ORGANIC LETTERS

2002
Vol. 4, No. 12
2083−2085

New Polyfluorinated Organotin Reagents. Stereoselective Synthesis of (*Z*)-α-Fluoro-*β*-trifluoromethylvinylstannanes

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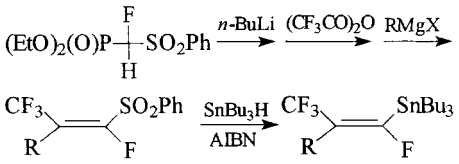
Received April 4, 2002

ABSTRACT



A new methodology for the synthesis of (*Z*)-α-fluoro-*β*-trifluoromethylvinylstannanes, which are useful polyfluorinated organotin reagents for the synthesis of fluorine-containing biologically active compounds, is described.

In the past several decades, much effort has been devoted to introducing a fluorine or trifluoromethyl functionality into organic molecules because of the dramatic effects of this functionality on their structure stability, reactivity, and biological activity of the resulting compounds.[1] Fluorinated organometallic reagents provide a useful and convenient methodology for the introduction of fluorine or trifluoromethyl functionality into organic molecules.[2] Organotin compounds are versatile reagents in synthetic organic chemistry. Among them, vinylstannanes have attracted special attention and emerged recently as highly valuable intermediates in organic synthesis.[3] In particular, a number of complex naturally occurring compounds have been synthesized by using the Stille palladium-catalyzed coupling reaction of vinylstannanes which were employed as key intermediates.[4]

Recently, the stereospecific synthesis of (*E*)- and (*Z*)-(1-fluorovinyl)stannanes was reported[5] and applied to the synthesis of enzyme inhibitors containing 2-fluoro terminal olefins.[6] The synthesis of 1,2-difluorovinylstannanes[7] and

(1) (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Welch, J. T.; Eswarakrishnam, S. *Fluorine in Biorganic Chemistry*; Wiley: New York, 1991. (c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (d) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds.; Elsevier Science Publishers B. V.: Amsterdam, 1993. (e) *Organofluorine Chemistry, Principles and Chemical Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (f) *Inventory of Industrial Fluorobiochemicals*; Becker, A., Ed.; Eyrolles: Pairs, 1996. (g) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555. (h) Resnatic, G.; Soloshnok, V. A. *Tetrahedron* **1996**, *52*, 1. (i) Hudlicky, M., Pavlath, A. E., Eds. *Chemistry of Organic Fluorine Compounds*; American Chemical Society: Washington, DC, 1996; #187.

(2) (a) Burton, D. J.; Yang, Z.-Y.; Morken, D. A. *Tetrahedron* **1994**, *50*, 2993. (b) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189.

(3) (a) Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, *37*, 1173. (b) Paley, R. S.; de Dios, A.; Estroff, L. A.; Lafontaine, J. A.; Montero, C.; McCulley, D. J.; Rubio, M. B.; Ventura, M. P.; Weers, H. L.; Fernandezde la Pradilla, R.; Castro. S.; Dorado, R.; Morente, M. *J. Org. Chem.* **1997**, *62*, 6326. (c) Kamlage, S.; Sefkow, M.; Peter, M. G. *J. Org. Chem.* **1999**, *64*, 2938. (d) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254. (e) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

(4) (a) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (b) Macdonald, G.; Alcaraz, L.; Wei, X.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1998**, *54*, 9823. (c) Paterson, I.; Lombart, H.-G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19. (d) Chakraborty, T. K.; Thippeswamy, D. *Synlett.* **1999**, 155. (e) Toshima, K.; Jyojima, T.; Miyamoto, N.; Katkhno, M.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **2001**, *66*, 1705.

(5) (a) McCarthy, J. R.; Mattews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lipper, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439. (b) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 360. (c) Matthews, D. P.; Millers, S. C.; Jarvi, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 3057. (d) Gross, R. S.; Mehdi, S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 7197. (e) Matthews, D. P.; Waid, P. P.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1994**, *35*, 5177.

(6) (a) Chen, C.; Wilcoxen, K.; Kim, K.-i.; McCarthy, J. R. *Tetrahedron Lett.* **1997**, *38*, 7677. (b) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.-i.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476.

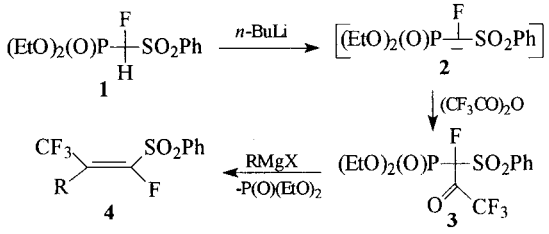
(7) (a) Xue, L.; Lu, L.; Pederson, S. D.; Liu, Q.; Narske, R. M.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 1064. (b) Lu, L.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 7673.

