

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

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ABSTRACT: This article describes the use of tetramethylammonium fluoride tetrahydrate (TMAF·4H₂O) for the large-scale preparation of a challenging 4-fluorothiazole. Commercially available TMAF·4H₂O 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·4H₂O 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 pharmaceutical 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.

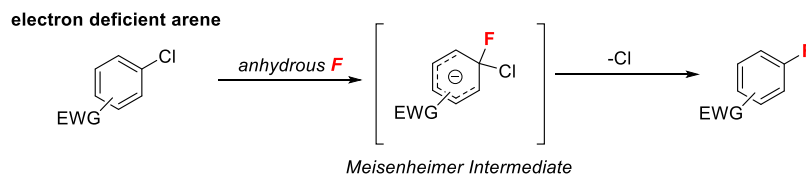
S_NAr fluorination is particularly challenging when used to prepare five-membered azoles with fluorine at the 4 or 5 position.⁵ The high π -electron density at these positions further exacerbates the requirement for forcing reaction conditions,⁶ which can limit functional group tolerance and lead to 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 DiMaggio

demonstrated that anhydrous tetrabutylammonium fluoride [TBAF (anh)] could be prepared in situ from tetrabutylammonium cyanide (TBACN) and hexafluorobenzene (C₆F₆) (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 (C₆F₆) 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.

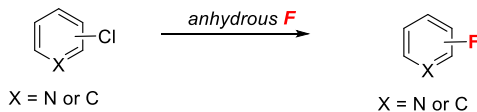
We realized that TMAF (anh) would be an attractive reagent to use for the large-scale production of a 4-fluorothiazole. However, even though TMAF (anh) is readily available in gram quantities, it does not have good bulk commercial availability, limiting its feasibility for use at a large scale.¹⁵ To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

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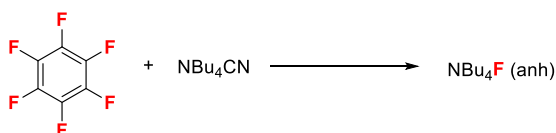
Scheme 1. S_NAr Fluorination MechanismScheme 2. Methods for S_NAr Fluorination Using Soluble, Anhydrous Nucleophilic Fluorination

Previous Work

electron-deficient arene



A) DiMaggio TBAF (anh)

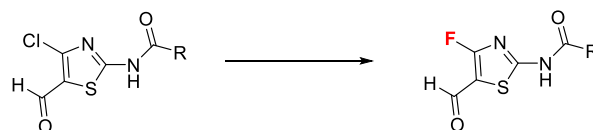
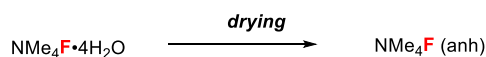
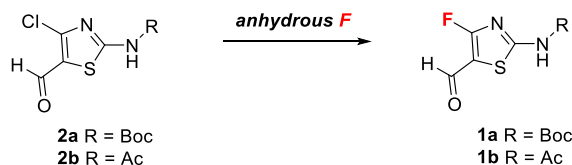


B) Sanford TMAF (anh)

NMe₄F (anh)

This work

5-membered heteroarene

C) TMAF·4H₂OTable 1. S_NAr Fluorination of Chlorothiazole 2a and 2b

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

^aUnless otherwise stated, reactions were completed on 50 mg of chlorothiazole 2a or 2b. ^bYield adjusted based on the amount of fluorothiazole 1a in the crude mixture of 1a and 2a. ^cIsolated yield after flash column chromatography. ^dTBAF (anh) was prepared in situ by the reaction of TBACN and C₆F₆.

4H₂O) for the production of a challenging five-membered heteroaryl fluoride (Scheme 2C). The readily available TMAF·4H₂O 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·4H₂O 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

