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Synthesis of a Sodium−Hydrogen Exchange Type 1 Inhibitor: An Efficient Cu-Catalyzed Conjugated Addition of a Grignard Reagent to an Acetyl Pyridinium Salt

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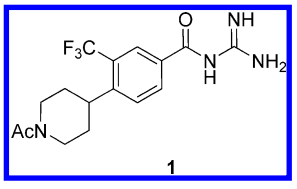
Supporting Information

ABSTRACT: A facile and economical five-step process for the synthesis of a sodium−hydrogen exchange type I inhibitor (NHE-1) was developed from readily available starting materials in 43% overall yield. Key transformations included a highly efficient copper-catalyzed conjugate addition of 2-trifluoromethylphenyl Grignard reagents to acetyl pyridinium salts, a facile hydrogenation of 4-aryl dihydropyridines, a regioselective aromatic bromination, an efficient palladium-catalyzed carbonylation of aryl bromides, and a high-yielding acyl guanidine formation. A safe and scalable protocol for preparation of 2-trifluoromethyl phenyl Grignard reagent was developed, and a facile method for controlling the palladium content with *N*-acetyl-*L*-cysteine as the scavenger was demonstrated. Process issues in controlling the formation of a key diacylation side product during acyl guanidine formation are also addressed.

INTRODUCTION

Sodium−hydrogen exchangers (NHEs) are ion transporters expressed in a variety of cells that maintain intracellular pH homeostasis by the electroneutral exchange of intracellular hydrogen for extracellular sodium.[1] Among the nine identified isoforms of NHEs, NHE type 1 (NHE-1) as the major subtype in myocardial cells is known to be deeply involved in ischemic and reperfusion injury. The NHE-1 inhibitors are proven to improve myocardial contractility and metabolic status as well as to reduce arrhythmia, apoptosis, necrosis, and intracellular overload of sodium and calcium ions. They can be effectively used for prevention and treatment of ischemic heart diseases such as acute myocardial infarction, arrhythmia, angina pectoris, etc., and they are also promising candidates for heart-protecting agents applied to reperfusion therapy or cardiac surgery including coronary artery bypass graft and percutaneous transluminal coronary angioplasty.[2] Our research department has recently discovered a potent NHE-1 inhibitor **1** for preclinical development to fully define safety and pharmacological properties. An efficient and economical process to acyl guanidine **1** was thus required in order to supply ample drug substances for preclinical studies.



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The original synthetic route to compound **1** from Medicinal Chemistry[3] (Scheme 1) consisted of 14 synthetic steps and, while suitable for medicinal chemistry's requirements, had a low overall yield (~20%). In addition to the requirement of several chromatographic purifications, some costly reagents such as triflimide **3**, octamethyl-2,2′-bi(1,3,2-dioxaborolane), and Boc-protected guanidine were also employed. We herein report an efficient and highly convergent synthesis of compound **1** from the readily available starting material 2-bromobenzotrifluoride (**7**) in only five synthetic steps and in 42% overall yield. Key transformations including an efficient copper-catalyzed conjugated addition of 2-trifluoromethylphenyl Grignard reagents to acetyl pyridinium salts, a facile hydrogenation of 4-aryl dihydropyridines, a regioselective aromatic bromination, an efficient carbonylation of aryl bromides, and a high-yielding acyl guanidine formation are described at multikilogram scales, and the key process issues are addressed.

RESULTS AND DISCUSSION

Choice of Synthetic Strategy. The original synthesis of NHE-1 inhibitor **1** from Medicinal Chemistry adopted a key Suzuki coupling reaction[4] between vinyl boronic ester **6** and trisubstituted aryl bromide **10** followed by a transfer hydrogenation to construct its 4-aryl piperidine framework. Although the Suzuki coupling was facile and proceeded in high yield (85%), the preparation of both vinyl boronic ester **6** and aryl bromide **10** were tedious and required several synthetic steps from readily available starting materials. Thus, this synthetic strategy was not ideal for further scale-up activity of compound **1**. Several alternative methods for the synthesis of 4-aryl piperidines were studied on the basis of the availability of starting materials and practicality (Scheme 2). These included

