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High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations

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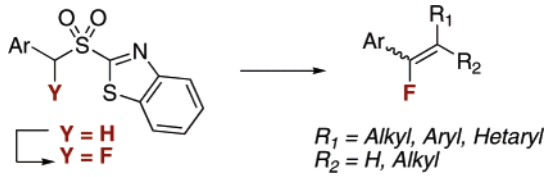
ABSTRACT



General, high-yield tandem electrophilic fluorination and modified Julia olefination for the synthesis of fluoro olefins is reported. A series of α-fluoro 1,3-benzothiazol-2-yl sulfone-based synthons were synthesized via deprotonation–fluorination. Of critical importance for high-yield fluorinations were heterogeneous reaction conditions, as under homogeneous conditions only starting sulfones were recovered. The α-fluoro 1,3-benzothiazol-2-yl sulfones so obtained were subjected to condensations with a variety of aldehydes and ketones to afford high yields of regiospecifically fluorinated olefins.

Vinyl fluorides are of considerable interest for their biological properties, such as enzyme inhibition,[1] as well as their use as versatile synthetic building blocks.[2] Therefore, several notable approaches have been developed for their synthesis, such as electrophilic fluorination of vinyllithiums[3] or stannanes,[4] fluorodesilylation of vinylsilanes,[5] the Horner−Wadsworth−Emmons condensation of α-fluorophosphonates with carbonyls,[6a−c] and Peterson fluoro olefination.[6d]

An attractive method for introduction of unsaturation is the modified (one-pot) Julia olefination.[7,8] For this, the 1,3-benzothiazol-2-yl sulfones (BT-sulfones) have been reported to provide the best yields and/or stereoselectivities.[9] We rationalized that synthesis of fluorinated BT-sulfones might provide new fluorinated synthons[2] for vinyl fluorides. To our knowledge, there is only a single example where a metalated α-fluoroethyl BT-sulfone has been used for the synthesis of vinyl fluorides.[10] In this case, direct fluorination of corresponding ethyl BT-sulfide with F-TEDA gave only 30−35% of the α-fluorosulfide. The requisite α-fluorosulfone was therefore synthesized either from commercially available 1-bromo-1-fluoroethane or from the α-chlorosulfide via chlorine−fluorine substitution.

Since direct fluorination is of a wider scope, we have evaluated a general method for the synthesis of α-fluoro BT-sulfones and studied their reactivities in the fluoro olefination.

(1) Bey, P.; McCarthy, J. R.; McDonald, I. A. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991; pp 105−133.

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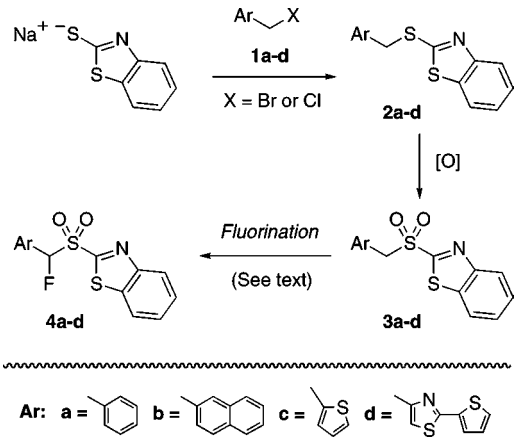
Described herein are initial results from this exploration and a novel, general avenue to vinyl fluorides.

At the onset, the sodium salt of 2-mercapto-1,3-benzothiazole was allowed to react with benzyl bromide in DMF to afford the corresponding sulfide (**2a** in Scheme 1) in 93%

Scheme 1. Synthesis of Fluorinated Benzothiazolyl Sulfones (BT-Sulfones)



yield. Initial unoptimized attempts were directed at introduction of fluorine into **2a** using various reagents. These, including the reported use of FTEDA-NEt_3 for fluorination of ethyl BT-sulfide,[10] were unsuccessful.[11]

