

Safe and Scaleable Oxidation of Benzaldoximes to Benzohydroximinoyl Chlorides†

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Abstract:

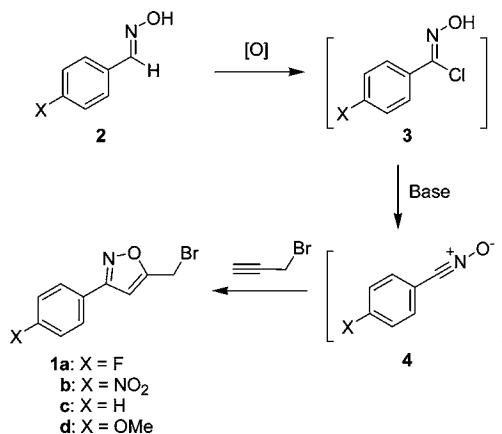
Benzohydroximinoyl chlorides are useful precursors to nitrile oxides used in the preparation of various heterocycles via 1,3-dipolar cycloadditions. These intermediates are typically accessed by oxidation of aldoximes using *N*-chlorosuccinimide. This simple and efficient reaction is highly exothermic and a significant induction period can be observed. The potential for a sudden and significant heat release makes large-scale reactions difficult to control and potentially hazardous. Herein we describe a thermal analysis of this reaction to determine the heat flow in the presence of common additives to determine the most effective means of safe scale-up. Of the additives screened, aqueous HCl consistently avoided an induction period and enabled a dose-controlled process to be developed.

Introduction

In a recent program we required kilogram quantities of the known compound 5-bromomethyl-3-(4-fluorophenyl)isoxazole **1a**.¹ Substituted isoxazoles of this type are well documented in the literature and are typically derived from the 1,3-dipolar cycloaddition of nitrile oxides with alkynes.² The highly reactive nitrile oxides are typically generated *in situ* from the hydroximinoyl chlorides which are readily available by oxidation of the corresponding aldoximes with *N*-chlorosuccinimide (NCS) (Scheme 1).^{3,4}

First, we adapted the known procedures for isoxazole synthesis^{4,5} to the scale-up of **1a**, deciding on a one pot, two-step synthesis that allows the reaction to be done in a single solvent. The benzonitrile oxide **4** is only generated in the presence of alkyne, thereby minimizing dimerization of this unstable intermediate. The procedure starts with the addition of a solution of **2a** in ethyl acetate to a slurry of NCS in the same solvent. Due to the low solubility of NCS in ethyl acetate, we opted for this mode of addition to avoid dosing of solid to the reactor. After the oxidation is complete, the excess NCS is quenched with aqueous sodium bisulfite. Propargyl bromide is then added as an 80 wt % solution in toluene.⁶ Generation of

Scheme 1. Synthesis of isoxazoles



the nitrile oxide and subsequent cycloaddition is achieved by addition of an aqueous solution of sodium carbonate. Ethyl acetate was found to be a suitable solvent for the oxime oxidation, the cycloaddition, and the subsequent aqueous workup and isolation which allows for a simple, streamlined procedure.

During the development of this process, a significant exotherm was observed for the oxidation step that occurred only after a considerable amount of the benzaldoxime had been added to the NCS. This poses a significant barrier to scale-up because of the safety issues involved with releasing a large amount of heat in an uncontrolled fashion. Consequently, we evaluated this reaction in the Mettler Toledo RC1 calorimeter to determine the heat output. 4-Fluorobenzaldehyde oxime **2a** was charged over 30 min as a 35 wt % solution in ethyl acetate using a dosing pump to the slurry of NCS in ethyl acetate at 25 °C. Figure 1 shows the dosing curve and the resulting heat output of the reaction. The integral of the heat curve corresponds to a heat of reaction of 114 kJ/mol and an adiabatic temperature rise (ΔT_{ad}) of 67 K. It is apparent from the graph that the vast majority of the reaction takes place after the dosing of the oxime is complete. The thermal conversion plot indicates that at the end of dosing, only 8% of the reaction has taken place.

In order to safely scale this reaction, it was apparent that the proper controls would need to be in place in order to prevent the sudden release of the reaction heat. Ideally, the induction period would be eliminated and the amount of heat controlled by the dosing of substrate. Attempts to achieve this by performing the reaction at higher temperatures (35 and 50 °C) were not successful in completely eliminating the induction period. A survey of the literature indicated that a catalytic amount of hydrochloric acid⁴ or pyridine⁷ are often used in this reaction; however, no systematic evaluation of the function of

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† Wyeth became part of Pfizer on October 16, 2009.

