Pergamon

Tetrahedron Letters, Vol. 35, No. 29, pp. 5177-5180, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01032-3

THE SYNTHESIS OF (1-FLUOROVINYL)TRIBUTYLTIN: A SYNTHETIC EQUIVALENT FOR THE 1-FLUOROETHENE ANION.

Donald P. Matthews, Philip P. Waid, Jeffrey S. Sabol* and James R. McCarthy*†
Marion Merrell Dow Research Institute, 2110 East Galbraith Rd., Cincinnati, OH 45215
†Neurocrine Biosciences, Inc., 3050 Science Park Rd., San Diego, CA 92121

Abstract: The synthesis of (1-fluorovinyl)tributyltin (1b) is reported, and the utility of 1b as a synthetic equivalent for the 1-fluoroethene anion 2 through palladium-catalyzed couplings is demonstrated.

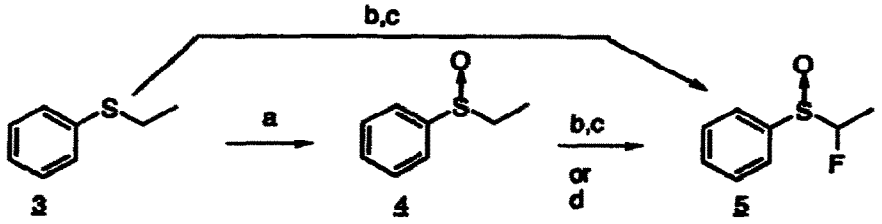
Previous publications from this laboratory have described routes to 2-fluoro-1-olefins[1] and a synthetic equivalent for the 1-fluoroethene anion 2.[2] In the latter case, (E)-tributyl(1-fluoro-2-trimethylsilyl)vinylstannane (1a) was prepared, and palladium catalyzed coupling with aryl halides and acid chlorides provided the trimethylsilyl protected fluoro olefins. Removal of the trimethylsilyl group was somewhat capricious, with conversion of the fluoro olefin to a methyl ketone observed on one occasion. In another instance, removal of the trimethylsilyl group required 2 weeks. Synthon 1b would avoid these problems and provide a more efficient synthetic equivalent for the 1-fluoroethene anion 2. In this letter, we report the synthesis of (1-fluorovinyl)tributyltin 1b and its utility in palladium catalyzed coupling reactions.

1a, R = $SiMe_3$
1b, R = H

2

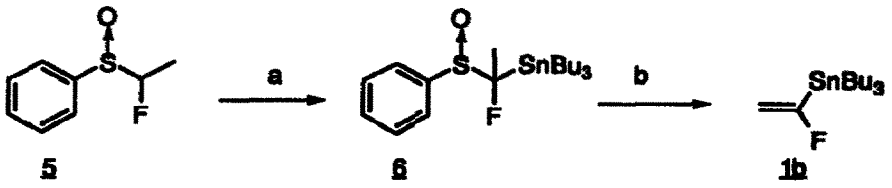
Commercially available ethyl phenyl sulfide 3 was converted via sulfoxide 4 to α-fluorosulfoxide 5 by a fluoro-Pummerer rearrangement[3,4] with diethylaminosulfur trifluoride (DAST)[5] followed by oxidation with 3-chloroperoxybenzoic acid (MCPBA) in 60% overall yield (Scheme 1). This procedure was used to prepare 20 grams of α-fluorosulfoxide 5. Alternate routes to 5 were examined. Conversion of 3 to 5 was also accomplished in 83% yield by direct transformation of thioether 3 to an α-fluorothioether with DAST using antimony trichloride as a catalyst;[6] MCPBA oxidation of this intermediate furnished product 5. Also, generation of the carbanion from sulfoxide 4 and electrophilic fluorination with N-fluorobenzenesulfonimide (NFSi)[7] produced α-fluorosulfoxide 5 in 40% yield. These alternate routes were examined on a 2-5 mmol scale, but not optimized for large scale preparations.

Scheme 1



Conditions: (a) $NaIO_4$, H_2O, CH_3OH, 0^0C (1 hr.); (b) DAST, $SbCl_3$, $CHCl_3$, RT (16 hr.); (c) MCPBA, CH_2Cl_2, -20^0C (1 hr.); (d) n-BuLi, THF, NFSI (1.5 eq.), -60^0C (0.5 hr.) to RT.

