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Diels-Alder Reactions of Oxygen-substituted Difluoroalkenes

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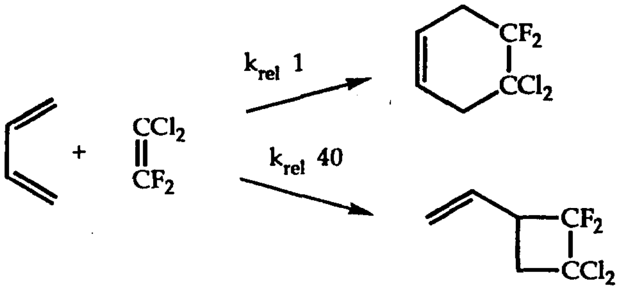
Abstract: We describe thermal [4+2] cycloaddition reactions of a difluoroenol acetal and carbamate with cyclopentadiene, which proceed in good yields.

The Diels-Alder reaction is one of enormous significance and versatility in synthetic organic chemistry; many natural products have been synthesised using this reaction as a key step.[1] However, we have found only one published example of a fluorinated alkene participating as a two electron component in a high-yielding [4+2] cycloaddition;[2] *trans*-1,2-difluorodinitroethylene adds to cyclopentadiene (dichloromethane, RT) and anthracene (benzene, reflux) under mild conditions albeit in moderate yield (49 and 47% respectively).

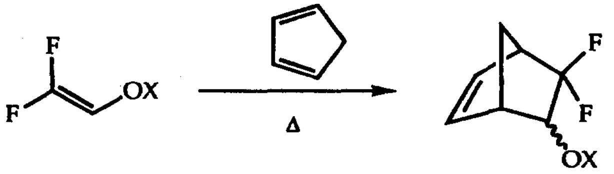
The concensus in the literature is that the fluoroalkenes lacking additional electron-withdrawing groups more readily undergo [2+2] reactions, often leading to dimers[3] and calculations[4] have suggested that the fluorine substituents act by stabilising diradical intermediates and thereby accelerating the [2+2] reaction. Even when products of the [4+2] addition are observed, they are usually only present in trace amounts. For example, 1,1-dichloro-2,2-difluoroethylene undergoes slow [4+2] addition to butadiene but the corresponding [2+2] addition occurs 40-times faster (Scheme 1).[5]



Scheme 1

Despite these discouraging precedents, the potential utility of Diels-Alder reactions with fluorine-substituted dienophiles for the construction of cyclic compounds containing -CHF- or $-CF_2$-groups prompted us to undertake this study as part of a continuing search for new fluorine-containing building blocks.

We have found that when the difluoroalkene bears an oxygen substituent as in **1** or **2**, [4+2] cycloadditions are observable. Heating cyclopentadiene with **1** (140°C, sealed tube, 12 hours) or **2** (150°C, sealed tube, 48 hours) affords bicyclic adducts **3** and **4** in 72 and 80% isolated yields as mixtures of *endo* and *exo* adducts (Scheme 2).[6]

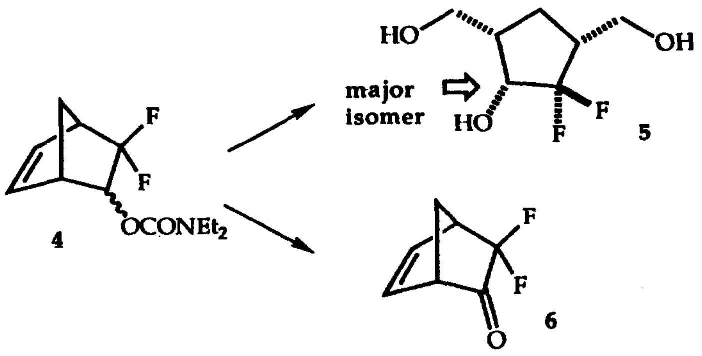


1; X = OMEM
2; X = $OCONEt_2$

3; X = OMEM
4; X = $OCONEt_2$

Scheme 2

The fluoroalkenes are readily available from trifluoroethanol using recently-developed chemistry.[7,8] Structural confirmation was provided by the SERC Ultra High Field NMR service at Edinburgh; difference nOe experiments on adduct 4 allowed the *endo*/*exo* ratio to be determined, the *endo* isomer predominating by a factor of 4:1.



Scheme 3

We have conducted some trial conversions on the adduct 4 (Scheme 3); ozonolytic cleavage ($O_3/CH_2Cl_2/-78^oC$; Me_2S work-up)[9] of the double bond, followed by reduction ($NaBH_4$ in methanol) of the unstable intermediate dialdehyde, and removal of the carbamate (NaOMe/MeOH/reflux)[10] affords highly functionalised diol 5 (90%), while removal of the carbamate group from 4[10] and Dess-Martin oxidation[11] allows isolation of bicyclic ketone 6 (65%), a potentially useful intermediate for the synthesis of more complex molecules.

It appears that the oxygen function masks the [2+2]-promoting effect of the two fluorine atoms to an extent sufficient for these alkenes to behave as effective two electron components in thermal [4+2] cycloadditions. However, these alkenes are still electron deficient; attempts to add 1 to crotonaldehyde in the presence of a Lewis acid catalyst after Danishefsky[11] resulted in the recovery of unreacted starting materials.[13] We also failed to isolate any adduct in the reaction between furan and 1. With the less reactive 2,3-dimethylbutadiene, we isolated a mixture of [2+2] and [4+2] adducts which we were unable to separate.

Current work in this laboratory is exploring the effect of diene structure on these reactions, and seeking to develop solvent-based and catalytic processes.

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