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(6) Propargyl bromide is shock sensitive as a neat liquid. See *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Elsevier: Boston, 2007; Vol. 1.

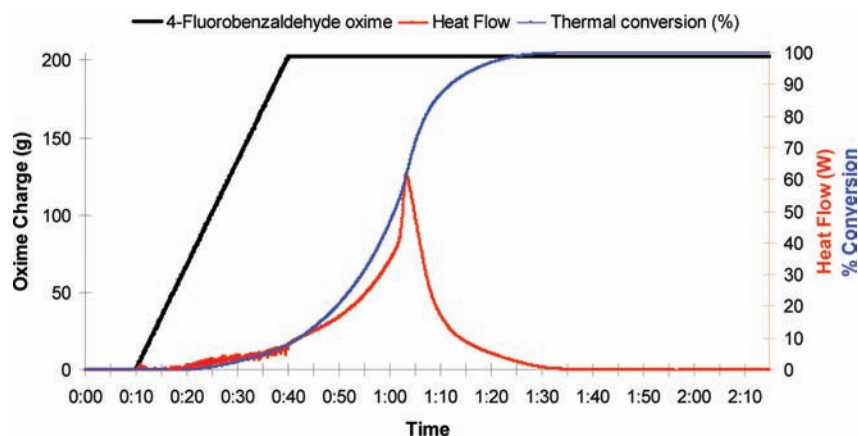


Figure 1. RC1 heat flow for oxidation of 2a.

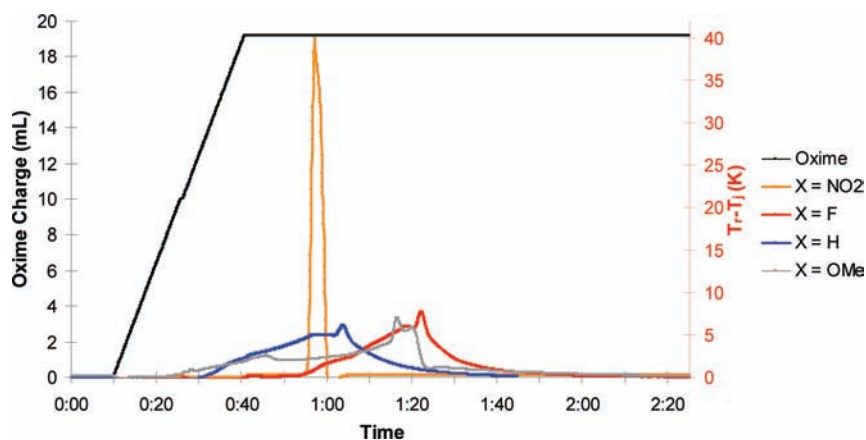


Figure 2. Oxidation of 2a-d with no initiator.

these additives has been reported. In an effort to determine their effect, we proposed to screen a variety of substrates in this oxidation in the presence of these initiators and to record the heat output vs dosing in order to get a qualitative picture of reaction rate over time. To do this, we utilized the Mettler Toledo EasyMax reactor. This system consists of two 100-mL glass reactors fitted in temperature-controlled reactor wells and equipped with overhead propeller stirring and internal temperature probes. Temperature can be controlled by either a set jacket temperature (T_j mode) or a set reaction temperature (T_r mode). While running in T_r mode, any rise in temperature due to an exothermic reaction is met with a proportional drop in jacket temperature in an attempt to remove the heat and maintain the reaction temperature. The resulting difference between reaction and jacket temperatures ($T_r - T_j$) is directly proportional to the heat of reaction and the reaction rate.^{8,9} The dosing pump attachment allows substrate dosing to be recorded and correlated with heat flow similar to the RC1 calorimeter setup. Using this apparatus, we evaluated the oxidation of a series of substituted benzaldoximes (**2a–d**) both with and without additives.

Figure 2 shows the oxidation of **2a–d** at 25 °C with no additives present. In all cases the substrate was charged over 30 min as a solution in ethyl acetate. Several trends are apparent from the heat flow curves. First, the more electron-rich substrates showed shorter initiation periods. The benzaldehyde oxime **2c** and *p*-methoxy substrate **2d** had induction times of

16 and 23 min, respectively, while substrates **2a** and **2b** containing electron-withdrawing groups had induction times of around 45 min. Second, following initiation, the reaction rate was much faster for the substrates with electron-withdrawing groups. Oxime **2b** showed complete reaction in less than 5 min, while **2d** took over 90 min to react completely. The small spike in heat flow observed in the latter half of the reaction was determined to be an exothermic crystallization of the succinimide byproduct from the reaction mixture.¹⁰