On the basis of these results as well as to avoid complications due to the potential instability of the α-fluorosulfide, functionalization of the sulfone appeared more desirable. Benzyl BT-sulfone **3a** was therefore prepared in 94% yield via *m*-CPBA oxidation of **2a**. To minimize difluorination,[12] the bulky *t*-BuLi was used for deprotonation of **3a** in THF at −78 °C, followed by addition of *N*-fluorobenzenesulfonimide (NFSi) in THF. However, no fluorinated products were formed, and only starting material and unidentified nonpolar byproducts were observed (Table 1, entry 1). Therefore, other conditions were studied for the monofluorination of **3a**, and Table 1 shows results of these experiments. Addition of *t*-BuLi to a mixture of NFSi and **3a** at −78 °C (entry 2) gave results similar to entry 1.[13] The use of toluene as solvent instead of THF (entries 3 and 4) gave the desired **4a**, along with recovered **3a** and unidentified nonpolar byproducts. The formation of **4a** increased substantially, when a suspension of NFSi in toluene was added to metalated **3a** (entry 5). Although not conclusive, the formation of nonpolar byproducts appears to be related to decomposition of **3a** in the presence of *t*-BuLi since such byproducts were not observed when LDA was used for proton abstraction (entry 6). To

Table 1. Conditions Tested for the Fluorination of **3a**

entry	rxn. mixture	addition of	products **3a**, **4a**, di-F, others
1	**3a**, THF, *t*-BuLi, −78 °C, 1 h	NFSi, THF solution, rt	√[a], −, −, √[a]
2	**3a**, THF, NFSi, −78 °C	*t*-BuLi	√[a], −, −, √[a]
3	**3a**, PhMe, *t*-BuLi, −85 °C, 0.5 h	NFSi, PhMe solution, rt	68[b], 32[b], trace, √[a]
4	**3a**, PhMe, NFSi, −85 °C	*t*-BuLi	62[b], 38[b], trace, √[a]
5	**3a**, PhMe, *t*-BuLi, −85 °C, 6 min	NFSi, PhMe suspension, −60 °C	7[b], 93[b], trace, √[a]
6	**3a**, PhMe, LDA, −85 °C, 11 min	NFSi, PhMe suspension, −70 °C	3[b], 97[b], trace[c], −
7	**3a**, PhMe, LDA, −85 °C, 11 min	solid NFSi	−[d], 90[e], 3[e], −

[a] Observed by TLC, not isolated. [b] Relative ratio determined by ^{1}H NMR. [c] Relative ratio of **4a** to difluoro derivative ~98:2, determined by ^{19}F NMR. [d] By TLC some **3a** was observed, but was not recovered. [e] Isolated yields of purified products.

ensure reproducibility of the reaction as well as feasibility on the large scale, solid NFSi was added to metalated **3a** at −85 °C rather than as a suspension in toluene.[14] These conditions were reproducible, and **4a** was routinely isolated in excellent yields (90%).[15]

An electron transfer (ET) mechanism leading to recovery of starting material is possibly a competing process to the S_N2 fluorination[16] (entries 1−4), and such recovery of starting materials has previously been observed when electron-rich systems were subjected to metalation−fluorination with NFSi.[17] In one instance, it has been shown that adventitious moisture is not the cause for the competing protonation.[17a] Therefore, it seems plausible that under the heterogeneous fluorination conditions (entries 5−7) the rate of the ET process is slower compared to the displacement leading to fluorination. To test the generality of this fluorination, sulfones **3b**−**d** (Scheme 1) were subjected to LDA deprotonation in toluene, followed by addition of solid NFSi. In every case, monofluoro derivatives **4b**−**d** were isolated in 82−87% yield (purified products).

(11) Reactions of **2a** using XeF_2, FTEDA-NEt_3, *N*-fluoropyridinium triflate, or DAST (with corresponding sulfoxide) resulted in little to only trace (with XeF_2) amounts of the fluorinated derivative. Attempts at obtaining the benzylic chloro derivative of **2a** for subsequent chlorine−fluorine substitution, as reported in ref 10 for ethyl BT-sulfide, were unsuccessful.

(12) Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052−8057.

(13) Hill, B.; Liu, Y.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 4285−4288.