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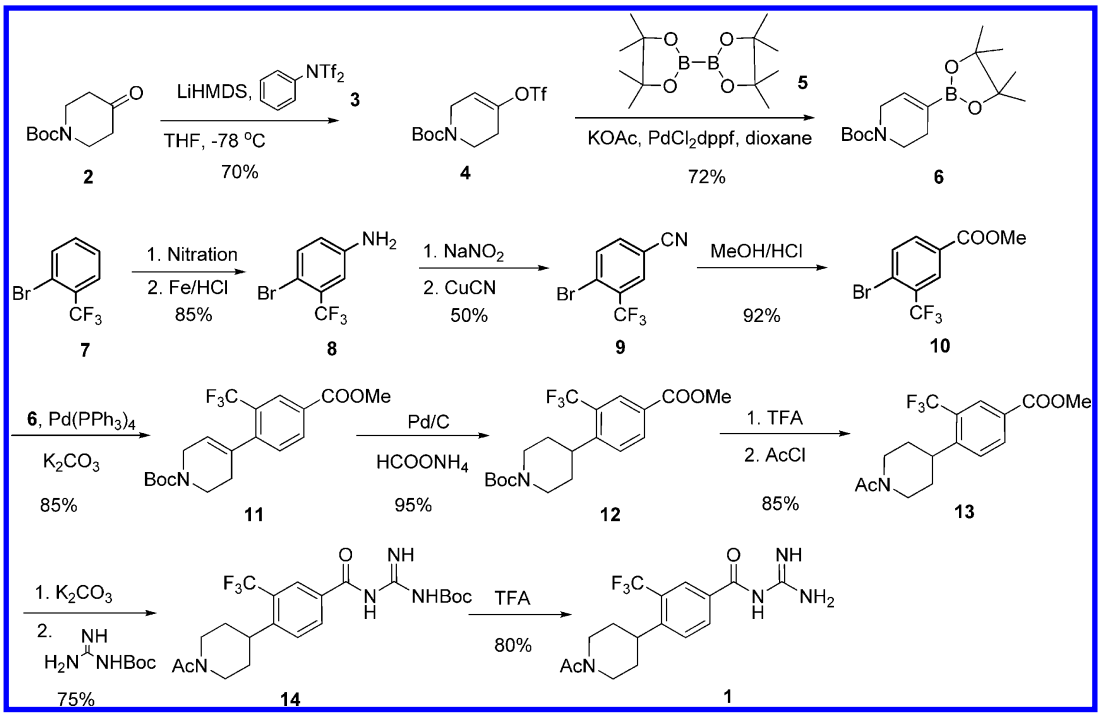
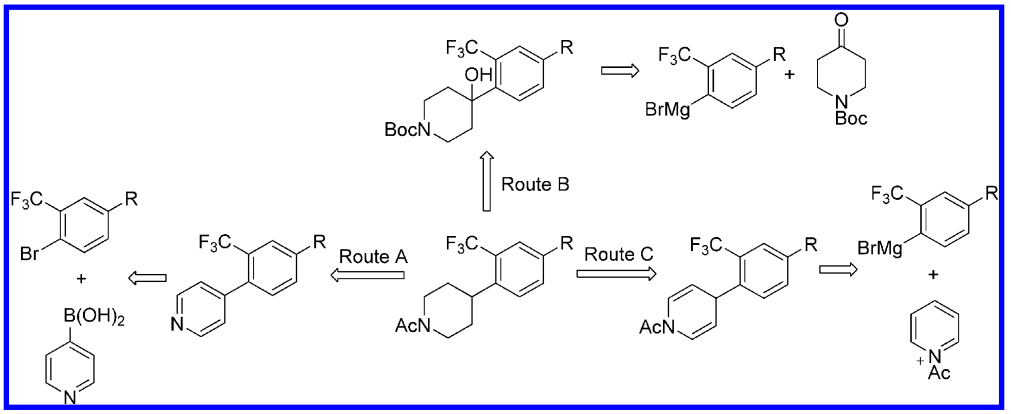
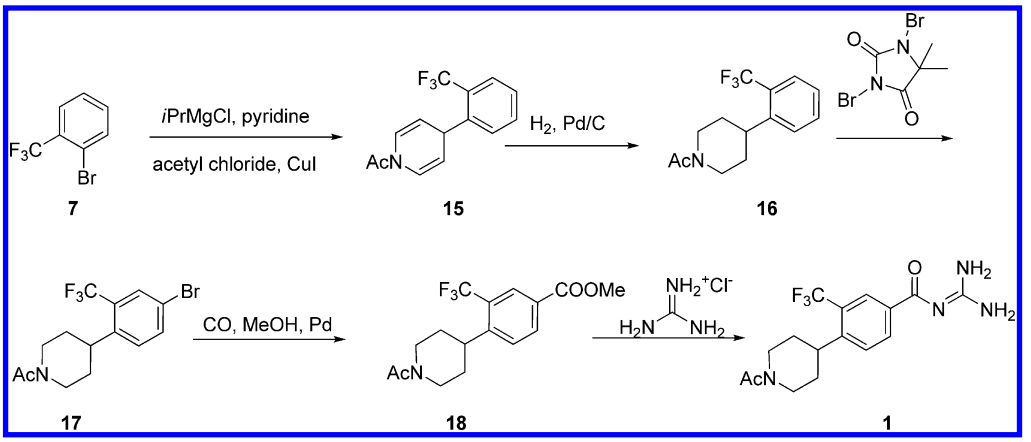
Scheme 1. Original synthetic route of compound 1 from Medicinal Chemistry



Scheme 2. Route scouting for the synthesis of 4-aryl piperidine framework



Scheme 3. Proposed new synthetic route to NHE-1 inhibitor 1



Suzuki coupling of an aryl halide with 4-pyridine boronic acid (Route A), nucleophilic attack by an aryl Grignard species on a protected piperidinone (Route B), and reaction of an aryl Grignard reagent with an acyl pyridium salt (Route C). Comin's nucleophilic addition of an aryl Grignard reagent to an acyl pyridium salt[5] to form a 4-aryl dihydropyridine is

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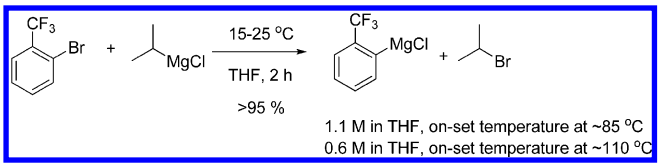
advantageous over the other two methods in terms of both convergence and cost-effectiveness. The product 4-aryl dihydropyridine is also easily reduced to form the corresponding 4-aryl piperidine derivative by catalytic hydrogenation. This method was thus adopted for the synthesis of compound **1**. Since the synthesis of trisubstituted phenyl bromide **10** was tedious and required five steps from the readily available starting material (Scheme 1), we proposed to synthesize the dihydropyridine **15** via Comin's reaction from 2-trifluoromethyl phenyl Grignard reagent, which can be prepared conveniently from 2-bromo benzotrifluoride (7) via Knochel's metal–halogen exchange protocol.[6] We expected that an aromatic bromination of the corresponding 4-aryl piperidine derivative **16** should furnish the bromination product **17** regioselectively (Scheme 3). A subsequent palladium-catalyzed carbonylation would provide its corresponding methyl ester **18**, which could further react with guanidine to form the acyl guanidine final product **1** in an overall five-step sequence.

