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COMMUNICATION

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Development of a Safe and Practical *N*-Oxidation Procedure Using *m*-CPBA in Acetic Acid

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ABSTRACT: A safe and practical procedure for the *N*-oxidation of pyrazolopyridine **4** using *meta*-chloroperbenzoic acid (*m*-CPBA) in acetic acid is described. Key safety experiments are outlined which have led to the development and implementation of this reaction on 28-kg scale in 98% isolated yield.

INTRODUCTION

During the course of a program to develop orally active non-nucleoside reverse transcriptase inhibitors (NNRTIs) against HIV reverse-transciptase mutation, compound **1** was brought forward for clinical development.[1] Amongst the key structural features of **1** is the pyrazolo-[3,4-β]-pyridine fragment. In particular, the 2-amino substituent on the pyrazolo-[3,4-β]-pyridine presented a considerable synthetic challenge that was not initially obvious from its apparently simple structure. The synthesis of **1** had evolved from its predecessor in clinical development, which did not contain the 2-amino substituent (Scheme 1).[2] Thus, the installation of the amino group was developed from a recent report which demonstrated that the reaction of pyridine *N*-oxides with tosic anhydride (Ts_2O) in the presence of *tert*-butylamine, followed by cleavage of the *tert*-butyl group with trifluoroacetic acid as an attractive method for the preparation of 2-aminopyridines from the parent unsubstituted pyridine.[3] In this case, the pyrazole nitrogen atom also required protection due to competitive tosylation; thus, **2** was the target from *N*-oxide **3**. In turn, the preparation of the key *N*-oxide intermediate **3** was required from pyrazolopyridine **4** using *m*-CPBA, a common reagent in organic synthesis used for heteroatom oxidations and epoxidations, but with safety concerns when used on scale. *m*-CPBA has been used frequently over the years with many examples of its use on pilot scale and pharmaceutical manufacturing.[4] However, the safety concerns with its use on scale are well-known, with the pure solid being shock-sensitive and potentially explosive in the condensed phase.[5,6] The commercial grade (70−77 wt %) although somewhat stabilised with chlorobenzoic acid and water still represents a significant concern when used on scale. The use of this reagent has been reported in many solvents, but *Bretherick's Handbook of Reactive Chemical Hazards* notes some incompatibility with certain solvents such as DMF and DMSO, with storage also recommended at 4 °C. The reagent's stability in solution has also been observed to be well below that of the solid form.[7]

Initial experimentation showed that the oxidation of pyrazolopyridine **4** to *N*-oxide **3** (Figure 1) was difficult due to a slow rate of reaction leading to incomplete conversion of starting material which, when coupled with the inherently poor physical properties of **3** and **4** leading to very thick slurries, made the reaction a concern for scale-up. An urgent program need for multikilogram quantities of **1**, combined with the challenging conversion of **4** to **3** and the safety concerns of using *m*-CPBA on scale, consequently necessitated the rapid development of a safe and scaleable protocol to prepare the key *N*-oxide intermediate **3** (Scheme 1).

RESULTS AND DISCUSSION

The initial conditions used for the preparation of *N*-oxide **3** employed *m*-CPBA in ethyl acetate (EtOAc) at 55 °C. The protocol consisted of the addition of 1.7 equiv of solid *m*-CPBA in multiple portions to a thick and inhomogeneous slurry of **4** in EtOAc at 55 °C. The limited solubility of starting material **4** and product **3** in EtOAc led to a poorly controlled slurry to slurry conversion, culminating in incomplete conversion (∼ 90%). This was reasoned to be due to entrainment of the starting material in the *N*-oxide product. In addition, the thick product slurry had very poor filtration properties, which significantly slowed the filtration and would have been impractical on scale. Also, the excess *m*-CPBA reagent was not quenched at the end of the reaction and was of concern.

Reaction Development. The first objective was to increase the conversion of **4** to **3** above 90% to positively impact the productivity through to **1** and simultaneously improve the safety profile of the reaction. As already noted, charging extra *m*-CPBA reagent did not increase conversion beyond 90%. This was also undesirable from a safety standpoint due to the inherent lack of control when adding an unstable solid oxidant to a thick, inhomogeneous slurry, thus giving the potential for accumulation of oxidant in the reaction vessel.

