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Cycloaddition reactions of 3-fluorobutenone

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ABSTRACT

3-Fluorobutenone (**8**) reacted as a dienophile with several dienes **9**, **11**, **13**, **15**, **17** to give cycloaddition products in moderate yields. The regio- and stereoselectivity of the reactions are given. Compound **8** is slightly less reactive than methyl vinyl ketone.

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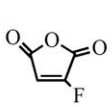
1. Introduction

Research into the use of fluorovinyl and α-fluoro-α,β-enones and esters-compounds as fluorodienophiles is of special interest with regard to using these materials in synthetic protocol [1]. Recently, Haufe [2] has reviewed his work and theory on Diels–Alder reactions of vinyl fluorides with dienes and indicates that fluorinated alkenes are less reactive than the non-fluorinated counterpart. For example *alpha*-(**1**) and *beta*-fluorostyrene (**2**) decrease the cyclization rate by approximately 30 and 10 times, respectively, with respect to styrene. Haufe concludes that simple vinyl fluorides are poor dienophiles in normal Diels–Alder reactions but are useful in inverse electron demand reactions. In addition α-fluoro-α,β-unsaturated carbonyl compounds, such as fluoromaleic anhydride (**3**) and 2-fluorooct-1-ene-3-one (**4**), are versatile dienophiles that react with preferred *exo*-selectivity.

PhCX=CHY

1, X = F, Y = H

2, X = H, Y = F



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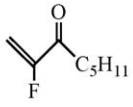

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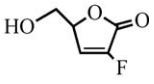

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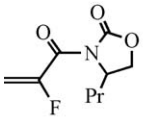
We observed that monofluorinated butenolide **5** reacts slowly in Diels–Alder reactions, but the non-fluorinated analog reacts well [3]. Taguchi and co-workers [4] found enhanced reactivity and *exo*-selectivity in the addition of fluoroacrylic acid derivatives (**6**) to cyclopentadiene. Percy and co-workers [5] demonstrated the facile cycloaddition of a monofluoro vinyl carbamate (**7**).



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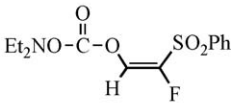

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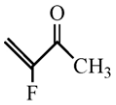
2. Results and discussion

We recently reported the preparation and synthetic utility of 3-fluorobutenone (**8**) in the Heck reaction [6] and in conjugate addition reactions [7]. Dienophile **8** is a fluorinated analog of methyl vinyl ketone. Now we report our results on cycloaddition chemistry with **8** with cyclopentadiene (**9**), furan (**11**), 2,3-dimethyl-1,3-butadiene (**13**), 1,3-diphenylisobenzofuran (**15**) and 4-bromo-2H-pyran-2-one (**17**).



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The cycloaddition of **8** with cyclopentadiene is kinetically controlled and provides *exo*/*endo* products (**10a**, **10b**) in a ratio of 3:1. These results are very similar to the results found by Haufe [2] and by Taguchi and co-workers [4]. The assignment of *endo* and *exo* structures is based on ^{19}F NMR results reported by Taguchi. This

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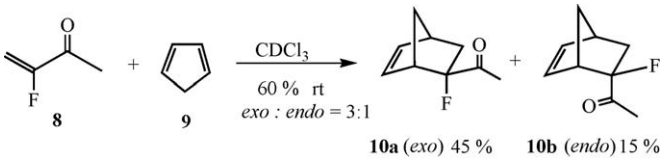
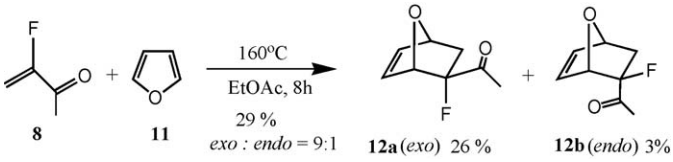
reaction occurred easily at room temperature in $CDCl_3$ or without solvent.

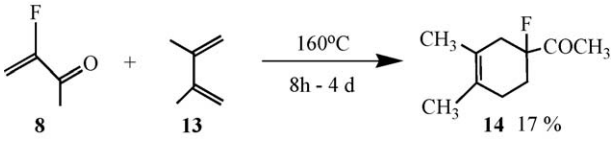


A competition reaction between 3-fluorobutenone (**8**) and methyl vinyl ketone (MVK) for cyclopentadiene showed that MVK is 8.5 times faster than **8** in agreement with Haufe [2] in showing that the fluorine atom decreases the reactivity of the dienophile.

