ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

pubs.acs.org/OPRD

Article

Tetramethylammonium Fluoride Tetrahydrate for S_NAr Fluorination of 4-Chlorothiazoles at a Production Scale

Mai Khanh Hawk,* Sarah J. Ryan,* Xin Zhang, Ping Huang, Jing Chen, Chuanren Liu, Jianping Chen, Peter J. Lindsay-Scott, John Burnett, Craig White, Yu Lu, and John R. Rizzo

Cite This: https://doi.org/10.1021/acs.oprd.1c00042

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: This article describes the use of tetramethylammonium fluoride tetrahydrate (TMAF·$4H_2O$) for the large-scale preparation of a challenging 4-fluorothiazole. Commercially available TMAF·$4H_2O$ was procured on a large scale and rigorously dried by distillation with isopropyl alcohol and then dimethylformamide at elevated temperature. This method of drying provided anhydrous TMAF [TMAF (anh)] containing <0.2 wt % water and <60 ppm isopropanol. The use of TMAF (anh) was essential for production of the 4-fluorothiazole. When the chlorothiazole starting material was treated with other anhydrous fluoride sources, poor conversion of the starting material or potential safety issues were observed. S_NAr fluorination using dried TMAF·$4H_2O$ was carried out at a 45.1 kg scale at 95−100 °C to produce 36.8 kg of 4-fluorothiazole **1b**.

KEYWORDS: *fluorination, S_NAr, tetramethylammonium fluoride, fluorothiazole, heteroarene, anhydrous fluoride*

INTRODUCTION

The substitution of hydrogen for fluorine can result in improved bioavailability or metabolic stability of bioactive molecules.[1] For this reason, the number of fluorinated heteroaromatics found in active pharmaceutic ingredients (APIs) and agrochemicals is increasing.[2] Despite the frequency that fluorine is incorporated into bioactive heteroarenes, large-scale production of these molecules remains challenging, particularly under mild, process-friendly conditions.[3]

One of the most common methods for the industrial-scale preparation of heteroaryl fluorides is nucleophilic aromatic substitution (S_NAr).[3,4] This reaction involves the substitution of an electron-deficient aryl halide with a nucleophilic fluoride source via the Meisenheimer intermediate (Scheme 1).[3b] The most commonly used fluoride source for S_NAr fluorination is an anhydrous alkali metal fluoride. However, the low solubility of alkali fluorides under anhydrous conditions often results in the requirement for high temperature and long reaction time.

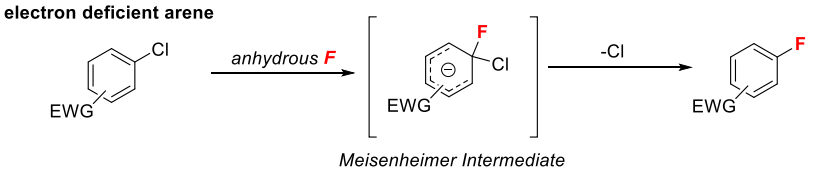
S_NAr fluorination is particularly challenging when used to prepare five-membered azoles with fluorine at the 4 or 5 position.[5] The high π-electron density at these positions further exacerbates the requirement for forcing reaction conditions,[6] which can limit functional group tolerance and lead to the formation of undesired impurities.[7] In fact, there are relatively few procedures of any kind that have been reported for the preparation of 4-fluoroazoles.[8,9] Moreover, many of these conditions involve the use of expensive electrophilic fluorinating reagents.[9] Thus, there is a need for the development of scalable, process-friendly methods for the production of five-membered fluoroarenes.

Many recent reports have demonstrated that electron-deficient aromatics can undergo S_NAr fluorination under mild conditions if a soluble anhydrous fluoride source is employed.[10−12] For example, the pioneering work of DiMagno demonstrated that anhydrous tetrabutylammonium fluoride [TBAF (anh)] could be prepared in situ from tetrabutylammonium cyanide (TBACN) and hexafluorobenzene (C_6F_6) (Scheme 2A).[11] This reagent was used for the room-temperature fluorination of a variety of electron-deficient aryl chlorides and nitroarenes. A 4-fluoroimidazole was even reported in the reaction scope, suggesting that this method could be applied to synthetically challenging 4-fluoroazoles.[11c] However, this method requires expensive (C_6F_6) and toxic (TBACN) as stoichiometric reagents, limiting its feasibility on an industrial scale. More recently, Sanford reported the room-temperature fluorination of electron-deficient aryl halides and nitroarenes using anhydrous tetramethylammonium fluoride [TMAF (anh)] (Scheme 2B).[12] This reagent is more stable than other anhydrous tetraalkylammonium salts.[13] Unlike TBAF (anh), it cannot undergo problematic Hofmann elimination as it lacks the β-protons required for E2 elimination.[14] For this reason, TMAF (anh) is commercially available and can be stored in its anhydrous form under ambient conditions.

We realized that TMAF (anh) would be an attractive reagent to use for the large-scale production of a 4-fluorothiazole. However, even though TMAF (anh) is readily available in gram quantities, it does not have good bulk commercial availability, limiting its feasibility for use at a large scale.[15] To address this challenge, we have pursued an approach that involves drying TMAF tetrahydrate (TMAF·

Received: February 4, 2021

Scheme 1. S_NAr Fluorination Mechanism



Scheme 2. Methods for S_NAr Fluorination Using Soluble, Anhydrous Nucleophilic Fluorination

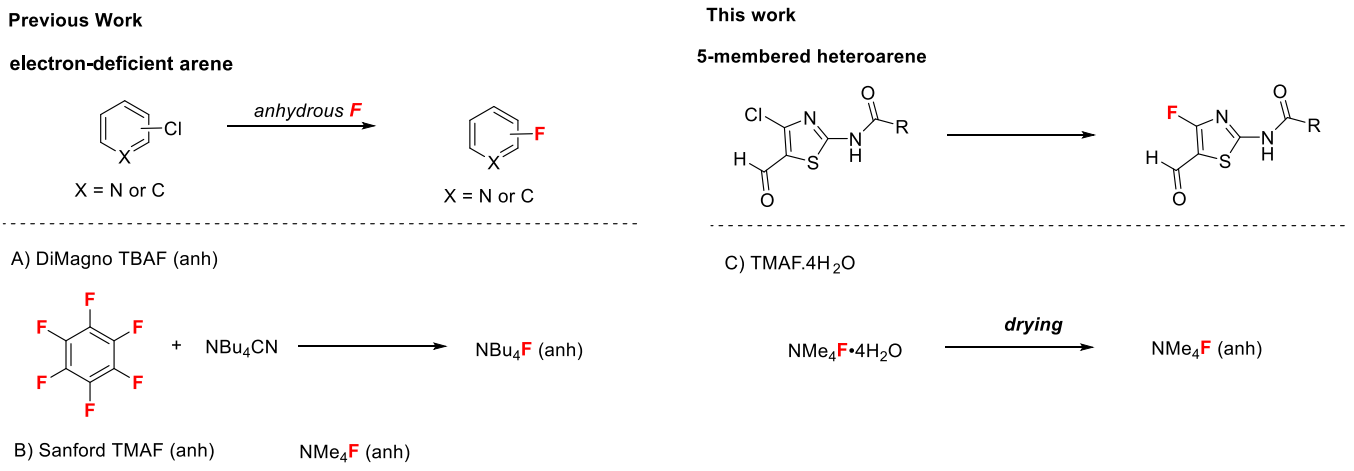
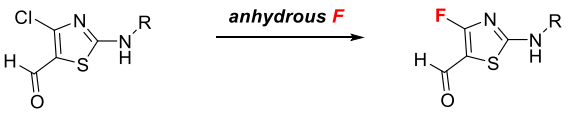


