A Scalable Oxidation for the Final Stage of Synthesis of Cathepsin K Inhibitor SB-462795

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Abstract:

In developing the manufacturing route for the cathepsin K inhibitor SB-462795, the oxidation of a secondary alcohol for the final chemical stage is described. Prospective conditions were limited by several factors, particularly general safety concerns of oxidation reactions, the requirement to control impurities and transition metals isolated in the final product, and the desire to reduce the environmental impact. Two *N*-oxy free radical approaches (TEMPO and PIPO) and Moffatt conditions were evaluated in depth for their potential to achieve the targets. For reasons of robustness, scalability, and cost-effectiveness, the Moffatt conditions were the best manufacturing option.

Introduction

SB-462795 (**1**),[1] an azepanone-based inhibitor of the cysteine protease cathepsin K, was under evaluation for the treatment of osteoarthritis and osteoporosis.[2] A critical step in the synthesis is oxidation of secondary carbinol **2** to ketone **1** in the final step (Scheme 1). Although a Moffatt oxidation (Ac$_2$O, DMSO) was sufficient to produce approximately 200 kg of active pharmaceutical ingredient (API), an extensive evaluation of alternative oxidation conditions was necessary to achieve commercial goals.
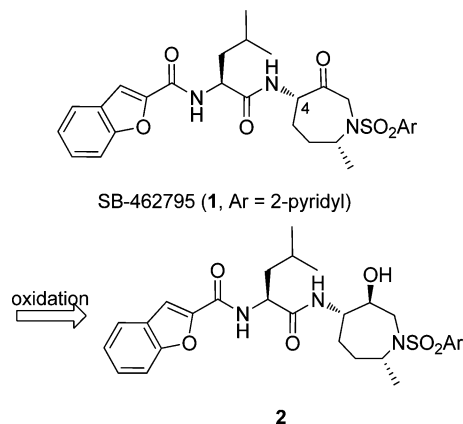
Results and Discussion

New oxidation conditions had to meet several criteria to be considered viable alternatives, including (1) conversions of >99.5%, to avoid purification issues associated with residual alcohol **2**; (2) mild conditions to avoid epimerization at the α-amido center (carbon 4, Figure 1); (3) low environmental impact, especially with respect to volume efficiency, waste streams, and solvent selection; and (4) low levels of any new impurities in the isolated product (particularly heavy metals).

Scheme 1. SB-462795 from oxidation of carbinol 2

SB-462795 (**1**, Ar = 2-pyridyl)

2

Unfortunately, scanning the literature proved that methods suitable for the oxidation of a secondary carbinol in the final step of a complex pharmaceutical agent were limited, especially given the requirements above.[3]

In total, 23 oxidation methods were investigated, including (but not limited to) Oppenauer-type oxidations, bleach/acetic acid, electrochemical, and dihalide (Br$_2$, I$_2$) methods. This screen identified five potential leads which afforded reasonable conversion and purity, specifically oxidations using Na$_2$WO$_4$−H$_2$O$_2$,[4] IBX-Oxone,[5] RuCl$_3$−NaBrO$_3$,[6] CrO$_3$−H$_5$IO$_6$,[7] and TEMPO−NaOCl.[8] After further evaluation of this collection of leads, only TEMPO−NaOCl showed the potential to achieve the required level of conversion and purity and, consequently, was chosen for additional development.

TEMPO−NaOCl Oxidation. Although NaOCl with catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) is a well-recognized procedure for generating carbonyl com-