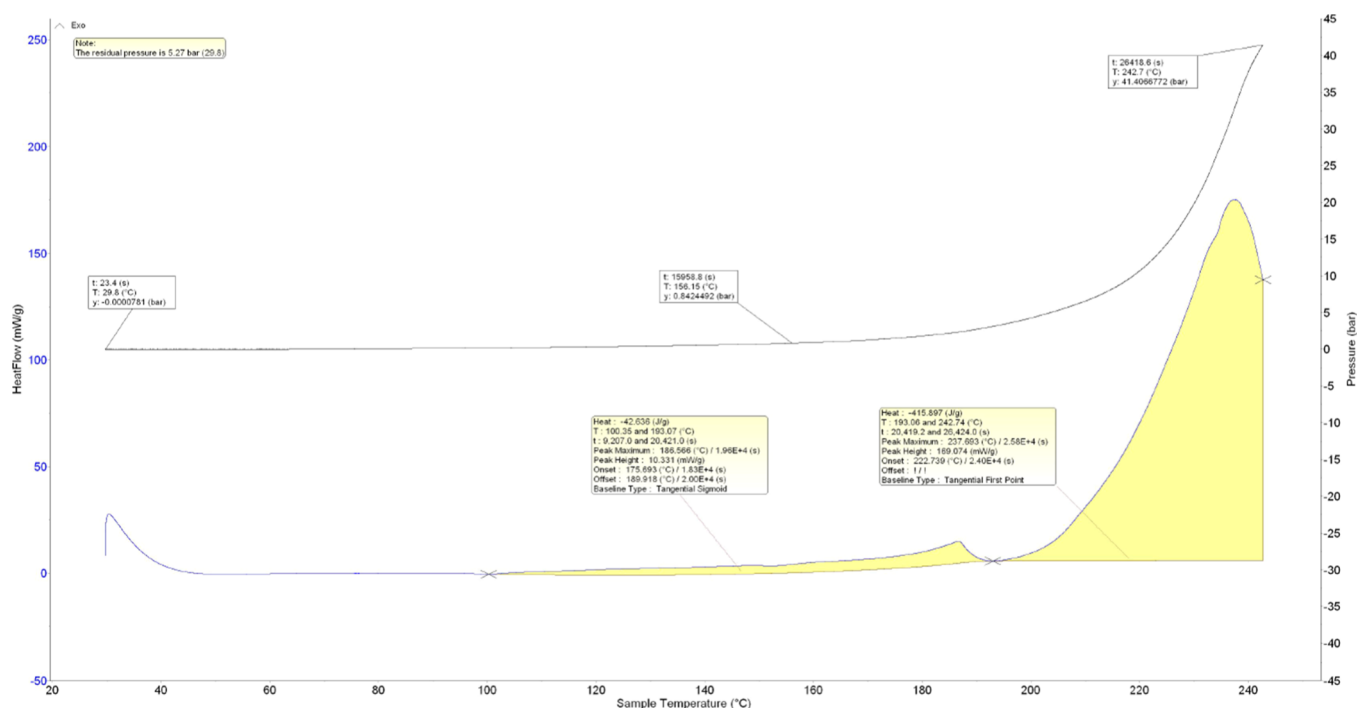


Figure 1. Scanning reaction calorimetry of the reaction of chlorothiazole **1b** with TMACl and CsF in DMSO. The safety data were collected on a 2.0 g scale reaction using 4 equiv of TMACl and 10 equiv of CsF in 20 vol of DMSO.

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.