Initial attempts to increase the conversion started with adding *m*-CPBA slowly as a solution in EtOAc to the pyrazolopyridine substrate **4** in EtOAc, however, these were not successful. Similarly, increasing the dilution of the reaction mixture up to 35 mL/g in EtOAc to aid mobility in the reaction system did not prove fruitful. Addition of cosolvents (ethanol (EtOH) and H_2O) also failed to facilitate an improvement in the conversion beyond 90%.

Next, a solubility screen was undertaken with both the starting material **4** and *N*-oxide **3** (Table 1) to assess the potential for better physical properties in the reaction and thus, push the reaction to completion with the added benefit of improving the safety profile. Most of the solvents in the screen unfortunately did

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not offer better solubility of either **4** or *N*-oxide **3**. Dimethylacetamide (DMAc) was also explored as a solvent (despite the known concerns over the compatibility of *m*-CPBA and dimethylformamide (DMF)[5]) as **4** and **3** were found to be fully soluble at 10 mL/g. However, the reaction still disappointingly only proceeded to 80% conversion after 5 h at 55 °C and resulted in a significantly worse purity profile.

Whilst the solubility of **4** and **3** was poor in most common solvents, solubility measurements in acetic acid (AcOH) indicated its potential use as a solvent, and pleasingly, with 1.6 equiv of *m*-CPBA at 55 °C in AcOH, > 99% conversion to *N*-oxide **3** was achieved. This was the first time this difficult reaction had been observed to reach full conversion, and with the starting material and product being more soluble at the start and end of the reaction, it gave much better potential for the development of a safer protocol to be used on scale. Further optimisation of this procedure resulted in the addition of 1.6 equiv of *m*-CPBA as a solution in AcOH (7 mL/g) to a thin slurry of **4** at 55 °C over 45 min to 1 h to maintain the reaction temperature. Typically, conversion at the end of the addition of the *m*-CPBA solution was 50−60%. By the end of the addition, the reaction mixture was completely homogeneous, which was a major improvement for the physical properties of the reaction, and as a result, after 3 h at 55 °C, the reaction reached completion (>99%). This protocol also offered good control of the reaction through limiting the potential for accumulation of oxidant.

Quench/Crystallization. With the reaction in satisfactory condition, isolation of the *N*-oxide product **3** now required some development. Variation was observed at the end of the reaction where the *N*-oxide product crystallized from some reaction mixtures after overnight ageing at 55 °C, whereas from other reactions, the *N*-oxide did not crystallize even upon cooling to ambient temperature and addition of seed. In addition, the spontaneous crystallization of **3** afforded a thick slurry with poor filtration properties and long time cycles due to the crystal morphology (long, hair-like needles). Where no crystallization was observed, up to 17−18 mL/g of H_2O was required as an antisolvent which gave better crystal morphology and a more filterable slurry, and this became the preferred isolation protocol. Further addition of H_2O to reduce mother liquor losses resulted in entrainment of 3-chlorobenzoic acid which could not be removed by the usual washing of the wetcake with EtOH/H_2O.

As part of the safety testing, the mother liquors from the crystallization were shown to contain residual *m*-CPBA. As a result, 13 mL of liquors from a laboratory experiment were shown an 18 mL Z-3 cell to pressurise to 1 psi over 23 h at 35 °C (vide infra). Therefore, to avoid pressurisation of waste drums of liquors, a sodium bisulfite quench was rapidly developed. Accordingly, 0.7 equiv of sodium bisulfite dissolved in H_2O (2 mL/g) was added directly to the reaction mixture at the end of reaction, after which testing with starch strips showed peroxide levels were below detectable limits. After addition of the sodium bisulfite solution, a further addition of H_2O (19.5 mL/g) was made, and this reliably resulted in agglomerated crystals of *N*-oxide **3** with an enhanced filtration rate.

Safety Testing. Given the known safety issues with using *m*-CPBA and the introduction of an uncommon solvent (AcOH) for the reaction, an extensive range of safety experiments were conducted to aid the development of a safe process amenable for a multikilogram scale reaction. Differential scanning calorimetry (DSC) was used to evaluate exothermic decompositions, advanced reaction system screening tool (ARSST) to characterize exothermic decomposition rates as a function of temperature, and accelerating rate calorimetry (ARC) to evaluate reaction mixture sample