Table 1. S_NAr Fluorination of Chlorothiazole 2a and 2b



2a R = Boc
2b R = Ac

1a R = Boc
1b R = Ac

entry[a]	anhydrous fluoride	solvent	temperature (scale)	2 area %	1 area % (yield)
1	CsF	DMSO	130−135 °C (38 g)	**2a** 36.8	**1a** 58.5 (36%)[b]
2	CsF	DMSO	130−135 °C (300 g)	**2a** 40.2	**1a** 48.2 (23%)[b]
3	TMAF (anh) (4 equiv)	DMF	RT	**2a** 100	**1a** ND
4	TMAF (anh) (4 equiv)	DMF	100 °C	**2a** 100	**1a** 94.4
				2b 12	**1b** 80.5 (69%)[c]
5	TMAF (anh) (4 equiv)	DMSO	100 °C	**2a** 100	**1a** ND
6	TBAF (anh)[d]	DMF	RT	**2a** 100	**1a** ND
			100 °C	**2a** 100	**1a** ND
			100 °C	**2b** 100	**1a** ND
7	TMAOPh + BzF	DMF	100 °C	**2a** 100	**1a** ND
8	TMACl + CsF	DMSO	110 °C	**2a** 14.0	**1a** 75.8
			130 °C	**2b** 5.0	**1b** 61.1 (32%)[c]
9	TMACl + CsF	DMF	130 °C	**2b** 79.8	**1b** 20.1

[a]Unless otherwise stated, reactions were completed on 50 mg of chlorothiazole **2a** or **2b**. [b]Yield adjusted based on the amount of fluorothiazole **1a** in the crude mixture of **1a** and **2a**. [c]Isolated yield after flash column chromatography. [d]TBAF (anh) was prepared in situ by the reaction of TBACN and C_6F_6.

$4H_2O$) for the production of a challenging five-membered heteroaryl fluoride (Scheme 2C). The readily available TMAF·$4H_2O$ is rigorously dried by distillation with isopropyl alcohol (IPA) and then dimethylformamide (DMF) at elevated temperature to provide TMAF (anh). The S_NAr fluorination using dried TMAF·$4H_2O$ was carried out at a 45.1 kg scale at 95−100 °C to produce 36.8 kg of aryl fluoride **1b**.

RESULTS AND DISCUSSION

We required 35 kg of the five-membered fluoroarene **1** (Scheme 2) as an intermediate for an API. The initial procedure developed by the discovery chemistry group involved the reaction of the Boc-protected chlorothiazole **2a** with CsF in dimethyl sulfoxide (DMSO) at elevated temperature (Table 1, entries 1 and 2). Unfortunately, these reaction conditions were not amenable to large-scale production. When the reaction was completed with 38 g of chlorothiazole **2a**, the reaction mixture needed to be heated to 130−135 °C for 48 h to achieve greater than 50% conversion (Table 1, entry 1). When the scale was increased to 300 g, the reaction mixture required 60 h of heating to achieve a similar level of conversion (Table 1, entry 2). The resulting mixture of

https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

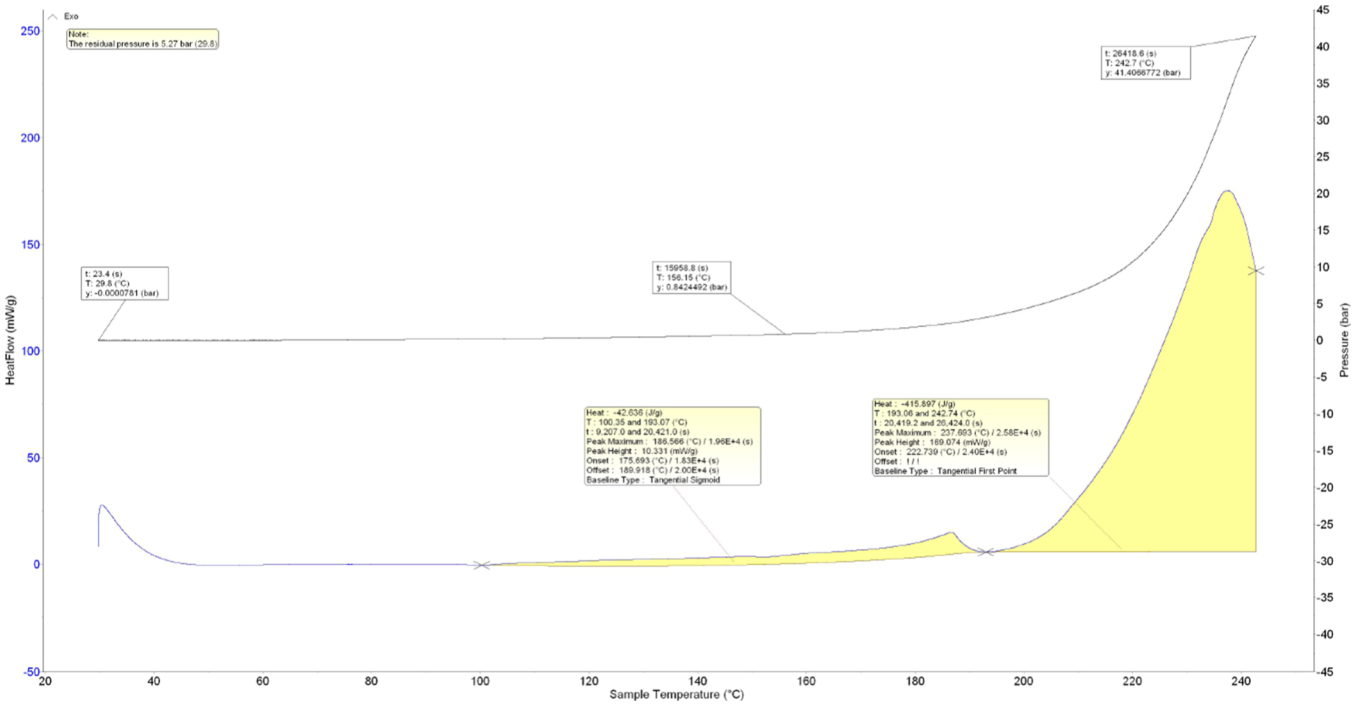


Figure 1. Scanning reaction calorimetry of the reaction of chlorothiazole **1b** with TMACl and CsF in DMSO. The safety data were collected on a 2.0 g scale reaction using 4 equiv of TMACl and 10 equiv of CsF in 20 vol of DMSO.

chlorothiazole **2a** and fluorothiazole **1a** could only be separated by supercritical fluid chromatography (SFC).[16] Moreover, a significant amount of decomposition was observed under the forcing reaction conditions, resulting in poor mass balance and low yield (Table 1, entries 1 and 2). These conditions provided access to hundreds of grams of the target fluorothiazole for preclinical development. However, the low conversion of the starting material, poor mass balance, and the need for SFC purification prompted us to investigate alternate S_NAr fluorination conditions.

