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Technical Notes

Process Development of an Inherently Safer Oxidation: Synthesis of 2-Chloro-6-methylbenzoic Acid in the R411 Manufacturing Process

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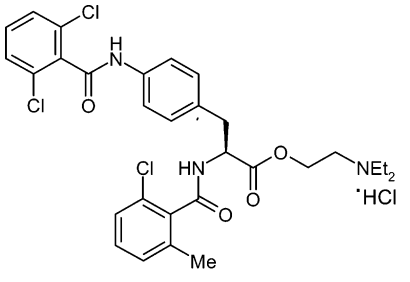
Abstract:

Many oxidation reactions can be hazardous when run on large scale. The manufacturing process for the production of R411, a developmental compound indicated for the treatment of asthma, includes the oxidation of 2-chloro-6-methylbenzaldehyde to the corresponding carboxylic acid. The use of sodium chlorite in this transformation was efficient and economical, but there were safety concerns regarding the use of hydrogen peroxide to scavenge unwanted hypochlorite, which was generated as a byproduct of the reaction. During the development of the R411 manufacturing process, an inherently safer oxidation system was discovered using a stoichiometric quantity of dimethyl sulfoxide (DMSO) as scavenger. The new process provided equivalent yields and purities to the hydrogen peroxide procedure, thus maintaining the economic viability of the process. The developed process was demonstrated in fixed equipment on a 300 gal scale.

Introduction

The integrin VLA-4 ($\alpha_4\beta_1$) is expressed on a variety of leukocytes including T-cells, eosinophils, and mast cells. Recruitment, activation, and retention of these types of cells are implicated in the inflammatory cascade associated with asthma by releasing a variety of substances that cause both acute and chronic damage to the airways.[1] R411 (*N*-(2-chloro-6-methylbenzoyl)-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine-2-(diethylamino)ethyl ester hydrochloride, **1**) has been found to be a potent and specific inhibitor of T-cell and eosinophil activation in vitro.[2] In animal models of asthma, R411 shows potential as a novel nonsteroidal approach for the treatment of asthmatic patients.



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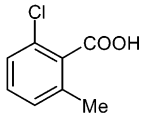

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2-Chloro-6-methylbenzoic acid (**2**) is a key raw material in the synthesis of **1**, but despite its simple structure there are currently no economical sources for commercial quantities of this material and the compound has been difficult to prepare in high yields and purities. Several synthetic routes to **1** were evaluated in Process Research, and the most commercially viable route was determined to be from 2-chloro-6-fluorobenzaldehyde (**3**). Protection of the aldehyde as the imine **4**, followed by introduction of a methyl group by a Grignard reaction, formed the 2-chloro-6-methylbenzaldehyde **5**. Oxidation of **5** to the corresponding benzoic acid was then carried out using sodium chlorite (Scheme 1).[3]

While this method provided good yields and was adequate for clinical supplies of multi-kilo quantities, there were safety concerns on scaling the reaction to a commercial process due to the use of hydrogen peroxide in the reaction. Hypochlorite, which forms as a byproduct of the oxidation, can cause side reactions as its concentration in the system increases (eq 1).[4] Hydrogen peroxide is added to the reaction to scavenge hypochlorite; however the use of this reagent leads to the loss of an inert atmosphere in the reactor due to the generation of oxygen during consumption of hypochlorite (eq 2).[4]

$$RCHO + HClO_2 \rightarrow RCO_2H + HOCl \quad (1)$$

$$HOCl + H_2O_2 \rightarrow HCl + O_2 + H_2O \quad (2)$$

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(1) (a) Abraham, W. M.; Gill, A.; Ahmed, A.; Sielczak, M. W.; Lauredo, L. T.; Botinnikova, Y.; Lin, K. C.; Pepinsky, B.; Leone, D. R.; Lobb, R. R.; Adams, S. P. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 603. (b) Lin, K. C.; Ateeq, H. S.; Hsiung, S. H.; Chong, L. T.; Zimmerman, C. N.; Castro, A.; Lee, W. C.; Hammond, C. E.; Kalkunte, S.; Chen, L. L.; Pepinsky, R. B.; Leone, D. R.; Sprague, A. G.; Abraham, W. M.; Gill, A.; Lobb, R. R.; Adams, S. P. *J. Med. Chem.* **1999**, *42*, 920. (c) Boer, J.; Gottschling, D.; Schuster, A.; Semmrich, M.; Holzmann, B.; Kessler, H. *J. Med. Chem.* **2001**, *44*, 2586.