Synthesis of 4-Aryl Dihydropyridine 15 via Comin's Reaction. In contrast to many reports on addition of organometallic reagents to 1-alkoxycarbonylpyridinium salts,[7,5a] the corresponding reaction on 1-acetyl pyridinium salt has received significantly less attention. An early report by Lyle et al[8] showed the addition of PhMgBr to 1-acetyl pyridinium salt occurred primarily at the 2-position of the pyridinium ring without using a copper catalyst. In the presence of a copper catalyst, the addition at the 4-position of the pyridinium ring was generally preferred.[5a,7a,b] We envisioned that the bulkiness of 2-trifluoromethyl phenyl Grignard reagent in conjunction with employment of a copper catalyst should facilitate the addition preferentially at the 4-position of the 1-acetyl pyridinium ring.

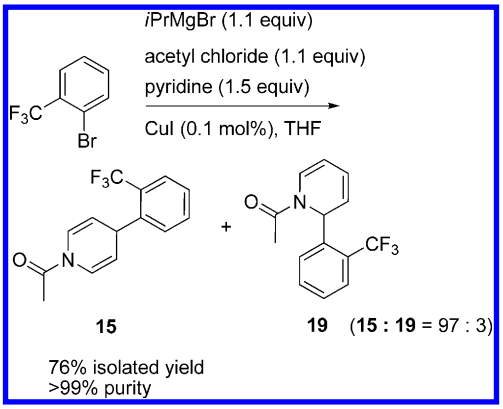
In order to study this reaction, it was required to scale up the formation of 2-trifluoromethyl phenyl Grignard reagent. It should be noted that the preparation of trifluoromethyl-substituted phenyl Grignard reagent from its corresponding aryl halide and magnesium metal is dangerous, and in fact several severe explosions have been reported.[9] Knochel's method of generating Grignard solutions via metal–halogen exchange has proven to be a better method with mild conditions. Applying this method, the formation of 3,5-bis(trifluoromethyl)phenyl Grignard reagent in kilogram scale was reported.[10] Thus, by using ^{i}PrMgCl (2.0 M in THF, 1.1 equiv) as the reagent and THF as the solvent, the magnesium–bromide exchange reaction of 2-bromobenzotrifluoride was run at 15–25 °C for 2 h and >95% conversion was observed. The resulting 2-trifluoromethyl phenyl magnesium chloride solution (~1.1 M) was stable over 24 h at ambient temperature (Scheme 4). However, an adiabatic calorimetry study of this solution in an Advanced Reactive Systems Screening Tool (ARSST, http://www.fauske.com) showed a highly exothermic event with an onset temperature at ~85 °C, leading to a safety concern for scale-up activities. Further studies showed that this exothermic event can be effectively moderated by decreasing its concentration. An important concentration effect on process safety was thus discovered, and the detailed results were reported by us separately.[11] ARSST studies showed much milder exothermic activity with a higher onset temperature (~110 °C) when the concentration was decreased to 0.5–0.6 M. Thus, the solution of 2-trifluoromethylphenyl magnesium chloride was recommended to be best prepared at a low concentration (<0.6 M). In our scale-up program, we successfully produced 83 L (50 mols) of a solution of 2-trifluoromethylphenyl magnesium bromide in THF at 0.6 M concentration.

Scheme 4. Formation of 2-trifluoromethyl phenyl Grignard reagent



With a scalable protocol for preparing 2-trifluoromethyl-phenyl Grignard reagent available, the Cu-catalyzed addition of 2-trifluoromethylphenyl Grignard reagent to acetyl pyridinium salts was explored (Scheme 5). The acetyl pyridinium salts were formed instantaneously and precipitated out while acetyl chloride was added to a light-yellow solution of pyridine and 10 mol % CuI in THF. 2-Trifluoromethylphenyl Grignard reagent was then added slowly into the slurry at −5–0 °C. The addition was highly exothermic, indicating the rapid reaction between 2-trifluoromethylphenyl Grignard reagent and the acetyl pyridinium salt. The reaction provided an excellent conversion (>90%), assay yield (~90%), and regioselectivity. The mole ratio of 1,4-addition adduct **15** to 1,2-addition adduct **19** was ~97:3. Further experiments showed that the excellent regioselectivity can even be maintained in the presence of only 0.1 mol % CuI. In order to understand the role of CuI in the regioselectivity of this reaction, a parallel study without CuI was studied. The regioselectivity decreased to 85:15 in the absence of CuI, demonstrating the importance of the copper catalyst for the regioselectivity. It is noteworthy that the CuI loading (0.1 mol %) for this reaction is among the lowest reported to date for addition of an organometallic reactant to an acyl pyridinium salt. With this protocol, we successfully produced over 10 kg of the dihydropyridine product **15** in 76% isolated yield and >99% purity.

Scheme 5. Synthesis of dihydropyridine 15



Hydrogenation of Dihydropyridine 15 and Bromination. The hydrogenation of dihydropyridine **15** with 10% Pd/C as the catalyst proceeded smoothly under 200 psi H_2 at 50–55 °C. The hydrogenation of the first double bond proceeded much faster than that of the second double bond, possibly due to the conformational and electronic change of the ring system during hydrogenation. With 1 mol % of 10% Pd/C as the catalyst, the hydrogenation of the second double bond reached >99% conversion after 10 h (Scheme 6). After filtration to

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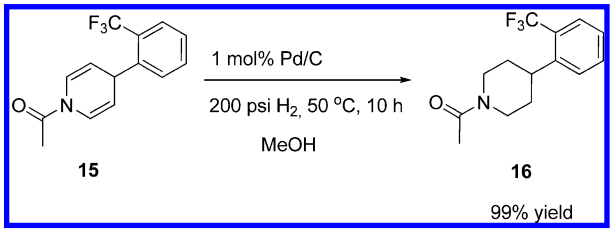
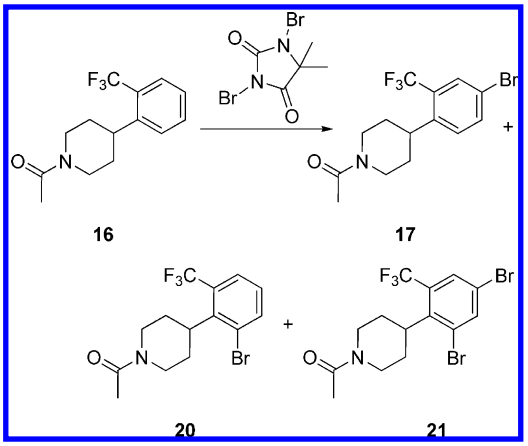
remove Pd/C catalyst, the filtrate was directly used for the ensuing bromination step.