We hypothesized that a soluble, anhydrous fluoride source would facilitate higher conversion under milder reaction conditions. To test this hypothesis, the chlorothiazoles **2a** and **2b** were reacted in the presence of commercially available TMAF (anh). The reaction did not proceed at room temperature (Table 1, entry 3). However, when the reaction mixture was heated to 100 °C, we were delighted to see good conversion of the starting material and high product area % in the high-performance liquid chromatography (HPLC) chromatogram (Table 1, entry 4). DMF was selected as a solvent as DMSO did not provide good conversion of the starting material (Table 1, entry 5). Interestingly, when TBAF (anh) was used as the fluoride source under the same reaction conditions, we did not see any conversion of the starting material (Table 1, entry 6). We propose that this is due to instability of TBAF (anh) at the elevated temperature required for thiazole S_NAr fluorination. This reagent can undergo competing Hofmann elimination with the very basic fluoride anion in its anhydrous form, leading to the formation of bifluoride (HF_2), which is significantly less nucleophilic than fluoride.[14]

Having established that TMAF (anh) could lead to full conversion of the starting material at the lab scale, we turned our attention to large-scale production. It became quickly evident that TMAF (anh) could not be procured in bulk.[14] To obtain large quantities of TMAF (anh), we began to investigate methods to prepare it in situ. Unfortunately, when TMAF (anh) was prepared in situ according to the procedure of Sanford, using tetramethylammonium phenoxide (TMAOPh) and benzoyl fluoride (BzF), we did not see any conversion of the starting material (Table 1, entry 7).[12b] We were initially excited to find moderate to good conversion of the starting material when tetramethylammonium chloride (TMACl) was used as a superstoichiometric phase-transfer reagent in the presence of CsF as the stoichiometric fluoride source in DMSO (Table 1, entry 8).[7b,14b] However, reaction calorimetry of these conditions indicated that the safety profile of this reaction was not desirable for scaleup (Figure 1). The reaction mixture was heated in a high-pressure Hastelloy cell from room temperature to 250 °C with a temperature increase of 0.5 °C/min. Two exothermic peaks were observed: the first peak (with an onset temperature of 100 °C) is likely to be the heat of the reaction of the desired reaction, and the second peak (onset temperature of 193 °C) indicates the thermal decomposition of the reaction mixture. Decomposition of DMSO is likely to be accelerated under these conditions due to the reaction with anhydrous fluoride with the solvent to produce the dimsyl anion and hydrogen fluoride (HF). Deprotonation of DMSO has previously been demonstrated to occur at 90 °C in the presence of TMAF (anh), leading to the formation of benzyne intermediates.[7a] It is well known that DMSO decomposes violently, and its decomposition is autocatalytic.[7c,d] The onset temperature of autocatalytic degradation of DMSO is lowered when in the presence of the dimsyl anion and in the presence of HF.[7c] The thermal stability of DMSO is also known to decrease over time in the presence of halides.[7c] Therefore, it was not recommended to hold this reaction mixture in DMSO at high temperature at a large scale.

In an attempt to improve the safety profile of the TMACl and CsF conditions, DMF was trialed as a solvent.

https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

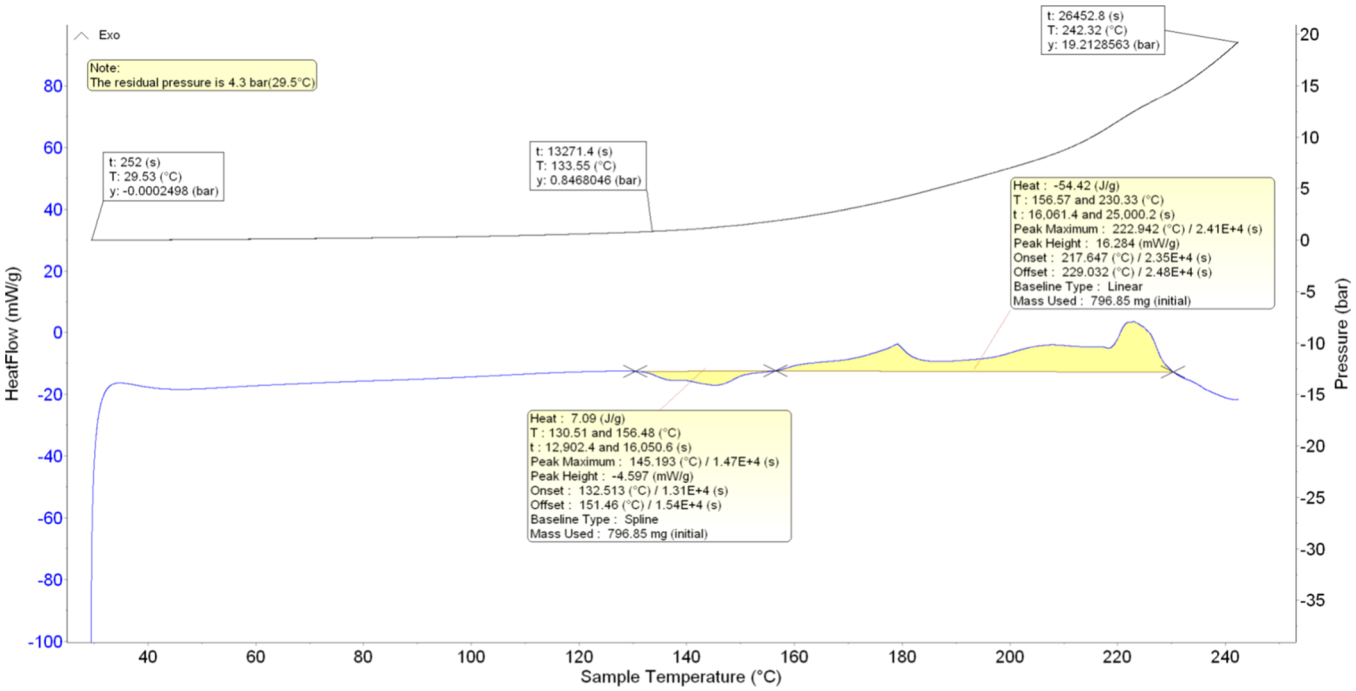
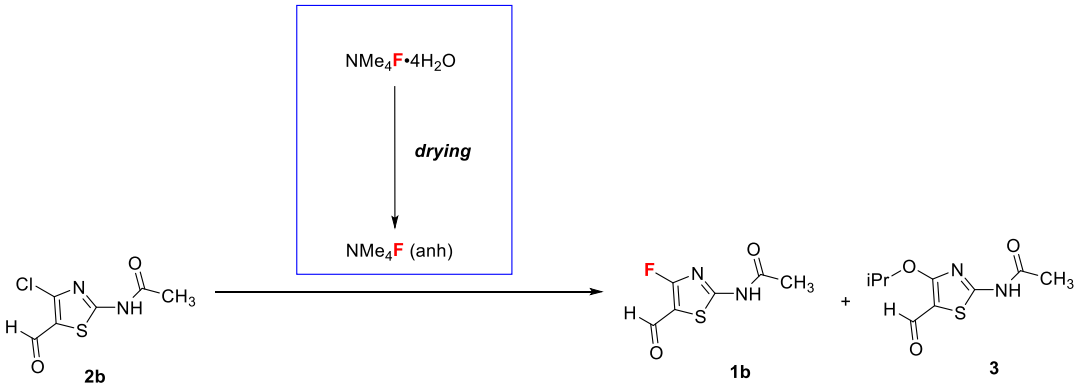


Figure 2. Scanning reaction calorimetry of the reaction of chlorothiazole **1b** with TMAF (anh) in DMF. The safety data were collected on a 1.3 g scale reaction using 6 equiv of TMAF in 24 vol of DMF.

Table 2. Methods for Drying TMAF·4H_2O



entry[a]	drying solvent	reaction solvent[b]	water content wt %[c] [molar equiv][d]	**2b** area %	**1b** area % (isolated yield)	**3** area %
1	none (TMAF·H_2O)	DMF	4.9% [7.0]	98	0	0
2	toluene	DMF	0.50% [0.7]	75	18	0
3	IPA	DMF	0.33% [0.5] (0.25% IPA)	2%	65%	17%
4	IPA[e]	NA	7.8% [11] (4.4% IPA)	NA[f]	NA[f]	0
5	IPA[g]	DMF	0.16% [0.2] (<60 ppm IPA)	0.9	79 (40%)	0

[a]All reactions were conducted on a 2 g scale using 6 equiv TMAF·4H_2O. [b]Reaction concentration after removal of the drying solvent is 24 mL/g DMF/TMAF. [c]Water content (wt %) remaining in the reaction mixture after removal of the drying solvent by distillation. [d]Molar equivalents relative to anhydrous TMAF. [e]TMAF was isolated by crystallization from THF after azeotropic drying with IPA. [f]Reaction was not completed due to the high water content and residual IPA. [g]Residual IPA was removed by distillation with DMF after azeotropic drying with IPA.

