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Reaction Safety: An Improved Procedure for the Preparation of 1,3,4,12a-Tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]benzodiazepine-6,12-dione with Iron in Acetic Acid

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Abstract:

This contribution describes the development of an improved scaleable process to prepare 1,3,4,12a-tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]benzodiazepine-6,12-dione, 2, in a safe and operationally simple procedure using iron powder in acetic acid. The original procedure being used to prepare initial quantities of this material also involves the use of iron with acetic acid. However, these original reaction conditions are not amenable to scale-up due to safety and operational issues. Reaction calorimetry is used to evaluate modifications to the original conditions that result in an improved procedure that has been developed and scaled to produce multikilogram amounts of material for initial development studies.

Introduction

Recently, we required a safe and scaleable synthesis of 1,3,4,12a-tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]benzodiazepine-6,12-dione, **2**, via reductive cyclization[1] from 4-(2-nitrobenzoyl)morpholine-3-carboxylate methyl ester **1** to supply intermediates for an ongoing project (Figure 1).

The original reduction procedure is not immediately amenable to scale-up for several reasons. The reaction is run very dilute (5% w/v), leading to very large volumes to manipulate during scale-up and needs 6.3 equiv of iron pellets that results in a significant agitation problem. Also, the reaction requires greater than 20 h to complete and needs a chromatographic purification after a laborious reaction workup. These result in a low yield for the reaction (62%).

We made improvements during the course of our initial optimization study, including doubling the reaction concentration to 10% (w/v), optimizing the use of only 2.5 equivalents of Fe powder (325 mesh size), and reducing the reaction time to only 1.5 h. These improvements increase the purity, simplify the reaction workup, and most importantly, eliminate the chromatographic purification. Moreover, these improvements result in a yield increase from 62% to 84% and improve product quality that is crucial for the success of the subsequent reaction steps. However, upon initial scale-up to prepare multigram quantities, we encountered a safety issue involving an uncontrollable exothermic reaction that we investigated using reaction calorimetry.[2−5]

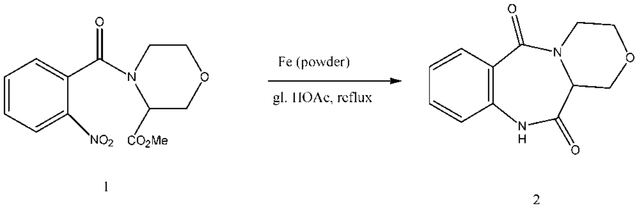

Figure 1.

Reaction Calorimetry Results and Discussion

Initially, we attempted to modify and scale-up the original procedure by mixing 4-(2-nitrobenzoyl)morpholine-3-carboxylate methyl ester **1** with 2.5 mol equiv of iron powder (325 mesh) in acetic acid at room temperature and then heating the reaction to reflux. However, we observed that, at 50−60 °C the temperature rose quickly, and in less than 1 min the temperature reached reflux (115−116 °C). A very thick precipitate formed, and the reaction mixture almost stopped stirring. The observed thickening of the reaction mixture surely diminished the heat transfer and thus enhanced the rapid heating to reflux. After 5−10 min at reflux the reaction mixture thinned out and became a stirrable suspension again. On the basis of these observations and the fact that reduction of nitroaromatic compounds is known to be exothermic,[6] we are of the opinion that a chemical reaction hazard exists for this reaction step and the reaction should not be scaled up without further investigation. This prompted us to investigate the current synthesis conditions using reaction calorimetry. Our goal is to optimize the current procedure to prepare **2** in multigram quantities quickly in a safe manner with a higher yield and purity.

All experiments are carried out in the Mettler RC-1 reaction calorimeter. The instrument is equipped with an SV01 1-L vessel, temperature sensor, calibration heater, and propeller stirrer. Essentially two different experimental protocols are evaluated in the RC-1 calorimeter that involve

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(2) *Guidelines for Chemical Reactivity Evaluation and Application to Process Design*; Center for Chemical Process Safety of the American Institute of Chemical Engineers: New York, NY, 1995; pp 117−119.