Scheme 6. Hydrogenation of dihydropyridine 15



Several reagents were initially screened for the bromination of **16**, and 1,3-dibromo-5,5-dimethylhydantoin (DBH) proved to be the best for its higher reactivity than Br_2 and *N*-bromosuccinimide (NBS) (Scheme 7). It was also found that an acidic

Scheme 7. Bromination of compound 16



media could enhance the reactivity, therefore various combinations of solvents and acids were tested, and the results are listed in Table 1. A combination of sulfuric acid and dichloromethane was found to be a good medium to promote the bromination (entry 6). Other than the desired product **17**, a major regioisomer **20** and a dibromo compound **21** were also identified, together with two other uncharacterized minor regioisomers. All experiments were run at ambient temperatures (20−25 °C); higher temperature was found to generate more impurities. It was found that addition of acetic acid provided a better regioselectivity between **17** and **20**.[12] The selectivity increased from ∼12:1 to 18:1 when 3 equiv of acetic acid was employed. Thus, with H_2SO_4/HOAc/DCM as the media and DBH (0.6 equiv) as the reagent, compound **17** was formed in ∼90−92% assay yield after 12 h at 20−22 °C (entry 10), along with the side products **20** (∼5%) and **21** (∼2%). These impurities could be easily controlled to <1.5% by a single crystallization of **17** from methylcyclohexane. We thus successfully produced 9.5 kg of **17** in 78−80% isolated yield and in >98.5% purity by HPLC.

Carbonylation of Bromide 17. The palladium-catalyzed carbonylation of bromide **17** to form methyl ester **18** was then studied.[13] With MeOH as the solvent and K_2CO_3 as the base at 70 °C under 100 psi CO, three common bidentate ligands DPPP, BINAP, and DPPF were screened and DPPP provided the best reactivity under otherwise identical conditions (entry 1, 3, Table 2). Thus, DPPP was chosen for further screening. Employment of a high reaction temperature (110 °C) greatly accelerated the reaction rate, and >99% conversion was observed after 20 h. However, the formation of the carboxylic acid **22** increased accordingly (27%). Further screening of bases revealed that an organic base such as triethylamine provided a decrease in the formation of **22** (5%). Fine tuning of the reaction temperature to 90 °C ensured the sufficient reactivity for this carbonylation and also controlled the formation of acid **22** to ∼3%. A small amount of the reduction product **16** (<2%) was also observed during the reaction. A simple workup procedure was developed, in which the reaction mixture was filtered over Celite and the filtrate then solvent-switched to an NMP-water system. The product was crystallized directly from this solution in 90−93% yield. In our scale-up program, we were able to employ only 0.2 mol % $Pd(OAc)_2$ and 0.22 mol % DPPP for this carbonylation, which not only allowed us to reduce costs but also facilitated the control of the Pd content within **18** (Scheme 8).

Several methods[14] were applied to control the Pd content including Cuno ZetaCarbon filters[15] and *N*-acetyl-*L*-cysteine[16,14a] (Table 3). While Cuno ZetaCarbon filters were ineffective with MeOH as the solvent, *N*-acetyl-*L*-cysteine was a fine scavenger for this process. Since the palladium complex of *N*-acetyl-*L*-cysteine is water-soluble, we simply added 3 mol % *N*-acetylcysteine to the NMP/water solution of the reaction mixture prior to crystallization and the Pd content of **18** was controlled to ∼10 ppm. No additional operations such as phase cuts or filtrations were then required for robust palladium content control. In our scale-up program, we successfully prepared 7.5 kg of methyl ester **18** in 90−93% isolated yield and 97% purity with <5 ppm residual Pd content.

Synthesis of Acyl Guanidine 1 and Its HCl Salt Formation. Next we studied the synthesis of acyl guanidine **1** from ester **18** and guanidine (Scheme 9).[17] Since anhydrous guanidine is not commercially available, it was generated *in situ* from guanidine·HCl salt by reaction with NaO^{t}Am as base in NMP solution. A more common base KO*t*Bu can also be used for generating guanidine on laboratory scale. However, its NMP solution proved to be too viscous for operations at larger scales. In addition to the desired product **1**, the two common side products during the reaction were acid **22** and diacylation product **23**, which were generally formed in about 3%. Abnormally high levels of the diacylation side product **23** (3−30%) were observed in some small batches. Investigation revealed that the heterogeneous reaction between guanidine·HCl salt and NaO^{t}Am was incomplete in those batches, leading to a strongly basic media at the time of addition of the ester **18**. The formed product **1** can be further deprotonated under the strong basic conditions used to promote the formation of the diacylation product **23** (Scheme 10). To avoid the incomplete reaction between guanidine·HCl salt and NaO^{t}Am, two strategies were enforced: (1) additional NMP solvent was employed to make the reaction more homogeneous, and (2) excess guanidine·HCl salt (2.2 equiv) was employed to ensure the complete consumption of NaO^{t}Am. In this way, the formation of diacylation side product **23** was consistently controlled to ∼3% and the acyl guanidine **1** was isolated by crystallization from NMP/water solution in 88% yield and 98.9 A% purity.

