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Process Development and Optimization for Production of a Potassium Ion Channel Blocker, ICA-17043

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Supporting Information

ABSTRACT: A scalable process for the manufacture of a potassium ion channel blocker was developed and optimized. Key features of the process include an optimized Grignard reaction, a direct cyanation of the intermediate trityl alcohol derivative, and an improved nitrile hydrolysis protocol, relative to the original acidic hydrolysis conditions, to generate the crude active pharmaceutical ingredient (API) with >95% HPLC purity. The Grignard and the cyanation reactions could be telescoped, resulting in an improved throughput compared to the original four-step process. An effective recrystallization of the API was also developed and the process scaled up to manufacture multiple batches at the pilot scale.

1. INTRODUCTION

Ion channels have emerged as attractive targets for the development of new therapies as they are implicated in the pathogenesis of several disease states, including vascular dysfunction, gastrointestinal dysmotility, memory disorders, neurological disorders, epilepsy, autoimmune and inflammatory diseases, to name a few.[1−4] In particular, the modulation of the intermediate conductance calcium-activated potassium ion channel, KCa3.1, a membrane protein found in lymphocytes, erythrocytes, fibroblasts, intestinal and airway epithelia, proliferating vascular smooth muscle, and vascular endothelium[3,5] offers avenues for potential pharmacological intervention, which can lead to the development of much needed therapies for several diseases. **ICA-17043** is a selective and potent inhibitor of KCa3.1 for which a practical and scalable synthesis was required.

The medicinal chemistry procedures used for producing the initial batches of the active pharmaceutical ingredient (API) for toxicological and formulation evaluation (Scheme 1) suffered from several drawbacks that precluded scale-up and required further development and optimization to establish an efficient and robust process.

The process development and optimization efforts needed to address several issues are summarized in Table 1.

Accordingly, the main development objectives were the following: (1) to optimize the Grignard reaction; (2) to evaluate a direct conversion of alcohol **2** to the penultimate nitrile **3**, thereby avoiding the moisture labile chloride **2′**; (3) to evaluate and optimize alternative hydrolysis conditions for the conversion of nitrile **3** to the API and optimize the yield, while improving its quality. Additionally, the process could be further optimized and streamlined by removing column chromatography, reducing the number of solvents used, and telescoping steps as appropriate.

2. RESULTS AND DISCUSSIONS

2.1. Optimization of the Grignard Reaction. Tetrahydrofuran (THF), methyl *tert*-butyl ether (MTBE) and toluene were evaluated as potential alternative solvents for the Grignard reaction. In all cases, the reaction was complete within 2 h (reversed phase HPLC, % area/area, UV detection at 220 nm), affording a quantitative yield of the crude alcohol. Toluene was chosen as the reaction solvent to facilitate azeotropic drying of the crude alcohol **2** and because it made it possible to telescope crude **2** into the next step. Phenylmagnesium bromide was chosen over phenylmagnesium chloride, as the former generally gave a cleaner reaction.[6] Reaction volumes in the range of 6−10 volumes of toluene relative to the volume of difluorobenzophenone showed no appreciable difference in the reaction outcomes, and so the lowest volume was chosen for scale-up. Likewise, the order of addition of the Grignard made no difference in the reaction time or product purity within the ranges studied.

Prior to scale-up, a calorimetric screening (RC1) of both the Grignard addition reaction and the quench was conducted. The screening indicated a moderately exothermic Grignard reaction, with an enthalpy of reaction of 151.5 kJ/mol, corresponding to a theoretical adiabatic temperature rise (ΔT_{ad}) of 66.9 K. The quench of the Grignard reaction was also exothermic (ΔT_{ad} of 47.9 K). Accordingly on scale, the difluorobenzophenone was dissolved in 12 volumes of toluene and approximately half of the solvent was stripped to azeotropically dry the reactor contents (KF <0.1%). On cooling to 30 °C, the Grignard reagent was added slowly, thereby allowing control of the resulting exotherm. Once complete (HPLC), the reaction was quenched by adding aqueous HCl over 1−2 h, while holding the reactor contents at 5−20 °C. The crude toluene solution obtained after the phase split was washed (aqueous sodium

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Scheme 1. Original synthesis of ICA-17043

