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Exceptionally Mild, High-Yield Synthesis of α-Fluoro Acrylates

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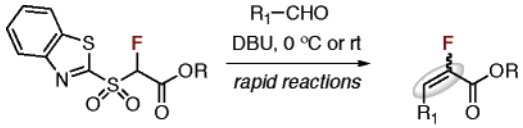
ABSTRACT



R = *tert*-Bu, Et or 8-Phenylmenthyl
R_1 = Alkyl, Aryl, Heteroaryl

Novel achiral and chiral alkyl α-(1,3-benzothiazol-2-ylsulfonyl)-α-fluoroacetates can be readily synthesized by metalation–fluorination of (1,3-benzothiazol-2-ylsulfonyl)acetates. DBU-mediated condensations of these fluorinated synthons with aldehydes proceed in a facile manner at 0 °C or at room temperature giving high yields of α-fluoro acrylates. Ketones are unreactive under these conditions. The presence of fluorine renders the synthon substantially more reactive compared to the unfluorinated analogue. Reactivity of α-(1,3-benzothiazol-2-ylsulfonyl)-α-fluoroacetate and the Horner–Wadsworth–Emmons reagent $(EtO)_2P(O)CHFCOOEt$ has also been compared.

α-Fluoro-α,β-unsaturated esters are useful synthetic intermediates[1] and key precursors to various biologically relevant molecules.[2] Several syntheses have been developed for their preparation, such as the Wittig and Horner−Wadsworth−Emmons reactions,[3] Peterson's olefination,[4] reactions of carbonyl compounds with alkyl esters of *tert*-butyl-[5a,b] as well as phenylsulfinyl[5c] fluoroacetates and with phenylselanyl fluoroacetate,[5d] as well as other methods.[6]

The one-pot Julia olefination[7] is widely used for the introduction of unsaturation; however, its use for the synthesis of vinyl fluorides has not received much attention.[8] Recently, we have developed an efficient synthetic method for the preparation of fluorinated 1,3-benzothiazol-2-yl benzyl sulfones (BT-sulfones).[8a] Upon condensation of these fluorinated synthons with aldehydes and ketones, high yields of regiospecifically fluorinated stilbene and styrene derivatives were formed.[8a] Herein, we report a simple synthesis of alkyl α-(1,3-benzothiazol-2-ylsulfonyl)-α-fluoroacetates as reagents for the synthesis of α-fluoro acrylates and their reactivity in the modified Julia olefination.

At the onset, we decided to synthesize the *tert*-butyl ester derivative because of its lower sensitivity toward hydrolysis. *tert*-Butyl bromoacetate was allowed to react with the sodium salt of 2-mercapto-1,3-benzothiazole, and the resulting sulfide

(1) (a) *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, DC, 2005. (b) Also see: Special Issue on Fluorinated Synthons. *J. Fluorine Chem.* **2004**, *125*, 477−645.

(2) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991; pp 105−133.

(3) For example, see: (a) Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2004**, *45*, 1679−1681. (b) Sano, S.; Saito, K.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 3987−3990. (c) Sano, S.; Teranishi, R.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 9183−9186. (d) Bargiggia, F.; Dos Santos, S.; Piva, O. *Synthesis* **2002**, 427−437. (e) Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777−779. (f) Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1990**, *55*, 4639−4642. (g) Etemad-Moghadam, G.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* **1985**, 448−454.

(4) Lin, J.; Welch, J. T. *Tetrahedron Lett.* **1998**, *39*, 9613−9616.

(5) (a) Chevrie, D.; Lequeux, T.; Pommelet, J.-C. *Tetrahedron* **2002**, *58*, 4759−4767. (b) Chevrie, D.; Lequeux, T.; Pommelet, J.-C. *Org. Lett.* **1999**, *1*, 1539−1541. (c) Allmendinger, T. *Tetrahedron* **1991**, *47*, 4905−4914. (d) Yoshimatsu, M.; Murase, Y.; Itoh, A.; Tanabe, G.; Muraoka, O. *Chem. Lett.* **2005**, *34*, 998−999.

