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A New Route To 1,1-Difluoroolefins From Carboxylic Acids

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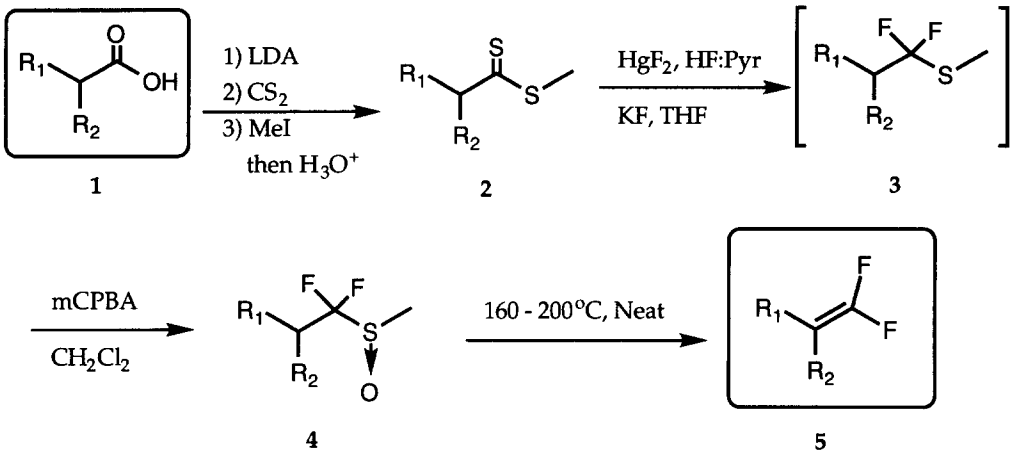
Abstract: Methodology is described for the conversions of carboxylic acids to 1,1-difluoroolefins via α, α-difluorothioethers (**3**).

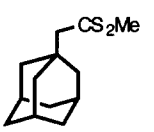
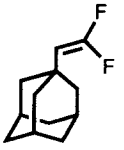
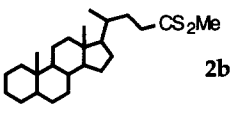
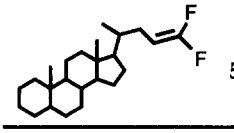
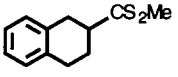
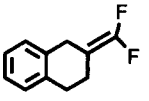
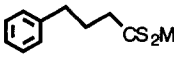
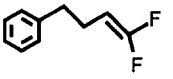
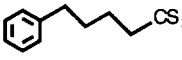
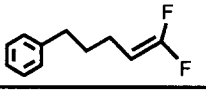
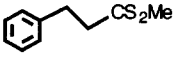
New methods for the synthesis of 1,1-difluoroolefins have attracted considerable attention, in large part due to the interest in the design of biologically active molecules incorporating this functional group.[1,2] The 1,1-difluoroolefin group is critical for certain mechanism-based enzyme inhibitors, [2,3] and can function as a bioisostere for aldehydes and ketones.[4]

Only a limited number of methods have been developed for the synthesis of 1,1-difluoroolefins and they rely on the addition of a reagent that adds the terminal carbon or the terminal two carbons containing the two fluorines to an electrophile or nucleophile. The most versatile method, and one that incorporates the terminal difluorocarbon, is the Wittig olefin synthesis.[5,6] Electrophilic fluorination of (fluorovinyl)stannanes, obtained from fluorovinyl sulfones *via* a Wittig reaction, offers an alternative method to 1,1-difluoroolefins that adds the terminal carbon initially with a single fluorine.[7] Other methods require incorporation of the two terminal difluoroolefin carbons into a precursor. These include the addition of stabilized difluorovinyl anions, (obtained from protected derivatives of 2,2,2-trifluoroethanol) to electrophiles,[8] addition of ethyl 4-chloro-4,4-difluorocrotonate to aldehydes *via* the Reformatsky reaction,[9] addition of organolithium reagents and other nucleophiles to 1,1-difluoromethylstyrene[10] and regioselective addition of carbon nucleophiles to 1,1-difluoro-p-allylpalladium complexes.[11] Recently, ethyl chlorofluoroacetate was utilized in a Wittig reaction to obtain chlorodifluoromethylepoxyethers that undergo butyllithium catalyzed rearrangement to 2-ethoxy-1,1-difluoroallylic alcohols.[12] A method that avoids the addition of the terminal difluorocarbon(s) to a preexisting electrophile or nucleophile from readily available starting material would be advantageous for the synthesis of a large number of 1,1-difluoroolefins.