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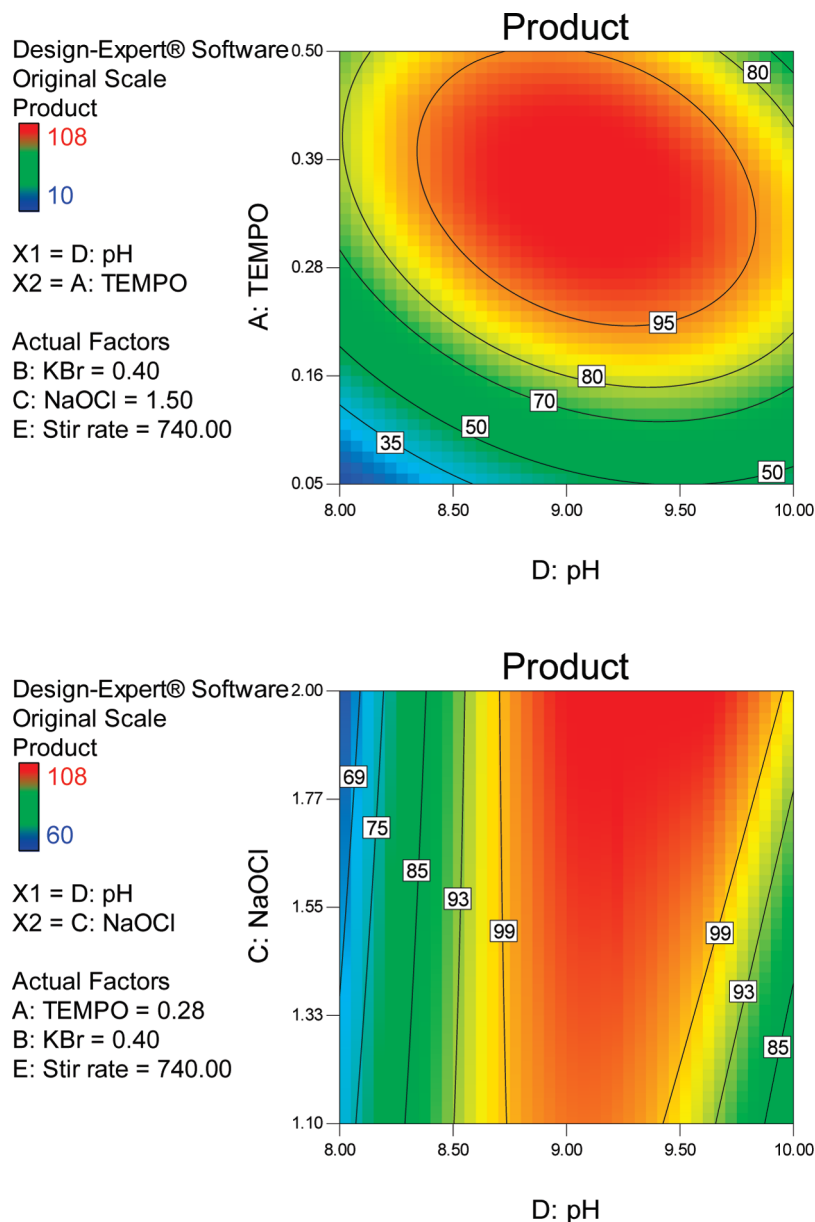
Figure 1. Response surface contour maps from CCD of TEMPO reaction, comparing (a) TEMPO vs pH of NaOCl, and (b) NaOCl vs pH of NaOCl for product levels (area %) after 1 h.

pounds from corresponding primary alcohols, it typically performs poorly with hindered secondary alcohols. Initial trials on **2** using standard literature conditions (0.01−0.1 equiv of TEMPO, 1.1−1.5 equiv of NaOCl (pH ≈ 8.6), 0.1 equiv of KBr, CH$_2$Cl$_2$, 0 °C) provided a maximum 80% of **1** and showed poor reproducibility. However, because the conversion could be increased by adding more catalyst and oxidant, continued investigation of this method using larger catalyst loadings was warranted as the cost of TEMPO is not prohibitively high.[9]

Further screening confirmed many findings from the literature: that CH$_2$Cl$_2$ is a superior solvent, that KBr—added to generate the reactive oxidant HOBr in situ—was required and superior to alternative bromide sources, and that 0 °C was the optimal temperature. From these scoping experiments, the oxidation was studied in detail using statistical design of experiments (DoE). After an initial 2^{5-1}-factorial screening design indicated significant curvature, a face-centered central composite design (CCD, $\alpha = 1.0$) was used to generate a response surface. The factors included in the design and their ranges are listed in Table 1.[10] Contour graphs from this DoE (Figure 1) indicate that the reaction is highly sensitive to TEMPO loading and pH of NaOCl (adjusted with solid NaHCO$_3$). As shown in Figure 1a, the expected yield declines dramatically as TEMPO and the pH of NaOCl are varied from 0.35 equiv and 9.0, respectively. While there was a significant (though lesser) effect from KBr and stir rate, it was interesting that the amount of NaOCl did not play a vital role in this reaction at the factor range studied (Figure 1b).

(9) The best price obtained to date for TEMPO is ∼$100/kg at metric ton scale.

(10) Factor ranges were set on the basis of scoping experiments to generate sufficient variation in response while still examining a reasonable potential operating space. Information on the DoE used in this study, including details on the design, methodology, and models generated, can be found in the Supporting Information.

Table 1. Factors and ranges for CCD ($\alpha = 1.0$) with TEMPO−NaOCl

factor	units	−1/−α	0	+1/+α
A: TEMPO	equiv	0.05	0.28	0.50
B: KBr	equiv	0.05	0.28	0.50
C: NaOCl	equiv	1.1	1.55	2.0
D: pH of NaOCl[a]	pH	8.0	9.0	10.0
E: stir rate[b]	rpm	300	600	900

[a] pH of NaOCl was adjusted using $NaHCO_3$. [b] Using RS-10 stemblock stirrer set points.

Verification runs of the optimal conditions determined from the CCD (0.35 equiv of TEMPO, 1.5 equiv of NaOCl at pH 8.8−9.2, 4 L·kg^{-1} CH_2Cl_2 at 0 °C, ∼1 h) gratifyingly confirmed the predicted model, providing ∼96−97% solution yields of **1**. It is believed that the steric hindrance around the secondary carbinol of **2** causes reduced reactivity and thus the need for such high loadings of TEMPO. Reduced reactivity raises the likelihood of some of the unstable catalytic species decomposing prior to complete conversion. Steric hindrance is a known limitation of TEMPO reactions and is one reason they are often used to selectively oxidize primary alcohols over secondary ones.[8a,11,12] With 0.35 equiv of TEMPO, the reactions typically achieved high conversion with few observed side products, and the catalyst was removed by a reductive aqueous workup with ascorbic acid.