Scheme 2



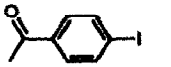
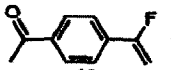
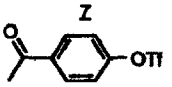
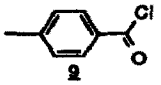
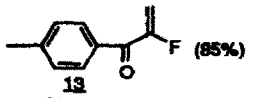
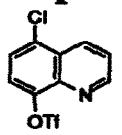
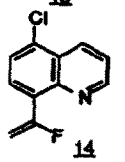
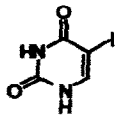
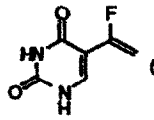
Conditions: (a) LDA (1.5-2.0 eq.),10% TMEDA-THF, Bu_3SnI, -70^0C (15 min.); (b) toluene, $(iPr)_2NEt$, 110^0C (2 hr.).

The conversion of sulfoxide 5 to α-stannylsulfoxide 6 was not straightforward, and considerable effort was expended to find the optimum conditions for this transformation (Scheme 2). A variety of parameters including bases (LDA, LHMDS, s-BuLi, KOtBu), solvents (THF, DME), co-solvents (HMPA, DMPU, TMEDA), and electrophiles (Bu_3SnI, Bu_3SnCl, Bu_3SnOTf) were examined, and inverse addition was also studied. The optimum conditions found were addition of a solution of sulfoxide 5 and Bu_3SnI (1.1 eq.) in THF to a cooled (-70°C) solution of LDA (1.5-2.0 eq.) in 10% TMEDA/THF with a reaction time of 15 minutes, work-up (ether/5% aq. $Na_2S_2O_3$) and flash chromatography afforded a 35% yield of α-stannyl sulfoxide 6 as a mixture of diastereomers[8,9] with starting material 5 (29%) also recovered. Several observations regarding the stability of sulfoxide 6 are worthy of mention. Facile pyrolysis of 6 to synthon 1b was observed during GC-MS analysis, and the complete protodestannylation of a solution of sulfoxide 6 in $CDCl_3$ was observed by proton NMR within a few hours at room temperature. Apparently, the presence of two geminal electron-withdrawing substituents weakens the carbon-tin bond and facilitates protonolysis. The completion of the synthesis of synthon 1b involved pyrolysis of sulfoxide 6, prepared by stannylation of the

carbanion generated from sulfoxide 5. Synthon 1b was obtained in 50% yield by pyrolysis of sulfoxide 6 in refluxing toluene in the presence of Hunig's base (5-10 eq.).[10] If desired, crude sulfoxide 6 obtained after workup and solvent removal may be used directly in the pyrolysis step to obtain 1b in 20% yield (5 --> 1b) after chromatography.

The palladium-catalyzed couplings of synthon 1b proceeded in fair to good yields for the substrates examined (Table 1). This sampling of coupling partners demonstrates the generality of the process and the utility of synthon 1b. It should be noted that the preparation of uracil derivative 15, without a protection-deprotection sequence, was a major impetus for the preparation of synthon 1b.[2]

TABLE I. PALLADIUM-CATALYZED COUPLINGS OF (1-FLUOROVINYL)TRIBUTYLTIN 1b.

SUBSTRATE	CONDITIONS	PRODUCT(YIELD)	^{19}F NMR
 7	$Pd(PPh_3)_4$ THF, 65°C(1h)	 12 (66%)	-108.8 (dd, J=17.8, 49.1)
 8	$Pd(PPh_3)_4$, LiCl THF, 65°C(1h)	12 (65%)	—
 9	$PdBnCl(PPh_3)_2$ THF, 65°C(0.5h)	 13 (85%)	-110.9(dd, J=15.4,45.5)
 10	$PdCl_2(PPh_3)_2$,LiCl THF, 65°C(18h)	 14 (61%)	-97.7(dd, J=20.3, 53.0)
 11	$Pd(PPh_3)_4$ DMF, 100°C(2h)	 15 (45%)	-108.7(dd, J=22.3, 56.7)

In summary, α-fluorosulfoxide 5 is prepared in large quantities and readily converted to synthon 1b. The utility of this synthon in transition metal mediated couplings provides a convenient route to 2-fluoro-1-olefins.

