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Cycloaddition reactions of ethyl (*E*)- and (*Z*)-3-fluoropropenoate

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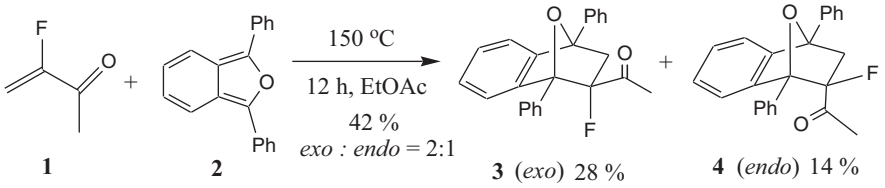
ABSTRACT

Ethyl (*Z*)-3-fluoropropenoate (**Z-5**) has been prepared in a pure state in 68% yield by a Wittig procedure developed by Burton. Ethyl (*E*)-3-fluoropropenoate (**E-6**) was prepared in 38% yield following the synthetic method of Purrington. The *Z* isomer gives cycloaddition with 1,3-diphenylisobenzofuran and cyclopentadiene to give a product with completely *endo* configurations. The *E* isomer also gives cycloadducts with same dienes to give mixtures of *endo* and *exo* products.

1. Introduction

Previously we reported that 3-fluorobutenone (**1**) underwent cycloaddition with the highly reactive 1,3-diphenylisobenzofuran (**2**) to give *exo*/*endo* (**3**/**4**) products in a ratio of 2/1, respectively (Eq. (1)) [1]. The literature on fluorodiene cycloadditions is scant but the major stereochemical outcome is that the fluorine atom is located in an *endo* position [2].

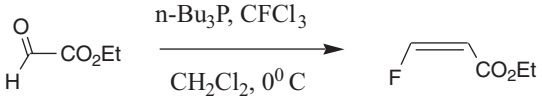


1 **2** **3** (*exo*) 28 % **4** (*endo*) 14 % (1)

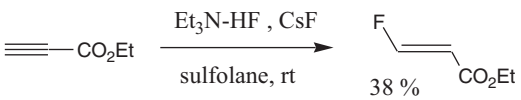
In this paper we describe cycloaddition reactions of ethyl (*Z*)-3-fluoropropenoate (**Z-5**) and ethyl (*E*)-3-fluoropropenoate (**E-6**). Purrington [3] described the preparation of pure **E-6** by the addition of fluoride ion to ethyl propiolate [3]. Wakselman described the **Z-5** isomer as a minor product but it was not isolated [4].

2. Results and discussion

We repeated the synthesis of **E-6** in 38% yield by the Purrington method (Eq. (3)). Only a slight amount (less that 1%) of the **Z-5** was observed. In order to prepare the pure **Z-5** isomer we used the Wittig-type reaction described by Burton which produces *cis* isomers in many cases [5]. Thus when ethyl oxylate was allowed to react with the ylid from tributylphosphine and fluorotrichloromethane the **Z-5** isomer was obtained in 68% yield (Eq. (2)). Occasionally we observed small amounts of the **E-6** isomer (less than 1%).



68 % **Z-5** (2)



38 % **E-6** (3)

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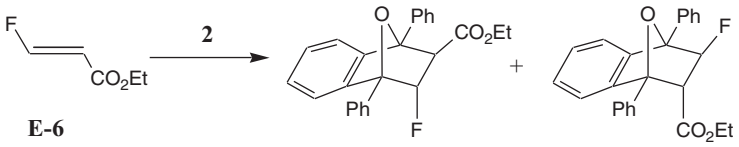
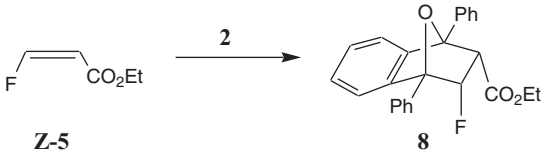
The reaction of **E-6** with the diene **2** required 18 h at 80 °C and produced the cycloadduct **7** as a mixture of *exo* and *endo* isomers in 90% yield after chromatography (Eq. (4)). The mixture could not be separated but the ratio of **7** *trans-exo* to **7** *trans-endo* is 3/1 by ^{19}F NMR spectroscopy.