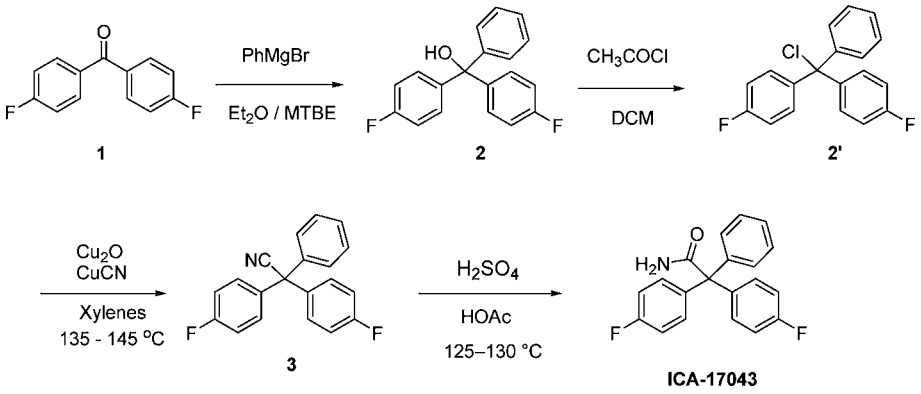


Table 1. Issues in original synthesis

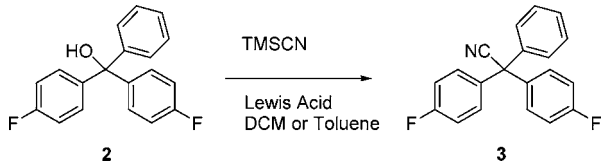
process step	issues
Grignard reaction	high volatility and flammability of diethyl ether
cyanation reaction	moisture lability of trityl chloride intermediate **2′**
	requirement for an extensive azeotropic drying of copper reagents to minimize hydrolysis of **2′** and yield losses
	high reaction temperatures
	Impractical workup and purification (decantation, triturations and filtration of crude extracts through silica gel to remove highly colored impurities)
nitrile hydrolysis	harsh reaction conditions
	loss of API through further hydrolysis to the corresponding acid and decarboxylation
	volume inefficient workup; emulsions during extraction; filtration of extracts through silica gel prior to isolation of crude API

bicarbonate, then deionized water), and then azeotropically distilled to dry the crude product (3−4 volumes of residual solution, KF <0.1%), which was used in the cyanation step without further purification.

2.2. Conversion of Alcohol 2 to Nitrile 3: Development of a Direct Catalytic Cyanation Reaction. *2.2.1. Cyanation Screening Experiments.* The original process for producing nitrile **3** relied on a classical procedure typically used for the preparation of triaryl halomethanes[7a−d] and proceeded *via* the moisture labile chloride **2′** (Scheme 1). Subsequent nucleophilic displacement of the chloride using CuCN in the presence of cuprous oxide in refluxing xylenes afforded the nitrile in moderate isolated yields. Inconsistent conversion profiles were observed due to hydrolysis of chloride **2′** back to alcohol **2**. Due to the anticipated difficulties in scaling up such a process, we sought to develop an alternative process that would obviate all the aforementioned issues. We briefly considered a Lewis acid-mediated cyanation of chloride **2′** using trimethylsilyl cyanide as a soluble cyanide source based on literature precedence for a related structure,[8] but we reasoned that a direct cyanation of the alcohol under similar reaction conditions would be simpler and might be achievable, as it would likely proceed through a stabilized carbenium species, affording the nitrile via S_N1 nucleophilic substitution.[9,10] We were encouraged by a report from Caron et al.[11] in which an aryl cyclohexanol intermediate was converted to the corresponding nitrile in near quantitative yields using a catalytic amount (25 mol %) of tin chloride and trimethylsilyl cyanide as the cyanide source.

Several Lewis acids were screened for their ability to mediate a direct cyanation of alcohol **2** using trimethylsilyl cyanide (TMSCN) as a soluble cyanide source and dichloromethane (DCM) or toluene as solvents (Scheme 2). The evaluated Lewis acids were $TiCl_4$, $BF_3{\cdot}Et_2O$, $InCl_3$, $ZnCl_2$, $Zn(CN)_2$, and Zn dust.

Scheme 2. Screening of Lewis acid-mediated direct cyanation of alcohol 2



Gratifyingly, a clean conversion of alcohol **2** to nitrile **3** was observed in all cases, except when zinc reagents ($ZnCl_2$, $Zn(CN)_2$, and Zn dust) were used as Lewis acids. In these cases, the reaction proceeded to approximately 50% conversion using roughly one molar equivalent of TMSCN. A single byproduct, determined to be the trimethylsilyl ether **4**, resulting from a competing silylation of alcohol **2** (Scheme 3) was generated in equal amounts (~50%).

Nonetheless, the cyanation reaction could be pushed to complete conversion in these cases by adding another equivalent of TMSCN. This indicates that the trimethylsilyloxy moiety is also a suitable leaving group under these reaction conditions.

In light of these screening experiments, indium trichloride proved to be the Lewis acid of choice for the desired cyanation reaction. Indeed, it afforded a clean reaction profile and it could be used catalytically. Furthermore, unlike the other Lewis acids ($TiCl_4$, $BF_3{\cdot}Et_2O$, and $ZnCl_2$), $InCl_3$ did not require stringently anhydrous conditions. Also, with the use of toluene as a reaction solvent for the cyanation reaction, the first two steps in the synthesis could be telescoped to improve the overall process throughput.

Concurrently with the optimization of the cyanation of alcohol **2**, the generality of this reaction toward the conversion of other benzylic alcohols to the corresponding nitriles was briefly examined (Scheme 4). A few representative examples are summarized in Table 2.