(2) (a) Sidduri, A.; Tilley, J. W.; Lou, J. P.; Chen, L.; Kaplan, G.; Mennona, F.; Campbell, R.; Guthrie, R.; Huang, T. N.; Rowan, K.; Schwinge, V.; Renzetti, L. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2479. (b) Hull, K. G.; Achytharao, S.; Tilley, J. W. Int. Patent Appl. WO200048994. (c) Chen, L.; Guthrie, R. W.; Huang, T. N.; Hull, K. G.; Achytharao, S.; Tilley, J. W. Int. Patent Appl. WO9910312.

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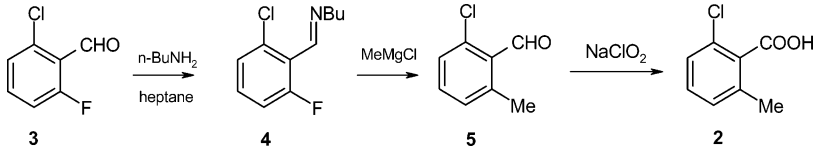
Scheme 1. **Synthesis of 2-chloro-6-methylbenzoic acid from 2-chloro-6-fluorobenzaldehyde**



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Another concern was the potential accumulation of hydrogen peroxide in the reactor. The decomposition of hydrogen peroxide is known to be highly exothermic, and while the decomposition rate depends strongly on both composition and temperature, it can also be catalyzed by the materials of construction used in the reactor or by various trace contaminants.[5,6] Although some hydrogen peroxide chemistry is routinely performed in properly passivated stainless steel or Hastelloy C reactors, exposure to unpassivated metal surfaces in the reactor train may result in highly accelerated decomposition even at ambient temperatures. Hydrogen peroxide is also known to form explosive mixtures with various organic compounds (including aldehydes and ketones) in certain concentration ranges.[5,6] For these reasons, the hazards of using hydrogen peroxide on this step along with potential alternates to hydrogen peroxide were investigated to improve the safety profile of this reaction for future commercial operation.

Results and Discussion

The energy release associated with the decomposition of hydrogen peroxide is well defined.[5] It was calculated that if the reaction was run on a 300 gal scale, 43 kg of aldehyde **3** and 37.6 kg of 35% H_2O_2 would be required per batch. Full decomposition of the H_2O_2 would produce 6.19 kg (or 193 mol or ~1250 gal @ 1 atm and 25 °C) of O_2 gas, accompanied by an adiabatic temperature rise of ~43 °C for a well-mixed system (281.5 kg total mass; ~3.15 kJ/kg K heat capacity). In this case, the oxygen release to the headspace and the associated risks of deflagration would pose a much greater threat than the temperature rise of the batch. The organic and aqueous layers quickly separate in the absence of agitation. If the peroxide partitioned entirely into the aqueous phase, the expected adiabatic temperature rise would be 66 °C (137.5 kg; ~4.18 kJ/kg K). If the peroxide partitioned entirely into the organic phase (worst case scenario), the anticipated adiabatic temperature rise would be ~122 °C (144 kg; ~2.175 kJ/kg K) without phase-change corrections. Using a value of 808.8 kJ/kg for the heat of vaporization, approximately 22 kg (~22%) of the acetonitrile in the system would be vaporized at the boiling point of the organic phase (~82 °C) in a vented system.

The effect of the organic components in the system was evaluated using adiabatic calorimetry. An accelerating rate calorimetry (ARC) test on the organic layer, run in a Hastelloy C bomb, showed an exotherm onset temperature of approximately 50 °C ($\varphi = 1.6$; $C_p = 2.175$ kJ/kg K), with a calculated adiabatic temperature rise of roughly 155 °C. This compared rather poorly with the ~122 °C that would be indicated exclusively from the decomposition of the peroxide if it had partitioned fully with the organic components. The excess energy indicated the occurrence of some undesired reaction in the system. A second exotherm was then observed, with an onset temperature of about 175 °C, which was tracked to ~250 °C before the experiment was terminated. Since this second exotherm was terminated while the self-heat rate was still increasing, we can only roughly estimate the associated energy release as ≥600 kJ/kg (≥ ~260 °C adiabatic temperature rise). The experimental temperature and pressure profiles for both exotherms are shown in Figure 1, and the associated self-heat and pressure rates are shown in Figure 2. Taken together, the two exotherms showed the potential for a very significant energy release.