However, even at such high loadings there were still reproducibility issues which led to incomplete conversions in certain experiments. After eliminating variables such as quality of input **2**, purity of TEMPO catalyst, concentration of NaOCl, exotherm during the NaOCl addition, and other parameters, we focused on the adjusted pH of the NaOCl solution. Using UV measurements to rapidly titrate the active chlorite concentration of our bleach, we were able to examine how various reaction conditions affected the oxidant species in solution. Interestingly, while commercial bleach at pH ≈12 appeared to be stable, NaOCl at pH ≈9.0 showed decay of chlorite content in a time- and temperature-dependent fashion. Most significantly, this decrease is appreciably accelerated in the presence of KBr and/ or TEMPO—for instance, mixtures of NaOCl and KBr at concentrations comparable to optimized reaction amounts lost all active oxidant within 60 min at 0 °C, even in the absence of substrate.

Clearly, competitive reactions were vying for active oxidant: one pathway productively oxidizing **2** to desired product **1** with other(s) consuming the stoichiometric oxidant (either in the form of NaOCl, HOCl, or HOBr) in unproductive manifolds. To date, the terminal product of the oxidant decomposition has not been confirmed, and the question of whether or not gases (e.g., O_2,
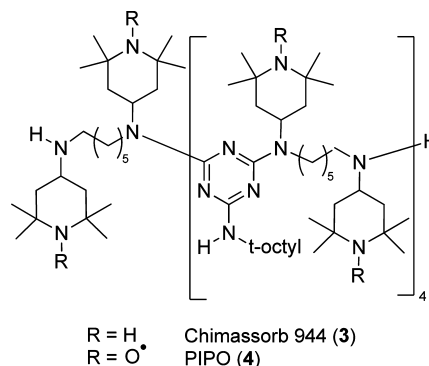

R = H, Chimassorb 944 (**3**)
R = O•, PIPO (**4**)

Figure 2. Structure of Chimassorb 944 (**3**) and PIPO (**4**).

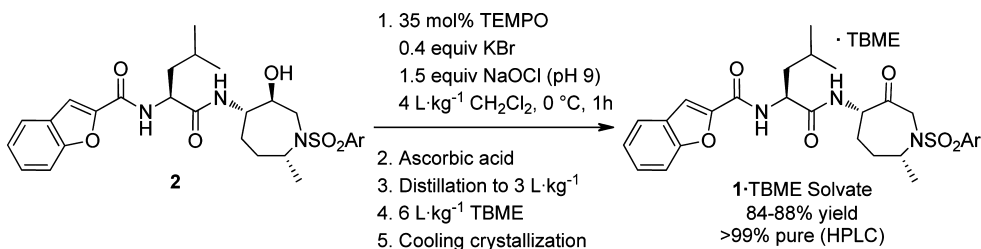**Table 2.** Factors and ranges for CCD ($\alpha = 1.5$) with PIPO−NaOCl

factor	units	−α	−1	0	+1	−α
A: PIPO	wt %	0.43	1.67	4.17	6.67	7.91
B: KBr	equiv	0	0.03	0.12	0.2	0.24
C: NaOCl	equiv	0.93	1.1	1.45	1.8	1.97
D: pH of NaOCl[a]	pH	8.05	8.4	9.1	9.8	10.15
E: stir rate[b]	rpm	276	400	650	900	1024

[a] pH of NaOCl was adjusted using $NaHCO_3$. [b] Using RS-10 stemblock stirrer set points.

Cl_2, Br_2) might be produced leaves a long-term safety question lingering over this reaction. Although addition of more NaOCl solution (adjusted to pH ≈ 9.0) to stalled reaction mixtures was an option for driving the reaction to completion, the overall process was clearly not considered robust. The best conditions with NaOCl−TEMPO, based upon the results from the CCD and some optimization of a reductive workup using ascorbic acid (to reduce excess NaOCl and oxidized catalyst), are shown in Scheme 2.

PIPO−NaOCl Oxidation. Concurrent with efforts to optimize the TEMPO protocol, we sought to identify alternative *N*-oxy free radical catalysts which might prove more robust or more reactive than TEMPO, and thus confer additional reliability to the process. Standard replacements for TEMPO (e.g., 4-hydroxy-TEMPO) proved inferior. Iwabuchi's observation[12] that reactive 2-azaadamantane *N*-oxyl (AZADO) radicals successfully oxidize secondary alcohols and resist decomposition pathways typical of TEMPO was inspiring, but the length of synthesis and projected cost of the catalyst precluded investigation. A polymer-immobilized piperidinyloxyl radical (PIPO, Figure 2) reported to be more active than TEMPO (per nitroxyl group) was a potentially attractive option.[13] This catalyst can be accessed by Na_2WO_4−H_2O_2 oxidation of Chimassorb 944, a sterically hindered amine which is marketed as an antioxidant and light stabilizer. The improved reactivity reported for PIPO