Unfortunately, this resulted in low conversion of the starting material (Table 1, entry 9), presumably due to the lower solubility of the CsF in DMF compared to DMSO (dielectric constant DMSO = 47.0, DMF = 38.3). Fortuitously, the safety profile of TMAF (anh) in DMF indicated that this reagent was suitable for large-scale production (Figure 2). As such, we focused our attention on drying commercially available TMAF·4H_2O to generate large amounts of TMAF (anh) for the production-scale S_NAr fluorination.

As expected, when TMAF·4H_2O was used "as is" without any drying procedure in place, there was no conversion of the starting material (Table 2, entry 1). Our initial attempt to drive off the water bound to the TMAF involved exploration of azeotropic distillation, followed by solvent swap to DMF to conduct the S_NAr fluorination. The use of toluene as an azeotropic solvent resulted in only 9 area % of the desired product **2a** (Table 2, entry 2). We suspect that the low yields were due to residual water that remained in the TMAF reaction solution after these drying methods were employed.

https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Karl Fischer (KF) analysis of the solution of TMAF in DMF that was obtained after solvent swap indicated that 0.50 wt % water was present in the DMF reaction solution when toluene was used as the azeotropic distillation solvent. To improve the yield of the product, a more efficient drying method needed to be implemented. A crystal structure of TMAF·4H_2O obtained by McLean and Jeffrey indicates that the water molecules are very tightly bound in the TMAF·4H_2O crystal lattice via H-bonding-type interactions with fluoride (Figure 3).[17] We

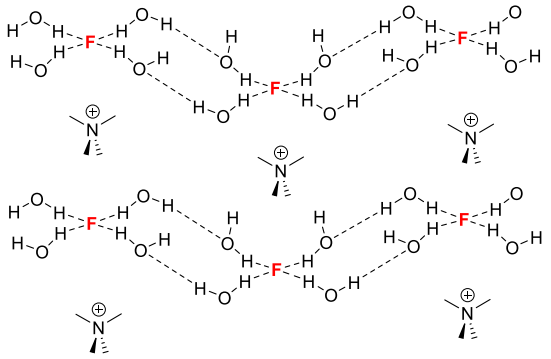


Figure 3. TMAF·4H_2O complex. Reproduced from ref 17, with permission from AIP publishing.

expect that these interactions would still be present in solution. To drive off the hydrate water molecules, we propose that they could be exchanged with an alcohol to produce an alcohol solvate of TMAF.[13,18] In 1990, Christe demonstrated that TMAF (anh) could be isolated as a crystalline solid from the TMAF isopropanol solvate by removal of the solvated alcoholate under dynamic vacuum at elevated temperature.[13] To avoid the need for isolation and drying, we propose that solvent exchange of the alcohol solution containing the TMAF·ROH with DMF would then allow removal of the alcohol to produce TMAF (anh).[19] To test this hypothesis, we turned to drying the TMAF·4H_2O with isopropanol (Table 2, entry 3). The resulting TMAF isopropanol complex was then solvent-exchanged to DMF to provide TMAF (anh). To our delight, this reagent allowed successful conversion of the chlorothiazole to provide the desired product (Table 2, entry 3). However, a major impurity had formed under these reaction conditions. This was identified as the isopropyl ether **3**. To control this impurity, the amount of residual IPA also needed to be controlled. Our initial attempt to control the IPA was by isolation of the dried TMAF·H_2O via crystallization from tetrahydrofuran (THF). Unfortunately, in our hands, the isolation of TMAF (anh) resulted in an increase in the water content in the DMF reaction solution to 7.8% (Table 2, entry 4). We suspect that this is due to the handling of the extremely hydroscopic solid. Gratifyingly, the IPA content could be controlled to <60 ppm by distillation with DMF (Table 2, entry 5). After distillation with DMF, the water content also remained very low (0.16%). This drying method provided 99.1% conversion of the starting material and 79 area % of the desired product when analyzed by HPLC. The fluorothiazole was isolated in 40.0% yield.

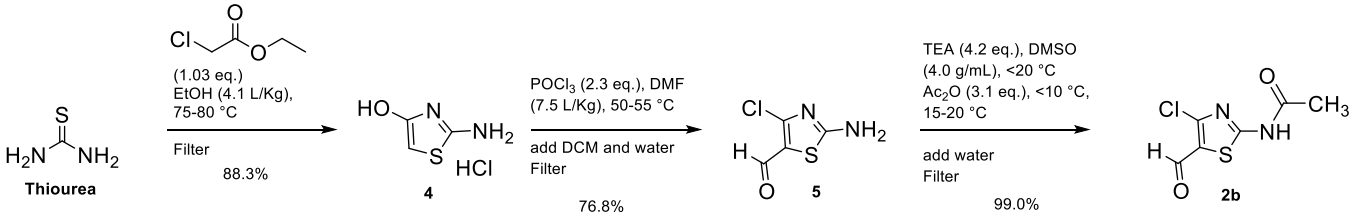
We were delighted that TMAF·4H_2O could be successfully dried on a lab scale. We next turned our attention to large-scale production. Chlorothiazole **2b** was selected for scaleup due to ease in the downstream chemistry. This substrate was prepared by cyclization of thiourea with ethyl chloroacetate to provide the amino thiazole **4** (Scheme 3). Vilsmeier haloformylation with $POCl_3$ and DMF then afforded chlorothiazole **5**, which was acylated with acetic anhydride to provide 139.2 kg of the target chlorothiazole **2b** in 97.3% purity and 98.1 wt % assay potency.

With chlorothiazole **2b** in hand, the S_NAr fluorination was completed with 45.1 kg of chlorothiazole. As such, 285.1 kg of TMAF·4H_2O was transferred to a 2000 L reactor and 1375 kg of IPA was added (Figure 4). The mixture was concentrated 6 times with IPA added back until the water content was measured to be <0.2 wt %. The water content was checked after the fourth distillation to be 0.5%, and after the sixth distillation, the water content was 0.12%. These results are in agreement with lab-scale experiments, which indicated that at least four IPA distillation/add-backs were required to achieve the desired water wt % (Chart 1). DMF was then added, and the mixture was concentrated until the IPA content was measured to be <60 ppm. This required multiple days under high vacuum (<−0.09 MPa). Chlorothiazole **2b** was then added to the TMAF (anh)/DMF solution, and the mixture was heated to 95−105 °C for 2 h to provide 36.8 kg of fluorothiazole in 70.4% purity (50.1 wt % purity) and 44% yield. Two major impurities were characterized as remaining chlorothiazole **2b** (3 area %) and dimethylamino thiazole **6** (3 area %). The formation of dimethylamine **6** was not observed in the lab-scale experiments. This suggested that DMF was decomposing to dimethylamine during the prolonged distillation time required at a larger scale. The purity of the fluorothiazole was successfully upgraded by conversion to the bisulfite adduct. The low mass balance is attributed to the formation of unknown decomposition products throughout the reaction progress. We suspect that the starting chloro-thiazole and the fluoro-thiazole undergo decomposition during the reaction.

