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Investigation of the Stability of the Corey–Kim Intermediate

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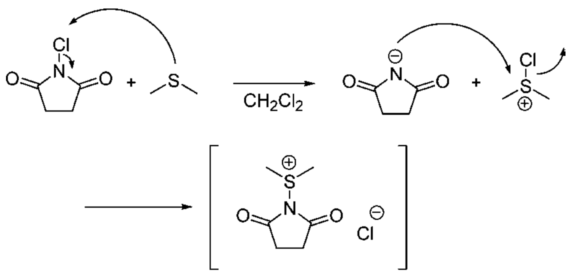
Introduction

The Corey–Kim oxidation[1] of alcohols is an important reaction used by synthetic chemists due to its reliability and the use of inexpensive reagents. Despite the more recent development of alternate oxidation methodologies, such as *o*-iodoxybenzoic acid (IBX),[2] Dess–Martin periodinane,[3] and tetrapropylammonium perruthenate (TPAP),[4] the Corey–Kim oxidation demonstrates selective reactivity[5] that continues to find application in synthesis. The Corey–Kim intermediate (**1**) is prepared by the reaction of *N*-chlorosuccinimide (NCS) with dimethyl sulfide (DMS) as shown in Scheme 1. The sequential addition of the starting alcohol and a tertiary amine, typically triethylamine, completes the oxidation to the ketone or aldehyde. The mechanism for the Corey–Kim oxidation was evaluated by McCormick[6] and found to be consistent with the mechanism of dimethyl sulfoxide oxidations.[7]

The Corey–Kim oxidation was essential for the large-scale production of the ketolide antibiotic ABT-773 (**4**, cethromycin).[5b] As shown in Scheme 2, the oxidation of the C-3 hydroxyl of compound **2** provided the ketone **3** as the final isolated intermediate. Final deprotection of the benzoate group in **3** completed the synthesis of ABT-773.

Scheme 1. **Preparation of the Corey–Kim intermediate**

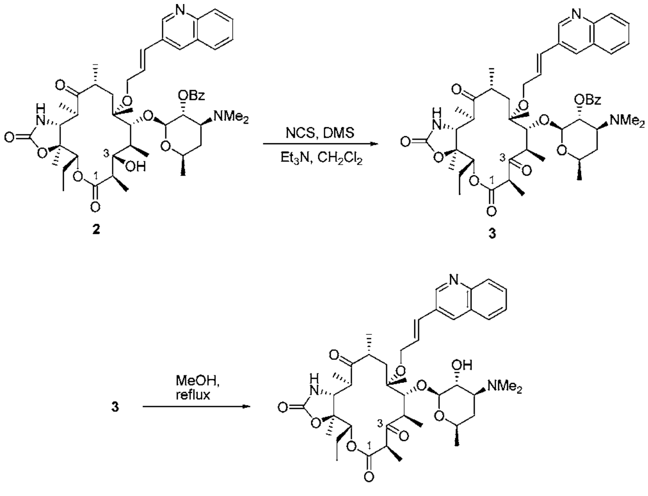


Corey-Kim Intermediate, **1**

For the application of the Corey–Kim oxidation at large scale, the stability of the intermediate **1** was a significant concern because Vilsmaier[8] has shown that intermediate **1** undergoes decomposition via two pathways. As shown in Scheme 3, intermediate **1** was converted into succinimide (**5**) and methylthiomethyl chloride (**6**) upon warming, and addition of triethylamine resulted in the formation of methylthiomethyl succinimide adducts **7a** and **7b**.

