A Novel Route to Polyfluorinated Alka-2E,4E-dienes

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Abstract: Treatment of (Z)-a-Fluoro-β-trifluoromethylvinylstannanes 3 with n-butyllithium gave tetrafluoropropene anion 4, which was reacted with α,β-unsaturated aldehydes affording 6. With or without isolation of 6, DAST was added and reacted with 6 to give polyfluorinated alka-2E,4E isomers, exclusively. It is noteworthy that the migration of the double bond occurred only at the non-fluorine-containing one.

Key words: polyfluorinated alka-2E,4E isomers, (diethylamino)sulfur trifluoride, polyfluorinated diallylic alcohols, double bond migration

Over the last several decades, much effort has been devoted to the introduction of a fluorine atom or trifluoromethyl group into organic molecules with biological properties, since the resulting compounds often lead to pronounced activity enhancement.1 Thus, fluorine-containing organic compounds have been applied increasingly in pharmaceuticals, agrochemicals and other fields,2 as exemplified in Vitamin A and pheromone chemistry.3,4 1,3-Dienes have been noted as important functionalities in naturally occurring compounds which show biological activity3 and they are also useful intermediates for the synthesis of some natural products.4 Furthermore, much attention has been paid to the synthesis of 1,3-dienes because they are important intermediates in cycloaddition reactions and Michael-type conjugate additions and can undergo many synthetic transformations.5 The fluorinated species were able to be employed as useful intermediates for the synthesis of biologically active compounds.6 The usual synthetic method for the preparation of 1,3-dienes is the cross-coupling reaction catalyzed by palladium.7 1,3-Dienes can also be prepared by nickel-catalyzed multiple-component reactions which are a promising new type of domino reaction.8 Very recently a ruthenium-catalyzed two-component coupling of an allene and an activated olefin to form 1,3-dienes has been developed.9 However, to the best of our knowledge a method for the synthesis of polyfluorinated alka-2E,4E-dienes has not been reported in the literature. Therefore, it would be valuable to develop an efficient method for the synthesis of the title compounds.

In our previous papers, the double olefination methodology was used to synthesize 3-trifluoromethyl 2Z,4E-pentadieninitriles,10 and a stereocontrolled method was used to synthesize 2E,4E- or 2Z,4E-pentadieninitriles.11 As part of our continuing investigation to explore new synthetic methodologies for the synthesis of functionalized dienes,12 we report herein alternatively a novel route to polyfluorinated alka-2E,4E-dienes.

It has been shown that the reaction of (diethylamino)sulfur trifluoride (DAST) with allylic alcohols to replace the hydroxyl group with fluorine appeared to undergo fluorination by an SN2 type substitution process.13 Before the synthetic route has been designed, the following reaction (Scheme 1) has been carried out using 114 as reactant in order to explore the reaction of DAST with polyfluorinated allylic alcohols.

Scheme 1

Fortunately the reaction proceeded smoothly at −78 °C and afforded the rearranged product 2 as Z isomer predominantly. On the basis of data reported in the literature,15 the coupling constants were observed as $J_{HF,cis} = 22.4$ Hz and $J_{HF,trans} = 33.5$ Hz. In our case we found a coupling constant of $J_{HF} = 36.6$ Hz. Thus, the major portion of 2 was ascertained as Z isomer.

Scheme 2

(Z)-a-Fluoro-β-trifluoromethylvinylstannane 316 was treated with n-butyllithium in THF at −78 °C to give a new synthetic intermediate, tetrafluoropropene anion 4, which was reacted with α,β-unsaturated aldehydes affording intermediate 6. With or without isolation of 6, DAST was added and reacted with 6 giving the desired product 7.
(Scheme 2). The results are summarized in Table 1. The reaction was stereospecific and 2E,4E isomers were obtained exclusively. No other isomer was isolated and detectable. Thus, proposed groups remained unchanged and the migration of the double bond containing the trifluoromethyl and fluorine electrons, to afford 6, while the latter is that of 7.

It can be assumed that there are four possible isomers, 7, 8, 9 and 10, which will be obtained in the reaction of dialylic alcohols 6 with DAST (Scheme 3).