After considering the potential for developing explosive compositions in the vapor space of the reactor, the magnitude of the potential energy release at elevated temperatures, and the potential for accidental catalysis of undesired chemistry, an investigation was carried out to find an inherently safer oxidation system. DMSO has been shown to be an effective HOCl scavenger when used as solvent since it is oxidized to dimethyl sulfone;[4] however the high boiling point of the solvent would present downstream processing issues if used in substantial quantities. To avoid the presence of excess DMSO, the compound was added as a stoichiometric charge, in the absence of hydrogen peroxide, and these conditions were found to be adequate to drive the reaction to completion. Under these reaction conditions, the oxidation of the aldehyde is performed as described before (eq 1) and the hypochlorite byproduct is consumed by oxidizing DMSO to dimethyl sulfone (eq 3).

$$\mathrm{RCHO + HClO_2 \rightarrow RCO_2H + HOCl} \qquad (1)$$

$$\mathrm{DMSO + HClO \rightarrow DMSO_2 + HCl} \qquad (3)$$

As an additional processing benefit, the process capacity was improved by a factor of 2 and waste was minimized using the DMSO procedure since buffer was no longer required in the reaction. The dimethyl sulfone byproduct of the oxidation was removed in the aqueous extractions during workup. The tandem base−acid purification workup was no longer required, and the products were isolated by direct crystallization from the reaction mixture, resulting in reduced process cycle time and additional reductions in waste. Overall, the new process provided better yields and similar purities to the hydrogen peroxide procedure, thus maintaining the economic viability of the process. To show the general

(3) Daniewski, A. R.; Liu, W.; Puntener, K.; Scalone, M. *Org. Process Res. Dev.* **2002**, *6*, 220−224.
(4) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.
(5) *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Urben, P. G., Ed.; Butterworth-Heinemann: 1995; Vol. 1, pp 1519−1538, Vol. 2, pp 291−296.
(6) Jeff, M. *Hydrogen Peroxide − The Safe Supply and Handling of HTP*; Solvay Interox, Inc.: 3333 Richmond Ave., Houston, Texas 77098.