Because of the temperature sensitivity of intermediate **1** and the exothermic nature of the reaction of DMS with NCS, control of the reaction temperature was considered critical to the successful scale-up of the Corey–Kim oxidation. Additionally, the time required to complete the oxidation was an important factor because the processing time would increase upon scale-up and intermediate **1** was expected to undergo decomposition during that time. In order to determine acceptable ranges for temperature and time, the stability of intermediate **1** was investigated at different temperatures by continuous FT–IR spectroscopy. A kinetic analysis on the rate of decomposition of intermediate **1** was conducted using a model system to quantify the concentration of **1** versus time. Because intermediate **1** was shown to undergo decomposition with triethylamine, the presence of a tertiary

Scheme 2. **Final Steps in the Synthesis of ABT-773**



ABT-773, Cethromycin, **4**

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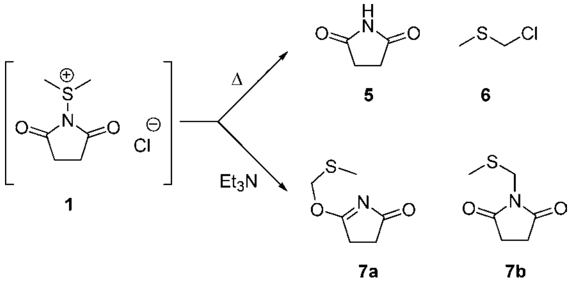
Scheme 3. **Decomposition pathways of the Corey−Kim intermediate**



amino group in compounds **2** and **3** was considered potentially problematic. The decomposition of intermediate **1** in the presence of triethylamine was monitored by FT−IR spectroscopy in order to estimate the rate of decomposition and to serve as a control experiment for the oxidation of compound **2**. The Corey−Kim oxidation of compound **2** was monitored by FT−IR spectroscopy, and the results are discussed.

Results and Discussion

The Corey−Kim intermediate was prepared according to the reaction shown in Scheme 1 at temperatures ranging from −8 to 30 °C. The reactions were conducted in a jacketed Mettler RC1 calorimeter equipped with a ReactIR probe and spectra of the mixture were recorded over a 20 h period. The FT−IR spectra of intermediate **1** were evaluated to identify bands that were distinct and well resolved from the bands of NCS, DMS and dichloromethane. Vilsmaier[8a] reported the carbonyl peak for intermediate **1** at 1735 cm^{-1}, but this was not well resolved from the carbonyl peak of NCS. It was observed that the bands at 1036 and 1011 cm^{-1} were increasing in intensity versus time when DMS was added to NCS in dichloromethane as shown in Figure 1. These two bands could not be attributed to either NCS or DMS, and were considered diagnostic for the presence of intermediate **1**. The bands at 1036 and 1011 cm^{-1} were most consistent with a CH$_3$ rocking vibration of the CH$_3$−S bond of intermediate **1**.[9]

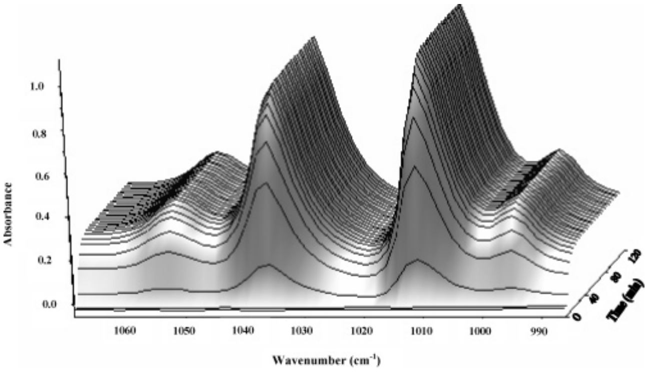


Figure 1. **FT−IR bands of the Corey−Kim intermediate at −8 °C at 2-min intervals.**

By monitoring the intensity of the diagnostic bands over time at different temperatures the decay of intermediate **1** could be observed. The analysis was based on the absorbance of the band at 1011 cm^{-1} due to its increased response relative to the 1036 cm^{-1} band. The absorbance of the band at 1011 cm^{-1} versus time was plotted in Figure 2 for each temperature evaluated.