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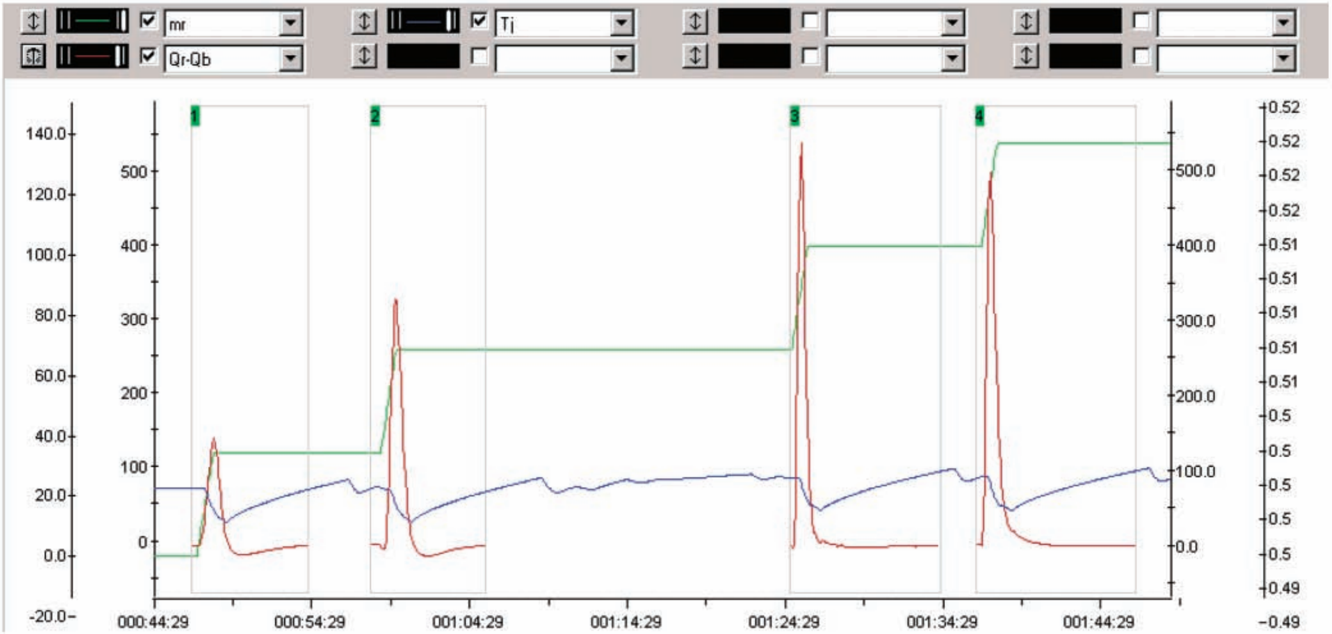

Figure 2. **Red = heat flow (*y*-axis in W). Blue = T_j jacket temperature (*y*-axis in °C). Green = iron addition (*y*-axis in kg). (*x*-axis is experiment time in hours.)**

different modes of addition in an attempt to control the reaction exotherm.

We first examined our modification of the original reaction conditions. This experiment was carried out using the addition of powdered iron to a heated solution of 4-(2-nitrobenzoyl)morpholine-3-carboxylate methyl ester, **1**, in acetic acid at 50 °C. The iron powder (325 mesh) was added portion-wise over 1 h to generate the heat flow curve shown in Figure 2.

The resulting heat flow curve (red curve in Figure 2) suggested that each iron addition step was very exothermic under the test conditions. Thickening of the reaction with poor stirring was again observed as the reaction progressed. The RC-1 program calculated a very large temperature rise potential (198 °C) that suggested that, if loss of reactor control (cooling and stirring) and full accidental mischarge of all the iron occurred, this would result in vigorous solvent reflux and, more likely, that spewing of the reaction mixture from the reaction vessel may occur. Also, DSC thermal screening tests that showed that the starting 4-(2-nitrobenzoyl)morpholine-3-carboxylate methyl ester **1** underwent an exothermic decomposition initiating at 176 °C, well beyond the operating temperature conditions for this reaction. (DSC showed that the final 1,3,4,12a-tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]benzodiazepine-6,12-dione, **2**, was thermally stable and did not undergo a thermal decomposition when tested to 300 °C.) On the basis of these results, we postulated that if any accumulated **1** remained as the reaction exotherm progressed and all the solvent evaporated, the nitro compound could also thermally decompose and compound an already hazardous situation. Therefore, it was our opinion that these reaction conditions represented a significant chemical reaction hazard due to the reaction thickening, poor stirring, large adiabatic temperature rise potential, and potential for the starting nitro compound to decompose if allowed to accumulate in the reaction mixture at very elevated temperatures. This led us to investigate a reverse addition where the starting ester **1** is added to a suspension of iron in acetic acid at elevated temperature.