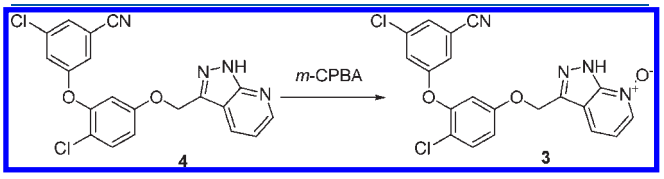
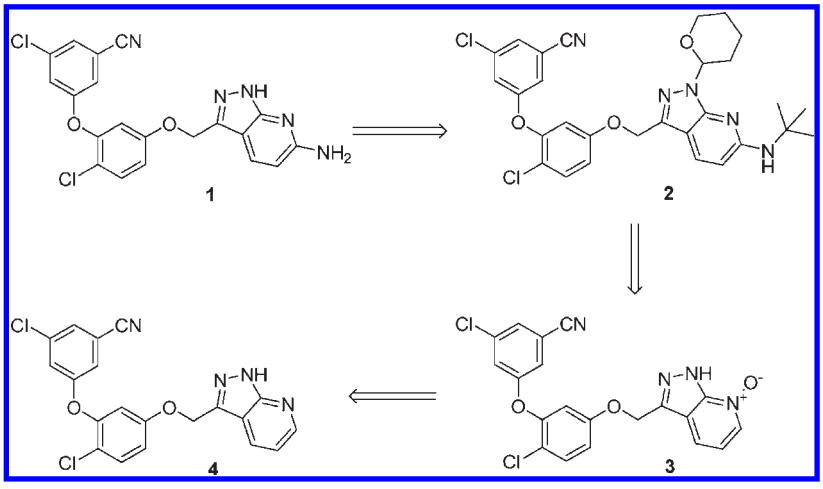


Figure 1. *N*-oxidation of pyrazolopyridine **1**.

Table 1. Solubility data for 3 and 4 at 20 °C

solvent	solubility of SM, **4** (mg/mL)	solubility of *N*-oxide, **3** (mg/mL)
ethyl acetate	10.7	<0.1
ethanol	2.5	<0.1
methanol	3.9	<0.1
dichloromethane	5.4	<0.1
acetonitrile	2.1	<0.1
acetic acid	19.4	7.5
dimethylacetamide	>100	>100

Scheme 1



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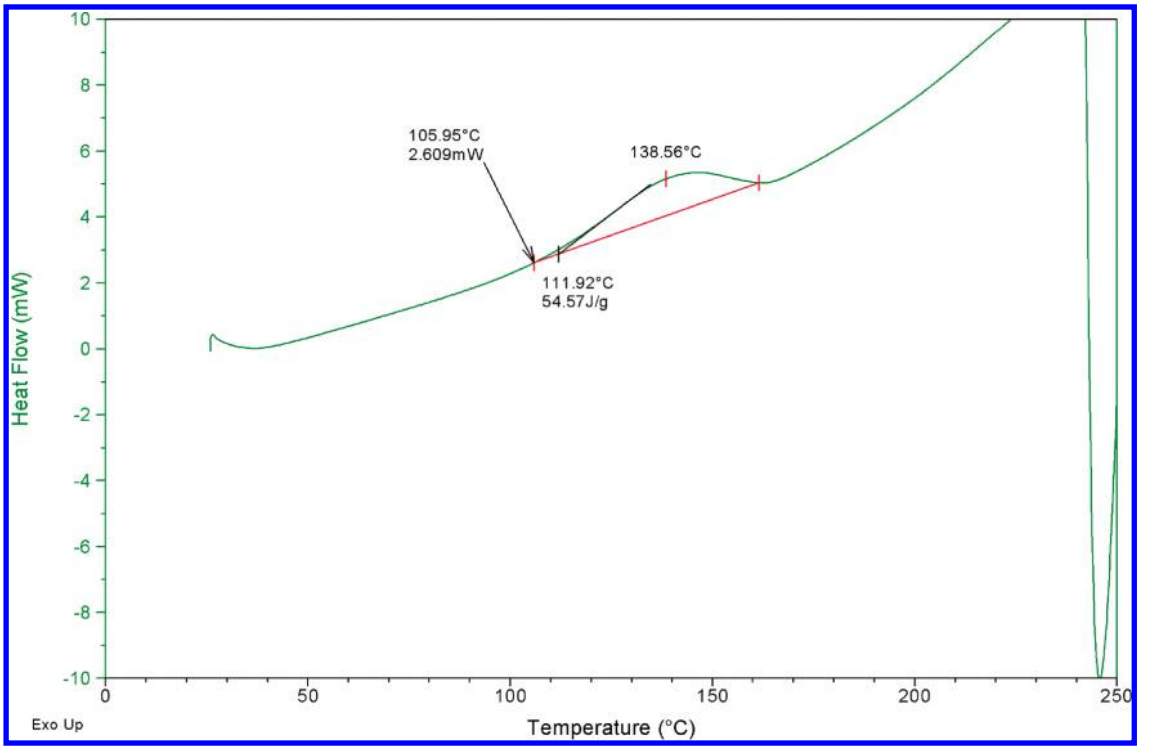

Figure 2. DSC of m-CPBA/AcOH solution.