The wet cake of acyl guanidine **1** was directly used for the formation of its HCl salt with isopropanol as the solvent and concentrated HCl as the reagent (Scheme 11). In order to consistently form the right polymorph and morphology of

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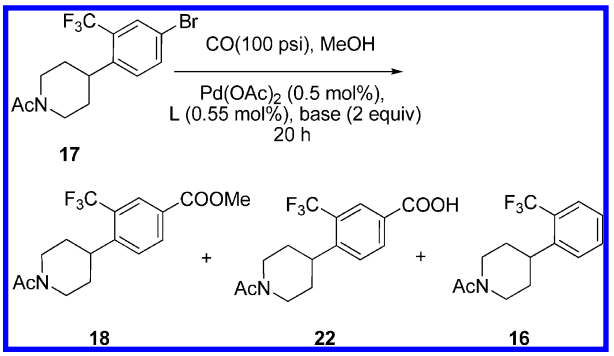
Table 1. Screening of reaction conditions for bromination of 16

entry	scale (g)	conditions	time (h)	product (**17**) (%)	SM (**16**) (%)	regioisomers (**20** + other two) (%)	dibromo (**21**) (%)
1	0.1	DCM (10 vol), DBH (0.5 equiv), $MeSO_3H$ (5 equiv)	12	32	61	2.0	0
						1.5	
						3.2	
2	0.1	DCM (10 vol), NBS (1.05 equiv), $MeSO_3H$ (5 equiv)	12	5	95	0	0
3	0.1	DCM (4 vol), DBH (0.75 equiv), $MeSO_3H$ (10−15 equiv)	12	80	8	7.4	0
						1.3	
						2.2	
4	0.1	TFA(2.5 vol), DBH (0.55 equiv), H_2SO_4 (1.0 equiv)	12	91	0	4.6	1.5
						2.1	
5	2	TFA(2.5 vol), DBH (0.55 equiv), H_2SO_4 (1.0 equiv)	12	90	2.8	4.7	0
						0.9	
						1.2	
6	0.1	DCM, DBH (0.62 equiv), H_2SO_4 (4 equiv)	8	82	3.2	7.2	4.6
						0.7	
7	0.1	DCM, DBH (0.62 equiv), H_2SO_4 (4 equiv)	8	75.3	14.8	4.1	0.6
						2.3	
8	0.1	DCM, DBH (0.62 equiv), AcOH (6 equiv), H_2SO_4 (2 equiv)	8	53	40.6	2.9	0
						1.0	
9	0.1	DCM, DBH (0.62 equiv), AcOH (4 equiv), H_2SO_4 (3.4 equiv)	3	88	4.0	5.9	0.5
						0.8	
10	**20**	**DCM, DBH (0.62 equiv), AcOH (4 equiv), H_2SO_4 (3.4 equiv)**	**8**	**92.2**	**0.0**	**5.5**	**1.5**
						0.6	
11	5.0	MeCN, DBH (0.65 equiv), AcOH (2.5 equiv), H_2SO_4 (5.0 equiv)	12	89.3	3.1	6.2	0.6
						0.6	
12	0.1	MCH, DBH (0.65 equiv), AcOH (5 equiv), H_2SO_4 (2 equiv)	15	40	56	1.5	0.8
						0.2	
13	0.1	^{i}PrOH, DBH (0.62 equiv), AcOH (4 equiv), H_2SO_4 (3.4 equiv)	15	–	100	–	–
14	0.1	THF, DBH (0.57 equiv), H_2SO_4 (2 equiv)	15	1	99	–	

Table 2. Screening of reaction conditions for carbonylation of 17



				HPLC yield (A%)	
entry	L	base	T (°C)	**18**	**22**
1	DPPF	K_2CO_3	70	20	–
2	BINAP	K_2CO_3	70	10	–
3	DPPP	K_2CO_3	70	44	–
4	DPPP	K_2CO_3	110	72	27
5	DPPP	TMEDA	110	87	8
6	DPPP	Et_3N	110	83	5
7	DPPP	Et_3N	90	92	3

Scheme 8. Carbonylation of aryl bromide 17

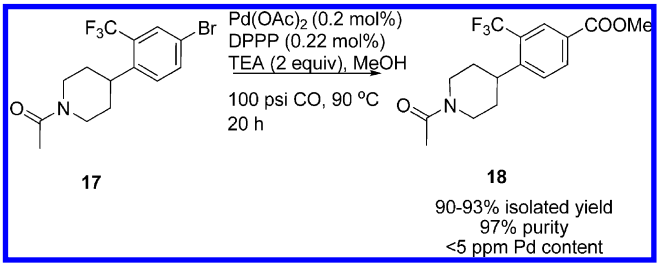


Table 3. Palladium content control in ester 18

$Pd(OAc)_2$ loading (mol %)	treatment	Pd content in **18** (ppm)
0.5	none	1557
0.5	CUNO ZetaCarbon R53 filter	1399
0.5	CUNO ZetaCarbon R55 filter	1255
0.5	1.5 mol % *N*-acetyl-*L*-cysteine	136
0.5	3 mol % *N*-acetyl-*L*-cysteine	83
0.2	3 mol % *N*-acetyl-*L*-cysteine	4

1·HCl salt, the water content of the isopropanol solution of **1** was controlled to below 1% prior to the addition of HCl. Thus, the HCl salt of **1** was isolated in ∼90% isolated yield and in 99.6% purity.