Since the reaction of diallylic alcohols 6 with DAST gave the products exclusively as 2E,4E isomers, the Sn2 mechanism shown in Scheme 4 was proposed.

It is reasonable to suggest that the carbon-3 atom is the less crowded place compared to carbon-1 and carbon-2. Thus, in the proposed mechanism the nucleophilic attack occurs at carbon-3 rather than at carbon-1 or carbon-2, followed by simultaneous movement of three pairs of electrons, to afford 7.

In conclusion, a synthetic route to polyfluorinated alka-2E,4E-dienes has been designed. It is noteworthy that the reaction of DAST with polyfluorinated diallylic alcohols afforded polyfluorinated alka-2E,4E isomers exclusively. No other isomers were isolated and detectable and the migration of the double bond occurred only at the non-fluorine-containing one. Thus, this methodology provides a simple and convenient route to the title compounds.

(2E)-2,4,4-Tetrafluoro-3-(4-methoxyphenyl)-1-(4-nitropheryl)but-2-en-1-ol (1) was prepared according to the reported method. Tri-tert-butyl[(Z)-1,3,3,3-tetrafluoro-2-arylprop-1-en-1-yl]stannanes 3 were prepared according to the known method. Petroleum ether (PE) used had a bp of 60–90 °C. IR spectra were recorded on a Digilab FTS-20E spectrometer. The spectra of all oil products were recorded as films. 1H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm, reference tetramethylsilane, in CDCl3, J values are given in Hz). The 19F NMR spectra were measured on a Varian EM-360 (60 MHz) spectrometer and re-calculated using the standard chemical shift of reference δ(F) (CFCl3) = −76.5 ppm with respect to δ(CFCl3) = 0.00 ppm. Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer using ionization and are reported as m/z (relative intensity). High resolution mass spectrometry data were obtained on a Finnigan-Mat 8430 high-resolution mass spectrometer. All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were evaporated under reduced pressure with a rotary evaporator and the residue was purified by column chromatography on a silica gel column (100–200 mesh). All solvents were purified before use. THF was purified by distillation from sodium benzenophene ketyl.

Fluorination and Rearranged Product 2; General Procedure

In an Schlenk tube previously purged with N2 was placed 1 (74 mg, 0.2 mmol) and DAST (0.035 mL, 0.26 mmol) was added at −78 °C. The reaction mixture was stirred for 0.5 h (TLC showed that the reaction was completed) and then poured into an aq sat. NaHCO3 solution (30 mL) and the aqueous layer was extracted with Et2O (3 × 10 mL). The combined organic layers were washed with H2O

### Table 1 Preparation of Polyfluorinated Alka-2E,4E-dienes 7

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)a</th>
</tr>
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<tr>
<td>7a</td>
<td>C6H5</td>
<td>H</td>
<td>CH3</td>
<td>67</td>
</tr>
<tr>
<td>7b</td>
<td>4-FC6H4</td>
<td>H</td>
<td>CH3</td>
<td>66</td>
</tr>
<tr>
<td>7c</td>
<td>4-CH3OC6H4</td>
<td>H</td>
<td>CH3</td>
<td>71</td>
</tr>
<tr>
<td>7d</td>
<td>C6H5</td>
<td>CH3CH2</td>
<td>n-C6H7</td>
<td>58</td>
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<td>CH3CH2</td>
<td>n-C6H7</td>
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<tr>
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<td>CH3CH2</td>
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<td>4-CH3C6H4</td>
<td>CH3CH2</td>
<td>n-C6H7</td>
<td>94, 89b</td>
</tr>
<tr>
<td>7h</td>
<td>4-CIC6H4</td>
<td>H</td>
<td>CH3</td>
<td>80, 98b</td>
</tr>
<tr>
<td>7i</td>
<td>3-CH3C6H4</td>
<td>H</td>
<td>CH3</td>
<td>70, 91b</td>
</tr>
</tbody>
</table>

a Isolated yields from one-pot method.
b Isolated yields from stepwise method, the former is the yield of 6, while the latter is that of 7.
Polyfluorinated alka-2E,4E-diens 7a–i; General Procedure