10.1021/ol0200697 CCC: $22.00
Published on Web 05/22/2002

1-trifluoromethylvinylstannanes[8] also has been reported. However, to the best of our knowledge, the synthesis of polyfluorinated organotin reagent has not been reported previously. We now wish to report the synthesis of polyfluorinated organotin reagents, (*Z*)-α-fluoro-*β*-trifluoromethylvinylstannanes, which we expect to be useful reagents in the synthesis of fluorine-containing biologically active compounds.

The reaction sequences are shown in Scheme 1. Treatment of diethyl (1-fluoro-1-phenylsulfonyl)methylphosphonate **1**[9a]

Scheme 1



with *n*-butyllithium in tetrahydrofuran (THF) at −78 °C gave carbanion **2** which was reacted with trifluoroacetic anhydride to form the trifluoromethylated phosphonate **3**. Without isolation, **3** was attacked by Grignard reagents followed by elimination of phosphonic acid anion to afford the desired product **4** in 77−98% yields (three steps). The results are summarized in Table 1. The reaction was stereospecific and the *Z*-isomer was obtained exclusively.

Table 1. (*Z*)-α-Fluoro-*β*-trifluoromethylvinyl Sulfones **4** Prepared

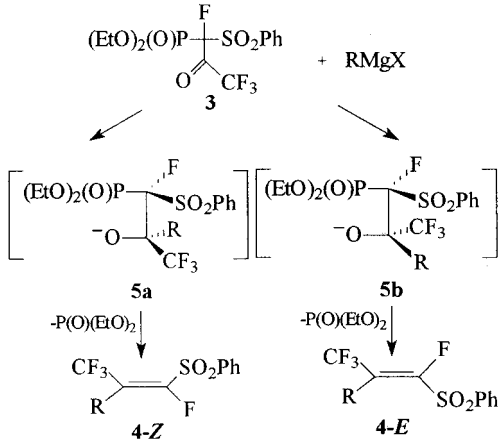
compd[10]	R	yield (%)[a]	*Z*:*E*[b]
4a	4-FC_6H_4	73	100:0
4b	4-ClC_6H_4	75	100:0
4c	2-$CH_3C_6H_4$	83	100:0
4d	3-$CH_3C_6H_4$	66	100:0
4e	4-$CH_3C_6H_4$	58	100:0
4f	2-$CH_3OC_6H_4$	72	100:0
4g	C_6H_5	64	100:0
4h	2-thienyl	78	0:100[c]

[a] Isolated yields. [b] The ratio of *E*- and *Z*-isomers is estimated on the basis of NMR spectra and TLC data. [c] According to the sequence rules, in **4h** (sulfur containing compound), when the trifluoromethyl group is trans with respect to the F group, the stereoisomer is assigned as the *E*-isomer, while in other cases they are assigned as the *Z*-isomer.

On the basis of F−CF_3 coupling constants across the double bond reported in the literature,[9b] if the trifluoromethyl group was trans with respect to the F group, the $^4J_{FFtrans}$ ranged from 7 to 13 Hz, while for those cis with respect to the F group, the $^4J_{FFcis}$ ranged from 21 to 31 Hz. In our cases, $^4J_{FF}$ is equal to 12 Hz; hence the configuration of the products **4** could be ascertained as the *Z*-isomer.

The stereochemical results may be rationalized as follows. The mechanism for the formation of trifluoromethylated α-fluoro-α,*β*-unsaturated sulfones is analogous to that of the intramolecular Horner−Wadsworth−Emmons reaction[11] and is shown in Scheme 2. The reaction is initiated by the

Scheme 2



nucleophilic attack of Grignard reagent on the carbon−oxygen double bond of the carbonyl group, and for the addition containing an asymmetric α-carbon, the Felkin−Anh model of asymmetric induction[12] predicts the predominant diastereomer. The incoming nucleophile preferentially attacks the less hindered side of the plane containing the C═O bond. Therefore, the relative steric bulk of F and SO_2-Ph play an important role in the stereoselectivity. The relative steric bulk of F is smaller than that of SO_2Ph, and the attack is from the rear (the side of plane containing the small group) of **3** forming the intermediate **5a**, while the reverse is true for the attack from the front, forming intermediate **5b**. Each of these intermediates decomposes via a syn elimination, giving **4-*Z*** or **4-*E***. In our case, formation of **5a** will be favored over **5b** and the *Z*-isomer was obtained exclusively.

