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TECHNICAL NOTE

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A Safe and Practical Procedure for the Difluoromethylation of Methyl 4-Hydroxy-3-iodobenzoate

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Supporting Information

ABSTRACT: The difluoromethylation of methyl 4-hydroxy-3-iodobenzoate has been demonstrated on multikilogram scale. Prior to execution, several issues had to be addressed. First, the difluorocarbene source had to be explored to avoid using highly toxic gases such as chlorodifluoromethane. After choosing sodium chlorodifluoroacetate as the difluororcarbene precursor and potassium carbonate as the base, a safety evaluation had to be performed to ensure this transformation could be carried out safely on multikilogram scale. Herein, we report a safe and practical difluoromethylation protocol of methyl 4-hydroxy-3-iodobenzoate. This procedure was successfully implemented on 7 kg scale to produce (**6**) in 99% yield and 99% purity after crystallization.

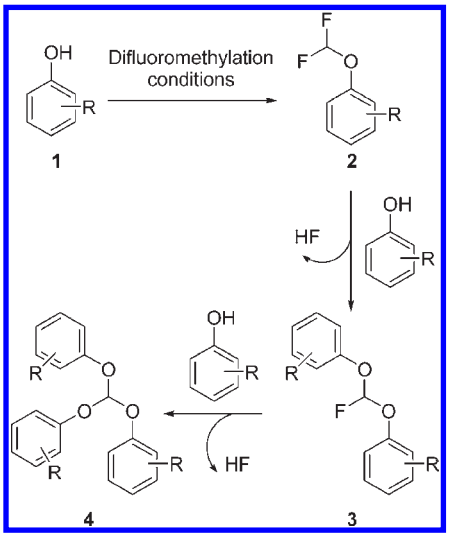
INTRODUCTION

Aryl difluoromethyl ethers are becoming increasingly prevalent in the pharmaceutical,[1] agrochemical,[2] and materials[3] industries. Recently, this functional group has been incorporated in selective phosphodiesterase-4 inhibitors,[4] PPAR-δ agonists,[5] treatments for cardiac arrhythmias,[6] and HCV inhibitors.[7] During the course of a cGMP campaign for a compound entering development, we required the conversion of an *o*-iodo phenol to the corresponding difluoromethyl ether. The original medicinal chemistry route utilized chlorodifluoromethane,[8] a highly toxic chlorofluorocarbon (CFC) gas, as the source of the difluorocarbene intermediate. This reagent could not be used on scale. Other reagents used for the difluoromethylation of phenols include those derived from chlorodifluoroacetic acid,[9] including the sodium salt and alkyl esters. These bench-stable solids are readily available in bulk and easier to handle than chlorodifluoromethane, however, the reactions must be carried out at elevated temperature, release an equimolar amount of carbon dioxide, and produce unwanted byproduct such as double-addition and triple-addition adducts. Alternative reagents do exist[10] for converting phenols to the corresponding difluoromethyl ether, but their lack of commercial availability, characteristically high toxicity, and/or inadequate efficiency limit their use in the pharmaceutical industry. Examination of the literature also suggests that difluoromethylation reactions are often plagued by low yields and/or limited scope.[9,10] We now report our efforts for the safe and efficient difluoromethylation of methyl 4-hydroxy-3-iodobenzoate carried out on multikilogram scale.

RESULTS AND DISCUSSION

The difluoromethylation of the free phenol moiety in **1** is first expected to provide the desired difluoromethyl ether (**2**). This product can be consumed by remaining phenol (**1**) to provide the double-addition adduct (**3**). This adduct can further react with free phenol (**1**) to generate a triple-addition adduct (**4**) (see Scheme 1). The easiest way to remove these impurities is via acidic hydrolysis to the parent free phenol, which can be extracted into aqueous base. Specifically, treatment with aqueous acid to hydrolyze (**3**) and (**4**) with partitioning into an organic solvent is followed by a phase split. Washing the organic layer with aqueous base to remove the parent phenol provides the desired product as a solution in organic solvent. It quickly became apparent that the ability to control, if not eliminate, the formation of (**3**) and (**4**) would greatly simplify the execution of this reaction on scale.