**Stepwise method:** n-Butyllithium (0.5 mmol in 0.31 mL of hexane) was added dropwise to a stirred solution of (Z)-a-fluoro-β-trifluoromethylyvinylstannane 3 (0.5 mmol) in absolute THF (10 mL) at –78 °C under nitrogen. The mixture was stirred at –78 °C for 0.5 h and a,b-unsaturated aldehyde (0.55 mmol) was added to it in one portion. The reaction mixture was allowed to warm to 25 °C and stirred for 1 h (TLC showed that the reaction was completed). The reaction mixture was poured into H2O (20 mL, containing few drops of 2 M HCl) and the aqueous layer was extracted with Et2O (3 × 10 mL). The combined organic layers were washed with H2O (3 × 10 mL) until the solution was neutral and dried (Na2SO4). After evaporation of the solvents the residue was purified by column chromatography (petroleum ether–EtOAc, 90:10) to give intermediate 6. In an Schlenk tube previously purged with N2 was placed 6 (0.3 mmol) and DAST (0.046 mL, 0.35 mmol) was added at –78 °C. The reaction mixture was stirred for 0.5 h (TLC showed that the reaction was completed). The reaction mixture was poured into an aq sat. NaHCO3 solution (30 mL) and the aqueous layer was extracted with Et2O (3 × 10 mL). The combined organic layers were washed with H2O (3 × 10 mL) until the solution was neutral and dried (Na2SO4). After evaporation of the solvents the residue was purified by column chromatography (petroleum ether–EtOAc, 99:1) to give product 7.

**One-pot method:** The procedure was similar as mentioned above but without isolation of intermediate 6, DAST (0.07 mL, 0.5 mmol) was directly added to the reaction mixture before the isolation step.

1.1.1.3.6-Pentafluoro-2-phenyl-hepta-2E,4E-diene (7a)

Yield: 67%, oil.

IR (neat): 1660, 1630, 1340, 1210, 1160, 1120, 970 cm⁻¹.  
1H NMR (CDCl3/TMS): δ = 7.43–7.29 (m, 5 H), 6.73 (ddd, J = 26.6, 15.7, 1.0 Hz, 1 H), 6.41 (ddd, J = 20.4, 15.8 Hz, 4.7 Hz, 1 H), 5.26 (dm, J = 47.7 Hz, 1 H), 1.48 (dd, J = 23.6, 6.5 Hz, 3 H).  
13C NMR (CDCl3/TFA): δ = –53.8 (d, J = 12 Hz, 3 F), –104.6 (q, J = 12 Hz, 1 F), –172.7 (m, 1 F).

MS: m/z (%) = 262 (M⁺, 2), 235 (4), 227 (15), 215 (100), 195 (85), 177 (36), 146 (10).

HRMS: m/z calcd for C13H10F3 (262.0781); found: 262.0814.

1.1.1.3.6-Pentafluoro-2-(4-fluorophenyl)-hepta-2E,4E-diene (7b)

Yield: 66%, oil.

IR (neat): 1660, 1630, 1510, 1340, 1240, 1160, 1120, 980 cm⁻¹.  
1H NMR (CDCl3/TMS): δ = 7.30–7.26 (m, 2 H), 7.13–7.07 (m, 2 H), 6.72 (ddd, J = 27.1, 15.6, 1.4 Hz, 1 H), 6.42 (ddd, J = 20.0, 15.7, 4.6 Hz, 1 H), 5.30 (dm, J = 47.8 Hz, 1 H), 1.49 (dd, J = 23.4, 6.5 Hz, 3 H).  
19F NMR (CDCl3/TFA): δ = –54.0 (d, J = 12 Hz, 3 F), –105.1 (q, J = 12 Hz, 1 F), –111.0 (s, 1 F), –165.0 (m, 1 F).

MS: m/z (%) = 280 (M⁺, 39), 261 (24), 245 (21), 233 (100), 213 (43), 195 (41).

HRMS: m/z calcd for C13H10F3 (280.21): 280.0687; found: 280.0697.

1.1.1.3.6-Pentafluoro-2-(4-methoxphenyl)-hepta-2E,4E-diene (7e)

Yield: 71%, oil.

IR (neat): 1660, 1610, 1460, 1340, 1290, 1250, 1160, 1120 cm⁻¹.