CONCLUSIONS

In conclusion, we have developed a method for drying readily available TMAF·4H_2O for the large-scale fluorination of a challenging five-membered heteroaryl fluoride. TMAF·4H_2O was procured in bulk from Changzhou Huadong Chemical Research Institute. The reagent was rigorously dried by

Scheme 3. Synthesis of Chlorothiazole 2b



https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

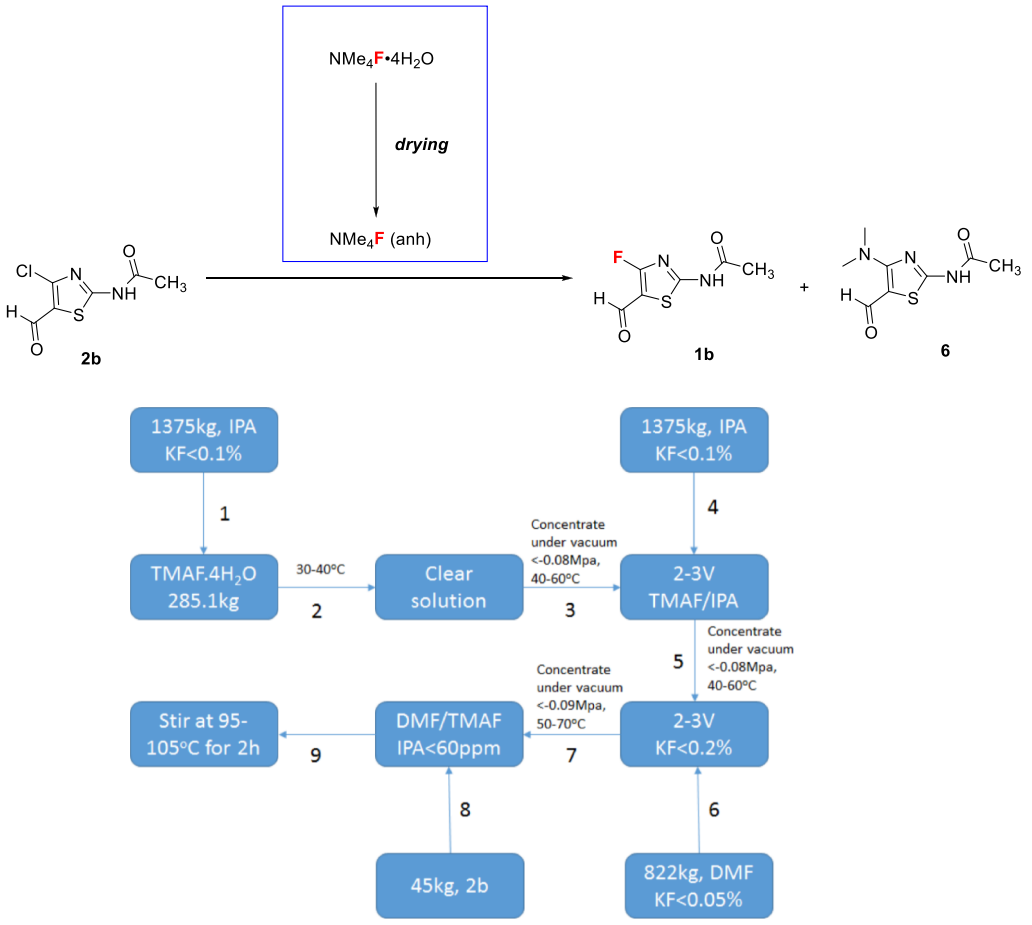
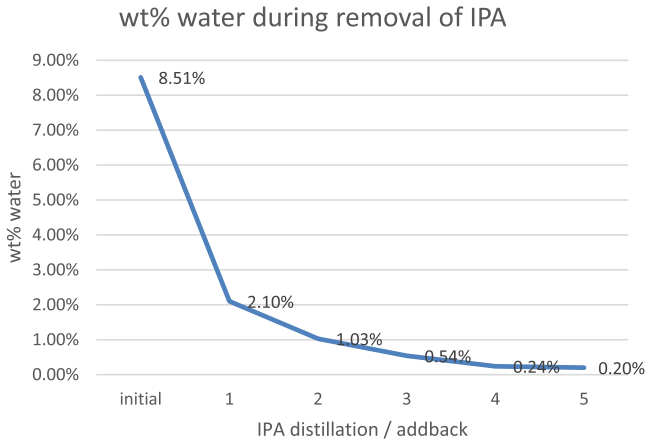


Figure 4. Reaction flow scheme for the production of fluorothiazole **1b**. Note: Repeat 4−5 until the KF of the mixture is below 0.2% and repeat 6−7 until the IPA content is below 60 ppm.

Chart 1. wt % of Water after Five IPA Distillations/Add-Back on a Lab Scale



distillation with IPA and then DMF at elevated temperature to provide TMAF (anh) containing <60 ppm water and <60 ppm isopropanol. The use of this reagent addressed the low conversion of the starting material and product decomposition that occurred when CsF was employed. The reaction conditions that included 6 equiv of dried TMAF·4H_2O in 24 vol of DMF were monitored by reaction calorimetry. These conditions were determined to be safe with no exothermic events or pressure buildup. The S_NAr fluorination using dried TMAF·4H_2O was carried out at a 45.1 kg scale at 95−100 °C to produce 36.8 kg of 4-fluorothiazole **1b**.

EXPERIMENTAL SECTION

General Experimental Section. Purchased starting materials and reagents were used without further purification. HPLC analysis (IPC and purity testing) were performed on a Shimadzu LC-20A instrument using a Waters XBridge C18 (75 mm × 4.6 mm, 3.5 μm) column. Liquid chromatography/mass spectrometry (LC/MS) analysis was performed on an Agilent HPLC 1200 with a 6120 Quadrupole LC/MS detector. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a Bruker Ultrashield 400, Avance II 400. Reaction calorimetry studies were performed using a Setaram C80 calorimeter with a Hastelloy high-pressure cell.

Step 1: Preparation of 2-Aminothiazol-4-ol Hydrochloride ***4.*** Thiourea (77.0 kg, 101 mol) and ethanol (250.4 kg, 4.12 L/kg) were charged into a 2000 L reactor, and the temperature was adjusted to 70−80 °C. Ethyl chloroacetate (127.5 kg, 104 mol, 1.03 equiv) was added dropwise below 80 °C, and the reaction mixture was stirred at 75−80 °C for 2−3 h. The reaction mixture was next cooled to 40−50 °C, and a sample was pulled for analysis to assure the reaction was complete. The temperature was adjusted to 5−10 °C, and the mixture was stirred for 1−2 h. The precipitate was collected by filtration, and the filter cake was washed with ethanol and dried under vacuum at 50−55 °C for 10−12 h to provide 137.5 kg of thiazole **4** as the hydrochloride salt in 88.3% yield (99.7%

https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

purity, 99.1 wt % potency). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 10.95 (s, 1H), 9.65 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 178.70, 177.60, 37.23. ESI-MS m/z: $C_3H_4N_2OS$ $[M + H]^+$, 117.0123; found, 117.0121.

Step 2: Preparation of 2-Amino-4-chlorothiazole-5-carbaldehyde ***5***. DMF (478.8 kg, 509 L, 7.5 L/kg), with a water content of 0.03 wt %, was charged into a 2000 L reactor. The solution was cooled to −5 to 2 °C, and $POCl_3$ (204.1 kg, 133 mol, 2.3 equiv) was added dropwise, maintaining the temperature below 5 °C. The reaction mixture was stirred at −5 to 2 °C for 0.5 h. Thiazole **4** (67.5 kg, 58 mol) was next added, maintaining the temperature below 20 °C. Once the addition was complete, the reaction mixture was heated to 50−55 °C and stirred at this temperature for 17−18 h. A sample was pulled for analysis to assure that the reaction was complete. Once the reaction was complete, the temperature was reduced to 25−30 °C and dichloromethane (DCM) (223.4 kg, 168 L, 2.5 L/kg) was added, followed by the addition of water (1822 kg, 27 L/kg). The temperature was adjusted to 0−5 °C, and the mixture was transferred to a 3000 L reactor, maintaining the temperature below 15 °C. The temperature was next adjusted to 30−35 °C, and the mixture was stirred for 16−18 h before cooling to 15−20 °C and centrifuging the mixture. The wet cake was dried under vacuum at 55−60 °C for 18−19 h to provide 60.45 kg of chlorothiazole **5** in 76.8% yield (93.0% purity, 92.6 wt % potency). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.64 (s, 1H), 8.74 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 179.90, 173.01, 147.32, 117.82. ESI-MS m/z: $C_4H_3ClN_2OS$ $[M + H]^+$, 162.9733; found, 162.9737.