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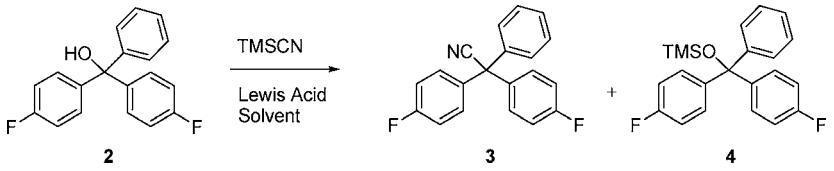
Scheme 3. Silylation side reaction using zinc reagents



Scheme 4. $InCl_3$-catalyzed cyanation of benzylic alcohols

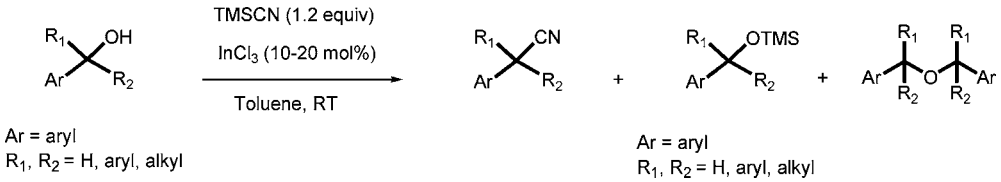
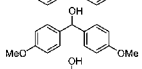
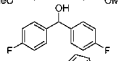


Table 2. $InCl_3$-catalyzed cyanation of benzylic alcohols

Entry	Substrate	Equiv $InCl_3$	Nitrile Product (% Yield)[1]	Byproducts (% AUC)[2]	
				OTMS	Dimer
1		0.2	0	99	0
2		0.2	76	0	0
3		0.2	23	30	26
4		0.2	74	0	0
5		0.1	44	0	56
6		0.2	89	0	0
7		0.2	80	0	0
8		0.2	75	0	0

[1]Isolated yields by column chromatography on silica gel (unoptimized). [2]Rough estimate by HPLC analysis (%AUC); clean reactions showed none of the OTMS or dimer byproducts and modest isolated yields of nitrile product in these cases reflect physical losses (1 mmol scale) or incomplete conversions in toluene at RT.

Triaryl methanols (entries 6–8) reacted readily to afford the corresponding nitriles in good isolated yields. Furthermore, substrates bearing electron donating groups (entries 2 and 4) reacted well to afford the expected nitriles in good yields (unoptimized). By contrast, benzyl alcohol and diaryl methanols bearing electron withdrawing groups or no substituents at all (entries 1, 3, and 5) afforded a mixture of products in which the desired nitrile was generated in low to fair yields (in the case of benzyl alcohol, no cyanation was observed). The main byproducts obtained in these reactions were the trimethylsilyl ethers derived by silylation of the alcohols and the symmetrical ethers resulting from a dehydrative dimerization of the alcohols, presumably via a nucleophilic attack of the alcohols on the less stabilized putative benzylic carbocations. That triaryl carbinols, as well as benzhydryl and benzylic alcohols bearing electron-donating substituents on the aromatic rings afforded the best reaction profiles strongly suggest the intermediacy of a carbenium ion that is highly resonance stabilized. These observations are consistent with those recently published by Ding et al.[10] on the cyanation of electron-rich benzylic alcohols using catalytic $InBr_3$ and TMSCN. No isonitrile products that could be potentially generated due to the ambident nature of the cyanide ion were observed,[12] consistent with mechanistic studies by Ziegler et al., who demonstrated that trityl isonitriles readily isomerize to the corresponding nitriles in the presence of trityl cations.[8] The nitrile product **3** obtained from alcohol **2** using $InCl_3$ and TMSCN was identical in all respects to the product derived from the cyanation of trityl chloride **2′** with CuCN/CuO.

This cyanation reaction further demonstrates the synthetic usefulness of indium in organic synthesis.[13]

2.2.2. Optimization of the Cyanation Reaction. The optimization of the cyanation of alcohol **2** focused on defining the mode of addition of TMSCN and the optimal reaction temperature, adjusting the TMSCN stoichiometry, and developing a suitable crystallization procedure to isolate the nitrile with high purity. While small-scale reactions conducted at ambient temperature in toluene typically afforded >60% conversion within the first hour, a complete conversion required 16–18 h. On the other hand, reactions run at higher temperatures (45–75 °C) afforded >85% conversion within the first hour, but required an additional 4–5 h to proceed to completion. It was suspected that due to its noticeable volatility (bp 118–119 °C) a substantial amount of the TMSCN was likely in the vapor phase and consequently only marginally available for reaction over time. A solution to circumvent this issue was to use slightly more TMSCN (1.35 mol equiv rather than 1.2 equiv) and to add it to the reaction mixture slowly over time (~1 h), while holding the reaction <40 °C (typically 25–35 °C). The reaction mixture was then agitated at ambient temperature for 1–2 h and sampled to assess the conversion of alcohol **2** to ketone **3**. The temperature was then raised to 40–50 °C to complete the conversion, usually within 1 h.

A calorimetric screening of the cyanation reaction was conducted prior to scale up. The study indicated a very exothermic reaction (enthalpy of reaction of 221.4 kJ/mol; ΔT_{ad} of 90.7 K). The thermal conversion profile at 40 °C showed the reaction to be essentially complete at the end of the trimethylsilyl cyanide addition (2 h), with no observed accumulation. On the basis of this calorimetric screening and consistent with the need to minimize losses of TMSCN to the vapor phase, a dose-controlled addition of the TMSCN was established and implemented on scale-up.

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A brief study to develop a suitable recrystallization of nitrile **3** was carried out using crude nitrile of 93.5% purity (Table 3).