CONCLUSIONS

In summary, we have successfully developed an economical and facile process for the synthesis of a NHE type I inhibitor, **1**, in five steps from readily available starting material and in 43%

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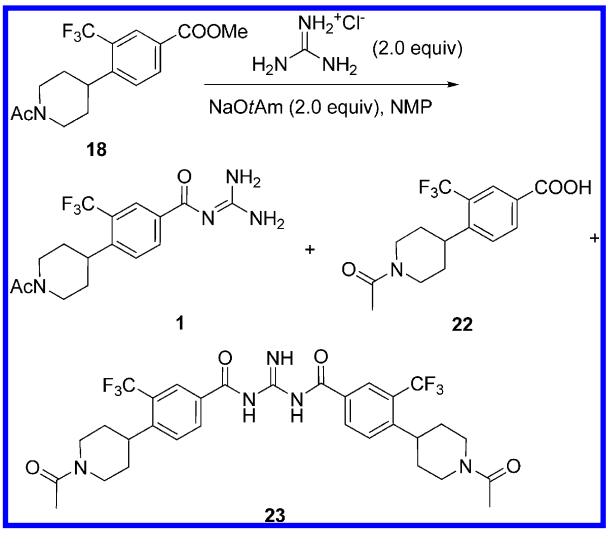
Scheme 9. Formation of acyl guanidine 1

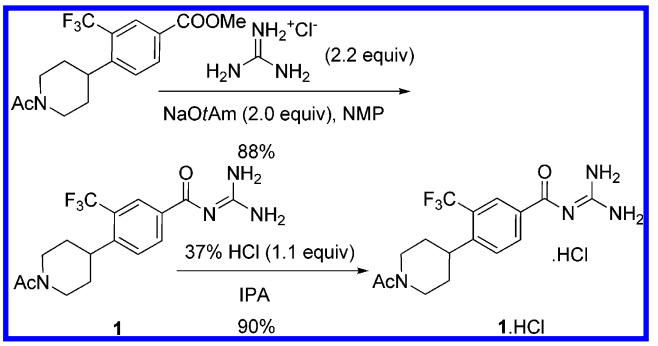


overall yield. This process allowed us to produce compound **1** in multikilogram scales in 3 months. Key transformations included a highly efficient copper-catalyzed conjugated addition of 2-trifluoromethylphenyl Grignard reagents to acetyl pyridinium salts at 0.1 mol % catalyst loading, a facile hydrogenation of 4-aryl dihydropyridines **15**, a regioselective aromatic bromination of **16**, an efficient palladium-catalyzed carbonylation of aryl bromide **17** at 0.2 mol % Pd loading, and finally a high-yielding acyl guanidine formation of **1**. In addition to the development of these key transformations, a safe and scalable protocol for the preparation and use of 2-trifluoromethyl phenyl Grignard reagent was developed, and a facile method for controlling the palladium content with *N*-acetyl-*L*-cysteine was defined.

EXPERIMENTAL SECTION

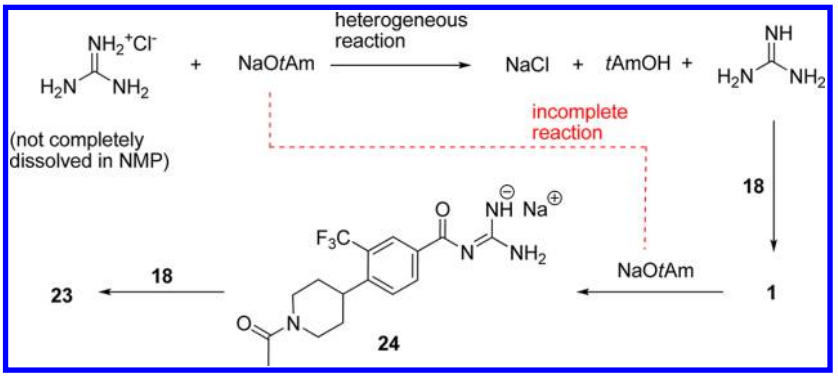
1-(4-(2-(Trifluoromethyl)phenyl)pyridin-1(4*H*)-yl)-ethanone (15). To a solution of 2-bromobenzotrifluoride (7, 5.0 kg, 22.0 mol) in THF (5 L) at 20−25 °C was added a solution of ^{i}PrMgBr in THF (26.2 kg, 13.6 wt %, 24.2 mol, 1.1 equiv) over 15 min while controlling the reaction temperature <30 °C (**CAUTION**: *For safety reasons, it is critical to add the ^{i}PrMgBr solution slowly and keep the temperature under 30 °C!*). After the addition, the mixture was stirred at 25−30 °C for 3−4 h. In a separate reactor was charged CuI (42 g, 0.022 mol, 0.1 mol %), THF (10 L) and pyridine (1.64 kg, 33.0 mol. 1.5 equiv). The resulting light yellow solution was stirred at 20−25 °C for 20 min. To this mixture at 0−5 °C was added acetyl chloride (1.94 kg, 24.2 mol, 1.1 equiv) over 10 min, while the temperature was controlled <25 °C. To the slurry at −5−5 °C was added the aforementioned 2-trifluoromethyl Grignard solution over 1.5 h, while the temperature was controlled at −5−5 °C. The mixture was kept at 0−5 °C for 0.5 h, warmed to 20−25 °C over 20 min, and further stirred at 20−25 °C for 1 h. To the cold reaction mixture at 10−15 °C was charged 2 N HCl solution (10 L) over 15 min while controlling the reaction temperature <35 °C. The two phases were separated, and the aqueous layer was discarded. To the organic phase was added methylcyclohexane (10 L) and 10% NaCl solution (10 L), and the mixture was stirred at 20−25 °C for 20 min. The organic phase was separated, and methylcyclohexane (5 L) was added. The mixture was distilled to ∼10 L to form a slurry, while the internal temperature was controlled <70 °C. Additional methylcyclohexane (7.5 L) was added, and the mixture was heated to ∼90 °C to form a clear solution, cooled to 40 °C over 1 h, held at 40 °C for 0.5 h, further cooled to 20−22 °C over 1 h, and finally stirred at 20−22 °C for 1 h to form a slurry. The slurry was filtered, and the cake was washed further with methylcyclohexane (2 L × 2) and then dried under vacuum at 20−25 °C for 12 h to give the desired product **15** (4.45 kg, 76% yield, >99% purity by HPLC) as a white crystalline solid. **15**: mp (DSC) 91 °C; ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.68 (m, 2H), 7.58 (m, 1H), 7.43 (m, 1H), 7.21 (d, J = 6.5 Hz, 1H), 6.96 (d, J = 6.0 Hz, 1H), 4.99 (br s, 1H), 4.87 (br s,1H), 4.46 (s, 1H), 2.23 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ166.4, 143.8, 133.1, 131.8, 127.1, 125.4 (m), 125.3 (m), 124.6, 124.4 (q, J = 272 Hz), 121.1, 109.5, 107.8, 34.5, 21.2; ESI-MS: m/z 268 $[M + H]^+$.