Step 3: Preparation of the Compound N-(4-Chloro-5-formylthiazol-2-yl)acetamide ***2b***. Chlorothiazole **5** (109.21 kg, 67 mol) and DMSO (483 kg, 440 L, 4 L/kg) were charged into a 3000 L reactor at 12−15 °C. Tetraethylammonium (TEA) (281.4 kg, 278 mol, 4.15 equiv) was next added into the reactor, maintaining the temperature below 20 °C. Once the addition was complete, the temperature was adjusted to 5−10 °C. Acetic anhydride (209.6 kg, 205 mol, 3.06 equiv) was then added dropwise, maintaining the temperature below 10 °C, and the reaction mixture was stirred at 15−20 °C for 2−3 h. A sample was pulled for analysis to assure the reaction had reached completion. Once the reaction was complete, the reaction mixture was cooled to 0−5 °C. Water was added dropwise, maintaining the temperature below 40 °C. Once the addition was complete, the temperature was adjusted to 5−10 °C, and the reaction mixture was stirred at this temperature for 6−8 h. The precipitate was collected by filtration and washed with H_2O (596 kg, 8.9 L/kg). The wet cake was dried under vacuum at 60−65 °C for 20−24 h to provide 139.2 kg of chlorothiazole **2b** in 99% yield (98.0% purity, 98.1 wt % potency). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.00 (1H, COHs), 9.90 (1H, s, CONH), 2.22 (3H, s, CH); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 182.81, 170.76, 163.40, 144.90, 123.03, 23.18. ESI-MS m/z: $C_6H_5ClN_2O_2S$ $[M + H]^+$, 204.9839; found, 204.9845.

Step 4: Preparation of N-(4-Fluoro-5-formylthiazol-2-yl)pivalamide ***1b***. TMAF·4H_2O (285.1 kg, 172 mol, 7.8 equiv) and IPA (1375 kg, 1740 L, 6.1 L/kg relative to TMAF·4H_2O) were charged into a 3000 L reactor. The temperature was adjusted to 40 °C, and the mixture was stirred for approximately 20 min until all of the solid had dissolved. The mixture was then concentrated to a final concentration of 300−360 L, maintaining the temperature below 70 °C. IPA was added back into the reactor to provide a final concentration of 6.1 L/kg relative to TMAF·4H_2O. The temperature was adjusted to 40 °C, and the mixture was stirred for approximately 20 min until all of the solid had dissolved. The mixture was concentrated to a final concentration of 300−360 L, maintaining the temperature below 70 °C. This azeotropic distillation (IPA add back and concentration) procedure was repeated several times until KF analysis indicated that the water content was <0.20%. Once the desired water content was achieved, DMF (822 kg, 900 L, 3.15 L/kg relative to TMAF·4H_2O) was charged into the reaction mixture. The mixture was concentrated to a final concentration of 300−360 L, maintaining the temperature below 90 °C. This distillation (DMF addition and concentration) was repeated until the residual IPA was measured to be <60 ppm. Once the desired IPA content was achieved, the reaction temperature was adjusted to 25−30 °C. Chlorothiazole **2b** (45.1 kg, 22 mol) was charged into the reactor under nitrogen protection, followed by DMF (442.0 kg, 451 L, 10 L/kg). The reaction mixture was stirred at 25−30 °C for 30 min, and then, the temperature was increased to 95−105 °C. The reaction mixture was stirred at this temperature for 2−4 h before cooling to 45−50 °C. A sample was pulled for analysis to assure complete conversion. Once complete conversion had been achieved, the reaction mixture was adjusted to 20−30 °C. 2-MeTHF (738.0 kg, 868 L, 19 L/kg) was charged into the reactor, followed by charging of aqueous NH_4Cl (1362.0 kg, 19 L/kg). The reaction temperature was adjusted to 25−30 °C and stirred at this temperature for 30−40 min. The layers were separated, and the aqueous phase was extracted with 2-MeTHF (730 kg, 858 L, 19 L/kg). The organic phases were combined and washed twice with saturated NH_4Cl (914.0 kg × 2). The combined organic phase was concentrated to a final concentration of 1−2 L/kg, maintaining the temperature below 55 °C. DCM (248 kg) was added, maintaining the temperature below 55 °C, and then, *n*-heptane (282 kg, 414 L, 9.2 L/kg) was added. The crystallization temperature was adjusted to 20−25 °C, and the mixture was stirred at this temperature for 1−2 h. The precipitate was collected by filtration, and the filter cake was rinsed with *n*-heptane (26.0 kg, 38 L, 0.8 L/kg). The wet cake was dried under vacuum at 55−65 °C for 10−24 h to provide 36.8 kg of fluorothiazole **1b** in 44% yield (70.4% purity, 50.1 wt % potency). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.00 (1H, COHs), 9.87 (1H, s, CONH), 2.22 (3H, s, CH); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 180.80, 171.09, 164.18, 162.10, 106.47, 23.22; ^{19}F NMR (400 MHz, DMSO-d_6, ppm): δ 98.79. ESI-MS m/z: $C_6H_5FN_2O_2S$ $[M + H]^+$, 189.0140.

Preparation of Compound N-(4-Chloro-5-formylthiazol-2-yl)pivalamide ***2a***. Chlorothiazole **5** (21.3 g, 123 mmol) and DCM (200 mL, 9.4 vol) were charged into a three-neck round-bottom flask. TEA (19.7 mL, 144 mol, 1.2 equiv) and 4-dimethylaminopyridine (0.60 g, 4.9 mmol, 0.04 equiv) were added. Boc-anhydride (26.8 g, 122.8 mmol, 1.0 equiv) was then added, and the reaction temperature was adjusted to 15 °C. The reaction mixture was stirred for 16 h. After this time, a sample was pulled for analysis to assure that the reaction had reached completion. Once complete conversion was achieved, water was added. The layers were separated, and the organic layer was flushed through a silica gel plug. The organic layer was then concentrated to dryness, and the resulting solid was dried under vacuum at 40 °C for 42 h to provide fluorothiazole **2a** (14.42 g) was in 99% yield (99.4% purity). ^{1}H NMR (400

https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

MHz, $CDCl_3$, ppm): δ 9.97 (1H, s, CHO), 1.567 (9H, s, CO_2CCH_3); ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 181.8, 166.2, 151.8, 145.0, 123.8, 84.7, 28.7. ESI-MS m/z: $C_9H_{11}ClN_2O_3S$ $[M + 1]^+$, 263.02.