Table 3. Nitrile crystallization screening

entry	solvent	water (vol)	mass recovery (%)	HPLC purity (% AUC)	remarks
1	EtOH	–	–	–	no crystallization
2	EtOH	0.5	60	–	crystallization on standing at RT for 10 h
3	EtOH	1	67	99.9	good crystallization
4	EtOH	2	69	99.7	good crystallization
5	IPA	–	–	–	no crystallization
6	IPA	0.5	61	99.1	crystallization on standing at RT for 10 h
7	IPA	1	55	99.2	good crystallization
8	IPA	2	70	99.9	good crystallization
9	IPA	3	72	97.6	good crystallization

Ethanol (EtOH) and isopropyl alcohol (IPA) were chosen as the primary solvents in an effort to limit the number of solvents used in the process, since these solvents were also concurrently being evaluated in the final crystallization of the API. Water was chosen as the preferred cosolvent. In a typical procedure, the crude nitrile was dissolved in 5 volumes of solvent at reflux (78−82 °C), water was added, then the reaction mixture was cooled to ambient temperature over 2 h. When crystallization was achieved the slurries were further cooled to 0 °C and stirred for 30 min then filtered, washed with chilled solvent (1 vol) and dried to afford the purified nitrile **3**. The nitrile did not crystallize from ethanol or IPA as single solvents (entries 1 and 5). The addition of 0.5 volumes of water in both cases induced a crystallization of the nitrile upon further standing at ambient temperature for 10 h. The best results in these screening experiments (1 g scale) were obtained using 5 volumes of IPA and 2 volumes of water, affording 70% mass recovery, with high purity (entry 8).

This crystallization procedure was successfully demonstrated at lab scale (starting from 300 g of 4,4′-difluorobenzophenone **1**) to afford pure nitrile **3** (>99% AUC) in >85% overall yield from the difluorobenzophenone **1**. Analysis of the nitrile **3** by ICP showed the material to contain <1 ppm of residual indium.

During the production of early batches at scale, severe emulsions were observed in the workup of the cyanation reaction. This issue was remedied by incorporating Rochelle's salt (sodium potassium tartrate) in the basic aqueous quench and filtering the batch through Celite impregnated filter pads. This modification suppressed the emulsions and streamlined the workup. The two-step telescoped process was scaled up at the pilot scale in multiple batches, with the largest batch run at 110 kg input of 4,4′-difluorobenzophenone **1** (1000 gallon reactor), affording 76−80% overall yields of the nitrile **3** (see Table 4 for representative batches).

Table 4. Representative pilot batches of nitrile 3

entry	ketone **1** input (kg)	nitrile **3** output (kg)	yield (%)
1	10.0	11.2	80.0
2	20.0	21.4	76.4
3	20.0	21.8	77.9
4	110.0	123.4	80.0

2.3. Development of an Alternative Hydrolysis Process. The hydrolysis process used to produce early batches of the API (concentrated sulfuric acid, refluxing glacial acetic acid) was evaluated as a baseline experiment and to generate samples of the API for optimization of the recrystallization. The nitrile **3** (10 g) was heated in refluxing H_2SO_4/HOAc (0.8 vol each) at 120−125 °C for 16 h to afford the amide with 87% purity (AUC), 5% residual unreacted nitrile **3** and 4.7% of a polar impurity determined to be carboxylic acid **5** (Scheme 5).

The reaction quench was very exothermic, which required a slow, inverse addition to chilled water while maintaining the temperature at 10−20 °C. To extract the crude product, the pH of the mixture was adjusted to 6.5−7.5 by slowly adding concentrated ammonium hydroxide. Dichloromethane was then added and the layers separated. The aqueous phase, which contained a substantial rag layer, was back extracted with DCM, resulting in significant emulsions. The combined extracts (including some undissolved solids) were filtered through a bed of Celite/silica gel. The filtrate was then concentrated under reduced pressure to afford the crude amide as a dark yellow powder (84% crude yield, 95% AUC). Further analysis of the isolated product and impurities showed that the main impurities observed in the hydrolysis reaction stemmed from further hydrolysis of the amide to the corresponding carboxylic acid **5** and subsequent decarboxylation of the acid to the corresponding 4,4′-difluorotriphenylmethane derivative **6** (Scheme 5).

2.3.1. Basic Hydrolysis Screening Experiments. The harsh acidic hydrolysis conditions and more importantly the impractical isolation and purification process were unattractive to scale without substantial development time. For this reason, we sought to develop a cleaner reaction with a simpler isolation protocol. A quick assessment of basic hydrolysis conditions[14,15] using powdered potassium hydroxide (5.5 molar equiv) in refluxing *tert*-butyl alcohol indicated a cleaner conversion profile that warranted a thorough evaluation (Scheme 6). *tert*-Amyl alcohol (*t-AmOH*) was then evaluated as an alternative tertiary alcohol, both because it was easier to handle at ambient temperature compared to *t*-BuOH (mp 24−25 °C) and because it made possible to run the hydrolysis reaction at higher temperatures (bp 103 °C).

A faster conversion was achieved in this solvent at 100 °C (67% conversion in 2 h in *t-AmOH vs* 65% conversion in 6 h in refluxing *t*-BuOH), with a complete conversion within 8 h.

Encouraged by these initial results we screened potentially suitable common alcoholic solvents. The results from this screen are summarized in Table 5.

The cleanest and fastest reaction profile was achieved in *t*-AmOH. Therefore, further process optimization was carried out using this solvent.