The polyfluorinated sulfones **4** could be easily converted to polyfluorinated stannanes **6** by treatment of **4** with

(8) Jeong, I. H.; Park, Y. S.; Kim, B. T. *Tetrahedron Lett.* **2000**, *41*, 8917.

(9) (a) Diethyl (1-fluoro-1-phenylsulfonyl)methylphosphonate **1** was prepared according to the known method (McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Org. Synth.* **1995**, *72*, 216). (b) Burton, D. J.; Krutzsch, H. C. *J. Org. Chem.* **1970**, *35*, 2125.

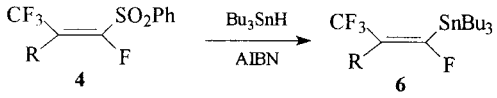
(10) **General procedure for the preparation of 4:** *n*-Butyllithium (1 mmol in 0.62 mL of hexane) was added dropwise over 10 min to a stirred solution of diethyl (1-fluoro-1-phenylsulfonyl)methylphosphonate **1**[9a] (310 mg, 1 mmol) in absolute THF (15 mL) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 0.5 h, and trifluoroacetic anhydride (0.14 mL, 1 mmol) was added to it in one portion. Stirring was continued at −78 °C for 1 h, and the reaction mixture was allowed to warm to 25 °C. After which the Grignard reagent (1.25 mmol) was added to the mixture which was stirred for another 0.5 h. The reaction mixture was poured into dilute HCl (2 M, 20 mL), and the water layer was extracted with ethyl ether (3 × 20 mL). The combined organic layer was washed with water (3 × 10 mL) until neutral and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography eluting with petroleum ether (60−90 °C)−ethyl acetate (95:5) to give the product **4**.

(11) Tasi, H.-J.; Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1994**, *59*, 7085.

(12) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

tributyltin hydride (2.0 equiv) and 2,2′-azobisisobutyronitrile (AIBN, 15 mol %) in high yields[13] (Scheme 3). The results

Scheme 3



are summarized in Table 2. This transformation was stereospecific and the *Z*-isomer was obtained exclusively. No

Table 2. (*Z*)-α-Fluoro-*β*-trifluoromethylvinylstannanes **6** Prepared

compd[14]	R	yield (%)[a]	*Z*:*E*
6a	4-FC_6H_4	98	100:0
6b	4-ClC_6H_4	83	100:0
6c	2-$CH_3C_6H_4$	93	100:0
6d	3-$CH_3C_6H_4$	93	100:0
6e	4-$CH_3C_6H_4$	98	100:0
6f	2-$CH_3OC_6H_4$	79	100:0
6g	C_6H_5	77	100:0
6h	2-thienyl	98	0:100[c]

E-isomer was detectable from the NMR spectra and TLC data. Similarly, the configuration of the products **6** was ascertained on the basis of their coupling constants ($^4J_{FF}$) as the *Z*-isomer. It has been reported that[5a] (fluorovinyl)sulfones obtained from ketones were transformed to (fluorovinyl)-stannanes with retention of configuration, while those obtained from aldehydes gave mixtures of [(*E*)- and (*Z*)-fluorovinyl]stannanes. In our studies, the retention of configuration was observed for the hemolytic cleavage of the vinyl phenylsulfonyl group with replacement by tributyltin. The stereochemical results of stannylation may be rationalized by a radical addition−elimination mechanism.[5a,13]

In summary, we have developed a new and convenient methodology for the synthesis of (*Z*)-α-fluoro-*β*-trifluoromethylvinylstannanes, which would be useful organotin polyfluorinated reagents for the synthesis of fluorine-containing biologically active compounds. The detailed application of this reagent in organic synthesis is being pursued.

Acknowledgment. Thanks are due to the National Natural Science Foundation of China and Academia Sinica for financial support.

Supporting Information Available: Spectral data for new compounds **4a**−**h** and **6a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0200697

(13) Khrimian, A. P.; Demilo, A. B.; Waters, R. M.; Liquido, N. J.; Nicholson, J. M. *J. Org. Chem.* **1994**, *59*, 8034.

(14) **General procedure for the preparation of 6:** Tributyltin hydride (0.54 mL, 2 mmol) was added to a mixture of sulfone **4** (1 mmol), AIBN (25 mg), and toluene (5 mL). The reaction mixture was heated at 85 °C for 4−6 h until completion of the reaction (by TLC). Evaporation of the toluene gave a residue, which was purified by column chromatography, eluting with petroleum ether (60−90 °C) to give the product **6**.