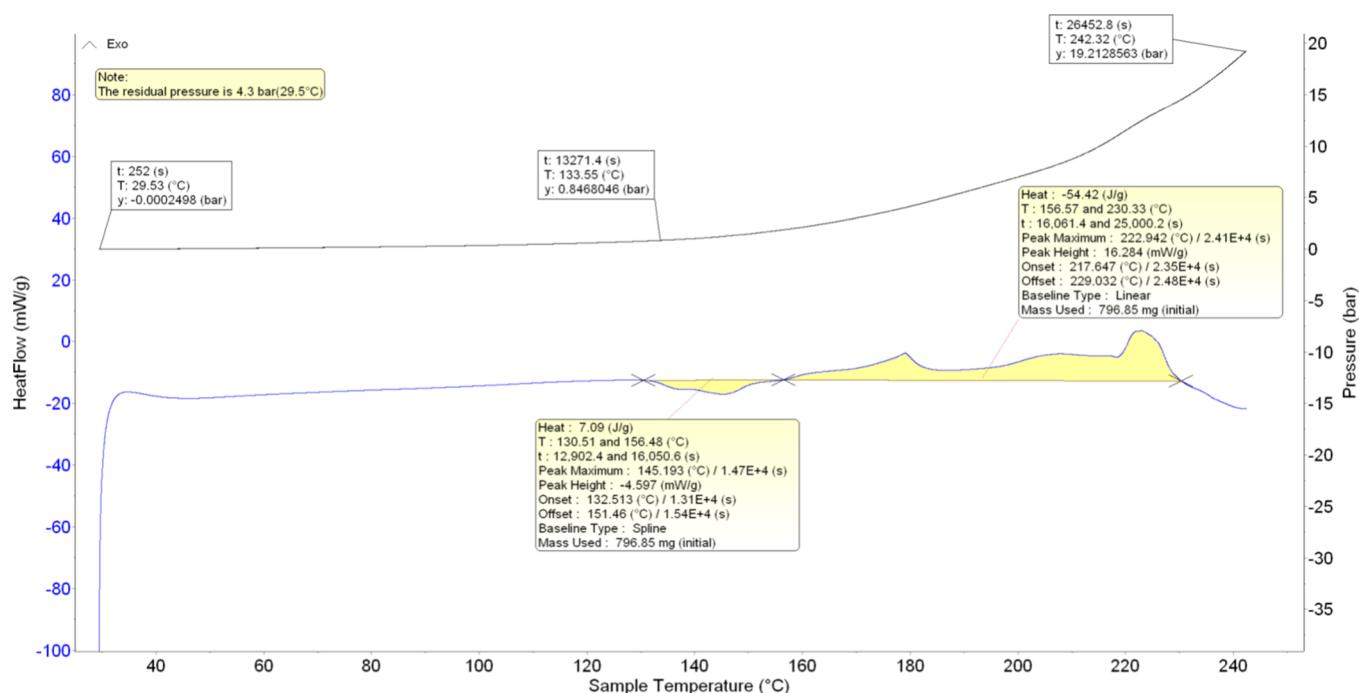


Figure 2. Scanning reaction calorimetry of the reaction of chlorothiazole **1b** with TMAF (anh) in DMF. The safety data were collected on a 1.3 g scale reaction using 6 equiv of TMAF in 24 vol of DMF.

Table 2. Methods for Drying TMAF·4H₂O

The reaction scheme illustrates the synthesis of compounds **1b** and **3** from compound **2b**. The starting material **2b** is 4-chloro-5-(acetamido)-1,3,4-thiadiazole-2-carbaldehyde. It reacts with anhydrous tetrabutylammonium fluoride ($\text{NMe}_4\text{F (anh)}$), which is prepared from $\text{NMe}_4\text{F} \cdot 4\text{H}_2\text{O}$ by drying. The reaction yields two products: **1b** (4-fluoro-5-(acetamido)-1,3,4-thiadiazole-2-carbaldehyde) and **3** (4-(isopropoxy)-5-(acetamido)-1,3,4-thiadiazole-2-carbaldehyde).

entry ^a	drying solvent	reaction solvent ^b	water content wt % ^c [molar equiv] ^d	2b area %	1b area % (isolated yield)	3 area %
1	none ($\text{TMAF} \cdot \text{H}_2\text{O}$)	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

^aAll reactions were conducted on a 2 g scale using 6 equiv TMAF·4H₂O. ^bReaction concentration after removal of the drying solvent is 24 mL/g DMF/TMAF. ^cWater content (wt %) remaining in the reaction mixture after removal of the drying solvent by distillation. ^dMolar equivalents relative to anhydrous TMAF. ^eTMAF was isolated by crystallization from THF after azeotropic drying with IPA. ^fReaction was not completed due to the high water content and residual IPA. ^gResidual 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). Fortunately, 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·4H₂O to generate large amounts of TMAF (anh) for the production-scale S_NAr fluorination.

As expected, when TMAF·4H₂O 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.

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·4H₂O obtained by McLean and Jeffrey indicates that the water molecules are very tightly bound in the TMAF·4H₂O crystal lattice via H-bonding-type interactions with fluoride (Figure 3).¹⁷ We

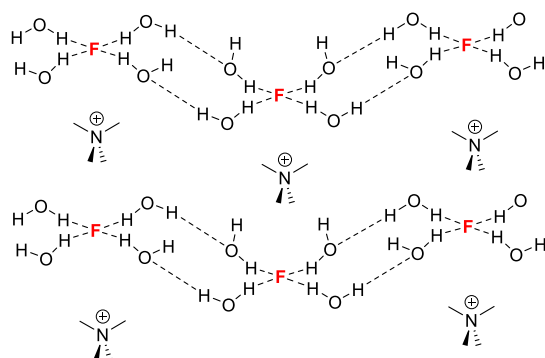


Figure 3. TMAF·4H₂O complex. Reproduced from ref 17, with permission from AIP publishing.