In the second RC-1 evaluation, a solution of 4-(2-nitrobenzoyl)morpholine-3-carboxylate methyl ester **1** in acetic acid was added manually using a liquid dropping funnel with a metering stopcock over 25 min to a mixture of iron powder (325 mesh) in acetic acid at 75 °C. In Figure 3 is shown the heat flow curve that was generated.

The heat flow curve (red curve in Figure 3) suggested that the addition of the acetic acid solution of the starting nitro ester **1** to iron was still exothermic, yet feed controlled under the test conditions. The thermal conversion rate (yellow curve) nearly matches the feed rate (green curve). No thickening or poor stirring was observed. The endothermic event at the end of the reaction period was most likely due to outgassing and hydrogen evolution (not measured as part of this study) as the reaction reached completion. Again, the RC-1 program calculated a very large worst-case temperature rise potential (158 °C) if full accidental mischarge of the entire acetic acid solution of the starting nitro ester **1** was accidentally added all at once. This slightly lower adiabatic temperature rise may be attributed to more solvent available during the initial stages of the reaction that results in a stirrable reaction mixture throughout the reaction period that allows for better heat transfer. However, the temperature rise potential again suggests that if all the acetic acid solution of the starting ester **1** is added all at once with loss of cooling and stirring in the reaction vessel then vigorous solvent reflux and spewing of the reaction mixture from the reaction vessel could occur. The caveats regarding the thermal instability of the starting nitro compound **1** are not as relevant here since the nitro compound is added in a semi-batch manner and is not present in the reactor to build up in any sufficient

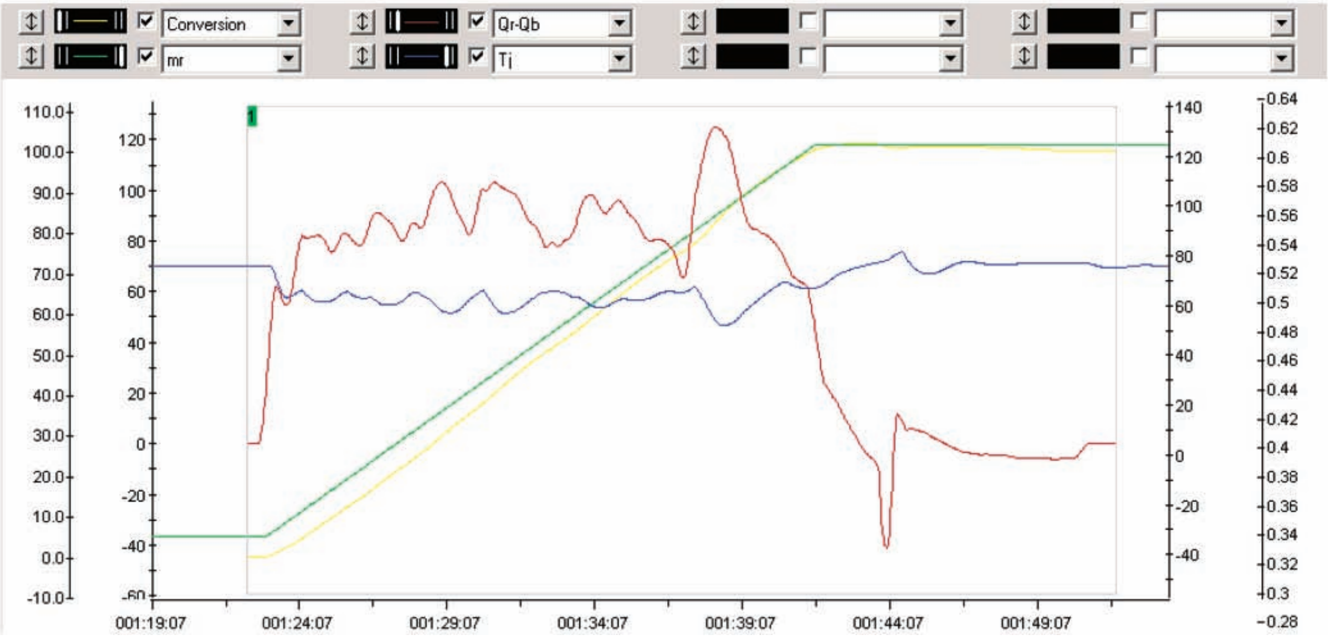

Figure 3. **Red = heat flow (*y*-axis in W). Blue = T_j jacket temperature (*y*-axis in °C).Yellow = thermal conversion to product (*y*-axis in %). Green = starting nitro ester 1 addition (*y*-axis in kg). (*x*-axis is experiment time in hours.)**