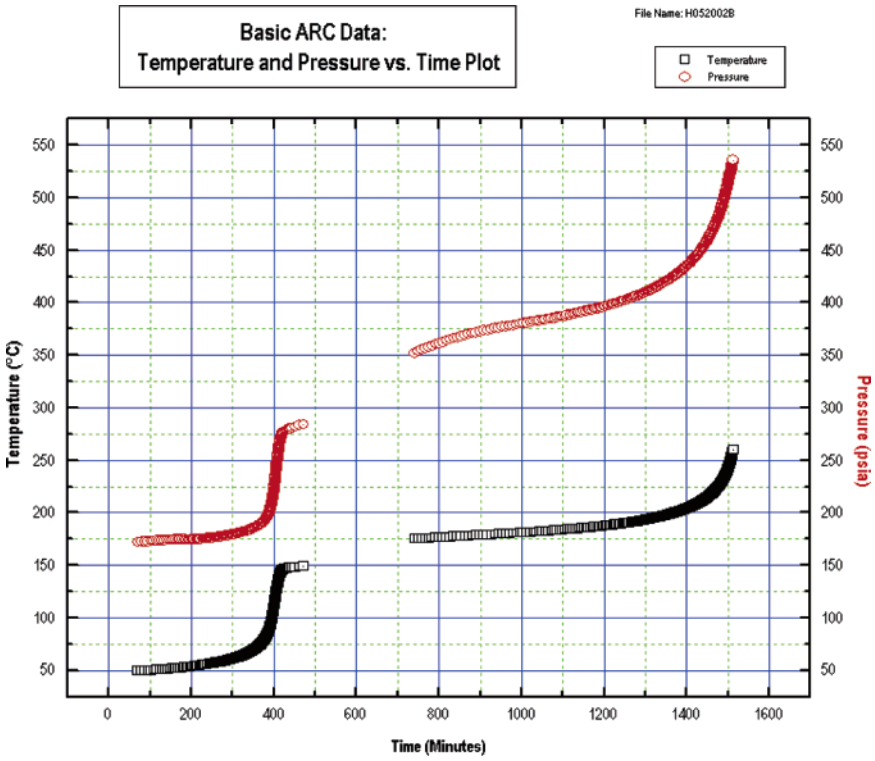


Figure 1. **Temperature and pressure profiles for two exotherms observed during the ARC screening of the organic phase, sampled after the hydrogen peroxide addition.**

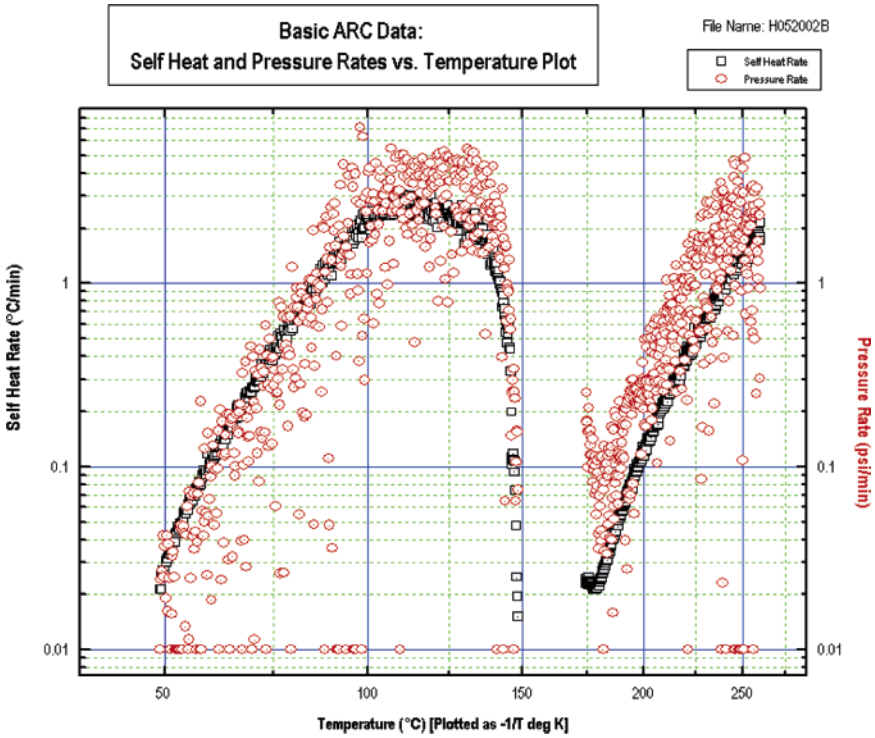
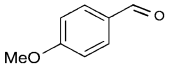
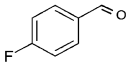


Figure 2. **Self-heat and pressure rates for two exotherms observed during the ARC screening of the organic phase, sampled after the hydrogen peroxide addition.**

applicability of the process, some simple aldehyde substrates were oxidized to their carboxylic acids using the DMSO procedure, and the results are shown in Table 1.

Prior to scale-up, the new process was tested for thermal stability. The first reaction mixture tested in the ARC (φ = 1.45) after the addition of sulfuric acid to a mixture of 2-chloro-6-methylbenzaldehyde, acetonitrile, water, and DMSO showed an onset at 84 °C with a calculated adiabatic temperature rise of approximately 8.4 °C. A second exotherm was observed with an onset of 134 °C and a calculated adiabatic temperature rise of >109 °C. (The ARC experiment was terminated at 250 °C.)

