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Nuclear fluorination of 2,4-diarylthiazoles with Accufluor®

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Abstract

A series of 2,4-diphenylthiazole derivatives were synthesized and directly fluorinated at the 5-position by reaction with the N–F fluorinating reagent Accufluor®. Although fluorination occurred selectively at the thiazole ring, it was always incomplete and thus yields for the novel fluorinated products were low to moderate (19–43%) following purification to remove starting material. Nonetheless, the target compounds were obtained in a convenient and straightforward manner. Selectfluor® was not as effective as Accufluor® as it gave a trace amount of the 5-chlorothiazole that was difficult to remove by chromatography.

Keywords: Thiazole; Fluorination; Accufluor®; Selectfluor®; Substituent effects

1. Introduction

Fluorinated compounds have become progressively incorporated into drug-discovery research as an approach to improving the physiochemical properties of drug candidates [1,2]. The synthesis and biological evaluation of fluorinated compounds is also widespread in agrochemical research [3]. Thiazoles, on the other hand, are known to possess a wide range of biological activities, including, among others [4], antibacterial [5], antiviral [6], anti-cancer [7], anti-diabetic [8], anti-obesity [9] and anti-psychotic [10] properties. Considering the diverse biological activity of thiazoles, and of fluorinated compounds in general, the development of methods for the direct fluorination of this ring system should be useful in drug development.

To date, most fluorinated thiazoles have been prepared indirectly using ring forming reactions [11,12], functional group conversions [13], or halogen exchange reactions [13,14]. In contrast, preparations employing direct, electrophilic fluorination, as often preferred in analogue preparation, are quite rare. For example, the only report we have been able to find involving thiazoles is the very recent fluorination of the highly activated 2-acetamidothiazole using Selectfluor® [15]. In addition, there has been a single report on the direct, electrochemical fluorination of some thiazoles using an HF adduct [4]. Considering the limited work with thiazoles, and that direct fluorination of certain heterocycles using either fluorine [16] or N–F reagents [15,17,18] is known to be difficult, or to lead to unexpected addition products [19], we have become interested in studying this ring system. Herein, we report the results of our initial work in this area, which has shown that 2,4-diarylthiazoles can be directly and selectively fluorinated at the 5-position of the thiazole, albeit in modest yield, by reaction with the N–F reagent Accufluor®.

2. Materials

The N–F fluorinating reagents tested in this study (all commercial) are shown in Fig. 1. As shown in Scheme 1, the starting 2,4 diarylthiazoles were readily prepared by reaction of variously substituted phenacyl bromides with thiobenzamide in refluxing EtOH (i.e., the Hantzsch thiazole synthesis) [20].

3. Results and discussion

Our first attempts at fluorination of our 2,4-diarylthiazoles involved reaction of the parent thiazole **7a** with Selectfluor® [21,22] (1.0–1.5 equiv.) in acetonitrile at about 50–60 °C (Scheme 2). After about 2–3 h, TLC showed significant formation of the 5-fluorothiazole, a trace byproduct, and a

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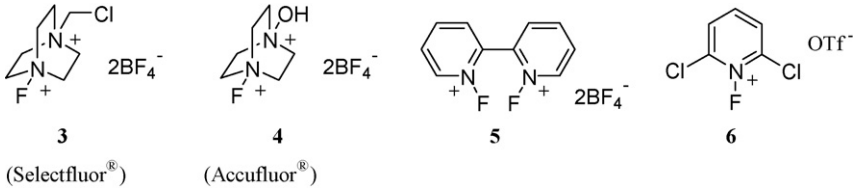
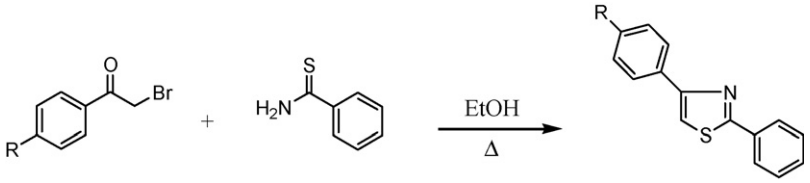
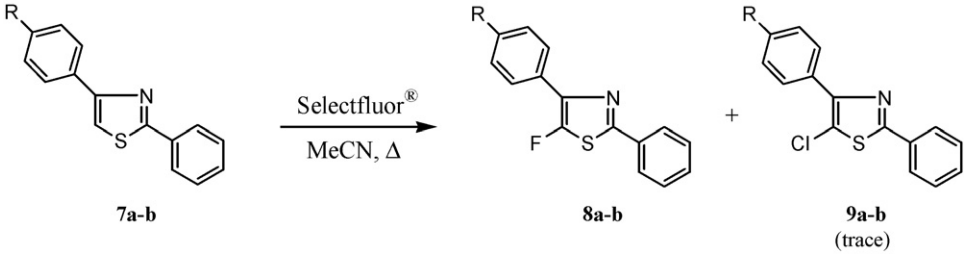


Fig. 1. Structures of N–F reagents tested.