Scheme 11. Synthesis of acyl guanidine 1 and its HCl salt



1-(4-(4-Bromo-2-(trifluoromethyl)phenyl)piperidin-1-yl)ethanone (17). To a 20 L autoclave was charged 1-(4-(2-

Scheme 10. Formation of unwanted diacylation side product 23



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(trifluoromethyl)phenyl)pyridin-1(4H)-yl)ethanone (**15**, 2.5 kg, 9.31 mol) and 10 wt % Pd/C (Degussa type E101 NE/W, wet, 50%, 0.2 kg). The system was purged with nitrogen three times and then MeOH (12.5 L) was charged. The mixture was further purged with hydrogen three times and then pressurized with 200 psi H_2. The resulting mixture was stirred at 50−55 °C for 12 h and then filtered over a Celite pad to give a crude MeOH solution of 1-(4-(2-(trifluoromethyl)phenyl)-piperidin-1-yl)ethanone (**16**) in 99% HPLC purity. A crude MeOH solution of 1-(4-(2-(trifluoromethyl)phenyl)piperidin-1-yl)ethanone (**16**) from hydrogenation (containing ∼5 kg **16**, 18.4 mol) was charged to a 50 L reactor. The mixture was distilled to ∼7 L, while the internal temperature was controlled at 50−55 °C. To the mixture was charged dichloromethane (16 L), and the resulting mixture was further distilled to ∼16 L to control the MeOH content <1 wt %. To the mixture at 20−25 °C was charged 1,3-dibromo-5,5-dimethylhydantoin (3.12 kg, 10.9 mol, 0.6 equiv) and acetic acid (3.28 kg, 54.6 mol, ∼3 equiv). After the mixture was cooled to ∼10 °C, conc. sulfuric acid (5.35 kg, 54.6 mol, ∼3 equiv) was added over 0.5 h, while the temperature was controlled at 15−20 °C. The resulting mixture was stirred at 20−23 °C for 10 h. Methylcyclohexane (25 L) and water (10 L) were added over 30 min, while the temperature was kept at <22 °C. The two phases were separated, and the aqueous layer was removed. To the organic layer at ∼10 °C was charged 10% NaOH solution (7.3 kg). The pH of the aqueous layer was adjusted to 8−10. To the mixture was further added 10% $Na_2S_2O_3$ solution (9.2 L). The two phases were separated, and the bottom aqueous layer was removed. The organic layer was further washed with 5% NaCl solution (12 L) and distilled under vacuum to ∼10 L. Methylcyclohexane (6.5 L) was added, and the mixture was warmed to ∼65 °C to form a clear solution, cooled to 20−22 °C over 8 h, and stirred further at this temperature for 1 h. The slurry was filtered, and the cake was washed with methylcyclohexane/heptane (1/1, 3 L × 2) and dried at 50 °C under vacuum for 12 h to provide the desired product **17** (4.93 kg, 78%, 99.0% purity by HPLC) as white solid. **17**: mp (DSC) 107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.4, 2.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 4.80 (d, J = 13.5 Hz, 1H), 3.93 (d, J = 13.4 Hz, 1H), 3.16 (m, 2H), 2.61 (t, J = 11.4 Hz, 1H), 2.13 (s, 3H), 1.83 (m, 2H), 1.62 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 168.7, 143.1, 135.1, 129.6, 129.6 (q, J = 119.6 Hz), 128.9 (q, J = 6.2 Hz), 123.5 (q, J = 272.8 Hz), 119.9, 46.9, 42.0, 38.1 (q, J = 1.9 Hz), 33.8, 32.7, 21.4; ESI-MS: m/z 350 $[M + H]^+$.