Table 1. **Oxidation of aldehydes using $HClO_2$ and DMSO as HOCl scavenger**

Item	Substrate	Rxn Time (Hrs) [a]	Carboxilic acid	Yield (%) [b]	Assay (Area %)
5a		2	2	95 (90)	99.9
5b		1	2b	98 (93)	99.1
5c		1.2	2c	98.6 (90)	99.5
5d		4	2d	87.5 (85)	99.2
5e		1	2e	98 (95)	99.9
5f		2	2f	90 (75)	99.0

A second ARC investigation was carried out on the reaction mixture after the addition of sodium chlorite. The ARC run ($\varphi = 1.34$) showed an initial minor exotherm with an onset of 139 °C and a calculated adiabatic temperature rise of 2.6 °C. On continued heating a second minor exotherm was detected with an onset of 154 °C and a calculated adiabatic temperature rise of 3.1 °C. On further heating and screening, a third exotherm with an onset of 164 °C and a calculated adiabatic temperature rise of 78 °C was measured giving a final calculated adiabatic temperature of 242 °C. Raw temperature and pressure tracking data of this ARC run and corresponding self-heat and pressure rise rates are shown in Figures 3 and 4. This process compares favorably with the first process using hydrogen peroxide where the exotherm onset temperature was approximately 50 °C and the adiabatic temperature rise > 155 °C.

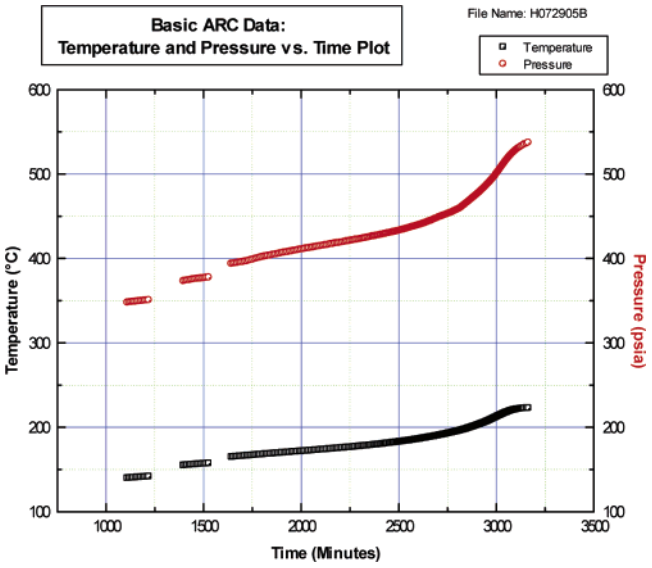


Figure 3. **Temperature and pressure profiles for exotherms observed during the ARC screening of the reaction mixture, sampled after the sodium chlorite addition.**

There are three additional exothermic events in the new process, which include the exothermic addition of sulfuric acid, the exothermic addition of sodium chlorite (aq), and the exothermic quench with sodium sulfite (aq). The addition of sulfuric acid is moderately exothermic with a measured reaction enthalpy of −56.9 kJ/kg (reaction mixture at addition end), and the adiabatic temperature rise is calculated at 19.3 °C. The addition is performed at 10 °C, and therefore this gives a maximum reaction temperature of 29.3 °C in the absence of cooling. The addition was performed over 4 min, and >95% of measured energy release was complete at the end of the addition of sulfuric acid. ARC screening reported above shows a mild self-heat exotherm with an onset temperature of 84 °C which is >60 °C over the maximum predicted adiabatic reaction temperature.

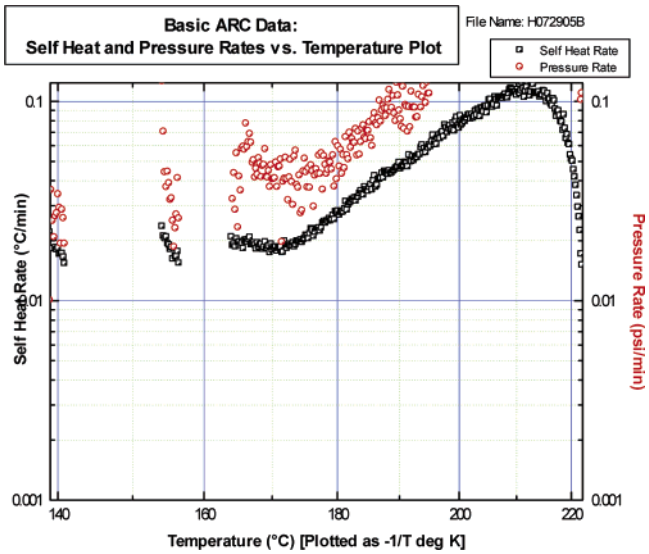


Figure 4. **Self-heat and pressure rate exotherms observed during the ARC screening of the reaction mixture, sampled after the sodium chlorite addition.**