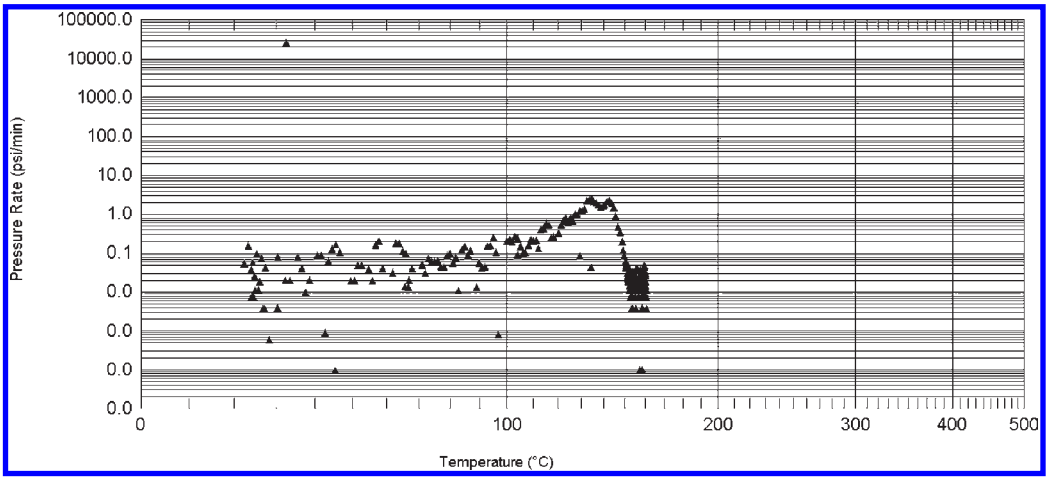

Figure 3. ARSST data: self-heat rate of *m*-**CPBA/AcOH solution.**

kinetics. Also, the chemical reaction calorimeter (CRC) was used to determine reaction stability and exothermic activity.

***m*-CPBA Solution Preparation.** As the oxidant was the main source of concern for the process, a significant number of experiments were performed to determine the stability of the *m*-CPBA in AcOH.

DSC analysis of *m*-CPBA in acetic acid showed a moderate exothermic decomposition of 14.5 cal/g with an onset at 105 °C (Figure 2). As this was well above the operating temperature (ambient) for handling of this solution, preparation of this solution was not a major concern; however, care was still required when warming up the solution for dissolution (see below).

Furthermore, an isothermal age experiment in the CRC of this *m*-CPBA solution at 55 °C (the reaction operating temperature) showed the total pressurization of the solution to be well within the venting capacity of the reaction vessel (150 L/min). Similarly, an ARSST experiment of the *m*-CPBA in AcOH showed the total pressurization from heating to decomposition to be within the venting capability of the reaction vessel (maximum pressure increase of 6.6 psi) (Figures 3 and 4).

With these observations, it was found that the dissolution of *m*-CPBA in AcOH was endothermic, with the temperature dropping between 9 and 11 °C. As the *m*-CPBA in AcOH was found to be thermally unstable, albeit at elevated temperature, care was required in warming it up to complete the dissolution. Overheating the solution risked lowering the assay of *m*-CPBA or triggering an exothermic decomposition; therefore, ~25 °C was maintained in the preparation vessel to prevent overheating of the *m*-CPBA solution.