(14) Typical fluorination procedure. A stirred solution of sulfone **3a** (1.00 g, 3.46 mmol) in dry toluene (25 mL) was cooled to −85 °C (dry ice/*iso*-PrOH) under nitrogen, and 2.07 mL (4.15 mmol, 1.2 molar equiv) of LDA (2 M solution in heptane/THF/EtPh) was added to the reaction mixture. After 11 min, solid NFSi (1.34 g, 4.25 mmol, 1.23 molar equiv) was added. The mixture was allowed to stir at −85 °C for 50 min, then warmed to room temperature, and the stirring continued for an additional 50 min. Saturated aq NH_4Cl was added to the mixture, and the layers were separated. The aqueous layer was extracted with EtOAc three times, and the combined organic layer was washed with saturated aq $NaHCO_3$ followed by brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to yield 0.951 g (90%) of fluorosulfone **4a** as a white solid.

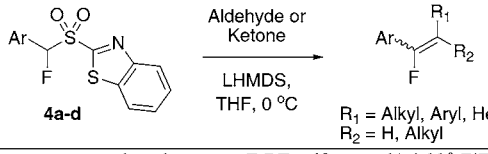
(15) Use of fresh LDA in these reactions is critical for good yields.

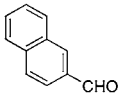
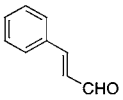
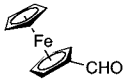
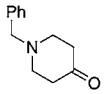
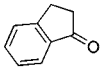
(16) (a) Differding, E.; Rüegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815−3818. (b) Differding, E.; Wehrli, M. *Tetrahedron Lett.* **1991**, *32*, 3819−3822.

(17) (a) Barnes, K. D.; Hu, Y.; Hunt, D. A. *Synth. Commun.* **1994**, *24*, 1749−1755. (b) Zajc, B. *J. Org. Chem.* **1999**, *64*, 1902−1907.

Olefination reactions of fluoro BT-sulfones **4a**−**d** were performed with a series of aldehydes and ketones. In a typical experiment, LHMDS (2.4 molar equiv) was added to a solution of **4a**−**d** (1.2 molar equiv) and a carbonyl compound (1 molar equiv) in THF at 0 °C, and the reaction mixture was stirred for 1.5−2 h at 0 °C.[18] Excellent yields were obtained in the condensation reactions, and these, along with *E*/*Z* ratios, are displayed in Table 2.

Table 2. General Synthesis of Vinyl Fluorides



entry	carbonyl	F-BT-sulfone	%yield,[a] *E*/*Z* ratio[b]
1		**4a**	**5a:** quant, 2.3:1
2		**4b**	**5b:** 98, 3.6:1
3		**4c**	**5c:** quant, 2.7:1
4		**4d**	**5d:** 97, 1:1.5
5		**4a**	**6a:** 90, 1:1
6		**4b**	**6b:** 90, 1:1.8
7		**4c**	**6c:** 86, 1:1.4
8		**4d**	**6d:** 87, 1:3.7
9		**4a**	**7a:** quant, 1.9:1
10		**4b**	**7b:** quant, 1.9:1
11		**4c**	**7c:** 95, 1.6:1
12		**4d**	**7d:** quant, 1:1.4
13		**4a**	**8a:** 98, 2.1:1
14		**4b**	**8b:** quant, 2.6:1
15		**4c**	**8c:** 91, 4.6:1
16		**4d**	**8d:** 93, 1:1.5
17		**4a**	**9a:** quant, *Z* only
18		**4b**	**9b:** quant, *Z* only
19		**4c**	**9c:** quant, 1:15.8
20		**4d**	**9d:** 96, 1:27.4
21		**4a**	**10a:** quant, N/A
22		**4b**	**10b:** quant, N/A
23		**4c**	**10c:** quant, N/A
24		**4d**	**10d:** quant, N/A
25		**4a**	**11a:** 91, 15.7:1[c]
26		**4b**	**11b:** 87, 17.2:1[c]
27		**4c**	**11c:** 85, 11.4:1[c]
28		**4d**	**11d:** 62, 3.6:1[c]