Evaluation of Figure 2 shows that intermediate **1** was present after 20 h for only the reactions run at −8 and 0 °C. This was further confirmed by adding isopropanol followed by triethylamine to the aged Corey−Kim intermediate, and by analyzing the reactions by GC−MS. For the reactions run at −8 and 0 °C, products corresponding to a Corey−Kim oxidation were detected. In this model system, the methylthiomethyl ether of isopropanol was the major product, and acetone was formed in small quantity. The propensity to form the methylthiomethyl ether over the carbonyl compound has already been documented[1a] and was attributed to a solvent as well as a substrate effect. For reactions run at and above 5 °C, no oxidation products of isopropanol were detected. Instead, the mass spectrum revealed the presence of **5**, **6**, and **7a**,**b**, consistent with the decomposition pathways shown in Scheme 3.

A kinetic analysis on the decomposition of intermediate **1** using the data in Figure 2 directly was not possible due to the fact that serial dilution revealed that intermediate **1** exhibited a nonlinear absorbance with respect to concentration. This nonlinearity was presumed to be due to the biphasic nature of intermediate **1** in methylene chloride. The nonlinearity of the absorbance, coupled with the instability of **1**, made quantifying the concentration of **1** by FT−IR not sufficiently accurate for a kinetic analysis.

Instead, the kinetic analysis was based on measuring the extent of a reaction mediated by intermediate **1** versus time. The reaction selected for the kinetic analysis was the conversion of benzyl alcohol to benzyl chloride, which has been shown to proceed in high yield.[1d] The concentration of **1** was determined by charging benzyl alcohol, one equivalent relative to the NCS charge, and measuring the amount of unreacted benzyl alcohol by HPLC. The concentration of **1** was equal to the amount of benzyl alcohol consumed. The process was repeated at multiple temperatures and NCS concentrations, $[C]_{NCS}$, to generate the decomposition profiles shown in Figure 3.

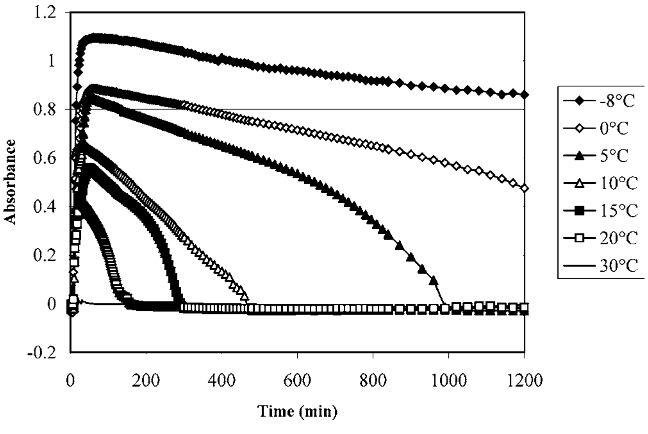


Figure 2. **Decay of the Corey−Kim intermediate versus time for the 1011 cm^{-1} band.**

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[9] Socrates, G. *Infrared and Raman Characteristic Group Frequencies: Tables and Charts*, 3rd ed.; John Wiley & Sons: New York, 2004; p 212.

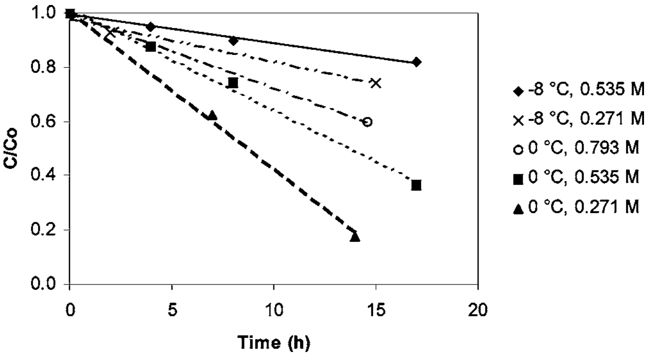


Figure 3. **Decomposition of the Corey−Kim intermediate versus time.**

Table 1. **Kinetic results summary**

temp (°C)	$[C]_{NCS}$ (M)	$[C]_o$ (M)	k_{obs} (1/h)	k (M/h)
−8	0.535	0.492	0.0104	0.00513
−8	0.271	0.239	0.0160	0.00383
0	0.793	0.725	0.0275	0.0199
0	0.535	0.480	0.0377	0.0181
0	0.271	0.235	0.0587	0.0138

