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Radical Additions to β,β-Difluoroacrylates

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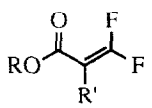
Abstract: Tetrahydrofuran, 1,3-dioxolane, hexanal, and benzaldehyde react readily with β,β–difluoroacrylates under free radical conditions to furnish adducts in moderate to high yield.

β,β–Difluoro derivatives of acrylic acids and esters **1** have shown great diversity as fluorinated substrates in various reactions. For example, **1** (R,R'= alkyl) has been used extensively as a precursor to



1

α–difluoromethylated[1], and α–trifluoromethylated carboxylic acid derivatives[2]; **1**(R=alkyl, R'=H) is a suitable substrate in Diels-Alder reactions[3] and in Michael additions[4]. However, Michael additions are limited due to the facile elimination of fluoride from the anionic intermediates derived from **1**(R=H, R'=alkyl) [5] and **1**(R,R'=-$CH_2C(CH_3)_2$-)[6]. Feeling that intermediate **2** would not readily loose a high energy fluorine atom, we examined radical addition to **1a** and found this to be a viable route to several 3,3-difluoroesters **3**, Figure 1.

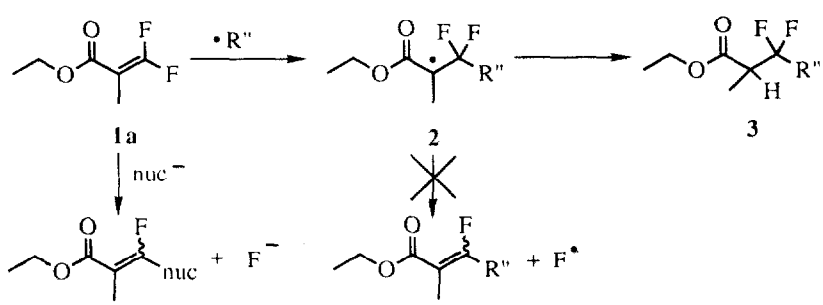
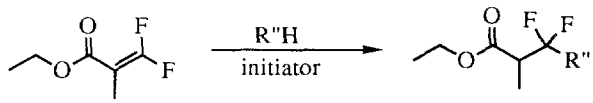


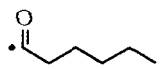
Fig. 1

Although radical additions to acrylates[7] and to terminal fluorolefins[8] are well known, no study of radical additions to β,β-difluoroacrylates, **1a**, has been reported. Acyl and α-alkoxy radical species were

chosen for initial study based on the facile additions of these radicals to 1-fluoro-1-(phenylsulfonyl) ethylene[9]. The results in table 1 show that α–alkoxy radicals and acyl radicals can be generated and added to **1** in useful yields. Refluxing **1a** (R=C_2H_5, R'=CH_3) in tetrahydrofuran with 1 mol% of 2,2'-azobis(2-methyl-propionitrile) (AIBN) and 1 mol% benzoyl peroxide (BPO) produces the fluoralkyl substituted tetrahydrofuran **4** in 73% yield. Gas chromatography revealed the product to be a 3:2 ratio of the diastereomers. Interestingly, neither AIBN nor BPO alone succeeded in producing the desired transformation, but the mixed initiator system performed satisfactorily.

Table 1. Radical Additions to Ethyl 3,3-difluoro-2-methyl propenoate,**1a** .



•R"	product	yield	^{19}F NMR of adduct
	**4**	73%	-114.2 ddd J_{FF}=252 Hz -119.7 ddd J_{FF}=252 Hz -114.8 ddd J_{FF}=256 Hz -118.6 ddd J_{FF}=256 Hz
	**5**	71%	-114.0 ddd J_{FF}=267 Hz -121.5 ddd J_{FF}=267 Hz
	**6**	53%	-106.4 dd J_{FF}=277 Hz -120.2 dd J_{FF}=277 Hz
	**7**	22%	-100.9 dd J_{FF}=287 Hz -110.7 dd J_{FF}=287 Hz

Similarly, refluxing **1a** with 1,3 dioxolane in the presence of 1mol% AIBN / 1 mol% BPO furnishes the fluoroalkyl substituted acetal **5** in 71% yield. An attempt to produce the ketal by similar methods from **1a** and 2-pentyl-1,3-dioxane failed under various conditions of time and initiator concentrations.

