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Technical Notes

Integrated Approach to the Development and Understanding of the Borane Reduction of a Carboxylic Acid[†]

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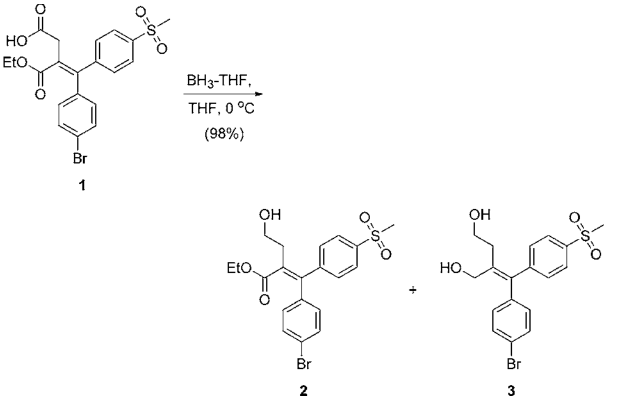
Abstract:

A delayed exotherm was recorded during the reduction of a carboxylic acid with BH$_3$·THF. This article will describe our efforts to explain and control the observed exotherm using a reactor integrated with a mass-flow meter, a reaction calorimeter, and an in situ FT-IR probe. In the end, a kinetic model is proposed that allows control of the addition rate of the reagent based on the known cooling capacity of the reaction vessel.

In the preparation of primary alcohol **2**, a key intermediate in our COX-2 inhibitor program,[1] a selective reduction of the carboxylic acid functionality was required in the presence of the α,β-unsaturated ester group (**1**, eq 1). Our early procedure relied on in situ generation of borane (BH$_3$) by reacting NaBH$_4$ with methanesulfonic acid (MSA) in DME solvent.[2] After several additional methods were screened,[3] reduction by both BH$_3$·THF (1.0M in THF) and BH$_3$·DMS (neat) was found to be more efficient. There are several inherent advantages for using commercially available BH$_3$·THF:[4] (1) the elimination of the hydrogen off-gas and the exotherm associated with in situ borane formation, (2) the elimination of DME as a reaction cosolvent, (3) the utilization of a single reaction vessel, and (4) the avoidance of the sulfide stench associated with BH$_3$·DMS.[5]



(1)

During the preparation of **2** on a multikilogram scale using BH$_3$·THF, we observed an unexpected exotherm. In particular, after the complete addition of 1.5 equiv of BH$_3$·THF (1.0 M in THF) at a rate of 1.6 L/min to a cold mixture of carboxylic acid **1** in THF, the temperature of the reaction steadily rose from 5 °C to 20 °C. Additionally, the diol impurity **3**, which is typically present in less than 0.8 area percent (AP) by HPLC, nearly exceeded our specification limit of 1.2 AP.

As a result of this observation, two immediate objectives were to determine the magnitude of the exotherm and to propose safety controls for future campaigns. The observation that the temperature of the reaction began to rise only after the addition of the reagent was complete was of particular concern. An integrated reactor, equipped with a Brooks mass-flow meter coupled with a Yokogawa Daqstation for off-gas measurements, a RC1e reaction calorimeter for heat flow data, and an in situ FT-IR probe for reaction monitoring, was used to investigate the reaction in more detail.[6]

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[†] This work was presented in part at the 20th SCI Process Development Symposium, December 11−13, 2002 in Cambridge, England.

(1) Nicolai, E.; Teulon, J.-M. Diarylmethylidenefuran Derivatives and Their Uses in Therapeutics. U.S. Patent 5,807,873, September 15, 1998.

(2) Wann, S. R.; Thorsen, P. T.; Kreevoy, M. M. *J. Org. Chem.* **1981**, *46*, 2579−2581.

(3) Various reagents and techniques have been employed to address the issue of reactivity and chemoselectivity. For lead references for the selective reduction of carboxyl-containing molecules, please see: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed; Wiley-VCH: New York, 1997. (b) Abdel-Magid, A. F., Ed. *Reductions in Organic Synthesis; Recent Advances and Practical Applications*; American Chemical Society: Washington, D.C, 1996. (c) Barrett, A. G. M. Reduction of Carboxylic Acid Derivatives to Alcohols, Ethers and Amines. In *Comprehensive Organic Synthesis, Vol. 8*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; pp 235−257.