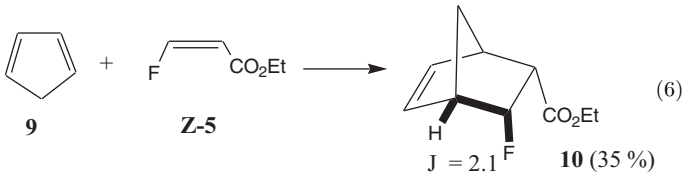
E-6 **7** ***exo*** **7** ***endo*** (4)

The reaction of **Z-5** with diene **2** required 48 h at 110 °C and gave a pure *cis-endo* product **8** in 70% yield as white crystals after chromatography and recrystallization (Eq. (5)). The structure was proven by X-ray crystallography as shown in Fig. 1.



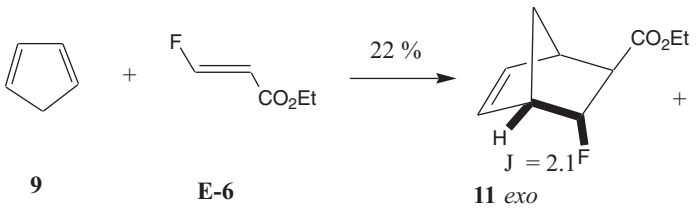
Z-5 **8** (5)

Reactions of **Z-5** and **E-6** with cyclopentadiene (**9**) required 3 days at 110 °C. The products in each case were oils that were difficult to purify. In the reaction of **9** with **Z-5** a 35% yield of cycloadduct **10** was obtained as a single isomer believed to be the *cis-endo* adduct **10** (Eq. (6)).



9 **Z-5** **10** (35 %) (6)

Reaction of **E-6** with **9** gave a mixture of two *trans* adducts (**11**) in equal amounts (Eq. (7)).



9 **E-6** **11** ***exo***

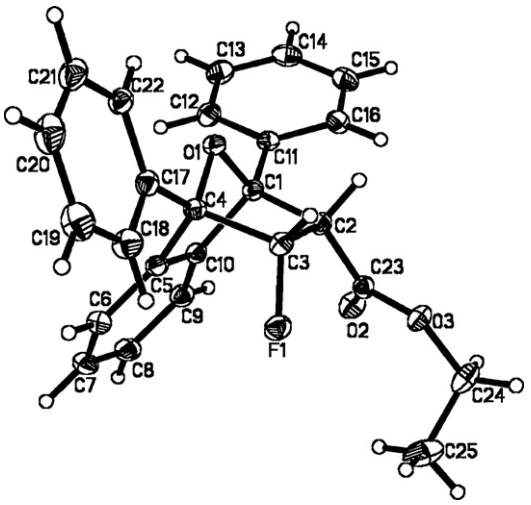
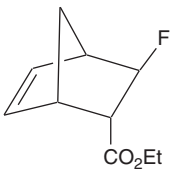


Fig. 1. Ortep representation of the X-ray crystal structure of **8**.

The *endo* position of the fluorine atom in structures **10** and **11**-*exo* (F-*endo*) was established by the coupling constants of the F to the bridgehead H that was 2.1 Hz in both cases. Williamson in 1966 presented results on coupling between bridgehead hydrogen atoms and fluorine atoms in norbornyl systems [6]. His finding, significant to this work, is that coupling between an *endo* F and a bridgehead proton is approximately 2 Hz. Coupling of a bridgehead proton and an *exo* F is zero.

The propensity for obtaining *exo* isomers (fluorine atom is *endo*) in Diels–Alder reactions when fluorinated dienophiles are used is well documented [2,7–10] and is observed here. Theoretical calculations by Haufe et al. [11] have shown that the stereoselectivity is kinetically controlled rather than thermodynamically controlled but the calculations do not resolve the problem. A somewhat qualitative approach to the selectivity can be obtained by applying the endo rule of Diels–Alder chemistry [12].