(6) For example, see: (a) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346−4353. (b) Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218−3219. (c) Clemenceau, D.; Cousseau, J. *Tetrahedron Lett.* **1993**, *34*, 6903−6906. (d) Shen, Y.; Zhou, Y. *J. Fluorine Chem.* **1993**, *61*, 247−251. (e) Fuchigami, T.; Hayashi, T.; Konno, A. *Tetrahedron Lett.* **1992**, *33*, 3161−3164. (f) Usuki, Y.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1148−1150. (g) Ishihara, T.; Kuroboshi, M. *Chem. Lett.* **1987**, 1145−1148. (h) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1981**, 1259−1260.

(7) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585.

(8) (a) Ghosh, A. K.; Zajc, B. *Org. Lett.* **2006**, *8*, 1553−1556. (b) Chevrie, D.; Lequeux, T.; Demoute, J. P.; Pazenok, S. *Tetrahedron Lett.* **2003**, *44*, 8127−8130.

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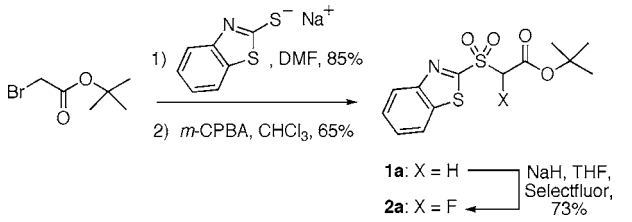
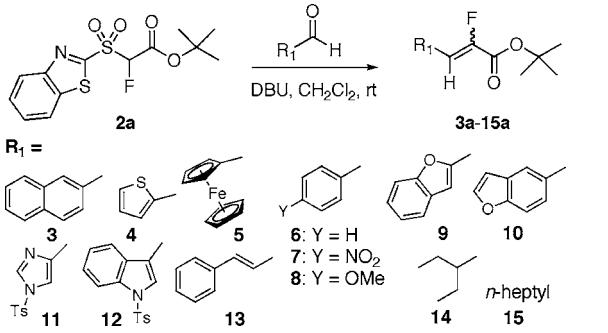
Scheme 1. Synthesis of **2a**



was subjected to oxidation with *m*-CPBA to afford sulfone **1a** (Scheme 1). Fluorination of **1a** using NaH−Selectfluor[9] resulted in the monofluoro derivative **2a** in 73% yield.

Initially, to find the optimal conditions, condensations of unfluorinated **1a** with 2-naphthaldehyde were attempted, using various bases (LHMDS, NEt_3, DBU) and solvents (THF, CH_2Cl_2). Among these, DBU gave the best results. While our work was in progress, Blakemore et al. reported the condensations of the unfluorinated ethyl ester analogue of **1a** with a series of aldehydes.[10] Although THF was also

Table 1. Mild Synthesis of α-Fluoro Acrylates



entry	R_1−CHO R_1 =	product: yield (%),[a] time[b]	% *E*/*Z* ratio[c]
1	**3**	**3a**: 93,[d] 35 min	77:23[d]
2	**3**	**3a**: 70, 3 h[e]	88:12[e,f]
3	**4**	**4a**: 88, 25 min	85:15 (S[g])
4	**5**	**5a**: 83,[d] 45 min	57:43[d] (S[g])
5	**6**	**6a**: 78,[d] 20 min	75:25[d]
6	**7**	**7a**: 84,[d] 30 min	72:28[d]
7	**8**	**8a**: 87,[d] 20 min	83:17[d]
8	**9**	**9a**: 93, 75 min	82:18 (S[g])
9	**10**	**10a**: 99, 90 min	80:20
10	**11**	**11a**: 99, 60 min	74:26 (S[g])
11	**12**	**12a**: 90, 45 min	83:17
12	**13**	**13a**: 93,[d] 25 min	76:24[d]
13	**14**	**14a**: 77[a] (98[h]), 40 min	64:36[d,f]
14	**15**	**15a**: 82[a] (quant[h]), 35 min	71:29[f]
15	**15**	**15a**: 75[a] (quant[h]), 3 h[e]	83:17[d,e,f]