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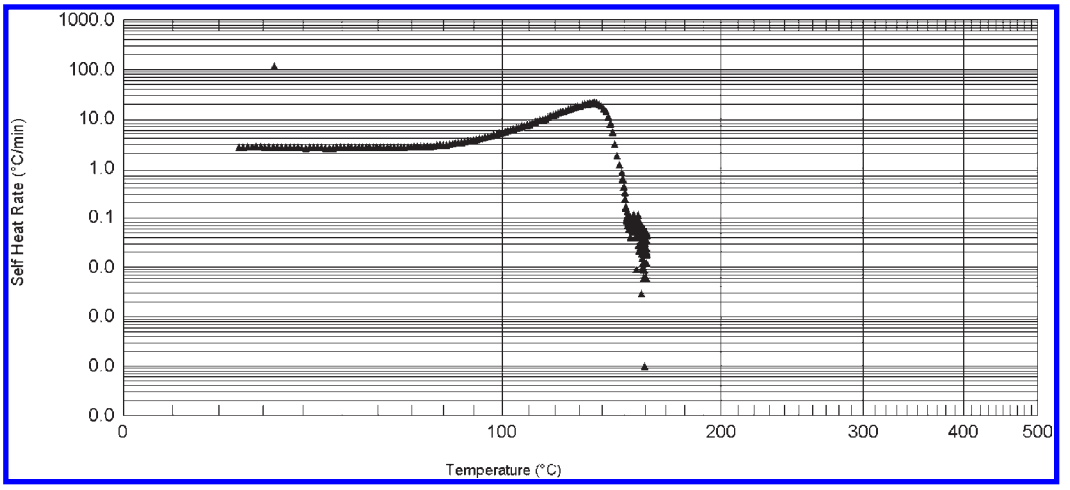

Figure 4. ARSST data: pressurisation rate of *m*-**CPBA/AcOH solution.**

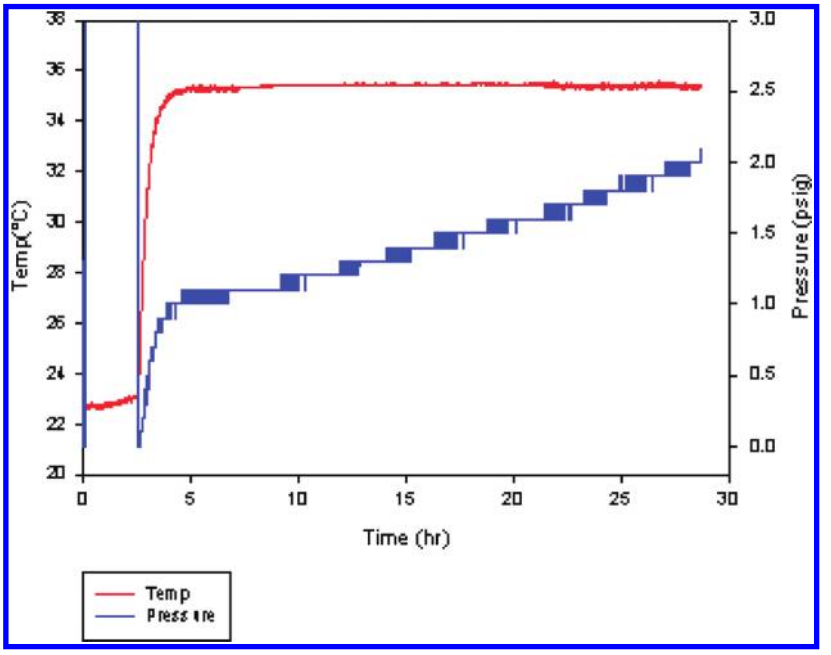

Figure 5. CRC of mother liquors without quenching at end of reaction.

In addition, from further testing it was calculated that the vessel vent was required to handle a gas flow of 0.47 L/h/kg of solution to provide emergency relief for the feed vessel in the case of a runaway decomposition. This was based on an EAC experiment which showed that the solution could run away if cooling was lost.[8] In this experiment, 4.24 g of *m*-CPBA in AcOH solution (prepared by dissolving 5 g of *m*-CPBA in 41 mL of AcOH) was loaded into a SS ARC cell (~10 mL volume; 12.7 g) and heated isothermally at 25 °C for ~15 h. The pressure slowly increased from 16.5 to 25.2 psi, which indicated the gas generation was from the decomposition of the *m*-CPBA. Next, the EAC was placed into adiabatic mode and a 5 °C step heat−wait−search experiment was run.[9] The sample began to exotherm at a self-heat rate of ~0.02 °C/min at 40 °C which continued to ~53 °C or a temperature rise of 13 °C. Correcting for a ϕ of 1.6, the adiabatic temperature rise was 20 °C. The maximum self-heat and pressure rise rates were 0.07 °C/min and 0.09 psi/min, respectively. Upon further heating to 78 °C the pressure was 55 psi, and no additional exothermic activity due to reaction was observed. Upon cool down to 20 °C, the pressure was 38 psi. A sample of this headspace gas was analysed using FT-IR and indicated the presence of CO_2 (O_2 not detected by this method).