Next, we evaluated the oxidation of **2a–d** in the presence of 5 mol % pyridine. To our surprise, the induction periods for **2a**, **2c**, and **2d** actually increased (Figure 3). Furthermore, once the oxidation initiated, the reaction rates were extremely fast, creating a large spike in heat flow. Substrate **2d**, which required approximately 90 min for completion in the uncatalyzed reaction, was complete in less than 30 min in the presence of pyridine. It quickly became apparent that this was not an improvement to the reaction conditions and in fact represents a worst-case scenario for scale-up of the reaction. Substrate **2b** showed very different behavior in the presence of pyridine. The induction period decreased slightly to 25 min and the reaction rate decreased significantly, requiring over 14 h to reach completion (Figure 4). Pyridine is typically used as an additive with DMF as solvent. When **2a**, **2c**, and **2d** were oxidized in the presence of pyridine using DMF as solvent, the reactions

(10) Filtration of the reaction mixture slurry identified pure succinimide as the solid phase. This small thermal event is not observed with reactions using DMF as solvent where the reaction remains homogeneous throughout.

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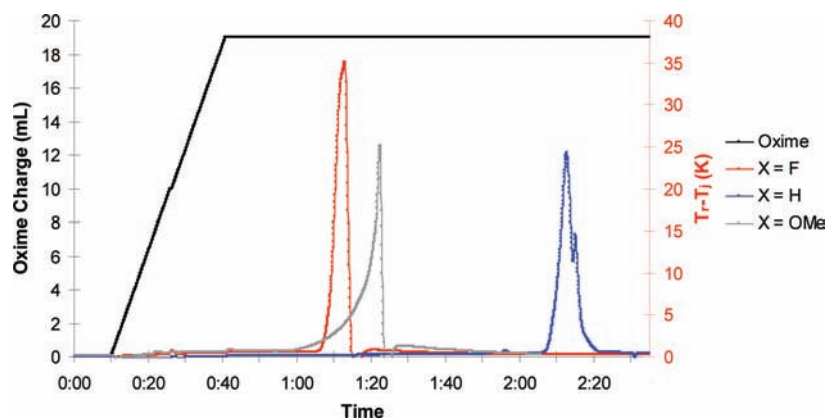


Figure 3. Oxidation of 2a, c, d with 5 mol % pyridine in ethyl acetate.

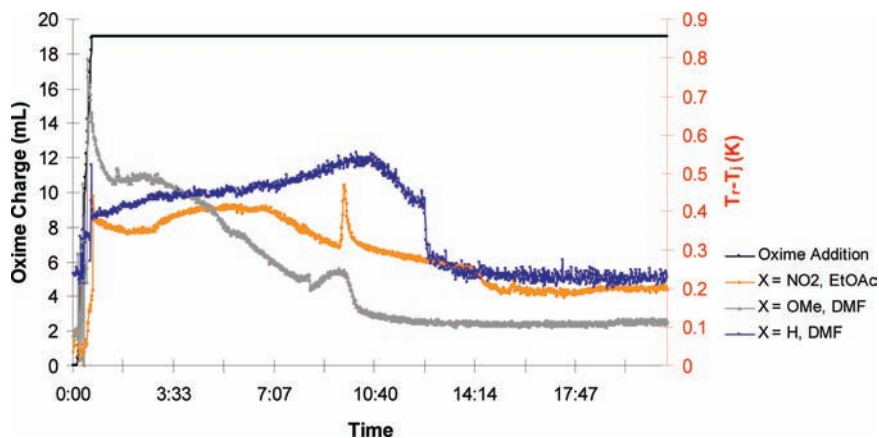


Figure 4. Oxidations with 5 mol % pyridine.

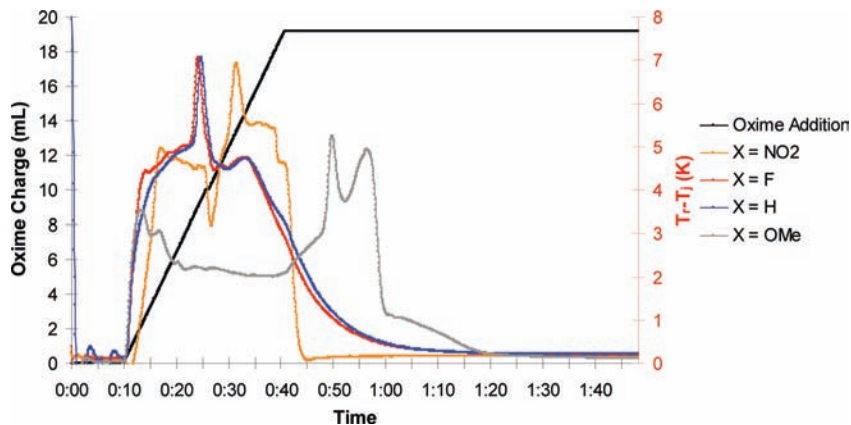


Figure 5. Oxidation of 2a–d with 5 mol % HCl.

proceeded similar to the reaction of **2b**—a very slow rate with a small heat output that extended 10–14 h was observed. The concern over initiation periods was effectively eliminated because the heat was released over an extended time. However, given the solvent dependence of this behavior, we determined this was not the ideal strategy for scaling the reaction.