Scheme 1. Byproduct formation in the difluoromethylation of phenols



In addition to these impurities, the use of reagents derived from chlorodifluoroacetic acid also generate an equivalent of carbon dioxide. The ability to control the release of carbon dioxide from the reaction was another critical safety parameter which

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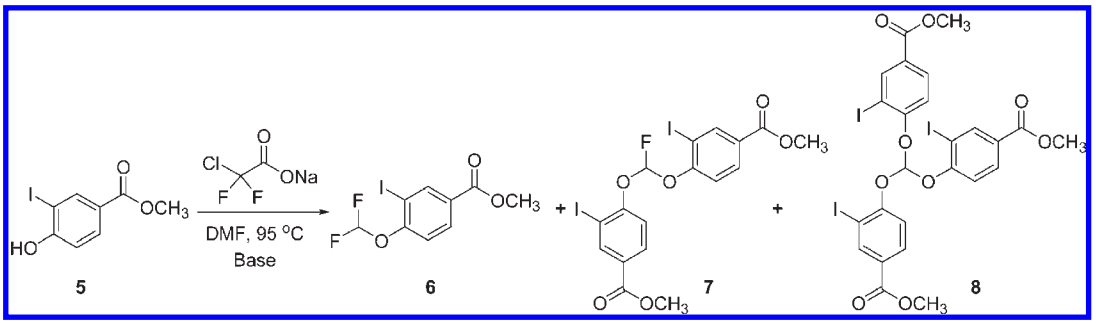
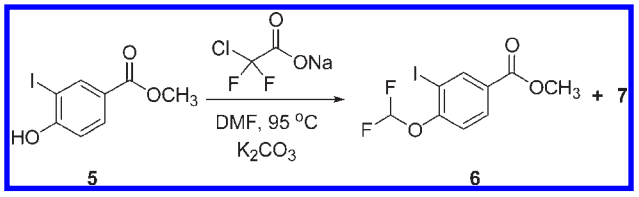
Table 1. Carbonate base screen for the difluoromethylation of 5[a]



base	5 (LC A%)	6 (LC A%)	7 (LC A%)	8 (LC A%)
Na_2CO_3	40	32	19	7
K_2CO_3	0.5	88	10	ND
Cs_2CO_3	39	52	5	ND

[a] These reactions were carried out with 2.0 equiv of sodium chlorodifluoroacetate and 1.5 equiv of carbonate base in 6 volumes of DMF in standard batch mode on a 1 g scale of **5**.

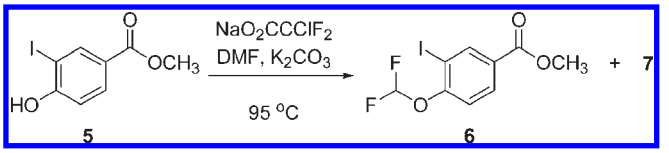
Table 2. Results of difluoromethylation of 5



scale (g of **1**)	addition time (min)	age time (min)	**6** (LC A %)	**7** (LC A %)	isolated yield (%)
126	60	15	98	1.8	92[a]
247	60	15	97	1	92[b]
1000	40	15	96	3.5	94[a]
7040[c]	240	15	>99	0.3	99[a]

[a] After crystallization from aq DMF. [b] After recrystallization from aq MeOH. All isolated yields adjusted for potency of product. [c] 2.0 equiv of SCDA used.

Table 3. Thermal stability study of 6[a]



entry	time after addition (min)	**5** (LC A %)	**6** (LC A %)	**7** (LC A %)	other impurities[b] (LC A %)
1	15	1.5	86	9.5	3.0
2	90	ND[c]	88	8.9	3.1
3	180	ND[c]	88	8.9	3.1
4	330	ND[c]	88	9.1	2.9

[a] This study was performed on 10 g scale with rapid addition of the reactive reagents to intentionally produce **7** and other impurities. [b] This includes **8** and other unknown baseline impurities. [c] ND = not detected.

needed to be addressed. The primary development goal was to develop a safe, simple, and reliable process that greatly minimized the generation of **3** and **4**.

The reagent of choice for the difluoromethylation reaction was sodium chlorodifluoroacetate (SCDA) due to its stability and availability in bulk. The reaction is typically run in a polar aprotic solvent such as DMF with sodium, potassium, or cesium carbonate as the base. A recent report suggested that water may be an important additive.[11] In our case, any additional water resulted in hydrolysis of the methyl ester in our substrate. A limited screen indicated potassium carbonate to be superior to sodium and cesium carbonate (see Table 1). Potassium carbonate was the only base that promoted near full consumption of starting material with formation of a small (~10%) amount of **7**.