Scheme 2. Conditions for producing 1 using optimized NaOCl−TEMPO chemistry

1. 35 mol% TEMPO
   0.4 equiv KBr
   1.5 equiv NaOCl (pH 9)
   4 L·kg^{-1} CH_2Cl_2, 0 °C, 1h
2. Ascorbic acid
3. Distillation to 3 L·kg^{-1}
4. 6 L·kg^{-1} TBME
5. Cooling crystallization

2 → **1**·TBME Solvate
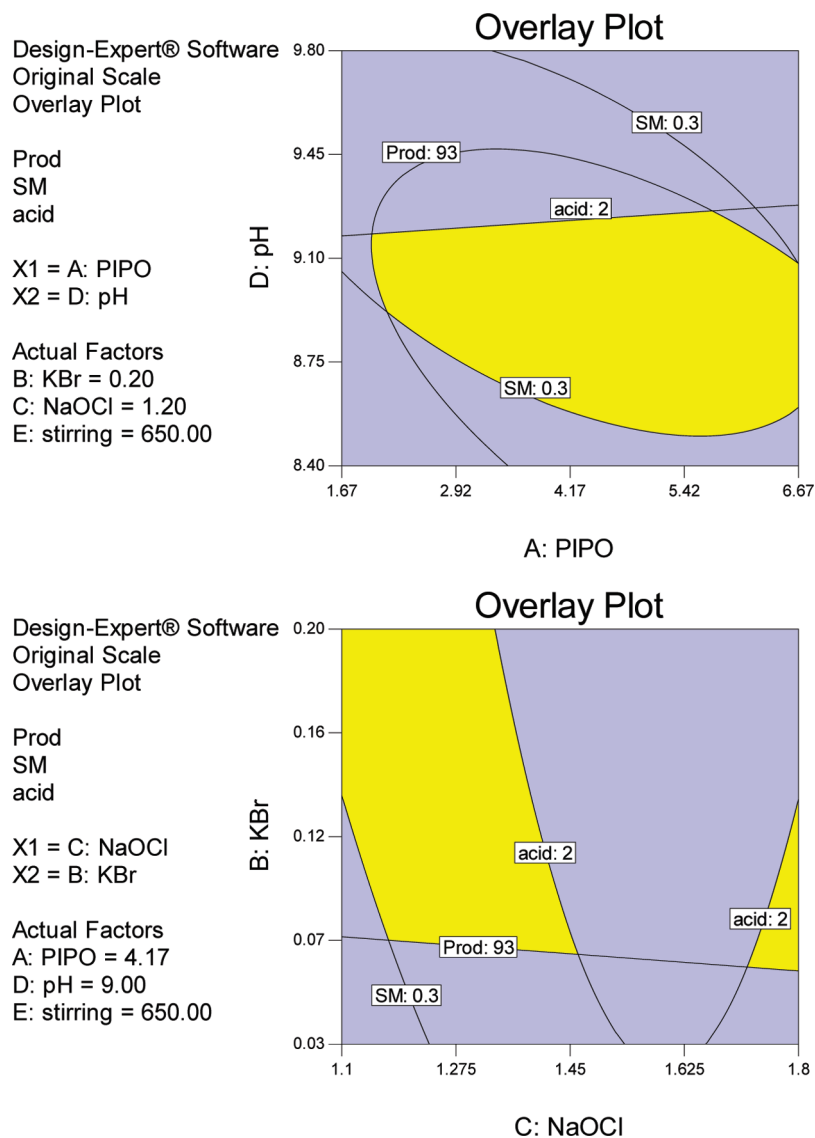84−88% yield
>99% pure (HPLC)

Figure 3. Optimization using contour overlay plots from the PIPO CCD, comparing (a) pH of NaOCl vs PIPO, and (b) KBr vs NaOCl. Areas in yellow achieve optimization target criteria to achieve solution measurements of product 1 (>93 area%), starting material 2 (<0.3 area%), and an acid impurity (from hydrolysis of the amide, <2 area %).

offers the possibility of reaction conditions with lower catalyst loadings, and solvent- and halide-free conditions, allowing the catalyst to be filtered and recycled.

