are commercially available and were used as is. THF, isopropyl alcohol, anisole, and methyl *tert*-butyl ether were used without further purification. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a weight/weight basis. Proton and carbon

NMR were run on a Bruker AC-300 spectrometer at 300 MHz for proton and 75 MHz for carbon in DMSO-d_6. In situ measurements were performed using a React-IR spectrometer (instrument model: Mettler-Toledo AutoChem ReactIR 1000 and ProcessIR) equipped with an immersion probe having a diamond internal reflection element. The probe was purged with nitrogen. The titration of the NaHMDS solution was performed in triplicate with 1,3-diphenylacetone tosylhydrazone. HPLC was run under the following conditions: column, YMC ODS-AQ 4.6 × 150 mm^2 s-3 μ; column temperature, ambient; flow rate, 1.0 mL/min; 236 nm (8 nm band); injection volume, 10 μL; mobile phase A, 0.05% NH_4OAc in 80:20 H_2O/MeOH; mobile phase B, 0.05% NH_4OAc in 75:20:5 ACN/MeOH/H_2O; recording time, 25 min. Gradient program: initial (30% B), 15 min (55% B), 17 min (100% B), 20 min (100% B), 22 min (30% B). RRT (retention times in minutes): buspirone **1** (starting material), 1.35 (typical T_r = 12.65 min); 6-hydroxybuspirone **2** (BMS-528215), 1.00 (typical T_r = 9.38 min); lactone **13**, 0.80 (typical T_r = 7.47 min); 6,10-dihydroxybuspirone **8**, 0.74 (typical T_r = 6.91 min). HPLC sample preparation: (1) For in-process samples of **2**, dilute ~10 μL of reaction mixture with ~1.5 mL of mobile phase B; (2) for isolated **2**, dissolve ~0.1 mg of solid in 1.5 mL of ACN (note: sonication may be necessary for solvation)

Procedures. A. 6-Hydroxybuspirone (2). Buspirone (8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro(4.5)-decane-7,9-dione) (**1**) (10 kg, 25.9 mol) was charged to a 500 L vessel under nitrogen. Tetrahydrofuran (142.4 kg, 161 L) was charged, and the mixture was agitated at ambient temperature until homogeneous. The water content of the solution was measured by Karl−Fischer titration (KF = 0.009%) (this enabled the base charge to be adjusted, compensating for the water present in the solution). Triethyl phosphite (15.1 kg, 90.9 mol, 15.6 L, 3.5 equiv) was added, and the mixture was cooled to <−60 °C. Sodium bis(trimethylsilyl)amide, 1.0 M in THF (22.9 kg, 25.4 mol, 25.4 L, 0.98 equiv) was charged to the mixture at such a rate so as to maintain the temperature at less than −60 °C. Ultra zero grade air was sparged into the reaction mixture. The initial rate of sparging was controlled so as to maintain the temperature of the reaction mixture at less than −60 °C. The sparging was continued until the reaction was complete by HPLC (<3% buspirone). Methyl *tert*-butyl ether (16.1 kg, 21.7 L) was added followed by hydrochloric acid (52.3 kg, 51.8 mol, 51.8 L, 1.0 M), and the solution was warmed to ambient temperature. The pH was adjusted to 6.0−7.0 (preferred range pH 6.5−6.9) using 1.0 M hydrochloric acid and/or 0.5 M Na_3PO_4 solution (final pH 6.6). The phases were separated, and the upper organic phase was washed twice with 25 wt % brine (30 kg, 27.3 L). The rich organic layer was then solvent swapped into isopropyl alcohol using three charges of 79.0 kg of IPA providing an IPA/THF ratio of 38:1 and KF = 0.37%. A final concentration of 8−10 mL/g was achieved. The solution was cooled to ambient temperature over 4 h to crystallize the material. The crystalline slurry was then filtered by centrifugation, and the wet cake was washed twice with isopropyl alcohol (2 × 7.7 kg, 9.8 L) and dried at 40 °C under vacuum to provide 6-hydroxybuspirone (**2**) (7.35 kg, 18.3 mol, 71%). Mp 109.5 °C; ^{1}H NMR ($CDCl_3$, ppm) δ 1.23−1.20 (m, 1H), 1.41−1.36 (m, 1H), 1.76−1.54 (m, 10H), 2.09−2.03 (m, 1H), 2.55−2.40 (m, 7H), 2.80 (d, J = 17.5 Hz, 1H), 3.55 (s, 1H), 3.83−3.72 (m, 5H), 4.20 (s, 1H), 6.48 (t, J = 4.7 Hz, 1H), 8.30 (d, J = 4.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, ppm): δ 24.3, 25.9, 26.2, 26.5, 30.6, 36.2, 40.5, 43.7, 44.8, 44.9, 53.2, 58.2, 72.8, 74.3, 109.6, 157.0, 160.9, 170.1, 173.0, 174.4. Anal. Calcd for $C_{21}H_{31}N_5O_3$: C, 62.82; H, 7.78; N, 17.44. Found: C, 61.41; H, 7.52; N, 17.13.