We report herein a new method for the synthesis of 1,1-difluoroolefins that avoids the addition of the terminal difluorocarbon(s) by using carboxylic acids as starting materials; in this route the carbonyl group of the acid is converted into the terminal difluoroolefin carbon. Carboxylic acids are converted to dithioesters (**2**) in high yield by a facile one-pot procedure (see Table).[13] We had hoped that **2** could be converted to a,a-difluorothioethers (**3**) with diethylaminosulfur trifluoride (DAST), based on the report that thioesters are converted to a,a-difluoroethers on treatment with DAST. [14] However, the conversion of **2** to **3** with DAST was unsuccessful in our hands. After exploring several different routes we proposed that HgF_2 [15] in the presence of excess HF-pyridine and KF would lead to the formation of the desired a,a-difluorothioethers (**3**).

Table. Synthesis of 1,1-Difluoroolefins.



Entry	2 (Yield from 1)	4 (yield from 2)	5 (Rxn. Temp., Rxn. Time and Yield*)
a	 **2a** (66%)	**4a** (65%)[17]	 **5a** (195°C, 4hr, 77%)[17]
b	 **2b** (80%)	**4b** (57%)[18]	 **5b** (195°C, 4hr, 87%)[18]
c	 **2c** (59%)	**4c** (45%)[19]	 **5c** (170°C, 5hr, 64%)[19]
d	 **2d** (78%)	**4d** (38%)[20]	 **5d** (200°C, 5hr, 89%)[20]
e	 **2e** (75%)	**4e** (43%)[21]	 **5e** (160°C, 5hr, 74%)[21]
f	 **2f** (38%)	Not successful.	

*Due to the volatility of most products, the yields of **5a**, **5c**, **5d** and **5e** were measured by GC analyses using 3,5-dimethoxybenzylalcohol as an internal standard. The yield for **5b** was based on isolated product.

Indeed, treatment of **2** under these conditions lead to good yields of **3**. Excess HF pyridine was required to obtain a high yield of desired product **3**. Subsequent oxidation of **3** to the corresponding sulfoxide **4** was readily accomplished with one equivalent of 3-chloroperbenzoic acid in good overall yield. Neat pyrolysis of **4** at 160 to 200 °C by a procedure similar to that reported by Reutrakukl and Rukachaisinkul[16] gave high yields of the title compounds (**4**) (see Table). It should be noted that phenethyl dithioester (see **2f** in Table) did not provide **3f** under the above reaction conditions.

The preparation of 1,1-difluoroolefins is illustrated by the synthesis of **5b**:

Preparation of **4b**. To a THF (10 ml) solution of HgF_2 (477 mg, 2.0 mmole) and anhydrous KF (58 mg, 0.5 mmole) under a N_2 atmosphere was added HF-pyridine (Aldrich) (3.2 g). After 5 min. stirring at RT, dithioester **2b** (812 mg, 2.0 mmole) (prepared by procedure in ref. 13) was added in one portion to the reaction mixture. After 4 hours at RT, the reaction mixture was poured into hexane (50ml) and 5% aqueous $NaHCO_3$ solution was added to the hexane solution until no gas evolution was observed. The hexane solution was dried ($MgSO_4$) and concentrated at below 25 °C. The concentrate of **3b** was dissolved in CH_2Cl_2 (10 ml) and mCPBA was added portionwise to this solution. The progress of the reaction (essentially a titration) was followed by TLC and on completion of the oxidation, the reaction mixture was washed with 5% aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated. Purification by prep-TLC (hexane/ether = 1/2) afforded 488 mg (57% from **2b**) of **4b** as a colorless oil.[18]