quantity to accumulate. Also, solvent reflux can be used as an effective barrier for safety. However, in our opinion, these reaction conditions again represent a chemical reaction hazard. Despite the exothermic nature of the reaction coupled with the potential chemical reaction hazard, these RC-1 modified conditions were recommended for scale-up for several reasons. The idea of a feed-controlled addition combined with the ability to meter in the acetic acid solution of the starting ester **1** is very appealing for reaction scale-up for this stage of early development to meet material demands. As part of the engineering controls for this reaction, mechanical safeguards including the use of metering pumps for all liquid additions were implemented to prevent full accidental mischarge of the starting ester solution of **1** that could result in the hazardous situation. No reaction thickening or stirring issues that can lead to poor heat transfer are evident using these conditions. Therefore, these reverse addition conditions offer a substantial improvement in reaction control and safety when compared to the original conditions where iron is added to the reaction mixture.

Using these improved reaction conditions we safely were able to successfully prepare kilogram amounts of **2**. For example, we would charge the reaction flask with acetic acid and iron powder (325 mesh) and warm the mixture to 35−40 °C. We then would add a 1 M solution of **1** as a premade solution in acetic acid in a controlled manner and allow the heat of reaction to warm the reaction mixture to reflux and drive it to complete the cyclization reaction. Using the improved inverse addition methodology for the iron reduction results in our ability to carry out large-scale reactions in a safe manner with high yield and purity.

Conclusions

We are pleased to find that we could achieve our goal by using an inverse addition method developed through the use of reaction calorimetry. Reaction calorimetry proved an invaluable tool in the development of an improved and safer procedure to prepare 1,3,4,12a-tetrahydro-11*H*-[1,4]-oxanio-[3,4-*c*][1,4]benzodiazepine-6,12-dione, **2**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All reagents and solvents were used as received from commercial sources. All reactions were performed under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker 300 MHz spectrometer. Spectra were recorded in $CDCl_3$. Elemental analyses were performed by QTI (Whitehouse, NJ).

1,3,4,12a-Tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]-benzodiazepine-6,12-dione (2). Add 325 mesh iron powder (500 g, 8.8 mol) and glacial acetic acid (5.4 L) to a nitrogen-purged 22-L, four-neck flask equipped with a reflux condenser, air stirrer, and addition funnel at room temperature. In a separate 5-L, three-neck flask equipped with an air stirrer dissolve **1** (1045 g, 3.56 mol) in glacial acetic acid (3.6 L) at room temperature. Warm the resulting dark iron/acetic acid suspension to 35−40 °C using a heating mantle. Discontinue heating and add the acetic acid solution of **1** in a controlled manner, allowing the exotherm to generate the initial heat source for the reaction. During the addition the reaction mixture becomes a stirrable, gray-black suspension. The addition of **1** is complete after 1 h and the reaction temperature increases to 105 °C. Turn on the heating mantle and continue heating the reaction to reflux (114−116 °C). At reflux the reaction mixture turns dark red and becomes a thin suspension. TLC analysis deems reaction completeness after 1 h at reflux. Cool the reaction mixture to 35−40 °C, filter off the solids over Celite, and wash with glacial acetic acid (7.5 L). Concentrate the filtrate in vacuo to a gray-black solid. Slurry this solid in water (10 L) overnight at room temperature, filter, wash with water (2.0 L), and dry in vacuo at 45−50 °C to yield **2** (707 g, 86%) as an off-white solid.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 8.40 (br s, 1 H), 7.92 (d, $J = 7.3$ Hz, 1 H), 7.50 (t, $J = 7.0$ Hz, 1 H), 7.30 (t, $J = 7.3$ Hz, 1 H), 7.01 (d, $J = 7.8$ Hz, 1 H), 4.50 (dd, $J = 12.2$, 13.5 Hz, 2 H), 4.12 (dd, $J = 11.3$, 3.4 Hz, 1 H), 4.0 (d, $J = 3.4$, 1 H), 3.73 (m, 2 H), 3.27 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.7, 168.9, 135.9, 132.9, 131.7, 127.1, 125.9, 121.0, 66.0, 63.2, 51.1, 40.1.

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.89; H, 5.16; N, 11.94.

TLC: mobile phase, ethyl acetate; stationary phase, silica gel 60F; R_f values: **1** = 0.3; **2** = 0.6.

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