R: **a** = H, **b** = Br, **c** = Me, **d** = OMe, **e** = NO_2

Scheme 1.



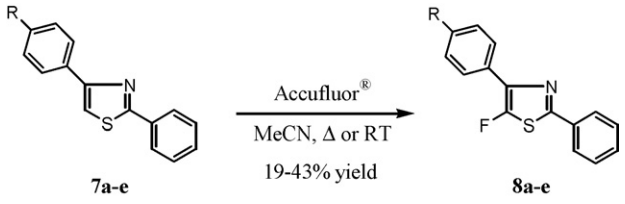
Scheme 2.

considerable amount of starting material. Continued heating after this point did not lead to any further reaction. The use of a larger excess of Selectfluor® did not help drive the reaction, nor did a change in solvent to nitromethane. Starch paper confirmed that the Selectfluor® was being consumed by some mechanism, perhaps involving attack by the thiazole nitrogen [17], although no other product could be observed. A similar incomplete conversion upon reaction of 2-acetamidothiazole with Selectfluor® was noted by others [15]. Despite our incomplete reaction, we were able to isolate 5-fluorothiazole (**8a**) in 23% yield following chromatography, with the structure being confirmed by GC–MS, ^{1}H, ^{13}C, ^{19}F NMR, IR, and elemental analysis (vida infra).

A similar reaction of 4-bromo thiazole (**7b**) with Selectfluor® gave fluorinated thiazole (**8b**) in 8.5% isolated yield, with the lower yield largely due to the tedious chromatographic separation from the trace byproduct (recrystallization was found to be an insufficient alternative). The trace byproduct was also isolated from this experiment and was identified using GC-MS and ^{1}H NMR as 5-chlorothiazole (**9b**). This assignment was confirmed by HRMS, and by GC–MS comparison with an authentic sample, which we prepared by reaction of thiazole (**7b**) with *N*-chlorosuccinimide [23]. Thus, the chlorine of Selectfluor® was being introduced into the thiazole, a side reaction of this reagent that has apparently not been described in the literature before.

In an attempt to improve the fluorination reaction and eliminate the formation of the chlorinated byproduct, other N–F reagents were examined. Compared to Selectfluor®, only a small amount of fluorination occurred when parent thiazole (**7a**) was reacted under similar conditions with *N*,*N*-difluoro-2,2-bipyridinium bis(tetrafluoroborate) (**5**) or with 1-fluoro-2,6-dichloropyridinium triflate (**6**). On the other hand, a similar to larger amount of fluorination occurred when Accufluor® [1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] [24] (**4**) was used, although the reaction still did not proceed to completion. However, considering that no chlorinated byproduct was formed, nor would it be expected using this reagent, chromatography to remove the residual starting material was simplified and a 43% yield of the 5-fluoro adduct **8a** was achieved (Scheme 3).

With this respectable outcome in hand, fluorination of the other thiazoles in the series was next examined. Using Accufluor®, the yield for **8b** was improved to 33% yield, and the 4-methyl analogue **8c** was obtained in 40% yield. The reaction with the activated 4-methoxy analogue **7d** was found to occur at room-temperature, with the Accufluor® being consumed after just 2 h (starch paper test). Purification gave



R: **a** = H, **b** = Br, **c** = Me, **d** = OMe, **e** = NO_2

Scheme 3.

34% yield of methoxy compound **8d**. Lastly, the reaction of the 4-nitro thiazole (**7e**) with Accufluor® (at 60 °C) did not proceed as much as did the other substrates, and fluoro adduct **8e** was obtained in only 19% yield. Nonetheless, this was satisfying as the strong electron withdrawing group could have inhibited the reaction altogether [19].