(4) For stability data, please see: Burkardt, E. R.; Corella, J. A. Borane−Tetrahydrofuran Complex Method of Storing and Reacting Borane−Tetrahydrofuran Complex. U.S. Patent 6,048,985, April 11, 2000. For handling information, please refer to BASF Corporation at http://www.basf.com/inorganics. BASF Corporation completed the acquisition of Callery Chemical in September, 2003. For an industrial incident involving 2 M BH$_3$·THF in a 400 L cylinder, please see *Chem. Eng. News*, July 1, 2002 and Safety Highlights in *Org. Process Res. Dev.* **2003**, *7*, 1029−1033.

(5) Although the cost of BH$_3$·THF, 1.0 M in THF exceeds the cost of NaBH$_4$, MSA, and DME used in the early process, when capital and labor expenses are considered, the cost is comparable. However, the true savings with the current process are realized when evaluating the processing and environmental aspects.

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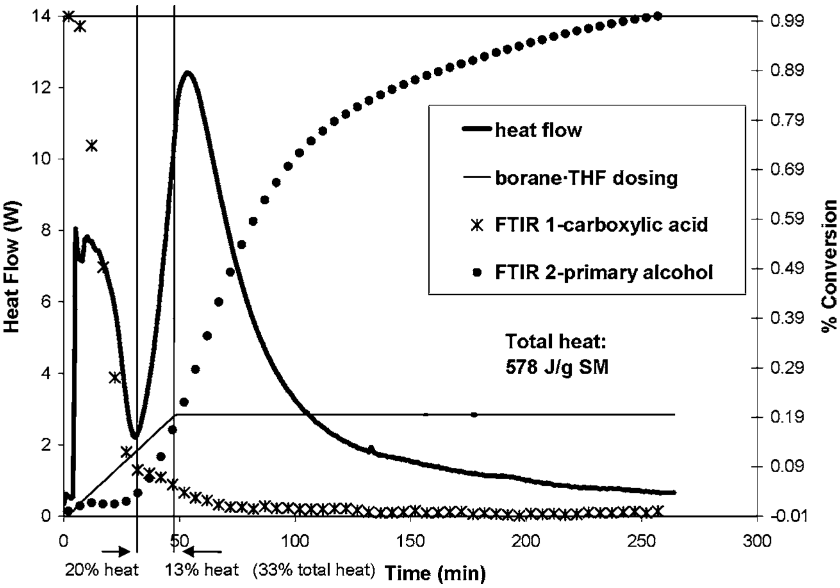

Figure 1. **RC1 integrated reactor, pilot plant simulation, 45 min addition, 1.4 equiv of BH_3·THF.**

The first experiment was designed to reproduce on a 50 g scale the reaction profile that was observed during the pilot plant campaign. The total heat liberated during the reaction, excluding quenching of the excess reagent, was 578 J/g of starting material (270 kJ/mol). During the course of the reaction, two discernible exotherms were observed (Figure 1). The first exotherm results from deprotonation of the carboxylic acid and accounts for about 20%, or 115.6 J/g (54 kJ/mol), of the total heat produced (vide infra). The second exotherm occurs during the reduction of the carboxylic acid. The fact that two distinct exotherms occurred was an indication that an intermediate was involved in the reaction. Also indicative of the existence of an intermediate was the observation that consumption of starting material and appearance of the product were not linearly related and that the product was not observed until after the first exotherm had subsided (Figure 1). It was presumed that the intermediate was an acyloxyborane, in accord with work done by H. C. Brown.[7]

The objective of the second experiment was to determine the nature of the acyloxyborane intermediate formed under our reaction conditions. Since borane has three active hydrides, the possibility exists to form mono-, di- or triacyloxyborane intermediates. If a triacyloxyborane were the intermediate in question then only 0.33 equivalents of borane would be necessary to generate one equivalent of hydrogen gas. However, if a monoacyloxyborane was the intermediate, then one full equivalent of borane would be required to liberate one equivalent of hydrogen gas. By utilizing the mass flow meter and dosing pumps with the integrated reactor, we found that 0.5 equiv of BH_3·THF was sufficient to evolve 1 equiv of hydrogen gas under our reaction conditions at 0 °C, indicative of a diacyloxyborane intermediate. Consumption of the starting material was monitored using the in situ FT-IR probe. The absorption at 1732 cm^{-1} is indicative of the carboxylic acid C═O stretching vibration (Figure 2). The appearance of the primary alcohol was evident by the deformation signal at 1420 cm^{-1}. We speculate that the formation of the triacyloxyborane intermediate is disfavored due to the bulkiness of the two acyloxy groups and decreased basicity of the third hydride as a result of the inductive-electron withdrawing ability and the bulkiness of the two acyloxy groups.[8]