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, Christie 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·4H₂O 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·H₂O 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 hygroscopic 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.

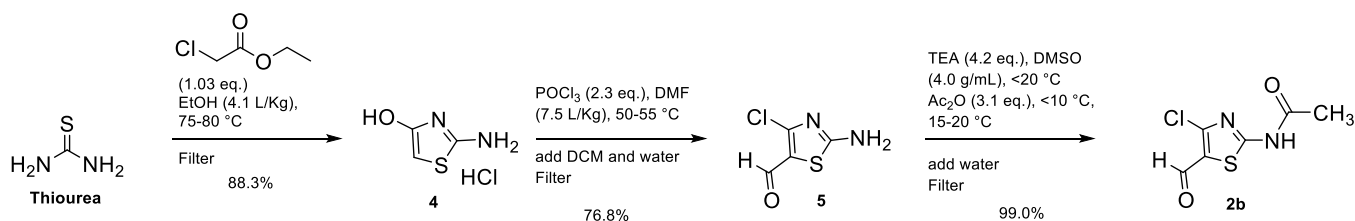
We were delighted that TMAF·4H₂O could be successfully dried on a lab scale. We next turned our attention to large-scale production. Chlorothiazole 2b was selected for scaleup due to ease in the downstream chemistry. This substrate was prepared by cyclization of thiourea with ethyl chloroacetate to provide the amino thiazole 4 (Scheme 3). Vilsmeier haloformylation with POCl₃ 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·4H₂O 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·4H₂O for the large-scale fluorination of a challenging five-membered heteroaryl fluoride. TMAF·4H₂O was procured in bulk from Changzhou Huadong Chemical Research Institute. The reagent was rigorously dried by

Scheme 3. Synthesis of Chlorothiazole 2b



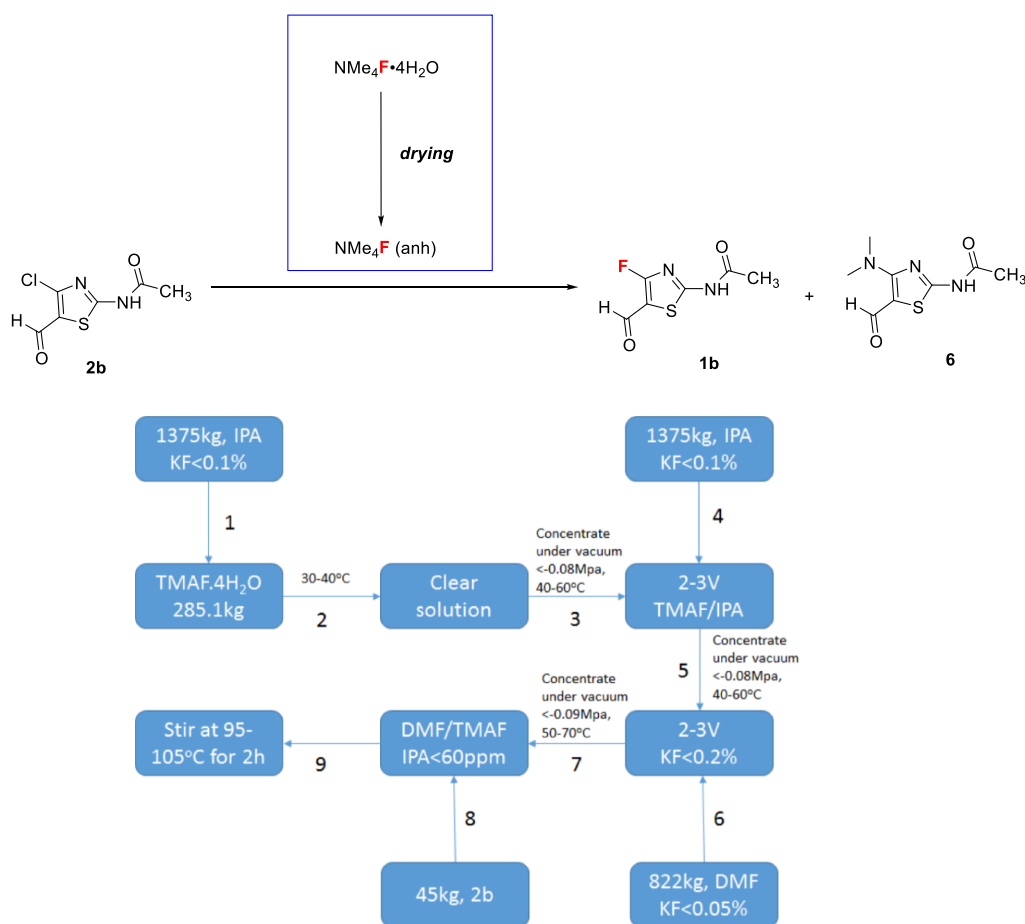
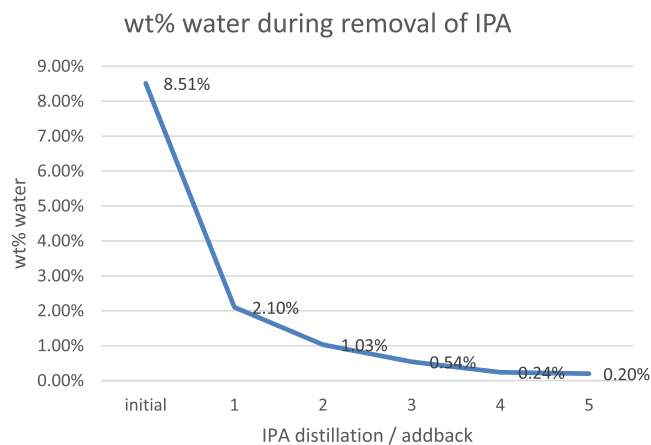