PIPO proved to be highly reactive in the NaOCl oxidation of **2**, although CH_2Cl_2 was still required. After an initial 2^{5-1}-factorial screening DoE, the design was augmented to a CCD ($\alpha = 1.5$) to optimize the reaction and obtain models to understand interactions and curvature (see Table 2 for factor ranges).[10] Figure 3 illustrates overlay plots which highlight key findings from this DoE. In this instance, the pH of NaOCl and the two-factor interaction of pH of NaOCl and PIPO loading had the largest impact on the reaction outcome, while mixing and PIPO loading had relatively little effect. From the graphical optimization, high levels of conversion and purity were predicted with 3 wt % PIPO (~6.6 mol % on N—O basis) and 0.2 equiv of KBr (1.1 eq equiv of NaOCl at pH 9.0 with normal agitation). This method represents a significant improvement in efficiency over the TEMPO process outlined above (approximately 10 wt % catalyst and 0.4 equiv of KBr).[14]

The PIPO conditions offered several advantages over the TEMPO process. Most importantly, significantly reduced catalyst loadings and low cost made this an attractive option. Additionally, existing commercial applications of Chimassorb 944 implied a reliable supply source for PIPO. Lastly, the conditions identified for PIPO appeared less dependent on mixing, a parameter which is notoriously difficult to scale with

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(14) To our best knowledge, Chimassorb 944 is used to coat plastic and is typically sold by the pallet. A full pallet (~1320 lbs) is priced at $12.70/lb, which is equivalent to ~$28/kg. The best price obtained to date for TEMPO is ~$100/kg at metric ton scale, making the PIPO catalyst approximately 1/10th the price of TEMPO per kg of substrate.

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Scheme 3. Original Moffatt reaction conditions

1. 10 L·kg^{-1} DMSO, 3 equiv Ac$_2$O, 60 °C, 3h
2. 10 L·kg^{-1} EtOAc 6 L·kg^{-1} H$_2$O
3. Wash 3 x 6 L·kg^{-1} H$_2$O
4. Conc to 3 L·kg^{-1} EtOAc

predicable results. However, a nearly intractable emulsion observed at the end of the reaction represented a significant obstacle to further development. Phase separation could only be achieved by elevating the temperature near the reflux temperature of dichloromethane. The polymeric oxy radical appears to act as a surfactant, which aids in the biphasic catalysis but disrupts normal partitioning for this two-solvent system.

Optimization of Moffatt Conditions. Although the TEMPO and PIPO oxidations of **2** held promise as greener alternatives to existing conditions, significant limitations associated with the hypochlorite procedures prompted us to revisit the original Moffatt oxidation[15] (see Scheme 3) to see whether drawbacks with this chemistry could be minimized. These shortcomings included the following:

(1) production of methyl sulfide (DMS), an odorous gas which requires complicated air and waste handling during processing and also contributes a detectable odor to the isolated product;

(2) the use of large amounts of DMSO, a solvent with known safety and handling issues which generates SO$_x$ gases upon incineration;

(3) volume inefficiency: to process one kilogram of **2** required a total of 20 L of organic solvents and 24 L of water;

(4) sensitivity to water, requiring the use of extremely dry (and thus very expensive) DMSO for processing.

The issue of odor was difficult to resolve largely because the human nose can detect DMS at parts per *billion* levels.[16] Washing the EtOAc product extracts with water or bleach did not reduce the amount of DMS in the organic layer. Fortunately, 32 wt % peracetic acid (AcOOH) and 3 wt % hydrogen peroxide both reduced DMS to below the limit of detection by GC. However, these results had two unforeseen implications. First, one of the only major impurities seen for the Moffatt chemistry, Pummerer byproduct **3**, gave rise to daughter impurities arising from oxidation of **3** to the sulfoxide and sulfone derivatives (Figure 4). Second, use of these oxidative workup conditions brought significant complications to the process in the form of safety concerns over levels of peroxide in both organic product layer and aqueous waste streams. Thus, both would have to undergo a reductive treatment (e.g., aqueous sulfite) prior to further processing. Given the fact that these peroxide workups reduced but did not eliminate odors in the
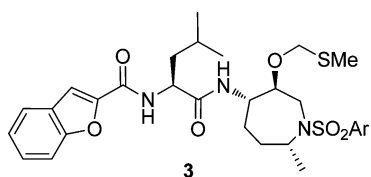
Figure 4. Structure of Pummerer impurity 3.

Table 3. Factors and ranges for CCD ($\alpha = 1.0$) for Moffatt oxidation

factor	units	−1/−α	0	+1/+α
A: concentration (DMSO)	L·kg^{-1}	3.5	4.0	4.5
B: Ac$_2$O	equiv	2.0	3.0	4.0
C: temperature	°C	50	60	70
D: water	equiv	0	0.5	1.0

process, the additional operations and increased waste streams were considered unjustified.

The remaining three issues with the process mostly centered on the use of DMSO; thus, optimization began by evaluating whether DMSO was needed as solvent. Given that only one equivalent of DMSO is theoretically required to perform the oxidation, reducing the amount used should positively impact many of the downstream processing issues such as waste handling and cumulative solvent usage. However, reduction of the amount of DMSO had a significant impact on the oxidation. Reducing the DMSO levels from 10 to 5 L·kg^{-1} led to nearly doubling the production of Pummerer byproduct **3** (from 1.2% to 2.1%). Believing this to be a concentration effect, it was unexpected to discover that performing the chemistry at half the total concentration, 10 L·kg^{-1} of DMSO/EtOAc (1:1 v/v), afforded the same composition of **3** in the product solution.