Secondary orbital interactions between the dienophile substituents and the π orbitals of the diene control the stereoselectivity of the reaction. Fig. 2 shows two alternative transition states possible: transition state **Z**[8] has an *endo* fluorine and an *endo* ester function while transition state **E**[8] has an *endo* fluorine atom and an *exo* ester group. Fluorine is unusual in that it contains a low anti-bonding sigma orbital (−13.5 eV) that can interact with the diene π system [13]. The anti-bonding π orbitals of the carbonyl group are somewhat higher at +0.8 eV [14]. Thus the π interaction when both atoms are *endo* is favored and places both the fluorine and ester in the *endo* positions, as in observed (transition state Z*). Thus because the fluorine interaction with the diene is greater than the interaction of the ester with the diene, the fluorine atom determines the stereoselectivity. This observation is consistent with the endo rule. We observed that when ethyl propenoate is used in reactions with **2** the *exo* and *endo* isomers are formed equally.



11 ***endo*** (7)

3. Experimental procedure

3.1. General

^{1}H NMR data were recorded at 300.0 MHz with tetramethylsilane (δ = 0.00 ppm) as internal reference. ^{13}C NMR spectra were recorded at 75.5 MHz with deuterated chloroform ($CDCl_3$ δ = 77.0 ppm) as internal reference. ^{19}F NMR spectra were recorded at 282.3 MHz with trifluoroacetic acid (TFA δ = 0.00 ppm) as external reference, and are corrected to $CFCl_3$. Deuterated chloroform was the solvent in all cases.

On cooling the reaction mixtures were concentrated by blowing a stream of nitrogen gas over the solution. The remaining mixtures were purified by flash column chromatography on silica gel with

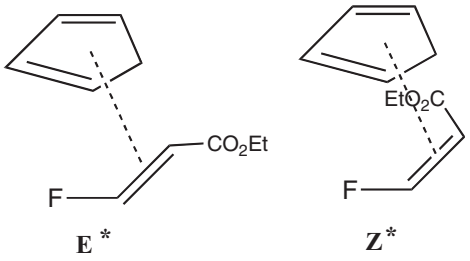


Fig. 2. Secondary orbital interactions.

hexane/ethyl acetate mixtures as the eluent solvents. Yields are reported with the equations.

3.2. Ethyl endo-2-fluoro-1,4-diphenyl-7-oxa-5,6-benzobicyclo[2.2.1]hept-5-ene-3-exo-carboxylate (7-exo) and ethyl exo-2-fluoro-1,4-diphenyl-7-oxa-benzobicyclo[2.2.1]hept-5-ene-3-endo-carboxylate (7-endo)

E-6 (100 mg, 1.7 mmol), 5 mL of ethyl acetate, and **2** (461 mg, 1.7 mmol) were placed in a Fischer pressure tube and tightly closed. The reaction was heated in an oil bath overnight at 80 °C. After 18 h the ethyl acetate was removed and a green oil was obtained. The oil was chromatographed on silica gel (60–100 mesh) with hexane eluent. A mixture of **7-exo** and **7-endo** was obtained in equal amounts in 95% yield.

^{19}F NMR: **7-exo** (F-*endo*, ester *exo*) δ 180.4 (dd, J_{gem} = 59.3, J_{vis} = 28 Hz) (*endo* fluorine atoms are observed at lower field that exo fluorine atoms). ^{1}H NMR: δ 7.2–7.8 (aromatic), 5.8 (*exo* 2-H, dd, J_{HF} = 59.3 Hz, J_{HH} = 2 Hz), 4.1 (CH_2, q, J = 7 Hz), 3.26 (3-H, d, J_{HF} = 28 Hz), 1.4 (CH_3, t); ^{13}C NMR: δ 97 (CF, J = 181.2 Hz), 170 (C=O), 120–148 (aromatic), 17 (CH_3), 58 (d, C3), 60 (CH_2), C1 and C4 quat not observed.