Preparation of **5b**. Neat **4b** (150 mg, 0.35 mmole) was heated in a sealed tube at 195 °C for 4 hours. The reaction mixture was cooled and dissolved in hexanes. The resulting solution was filtered through silica gel. Concentration of the filtrate afforded 111 mg (87%) of **5b** as a colorless oil.[18]

In summary, a new method for the synthesis of 1,1-difluorolefins is reported which compliments the Wittig reaction methods and provides the homodifluoroolefin relative to the Wittig reaction product.

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16. Reutrakukl, V.; Rukachaisinkul, V. *Tetrahedron Lett.* **1983**, *24*, 725-727.
17. Methyl adamantyldifluoromethyl sulfoxide (**4a**): R_F 0.65 (Ether); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 1.67-1.76(12H, m, CH_2), 1.99(3H, m, CH), 1.91-2.23(2H, m, CH_2), 2.63(3H, s, CH_3); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -107.12(1F, ddd, J_1 = 217.1, J_2 = 34.4, J_3 = 6.2, CF_2), -99.90(1F, ddd, J_1 = 217.1, J_2 = 38.9, J_3 = 11.0, CF_2); M.S.(EI) m/z 261(M-1), 135.
1-Adamantyl-2,2-difluoroethylene (**5a**): R_F ^{1}H-NMR (300 MHz, C_6D_6, J in Hz) d 1.67-1.74(12H, m, CH_2), 1.97(3H, m, CH), 3.94(1H, dd, J_1 = 29.3, J_2 = 5.8, CH); ^{19}F-NMR (282 MHz, C_6D_6, $CFCl_3$, J in Hz) d -88.65(1F, dd, J_1 = 52.9, J_2 = 5.8, CF_2), -87.51(1F, dd, J_1 = 52.9, J_2 = 29.3, CF_2); HRMS (EI) M^+ 198.1225 (observed), 198.1220 (calculated).
18. Methyl 5b-24,24-difluorocholan-24-sulfoxide (**4b**): R_F 0.25 (Hexane/Ether = 1/1); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 0.65(3H, s, CH_3), 0.92(3H, s, CH_3), 0.96(3H, d, J = 6.4, CH_3), 1.00-1.95(28H, m, CH & CH_2), 2.00-2.45(2H, m, CH_2), 2.66(3H, s, CH_3); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -108.49(1F(diastereomer-A), ddd, J_1 = 102.5, J_2 = 13.0, J_3 = 5.2, CF_2), -108.16(1F(diastereomer-B), ddd, J_1 = 102.5, J_2 = 13.0, J_3 = 5.2, CF_2), -104.93 (1F(diastereomer-A & B), dm, J = 102.5, CF_2); MS (EI) m/z 364, 349, 287, 257, 217.
Methyl 5b-24,24-difluoro-24-cholene (**5b**): ^{1}H-NMR (300 MHz, C_6D_6, J in Hz) d 0.59(3H, s, CH_3), 0.84(3H, d, J = 6.6, CH_3), 0.96(3H, s, CH_3), 0.85-1.90(28H, m, CH & CH_2), 3.95(1H, dddd, J_1 = 26.0, J_2 = 7.0, J_3 = 2.8, J_4 = 1.0, CH); ^{19}F-NMR (282 MHz, C_6D_6, $CFCl_3$, J in Hz) d -92.34(1F, dd, J_1 = 48.8, J_2 = 26.0, CF_2), -88.85(1F, d, J = 48.8, CF_2); HRMS (EI) M^+ 364.2930(observed), 364.2942(calculated).