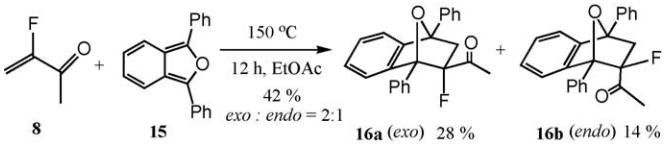
The reaction of **8** with furan (**11**) gave the *exo* product (**12a**) predominantly with *exo*/*endo* selectivity of 9:1 in moderate yield. Cycloaddition of fluorinated dienophiles with furan is rare but has been accomplished with **8** with *exo*/*endo* selectivity of approximately 8:1.



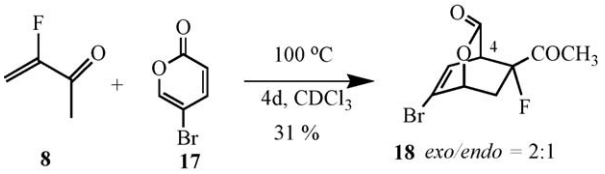
2,3-Dimethyl-1,3-butadiene (**13**) gave a pure cycloaddition product (**14**) with **8** by heating in ethyl acetate at 160 °C overnight in 17% yield. Attempts to improve the yield using longer reaction times or the use of Lewis acid catalysts were unsuccessful.



3-Fluorobutenone (8) underwent cycloaddition with the highly reactive 1,3-diphenylisobenzofuran (15) to give products **16a** (*exo*) and **16b** (*endo*) with *exo*/*endo* ratio of 2:1. Nice white crystals were obtained for X-ray analysis (Fig. 1) for *exo* **16a**. The F NMR for the *exo* isomer shows a singlet at δ −155.6 ppm while the *endo* isomer is observed as a singlet at δ −166.5 ppm ($CFCl_3$ reference). This observation aided in confirming the *exo*/*endo* structures for the other compounds reported here as the *exo* isomer shows its ^{19}F shift at lower field that the *endo* isomer.



Halogenated 2(H)-pyran-2-ones are interesting dienes with much synthetic potential for natural products [8–10]. Computational predictions for the regio- and stereoselectivity of several halogenated 2(H)-pyran-2-ones are known from the work of Afarinkia et al. [8]. We studied the cycloaddition of **8** with 5-bromo-2(H)-pyran-2-one (**17**). The only regio isomer observed contains the fluorine and acyl groups in the 5-position, as predicted by Afarinkia. The ratio of *exo*/*endo* isomers is 2:1 with the *exo* isomer being the major product. Fluorine coupling with C-4 and H-4 established the regiochemistry.



The propensity for obtaining *exo* isomers in Diels–Alder reactions when fluorinated dienophiles are used is well documented [2,4,5] and also observed here in the chemistry of **8**. Theoretical calculations by Haufe and co-workers [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 **A** has an *endo* fluorine and transition state **B** has an *endo* acetyl 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 with the endo fluorine atom is favored and places the fluorine in the *endo* position and the acetyl in the *exo* position, as in observed (transition state A). Thus, because the fluorine interaction with the diene is greater that the interaction of the acetyl with the diene, the fluorine atom determines the stereoselectivity, and the observation is consistent with the endo rule.

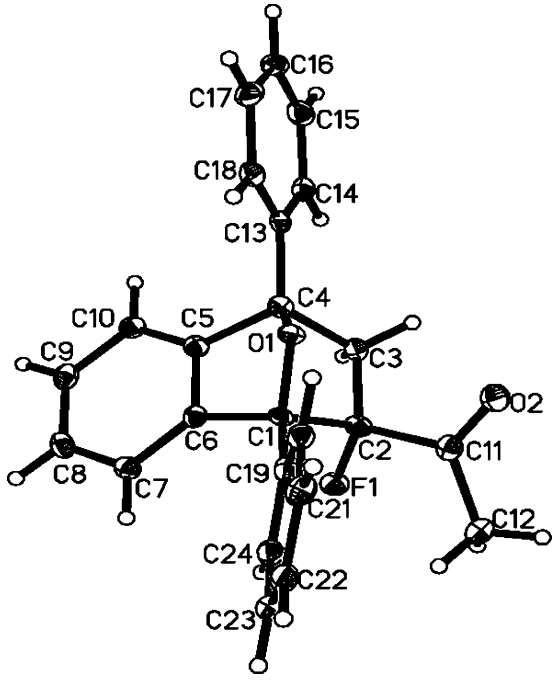


Fig. 1. ORTEP representation of the X-ray crystal structure of **16a** (*exo*).