Physical and analytical data for the 5-fluorothiazoles prepared are shown in Tables 1 and 2. Purity and formula were confirmed by GC–MS, combustion analysis, and NMR data. Confirmation that fluorination occurred on the thiazole nucleus is based on the fluorine signal in the ^{19}F NMR being a singlet, and by the absence of the singlet for the original 5-H proton in the ^{1}H NMR. The relatively large C–F coupling constants (~300 Hz) observed for the fluorine bearing carbon in the ^{13}C NMR of the products is further evidence that the fluorine is not located on a phenyl ring. Finally, the presence of a peak for $M^+ - 103$ ($M^+ - PhCN$) in the mass spectrum of each product indicates that fluorination did not occur on the 2-phenyl ring.

4. Conclusion

In conclusion, we have described the synthesis and characterization of a series of 2,4-diaryl-5-fluorothiazoles via direct, electrophilic fluorination with Accufluor®. Fluorination of this triaryl system occurred selectively at the 5-position of the thiazole; however, as the reaction could not be driven to completion, the yields were low to moderate (19–43%). Nonetheless, as the compounds can be readily purified by

Table 1
Yield, mp, combustion analysis and mass spectral data for 5-fluorothiazoles (**8a–e**)

Product	R	% yield	mp (°C)	Formula (MW)	Combustion analysis calculated and found	*m/z*
8a	H	43	84–85	$C_{15}H_{10}NSF$ (255.32)	C: 70.57, H: 3.95, N: 5.49; C: 70.81, H: 3.99, N: 5.42	255 (M^+)
8b	Br	33	114–115	$C_{15}H_9BrFNS$ (334.21)	C: 53.91, H: 2.71, N: 4.19; C: 53.89, H: 2.87, N: 4.12	333 (M^+), 335 (M^+)
8c	CH_3	40	81–83	$C_{16}H_{12}NSF$ (269.34)	C: 71.35, H: 4.49, N: 5.20; C: 71.68, H: 4.77, N: 4.92	269 (M^+)
8d	OCH_3	34	62–63	$C_{16}H_{12}NOSF$ (285.34)	C: 67.35, H: 4.24, N: 4.91; C: 67.18, H: 4.30, N: 4.88	285 (M^+)
8e	NO_2	19	140–141	$C_{15}H_9N_2O_2SF$ (300.31)	C: 59.99, H: 3.02, N: 9.33; C: 59.75, H: 2.93, N: 9.19	300 (M^+)

Table 2
IR, ^{1}H, ^{13}C, and ^{19}F NMR data for 5-fluorothiazoles (**8a–e**)

Product	IR (KBr) (cm^{-1})	^{1}H NMR (DMSO-d_6)	^{13}C NMR (DMSO-d_6)	^{19}F NMR (DMSO-d_6)
8a	3086, 3062, 3026, 1556, 1490, 1351, 1305, 1198, 970, 759, 706 690, 661	7.38–7.43 (m, 1H), 7.49–7.54 (m, 5H), 7.90–7.93 (m, 4H)	156.7 (d, J = 302 Hz), 154.8 (d, J = 12 Hz), 135 (d, J = 4.6 Hz), 132.6 (s), 131.1 (d, J = 5.7 Hz), 130.7 (s), 129.3 (s), 129.0 (s), 128.4 (s), 126.6 (d, J = 5.7 Hz), 125.7 (d, J = 1.1 Hz)	−147.0 (s)
8b	3057, 3021, 1551, 1484, 1338, 1297, 1196, 1076, 827, 758, 689, 657	7.52–7.54 (m, 3H), 7.73 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.88–7.95 (m, 2H)	157.2 (d, J = 303 Hz), 155.2 (d, J = 9.8 Hz), 134.0 (d, J = 4.6 Hz), 132.5 (s), 132.0 (s), 130.8 (s), 130.3 (d, J = 5.7 Hz), 129.4 (s), 128.5 (d, J = 5.8 Hz), 125.7 (s), 121.6 (d, J = 2.55 Hz)	−145.5 (s)
8c	3063, 3029, 2923, 2857, 1558, 1502, 1477, 1339, 1303, 1190, 975, 815, 756, 687, 661, 490	2.34 (3H), 7.31 (d, J = 8.1 Hz, 2H), 7.50–7.52 (m, 3H), 7.79 (d, J = 8.1 Hz, 2H), 7.90–7.92 (m, 2H)	156.2 (d, J = 302 Hz), 154.7 (d, J = 9.8 Hz), 138.0 (d, J = 1.1 Hz), 135.2 (d. J = 4.6 Hz), 132.7 (s), 130.7 (s), 129.5 (d, J = 16.6 Hz), 128.5 (d, J = 5.2 Hz), 126.5 (d, J = 5.7 Hz), 125.7 (d, J = 1.2 Hz), 20.9 (s)	−147.8 (s)
8d	3076, 3040, 2998, 2957, 2835, 1559, 1501, 1466, 1250, 1031, 835, 767, 696 668	3.81 (3H), 7.07 (d, J = 8.7 Hz, 2H), 7.50–7.53 (m, 3H), 7.85 (d, J = 8.7 Hz, 2H), 7.86–7.93 (m, 2H)	159.2 (d, J = 1.2 Hz), 155.3 (d, J = 300 Hz), 154.5 (d, J = 9.8 Hz), 135.0 (d, J = 4.6 Hz), 132.7 (s), 130.6 (s), 129.3 (s), 128.0 (d, J = 5.2 Hz), 125.6 (s), 123.8 (d, J = 5.7 Hz), 114.4 (s), 55.2 (s)	−149.3 (s)
8e	3060, 1600, 1517, 1487, 1343, 859, 847, 756, 686	7.51–7.54 (m, 3H), 7.90–7.93 (m, 2H), 8.14 (d, J = 8.7 Hz, 2H), 8.33 (d, J = 8.4 Hz, 2H)	159.6 (d, J = 307 Hz), 156.5 (d, J = 9.15 Hz), 146.8 (s), 137.3 (d, J = 5.7 Hz), 133.3 (d, J = 3.3 Hz), 132.5 (s), 131.3 (s), 129.6 (s), 127.8 (d, J = 6.8 Hz), 126.1 (s), 124.6 (s)	−141.3 (s)