[a] Yields of isolated, purified products. [b] Time at isolation. [c] Relative ratio of purified *E*/*Z* isomers determined by ^{19}F NMR (reactions were performed under similar conditions but were not optimized for individual cases). [d] Average of two runs. [e] Experiment at −78 °C and aqueous workup;[10] see the Supporting Information for details. [f] No change in ratio was observed prior to and after purification. [g] S: Separation of *E*/*Z* isomers was observed by TLC while monitoring the reactions. [h] Yield determined with internal standard C_6F_6 prior to complete solvent removal.

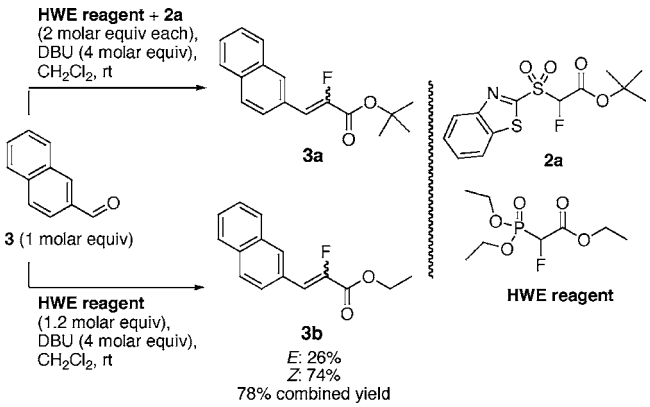
a suitable solvent, for purposes of comparison, condensations of **2a** were performed in CH_2Cl_2. In a typical experiment, aldehyde (**3**−**15**, Table 1, 1 molar equiv) and **2a** (1.2 molar equiv) were dissolved in CH_2Cl_2 while stirring at room temperature, and DBU (4 molar equiv) was added.

Reactions were monitored by TLC, and upon disappearance of the aldehyde, the reaction mixtures were directly loaded onto a dry silica gel column; the products were eluted (except for **14** and **15** which were subjected to aqueous workup; see the Supporting Information for details).[11] The combined *E*/*Z* product mixture was collected, and the ratio was analyzed by ^{19}F NMR. The yields obtained in the condensations and *E*/*Z* ratios are displayed in Table 1.

Aldehydes **11** and **12** gave high yields of products only upon N-protection (Table 1, entries 10 and 11). Whereas aldehydes gave generally high yields of products, ketones were unreactive under these mild conditions.

Further, the reactivities of **2a** and the Horner−Wadsworth−Emmons (HWE) reagent $(EtO)_2P(O)CHFCOOEt$ were compared in a competitive reaction with 2-naphthaldehyde (**3**) (Scheme 2). This reaction was monitored by ^{19}F

Scheme 2. Comparison of Reactivity and Selectivity of **2a** and the Horner−Wadsworth−Emmons Reagent