Surprised by these results, a face-centered CCD ($\alpha = 1.0$) was carried out to study the impact the three main parameters for the chemistry (concentration, Ac$_2$O, and temperature) had on the reaction rate and impurity profile. Additionally, water was added as a factor for investigation as it had previously been identified as detrimental to the oxidation. The factor settings are shown in Table 3.[10] Interestingly, both product **1** and byproduct **3** are most significantly impacted by the amount of Ac$_2$O and water present in the reaction. Those two factors alone, and the interaction between them, account for approximately 55−65% (adjusted R^2) of these models (4 h time point). As can be seen in Figure 5a, conversion drops precipitously when >0.5 equiv of water (which represents a loading of just 1.7 wt % relative to **1**) and <3 equiv of Ac$_2$O are used. Likewise, **3** is formed with increased water and anhydride amounts (Figure 5b). Although the graph in Figure 5b would imply that Pummerer formation is not sensitive to water when 2 equiv of Ac$_2$O is present, this is simply a reflection of the overall low conversion under these conditions.

The effect of water (and that of Ac$_2$O, as they are interrelated) is best understood in the context of attempts to make an authentic sample of Pummerer compound **3** to study its solubility. Some standard ways to install the methylthiomethyl (MTM) ether were not particularly
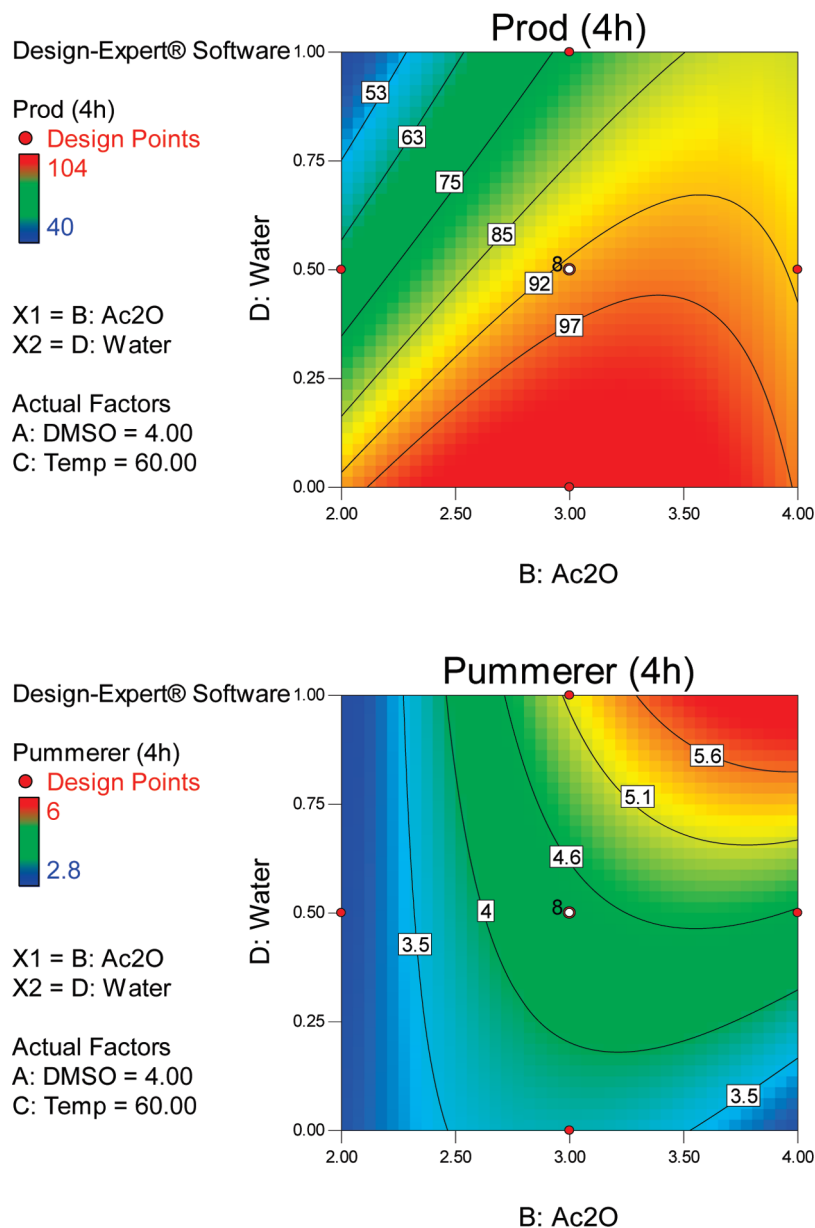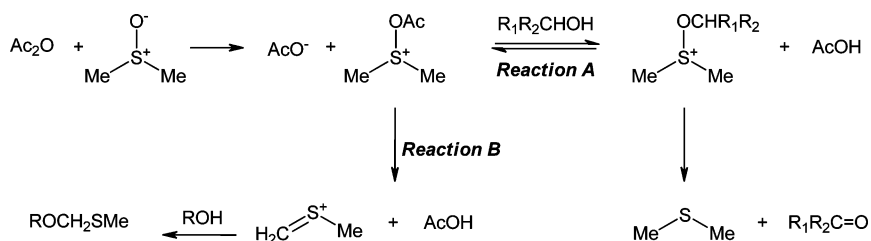
Figure 5. Response surface contour plots from CCD of (a) product 1 (area %, 4 h time point) and (b) Pummerer 3 (area %, 4 h time point) with respect to water and Ac₂O amounts.