The addition of sodium chlorite is also exothermic with a measured reaction enthalpy of −458.7 kJ/kg (of reaction mixture at addition end), and the adiabatic temperature rise is calculated at 141.6 °C. The addition is performed at 10 °C, and this gives a maximum reaction temperature of 151.6 °C under complete containment. There exists the potential of uncontrolled boiling and release of reactor contents from the reactor if all sodium chlorite were to be added at once. In the laboratory the addition was performed over 30 min, and energy release was found to be approximately linear with the addition mass with >95% of total energy released at the end of addition. No accumulation of reaction enthalpy was measured. In the plant because of potential limits in cooling capacity, the rate of addition is adjusted to ensure that reactor contents are maintained at 10 °C. Additionally, in ARC testing reported above, the first major self-heat exotherm was measured at an onset of 164 °C.

The addition of sodium sulfite is mildly exothermic, and the reaction enthalpy was measured at −14.4 kJ/kg (of reaction mixture at addition end). The predicted adiabatic temperature rise is 4.4 °C. Approximately 75% of reaction enthalpy is released over the addition time of 10 min. The residual accumulated reaction enthalpy is predicted to cause an adiabatic temperature rise of ∼1 °C, which was considered insignificant.

Based on this favorable thermal data, the DMSO process was run on a 300 gal scale. Yields and purities were similar to those in the lab.

Conclusion

Hydrogen peroxide was successfully removed from the R411 process by substituting DMSO as a HOCl scavenger in the oxidation of 2-chloro-6-methylbenzaldehyde to its carboxylic acid. In addition to the improved safety profile for the reaction step, the new process had improved process cycle times, reduced waste, and better yields with similar purities to those of the hydrogen peroxide procedure, thus maintaining the economic viability of the process. The developed process was demonstrated in fixed equipment on a 300 gal scale.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR were performed on a Varian 400 MHz spectrometer. HPLC analysis was performed on a Hewlett-Packard 1100 HPLC using a Zorbax SB-CN (4.6 mm × 250 mm, 5 μ) column; mobile phase was a gradient of A (water/TFA 1000:1 (v/v)) and B (acetonitrile/TFA 1000:1 (v/v)) in ratios (%A) of 95% (25 min), 20% (10 min), and 95% (5 min); ambient temperature; flow rate = 1.0 mL/min; UV detection at 220 nm.

Oxidation of 2-Chloro-6-methylbenzaldehyde (5a) with Hydrogen Peroxide Scavenger: To a 2 L reactor was added 2-chloro-6-methylbenzaldehyde (139.1 g, 0.89 mol), acetonitrile (417 mL), and a solution of sodium dihydrogenphosphate monohydrate (36.8 g) in water (126.54 mL). The mixture was agitated and brought to a temperature of 15 °C ± 5 °C. Water (125.1 mL) was added followed by concentrated sulfuric acid (33.92 g) while continuing to maintain the temperature at 15 °C ± 5 °C (slightly exothermic). Hydrogen peroxide (121.8 g of 35% solution) was then charged, while maintaining 15 °C ± 5 °C (slightly exothermic). A solution of sodium chlorite (141.6 g) in water (368 mL) was then carefully charged while maintaining the batch below 20 °C (highly exothermic). When less than 0.5% starting material remained, the reaction was carefully quenched with a solution of sodium sulfite (112.7 g) in water (448 mL) while maintaining the batch below 20 °C (highly exothermic). After a 3 h hold, the batch was distilled under vacuum at 40 °C and diluted with toluene (500 mL), and then the phases were separated. The toluene solution of crude product was extracted with 9% NaOH (780 mL), and the organic phase was discarded. The aqueous extract was then acidified with 37% HCl (186.7 mL) and diluted with water (500 mL), and the product crystallized by cooling from 35 °C to 6 °C. After filtering, the batch was washed with water and dried under vacuum at <40 °C for 24 h to provide **2** in 85% yield and 99.9 area% purity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.56 (d, 1H), 7.33 (d, 1H), 7.61 (d, 1H), 7.97(d, 1H), 8.27 (d, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 33.14, 102.03, 106.24, 114.68, 120.58, 133.16, 134.54, 135.14, 142.78.