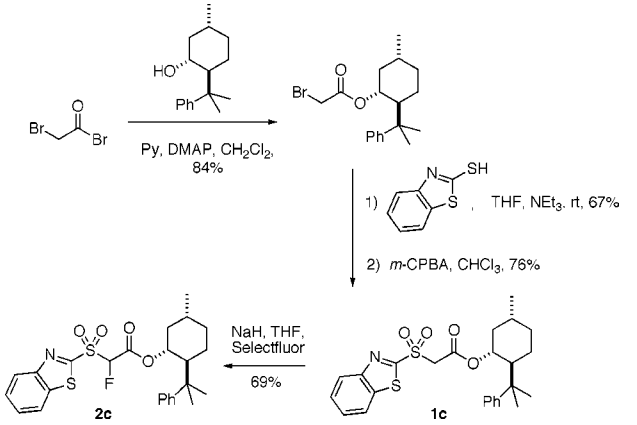
NMR, and upon consumption of **2a**, exclusive formation of **3a** was observed. Neither ^{19}F NMR nor TLC analysis showed any trace of olefins **3b** arising via reaction with the HWE reagent.[12] This result shows a higher reactivity of **2a** compared to the HWE reagent. In an independent condensation of the HWE reagent with **3** under these conditions, the olefin mixure **3b** was isolated in 78% yield with an *E*/*Z* ratio of 26%:74%. When comparing this to entry 1 in Table 1, under comparable conditions, a reversal in olefin geometry occurs in the reaction with 2-naphthaldehyde.

Subsequently, the influence of the ester moiety on the reactivity was studied. The known ethyl (1,3-benzothiazol-

(9) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791−2796.
(10) Blakemore, P. R.; Ho, D. K. H.; Nap, W. M. *Org. Biomol. Chem.* **2005**, *3*, 1365−1368.
(11) To assess the influence of the workup on the *E*/*Z* ratio, **3** was allowed to react with **2a** and the products were isolated via conventional aqueous workup; **3a** was isolated in a somewhat lower 75% yield in a nearly identical *E*/*Z* ratio of 78:22 (compared to 77:23, Table 1, entry 1).
(12) TLC (silica gel, 10% EtOAc in hexane). R_f **3a** = 0.44. R_f **3b** = 0.36.

2-ylsulfonyl)acetate **1b** was synthesized[10] and subjected to fluorination using NaH−Selectfluor to afford **2b** in 71% yield. The 8-phenylmenthyl ester **1c** was prepared from (−)-8-phenylmenthol as shown in Scheme 3 and converted to

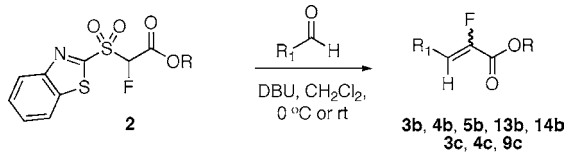
Scheme 3. Synthesis and Fluorination of **1c**



α-fluoro derivative **2c** (Scheme 3). Specifically, **2c** is of interest for the synthesis of optically active α-fluoro acrylates that were shown to form optically active products in Diels−Alder reactions.[13]

Condensation reactions of **2b** and **2c** with selected aldehydes gave good to excellent yields and *E*/*Z* ratios of products comparable to those from **2a** (Table 2). With **2c**,

Table 2. Condensations of **2b** and **2c** with Aldehydes



b: R = Et
c: R = 8-Phenylmenthyl

entry	BT− sulfone	R_1−CHO R_1 =	product: % yield,[a] time[b]	% *E*/*Z* ratio[c]
1	**2b**	**3**	**3b**: 78,[d] 60 min	78:22[d]
2	**2c**	**3**	**3c**: 92, 30 min	73:27 (S[e])
3	**2b**	**4**	**4b**: 94, 45 min	87:13
4	**2c**	**4**	**4c**: 70, 25 min	86:14 (S[e])
5	**2b**	**5**	**5b**: 71, 60 min	54:46 (S[e])
6	**2c**	**9**	**9c**: 79, 30 min	85:15 (S[e])
7	**2b**	**13**	**13b**: 80, 45 min	75:25
8	**2b**	**14**	**14b**: 65[a,d] (87[d,f]), 30 min	61:39[d,g]