For this analysis, the data was plotted as $[C]/[C]_o$ versus time, where $[C]_o$ was the measured concentration at time zero determined by adding the benzyl alcohol immediately after the DMS addition. Ideally the concentration at time zero would be equivalent to the starting NCS concentration. However, the measured concentration at time zero was approximately 90% of the NCS concentration due to the less than quantitative yield for the formation of **1** and the reaction with benzyl alcohol. Figure 3 shows a linear decomposition profile for intermediate **1** with the rate of decomposition increasing with temperature, consistent with the FT−IR analysis. The data also show that the rate of decomposition, k_{obs}, increases as the concentration decreases. These three findings were consistent with zero-order kinetics, as described by eqs 1 and 2 below, where the observed rate constant k_{obs} was inversely related to the initial concentration.

$$[C]/[C]_o = 1 - k_{obs}t \tag{1}$$

$$k_{obs} = k/[C]_o \tag{2}$$

$$k = A\,e^{-E_a/RT} \tag{3}$$

The data from Figure 3 were summarized in Table 1 in terms of the time zero concentration and observed rate constant for each temperature and NCS concentration combination examined. Equation 2 above was used to calculate k for evaluation of the Arrhenius equation, eq 3 above, to account for the temperature dependence of the rate constant. A plot of ln k versus $1/T$ (K) provided the activation energy, E_a, at 101.5 kJ/mol from the slope of the line, and the pre-exponential factor A at 4.31×10^{17} M/h as the intercept.

In order to develop a predictive model for the concentration of **1**, a relationship between the NCS concentration and the time zero concentration was required. A plot of $[C]_o$ versus $[C]_{NCS}$ resulted in a the linear relationship shown in eq 4 below. Using the empirical relationship between $[C]_o$ and $[C]_{NCS}$, transforming eq 1 into eq 5, and then inserting the Arrhenius equation resulted in the model for the concentration of the Corey−Kim intermediate described by eq 6.

Table 2. **Test experiments on the predictive model**

temp (°C)	$[C]_{NCS}$ (M)	time (h)	[C] (M) calcd	[C] (M) exp
−12	0.254	4	0.221	0.207
−4	0.360	4.5	0.287	0.284
5	0.895	4.5	0.641	0.626

$$[C]_o = 0.9079[C]_{NCS} \tag{4}$$

$$[C] = [C]_o - kt \tag{5}$$

$$[C] = 0.9079[C]_{NCS} - \{A\,e^{-E_a/RT}\}t \tag{6}$$

One of the major drawbacks to a kinetic model that incorporates an empirical factor is the accuracy of the prediction is poor when extrapolated outside the parameter ranges used to develop the model. In order to test the accuracy of the model, several experiments were run outside the concentration and temperature range, along with a control experiment within the range. The results of these test experiments, shown in Table 2, demonstrate the calculated concentration being within 7% of the experimental concentration. Comparing the model to the data shown in Figure 3 revealed that the accuracy of the model decreases significantly at $[C]/[C]_o$ values less than 0.3.

The two main conclusions drawn from the experimental results were that in order to maximize the concentration of the Corey−Kim intermediate the temperature should be maintained as low as possible, as expected, and that the concentration should be as high as possible. There was a practical upper limit for the concentration used in the preparation of **1**; a sufficient solvent volume was required to act as a heat sink due to the exothermic nature of the reaction. The time required to complete the Corey−Kim oxidation step at the manufacturing scale was estimated at 4 h or less, from the addition of dimethyl sulfide to the addition of triethylamine. Based on the model developed for the decay of intermediate **1**, at $[C]_{NCS}$ of 0.535 M less than 25% degradation would occur during the 4 h required to complete the process when the temperature was maintained at or below 0 °C.

With the evaluation of the decomposition of the intermediate **1** versus temperature complete, the decomposition in the presence of tertiary amines was evaluated by FT−IR. Intermediate **1** was generated at −8 °C as shown in Scheme 1, followed by addition of triethylamine at the same temperature. As shown by the disappearance of the 1011 cm^{-1} band in Figure 4, tertiary amines destroy intermediate **1** even at low temperatures in the absence of an alcohol substrate. GC−MS analysis of the reaction mixture confirmed the decomposition of the intermediate, showing the main product to be **7a,b**, as shown in Scheme 3.