Acyl radicals from both aliphatic and aromatic aldehydes also add to **1a**. Refluxing **1a** with hexanal and 5 mol% AIBN/ 5 mol% BPO in benzene provides the α,α-difluoroketone **6** in 52% yield. The use of 5 mol% AIBN and BPO was required to produce reasonable yields. Likewise refluxing **1a** and benzaldehyde with 5 mol% AIBN/ 5 mol% BPO in benzene produces the α,α-difluoroketone **7** which was isolated in 22% yield.

In conclusion, radicals from ethers and aldehydes add to the β carbon of β,β-difluoroacrylates. Since we have recently published a general method for synthesizing β,β-difluoroacrylates[10] in multigram quantities, free radical additions to these substrates constitute a new and useful route to a variety of fluorinated compounds not readily available by conventional methods.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a GE GN-300 NMR spectrometer operating at 300.52 MHz for ^{1}H and 75.57 MHz for ^{13}C. Spectra were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to internal TMS. ^{19}F NMR spectra were obtained on a Bruker AR-100 spectrometer operating at 95.52 MHz for ^{19}F. Spectra were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to external $CFCl_3$. Negative chemical shifts indicate that the resonances are upfield relative to $CFCl_3$.

Ethyl 3,3-difluoro-2-methyl propenoate, **1a**, was prepared by previously described methods[10]. 1,3-Dioxolane and hexanal were purchased from Aldrich and distilled prior to use. Benzaldehyde, from Aldrich, was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and distilled prior to use. Tetrahydrofuran was distilled from sodium/benzophenone. Benzene, from Fisher, was washed with concentrated H_2SO_4 and then distilled. AIBN from Polyscience and BPO from Aldrich were used as purchased.

Synthesis of **4** 0.821g (5.00 mmols) of ethyl 3,3-difluoro-2-methyl propenoate, **1a**, 0.008g (0.05 mmols) of AIBN, and 0.012g (0.05 mmols) of BPO, were combined in 10 ml of THF and brought to reflux under N_2. The mixture was refluxed for 12 hrs then cooled to RT. The volatile materials were removed by rotary evaporation. The residue was taken up in ether and washed with saturated $NaHCO_3$ several times. The organic fractions were combined and dried over anhydrous $MgSO_4$. After filtration and solvent removal by rotary evaporation the light yellow oil was flash chromatographed using 15% methylene chloride in hexanes to provide 0.810g (73% yield) of **4** in >95 % purity as a 3:2 mixture of diastereomers. MS: base peak 177 $[M- C_2H_5O]^+$; ^{1}H NMR (δ) : 1.20 (t, 3H, $^{3}J_{HH}$=7.0 Hz); 1.23 (d, 3/2 H, $^{3}J_{HH}$=3.7 Hz); 1.26 (d, 3/2 H, $^{3}J_{HH}$=3.7 Hz); 1.90 (mult, 4H); 3.10 (mult, 1H); 3.75 (mult, 2H); 4.10 (mult, 3H). ^{13}C NMR (δ): 9.9 (t, $^{3}J_{CF}$=3 Hz); 11.0 (t, $^{3}J_{CF}$=3 Hz); 13.5; 25.0; 26.5; 44.0 (mult); 60.5; 69.0; 78.2 (mult); 122 (t, $^{1}J_{CF}$=272 Hz); 170 (mult). ^{19}F NMR (δ): -114.2 (ddd, $^{2}J_{FF}$=252 Hz, $^{3}J_{HF}$=18.1 Hz, $^{3}J_{HF}$=5.0 Hz); -119.7 (ddd, $^{2}J_{FF}$=252 Hz, $^{3}J_{HF}$=21.1 Hz, $^{3}J_{HF}$=11.3 Hz); -114.8 (ddd, $^{2}J_{FF}$=256 Hz, $^{3}J_{HF}$=21.4 Hz, $^{3}J_{HF}$=4.0 Hz); -118.6 (ddd, $^{2}J_{FF}$=256 Hz, $^{3}J_{HF}$=20.9 Hz, $^{3}J_{HF}$=9.2 Hz).