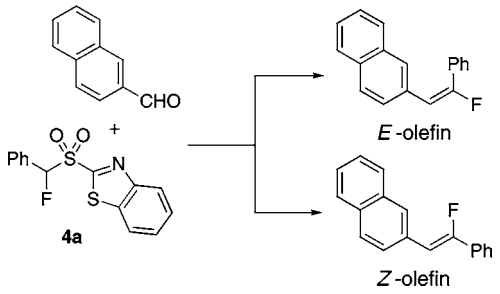
[a] Yields of isolated, purified products. [b] Relative ratio of purified diastereomers determined by ^{19}F NMR (reactions were performed under similar conditions but were not optimized for individual cases). [c] Ratio of isomers (more downfield : more upfield resonance); *E*,*Z* configuration was not determined (however, in the reactions with aldehydes, the ^{19}F resonance of *E* isomer appeared more downfield consistently).

Appropriate choice of coupling partners leads to regioisomeric vinyl fluorides via this method. This is exemplified by the synthesis of fluoroalkenes **5c** and **8b**.

We then studied the effect of reaction conditions, reported by Liu and Jacobsen[19] as well as Albrecht and Williams,[9b] on the *E*/*Z* ratio in the condensation reactions of **4a** with naphthaldehyde. These results are shown in Table 3.

The use of LHMDS in DMF/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) favored formation of the *Z* isomer, and the stereoselectivity increased significantly as temperature was lowered (entries 1−3). On the other hand, in this particular case, the *E* isomer was favored with

Table 3. Stereoselectivity in the Condensation of **4a** with 2-Naphthaldehyde



entry	conditions	*E*/*Z* ratio[a]
1	LHMDS, DMF-DMPU (1:1), rt, 2 h	1:1.4
2	LHMDS, DMF-DMPU (1:1), 0 °C, 1.5 h	1:3.6
3	LHMDS, DMF-DMPU (1:1), −78 °C[b]	1:11.9
4	LHMDS, THF, 0 °C, 2 h	2.3:1
5	LHMDS, THF, −78 °C[b]	2.2:1
6	NaHMDS, THF, −78 °C[b]	2.0:1

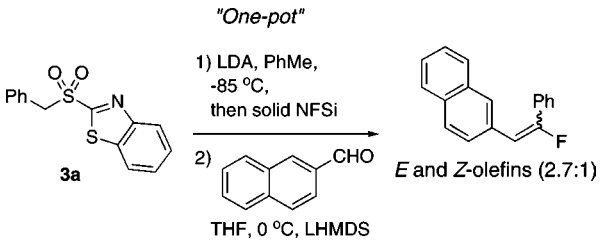
[a] Relative isomer ratio from the crude reaction mixtures determined by ^{19}F NMR. [b] Reactions were stirred at −78 °C for 40 min, −45 °C for 35 min, rt for 2 h.

LHMDS and THF, and temperature had little effect on the isomer ratio (entries 4 and 5). Similar stereoselectivity was observed with NaHMDS (entry 6).

To assess the influence of the fluorine substituent on stereochemical outcome of the olefination step, a condensation of unfluorinated **3c** with octanal was performed under conditions identical to those that yielded **7c**. In this case, the *E*/*Z* ratio was ∼1:10, indicating that presence of fluorine alters the stereoselectivity of the olefination.

Finally, in an attempt at simplifying the two-step fluorination−olefination method, an unoptimized one-pot reaction was performed (Scheme 2). After fluorination of **3a**, the

Scheme 2. A Two-Step, One-Pot Synthesis of Vinyl Fluorides

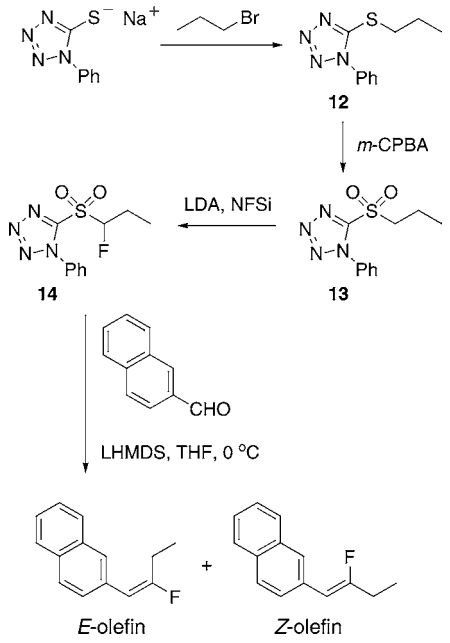


resulting **4a** was subjected to olefination without isolation, by addition of a THF solution of 2-naphthaldehyde at 0 °C to the reaction mixture, followed by addition of LHMDS. The yield of purified **5a** was 72% (93% based on recovered aldehyde), and the *E*/*Z* ratio (2.7:1) was similar to the sequential transformation.