For alcohol substrates containing a tertiary amino group, such as **2**, two competing pathways would exist; the amine

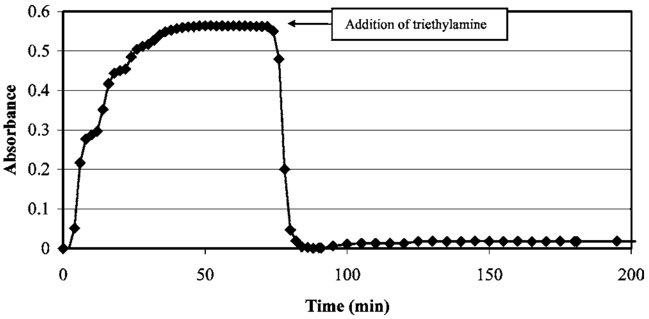
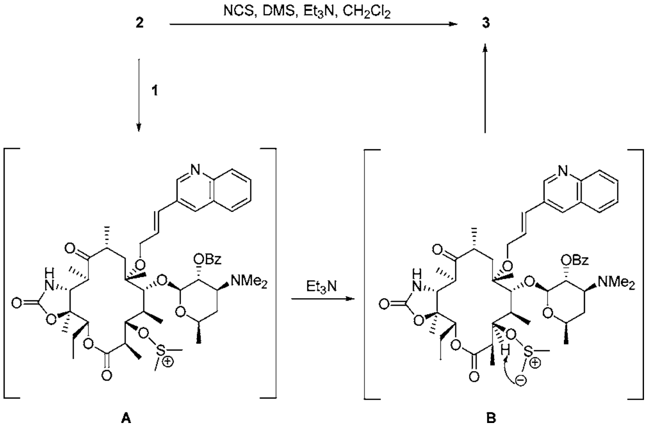


Figure 4. **Peak intensity of the 1011 cm^{-1} band upon addition of triethylamine to intermediate 1.**

could cause decomposition of intermediate **1** or act as the base and cause oxidation to the desired product. If the amino group caused decomposition, the reaction would likely require an excess of intermediate **1** to counter the negative effect of the amine and allow the oxidation to go to completion. If the amino group of the substrate was functioning as a base in the reaction, product would be formed prior to the addition of triethylamine and a substoichiometric amount of triethylamine would be required.

The Corey−Kim oxidation of the C-3 hydroxyl of compound **2**, as shown in Scheme 4, was evaluated using FT−IR spectroscopy. The Corey−Kim intermediate was prepared at −8 °C using 1.6 equiv of *N*-chlorosuccinimide relative to **2**. The addition of compound **2** to the Corey−Kim intermediate did not result in a change in FT−IR spectrum that could be attributed to the formation of intermediate **A** in Scheme 4. It was possible that both the Corey−Kim intermediate and intermediate **A** exhibited bands at 1036 and 1011 cm^{-1}.

Scheme 4. **Corey−Kim oxidation of compound 2**



The addition of compound **2** to the Corey−Kim intermediate resulted in a slow but steady decrease in the intensity of the 1011 cm^{-1} FT−IR band, as shown in Figure 5. HPLC analysis of this reaction revealed that the desired product, ketone **3**, is formed in ~20% *prior to the addition of triethylamine*. In this instance, the tertiary amine in compound **2** was acting as the base to cause the oxidation. The partial conversion of compound **2** to **3** would consume a fraction of the Corey−Kim intermediate and was consistent with the slow decrease in the intensity of the 1011 cm^{-1} FT−IR band shown in Figure 5.