To determine the most important parameters in the hydrolysis reaction we relied on a design of experiments (DoE) methodology.[16a−c] The goals of the study were: (1) to identify reaction conditions that afforded the highest conversion of the nitrile **3** to the API and (2) to identify key parameters that minimized the formation of impurities. Two factors, the amount of KOH and the solvent volume, were evaluated in the DoE study. All experiments were run at 100 °C. The experimental details and the complete set of DoE data are provided in the Supporting Information [SI].

The DoE study helped gain the following insights into the performance of this hydrolysis reaction: (1) both the amount of KOH and the solvent volume, as well as the interaction

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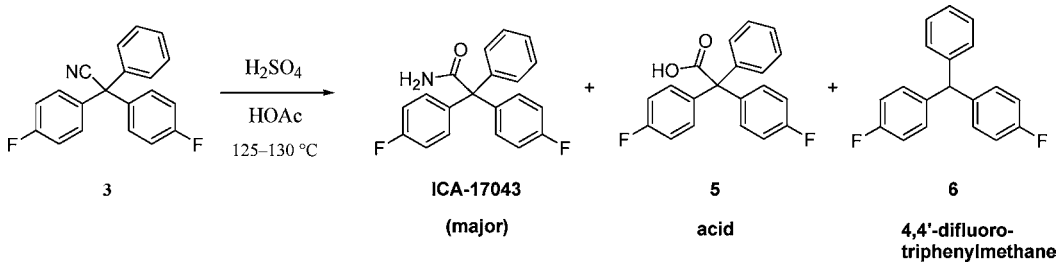
Scheme 5. Original acidic hydrolysis conditions



Scheme 6. Alternative basic hydrolysis conditions

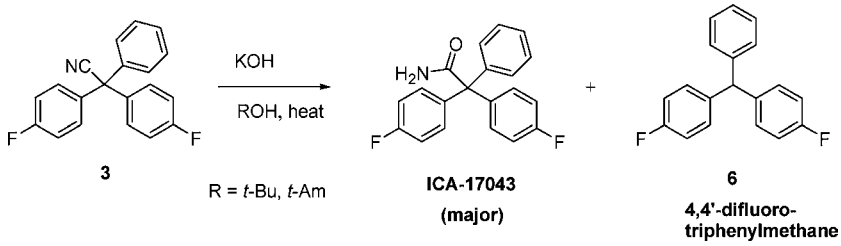


Table 5. Basic hydrolysis solvent screen

entry	solvent	temp (°C)	time (h)	% amide[a]	% unreacted nitrile[a]	% total impurities[a]
1	*t*-BuOH	82	6	69.7	29.2	1.1
2	***t*-AmOH**	**100**	**5**	**90.2**	**5.5**	**4.3**
3	IPA	82	10	51.7	41.4	6.9
4	*n*-BuOH	100	7	47.9	15.4	36.7
5	*i*-BuOH	100	7	61.3	14.6	24.1
6	*i*-AmOH	100	7	61.6	17.7	20.7
7	*n*-pentanol	100	6	44.6	15.8	39.6
8	2-BuOH	98	6	73.9	10.8	15.3

[a]% AUC by HPLC analysis.

Table 6. Effect of temperature and concentration on reaction profile

			API (% AUC)			4,4′-difluoro- triphenylmethane **6** (%AUC)			total impurities (% AUC)		
entry	solvent volumes	temp (°C)	**5 h**	**9 h**	**12 h**	**5 h**	**9 h**	**12 h**	**5 h**	**9 h**	**12 h**
1	10	100	90	–	86.1	3.3	–	8.9	4.4	–	12.3
2	**10**	**90**	**74**	**87.8**	**90.2**	**0.6**	**1.4**	**2.0**	**4.9**	**6.1**	**7.3**
3	15	100	86.6[a]	–	89.8	2.6[a]	–	5.4	7.3[a]	–	9.4

[a]HPLC analysis after 5.5 h.

between these two factors have a significant impact on the reaction profile and the amount of impurities generated; (2) the fastest conversion is achieved at high KOH loading and low solvent volumes (i.e., high concentration); (3) impurities are minimized under dilute reaction conditions; (4) the amide is gradually depleted over time when the reaction is allowed to proceed over an extended time. This loss is most significant at high reaction concentration and high KOH loading. These conclusions agreed well with the results achieved under typical conditions in most preliminary preparative-scale experiments in *t*-AmOH (5.5 molar equiv KOH, 10 vol solvent, 100 °C). Indeed, these conditions consistently provided the highest conversion of nitrile **3** to the API within 6−8 h with minimal impurities; however, it showed increasing API degradation through hydrolysis to the acid **5** and decarboxylation to the triphenylmethane derivative **6** when the reaction was allowed to proceed at 100 °C for 12 h.

2.3.2. Hydrolysis Process Optimization. Additional experiments were conducted to determine the best reaction temperature, concentration, and time that would maximize the conversion while minimizing the amount of impurities. The experiments were conducted at 10 g scale, using 5.4 mol equiv of KOH and the solvent volumes and temperatures shown in Table 6.

As expected and consistent with the DoE study, a slower conversion was observed at lower concentration (compare entries 1 and 3) and at lower temperature (compare entries 1 and 2). Overall, the hydrolysis reaction conducted at 90 °C using 10 volumes of solvent (entry 2) afforded the best balance for the highest conversion and the lowest amount of impurities, particularly residual unreacted nitrile **3**, which was the most difficult process impurity to purge out during the final crystallization of the API. These reaction conditions were selected for further scale-up.