^{19}F NMR: **7-endo** (F-*exo*, ester-*endo*) δ −181.5 (dd, J_{gem} = 51 Hz, J_{vis} = 21 Hz); ^{1}H NMR: δ 7.2–7.8 (aromatic), 5.6 (*endo* 2-H, dd, J_1 = 52 Hz, J_2 = 3 Hz), 3.83 (CH_2, q, J_1 = 6.6 Hz), 3.2 (3-H, d, J_{HF} = 21 Hz), 1.4 (CH_3, t); ^{13}C NMR: δ 89.7 (CF, J = 196.3 Hz), 168 (C=O), 120–148 (aromatic), 17 (CH_3), 58 (d, 3-C), 61 (CH_2), C1 and C4 quat not observed. Mass spectrum of mixture calcd for $C_{25}H_{21}FO_3$: m/z 388. Found 388.

3.3. Ethyl endo-2-fluoro-1,4-diphenyl-7-oxa-5,6-benzobicyclo[2.2.1]hept-5-ene-3-endo-carboxylate (8)

Z-5 (100 mg, 1.7 mmol), 5 mL of ethyl acetate, and **2** (461 mg, 1.7 mmol) were placed in a Fischer pressure tube and tightly closed. The reaction was heated in an oil bath for 48 h at 110 °C. The ethyl acetate was removed and a yellow solid was obtained. The material was chromatographed on silica gel (60–100 mesh) with hexane eluent. Pure **8**, mp 130–133 °C was obtained as pale yellow crystals. After recrystallization slowly from ethyl acetate/hexane crystals for X-ray analysis were obtained (see Fig. 1). The X-ray data is deposited with the Journal. The results show that both the F atom and the ester function are *cis* and *endo*. ^{1}H NMR: δ 7.2–7.8 (aromatic), 5.75 (2-H, dd, J_{gem} = 57 Hz, J_{vis} = 9 Hz), 4.14 (CH_2 of ethyl, q), 3.92 (3-H, dd, J_{HF} = 15 Hz, J_{HH} = 9 Hz), 1.2 (CH_3 of ethyl, t); ^{19}F NMR: δ −185.4 (J_{gem} = 57 Hz, J_{vis} = 15 Hz); ^{13}C NMR: δ 168 (C=O), 120–146 (aromatic), 94.2 (CF, d, J = 189 Hz), 64.5 (C-3), 60.5 (CH_2), 17 (CH_3). MS calcd for 388. Found, 388.

3.4. Reaction of E-6 with cyclopentadiene (9)

Ethyl (*E*)-2-fluoropropenoate (**E-6**, 100 mg, 1.7 mmol) was placed in a Fischer pressure hydrolysis tube with ethyl acetate (5 mL). Fresh cyclopentadiene (**9**, 431 mg, 1.7 mmol) was added and the mixture was allowed to stir for 48 h at 115 °C. The contents became dark yellow and after evaporation gave a yellow semisolid that contained presumably some insoluble polymeric material. The semisolid was chromatographed on silica gel (60–100 mesh) with hexane eluent to give a 22% isolated yield of **11**-*exo* and **11**-*endo* in equal amounts by NMR. ^{1}H NMR: δ 6–6.4 (alkene, m), 5.5 (H-2, dm, J = 57 Hz, J_{12} = 2.1, $J_{2,3}$ = 6 Hz, 11 F-*endo*), 4.9 (H-2, J_{HF} = 60 Hz, $J_{2,3}$ = 3.5, 11 F-*exo*), 4.2 (CH_2 of ethyl), 3.1 (4-H, methine next to F, broad), 2.8 (1-H, m, J_{HF} = 2.1 Hz, **11**-*exo*), 2.9 (4-H, m, **11**-*endo*), 2.6 (3-H, m, mixture), 2.25 (dt, 7-H); ^{19}F NMR: δ −174 (dm, F-*endo*, J_{HF} = 57 Hz), 180.5 (dm, F-*exo*, J_{HF} = 60 Hz); ^{13}C NMR: 173.1, 173.4 (C=O), 130–140 (alkene), 96.3 (d, CF, J = 196 Hz), 96.0 (d, CF, J = 190), 60 (CH_2), 17 (CH_3), 42–52 (C1, C3, C4, all with some F coupling), 37 C7. Mass spectrum of mixture calculated for m/z 184. Found 184.