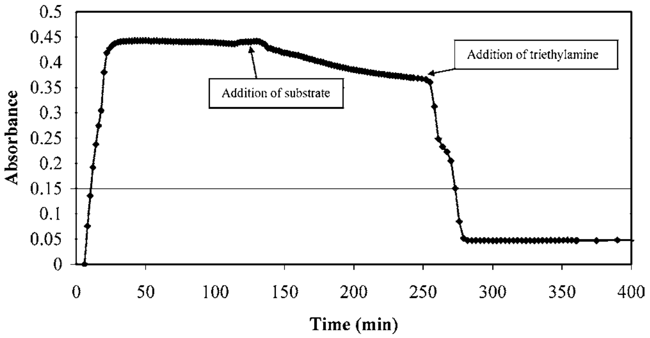


Figure 5. **Peak intensity of 1011 cm^{-1} band of the Corey−Kim oxidation of compound 2.**

Upon addition of 1.9 equiv of triethylamine, the FT−IR band at 1011 cm^{-1} completely disappeared within minutes. HPLC analysis showed the reaction was complete within 1 h after the addition of the triethylamine. It should be noted that, while the addition of triethylamine is necessary to complete the oxidation step, the use of excess triethylamine relative to *N*-chlorosuccinimide consumed the excess Corey−Kim intermediate. In order to maintain active Corey−Kim intermediate after the addition of triethylamine, the amount of triethylamine was reduced to the minimum required to complete the oxidation. Range-finding experiments revealed that 1.0 equiv of triethylamine resulted in complete oxidation within 2 h, and as little as 0.5 equiv of triethylamine caused complete oxidation after 19 h. When 1.0 equiv of triethylamine was used in the oxidation of compound **2** and after the reaction was complete by HPLC analysis, an additional 10 mol % of **2** could be added to the reaction and undergo oxidation to **3**. This result showed that active Corey−Kim intermediate was still present when 1.0 equiv of triethylamine was used. These results indicated that for a substrate containing a tertiary amine, the Corey−Kim oxidation can be completed with substoichiometric amounts of base; however, the reaction rate was slower, and stability of the intermediate might be problematic. The tertiary amino group of **2** was not likely causing significant degradation of the Corey−Kim intermediate because the oxidation could be completed with less *N*-chlorosuccinimide (1.4 equiv)[5b] than described in the original Corey−Kim procedure (1.5 equiv).[1a]

In conclusion, the Corey−Kim intermediate was found to decompose over time, and the rate of decomposition was related to temperature and concentration. A model was developed to predict the concentration of the Corey−Kim intermediate as a function of time, temperature, and NCS concentration. The temperature dependence of the decomposition rate was defined using the Arrhenius equation. Based on the model developed, less than 25% decomposition of the Corey−Kim intermediate would occur under typical reaction conditions when the temperature was maintained at or below 0 °C. The addition of triethylamine to complete the oxidation process, typically in excess relative to NCS, also destroyed the excess Corey−Kim intermediate. In order to maintain active Corey−Kim intermediate, the amount of triethylamine was reduced to the minimum required to complete the oxidation of compound **2** within 2 h. The oxidation of compound **2** was successful at large scale (>300 kg) maintaining the temperature below 0 °C with a slight excess of the Corey−Kim intermediate.

Experimental Section

General Experimental. The reactions were carried out in a Mettler-Toledo reaction calorimeter (RC1), and the FT−IR spectra were recorded using a Mettler-Toledo AutoChem ReactIR 1000. An air background spectrum was recorded before starting each FT−IR experiment. The GC−MS spectra were recorded on a Hewlett-Packard 5890/5972 with a jet separator interface, fitted with a J&W, DB-624 30 m × 0.53 mm, 3 μm column; helium carrier gas, flow rate 6.8 mL/min; injector 150 °C, jet separator 210 °C, detector 280 °C, oven program: 45 °C, hold 7 min, rate 20 °C/min, 210 °C, hold 10 min. The HPLC analyses were performed on a Zorbax or Phenomenex C8 column, eluting with a gradient of acetonitrile and water (0.1% phosphoric acid). The chemicals and solvents were purchased form the Aldrich Chemicals and EM Science companies and used as received. Compound **2** was prepared according to the known procedure.[5b]