With the knowledge that the difluoromethylation reaction was both fast and high-yielding, it was hypothesized that keeping the concentration of the SCDA higher than the concentration of **5** throughout the course of the entire experiment would minimize the formation of dimer and trimer (as well as HF formation). On the other hand, the issue of carbon dioxide release also had to be addressed before large-scale production could begin. Our proposed 7 kg scale-up batch would produce 1,500 L[12] of CO_2, thus vent capacity and off-gas rate needed to be evaluated and safely controlled. Adding a solution of SCDA (2.0 to 2.5 equivalents) and **5** in DMF (3 volumes) to a hot (95 °C) suspension of potassium carbonate and DMF (2 volumes) addressed both of these requirements. By controlling the addition rate of the solution of SCDA and **5**, the rate of CO_2 release was effectively managed and the concentration of SCDA (and the proposed difluorocarbene intermediate) was kept higher than the concentration of **5** throughout the course of the reaction.

As seen in Table 2, this process proved highly efficient and was essentially complete once addition of the SCDA/ **5** solution was finished. In addition, the formation of **7** was minimized, typically <4% by area. The final entry in Table 2 shows the kilo-lab run. With a slow addition of the SCDA/ **5** solution, the formation of **7** (and all other impurities) was minimized and provided the desired product in near quantitative yield and 99% HPLC purity

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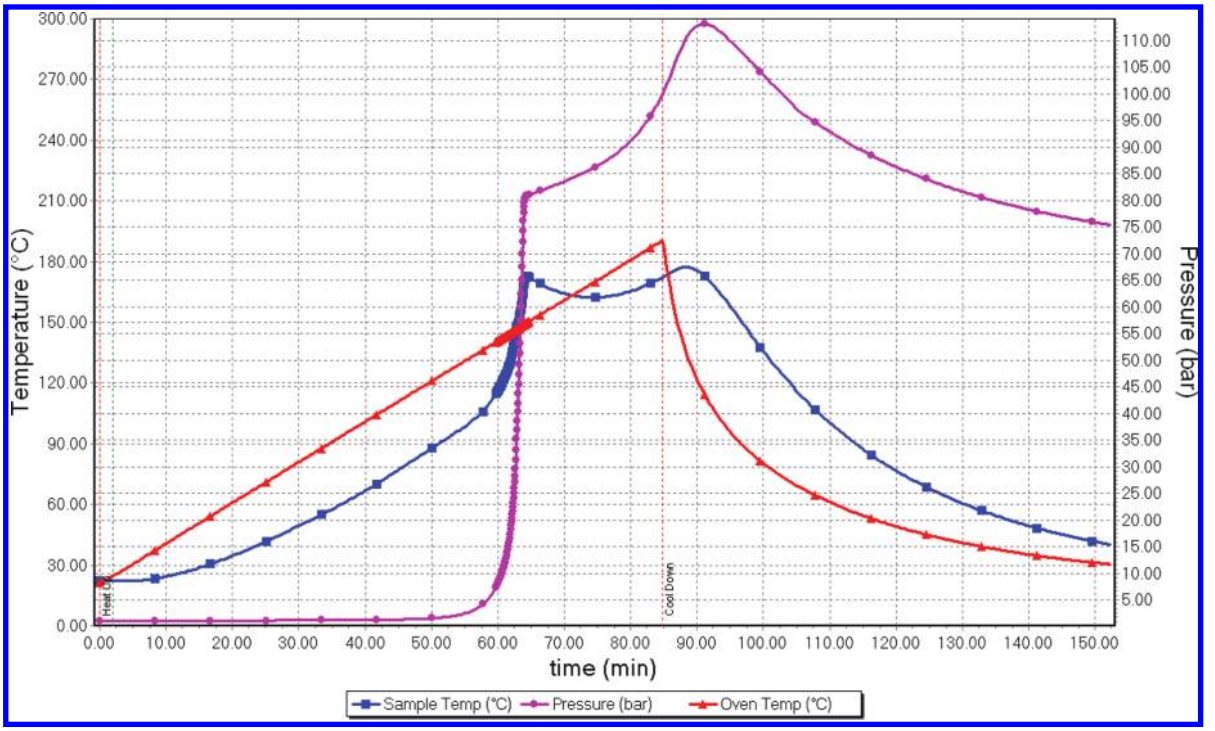

Figure 1. TSu evaluation of a solution of **5** and SCDA in DMF.

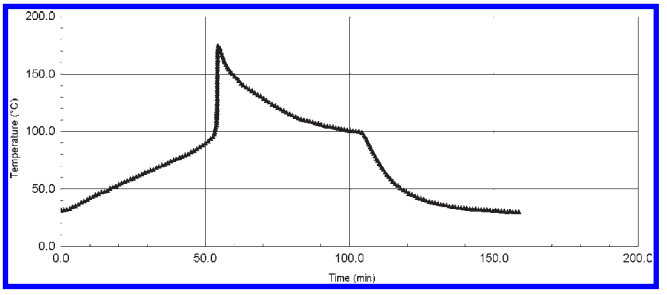

Figure 2. ARSST data (time versus temperature) for the reaction suspension.