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In contrast to the original sulfuric acid-mediated hydrolysis in glacial acetic acid, the isolation of the crude API from the basic hydrolysis process was simpler and straightforward. A comparison between the workup and isolation procedures is provided in Table 7.

Table 7. Comparison of workup and isolation procedures of crude API

processing step/ appearance	hydrolysis in H_2SO_4/AcOH	hydrolysis in KOH/*t*-AmOH
quench	cool reaction mixture to RT; inversely add it to cold water (5−10 °C) over 60−90 min	cool reaction mixture to 5−10 °C; add 3 volumes of cold (5 °C) 6 N HCl over 30−60 min
isolation of crude API	add conc. NH_4OH and adjust pH to 6.5−7.5; extract with DCM (severe emulsions); filter DCM extracts through Celite/silica gel; strip to a solid residue	filter and wash cake with water; dry under reduced pressure
appearance	dark yellow powder	off-white to white powder

Further process optimization focused on developing a robust crystallization procedure to purify the API. Both single solvents and binary solvent systems were evaluated in screening experiments (Table 8).

Table 8. Recrystallization Screening

entry	solvent (mL/g)	antisolvent (mL/g)	total volume (mL)	recovery (%)	HPLC (% AUC)
1	EtOH (16.4)	–	16.4	74	95.3
2	IPA (24)	–	24	74	94.3
3	EtOH (18)	H_2O (4)	22	80	81.2
4	MEK (10)	*n*-heptane (12)	22	58	93.1
5	EtOAc (8)	*n*-heptane (10)	18	60	97.4
6	toluene (14)	*n*-heptane (8)	22	86	96.2

Saturated solutions of the crude API (93.5% AUC; material from acidic hydrolysis) were prepared near the boiling point of the chosen primary solvent. In experiments using a single solvent, crystallization was induced by cooling the solution, whereas in the case of binary solvent systems, it was achieved by adding the chosen antisolvent to the hot solution. The crystallizing mixtures were then cooled to 0 °C over 2 h and filtered. Conditions that afforded materials of lower purity than that of the starting crude API (entries 3 and 4) and those yielding low recoveries (entries 4 and 5) were eliminated from further consideration. The best solvent systems (entries 1, 2, and 6) were reevaluated at higher concentrations using crude API from the basic hydrolysis process (96% AUC), with the goal of improving the mass recoveries. Results are summarized in Table 9.

We chose IPA as the preferred solvent for purifying the API since it afforded the best combination of mass recovery and product purity and since it was used upstream in the purification of nitrile **3**. This was an important consideration in order to minimize the number of organic volatile impurities

Table 9. Further recrystallization screening experiments

entry	solvent (mL/g)	antisolvent (mL/g)	total volume (mL)	recovery (%)	HPLC (% AUC)
1	EtOH (11)	–	11	82.0	99.6
2	IPA (13)	–	13	88.2	99.7
3	toluene (8)	*n*-heptane (4)	12	86.0	99.6

in the API. Finally, a polish filtration of the hot solution of the API through a 1.2 μm Teflon filter was incorporated into the crystallization process to remove inorganics (KCl) trapped in the crude API at the quench of the hydrolysis reaction.

2.3.3. Process Demonstration and Pilot-Scale Production. The optimized, alternative chemistry is shown in Scheme 7. Prior to technology transfer for pilot-scale production, incremental scale-up experiments were conducted at 25-, 80-, and 300-g scale. Results from the 300-g batch are provided below.

The Grignard reaction followed by the telescoped indium trichloride-mediated cyanation of crude alcohol **2** performed well, consistent with smaller scale reactions, affording 345 g of nitrile **3** as an off-white, crystalline solid (89% overall yield, >99% AUC by HPLC analysis). Subsequent base-mediated hydrolysis of the nitrile (345 g scale) afforded 307 g of crude API (94% AUC). The crude (300 g) was recrystallized from 13 volumes of IPA to afford the purified API as a white, crystalline solid (280 g, 77.1% overall yield from nitrile **3**, 99.2 wt % by validated HPLC assay). The overall yield from 4,4′-difluorobenzophenone **1** was ∼68.5%. Other analytical data were consistent with smaller scale batches (<1 ppm residual indium, 876 ppm residual IPA).

The process was further scaled up at pilot scale to produce several batches of the API. Representative results from pilot scale production are shown in Table 10.

3. CONCLUSIONS

In conclusion, an improved process suitable for the pilot-scale production of a potassium ion channel blocker from 4,4′-difluorobenzophenone, **1**, was developed and optimized to produce multiple batches of the API. The Grignard reaction was conveniently conducted in toluene rather than diethyl ether to afford crude alcohol **2** suitable for processing without further purification. The original two-stage cyanation reaction employing a moisture labile tertiary chloride intermediate **2′** was replaced with a direct cyanation employing a catalytic amount of indium trichloride as the Lewis acid and trimethylsilyl cyanide as the cyanide source. The process throughput was further enhanced by telescoping the alcohol into the cyanation reaction. A basic hydrolysis of the intermediate nitrile **3** was developed and optimized using potassium hydroxide in *tert*-amyl alcohol and employing a direct drop isolation process instead of an extractive workup. An improved crystallization process using isopropyl alcohol as the solvent was implemented to afford the API in good yield and high purity.