3. Experimental procedure

3.1. General

^1H NMR data were recorded at 300.0 MHz with tetramethylsilane (δ = 0.00 ppm) as internal reference. ^{13}C NMR spectra were

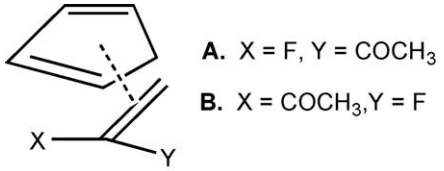


Fig. 2. Secondary orbital interactions.

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 hexane/ethyl acetate mixtures as the eluent solvents. Yields are reported with the equations. A complete material balance was not achieved but minor amounts of **8** were observed in crude NMR spectra and some polymeric residues were observed (carbon, hydrogen and fluorine analysis were satisfactory for the *exo* isomers).

3.2. (Exo.endo)-1-(2-Fluorobicyclo[2.2.1] hept-5-en-2-yl)ethanone (10a, 10b)

(**exo-10a**) ^1H NMR δ 1.1–2.2 (m, 3-CH_2, 7-CH_2, 4H), 2.22 (d, CH_3, J = 2.4 Hz, 3H), 2.24 (m, 4-CH, 1H) 3.08 (d, 1-CH, $J \sim 0$.1 Hz, 1H), 5.8 (m, 5-CH, 1H), 6.3 (m, 6-CH, 1H); ^{113}C NMR δ 26.3 (s, CH_3), 39.0 (m, 3-CH_2), 42.3 (s, 4-CH), 50.6 (7-CH_2), 51.08 (d, 1-CH, J = 7 Hz), 107.2 (d, J = 193 Hz, 2-C), 132.5 (5-CH), 142.3 (6-CH), 209.5(d, CO, J = 35.1 Hz); ^{19}F NMR δ −149.7 (m).

(**endo-10b**) (obtained from impure sample) ^1H NMR δ 1.2–2.2 (m, 3-CH_2, 7-CH_2, 4H), 2.2 (m, 4-CH, 1H), 2.38 (d, CH_3, J = 2.4 Hz, 3H), 3.0 (d, 1-CH, J = 0.5 Hz, 1H), 6.1 (m, 5-CH, 1H) 6.5 (m, 6-CH, 1H); 13 C NMR (not obtained); ^{19}F NMR δ −157.2 (m). An *exo*/*endo* ratio of 3:1 was obtained from ^{19}F analysis of the crude reaction mixture.

3.3. 1-(2-Fluoro-7-oxa-bicyclo [2,2,1] hept-5-en-2-yl)ethanone (12a, 12b)

exo-12a; ^1H NMR; δ 2.2 (d, J = 2.0 Hz, CH_3, 3H), 3.2 (m, 3-CH_2, 2H), 4.9 (m, 4-CH, 1H), 5.05 (m, 1-CH, 1H), 6.1 (m, 5-CH, 1H), 6.3 (m, 6-CH, 1H); ^{13}C NMR δ 26.2 (s, CH_3), 31.0 (d, 3-C, J = 21.4 Hz), 64.0 (4-C), 69.0 (d, 1-CH, J = 9 Hz), 130 (d, J = 1 95.1, 2-C), 141 (s, 5-c), 142 (s, 6-C), 207.3 (d, CO, J = 25.9 Hz); ^{19}F NMR^{TM} −189.5 (m, CF). *endo*-**12b**: ^1H and ^{13}C NMR data for the *endo* isomer were not observed because of the trace amounts of **12b** obtained but a ^{19}F peak at −194.0 (m, CF, *endo*) could be observed and was used to calculate the exo/endo ratio of >20:1.

3.4. 1-(1-Fluoro-3,4-dimethylcyclohex-3-enyl)ethanone (14)

^1H NMR: δ 1.6 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 2.3 (s, CH_3, 3H), 1.7 −2.6 (m, CH_2, 6H); ^{13}C NMR: δ 24.8 (d, CH_3, J = 3.0 Hz), 24.0 (3-CH_3), 24.3 (m, 4-CH_3), 24.5 (s, 5-C), 36.7 (6-C), 37.6 (s, 2-C), 120.9 (s, 3-C), 125.1 (s, 4-C), 210.6 (d, CO, J = 30.2 Hz), quaternary carbon 1 not observed; ^{19}F NMR: δ −162.0 (m, CF).

