A Stereoselective Access to Functional Dienes Containing a Trifluoromethyl Group *via* Stille Cross Coupling of Ethyl 4,4,4-Trifluoro-3-iodobutenoate

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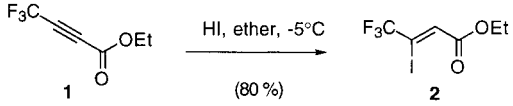
Received 27 March 1998

Abstract: Stereoselective construction of 3-trifluoromethyl conjugated dienoates or enynoates was achieved from ethyl (*Z*)-4,4,4-trifluoro-3-iodobutenoate and alkenyltin or alkynyltin reagents through the Stille reaction. Reduction of ethyl 3-trifluoromethyldienoates using DIBAL-H selectively afforded allylic alcohols.

Functionalized molecules bearing fluorine atoms, which modify their bioactivity by enhancement of both nucleophilicity and electronic properties, are often required in medicinal chemistry.[1,2,3] Among these molecules, trifluoromethyl substituted α,β-unsaturated esters are important.[4,5] Trifluoromethyl substituted polyenes have previously been obtained by Wittig Horner olefination of trifluoromethyl ketones or phosphonates,[6] or through sulfone-based cross coupling.[7] These major routes have been successfully applied to the synthesis of a trifluoromethyl substituted juvenile hormone,[8] retinal or retinoic acid.[9] Nevertheless, the weak *E*/*Z* selectivity of the created trisubstituted double bond containing a trifluoromethyl group constitutes the major drawback of such approaches.

Following our previous work describing the synthesis of (*Z*)- or (*E*)-3-methylalk-2-enoic or 3-substituted but-3-enoic acids,[10] we decided to examine the possibility of extending this methodology to the direct synthesis from 4,4,4-trifluoro-3-iodobutenoate esters of dienoic esters bearing a trifluoromethyl group. Moreover, a recent paper describing the synthesis of trifluoromethyl substituted enynes from **2** under Heck-Sonogashira conditions prompted us to report our results in this field.[11] In this paper we report the stereoselective synthesis of functional dienes from ethyl (*Z*)-4,4,4-trifluoro-3-iodobutenoate **2** *via* the Stille reaction.

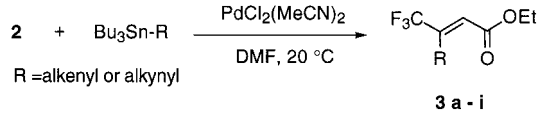
The starting ethyl (*Z*)-4,4,4-trifluoro-3-iodobutenoate **2** was obtained by addition of hydroiodic acid[12] on **1**.[13]



Scheme 1

The addition on the triple bond occurs with clean *Z*-stereoselectivity.[14] It should be noted that temperature, reaction time and purity of hydroiodic acid are critically important parameters in obtaining a pure *Z*-stereoisomer. Because of the high volatility of **1**, the use of a hydroiodic solution at 0°C instead of the sodium iodide/acetic acid system was an appealing procedure.[15]

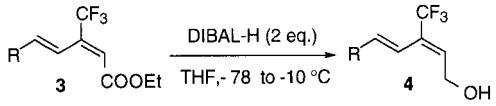
Attention was next directed to the synthesis of trifluorodienoates by palladium complex mediated cross-coupling between **2** and organotin reagents as described in Scheme 2.[16]



Scheme 2

Vinyltin compounds were used with 3% of dichlorobis-(acetonitrile)palladium(II) using DMF as solvent. The mild experimental conditions of the Stille cross-coupling reaction resulted in good yields of dienes **3** and no polymerisation products were detected. Results are shown in Table 1. NMR studies on **3a** confirmed the retention of the *Z* stereochemistry of the α-double bond.[14] Cross coupling of **2** with (*E*)-1,2-bis(tributylstannyl)ethylene (1.6 eq.) (entry 6) under the same experimental conditions, provided a separable mixture of dienyltin compound **3f** and bis coupling product **3g**. When 0.51 equivalent of (*E*)-1,2-bis(tributylstannyl)ethylene was used (entry 7), **3g** was obtained as the sole product, indicating the high reactivity of **2** towards vinyltin in comparison with our previous results where no bis-cross-coupling product was obtained.[17] Finally, to extend this methodology to other tin reagents, we found that alkynyltin reagents led to functional enynes (entries 8 and 9) in good yields and with a complete retention of the double bond configuration.