4. EXPERIMENTAL SECTION

General. HPLC data during process development (nonvalidated method) was collected using a LUNA C8 (3 μm) column using water (modified with 0.1% TFA) and acetonitrile (modified with 0.1% TFA) as mobile phases. The following gradient was used: 30% acetonitrile isocratic for 1 min, 30% to 90% acetonitrile over 7 min, 90% acetonitrile isocratic for 5

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Scheme 7. Alternative chemistry to ICA-17043

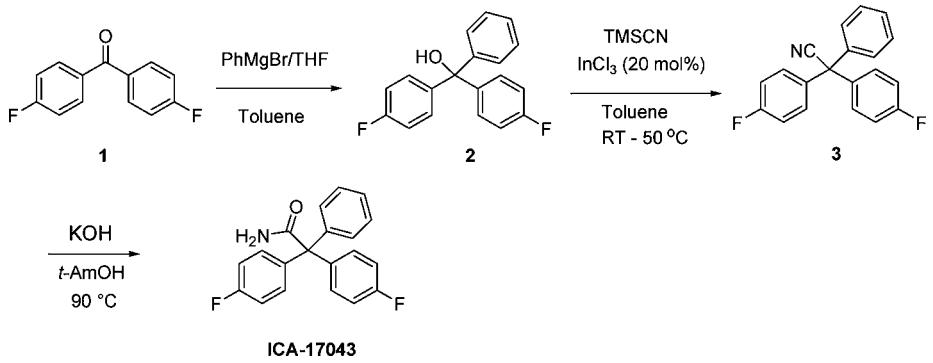

Table 10. Representative pilot-scale production results

entry	input	output	yield (%)	reactor size (gal)
1	ketone **1**	nitrile **3**	80.1	1000
	110.0 kg	123.4 kg		
2	nitrile **3**	crude **API**	95.2[a]	300
	60.0 kg	60.5 kg[a]		
3	nitrile **3**	crude **API**	93.3[b]	300
	63.4 kg	62.7 kg[b]		
4	crude **API**	pure **API**	78.3	300
	54.0 kg[a]	42.3 kg		
5	crude **API**	pure **API**	80.3	300
	54.0 kg[a]	43.4 kg		

[a]KF = 6.5% and ROI = 7.2%. [b]ROI = 10.0%.

min, 90% to 30% acetonitrile over 2 min and 30% acetonitrile isocratic for 2 min, detector at 220 nm; RT for API is 9.7 min, alcohol **2** is 10.7 min and nitrile **3** is 11.8 min. HPLC data during pilot scale production (validated method) was collected using a Waters Symmetry Shield RP18 (5 μm) column using water and acetonitrile as mobile phases. The following gradient was used: 50% acetonitrile isocratic for 25 min, 50% to 100% acetonitrile over 15 min, 100% acetonitrile isocratic for 10 min, 100% to 50% acetonitrile over 1 min and 50% acetonitrile isocratic for 15 min, detector at 210 nm; RT for API is 16.9 min, alcohol **2** is 32.7 min and nitrile **3** is 36.0 min.

Preparation of Bis-(4-fluorophenyl)phenylmethanol 2. A glass-lined stainless steel reactor was charged with 4,4′-difluorobenzophenone **1** (110.0 kg, 504.1 mol), followed by toluene (1320 L). Approximately half the amount of toluene was distilled under reduced pressure (50 °C, 25 in. vacuum), leaving approximately 770 L of residual solution, which was then cooled to 30 °C. A solution of phenylmagnesium bromide in tetrahydrofuran (1 M, 609.4 kg) was added to the batch over 1 h and 30 min, while maintaining a temperature of 20−40 °C. The reaction mixture was further agitated at 20−30 °C for 1 h, whereupon in-process analysis by HPLC indicated <3% (AUC) ketone remaining (reaction considered complete when no more than 3% ketone remains). The batch was cooled to 5 °C, and the reaction quenched with 5 °C aqueous HCl (prepared by mixing 128.7 kg of conc. HCl with 160.3 kg of deionized water) over 1 h 15 min, while maintaining the batch temperature between 5 and 20 °C. The batch was allowed to warm to 25−30 °C and further agitated for 1 h. The bottom layer was separated and the organic layer was washed with aqueous sodium bicarbonate (prepared by dissolving 33 kg of sodium bicarbonate in 78.6 gal of deionized water) then deionized water (2 × 87.3 gal). The crude alcohol **2** solution was then concentrated by distillation under reduced pressure (50 °C, 25 in. vacuum) to approximately 440 L of residual solution. Toluene (1,100 L) was added and the batch was further distilled to approximately 440 L of residual solution. Analysis of an aliquot from the residual solution by Karl Fisher titration indicated 0.0% (w/w) water. The residual toluene solution of alcohol 2 was used in the cyanation step without further processing.