3.5. Exo-5-fluoro-7-oxo-5-exo-acetyl-1, 3-diphenyl-2, 3-benzobicyclo[2.2.1]-2-heptene (16a, 16b)

The exo/endo ratio of 2:1 was determined from integration of the ^{19}F spectrum. Recrystallization of the solid reaction mixture from ethyl acetate gave the pure *exo*-**16a** product as white needles, mp 170–172 °C. The ORTEP diagram for **16a** is shown in Fig. 1.

^1H NMR: δ 2.05 (s, CH_3, 3H), 2.20 m (CH of CH_2, 1H), 3.0 (m, CH of CH_2, 1H), 7.0–7.8 (m, aromatic, 14H); ^{13}C NMR δ 27.0 (s, CH_3), 46.8 (d, CH_2, J = 8.24 Hz, 3-C), 74.9 (s, 4-C;) 91.4 (d, C, J = 25.0 Hz, 1-C), 119.2 (d, C, J = 10.0 Hz), 112.2–148.6 (aromatic peaks) 205 (d, CO, J = 26.9 Hz); ^{19}F NMR δ −155.6 (m, CF). The *endo* isomer **16b** showed ^{19}F −165.7 (m, CF, *endo*).

3.6. Exo-8-acetyl-6-bromo-8-fluoro-2-oxa-bicyclo[2.2.2]oct-5-en-3-one (18a)

Column chromatography on silica gel with hexane/ethyl acetate eluent gave the pure exo isomer **18a**. ^1H NMR: δ 2.4 (d, J = 2.2 Hz, CH_3, 3H), 2.42 (m, CH of CH_2, 1H), 2.85 (m, CH of CH_2, 1H), 3.8 (d, J = 4 Hz, CH next to CO, 1H), 5.3 (m, CH next to O, 1H), 6.4 (m, vinyl-CH, 1H); ^{13}C NMR: δ 25.3 (d, CH_3, J = 3.3 Hz), 29.9 (m, 7-CH_2), 40.6 (d, 4-CH, J = 7.5 Hz), 68.0 (s, 1-CH), 96.8 (d, 8-C, J = 196.5 Hz), 126.0 (s, 6-CH), 131.9 (s, 5-CH), 166.0 (s, CO of lactone), 204.5 (d, J = 31 Hz, CO of ketone); ^{19}F NMR: δ −148.6 (*exo*). The endo isomer was observed in the mixture but not obtained pure. It showed ^{19}F NMR at −154.3 (*endo*). The *exo*/*endo* ratio determined from integration of the ^{19}F NMR spectrum of the mixture was 2:1.

Acknowledgments

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References

[1] J.M. Percy, Topics in Current Chemistry, in: R.D. Chambers (Ed.), Organofluorine Chemistry. Techniques and Synthons, Springer-Verlag, Germany, 1997, p. 193.
[2] G. Haufe, in V. Soloshonok (Ed.), Fluorine Containing Synthons, ACS Symposium Series, vol. 911, 2005 (Chapter 7).
[3] T.B. Patrick, C. Finau, E. Pak, K. Zaksas, B. Neal, J. Fluorine Chem. 127 (2006) 861.
[4] (a) H. Ito, A. Saito, T. Taguchi, Tetrahedron: Asymmetry 9 (1998) 1979;
(b) H. Ito, A. Saito, T. Taguchi, Tetrahedron: Asymmetry 9 (1998) 1989.
[5] P.J. Crowley, J.M. Percy, K. Stansfield, Tetrahedron Lett. 37 (1996) 8237.
[6] T.B. Patrick, T.Y. Agboka, K. Gorrell, J. Fluorine Chem. 129 (2008) 983.
[7] T.B. Patrick, U.P. Dahal, J. Fluorine Chem. (2009). doi:10.1016/j.jfluchem.2009.02.007.
[8] K. Afarinkia, M.J. Bearpark, A. Ndibwami, J. Org. Chem. 70 (2005) 1122.
[9] (a) C.G. Cho, J.S. Park, I.H. Jung, H. Lee, Tetrahedron 42 (2001) 1065;
(b) C.G. Cho, Y.W. Kim, Y.K. Lim, J.S. Park, J. Org. Chem. 67 (2002) 290.
[10] G.H. Posner, T.D. Nelson, Tetrahedron 46 (1990) 4573.
[11] M. Essers, C. Muck-Lichtenfeld, G. Haufe, J. Org. Chem. 67 (2002) 4715.
[12] K. Alder, G. Stein, Angew. Chem. 50 (1937) 510.
[13] K. Uneyama, Organofluorine Chemistry, Blackwell Publishing, UK, 2006 (Chapter 1).
[14] A. Rauk, Orbital Interactions: Theory of Organic Chemistry, second ed., John Wiley and Sons, New York, 2004, p. 124.