To examine the thermal stability of both **6** and **7** during the difluoromethylation reaction, an experiment was conducted that intentionally formed a traceable amount of dimer and held the mixture at 95 °C for an extended period of time (Table 3). In this case, the solution of SCDA/ **5** was added over 3 min (10 g scale) and formed ~10 area % of the dimer. No change was observed in the formation of dimer or impurities after holding the contents of the reactor at 95 °C for 5.5 h. This gave us confidence that our upcoming kilo-lab run, which would involve a 4-h addition of the SCDA and iodophenol could be completed without significant thermal degradation of our product (**6**) (Table 2).

Crystallization and Isolation. The isolation of **6** proved relatively straightforward as solubility studies indicated that crystallization from water was the best option. Compound **6** is soluble (>200 mg/mL) in almost every common organic solvent but is insoluble in water. Initially, the crude DMF product solution was partitioned between MTBE and water. After extraction, the MTBE was switched to methanol, and the product was readily crystallized from a methanol/water mixture. Later, it was discovered that the direct addition of water (8 volumes) to the crude DMF product mixture resulted in crystallization. Although this direct method simplified the workup, the direct crystallization resulted in significantly slower filtration rates, which we presumed was due to residual potassium carbonate present as a fine powder. Once filtered, the cake could be washed with water until the pH of the filtrate was neutral. This facilitates removal of residual DMF and potassium carbonate. As **6** is insoluble in water, no product loss was observed in the water washes. Mother liquor losses from the direct crystallization procedure were typically ≤1%.

Safety Evaluation. With our slow-addition protocol in hand, we hoped the issues associated with CO_2 off-gassing and heat generation would be well controlled; however, all aspects of the procedure had to be examined by Process Safety before beginning. Since a solution of **5** and SCDA was being added to a hot suspension of potassium carbonate in DMF, the thermal stability of this mixture was first examined by a thermal screening unit (TSu) to determine if the solution of **5** and SCDA would be safe to prepare and store at ambient temperature. TSu data showed a very strong exotherm beginning at about 96 °C, corresponding to a maximum dT/dt of 23 °C/min at 170 °C (Figure1). The increase in temperature was also followed by an initial increase in pressure to 80 bar, a second increase to 115 bar at oven temperatures above 150 °C, and a maximum dP/dt of 68 bar/min at 160 °C. A residual pressure of 75 bar was also observed (Figure1). This TSu suggested that preparing and storing a solution of **5** and SCDA at ambient temperature would not result in an unwanted thermal event. Upon reaction completion, the crude DMF solution of (**6**) displayed no significant exotherm or increase in pressure (see Supporting Information for graphs).

We also evaluated the "worst case scenario" (all reactants added together) by the advanced reactive system screening tool (ARSST). The reaction mixture exhibited a large exotherm at 84 °C, eventually rising to 180 °C (Figure 2). In addition, this

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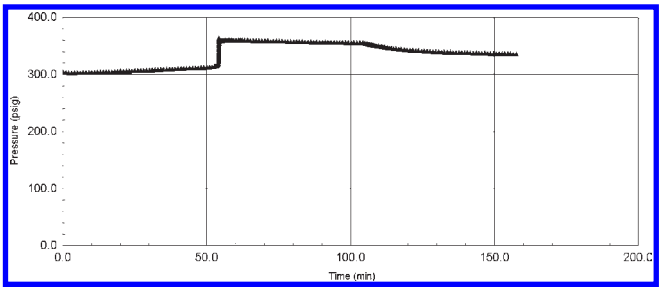

Figure 3. ARSST data (time versus pressure) for the reaction suspension.

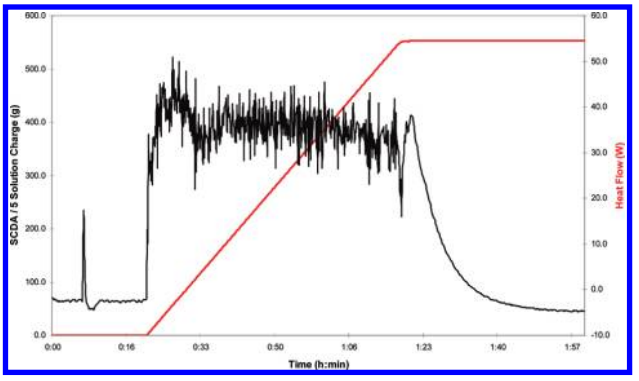

Figure 4. RC1 study of controlled addition process.

exotherm was also accompanied by an increase in pressure from 314 psig to 360 psig (Figure 3). Taken together, the dT/dt of 426 °C/min and dP/dt of 546 psi/min highlight the safety concerns associated with this reaction (see Supporting Information for graphs). Although the difluoromethylation reaction would never be carried out in this way, the ARSST studies provide additional data to support our initial safety concerns.