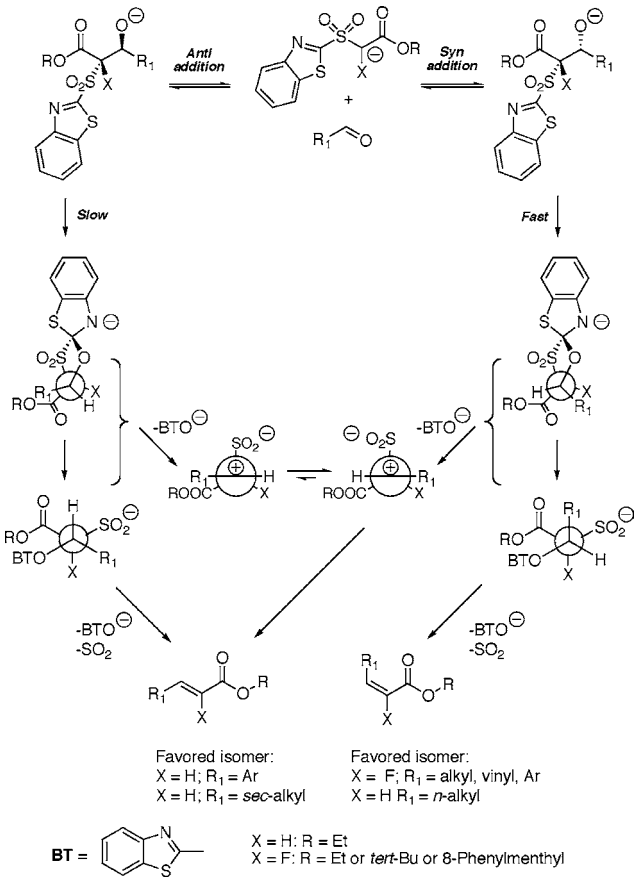
[a] Yields of isolated, purified products. [b] Time at isolation. [c] Relative ratio of purified *E*/*Z* isomers determined by ^{19}F NMR (reactions were performed under similar conditions but were not optimized for individual cases). [d] Average of two runs. [e] S: Separation of *E*/*Z* isomers was observed by TLC while monitoring the reactions. [f] Yield determined with internal standard C_6F_6 prior to complete solvent removal. [g] No change in ratio was observed prior to and after purification.

higher yields were obtained when the reactions were performed at 0 °C rather than at room temperature.

Next, we were interested in evaluating the effect of fluorine substitution on the reactivity of BT-sulfone in the olefination reaction. In a competitive experiment, fluorinated synthon **2b** (1.2 molar equiv) and its unfluorinated analogue **1b** (1.2 molar equiv) were reacted with 2-naphthaldehyde (1 molar equiv) in the presence of DBU (4 molar equiv). Only fluorinated alkene **3b** was formed, and the ^{1}H NMR spectrum of the product mixture showed no signals corresponding to the unfluorinated alkene. This indicates that fluorine substitution substantially increases the reactivity of the sulfone.

The stereochemistry of products formed in the Julia olefination depends on various factors which can have opposing effects and is thus often difficult to predict.[7] On the basis of the mechanism proposed by Julia,[14] Scheme 4

Scheme 4. Mechanism of Julia Olefination



shows the pathways that can be operative in the present reactions. In the case of stabilized BT-sulfone anions, such as the enolate formed here, the initial addition can be reversible. Further, the *syn*-β-alkoxy sulfone has been suggested to undergo a Smiles rearrangement faster than the *anti*-β-alkoxy sulfone.[7,15] When these two factors are com-

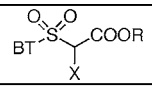
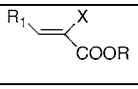
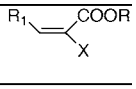
(13) Ito, H.; Saito, A.; Taguchi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1989−1994.
(14) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856−878.
(15) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336−357.

bined, the overall mechanism can account for the predominantly cis stereoselectivity observed. However, in the case of aryl and vinyl aldehydes, possible formation of a stabilized zwitterionic intermediate has been proposed.[14] In these cases, formation of an isomer with trans arrangement of R_1 and COOR is favored.