Finally, the oxidation was performed in the presence of 5 mol % HCl that was added to the reaction mixture as an ether solution prior to dosing of the oxime. Figure 5 shows that these reactions had essentially no induction periods and the heat curves showed the roughly square heat output indicative of an addition controlled reaction. Oxime **2d** still showed a much slower reaction rate with a heat curve extending beyond the

end of the addition. Accumulation of oxime in this case could be mitigated by slowing the addition rate. The lack of induction period in all cases allowed the rate of heat to be controlled by the rate of addition.

Given these positive results, we reevaluated the oxidation of **2a** in the RC1 calorimeter in the presence of HCl. For large-scale reactions, concentrated HCl was used with no detrimental effects. Figure 6 shows the heat output vs dosing. As expected, no induction period was observed, and the heat curve is typical of a dose-controlled reaction. The dosing was done in two equal portions to demonstrate that the dosing can be paused and restarted without the presence of a second induction period. The similarity of the thermal conversion and dosing plots further

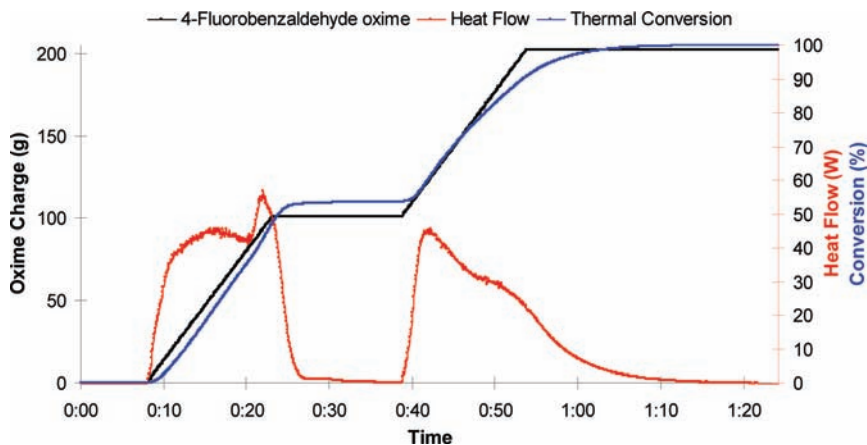
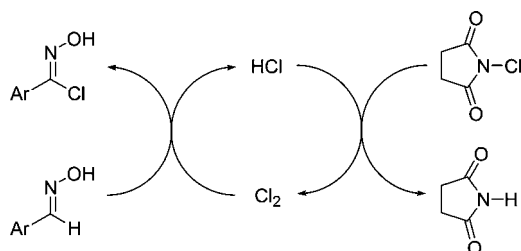


Figure 6. RC1 calorimetry with 5 mol % HCl.

Scheme 2. Proposed mechanism of the NCS oxidation of oximes



confirms that there was no accumulation of oxime in the reaction. Interestingly, the calorimeter records the small exotherm corresponding to the crystallization of succinimide near the end of the first dosing period.

Using this method we were able to safely synthesize our target compound **1a** on 1 kg scale. The oxime was added over 1.5 h, maintaining a reaction temperature between 20–30 °C using a jacket temperature between 5–20 °C.

Mechanism. The potency of HCl as an initiator can be explained by considering the reaction mechanism proposed in Scheme 2. We believe that the HCl reacts with NCS to form chlorine which is the reactive oxidant.¹¹ The reaction between chlorine and the oxime generates one equivalent of HCl which propagates the catalytic cycle. The presence of chlorine is consistent with the deep blue-green color observed in several of the reactions described above. This hypothesis is further supported by the fact that the addition of a catalytic amount of chlorine gas to the reaction is equally as effective at initiating the catalytic cycle.

The presence of pyridine in the reaction is likely to buffer the HCl and reduce the rate at which the active oxidant is generated, thereby slowing the overall reaction rate as observed in Figure 4. The dependence of the induction period and reaction rate on the reaction solvent, as demonstrated in Figure 3, highlights that adding pyridine is a risky strategy for scale-up of this reaction.

