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Technical Notes

Practical Synthesis of 2-Amino-5-fluorothiazole Hydrochloride

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Abstract:

The first synthesis of 2-amino-5-fluorothiazole hydrochloride is reported from 2-aminothiazole. The synthesis proceeds in 35% overall yield, involves no chromatographic purification, and has been employed to prepare multikilogram quantities of the title compound. The key fluorine-introducing step comprises the reaction of dilithiated 2-*tert*-butoxycarbonylaminothiazole with *N*-fluorobenzenesulfonimide.

Recently, we discovered a range of novel glucokinase activators, bearing a 2-aminothiazole moiety, that are potential medicaments for Type 2 Diabetes.[1] It proved necessary to site a fluorine atom[2] on the 5-position of the thiazole ring system in these compounds to restrict oxidative ring-opening metabolism,[3] a phenomenon that could lead to toxicity in vivo. Thus, we required a practical preparation of amides of 2-amino-5-fluorothiazole (**3**, Table 1). Surprisingly, little information is available on this "simple" organic molecule in the chemical literature. In the late 1970s, **3** was described[4] in the patent literature as a building block for a number of herbicides. Nonetheless, the compound's synthesis was not outlined, nor were any characterization data reported. More recently, it was stated[5] that the trifluoroacetate salt of **3** had been prepared by deprotection of 2-*tert*-butoxycarbonylamino-5-fluorothiazole (**2c**) with TFA. However, details of the characterization of **3**·TFA, as well as the synthetic procedure employed to prepare **2c**, were not furnished. Previously,[1] we synthesized the hydrochloride salt of **3** from the trifluoroacetamide **2a**. This amide was made by quenching the dilithio species, formed by treating 5-bromo-2-trifluoroacetamidothiazole (**1a**) with 2.2 equiv of *n*-BuLi, with *N*-fluorobenzenesulfonimide (NFSi),[6] as delineated by Route **a** in Table 1. By employing this approach, 10.9 g of **3**·HCl was isolated from 50.0 g of bromide **1a**. However, this route required a difficult chromatographic separation following the fluorination step and was unreliable, especially when carried out on a larger scale. Here, we report a substantially improved route for the synthesis of **3**·HCl that does not rely on column chromatography and allows its preparation on a multikilogram scale.

Initial attempts to prepare **3**, or a suitable precursor, via a number of routes either failed or had limited success. These routes included the Balz−Schiemann fluorodediazoniation[7] of 2-acetamido-5-aminothiazole[8] and the direct formation of the 2-amino-5-fluorothiazole ring system[9] via the condensation of chlorofluoroacetaldehyde hydrate[10] with thiourea by a process analogous to that employed previously for the synthesis of 2-amino-5-chlorothiazole.[11] Nucleophilic aromatic substitution reactions of fluoride[12] with 2-amino-[13] or 2-acetamidothiazoles[14] bearing a leaving group at the 5-position were also not useful.

A partially successful route involved the fluorination of 2-acetamidothiazole (**1b**) by 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [F-TEDA, Selectfluor][15] followed by amide hydrolysis (Route **b**, Table 1). On a small scale (1.5 mmol **1b**), the key fluorination step worked in moderate yield (48%). However, on a larger scale (35.2 mmol **1b**), the isolated yield was much lower (7%) and the maximum conversion of 2-acetamidothiazole that could be obtained was only 60%, as ascertained by both

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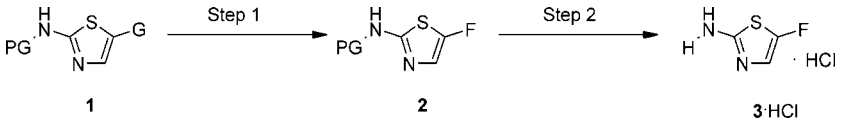
Table 1. **Routes to the synthesis of 3·HCl**