The synthetic potential of compounds **3a-i** has not been completely studied to date. However, saponification reaction with lithium hydroxide in a 1/1 water/ethanol mixture at 20°C gave the corresponding acids in fair yields [**3c'**(83%), **3d'**(73%), **3e'**(69%)].[18] Finally, selective reduction of the ester function into the primary alcohol was investigated in order to preserve the trifluoromethyl diene moiety. Treatment of dienes **3** with DIBAL-H (2 eq.) at -78° C afforded quantitatively dienyl alcohols **4** (Scheme 3).[19]



4a: R = H (92%), **4b**: R=SiMe$_3$ (96%),
4c: R=Ph (87%), **4d**: R=CH$_2$-CH(OEt)$_2$ (95%)

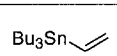
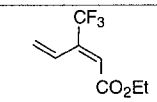
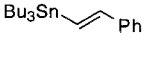
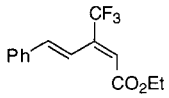
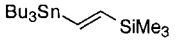
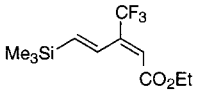
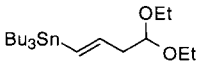
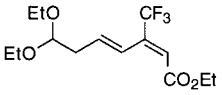
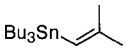
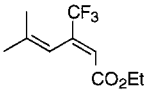
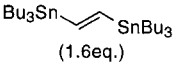
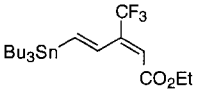
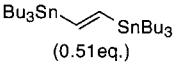
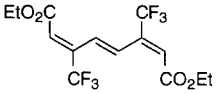
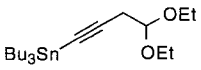
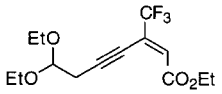
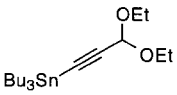
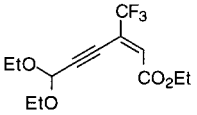
Scheme 3

DIBAL-H treatment of **2** under the same experimental conditions also gave the corresponding (*Z*)-4,4,4-trifluoro-3-iodobutenol in 50 % yield.

In summary, we have shown that Stille cross-coupling of ethyl (*Z*)-4,4,4-trifluoro-3-iodobutenoate with tin reagents constitutes a facile method for a selective synthesis of functional dienes or enynes bearing a trifluoromethyl group. Application to the synthesis of trifluoroterpenoic structures are in progress and will be reported in due course.

Acknowledgements*:* We thank CNRS and MESR for providing financial support, the "Service d'analyse chimique du vivant de Tours" for recording NMR and mass spectra, and the "Conseil Régional de la Région Centre" for awarding a fellowship to one of us (J.T.).

Table 1. Stille cross coupling of **2** with tin reagents

entry	Tin reagent	**3**	N°	Yield (%)
1			**3a**	77
2			**3b**	78
3			**3c**	88
4			**3d**	41
5			**3e**	47
6*	 (1.6eq.)		**3f**	84
7	 (0.51eq.)		**3g**	55
8			**3h**	74
9			**3i**	78

*: obtained as a separable 81/19 mixture of **3f** and **3g**

References and Notes

1 a) Welch, J.T. *Tetrahedron* **1987,** *4*, 3123-3136 and references cited therein; b) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Filler, R.; Kobayashi, Y.; Yagupolskii, L.; Eds., Elsevier, Amsterdam, 1993.

2 *Fluorine in Bioorganic Chemistry*, Welch J.T., Eswara-Krishnan S., Eds., Wiley, New York, 1991.

3 a) Francesch, A.; Alvarez, R.; Lopez, S.; de Lera, A.R. *J. Org. Chem.* **1997,** *62*, 310-319; b) Groesbeck, M.; Smith, S.O. *J. Org. Chem.* **1997,** *62*, 3638-3641.

4 *Fluorine-Containing Aminoacids, Synthesis and Properties*, Kukhar VP, Soloshonok VA, Eds., Wiley, New York, 1995.

5 Bensadat, A.; Félix, C.; Laurent, A.; Laurent, E.; Faure, R.; Thomas, T. *Bull. Soc. Chim. Fr.* **1996,** *133*, 509-514.

6 Poulter, C.D.; Wiggins, P.L.; Plummer, T.L. *J. Org. Chem.* **1981,** *46*, 1532-1538.

7 Welch, S.C.; Gruber, J.M. *J. Org. Chem.* **1982,** *47*, 385-389.

8 Siddal, J.B.; Biskup, M.; Fried, J.H. *J . Am. Chem. Soc.* **1969,** *91*, 1853-1854.

9 Mead, D.; Asato, A.E.; Denny, M.; Liu, R.S.H.; Hanzawa,Y.; Taguchi, T.; Yamada, A.; Kobayashi, N.; Hosoda, A.; Kobayashi, Y. *Tetrahedron Lett.* **1987,** *28* , 259-262 and references cited therein.