Oxidation of 2-Chloro-6-methylbenzaldehyde (5a) with DMSO Scavenger: To a 1 L reactor was added 2-chloro-6-methylbenzaldehyde (40.0 g, 257 mmol), acetonitrile (100 mL), DMSO (24.28 g, 311 mmol), and water (33 mL). The mixture was agitated and brought to a temperature of 10 °C ± 5 °C. Concentrated sulfuric acid (14 g) was added while continuing to maintain the temperature at 10 °C ± 5 °C (slightly exothermic). A solution of sodium chlorite (34.85 g) in water (170 mL) was then carefully added while maintaining the batch below 10 °C (highly exothermic). When less than 0.5% starting material remained, the reaction was carefully quenched with a solution of sodium sulfite (6.7 g) in water (40 mL) while maintaining the batch below 20 °C (highly exothermic). After a 30 min hold, the batch was distilled under vacuum at 40 °C until a slurry was observed. The mixture was then diluted with toluene (300 mL), and the phases were separated. The organic phase was washed with water (2 × 60 mL), and then the volume was reduced by removing ∼200 mL of toluene by vacuum distillation. The resulting solution was assayed for both product and water content; usually 0.2% g of **5a**/mL and water <0.01%. Alternatively, the carboxylic acid **2** can be isolated from toluene−heptane crystallization to provide ∼90−95% yield and assay >99 area%.

2-Chlorobenzoic Acid (2b). Prepared as described above and isolated from acetonitrile−water.

^{1}H NMR (500 MHz, DMSO): δ 7.41 (m, 1H), 7.50−7.55 (m, 2H), 7.78 (m, 1H), 13.36 (bs, 1H). ^{13}C NMR (500 MHz, DMSO): δ 127.1, 130.5, 130.7, 131.4, 131.6, 132.5, 166.6.

2-Methylbenzoic Acid (2c). Prepared as described above and isolated from methylene chloride.

^{1}H NMR (500 MHz, DMSO): δ 7.27 (t, 1H, ovlp), 7.28 (d, 1H, ovlp), 7.42 (td, 1H), 7.82 (d, 1H), 12.78 (bs, 1H). ^{13}C NMR (500 MHz, DMSO): δ 21.1, 125.7, 130.1, 130.4, 131.4, 131.6, 138.9, 168.6.

4-Methoxybenzoic Acid (2d). Prepared as described above and isolated from methylene chloride.

^{1}H NMR (500 MHz, DMSO): δ 7.00 (d, 1H), 7.91 (d, 1H), 12.6 (bs, 1H). ^{13}C NMR (500 MHz, DMSO): δ 55.3, 113.7, 122.9, 131.3, 162.8, 166.9.

4-Fluorobenzoic Acid (2e). Prepared as described above and isolated from acetonitrile−water.

^{1}H NMR (500 MHz, DMSO): δ 7.29 (t, 2H), 8.00 (dd, 2H), 13.02 (bs, 1H). ^{13}C NMR (500 MHz, DMSO): δ 115.5, 127.3, 132.1, 164.8, 166.3.

1-Naphthoic Acid (2f). Prepared as described above and isolated from methylene chloride−toluene.

^{1}H NMR (500 MHz, DMSO): δ 7.60−7.55 (m, 2H), 7.64 (td, 1H), 8.00 (d, 1H), 8.14 (d, 1H), 8.17 (dd, 1H), 8.89 (d, 1H), 13.15 (bs, 1H). ^{13}C NMR (500 MHz, DMSO): δ 124.8, 125.4, 126.1, 127.5, 127.6, 128.5, 129.8, 130.6, 132.9, 133.4, 168.9.

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Note Added after ASAP Publication: There was an error in Scheme 1 in the version published on the Web October 14, 2005. The version published October 19, 2005 and the print version are correct.

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