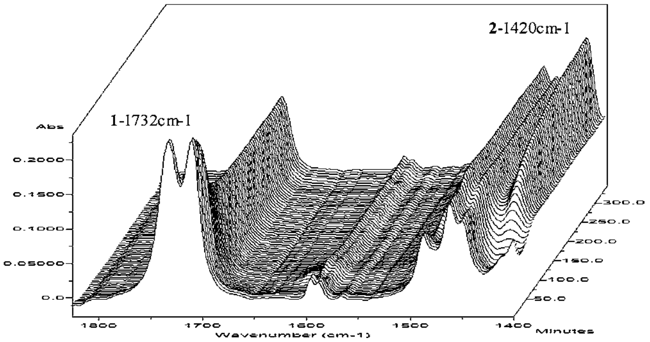

Figure 2. **Monitoring the reduction by in situ FT-IR.**

From these two experiments and literature precedence, a detailed mechanism for the reduction of carboxylic acid **1** by 1.5 equiv of BH_3·THF (1.0M in THF) in THF at 0 °C can be proposed (Figure 3). The first 0.5 equiv of borane deprotonates the carboxylic moiety of **1** generating diacyloxyborane intermediate **I** and 1.0 equiv of hydrogen gas. Diacyloxyborane **I** is stable and does not undergo reduction or decomposition when held at 0 °C for 20 h. The second 0.5 equiv of the reagent induces redistribution to monoacyloxyborane intermediate **II** which is subsequently reduced to trialkoxyboroxine intermediate **III**, characterized by the frequency at 718 cm^{-1}.[9] The third 0.5 equiv of BH_3·THF (excess) drives the reduction to completion in a timely manner. When only 1.0 equiv of reagent was employed at 0

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(6) See the Supporting Information for a schematic diagram of the integrated reactor.

(7) (a) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786−2792. (b) Brown, H. C.; Stocky, T. P. *J. Am. Chem. Soc.* **1977**, *99*, 8218−8226.

(8) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317−384.

(9) Lappert, M. F. *J. Chem. Soc.* **1958**, 2790.