B. In Situ Monitoring with FTIR for the Conversion of Buspirone (1) to 6-Hydroxybuspirone (2). Buspirone (8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro(4.5)-decane-7,9-dione) (**1**) (246.5 g, 639.6 mmol) was charged to a 12 L flask equipped with a mechanical stirrer and a React-IR probe under inert gas. Tetrahydrofuran (4.383 kg, 60.8 mol, 4.930 L) was charged, and the mixture was agitated at ambient temperature until homogeneous. Triethyl phosphite (371.9 g, 2.238 mol, 383.8 mL, 3.5 equiv) was added, and the mixture was cooled to −68 to −75 °C. The mixture was agitated at this temperature for at least 10 min to allow the React-IR signal to stabilize. Sodium bis-(trimethylsilyl)amide, ~1.0 M in THF (1.00 equiv) was charged to the mixture at such a rate to maintain the temperature at less than −60 °C. Small amounts of sodium bis(trimethylsilyl)amide were charged to the mixture until the IR signal for buspirone reached a minimum, indicating complete deprotonation of buspirone. Additional buspirone in THF (10−20 mL/g) was then charged to the reaction mixture in small increments until the IR signal indicated a 0.5%−5% excess of buspirone. Air was sparged into the reaction mixture, controlling the initial rate of sparging so as to maintain the temperature of the reaction mixture at less than −60 °C. The sparging was continued until the reaction was complete as indicated by HPLC. Methyl *tert*-butyl ether (384.8 g, 4.365 mol, 520.0 mL) was added followed by 1 M hydrochloric acid (1350.8 g, 1.328 mmol, 1328 mL), and the solution was warmed to ambient temperature. The pH was adjusted to between 6.5 and 6.9 using hydrochloric acid and Na_3PO_4. The phases were separated, and the organic phase was washed twice with brine (542.3 g, 493 mL). The solvent of the rich organic layer was then replaced by isopropyl alcohol, and the solution was cooled to crystallize the reaction product (there is an option to seed with 0.01−5% 6-hydroxybuspirone (**2**) at approximately 54−56 °C). The crystalline slurry was then filtered, and the wet cake was washed with isopropyl alcohol and dried to provide 6-hydroxybuspirone **2** (220.0 g, 82%), mp 109.5 °C.

C. Crystallization of 6-Hydroxybuspirone (2) to Reduce 6,10-Dihydroxybuspirone (8) and Buspirone (1). 6-Hydroxybuspirone (**2**) (8.0 kg, 20.8 mol) was slurried with anisole (80 L, 10 L/kg, 10−15 L/kg may be used). The mixture was heated to 80−100 °C and stirred to obtain a clear solution. The solution was then cooled to 75−85 °C

before 6,10-dihydroxybuspirone (**8**) seeds (20 g, 0.25 wt %, 0−2 wt % may be used) were added. The mixture was then cooled to ambient temperature over 2−6 h and stirred overnight. The resulting slurry was filtered, and the filtrate was concentrated to approximately half its initial volume. Heptane (1 volume relative to the initial volume of anisole) was then added over ∼5 h, and the resulting slurry was stirred at ambient temperature overnight. The slurry was filtered, and the resulting filter cake was washed with heptane. After drying, 5.56 kg of 6-hydroxybuspirone (**2**) was obtained (70% recovery). The level of diol **8** was reduced from 13 area % to 0.6 area % and buspirone (**1**) from 1.35 to 0.17 area %.

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