For a controlled procedure, the *m*-CPBA solution had to be charged at a rate to maintain 55 °C ± 5 °C, and the venting capacity of the reaction vessel was required to be at least 0.30 L/h/kg of starting material.

Oxidation Reaction. CRC analysis of the reaction showed that gas was slowly evolved during the reaction (rate of 0.30 L/h/kg substrate). On the basis of the TG/MS data, this was expected to be CO_2 with some O_2; therefore, adequate venting was required during the reaction. The total pressurization was measured at 8.6 L/h over 3.5 h = 30.1 L, which was well within venting capability of the vessel (150 L/min). As a precaution,

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blanket sweep control was used in the vessel as the gas was most likely to contain oxygen from decomposition of *m*-CPBA.

Although the reaction was moderately exothermic (−20.8 kcal/mol substrate), part of the exotherm was masked by the addition of the cooler feed solution (*m*-CPBA in AcOH) to the warm batch. The overall heat of reaction was found to be endothermic, but the temperature was calculated to rise above the jacket during the age. The reaction had a pseudo-first-order half-life of 25.8 min at 52 °C, and was expected to take ∼3 h to reach 99% conversion at 52 °C.

Quench. A reaction was performed where, at the end of the reaction, product **3** was crystallized without quenching of the excess *m*-CPBA and the slurry filtered. CRC analysis showed in an 18 mL Hastelloy vessel, that these mother liquors generated 1.077 psi/day of pressure at 35 °C and 72% fill (3.77 psi/day at 90% fill). There was no evidence of the rate decreasing with time over the 24 h of the test (Figure 5). The quench of the excess oxidant using sodium bisulfite was therefore necessary to address this pressurization in the waste liquors. The quench was also characterized and calculated to be exothermic (dH_r = −67.6 kcal/mol, lit., modelled as quenching perbenzoic acid). In the CRC, a total heat of 2.73 kcal/L of batch was measured during the quench (ΔT_{ad}=4 K). Assuming all of the heat was from quenching unreacted *m*-CPBA, the concentration was ∼0.04 mol/L *m*-CPBA at the time of the quench (∼66% of the theoretical excess). Even if the full amount of excess *m*-CPBA was quenched, the ΔT_{ad} would only be 7 K.

The quench was found not to be instantaneous but took ∼90 min to reach completion. Testing for completion of the quench was therefore essential, especially in view of the unquenched mother liquors generating gas in the CRC experiment.

After the addition of sodium bisulfite, small quantities of gas were formed after the $NaHSO_3$ addition. If this gas was assumed to be SO_2 then 0.3 g of SO_2/ L of solution were formed at a slow rate (0.2 g/L/h), and this rate of gas release was also not a concern.

Thermal Stability of Product and Intermediates. The *N*-oxide product was thermally characterized and found to decompose exothermically above 200 °C (well above the operating temperature of drying), and was also not shock sensitive. None of the intermediate streams tested possessed hazardous exotherms

CONCLUSION

In summary, a safe and practical procedure for the *N*-oxidation of pyrazolopyridine **4** was developed and successfully implemented on 28-kg scale using *m*-CPBA in AcOH to achieve >99% conversion and 98% yield of *N*-oxide **3** from a simple, direct, and controlled crystallization procedure. Extensive safety testing and analysis were conducted to determine safe operating parameters for the use of *m*-CPBA in acetic acid at elevated reaction temperature.

EXPERIMENTAL SECTION

General. Melting points were determined by closed cell DSC. HPLC assays were carried using a C-18 reversed-phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile. Assay yields were obtained by HPLC using pure compounds as standards. Isolated yields refer to yields corrected for purity based on HPLC assay using purified standards. All reagents and solvents were used as received without further purification.

N-Oxide, 3. *m*-CPBA (27.1 kg) was charged to a 400-L vessel followed by AcOH (198 L; 208 kg) and stirred for 20 min to fully dissolve the solid *m*-CPBA. (Jacket used to counter dissolution endotherm.)