Conclusion

A safe and effective means of scaling the oxidation of benzaloximes to hydroximinoyl chlorides has been developed.

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The large exotherm can be controlled by introduction of a suitable initiator that allows an addition-controlled release of heat from the reaction. Hydrochloric acid was identified as the most effective initiator by using the EasyMax reactor to perform small-scale “pseudo” calorimetry. This method has been used to synthesize kilogram quantities of isoxazole **1a**.

Experimental Section

General. Oxime **2a** was purchased from Wychem Ltd. and **2c** was purchased from Aldrich. Oximes **2b,d** were synthesized from the corresponding aldehydes using standard methods (NH₂OH·HCl, pyridine, EtOH). Reaction monitoring was carried out on a Waters Aquity UPLC with PDA monitoring (210 nm) equipped with an Aquity UPLC BEH C-18 (1.7 μm) column (2.1 mm × 100 mm) at 50 °C. Elution was performed with a flow rate of 0.9 mL/min and a gradient method using water containing 0.1% H₃PO₄ (mobile phase A) and acetonitrile (mobile phase B) (Initial: 90% A, 0.1 min: 90% A, 3.0 min: 10% A, 3.75 min: 10% A). Observed retention times were as follows: Compound **2a** (1.38 min); **3a** (1.80 min); **2b** (1.37 min); **3b** (1.80 min); **2c** (1.26 min); **3c** (1.75 min); **2d** (1.28 min); **3d** (1.73); **1a** (2.20 min).

Procedure for EasyMax Calorimetry. In the 100-mL cylindrical EasyMax reaction vessel fitted with propeller stirring, temperature probe, and nitrogen inlet was charged NCS (5.11 g, 37.13 mmol) and ethyl acetate (20 mL). The temperature was adjusted to 25 °C (*T_r* mode), and the initiator (5 mol %) was added. A stock solution of oxime in ethyl acetate was prepared (1.83 M). The oxime solution (19 mL) was charged over 30 min using the dosing pump attachment. The data for dosing, *T_r* and *T_j* measurements, were collected by the internal computer and exported to Excel.

Scale-Up of 1a. *N*-Chlorosuccinimide (1.2 kg, 8.37 mol) and ethyl acetate (4.0 L) at 20 °C were treated with concentrated HCl (29 mL, 0.35 mol). An oxime solution of **1a** (1.0 kg, 7 mol) in ethyl acetate (2.0 L) was then added to the slurry of NCS over 1.5 h at a constant rate. The jacket temperature was adjusted between 5–20 °C in order to maintain a reaction temperature in the range 20–30 °C. The reaction was stirred 30 min to ensure complete conversion to **2a** as determined by HPLC. A solution of sodium sulfite (145 g in 350 mL water) was then added over 3 min. Propargyl bromide (1.24 kg, 80 wt

% in toluene **Caution: Neat propargyl bromide is shock sensitive. This reagent must be handled as a stock solution. See reference 6.**) was added over 20 min. The temperature was adjusted to 20 °C, and a solution of sodium carbonate (750 g in 2.5 L water) was added over 1.5 h. The reaction temperature was maintained in the range 17–27 °C, using a jacket temperature of 5–20 °C. The reaction was stirred 5 min at 24 °C, and complete reaction was confirmed by HPLC. Water (1.6 L) was added, and the layers were separated. The organic layer was washed a second time with water (4 L). Sodium chloride (20 g) was added to the second wash to aid in layer separation. The solution was concentrated to a volume of ~4.0 L, and heptane (8.0 L) was added over 1 h as the distillation continued. The resulting slurry was filtered and washed with heptane (500 mL). The solids were dried in a vacuum oven at 50 °C for 24 h.

Isolated 1.08 kg (60%) as an off-white solid (97 area % purity and 95 wt %). **¹H NMR:** (400 MHz, CDCl₃) δ 7.78 (dd, $J_{\text{H-H}} = 8.7$ Hz, $J_{\text{H-F}} = 5.2$ Hz, 2 H); 7.15 (t, $J_{\text{H-H}} \approx J_{\text{H-F}} = 8.7$ Hz, 2 H); 6.60 (s, 1 H); 4.51 (s, 2 H); **¹³C NMR:** (100 MHz, CDCl₃): δ 168.2, 163.9 (d, $^1J_{\text{C-F}} = 250$ Hz, 1 C), 161.9, 128.8, 124.8, 116.1 (d, $^2J_{\text{C-F}} = 22$ Hz, 2 C), 101.8, 18.6.

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