1H NMR (CDCl3/TMS): δ = 7.30–7.27 (m, 2 H), 6.98–6.94 (m, 2 H), 6.75 (ddd, J = 26.6, 15.4, 1.5 Hz, 1 H), 6.56 (ddd, J = 20.2, 15.5, 4.5 Hz, 1 H), 5.30 (dm, J = 47.8 Hz, 1 H), 3.82 (s, 3 H), 1.53 (dd, J = 23.6, 6.5 Hz, 3 H).

19F NMR (CDCl3/TFA): δ = –55.4 (d, J = 12 Hz, 3 F), –106.8 (m, 1 F), –175.5 (m, 1 F).

MS: m/z (%) = 280 (M⁺, 39), 261 (24), 245 (21), 233 (100), 213 (43), 195 (41).

Anal. Calcd for C14H13F5O (292.24): C, 57.54; H, 4.84. Found: C, 57.85; H, 4.60.

1.1.1.3.6-Pentafluoro-2-phenyl-5-ethylhiona-2E,4E-diene (7d)

Yield: 58%, oil.

IR (neat): 1660, 1610, 1340, 1220, 1160, 1120, 970 cm⁻¹.

1H NMR (CDCl3/TMS): δ = 7.54–7.27 (m, 5 H), 6.40 (dd, J = 29.5, 1.2 Hz, 1 H), 4.93 (dt, J = 47.5, 5.9 Hz, 1 H), 2.30 (dm, J = 59.6 Hz, 2 H), 1.81–1.39 (m, 4 H), 1.10 (t, J = 7.5 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H).

19F NMR (CDCl3/TFA): δ = –54.6 (d, J = 12 Hz, 3 F), –95.4 (q, J = 12 Hz, 1 F), –170.0 (m, 1 F).

MS: m/z (%) = 318 (M⁺, 21), 289 (22), 275 (21), 255 (26), 243 (100), 227 (51), 215 (67), 201 (60), 177 (29), 151 (21), 133 (25), 109 (9), 41 (27).


The NOESY spectrum shows that the vinyl H is cis with respect to the HFR group.

1.1.1.3.6-Pentafluoro-2-(4-methoxyphenyl)-5-ethylhiona-2E,4E-diene (7e)

Yield: 66%, oil.

IR (neat): 1660, 1610, 1510, 1330, 1290, 1250, 1160, 1120 cm⁻¹.

1H NMR (CDCl3/TMS): δ = 7.30–7.25 (m, 2 H), 6.97–6.93 (m, 2 H), 6.42 (d, J = 29.4 Hz, 1 H), 4.95 (dt, J = 46.7, 5.9 Hz, 1 H), 3.87 (s, 3 H), 2.46–2.20 (m, 2 H), 1.84–1.43 (m, 4 H), 1.15 (t, J = 7.8 Hz, 3 H), 1.04 (t, J = 7.3 Hz, 3 H).

19F NMR (CDCl3/TFA): δ = –56.1 (d, J = 12.7 Hz, 3 F), –96.7 (m, 1 F), –178.8 (m, 1 F).

MS: m/z (%) = 348 (M⁺, 100), 329 (14), 305 (11), 273 (17).

1H NMR (CDCl3/TMS): δ = 7.42–7.37 (m, 2 H), 7.26–7.22 (m, 2 H), 6.71 (dd, J = 26.8, 15.7, 1.1 Hz, 1 H, 1), 6.43 (dd, J = 19.7, 15.6, 4.5 Hz, 1 H), 5.28 (dm, J = 47.8 Hz, 1 H), 1.49 (dd, J = 23.6, 6.5 Hz, 3 H).

19F NMR (CDCl3/TFA): δ = –54.4 (d, J = 12 Hz, 3 F), –105.8 (q, J = 12 Hz, 1 F), –172.2 (m, 1 F).

MS: m/z (%) = 298 (M^+ + 2, 7), 296 (M^+, 23), 276 (8), 261 (23), 249 (100), 229 (61), 211 (17), 201 (31).

HRMS: m/z calc for C_{18}H_{18}ClF_{5} (296.66): 296.0416; found: 296.0416.

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References