Preparation of N-(4-Fluoro-5-formylthiazol-2-yl)-pivalamide ***1a***. TMAF·$4H_2O$ (32.5 g, 200 mmol, 10.5 equiv) was charged into a three-neck round-bottom flask followed by IPA (200 mL, 6.1 mL/g relative to TMAF·$4H_2O$). The reaction mixture was concentrated and azeotropically distilled with IPA 10 times until the water content was measured to be <0.2% (by KF analysis). DMF (200 mL, 6.1 mL/g) was next added to the reaction mixture. The mixture was concentrated with DMF added back 10 times until the IPA concentration was measured to be <60 ppm. The TMAF/DMF solution was adjusted to provide a final concentration of 20 mL/g DMF relative to compound **2a** (100 mL). Compound **2a** (5.0 g, 19.0 mmol) was charged into the flask. The reaction mixture was heated to 100 °C for 2 h and then cooled to 25 °C. 2-MeTHF (100 mL, 20 mL/g) was added, followed by addition of saturated NH_4Cl (150 mL, 30 mL/g). The mixture was stirred for 17 h, and then, the layers were separated. The organic layer was concentrated to dryness, and the residue was purified via flash column chromatography (2:1 petroleum ether/EtOAc). Fractions containing the desired product were combined and concentrated to provide fluorothiazole **1a** (1.4 g) as a yellow solid in 30% isolated yield (96.2% purity). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.933 (1H, s, CHO), 1.567 (9H, s, CCH_3); ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 179.2, 164.9, 164.7, 164.1, 161.4, 151.7, 107.2, 107.1, 84.7. ESI-MS m/z: $C_9H_{11}FN_2O_3S$ $[M + 1]^+$, 247.05.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00042.

^1H, ^{13}C, and ^{19}F NMR spectra of compounds **4**, **5**, **2a**, **2b**, **1a**, and **1b** and the development of preparative SFC conditions (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Mai Khanh Hawk − *Small Molecule Design and Development (SMDD), Lilly Technology Center North, Eli Lilly and Company, Indianapolis, Indiana 46221, United States*; Email: hawk_mai_khanh_n@lilly.com

Sarah J. Ryan − *Small Molecule Design and Development (SMDD), Lilly Technology Center North, Eli Lilly and Company, Indianapolis, Indiana 46221, United States*; orcid.org/0000-0002-9633-5299; Email: Ryan_sarah_j@lilly.com

Authors

Xin Zhang − *STA Pharmaceutical (WuXi STA), WuXi AppTec., Shanghai 200131, People's Republic of China*

Ping Huang − *STA Pharmaceutical (WuXi STA), WuXi AppTec., Shanghai 200131, People's Republic of China*

Jing Chen − *STA Pharmaceutical (WuXi STA), WuXi AppTec., Shanghai 200131, People's Republic of China*

Chuanren Liu − *STA Pharmaceutical (WuXi STA), WuXi AppTec., Shanghai 200131, People's Republic of China*

Jianping Chen − *STA Pharmaceutical (WuXi STA), WuXi AppTec., Shanghai 200131, People's Republic of China*

Peter J. Lindsay-Scott − *Eli Lilly and Company Limited, Surrey GU20 6PH, U.K.*; orcid.org/0000-0002-4721-3594

John Burnett − *Eli Lilly and Company Limited, Surrey GU20 6PH, U.K.*

Craig White − *Eli Lilly and Company Limited, Surrey GU20 6PH, U.K.*

Yu Lu − *Small Molecule Design and Development (SMDD), Lilly Technology Center North, Eli Lilly and Company, Indianapolis, Indiana 46221, United States*; orcid.org/0000-0002-6411-9954

John R. Rizzo − *Small Molecule Design and Development (SMDD), Lilly Technology Center North, Eli Lilly and Company, Indianapolis, Indiana 46221, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.1c00042

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Kevin Cole for his help in reviewing this manuscript.

■ ABBREVIATIONS

API, active pharmaceutical ingredient; BzF, benzoyl fluoride; KF, Karl Fischer; MF, metal fluoride; NMR, nuclear magnetic resonance; SFC, supercritical fluid chromatography; S_NAR, nucleophilic aromatic substitution; TBACN, tetrabutylammonium cyanide; TBAF, tetrabutylammonium fluoride; TMACl, tetramethylammonium chloride; TMAF (anh), anhydrous tetramethylammonium fluoride; TMAF·$4H_2O$, tetramethylammonium fluoride tetrahydrate; TMAOPh, tetramethylammonium phenoxide

■ REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881−1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (c) Jeschke, P. The Unique Role of Halogen Substituents in the Design of Modern Agrochemicals. *Pest Manage. Sci.* **2010**, *66*, 10−27. (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359. (e) Wang, B.-C.; Wang, L.-J.; Jiang, B.; Wang, S.-Y.; Wu, N.; Li, X.-Q.; Shi, D.-Y. Application of Fluorine in Drug Design During 2010−2015 Years: A Mini Review. *Mini-Rev. Med. Chem.* **2017**, *17*, 683−692. (f) Kirk, K. L. Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments. *Org. Process Res. Dev.* **2008**, *12*, 305−321.

(2) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals to Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832−2842. (c) O'Hagan, D. Fluorine in Health Care:

Organofluorine Containing Blockbuster Drugs. *J. Fluorine Chem.* **2010**, *131*, 1071−1081.

(3) (a) Langolis, B.; Gilbert, L.; Forat, G. Fluorination of Aromatic Compounds by Halogen Exchange with Fluoride Anions ("Halex" Reaction). In *Industrial Chemistry Library*; Jean-Roger, D., Serge, R., Eds.; Elsevier: New York, 1996; pp 244−292. (b) Clark, J. H.; Wails, D.; Bastock, T. W. *Aromatic Fluorination*; CRC Press: Boca Raton, FL, 1996. (c) Adams, D. J.; Clark, J. H. Nucleophilic Routes to Selectively Fluorinated Aromatics. *Chem. Soc. Rev.* **1999**, *28*, 225−231. (d) Siegemund, G.; Schwertfeger, W.; Feiring, A.; Smart, B.; Behr, F.; Vogel, H.; McKusick, B.; Kirsch, P. Fluorine Compounds, Organic. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2016. (e) Furuya, T.; Klein, J. E.; Ritter, T. C−F Bond Formation for the Synthesis of Aryl Fluorides. *Synthesis* **2010**, 1804−1821.

(4) (a) Finger, G. C.; Kruse, C. W. Aromatic Fluorine Compounds. VII. Replacement of Aromatic −Cl and −NO2 Groups by −F1,2. *J. Am. Chem. Soc.* **1956**, *78*, 6034−6037. (b) Boechat, N.; Clark, J. H. Fluorodenitrations using Tetramethylammonium Fluoride. *J. Chem. Soc., Chem. Commun.* **1993**, 921−922. (c) Gottlieb, H. B. The Replacement of Chlorine by Fluorine in Organic Compounds. *J. Am. Chem. Soc.* **1936**, *58*, 532−533. (d) Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. Tetrabutylammonium Salt Induced Denitration of Nitropyridines: Synthesis of Fluoro-, Hydroxy-, and Methoxypyridines. *Org. Lett.* **2005**, *7*, 577−579.

(5) (a) Arimoto, S.; Kubota, M.; Kurahashi, M.; Ohira, D. Amide Compound and use Thereof. Japanese Patent JP 2011001353 A, Jan 6, 2011. (b) Uchibori, Y.; Umeno, M.; Yoshioka, H. Nucleophilic fluorination of chlorinated *N*-Heterocycles with Tetrabutylphosphonium Hydrogendifluoride and dihydrogentrifluoride. *Heterocycles* **1992**, *34*, 1507−1510. (c) Forster, H.; Beck, G.; Klauke, E.; Santel, H.-J.; Schmidt, R. R. Novel 4,5-di-substituted 1,3-thiazol-2-yloxyacetamide herbicides. U.S. Patent 4,929,743 A, May 29, 1990.

(6) Metzger, J. V. 4.19—Thiazoles and their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon, 1984; pp 235−331.