Figure 4. Reaction flow scheme for the production of fluorothiazole **1b**. Note: Repeat 4–5 until the KF of the mixture is below 0.2% and repeat 6–7 until the IPA content is below 60 ppm.

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 $\text{TMAF} \cdot 4\text{H}_2\text{O}$ 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 $\text{S}_{\text{N}}\text{Ar}$ fluorination using dried

$\text{TMAF} \cdot 4\text{H}_2\text{O}$ 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. ^1H 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%

purity, 99.1 wt % potency). ^1H 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 : $\text{C}_3\text{H}_4\text{N}_2\text{OS}$ $[\text{M} + \text{H}]^+$, 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). ^1H 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 : $\text{C}_4\text{H}_3\text{ClN}_2\text{OS}$ $[\text{M} + \text{H}]^+$, 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). ^1H 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 : $\text{C}_6\text{H}_5\text{ClN}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$, 204.9839; found, 204.9845.

Step 4: Preparation of N-(4-Fluoro-5-formylthiazol-2-yl)pivalamide 1b. TMAF· $4\text{H}_2\text{O}$ (285.1 kg, 172 mol, 7.8 equiv) and IPA (1375 kg, 1740 L, 6.1 L/kg relative to TMAF· $4\text{H}_2\text{O}$) 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· $4\text{H}_2\text{O}$. 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· $4\text{H}_2\text{O}$) 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 $\times$ 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). ^1H 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 : $\text{C}_6\text{H}_5\text{FN}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$, 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). ^1H NMR (400

MHz, CDCl₃, ppm): δ 9.97 (1H, s, CHO), 1.567 (9H, s, CO₂CCH₃); ¹³C NMR (400 MHz, CDCl₃, ppm): δ 181.8, 166.2, 151.8, 145.0, 123.8, 84.7, 28.7. ESI-MS *m/z*: C₉H₁₁ClN₂O₃S [M + 1]⁺, 263.02.

Preparation of N-(4-Fluoro-5-formylthiazol-2-yl)-pivalamide 1a. TMAF·4H₂O (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·4H₂O). 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 NH₄Cl (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, CDCl₃, ppm): δ 9.933 (1H, s, CHO), 1.567 (9H, s, CCH₃); ¹³C NMR (400 MHz, CDCl₃, ppm): δ 179.2, 164.9, 164.7, 164.1, 161.4, 151.7, 107.2, 107.1, 84.7. ESI-MS *m/z*: C₉H₁₁FN₂O₃S [M + 1]⁺, 247.05.

■ ASSOCIATED CONTENT

SI Supporting Information

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

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

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■ Notes

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■ 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·4H₂O, tetramethylammonium fluoride tetrahydrate; TMAOPh, tetramethylammonium phenoxide

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