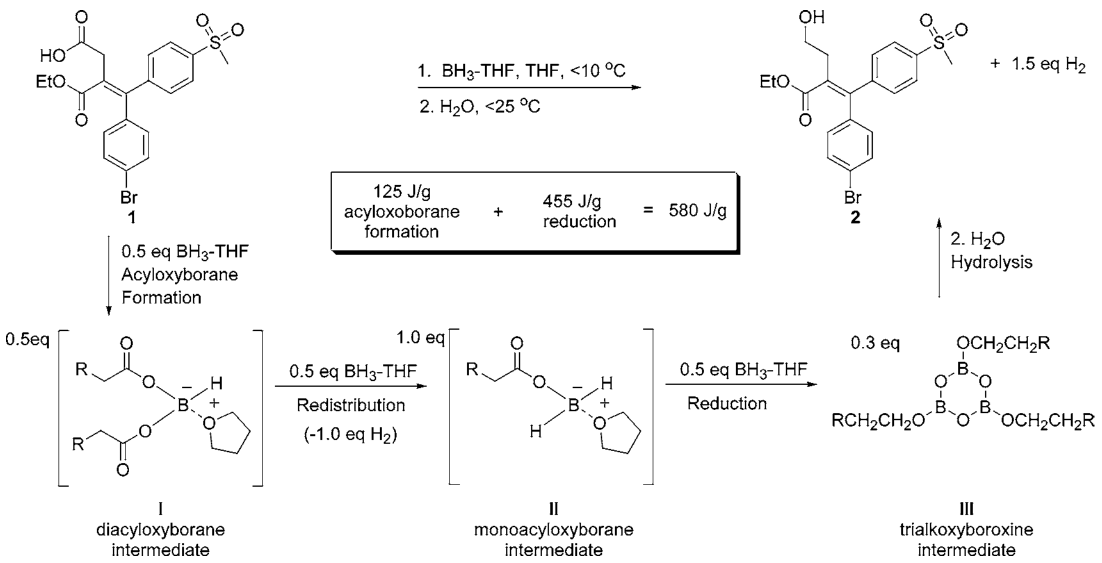

Figure 3. **Proposed mechanism for the borane reduction of 1.**

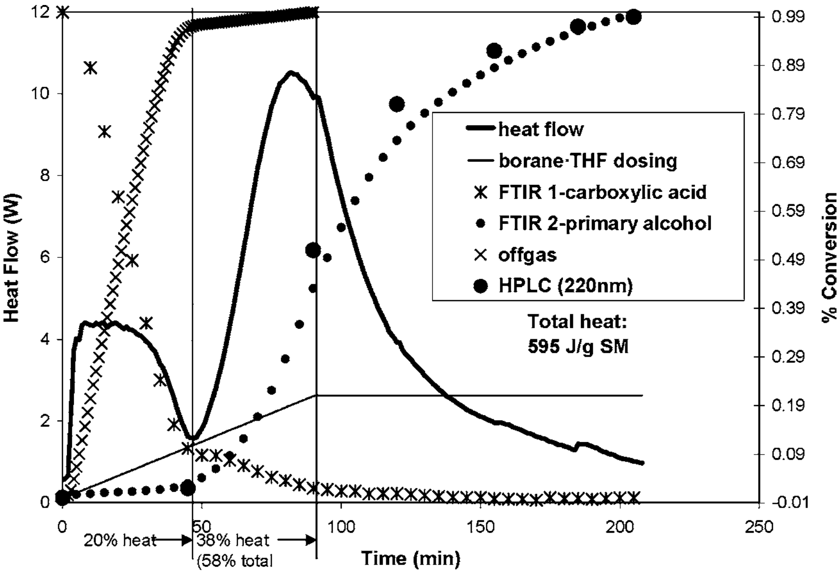

Figure 4. **RC1 integrated reactor, extended addition time to 90 min, 1.5 equiv of BH_3·THF.**

°C, the reaction took 28 h to reach 90% conversion. However, with 1.5 equiv, 90% conversion is typically obtained in 3 h, and complete conversion occurs in 5 h. For the final step of the reaction, the trialkoxyboroxine intermediate **III** and excess borane reagent are hydrolyzed with water to afford alcohol **2**, boric acid, and an additional 1.5 equiv of hydrogen gas. In situ FT-IR spectroscopy was used to monitor the disappearance of the starting material, and HPLC (220 nm) is used to accurately determine the endpoint of the reaction.

From a safety perspective, we desired to have a comfortable level of control over the process and, in particular, the ability to slow or halt the addition of the reagent to control the reaction temperature. It is readily apparent from Figure 1 that the heat flow maximum occurs after the 45 min addition of the reagent is complete, yet this coincides with only about 33% of the total heat produced during the reaction. With this addition protocol, there exists little or no control over the ensuing exotherm because nearly the entire amount of reagent is dispensed by the time the temperature increase might be observed. We felt this goal could be achieved by extending the addition time of the borane reagent such that the second exotherm lies within the addition time window.

For the third and final experiment in the integrated reactor, the addition time of the reagent was extended to 90 min (Figure 4). Consequently, the heat flow maximum was shifted towards the center, occurring at about 80 min but now encompassing 58% of the total heat produced during the reaction. With this modification, the total heat produced after the complete addition of the reagent was reduced by 37%. This adjustment should provide sufficient time to mitigate the exotherm and preclude any unwanted heat excursion.

The proposed mechanism and the exotherm data were used to develop a five-step kinetic model. In this model, carboxylic acid **1** reacts with borane to form the transient monoacyloxyborane intermediate **II** followed by subsequent transformation to the diacyloxyborane intermediate **I** by reaction with another molecule of the starting material, k_1 and k_2, respectively. Diacyloxyborane **I** is reduced by another 0.5 equiv of BH_3 to regenerate monoacyloxyborane **II**, k_3.

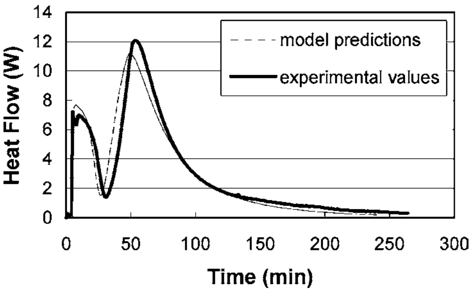

Figure 5. **Comparison of the heat flow data generated from the model and from the 45 min addition experiment.**

Two pathways now exist for the reduction of intermediate **II**, either by the reactive B−H bonds (inter- or intramolecular) or by the excess equivalents of $BH_3 \cdot THF$, k_4 and k_5, respectively. The reactive B−H bonds of **II** are represented by a pseudo species (B−H). The five steps and the associated rate expressions are as follows:

Formation of acyloxyborane intermediates **I** and **II**

$(\mathbf{1}) + (BH_3) \rightarrow (\mathbf{II}) + (H_2) + 2(B{-}H) \qquad \text{Rate: } k_1(\mathbf{1})^*(BH_3)$

$(\mathbf{II}) + (\mathbf{1}) + (B{-}H) \rightarrow (\mathbf{I}) + (H_2) \qquad \text{Rate: } k_2(\mathbf{1})^*(\mathbf{II})$

$(B{-}H) + (\mathbf{I}) + (BH_3) \rightarrow 2(\mathbf{II}) + 4(B{-}H) \qquad \text{Rate: } k_3(\mathbf{I})^*(BH_3)$