The benzothiazolyl sulfone derivatives clearly are excellent substrates for benzylic fluorination−olefinations. On the basis of the purported higher stability of metalated 1-phenyl-1*H*-

tetrazol-5-yl sulfone derivatives (PT-sulfones) and the fact that these are less prone to self-condensation,[8,9a] we have briefly investigated fluorination of this system as well. Furthermore, *n*-alkyl PT-sulfones are reported to produce higher yields of alkenes in condensation reactions compared to their *n*-alkyl BT-sulfone counterparts.[9a] Thus, in our preliminary experiments, as shown in Scheme 3, we synthesized 1-phenyl-1*H*-tetrazol-5-yl *n*-propyl sulfide **12** (quantitative). Oxidation of **12** with *m*-CPBA yielded the sulfone **13** in 89% yield, which was subjected to fluorination with LDA/NFSi. The α-fluoro derivative **14** was isolated in 80% yield. Subsequent condensation of 1-fluoropropyl PT-sulfone **14** with 2-naphthaldehyde using LHMDS in THF afforded the *E*/*Z* product mixture in 92% yield after chromatographic purification. The ratio of *E*/*Z* isomers in this case was 1.3:1.

Scheme 3. Synthesis and Condensation of 1-Fluoropropyl PT-Sulfone



This experiment demonstrates that PT-sulfones can potentially also be subjected to the metalation and fluorination conditions described herein. The overall sequence may be suitably applicable to other alkyl systems, and work is ongoing in our laboratories to delineate the scope.

Introduction of fluorine atom into organic molecules poses a considerable challenge. This communication reports a general, high-yield tandem electrophilic fluorination and modified Julia olefination to yield fluoro olefins. Heterogeneous reaction conditions appear critical for successful fluorination of metalated BT-sulfones affording the α-fluoro 1,3-benzothiazol-2-yl sulfone derivatives in excellent yields. Condensation of the α-fluoro benzothiazolyl synthons prepared via this method with a variety of aldehydes and ketones afforded high yields of regiospecifically fluorinated olefins. Current work in our laboratories is aimed at a more detailed understanding of the BT- and PT-sulfone-based synthons as general reagents for synthesis of fluoroalkenes as well as the stereochemical outcome from these reactions.

Acknowledgment. This work was supported by NSF Grant CHE-0516557 and by NIH RCMI Grant 5G12 RR03060-20. Acquisition of a 500 MHz NMR spectrometer and a mass spectrometer has been funded by NSF Grants CHE-0210295 and CHE-0520963. We thank Dr. B. Boggess and Ms. N. Sevova (U. of Notre Dame) for mass spectral analyses, and Dr. G. Shia (Honeywell) for a sample of NFSi.

Supporting Information Available: Experimental details, ^{1}H NMR spectra of **3a**−**d** to **11a**−**d**, and ^{1}H and ^{19}F NMR spectra of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Typical olefination procedure. A stirred solution of 2-naphthaldehyde (43.0 mg, 0.275 mmol) and 1,3-benzothiazol-2-yl (phenyl)fluoromethyl sulfone **4a** (101.5 mg, 0.330 mmol, 1.2 molar equiv) in dry THF (3.5 mL) was cooled to 0 °C under nitrogen, and 0.660 mL (0.660 mmol, 2.4 molar equiv) of LHMDS (1 M solution in THF) was added. The reaction mixture was allowed to stir at 0 °C for 1.5 h. Saturated aq NH_4Cl (5 mL) was added to the mixture, and the mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude *E*/*Z* product mixture was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to yield 68.3 mg (quantitative yield) of **5a** as an off white solid.

(19) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772−10773.