Evaluation of Corey−Kim Intermediate at Different Temperatures over Time. To the 1-L RC-1 calorimeter were charged *N*-chlorosuccinimide (41 g, 0.31 mol) and dichloromethane (681 g). The mixture was stirred and adjusted to the desired temperature. Dimethyl sulfide (20 g, 0.32 mol, 24 mL) was added dropwise via addition funnel. The mixture was then stirred for 20 h at the desired temperature while being periodically monitored by FT−IR. Following the 20 h mix, isopropanol (11 g, 0.18 mol, 14 mL) was added dropwise via addition funnel. The resulting mixture was stirred at the desired temperature for approximately 1 h, and then triethylamine (35 g, 0.35 mol, 48 mL) was added dropwise via addition funnel. The mixture was stirred for 1 h, and a sample was analyzed by GC−MS.

Determination of the Amount of Corey−Kim Intermediate by Reaction with Benzyl Alcohol. The Corey−Kim intermediate was prepared as described above at 20% scale using a jacketed reactor at the desired temperature. The mixture was stirred for the desired amount of time, and then benzyl alcohol (6.641 g, 0.06141 mol, 1.0 equiv) was added. The mixture was warmed to 20 °C over 45 min and then quantitatively transferred to a volumetric flask, diluting to volume with acetonitrile. After serial dilution, the amount of unreacted benzyl alcohol was quantified by HPLC relative to a benzyl alcohol standard. The amount of Corey−Kim intermediate was equal to the amount of benzyl alcohol consumed.

Evaluation of the Effect of Triethylamine on the Corey−Kim Intermediate. The Corey−Kim intermediate was prepared in the 1-L RC-1 calorimeter at −8 °C as described above. The mixture was then stirred for 40 min while being periodically monitored by FT−IR. Triethylamine (35 g, 0.35 mol, 48 mL) was added dropwise via addition funnel while maintaining the internal temperature in the vessel at −8 °C. The mixture was stirred for 1 h, and a sample was analyzed by GC−MS.

Evaluation of the Corey−Kim Oxidation of Compound 2. The Corey−Kim intermediate was prepared in the 1-L RC-1 calorimeter at −8 °C as described above using *N*-chlorosuccinimide (31.6 g, 0.237 mol), dichloromethane (525 g), and dimethyl sulfide (15.4 g, 0.248 mol). The mixture was stirred for 1.5 h while being periodically monitored by FT−IR. A solution of compound **2** (131.2 g, 0.15 mol) in dichloromethane (457 g) was added over 1 h. The mixture was stirred for 1 h, and then triethylamine (28.7 g, 0.284 mol) was added dropwise via addition funnel over 20 min while maintaining the internal temperature in the vessel at −8 °C. The mixture was stirred and periodically monitored by FT−IR.

GC−MS analysis of major components: compound: formula, formula weight; GC: retention time; MS: *m*/*z* (intensity, rel %), molecular ion, M^+. Triethylamine: $C_6H_{15}N$, FW = 101; GC RT = 5.8 min; MS: 86 (100%), M^+ 101 (18%). Methylthiomethyl chloride, **6**: C_2H_5ClS, FW = 96; GC: RT = 8.7 min; MS: 35 (17%), 45 (35%), 47 (8%), 49/51 (8%/3%), 61 (100%), 81/83 (3%/1%), M^+ 9 6/98 (46%/18%). Isopropyl methylthiomethyl ether: $C_5H_{12}OS$, FW = 120; GC: RT = 10.6 min; MS: 43 (100%), 61 (45%), 73 (45%), 105 (1%), M^+ 120 (18%). Succinimide, **5**: $C_4H_5NO_2$, FW = 99; GC: RT = 15.2 min; MS: 42 (11%), 56 (74%), 70 (6%), M^+ 99 (100%). Methylthiomethyl succinimide, **7a,b**: $C_6H_9NO_2S$, FW = 159; GC: RT = 18.2 min; MS: 47 (8%), 55 (100%), 61 (11%), 84 (65%), 100 (12%), 112 (76%), 144 (26%), M^+ 159 (71%).

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