Synthesis of **5**. **5** was prepared by a procedure similar to **4**. ^{1}H NMR (δ): 1.21 (t, 3H, $^{3}J_{HH}$=7.3 Hz); 1.25 (d, 3H, $^{3}J_{HH}$=7.6 Hz); 3.05 (mult, 1H); 3.93 (mult, 2H); 4.00 (mult, 2H); 4.15 (q, 2H, $^{3}J_{HH}$=7.3 Hz); 5.23 (dd, 1H, $^{3}J_{HF}$=6.6 Hz, $^{3}J_{HF}$=9.5 Hz). ^{13}C NMR (δ): 10.7 (t, $^{3}J_{CF}$=1.7 Hz); 14.1; 44.7 (t, $^{2}J_{CF}$=47.5 Hz); 62.1; 66.3; 101.1 (t, $^{2}J_{CF}$=65.8 Hz); 120.0 (t, $^{1}J_{CF}$=257 Hz); 170.1 (mult). ^{19}F NMR (δ): -114.0 (ddd, $^{2}J_{FF}$=267 Hz, $^{3}J_{HF}$=12.5 Hz, $^{3}J_{HF}$=9.0 Hz); -121.5 (ddd, $^{2}J_{FF}$=267 Hz, $^{3}J_{HF}$=16.0 Hz, $^{3}J_{HF}$=7.0 Hz).

Synthesis of **6**. 1.044g (7.00mmol) of **1a**, 0.697g (7.00mmol) of hexanal, 0.006g (.35 mmol) of AIBN and 0.008g (.35 mmol) of BPO were combined in 10 ml of dry benzene and refluxed for 2 days under N_2. The mixture was cooled to RT and the volatile materials were removed by rotary evaporation. The residue was taken up in ether and extracted with several portions of saturated $NaHCO_3$. The organic fractions were

combined over anhydrous $MgSO_4$. After filtration and solvent removal by rotary evaporation yellow oil was Kugelrohr distilled providing 0.991g (52% yield) of **9** as a colorless oil. MS: 205 $[M-C_2H_5O]^+$, 230 $[M-HF]^+$; ^1H NMR (δ): .90 (mult, 3H); 1.22 (t, 3H, $^3J_{HH}$=7.3 Hz); 1.30 (mult, 4H); 1.37 (d, 3H, $^3J_{HF}$=7.2 Hz); 1.62 (mult, 2H); 2.75 (mult, 2H); 3.40 (mult,1H, $^3J_{HF}$=22.0 Hz, $^3J_{HF}$=7.2 Hz, $^3J_{HH}$=7.2 Hz); 4.15 (q, 2H, $^3J_{HH}$=7.3 Hz). ^{13}C NMR (δ): 9.0 (t, $^3J_{CF}$=3.0 Hz); 13.9; 14.0; 22.0; 25.2; 32.1; 44.0; 44.3 (t, $^2J_{CF}$=24.4 Hz); 44.0; 62.0; 117.7(t, $^1J_{CF}$=256 Hz); 172.8 (d, $^3J_{CF}$=12.2 Hz); 203.3 (t, $^2J_{CF}$=26.8 Hz). ^{19}F NMR (δ): -106.4 (dd, $^2J_{FF}$=277 Hz, $^3J_{HF}$=7.2 Hz); -120.2 (dd, $^2J_{FF}$=277 Hz, $^3J_{HF}$=22.0 Hz).

Synthesis of 7. **7** was produced by a procedure similar to **6**. ^1H NMR (δ): 1.18 (t, 3H, $^3J_{HH}$=7.3 Hz); 1.46 (d, 3H, $^3J_{HH}$=7.3 Hz); 3.58 (mult, 1H); 4.15 (q, 2H, $^3J_{HH}$=7.3 Hz); 7.48 (mult, 3H); 8.10 (mult, 2H). ^{13}C NMR (δ): 9.6 (t, $^3J_{CF}$=4.9 Hz); 13.7; 43.7 (t, $^2J_{CF}$=24.4 Hz); 61.1; 128.4; 129.9; 130.0 (t,$^1J_{CF}$=258 Hz); 133.9; 134.2; 170.0 (t, $^3J_{CF}$=12.0 Hz); 180.0 (mult). ^{19}F NMR (δ): -100.9 (dd, $^2J_{FF}$=287 Hz, $^3J_{HF}$=9.4 Hz); -110.7 (dd, $^2J_{FF}$=287 Hz, $^3J_{HF}$=19.8 Hz)

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