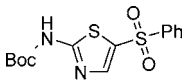


1 2 3·HCl

starting material	PG/G	step 1 product/conditions [yield (%)]	step 2 conditions [yield (%)]
1a	CF_3CO/Br	**2a**/(i) *n*-BuLi, THF, −78 °C; (ii) NFSi [40%]	AcCl, MeOH, reflux [96%]
1b	Ac/H	**2b**/F-TEDA, MeCN, reflux [48%]	HCl, H_2O, 70−75 °C [quant]
1c	Boc/H	**2c**/(i) *t*-BuLi, THF, −50 °C; (ii) NFSi [36%]	HCl, dioxane [96%]

HPLC analysis and ^{19}F NMR. Changing the order of addition, the reaction time, the concentration, or the rate of addition of F-TEDA did not increase the degree of conversion, as ^{19}F NMR analysis indicated that unreacted fluorinating agent was still present. Additives such as TfOH[16] or Lewis acids[17] gave no improvement, and complete conversion of starting material was observed only when the reaction was carried out at 150 °C in an autoclave. However, in this instance, the isolated yield of product **2b** following column chromatography was only 15%. As a result of this route's reliance on column chromatography and the low isolated yields obtained on scale-up,[18] an alternative method was sought.

Our attentions refocused on the fluorination of an organolithium[19] reagent with NFSi since, along with F-TEDA, this compound is one of the few electrophilic fluorinating agents commercially available in bulk.[20] It was suspected that the utility of Route **a** (Table 1) had been compromised by the instability of the trifluoroacetyl protecting group in the presence of *n*-BuLi. Consequently, the amino protecting group was changed to Boc to provide a moiety much more stable under the strongly basic reaction conditions. Indeed, deprotonation of 2-*tert*-butoxycarbonylaminothiazole[21] (**1c**) with 2.2 equiv of *t*-BuLi gave a dianion that was stable for several hours at −50 to 0 °C, as only starting material was isolated following a MeOH quench. Reaction of the dianion with NFSi furnished a mixture of the desired fluorinated thiazole **2c** (70%), the sulfone **4** (15%),[22] and the starting material **1c** (10%).[23] Use of additives, such as TMEDA, DMPU, or HMPA, had a negative influence on the reaction, either lowering the conversion rate or increasing the amount of **4** generated. The ratio of the three products was unaltered by changing the order of addition of the reactants, the reaction time, or the reaction temperature.[24] Three consecutive recrystallizations employing CF_3CH_2OH−HCO_2H (100:1) were required to remove the impurities **4** and **1c** from the product mixture. In this fashion, **2c** could be obtained in 35−40% yield (>98% purity containing <1% **1c**). The Boc-protected compound **2c** was smoothly deprotected in HCl-saturated dioxane to furnish **3**·HCl. The synthesis exemplified by Route **c** of Table 1 provides the title compound in 35% overall yield, without any chromatographic purification, and has been used to prepare multikilogram quantities of **3**·HCl.



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In summary, we have developed the first practical, large-scale synthesis of **3**·HCl, the hydrochloride salt of an important heteroaromatic amine component of novel glucokinase activators.[1] The difficulties encountered in making this seemingly simple, fluorinated, heteroaromatic amine highlight the importance of developing new, reliable methods for the chemo- and regioselective preparation of fluorine-substituted organic molecules.[25]

Experimental Section

2-*Tert*-butoxycarbonylamino-5-fluorothiazole (2c). A stirred solution of **1c** (0.75 kg, 3.75 mol) in anhydrous THF (15 L) at −50 °C was treated with *t*-BuLi[26] (2.87 kg of an 18% solution in *n*-C_5H_{12}, 8.06 mol) over 60 min, the temperature being kept below −40 °C. The bright yellow suspension thus obtained was stirred for 30 min at −50 °C before being treated with a solution of NFSi (1.24 kg, 3.93 mol) in anhydrous THF (3.75 L) over 60 min, the temper-