In all condensations of fluoro BT-sulfones **2**, a cis arrangement of R_1 and COOR prevailed (*E* isomer major), and stereoselectivity decreased with bulky aldehydes such as ferrocene carbaldehyde and 2-ethylbutanal (Table 1, entries 4 and 13). On the other hand, cis stereoselectivity increased with lower temperature (Table 1, entries 2 and 15).

Comparison of stereoselectivity of reactions of fluorinated and unfluorinated BT-sulfones revealed some interesting features. An opposite trend in stereoselectivity was observed in the condensations of fluorinated BT-sulfones **2**, compared to the reported reactions of the unfluorinated analogue **1b**[10] with aromatic aldehydes (Table 3 shows some representative examples, entries 1−4). This same reversed trend was also observed for a *sec*-alkyl aldehyde (entries 5 and 6), although stereoselectivity in the case of **2** was modest. On the other hand, a similar trend in stereoselectivity was observed in the condensations of **1b** and fluorinated sulfone **2a** with *n*-alkanals (entries 7 and 8).

Table 3. Comparison of Stereoselectivity of Reactions of Fluorinated (**2**) and Unfluorinated (**1b**)[a] BT-Sulfones

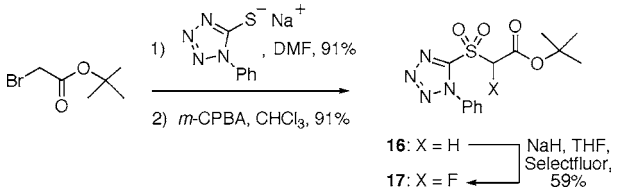
entry		R_1-CHO R_1 =		
1	X = H; R = Et	**3**	93%	7%
2	X = F; R = Et	**3**	22%	78%
3	X = H; R = Et	**8**	92%	8%
4	X = F; R = *t*-Bu	**8**	17%	83%
5	X = H; R = Et	**14**	<98%	2%
6	X = F; R = Et	**14**	39%	61%
7[b]	X = H; R = Et	*n*-pentyl	8%	92%
8[b]	X = F; R = *t*-Bu	**15**	17%	83%

[a] Data obtained from ref 10. [b] *E*/*Z* ratio of experiment at −78 °C.

A plausible reason for the reversal of stereoselectivity in condensations of aromatic aldehydes with fluorinated sulfones **2** compared to the unfluorinated sulfone **1b** could be the formation of a stabilized zwitterionic intermediate in the case of **1b** (Scheme 4, X = H), leading to the alkene with trans disposition of Ar and COOR moieties. However, such an intermediate could be disfavored in the case of the fluorinated sulfones **2** (Scheme 4, X = F), due to the destabilizing effect that a β-fluorine substituent has on carbocation stability. This may contribute to the overall cis stereoselectivity. With *n*-alkanals, stabilization of the zwitterionic intermediate is not possible in either the fluorinated or the unfluorinated case. Thus, the same overall stereochemical disposition is obtained with both **2** and **1b** (Table 3, entries 7 and 8).

Finally, a fluorinated derivative of 1-phenyl-1*H*-tetrazol-5-yl sulfone (PT-sulfone) **17** was synthesized (Scheme 5).

Scheme 5. Synthesis of the Fluorinated PT-Sulfone Derivative



The unfluorinated tetrazolyl sulfones[16] were reported to be unreactive toward aldehydes under mild conditions.[10] We reasoned that fluorine substitution would lead to higher reactivity of **17**. Indeed, **17** reacted with 2-naphthaldehyde and provided **3a** in 95% yield and an *E*/*Z* ratio of 75:25, comparable to the result with **2a**.

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Supporting Information Available: Experimental details and ^{1}H NMR spectra of **1a**−**c**, **2a**−**c**, **3a**−**15a**, **3b**−**5b**, **13b**, **14b**, **3c**, **4c**, **9c**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Blakemore, P. R.; Cole, W. J.; Kociénski, P. J.; Morley, A. *Synlett* **1998**, 26−28.