Scheme 4. Mechanism proposed by Pojer and Angyal[18] for formation of MTM ethers versus oxidation using Moffatt oxidation conditions

effective,[17] but a procedure using DMSO−Ac₂O *plus AcOH* worked quite well.[18] As illustrated in Scheme 4,

the authors propose that the effect of AcOH is to shift the equilibrium of **Reaction A** to the left and drive the reaction toward formation of the MTM ether. Given this mechanism and the effect of AcOH, the role of water appears simply to be to hydrolyze Ac₂O to generate more AcOH and shift the equilibrium. This consumption of reagent also impacts the rate of conversion. This finding

(16) Tsai, C.-J.; Chen, M.-L.; Ye, A.-D.; Chou, M.-S.; Shen, S.-H.; Mao, I.-F. *Atmos. Environ.* **2008**, 8246.
(17) For example, (a) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269. (b) Suzuki, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1979**, 1277.
(18) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.

Table 4. Summary of solvent use improvements for Moffatt oxidation chemistry

	old process [L·kg⁻¹]	new process [L·kg⁻¹]	improvement [%]
DMSO	10	4	60
EtOAc	10	4	60
water	24	7	71
V_{max}	27	13	52
V_{total}	44	16	64

also helps explain the earlier observation that lower amounts of DMSO cause an increase in Pummerer formation, as this increases the effective (localized) concentration of AcOH to further alter the equilibrium of **Reaction A**.

Given the sensitive nature of the reaction to adventitious water, investigating a means to control this factor became a priority. Although efforts to remove AcOH during the course of the reaction—including addition of a base scavenger or distillation under vacuum—were unsuccessful, azeotropic removal of water proved more promising. Thus, adventitious water brought in with **2** or wet DMSO can be removed to low levels by first performing a vacuum distillation with toluene prior to charging of Ac₂O. This allowed lowering the specification of water in the solvent and starting material to reduce cost associated with purchasing extremely dry DMSO and the cycle time for drying **2**.

Having optimized the chemical transformation to 4 L·kg⁻¹ DMSO, the amount of water and EtOAc required to extract out the product could be drastically reduced: 4 L·kg⁻¹ EtOAc easily dissolved all of **1**, and 4 L·kg⁻¹ water was used for the initial extraction, followed by one 4 L·kg⁻¹ water wash of the organic layer to ensure removal of DMSO and AcOH while minimizing yield loss.[19] The sum of these changes reduced the overall solvent usage in the process to 16 L·kg⁻¹ from 44 and brought the V_{max} to 13 L·kg⁻¹, more than doubling the throughput. The overall improvements to the process are shown in Table 4.

Conclusion

Extensive screening of alternative oxidations to convert **2** to **1** highlighted five primary leads. Further investigation demonstrated the TEMPO- or PIPO-catalyzed oxidation with NaOCl to be promising procedures which offer several advantages over the existing Moffatt-type oxidation. These include no odorous emissions, elimination of DMSO from aqueous waste, and greater volume efficiency. Unfortunately, increased sensitivity to processing conditions and reagent instability made the chemistry less robust for manufacturing. Meanwhile, significant improvements to the modified Moffatt oxidation made this procedure less onerous on the environment and more reliable as a manufacturing process. Given considerations such as environmental impact, process safety, product quality, as well as cost of goods, this work clearly highlights the significant challenges of developing a carbinol oxidation suitable for manufacturing scale.

(19) Excess Ac₂O had to first be quenched prior to extraction to ensure a consistent product mixture going in to the crystallization. This was easily achieved by treating the 60 °C reaction mixture with 2 L·kg⁻¹ water for 1 h prior to performing the EtOAc extraction.

Experimental Section

General. Unless otherwise indicated, all reactions were conducted under a nitrogen atmosphere. Reaction in-process monitoring was conducted by reversed phase HPLC using an YMC ODS-AM 250 mm ×4.6 mm (5 μm) column using a 30 min isocratic method: 1:1 acetonitrile/water containing 0.05% TFA with 1 mL/min flow, detection at 265 nm. HPLC determination of API purity was done using an ACE 3 C18 150 mm ×4.6 mm (3 μm) using a step-down gradient method over 38 min: 95:5 to 5:95 mobile phases A/B (A = acetonitrile/water (80:20 v/v with 0.01% TFA); B = acetonitrile/IPA (95:5 v/v). More detail of HPLC conditions with gradients and retention times can be found in the Supporting Information. All DoE data were processed using Design-Expert Version 7.0.3.