Safety assessment of the controlled addition process was also evaluated via RC1 calorimetry (see Figure 4). As expected, the difluoromethylation reaction exhibited a short incubation period of less than 5 min. In addition, the exotherm stayed constant during the course of the experiment, which is consistent with a fast reaction rate. Once the dose-controlled addition of the reactive materials was complete, heat generation ceased after less than 5 min, indicating a complete reaction. Utilizing the RC1 also allowed for the determination of both the ΔT_{ad} and ΔH for the process. The thermal profile observed during the course of the reaction resulted in a net output of −159 kJ/mol with a ΔT_{ad} of 193 K. Although a significant and potentially dangerous amount of heat and CO_2 are generated during the course of the reaction, proper dose control allowed for successful implementation of this process on the 7 kg scale.

CONCLUSIONS

A scalable procedure for the difluoromethylation of methyl 4-hydroxy-3-iodobenzoate (**5**) has been developed, and the major safety issues that accompany this type of reaction have been evaluated. The dosing of a solution of SCDA and **5** in DMF to a 95 °C suspension of potassium carbonate in DMF allowed for the careful control of both the exotherm and the release of carbon dioxide. TSu and ARSST data show that performing this reaction under standard batch conditions is not advisible. Also, RC1 data showed that the dose-controlled addition of the reactive reagents can minimize the thermal hazards associated with this reaction.

EXPERIMENTAL SECTION

General Methods. Reaction progress and chemical purity were evaluated by HPLC analysis using an Agilent Eclipse XDB-C18 column (4.6 mm × 250 mm) with mobile phases A (25 mM NH_4OAc in water) and B (acetonitrile). Dual detection was at 210 and 254 nm, flow was set at 1.5 mL/min, and the temperature was 30 °C. Gradient: 0 min: A = 10%; B = 90%; 10 min: A = 90%; B = 10%; 12 min A = 90%; B = 10%. Retention time of **5**: 6.83 min. Retention time of **6**: 9.09 min.

Large-Scale Difluoromethylation Procedure. A solution of sodium chlorodifluoroacetate (9.6 kg, 63 mmol, 2.0 equiv) and methyl 4-hydroxy-3-iodobenzoate (**5**) (7.0 kg, 31 mmol, 1.0 equiv) in DMF (22.1 kg) was added in two portions[a] over a period of 4 h to a 95 °C suspension of potassium carbonate (5.2 kg, 47 mmol, 1.5 equiv) in DMF (13.2 kg). The addition was controlled to maintain an internal temperature range of 93−98 °C. After complete addition, the suspension was stirred for 15 min and cooled to 30 °C. Water (17.5 kg) was added, and the contents of the reactor were transferred to a 180 L reactor for further processing. The remaining 52.5 kg of water was added, and the batch was cooled to 10−15 °C. After stirring at this temperature for 1 h, the suspension was filtered on a Nütsche filter. The crystals were washed with water (3 × 22.4 kg) and dried under nitrogen.

4-Difluoromethoxy-3-iodobenzoic acid methyl ester (6). Isolated as a white solid (mp = 56 °C) 99.6% pure by LC analysis. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 8.5, 2.0 Hz, 1H), 6.96 (dt, J = 8.5, 1.0 Hz, 1H), 6.39 (t, J = 72.6 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 154.7, 140.85, 131.4, 128.0, 117.8, 116.5 (t, J = 260 Hz), 88.8, 52.8. HRMS calculated for $C_9H_8O_3F_2I$: 328.94807 [M + H]; found: 328.94768.

ASSOCIATED CONTENT

Supporting Information. Additional ARSST and TSu data for the reaction described. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ADDITIONAL NOTE

[a] The large-scale addition of the SCDA/**5** solution was charged through a pressure can. Due to the limited capacity of the pressure can, two batches of SCDA and **5** in DMF were generated and added consecutively. Once the first charge was complete, the second batch was dissolved and charged to the same pressure can. The time between the completion of the first charge and the beginning of the second charge was about 10 min.

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(12) This value assumes that complete thermal decomposition of SCDA occurs and was calculated using the molar volume of CO_2 at 24.6 L/mol at 298 K and 1 bar.