Pyrazolopyridine **4** (28.3 kg) was then charged to a 1000-L vessel followed by AcOH (425 L; 445 kg), and the slurry was heated to ∼55 °C to obtain a thin slurry.

The *m*-CPBA in AcOH was then transferred to the 1000-L vessel over 45 min whilst maintaining the temperature in 1000-L vessel as close to 55 °C as possible using jacket heating and rate of addition. The line was rinsed with AcOH (5 kg) into the 1000-L vessel. The reaction mixture was aged at 55 °C, and after 3 h, HPLC analysis confirmed complete reaction (>99% conversion).

The batch was cooled to 30 °C, and a sodium bisulfite solution (5.01 kg in 8.0 kg water) was charged over a period of ∼20−40 min whilst maintaining a batch temperature of 30 ± 5 °C using jacket control. A sample of the reaction mixture was tested for oxidant using starch test-strips and found to be below the detectable limit.

Water (550 kg), (19.4 mL/g wrt SM) was then charged over 1 h, maintaining a batch temperature of ∼20−25 °C, and aged for 30 min. The slurry was filtered and washed with ethanol (140 kg)/water (90 kg), and dried in a vacuum oven at 40 °C with a nitrogen bleed for 18 h to afford 32.2 kg (97.9% yield, 97.8 LCAP, 90.0 LCWP, 8.1 wt % H_2O) of *N*-oxide **3** as an off-white solid: mp 197−198 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.49 (s, 2H), 7.09 (dd, 1H, J = 8.8, 2.8 Hz), 7.12 (d, 1H, J = 2.7 Hz), 7.19 (dd, 1H, J = 8.0, 6.0 Hz), 7.35 (t, 1H, J = 2.2 Hz), 7.45 (dd, 1H, J = 2.2, 1.4 Hz), 7.55 (d, 1H, J = 8.8 Hz), 7.78 (t, 1H, J = 1.4 Hz), 7.89 (d, 1H, J = 8.0 Hz), 8.40 (d, 1H, J = 6.0 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 64.1, 110.0, 114.5, 114.6, 117.4, 117.5, 118.5, 118.6, 119.6, 120.1, 122.2, 127.1, 131.8, 135.8, 136.0, 150.5, 152.2, 158.5. Anal. Calcd for $C_{20}H_{12}Cl_2N_4O_3$: C, 56.22; H, 2.83; N, 13.11. Found: C, 56.14; H, 2.79; N, 12.99.

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REFERENCES

(1) (a) Tucker, T. J.; Saggar, S.; Sisko, J. T.; Tynebor, R. M; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M.-T.; Liang, Y.; McGaughey, G.; Liu, M.; Miller, M.; Moyer, G.; Munshi, V.; Perlow-Poehnelt, R.; Prasad, S.; Sanchez, R.; Torrent, M.; Vacca, J. P.; Wan, B. L.; Yan, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2959–2966. (b) Tucker, T. J.; Sisko, J. T.; Tynebor, R. M.; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M.-T.; Liang, Y.; McGaughey, G.; Liu, M.; Miller, M.; Moyer, G.; Munshi, V.; Perlow-Poehnelt, R.; Prasad, S.; Reid, J. C.; Sanchez, R.; Torrent, M.; Vacca, J. P.; Wan, B. L.; Yan, W. *J. Med. Chem.* **2008**, *51*, 6503–6511.

(2) Kuethe, J. T.; Zhong, Y-Li.; Alam, M.; Alorati, A. D.; Beutner, G. L.; Cai, D.; Fleitz, F.; Gibb, A. D.; Kassim, A.; Linn, K.; Mancheno, D.; Marcune, B.; Pye, P. J.; Scott, J. P.; Tellers, D. M.; Xiang, B.; Yasuda, N.; Yin, J.; Davies, I. W. *Tetrahedron* **2009**, *65*, 5013–5023.

(3) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554–4557.

(4) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106* (7), 2943–2989.
(5) Sigma-Aldrich MSDS for *m*-CPBA, available on http://www.sigmaaldrich.com.
(6) Kubota, A.; Takeuchi, H. *Org. Process Res. Dev.* **2004**, *8*, 1076–1078.
(7) Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Elsevier: Oxford, 2007; Vol. 1; p 944.
(8) EAC stands for "enhanced adiabatic calorimeter" and is a larger version of the ARC.
(9) The "heat−wait−search" experiment takes into account the thermal mass of the reaction cell.