(7) (a) Grushin, V. V.; Marshall, W. J. Fluorination of Nonactivated Haloarenes via Arynes under Mild Conditions, Resulting from Further Studies toward Ar−F Reductive Elimination from Palladium(II). *Organometallics* **2008**, *27*, 4825−4828. (b) Allen, L. J.; Lee, S. H.; Cheng, Y.; Hanley, P. S.; Muhuhi, J. M.; Kane, E.; Powers, S. L.; Anderson, J. E.; Bell, B. M.; Roth, G. A.; Sanford, M. S.; Bland, D. C. Developing Efficient Nucleophilic Fluorination Methods and Application to Substituted Picolinate Esters. *Org. Process Res. Dev.* **2014**, *18*, 1045−1054. (c) Yang, Q.; Sheng, M.; Li, X.; Tucker, C.; Vásquez Céspedes, S.; Webb, N. J.; Whiteker, G. T.; Yu, J. Potential Explosion Hazards Associated with the Autocatalytic Thermal Decomposition of Dimethyl Sulfoxide and its Mixtures. *Org. Process Res. Dev.* **2020**, *24*, 916−939. (d) Deguchi, Y.; Kono, M.; Koizumi, Y.; Izato, Y.-i.; Miyake, A. Study on Autocatalytic Decomposition of Dimethyl Sulfoxide (DMSO). *Org. Process Res. Dev.* **2020**, *24*, 1614−1620.

(8) (a) Milner, P. J.; Yang, Y.; Buchwald, S. L. In-Depth Assessment of the Palladium-Catalyzed Fluorination of Five-Membered Heteraryl Bromides. *Organometallics* **2015**, *34*, 4775−4780. (b) *Fluorine in Heterocyclic Chemistry: 5-Membered Heterocycles and Macrocycles*; Nenajdenko, V., Ed.; Springer: New York, 2014; Vol. *1*. (c) Kirk, K. L. Fluorinated Five-Membered Nitrogen-Containing Heterocycles. In *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Petrov, V. A., Ed.; Wiley: Hoboken, NJ, 2009; pp 91−158. (d) Shermolovich, Y. Fluorinated Five-Membered Heterocycles Containing Oxygen, Sulfur, Selenium, and Phosphorus. In *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Petrov, V. A., Ed.; Wiley: Hoboken, NJ, 2009; pp 159−225.

(9) (a) Grineva, A. A.; Filippov, O. A.; Nefedov, S. E.; Lugan, N.; César, V.; Valyaev, D. A. Direct Access to IMesF and IMesF2 by Electrophilic Fluorination of Abnormal *N*-Heterocyclic Carbenes. *Organometallics* **2019**, *38*, 2330−2337. (b) Lu, S.; Tian, L.-L.; Cui, T.-W.; Zhu, Y.-S.; Zhu, X.; Hao, X.-Q.; Song, M.-P. Copper Mediated C-H Amination of Imidazopyridines with *N*-Fluorobenzenesulfonimide. *J. Org. Chem.* **2018**, *83*, 13991−14000. (c) Albertshofer, K.; Mani, N. S. Regioselective Electrophilic Fluorination of Rationally Designed Imidazole Dericatives. *J. Org. Chem.* **2016**, *81*, 1269−1276. (d) Hatfield, J. M.; Eidell, C. K.; Stephens, C. E. Mono-and Trifluorination of the Thiazole Ring of 2,5-diarylthiazoles using *N*-Fluorobenzenesulfonimide (NFSI). *Tetrahedron Lett.* **2013**, *54*, 1025−1028. (e) Yamada, S.; Gavryushin, A.; Knochel, P. Convenient Electrophilic Fluorination of Functionalized Aryl and Heteroaryl Magnesium Reagents. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215−2218.

(10) (a) Allen, L. J.; Muhuhi, J. M.; Bland, D. C.; Merzel, R.; Sanford, M. S. Mild Fluorination of Chloropyridines with in Situ Generated Anhydrous Tetrabutylammonium Fluoride. *J. Org. Chem.* **2014**, *79*, 5827−5833. (b) Ryan, S. J.; Schimler, S. D.; Bland, D. C.; Sanford, M. S. Acyl Azolium Fluorides for Room Temperature Nucleophilic Aromatic Fluorination of Chloro- and Nitroarenes. *Org. Lett.* **2015**, *17*, 1866−1869.

(11) (a) Sun, H.; DiMagno, S. G. Anhydrous Tetrabutylammonium Fluoride. *J. Am. Chem. Soc.* **2005**, *127*, 2050−2051. (b) Sun, H.; DiMagno, S. G. Room-Temperature Nucleophilic Aromatic Fluorination: Experimental and Theoretical Studies. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720−2725. (c) Sun, H.; DiMagno, S. G. Fluoride Relay: A New Concept for the Rapid Preparation of Anhydrous Nucleophilic Fluoride Salts From KF. *Chem. Commun.* **2007**, 528−529.

(12) (a) Schimler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S. Anhydrous Tetramethylammonium Fluoride for Room-Temperature SNAr Fluorination. *J. Org. Chem.* **2015**, *80*, 12137−12145. (b) Cismesia, M. A.; Ryan, S. J.; Bland, D. C.; Sanford, M. S. Multiple Approaches to the In Situ Generation of Anhydrous Tetraalkylammonium Fluoride Salts for SNAr Fluorination Reactions. *J. Org. Chem.* **2017**, *82*, 5020−5026.

(13) (a) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. A. Synthesis, Preparation, and Structures and Anhydrous Tetramethylammonium Fluorinde and its 1:1 Adduct with Trans-3-amino-2-butenenitrile. *J. Am. Chem. Soc.* **1990**, *112*, 7619−7625.

(14) (a) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. "Anhydrous" Tetrabutylammonium Fluoride: A Mild but Highly Efficient Source of Nucleophilic Fluoride Ion. *J. Org. Chem.* **1984**, *49*, 3216−3219. (b) Elias, S.; Karton-Lifshin, N.; Yehezkel, L.; Ashkenazi, N.; Columbus, I.; Zafrani, Y. Synthesis, Characterization, and Reactivity of Thermally Stable Anhydrous Quaternary Ammonium Fluorides. *Org. Lett.* **2017**, *19*, 3039−3042. Hong, C. M.; Xu, Y.; Chung, J. Y. L.; Schultz, D. M.; Weisel, M.; Varsolona, R. J.; Zhong, Y.-L.; Purohit, A. K.; He, C. Q.; Gauthier, D. R.; Humphrey, G. R.; Maloney, K. M.; Lévesque, F.; Wang, Z.; Whittaker, A. M.; Sirota, E.; McMullen, J. P. Development of a Commercial Manufacturing Route to 2-Fluoroadinine, The Key Unnatural Nucleobase of Islatravir. *Org. Process Res. Dev.* **2021**, *25*, 395−404.

(15) The largest bulk source of TMAF (anh) was 15 kg with a cost of $15,000/kg. In comparison, the bulk cost of TMAF·4H_2O is $70/kg to provide a total amount of 800 kg of material.

(16) See Supporting Information for SFC purification development and conditions.

(17) McLean, W. J.; Jeffrey, G. A. Crystal Structure of Tetramethylammonium Fluoride Tetrahydrate. *J. Chem. Phys.* **1967**, *47*, 414−417.

(18) For TBAF alcohol complexes and their reactivity see; Engle, K. M.; Pfeifer, L.; Pidgeon, G. W.; Giuffredi, G. T.; Thompson, A. L.; Paton, R. S.; Brown, J. M.; Gouverneur, V. Coordination diversity in hydrogen-bonded homoleptic fluoride-alcohol complexes modulates reactivity. *Chem. Sci.* **2015**, *6*, 5293−5302.

(19) For drying of TMAF alcohol complexes in alcohol solvent see; Bland, D. C.; Yang, C. Method for Preparing Tetramethylammonium Fluoride. U.S. Patent 20,180,050,980 A1, Feb 22, 2018.

https://doi.org/10.1021/acs.oprd.1c00042
Org. Process Res. Dev. XXXX, XXX, XXX−XXX