Preparation of Bis-(4-fluorophenyl)phenylacetonitrile 3. A slurry of indium trichloride (22.44 kg) in toluene (308 L) was added to the residual solution of alcohol **2** from above, which was agitated at ambient temperature for 30 min. Trimethylsilyl cyanide (68.2 kg) was then added over 1 h, while maintaining the temperature at 20−40 °C. The reaction mixture was further agitated for 1.5 h at ambient temperature and analyzed by HPLC for residual alcohol **2** (~60% AUC). The batch was then heated and agitated at 40−50 °C for 1 h and analyzed by HPLC (3% AUC for residual alcohol **2**; reaction considered complete when no more than 3% alcohol **2** remains). After further reaction at 40−50 °C for 1 h, the reaction was quenched with aqueous KOH containing Rochelle's salt (74.8 kg KOH and 74.8 kg of sodium potassium tartrate dissolved in 176.5 gal of deionized water), maintaining the temperature at 20−30 °C. The quenched reaction mixture was further agitated overnight (16 h) and the layers separated. The organic layer was filtered through Celite impregnated filter pads into a glass-lined reactor, and further washed with deionized water (3 × 145.5 gal). The crude nitrile **3** solution was distilled under reduced pressure (50 °C, 25 in. vacuum) to the minimum stir volume (until no further toluene distilled). Isopropyl alcohol (157.1 gal) was added, followed by deionized water (78.6 gal), and the resulting suspension was heated to 65−75 °C and held at that temperature for an additional 30 min. The hot solution was then cooled to 5 °C at a rate of 10 °C/h (9.5 h) to crystallize the product. The resulting slurry was aged at 5 °C for 1 h, then transferred to a stainless steel centrifuge and filtered in sections. The reactor was rinsed with isopropyl alcohol (26.5 gal) and the rinse transferred to the centrifuge to wash the wet cake. The wet solids were spun to dryness, transferred to a tray dryer, and dried at 40−45 °C for 17 h to afford nitrile **3** as a white crystalline powder (123.4 kg, 80.2% isolated yield over two steps). Analytical data: HPLC assay: 97.4% AUC; residue on ignition (sulfated ash): 0.04% (w/w); residual indium: none detected (ICP; limit of detection: 1 ppm); ^{1}H NMR (300 MHz, $CDCl_3$): 7.01−7.08 (m, 4H); 7.15−7.34 (m, 6H); 7.34−7.39 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 56.6; 116.0; 116.2; 123.5; 128.8; 128.9;

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129.2; 130.8; 131.0; 136.3; 140.2; 161.1; 164.4. ^{19}F NMR (282 MHz, $CDCl_3$): −113.71.

Preparation of 2,2-Bis-(4-fluorophenyl)-2-phenylacetamide, ICA-17043. A Hastelloy reactor was charged with nitrile intermediate **3** (60.0 kg, 196.5 mol), followed by potassium hydroxide flakes (60.0 kg) and *tert*-amyl alcohol (480 kg). The resulting mixture was then heated and agitated at 85−95 °C for 10.5 h, whereupon in-process analysis by HPLC indicated 1.1% (AUC) nitrile **3** remained. The batch was cooled to 5 °C and the reaction quenched with 5 °C aqueous HCl (prepared by diluting 104.7 kg of conc. HCl with 93 L of deionized water) over 1 h and 30 min, maintaining the batch temperature at 5−15 °C. The resulting slurry was further agitated at 15−25 °C for 45 min, then transferred to a pressure filter dryer and filtered. The wet cake was washed with deionized water (3 × 300 L), conditioned for 3 h then further dried at 45−50 °C for 12 h to constant weight, affording crude **ICA-17043** as a white crystalline powder (60.5 kg, 95.2% crude yield). HPLC assay: 99.3% AUC; KF: 6.5% (w/w); residue on ignition (sulfated ash): 7.2% (w/w); residual indium: none detected (ICP; limit of detection: 1 ppm).

Crude **ICA-17043** (54.0 kg) was charged into a glass-lined reactor, followed by isopropyl alcohol (847.8 kg), and the batch was heated and held at 75−85 °C for 1 h to dissolve the solids. The resulting solution was polish-filtered through a 1.2 μm in-line Teflon filter (with the filter housing held at 80 °C) into a Hastelloy reactor, then distilled at atmospheric pressure to approximately 756 L of residual solution. The batch was cooled to 5 °C over 8 h to crystallize the API. The resulting slurry was transferred to a pressure filter dryer and filtered. The wet cake was washed with 5 °C isopropyl alcohol (52.8 kg), conditioned at ambient temperature for 3 h, then further dried at 45−50 °C to constant weight for 12 h to afford **ICA-17043** as a white crystalline powder (43.4 kg, 80.3% recovery; 61.3% overall yield from the difluorobenzophenone **1**). Analytical data: DSC melting endotherm: 187.2 °C; HPLC assay: 100.5% w/w (specifications: 98.0−102.0% w/w); total related impurities: 0.25% (AUC); residue on ignition (sulfated ash): 0.09% w/w; residual IPA: 461 ppm; residual *tert*-amyl alcohol: none detected; residual indium: none detected (ICP; limit of detection: 1 ppm); particle size distribution by laser diffraction: D10 = 8.2 μm, D50 = 26.9 μm, and D90 = 53.6 μm; KF = 0.0% w/w; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.71(bs, 1H); 6.73 (bs, 1H); 6.95−7.00 (m, 4H); 7.19−7.32 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.8; 115.0; 115.3; 127.8; 128.6; 130.5; 132.4; 132.5; 139.2; 143.3; 160.4; 163.7; 176.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.66.

■ ASSOCIATED CONTENT

Supporting Information

(1) DoE study data, including 2 tables and 12 figures; (2) NMR and HPLC data for laboratory scale (300 g) process demonstration batch (alcohol **2**, nitrile **3**, and **ICA-17043**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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