10 a) Abarbri, M.; Parrain, J.L.; Duchêne A. *Tetrahedron Lett.* **1995,** *36*, 2469-2472; b) Abarbri, M.; Parrain, J.L.; Cintrat, J.C.; Duchêne A. *Synthesis* **1996,** 82-86; c) Thibonnet, J.; Abarbri, M.; Parrain, J.L.; Duchêne, A. *Tetrahedron Lett.* **1996,** *37*, 7507-7510.

11 Qing, F.L.; Zhang, Y. *Tetrahedron Lett.* **1997,** *38* , 6729-6732.

12 a) Chalcat, J.C.; Théron, F.; Vessière, R. *C. R. Acad Sci. série C* **1971,** *273*, 763-765. b) Preparation of **2**: 14.6 mL (0.065 mol) of an aqueous solution of hydroiodic acid(57%) are added dropwise to 8.3 g (0.05 mol) of **1** with stirring at 0,-5 °C. After work-up (5% aq. $Na_2S_20_3$, brine solution, $MgSO_4$), **2** (11.8 g, 0.04 mol, 80%) is pure enough and can be used without purification.

13 Hamper, B.C. *Org. Synth*. **1991**, *70*, 246-253.

14 For assignment of *Z* stereochemistry see: a) Camps, F.; Canela, R.; Coll, J.; Messeguer, A.; Roca, A. *Tetrahedron* **1978**, *34*, 2179-2182; b) Begue, J;-P.; Bonnet-Delpon, D.; Mesureur, D.; Ourevitch, M. *Magn. Reson. Chem.* **1991**, *29*, 675-678; c) Tamura, K.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **1994**, *68*, 25-31; d) Bouillon, J.-P.; Maliverney, C.; Janousek, Z.; Viehe, H.G. *Bull. Soc. Chim. Fr.* **1997**, *134*, 47-57. All the coupling constants $^3J_{C\text{-}F}$ for carbon 2 of compounds **3a-f** are up to 5.1 Hz. This strongly supports the *Z* stereochemistry of the double bond (ref. 14b).

15 a) Ma, S.; Lu, X.; Li, Z. *J .Org. Chem.* **1992**, 57, 709; b) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643; c) Lu, X.; Wang, Z.; Ji, J. *Tetrahedron Lett.* **1995**, *35*, 613-616.

16 a) Stille, J.K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508-524; b) Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc.* **1987**, *109*, 813-817; c) Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, *105*, 669-670; d) Mitchell, R.N. *Synthesis* **1992**, 803-815.

17 Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771-772.

18 ^{19}F NMR δ (ppm) (183.3 MHz, $CDCl_3$) (using CF_3COOH as external standard, upfield positive): -9.85 (**3b**), -9.75 (**3c**), -9.45 (**3d**), -4.85 (**3d**), -9.45 (**3g**), -5.55 (**3**h), -9.45 (**3d'**), -4.85 (**3e'**)

19 Sen, S.E.; Ewing, G.J. *J. Org. Chem.* **1997**, *62*, 3529-3536.

20 **Typical procedure**: Preparation of compound **3c**. To a DMF solution (15mL) of **2** (1.77 g, 7 mmol), (*E*)-2-tributylstannyl-1-trimethylsilylethene (2.81 g, 7.2 mmol) and 55 mg (0.21 mmol) of dichlorobis(acetonitrile)palladium(II) were added. The mixture was stirred for 6h at 20°C, then hydrolysed with 25 mL of a 0.5M solution of potassium fluoride and 25 mL of ethyl acetate to precipitate the tribuyltin fluoride formed. After strongly stirring for 2h, the reaction mixture was filtered and extracted with diethyl ether (3x30 mL). After usual work-up, the crude ester **3c** was purified by column chromatography (hexane/diethylether = 97/3 to 70/30). IR (cm^{-1}): 3060, 2963, 1725, 1637, 1251; ^1H NMR δ (ppm) (200 MHz): 0.19 (9H, s), 1.37 (3H, t, $^3J_{2H}$ = 7.1Hz), 4.3 (2H, q, $^3J_{3H}$ = 7.1Hz), 6.31 (1H, s), 6.62 (1H, dq, $^3J_{1H}$ = 20Hz, $^4J_{H\text{-}F}$ = 2.2Hz), 7.65 (1H, bd, $^3J_{1H}$ = 20Hz); ^{13}C NMR δ (ppm) (50 MHz): -1.2, 14.7, 61.7, 121.2 (q, ^{3}JC-F = 6Hz), 123.1 (q, ^{1}JC-F = 277Hz), 132.7, 141.3 (q, ^{2}JC-F = 28Hz), 143.5, 165.2; MS (70 eV): m/z = 251 (M-Me, 1), 237 (15), 174 (23), 146 (38), 129 (11), 81 (13), 79 (15), 77 (56), 75 (78), 73 (100), 59 (10), 45 (19), 43 (13)