Methyl 4-(1-Acetylpiperidin-4-yl)-3-(trifluoromethyl)-benzoate (18). To a 20 L autoclave was charged 1-(4-(4-bromo-2-(trifluoromethyl)phenyl)piperidin-1-yl)ethanone (**17**, 2.5 kg, 7.1 mol) followed by MeOH (10 L) and triethylamine (1.44 kg, 14.1 mol, 2 equiv). The mixture was purged with nitrogen (5 psi) three times before a solution of $Pd(OAc)_2$ (3.2 g, 14 mmol, 0.2 mol %) and DPPP (6.6 g, 16 mmol, 0.22 mol %) in degassed MeOH (2 L) was charged. The resulting solution was purged with CO three times, pressurized with 100 psi CO, and then heated to 90−92 °C for 20 h. After cooling to rt, the mixture was filtered through a Celite pad to provide a crude solution of methyl 4-(1-acetylpiperidin-4-yl)-3-(trifluoromethyl)benzoate (**18**) in MeOH in 93.6% assay yield. The solution was distilled to ∼2 L, while the internal temperature was controlled at <65 °C. NMP (6.5 kg) was added, and the resulting mixture was further distilled at ∼55 °C under reduced pressure to remove most of MeOH. To the mixture at ∼60 °C was charged *N*-acetyl-*L*-cysteine (35.5 g, 0.22 mol, 3 mol %), and the mixture was further stirred at ∼60 °C for 30 min before water (20 L) was charged. To the mixture at ∼40 °C was charged seed crystals (12 g, ∼0.5% of theoretical yield), and the resulting solution was cooled to 20−22 °C over 3 h and held at this temperature for 6−8 h. Water (5 L) was added, and the resulting slurry was further stirred at 20−22 °C for 1 h. The slurry was filtered, and the wet cake was washed with water (2 L × 3) and dried at 50 °C under house vacuum to provide the desired product **18** (2.12 kg, 93.6% 96.5 A% purity by HPLC, Pd content: 4.1 ppm) as white solid. **18**: mp (DSC) 105 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, J = 8.2 Hz, 1H), 8.13 (s, 1H), 7.80 (d, J = 8.1 Hz, 1H), 4.56 (d, J = 13.2 Hz, 1H), 3.94 (d, J = 13.7 Hz, 1H), 3.87 (s, 3H), 3.13 (m, 2H), 2.57 (td, J = 12.9, 2.6 Hz, 1H), 2.04 (s, 3H), 1.50−1.85 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 164.9, 149.6, 133.1, 129.6, 128.1, 126.9 (q, J = 29.0 Hz), 126.0 (q, J = 5.9 Hz), 124.0 (q, J = 272.5 Hz), 52.4, 46.1, 41.2, 38.4, 32.9, 32.4, 21.2; ESI-MS: m/z 330 $[M + H]^+$.

4-(1-Acetylpiperidin-4-yl)-*N*-(diaminomethylene)-3-(trifluoromethyl)benzamide (1). To a 50 L reactor was charged guanidine·HCl (2.39 kg, 24.5 mol, 2.2 equiv) followed by NMP (11.7 kg). The mixture was cooled to 10−15 °C. A solution of sodium *tert*-pentoxide (2.58 kg, 22.3 mol, 2.0 equiv) in NMP (7.8 kg) was charged over ∼20 min, while the reaction temperature was controlled at <25 °C. The resulting mixture was stirred at 20−25 °C for 1 h. To the mixture at 20−25 °C was charged a solution of methyl 4-(1-acetylpiperidin-4-yl)-3-(trifluoromethyl) benzoate (**18**) over 1 h, while the temperature was controlled at <25 °C. The resulting mixture was stirred at 20−25 °C for 2 h. Water (39.9 kg) was added over 20 min, while the temperature was controlled <40 °C. The solution was cooled to 30 °C, and seed crystals (30 g, ∼0.6% of theoretical yield) were charged. The resulting mixture was cooled to 20−22 °C over 3 h and stirred at this temperature for 12 h. The slurry was filtered, and the cake was rinsed with water (2 L × 3), air-dried for 2 h, and further dried under house vacuum at 20−25 °C for 12 h to provide the wet desired product **1** (4.18 kg, 88.4% yield, 98.9 A% purity by HPLC, containing 15.5% water and 0.9% NMP) as a white crystalline solid. **1**: mp (DSC) 219 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 4.56 (d, J = 13.0 Hz, 1H), 3.92 (d, J = 13.3 Hz, 1H), 3.09 (m, 2H), 2.56 (t, J = 12.7 Hz, 1H), 3.10 (s, 3H), 1.45−1.80 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.0, 168.1, 163.1, 145.5, 137.5, 132.4, 128.3, 126.1, 125.6 (q, J = 6.0 Hz), 124.6 (q, J = 243.7 Hz), 46.3, 41.4, 38.2, 33.2, 32.7, 21.3; ESI-MS: m/z 357 $[M + H]^+$.

4-(1-Acetylpiperidin-4-yl)-*N*-(diaminomethylene)-3-(trifluoromethyl)benzamide HCl Salt (1·HCl). To a 50 L reactor was charged wet 4-(1-acetylpiperidin-4-yl)-*N*-(diaminomethylene)-3-(trifluoromethyl)benzamide (**1**, 4.1 kg, 84.0%, 9.66 mol) followed by isopropanol (41.3 L). The mixture was stirred at 20−25 °C for 15 min to form a clear solution and then polish filtered. The filtrate was distilled under vacuum to ∼25 L, while the temperature was controlled at 50−65 °C. A sample was taken to confirm the water content of the solution was <1.5% (actual: 1.38%). Additional isopopanol (20 L) was added, and the mixture was cooled to ∼40 °C. Conc. HCl solution (1.05 kg, 37%, 10.63 mol, 1.1 equiv) was charged to the mixture over 15 min followed by seeding (19 g, ∼0.5% of theoretical yield). The mixture was held at ∼40 °C for 2 h, cooled to 20−22 °C over 3 h, and further stirred at this

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temperature for 10 h. The slurry was filtered and the wet cake dried under house vacuum at 80 °C for 24 h to provide the desired product **1**·HCl (3.40 kg, 90% yield, 99.6 A% purity by HPLC) as a white crystalline solid. **1**·HCl: mp (DSC) 238 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (s, 1H), 8.81 (br s, 2H), 8.69 (br s, 2H), 8.42 (d, J = 8.36 Hz, 1H), 8.38 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 4.56 (d, J = 12.7 Hz, 1H), 3.95 (d, J = 13.3 Hz, 1H), 3.13 (m, 2H), 2.57 (t, J = 11.0 Hz, 1H), 2.03 (s, 3H), 1.50−1.90 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 166.1, 155.6, 150.2, 132.5, 129.7, 129.6, 127.0 (q, J = 29.5 Hz), 125.9 (q, J = 5.8 Hz), 124.0 (q, J = 273 Hz), 46.1, 41.2, 38.5, 32.8, 32.3, 21.3.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR of compounds **15**, **17**, **18**, **1**, and **1**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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