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(23) It is believed that the proton source for the formation of **1c** is NFSi itself, as quenching of the dianion with DMF gave a quantitative yield of the appropriate aldehyde.
(24) The difluorinated compound 2-*tert*-butoxycarbonylamino-4,5-difluorothiazole (**5**) was produced in 5−10% yield (determined by HPLC at 275 nm) when a larger quantity of *t*-BuLi (2.4 equiv) was employed.
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(26) This organometallic reagent was purchased on a multikilogram scale from Chemetall GmbH (Frankfurt a. M., Germany). CAUTION: *t*-BuLi is extremely pyrophoric and should be handled on a large scale only by experienced personnel. Solutions of *t*-BuLi react vigorously and often violently with oxygen, water, and other protic solvents. As a result, the reaction must be conducted with extreme care under a dry, oxygen free, inert atmosphere. Appropriate protective clothing should be worn, and a suitable safety shield should be employed. In case of fire, a dry-powder extinguisher should be used. For further information on the handling of *t*-BuLi solutions in large quantities, see: Bailey, W. F.; Longstaff, S. C. FMC Lithium Link, Fall 2000, *tert*-Butyllithium in Organic Synthesis (available via the Internet at http://www.fmclithium.com).

ature being maintained under −40 °C. After a further 30 min at −50 °C, the reaction was transferred cold to a vessel containing NH_4Cl (0.60 kg) and H_2O (6 L). The mixture was stirred for 15 min at ambient temperature, before being extracted with Et_2O (21 L + 9 L). The combined organic extracts were washed with brine (12 L) and dried (Na_2SO_4), before being filtered and concentrated under reduced pressure. The residue was dissolved in a mixture of CF_3CH_2OH (2.5 L) and HCO_2H (25 mL) at 65 °C. The precipitate formed on cooling to ambient temperature was collected by filtration and dried under high vacuum. This solid was treated with CH_2Cl_2 (7 L), and then the mixture was filtered through Celite. The clear solution obtained was evaporated to dryness under reduced pressure. Two further recrystallizations employing $CF_3CH_2OH-HCO_2H$ (100:1) yielded the title compound (0.29 kg, 36% yield, HPLC purity >98.5%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90 (d, J = 2.6 Hz, 1 H), 1.55 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 158.1 (d, J = 292.0 Hz), 153.0 (s), 152.1 (d, J = 9.7 Hz), 116.8 (d, J = 13.2 Hz), 82.7 (s), 28.4 (s); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −159.0; MS (ES^+) m/z 219.0 $[M + H]^+$; Anal. Calcd for $C_8H_{11}FN_2O_2S$: C, 44.03; H, 5.08; N, 12.84; Found: C, 43.80; H, 4.91; N, 12.76.

2-Amino-5-fluorothiazole Hydrochloride (3·HCl). HCl gas was bubbled through a stirred solution of **2c** (1.21 kg, 5.54 mol) in dioxane (7.2 L) for 5 h, the reaction temperature being kept at <35 °C. The solution was stirred at ambient temperature overnight, then Et_2O (12 L) was added. The white precipitate produced was collected by filtration and dried (50 °C, 200 mbar) to afford the title compound (0.83 kg, 96% yield, HPLC purity = 98.5%), mp 135 °C; ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ 7.25 (d, J = 1.0 Hz, 1 H), 5.80−4.60 (br, 3 H); $^{13}C\{^1H\}$ NMR (CD_3OD, 75 MHz) δ 166.5 (s), 151.1 (d, J = 285.0 Hz), 109.8 (d, J = 24.5 Hz); ^{19}F NMR ($(CD_3)_2SO$, 282 MHz) δ −159.0; MS (ES^+) m/z 119.0 $[M + H]^+$; Anal. Calcd for $C_3H_4ClFN_2S$: C, 23.31; H, 2.61; N, 18.12; Found: C, 23.11; H, 2.72; N, 17.77.

Supporting Information Available

Experimental procedures for the synthesis of **3**·HCl by Route **b** of Table 1 and spectral data for **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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