Reduction by reactive B−H bonds of (**II**)

$(\mathbf{II}) + 2(B{-}H) \rightarrow {}^1/_3(\mathbf{III}) \qquad \text{Rate: } k_4(\mathbf{II})^*(B{-}H)$

Reduction by excess equivalents of BH_3

$2(B{-}H) + (\mathbf{II}) + (BH_3) \rightarrow {}^1/_3(\mathbf{III}) + 3(B{-}H)$

$\text{Rate: } k_5(\mathbf{II})^*(BH_3)$

Based on the measured heats of reaction, off-gas data, and in-line FT-IR data, the kinetic rate constants were regressed on the experimental data of the 90 min addition experiment using the software BatchCAD, version 7 (GSE Systems, Inc., Columbia, MD). The following rate constants were obtained: $k_1 = 13.9$ M min^{-1}, $k_2 = 2.08$ M min^{-1}, $k_3 = 459$ M min^{-1}, $k_4 = 0.0129$ M min^{-1}, $k_5 = 0.245$ M min^{-1}. Good agreement was found between the simulated model and the laboratory data gathered from the 45 min addition experiment (Figure 5). The model further allows us to simulate temperature profiles and addition protocols on-scale and determine the optimum addition rate of the borane reagent by simply knowing the heat capacity of the reaction vessel.

From only three reactions in the integrated reactor, equipped with a mass-flow meter, an in situ FT-IR, and a calorimeter, sufficient data were collected to explain the observed temperature increase recorded during our pilot plant campaign. Additionally, with these data we were able to propose a detailed mechanism and provide solutions to control the exotherms during future campaigns. In summary, the first stage of the reaction is punctuated by the vigorous evolution of 1.0 equiv of hydrogen, the generation of a diacyloxyborane intermediate, and the production of 125 J/g of starting material. A stronger exotherm of approximately 455 J/g typifies the second stage during the reduction of the carboxylic acid. A kinetic model was developed, and the rate constants for each step have been estimated. With this model, and by knowing the heat capacity of the reaction vessel, the safest addition protocol for the borane can be calculated for future scale-up endeavors.

Experimental Section

$BH_3 \cdot THF$ (1.0 M in THF) was purchased from Callery Chemical Company. For stability data, please see Burkardt, E. R.; Corella, J. A. U.S. Patent 6,048,985. Stability, handling, and safety concerns have been documented.[4]

(*Z*)-Ethyl-3-(4-bromophenyl)-3-(4-methanesulfonylphenyl)-2-(2-hydroxyethyl)-2-propenoate (2). Under an inert atmosphere, $BH_3 \cdot THF$ (1.5 L, 1.5 mol, 1.0 M in THF) was added at a rate of about 33 mL/min to a slurry of carboxylic acid **1** (0.50 kg, 1.1 mol) and THF (1.0 L). The temperature was maintained below 10 °C throughout the addition. CAUTION: Hydrogen gas evolution is nearly instantaneous but markedly decreases after the first 0.75 equiv of the reagent is added! The resulting homogeneous reaction mixture was stirred at less than 10 °C for 3−5 h.[10] The reaction mixture was quenched by the slow addition of water (0.24 L) and heated to 65 °C. Water (2.5 L) was slowly added at approximately the same rate as that of the removal of THF under reduced pressure in order to maintain the original volume of approximately 3.2 L. The temperature was maintained between 55 and 65 °C during the distillation. The reaction mixture was diluted with additional water (2.0 L) and cooled to room temperature. The product was collected by filtration, washed with water and *n*-heptane, and dried in a vacuum oven (25−30 in Hg, 50−60 °C) to afford **2** as an off-white solid (0.47 kg 98%), mp 136−137 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, $J = 8.1$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.40 (dd, $J = 8.3$, 2.4 Hz, 2H), 6.98 (dd, $J = 8.7$, 2.6 Hz, 2H), 3.99 (dd, $J = 14.2$, 7.0 Hz, 2H), 3.74 (br s, 2H), 3.07 (s, 3H), 2.59 (t, $J = 6.2$ Hz, 2H), 2.11 (br s, 1H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.2, 145.4, 144.6, 139.9, 132.6, 131.4, 130.3, 130.1, 127.6, 122.3, 109.6, 61.2, 61.0, 44.4, 34.9, 13.6.

Acknowledgment

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Supporting Information Available

A schematic diagram of the integrated reactor and copies of ^1H and ^{13}C NMR for compounds **1**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The reaction rate is dependent on the concentration and temperature of the reaction mixture as well as the equivalents of reagent.