REFERENCES AND NOTES

1. McCarthy, J.R.; Matthews, D.P.; Barney C.L. *Tetrahedron Lett.* **1990**, 31, 1973.
2. Matthews, D.P.; Gross, R.S.; McCarthy, J.R. *Tetrahedron Lett.* **1994**, 35, 1027.
3. McCarthy, J.R.; Peet, N.P.; Le Tourneau, M.E.; Inbasekaran, M. *J. Am Chem. Soc.* **1985**, 107, 735.
4. McCarthy, J.R.; Matthews,D.P.; Paolini, J.P. *Org. Syn.*, **1993**, 72, 209.
5. Hudlicky, M. *Org. React.* (N.Y.), **1988**, 35, 513.
6. Robins, M.J.; Wnuk, S.F. *J. Org. Chem.* **1993**, 58, 3800.
7. Information regarding availability and applications of NFSi is available from Dr. George A. Shia, Allied Signal Inc., Buffalo Research Laboratory, 20 Peabody Street, Buffalo, NY 14210.
8. Preparation of 6: To a solution of 2.8 ml (20 mmol) diisopropylamine in 45 ml of THF at -5°C under Ar was added 8 ml (20 mmol) of 2.5M nBuLi/hex dropwise and the mixture stirred for 10 min. TMEDA (5 ml) was then added and the mixture was cooled to -70°C. A solution of 1.72 g (10 mmol) sulfoxide 5 and 3.14 ml (11mmol) tributyltin iodide in 5 ml of THF was added dropwise keeping the temperature below -60°C. The resulting pale yellow chalky mixture was stirred for 15 min. and then partitioned between ether-5% aq. $Na_2S_2O_3$. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography on silica gel (6% ethyl acetate/hexanes, R_f=0.19, 0.24) affording 1.60 g (35%) of α-stannylsulfoxide 6 as a 2:1 mixture of diastereomers; ^{19}F NMR ($CDCl_3$) δ -166.99 (m, major), -167.57 (m, minor). Further elution with ether afforded 0.5 g (29%) of recovered sulfoxide 5.
9. For a reverse-phase chromatographic technique for the purification of organic stannanes, see Farina, V. *J. Org. Chem.* **1991**, 56, 4985.
10. Preparation of 1b: A solution of 0.46 g (1 mmol) 6 and 1 ml (5.74 mmol) of N,N-diisopropylethylamine in 10 ml of toluene was placed in an oil bath at 110°C and heated under an Ar atmosphere for 2 h. The mixture was then cooled and the solvent removed. The crude product was purified by flash chromatography on silica gel (hexane, R_f=0.8) affording 165 mg (50%) of 1b as an oil of >90% purity (GC); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, 9H, J=7.3 Hz), 1.01 (m, 6H), 1.33 (m, 6H), 1.54 (m, 6H), 4.55 (m, 1H, J_{H-H}=2.8 Hz, J_{H-F}=38.1 Hz, J_{H-Sn}=67.0, 69.8 Hz), 5.31 (m, 1H, J_{H-H} =2.8 Hz, J_{H-F}=67.6 Hz, J_{H-Sn}=15.1 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -84.77 (m, dd (84%), J=38.1, 67.6 Hz), J=(7.6%)$_{F-}{}^{117}Sn$, J=(8.6%) $_{F-}{}^{119}Sn$, = 228, 238 Hz; ^{13}C NMR ($CDCl_3$, 76 MHz) δ 9.91 (J_{F-C}=2.0 Hz, J_{Sn-C} = 338.8, 354.3 Hz), 13.63, 27.15 (J_{Sn-C}=57.4 Hz), 28.80 (J_{Sn-C}=21.6 Hz), 107.59 (J_{F-C}=1.6 Hz, J_{Sn-C}=64.2 Hz), 178.92 (J_{F-C}=319.5 Hz). The authors thank William J. Magner and Dr. Edward W. Huber for obtaining the NMR data.

(*Received in USA* 6 *May* 1994; *accepted* 25 *May* 1994)