chromatography, this represents a convenient method for preparation of these fluorinated derivatives. Finally, Accufluor® was found to be superior to Selectfluor® for fluorination of these compounds as the latter gave a trace amount of the 5-chloro adduct that was difficult to remove by chromatography.

5. Experimental

Accufluor® (50% on alumina) was purchased from SynQuest Laboratories, Inc. and Selectfluor® was obtained as a gift from Air Products and Chemicals, Inc. Acetonitrile was distilled from calcium hydride. Selecto silica gel (230–400 mesh) was used for column chromatography. All NMR spectra were recorded on a Varian Unity +300 instrument at ambient temperature. Chemical shifts for ^{19}F-NMR were measured from hexafluorobenzene as internal standard and converted to the δ-scale with $CFCl_3$ as reference by the conversion relation $\delta(CFCl_3) = \delta(C_6F_6) - 162.9$ ppm [19]. GC–MS data were obtained on a Shimadzu GC-17A/QP-5000 instrument operating in EI mode (70 eV). Other details are as previously described [19].

5.1. General procedure for synthesis of 2,4-diaryl-5-fluorothiazoles (8a–e)

A mixture of the 2,4-diphenylthiazole (**7a–e**) (1 mmol) and Accufluor® (50% on alumina) (0.77 g, 1.2 mmol) in acetonitrile (3 ml) was heated at ~60 °C (oil bath temperature) under nitrogen until KI/starch paper indicated the N–F reagent was consumed (1–2 h). Excess water was then added to give a solid, which was filtered off and dried. The compound was then absorbed onto silica gel using acetone, and the dried (high vacuum) mixture was eluted from a silica gel column using petane or 1% tert-butyl methyl ether in pentane to give, following concentration of the homogeneous fractions, the pure 5-fluorothiazole (yields following this step given in Table 1). The products were recrystallized from MeOH (or EtOH in the case of **8e**) to give analytical samples as white to off-white solids (or yellow in the case of **8e**).

A similar reaction of thiazoles **7a–b** with Selectfluor® (1.5 equiv.) for 2–3 h at 50–60 °C gave 5-fluorothiazoles (**8a**) (23% yield) and **8b** (8.5% yield), respectively, after chromatographic purification to remove residual starting material and trace byproduct. In the reaction of **7b** with Selectfluor®, a trace amount of 5-chlorothiazole **9b** was also isolated and characterized. HRMS calculated for **9b** ($C_{15}H_{10}NSCl^{35}Br^{79}$) ($MH^+$): 349.9406. Observed: 349.9394. The GC–MS and ^{1}H NMR data of **9b** were also identical to that of an authentic sample [23].

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