3.5. Reaction of Z-5 with cyclopentadiene (9)

Ethyl (*Z*)-2-fluoropropenoate (**Z-5**, 100 mg, 1.7 mmol) was placed in a Fischer pressure hydrolysis tube with ethyl acetate (5 mL). Fresh cyclopentadiene (**9**, 431 mg, 1.7 mmol) was added and the mixture was allowed to stir for 48 h at 115 °C. The contents became dark yellow and after evaporation gave a yellow semisolid that contained some presumably polymeric material. The semisolid was chromatographed on silica gel (60–100 mesh) with hexane eluent to give a 35% isolated yield of **10**. The sample contained about 0.2% of the *endo* isomer. ^{1}H NMR: δ 6.6, 6.1 (m, alkene), 5.5 (CHF, dq, J_{HF} = 57 Hz, $J_{H1,F}$ = 2.1 Hz, $J_{H3,F}$ = 3.9), 4.1 (CH_2 of ethyl), 3.0–3.2 (m, H1, H3, H4), 1.2 (CH_3), 3.0–3.2 (m, H1, H3, H4); ^{19}F NMR: −112.6 (dm, J = 57 Hz); ^{13}C NMR: δ 171 (C=O), 131, 129 (alkene), 93.7 (d, CF, J = 198 Hz), 60 (CH_2 of ethyl), 51, 45.5, 45, 44 (ring C), 17 (CH_3 of ethyl). Mass spectrum of **10**: Calculated for $C_{10}H_{13}FO_2$; 184.088. Found: 184.090.

3.6. Preparation of ethyl (Z)-3-fluoropropenoate (Z-5)

A 250 ml round-bottom flask containing a stirring bar was sealed with a rubber stopper and placed under an argon atmosphere. Methylene chloride (25 mL) and then tributylphosphine (18.5 g, 23 mL, 0.091 mol) were added to the flask by syringe. The solution was cooled in an ice bath and trichlorofluoromethane (3.4 mL, 4.2 g, 0.031 mol) was added dropwise by syringe. The solution was stirred for 1 h in the ice bath and then for 3 h at room temp. To the yellow phosphonium salt mixture in an ice bath, ethyl glyoxalate (5 mL, 2.4 g, 0.024 mol) was added dropwise by syringe. The mixture was not allowed to become hot to touch. The rapid reaction shows color change from orange to dark brown. The mix was stirred overnight at room temperature. Sodium hydroxide (6% solution, 30 mL) was added very slowly dropwise to the mixture in an ice bath so as not to allow any warming. If the solution becomes warm then some *E* isomer is obtained. The solution is stirred at room temperature from 1 to 2 h. The mixture was extracted with two 50 mL portions of methylene chloride. The methylene chloride was then washed with two portions of 30 mL of water, followed by two portions of 30 mL of brine, and finally by two portions of 30 mL or sodium bicarbonate. The organic layer was dried with magnesium sulfate and distilled at 50–60 °C to remove the methylene chloride. The final product was obtained from column chromatography on silica gel (hexane) to give 38% of **Z-5**. The spectral parameters are identical with those reported by Wakselman et al. [4] on a mixture of *Z* and *E* products.^{1}H NMR: δ 6.77 (3-H, dd, J_{HF} = 72 Hz, J_{HH} = 6 Hz), 5.33 (2-H, dd, J_{HF} = 15.6 Hz, J_{HH} = 6 Hz), 4.28 (q, CH_2 of ethyl, J = 6 Hz), 1.3 (CH_3 of ethyl, J = 6 Hz); ^{19}F NMR: δ −178.1 (dd, J_{H3} = 72 Hz,

J_{H1} = 15.6 Hz); ^{13}C NMR: 163.3 (C=O), 157.8 (d, J = 267 Hz), 104 (d, J = 15 Hz), 61 (CH_2), 14 (CH_3).

Acknowledgment

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