N-[(1*S*)-3-Methyl-1-({[(4*S*,7*R*)-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)hexahydro-1*H*-azepin-4-yl]amino}carbonyl)butyl]-1-benzofuran-2-carboxamide-1,1-dimethylethyl Methyl Ether (1:1) [TBME Solvate of 1]. *TEMPO Conditions.* Commercial NaOCl (5.58%, 70.0 mL, 0.06 mol) was adjusted to pH ≈ 9.5 with solid NaHCO₃ (3.0 g). The NaOCl solution was cooled to 0 °C and then added over 40 min to a 0 °C mixture of carbinol **2** (21.7 g, 0.04 mol), TEMPO (2.16 g, 0.014 mol), and KBr (16.0 mL of a 0.5 M aq solution) in CH₂Cl₂ (87 mL) at <5 °C. After 1 h, the reaction was deemed complete and the phases were separated. The organic phase was returned to the reactor and stirred at 20 °C while solid ascorbic acid (2.4 g, 0.014 mol) was added to reduce any active oxidant and remove some of the dark color. After 20 min, water (43 mL) was charged, and stirring was continued for 20 min as the solids dissolved. The phases were separated and the organic phases washed again with water (87 mL). Analysis showed a 97% solution yield of **1**. The product solution was concentrated under vacuum to 3 L·kg⁻¹ (65 mL) and heated to 45 °C. *tert*-Butyl methyl ether (TBME) (109 mL) was added and the solution cooled to 40 °C, and seeds of **1**·TBME solvate (11 mg) were added as a slurry in TBME. After holding for 1 h, the product slurry was cooled to 24 °C at 0.5 °C/min. To the thick slurry was added additional TBME (65 mL) over 30 min. The mixture was further cooled to 5 °C over 2 h and then filtered, and the product was rinsed with TBME (2 × 43 mL). The product was dried under vacuum to give 21 g (84% yield) of white powder. Reverse-phase HPLC indicated ≥99 area % purity. ¹H NMR δ (CDCl₃, 300 MHz) 8.70 (dq, 1H, 4.7, 0.9 Hz), 7.99 (dt, 1H *J* = 7.9, 1.0 Hz), 7.92 (dt, 1H, *J* = 10.1, 1.7 Hz), 7.64 (d, 1H, *J* = 7.4 Hz), 7.51 (dt, 1H, *J* = 6.1, 1.4 Hz), 7.48 (dd, 2H, *J* = 5.7, 0.9 Hz), 7.41 (dt, 1H, *J* = 7.2, 1.3 Hz), 7.28 (dt, 1H, *J* = 6.8, 1.0 Hz), 7.17 (d, 1H, *J* = 8.5 Hz), 7.06 (d, 1H, *J* = 6.5 Hz), 5.13 (m, 1H), 4.76 (m, 2H), 4.41 (m, 1H), 3.85 (d, 1H, *J* = 19.5 Hz), 3.20 (s, 3H, CH₃OtBu), 2.14 (m, 2H), 1.74 (m, 3H), 1.5 (m, 2H), 1.18 (s, 9H, MeOC(CH₃)₃), 0.99 (d, 6H, *J* = 5.5 Hz), 0.95 (d, 3H, *J* = 7.0 Hz). ¹³C NMR δ (CDCl₃, 75 MHz) 206.8, 171.1, 159.0, 158.1, 155.2, 150.7, 148.6, 138.5, 127.9, 127.5, 127.3, 124.1, 123.1, 122.7, 112.3, 111.3, 57.6, 52.6, 52.5, 51.9, 49.8, 42.3, 33.7, 27.6, 27.4, 25.2, 23.3, 22.6, 15.9.

Moffatt Conditions. Carbinol **2** (100.0 g, 0.184 mol) was charged to a flask with a gas outlet to a bleach scrubber.

Anhydrous DMSO (400 mL) and Ac$_2$O (56.4 g, 0.553 mol) were added, and the vessel contents were heated to 60 °C over 30 min. After 2 h, the reaction was complete. The excess Ac$_2$O was hydrolyzed by the addition of water (200 mL) and stirring at 60 °C for 1 h. The mixture was diluted with EtOAc (400 mL) and water (200 mL) and cooled to 20−25 °C. The phases were separated, and the top organic phase was washed with a 1 wt % brine solution (400 mL). Analysis of the organic layer showed a ≥95% solution yield of **1**. The organic phase was distilled under vacuum to 300 mL (3 L·kg^{-1}) and the solution warmed to 50 °C. TBME (500 mL) was added, the solution was cooled to 40 °C, and seeds of **1**·TBME solvate (160 mg) were added. The resultant slurry was held at 40 °C for 2 h, then cooled to 5 °C and isolated by filtration. The cake was washed with TBME (2 × 200 mL) and dried under vacuum to afford 93.4 g (81% yield) of white powder which was 99.7 area % pure by HPLC and had spectroscopic data identical to those of the product generated via the TEMPO method.

Supporting Information Available

More detailed description of the experimental designs conducted in this study and the models generated, as well as details on the analytical methods. This material is available free of charge via the Internet at http://pubs.acs.org.