19. Methyl difluoro-(2-(1,2,3,4-tetrahydronaphthyl))methyl sulfoxide (**4c**): R_F 0.73 (Ether); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 1.77(2H, m, CH_2), 2.28(1H, m, CH_2), 2.72(3H, s, CH_3), 2.62-3.20(5H, m, CH_2), 7.05-7.15(4H, m, aromatic); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -118.04(1F, ddd, J_1 = 221.4, J_2 = 32.7, J_3 = 5.6, CF_2), -113.24(1F, ddd, J_1 = 221.4, J_2 = 20.0, J_3 = 20.0, CF_2).
2-Difluoromethylene-1,2,3,4-tetrahydronaphthalene (**5c**): R_F 0.70 (Hexane); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 2.40(2H, t, J = 7.5, CH_2), 2.80(2H, t, J = 7.5, CH_2), 3.44(2H, m, CH_2), 7.10-7.15(4H, m, aromatic); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -97.40(1F, d, J = 59.4, CF_2), -95.66(1F, d, J = 59.4, CF_2); H.R.M.S.(EI) M^+ 180.0758(observed), 180.0751(calculated).
20. Methyl 4-phenyl-1,1-difluoro-1-butyl sulfoxide (**4d**): R_F 0.47 (Ether); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 1.99(2H, m, CH_2), 2.29(2H, m, CH_2), 2.66(3H, s, CH_3), 2.73(2H, t, J = 7.5, CH_2), 7.18-7.33(5H, m, aromatic); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -111.58 (1F, dt, J_1 = 220.0, J_2 = 15.2, CF_2), -104.70(1F, dt, J_1 = 220.0, J_2 = 21.4, CF_2).
4-Phenyl-1,1-difluoro-1-butene (**5d**): R_F 0.90 (Hexane/Ether = 40/1); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 2.30(2H, td, J_1 = 8.0, J_2 = 7.8, CH_2), 2.69(2H, t, J = 8.0, CH_2), 4.15(1H, dtd, J_1 = 25.5, J_2 = 7.8, J_3 = 2.5, CH), 7.17-7.30(5H, m, aromatic); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -91.67(1F, dd, J_1 = 46.5, J_2 = 25.9, CF_2), -89.62(1F, d, J = 46.5, CF_2); HRMS(EI) M^+ 168.0747(observed), 168.0751(calculated).
21. Methyl 5-phenyl-1,1-difluoro-1-pentyl sulfoxide (**4e**): R_F 0.65 (Ether); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 1.72(4H, m, CH_2), 2.30(2H, m, CH_2), 2.63(2H, t, J = 8, CH_2), 2.66(3H, s, CH_3), 7.16-7.30(5H, m, aromatic); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -111.40(1F, ddd, J_1 = 220, J_2 = 15.6, J_3 = 15.6, CF_2), -104.80(1F, dt, J_1 = 220, J_2 = 20.3, J_3 = 20.3, CF_2).
5-Phenyl-1,1-difluoro-1-pentene (**5e**): R_F 0.90 (Hexane/Ether = 40/1); ^{1}H-NMR (300 MHz, $CDCl_3$, J in Hz) d 1.72(2H, tt, J_1 = 7.6, J_2 = 7.6, CH_2), 2.01(2H, td, J_1 = 7.6, J_2 = 7.7, CH_2), 2.62(2H, t, J = 7.6, CH_2), 4.16(1H, dtd, J_1 = 25.4, J_2 = 7.6, J_3 = 2.7, CH), 7.16-7.30(5H, m, aromatic); ^{19}F-NMR (282 MHz, $CDCl_3$, $CFCl_3$, J in Hz) d -92.13(1F, dd, J_1 = 47.6, J_2 = 25.4, CF_2), -89.81(1F, d, J = 47.6, CF_2); HRMS (EI) M^+ 182.0913 (observed), 182.0907 (calculated).

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