Tetrahedron Letters,Vol.30,No.41,pp 5571-5574,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

PREPARATION OF α-FLUORO-α,β-UNSATURATED ESTERS VIA TWO CARBON HOMOLOGATION OF ESTERS[1]

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Abstract: In the presence of diisobutyl aluminum hydride, esters react with an anion derived from $(EtO)_2P(O)CFHC(O)OEt$ to give the title compounds in good yields. The scope of this method and the factors which influence the stereochemistry of the products are discussed.

α-Fluoro-α,β-unsaturated esters of defined stereochemistry are useful building blocks for the synthesis of biologically active 12-fluororetinal and 12-fluororhodopsin,[2] fluorinated mimics of insect sex pheromones of the silkworm moth Bombyx mori,[3] and in the field of pyrethroids.[4]

The methods reported for the preparation of the title compounds include 1) condensation of carbonyl compounds with either fluoroacetate or fluorooxaloacetate,[5] 2) the Horner-Wadsworth-Emmons reaction of fluorocarboalkoxy substituted dialkylphosphonate anions and carbonyl compounds,[6] 3) spray-dried potassium fluoride fluorination of chloromalonates in the presence of aldehydes and ketones,[7] 4) addition of chlorofluorocarbene to enoxysilanes and subsequent rearrangement of the cyclopropanes,[8] 5) addition of carbonyl compounds to perfluorovinyl organometallic reagents,[9] and 6) zinc(0)-copper(I) chloride promoted reaction of methyl dichlorofluoroacetate with carbonyl compounds.[10] Although many of these methods offer a convenient route to introduce a fluorine atom at the α-position with a concomitant elongation of the chain by two carbon atoms, the generality of these methods depends upon the availability of the carbonyl compounds. All of the reported unsaturated esters were derived from fluorine-free aldehydes, and reaction of fluorinated aldehydes with $[(EtO)_2P(O)C^{-}FC(O)OEt\ M^{+}]$ has not been reported. The lack of a general synthetic procedure for the preparation of fluorinated aldehydes may be the main reason for this paucity. Herein, we describe a synthesis of α-fluoro-α,β-unsaturated esters (2) via the Horner-Wadsworth-Emmons reaction between the anion generated from $(EtO)_2P(O)CFHC(O)OEt$ and the aldehydes produced in situ from esters (1).

Recently, Takacs[11] has reported that diisobutylaluminum hydride (DIBAL) reduction of esters and lactones in the presence of lithio triethylphosphonoacetate leads to the corresponding homologated unsaturated esters in good yields. The overreduction of in situ generated aldehyde or the product unsaturated ester is minimal (<3%) when a stoichiometric quantity of DIBAL is used for reduction. Takacs' report led us to investigate the related carbon homologation reaction with $(EtO)_2P(O)CFHC(O)OEt$, a fluorinated analogue of $(EtO)_2P(O)CH_2C(O)OEt$. In the presence of DIBAL, esters react with an anion derived from $(EtO)_2P(O)CFHC(O)OEt$ to afford the corresponding unsaturated esters in good yields (Scheme I). Perfluorinated, partially fluorinated, aliphatic, aromatic, cyclic and α,β-unsaturated esters were converted to the title compounds in good yields (Table I). Homologation of an ester *via* this reduction/olefination sequence thus permits the use of readily accessible esters in place of aldehydes, which is invaluable in fluorocarbon chemistry where fluorinated esters can be used as a convenient and inexpensive source of fluorinated aldehydes.

$$\underset{(1)}{RC(O)OR'} \xrightarrow[\text{1) DIBAL}\quad \text{2) }[(EtO)_2P(O)C^{-}FC(O)OEt]\ M^{+}]{THF/-78^{o}C} \underset{(2\ E\ \text{and}\ Z)}{RCH{=}CFCOOEt}$$

R = alkyl, aryl, alkenyl, perfluoro and partially fluorinated alkyl

R' = Me, Et, and *n*-Bu; M = Li, Na, and K

Scheme I

Observations in our laboratory indicate that the conversion of esters to final products is low (60-65%) *via* the Takacs procedure, i.e. when the reduction of esters to aldehydes was performed in the presence of $[(EtO)_2P(O)C^{-}FC(O)OEt\ Li^{+}]$ (Method B). However, the conversion can be improved (80-90%) by addition of a THF solution of the anion to the *in situ* pre-generated aldehyde (Method A).

The stereochemistry of the unsaturated esters (2) obtained in the homologation reaction depends on the counter ions present in the reaction mixture. With lithium ion, the *E* isomer (E/Z = 83/17) predominates, while in the presence of sodium and potassium ions, there was little selectivity (E/Z = 55/45). The effect of metal ions on the isomer ratio may best be explained by the degree of association of M^{+} with the intermediate alkoxide ion, which affects the interconversion between the two diastereoisomeric alkoxide ions. Solvents such as THF, diethyl ether or *n*-hexane have very little influence on the stereochemistry of the products.

The stereospecific formation of *E*,*Z*-$CH_3CH{=}CHCH{=}CFCOOEt$ and *E*,*E*-$PhCH{=}CFCH{=}CFCOOEt$ from *E*-$CH_3CH{=}CHCOOEt$ and *E*-$PhCH{=}CFCOOEt$ indicates that the above methodology may also be used to prepare α-fluoro dienic esters in good yields. In addition, the transformation of $PhCOOBu^{n}$ to *E*-$PhCH{=}CFCOOEt$ and then to *E*,*E*-$PhCH{=}CFCH{=}CFCOOEt$ exemplifies the synthetic utility of this method in sequential two carbon chain extension reactions.

Table I: Preparation of $RCH{=}CFCOOEt$

$$RCOOR' \xrightarrow[\substack{1)DIBAL \\ 2)[(EtO)_2P(O)C^-FC(O)OEt]\ Li^+}]{THF/-78^oC} RCH{=}CFCOOEt \quad \text{(Method A)}$$

$$(EtO)_2P(O)CFHC(O)OEt \xrightarrow[\substack{1)n\text{-}BuLi \\ 2)RCOOR' \\ 3)DIBAL}]{THF/-78^oC} RCH{=}CFCOOEt \quad \text{(Method B)}$$

No	R	R'	Method	Isolated[a] yield	E/Z[b]	bp (^{o}C/mmHg)
1	CF_3	C_2H_5	A	63	83/17	60-63/144
2	C_2F_5	C_2H_5	A	44	80/20	50-55/140
3	C_3F_7	C_2H_5	B	66	77/23	61-65/101
4	CF_2Cl	C_2H_5	A	64	89/11	64-67/98
5	CF_2Br	C_2H_5	A	64	88/12	55-60/67
6	CFHBr	C_2H_5	B	66	88/12	52-54/12
7	$\underline{n}$-C_5H_{11}	C_2H_5	B	57	93/7	67-70/3
8	$(CH_3)_2CH$	CH_3	A	54	95/5	52-58/80
9	C_6H_5	$\underline{n}$-C_4H_9	A	56	100/0	73-77/0.7
10	$\underline{E}$-$CH_3CH{=}CH$	CH_3	A	55	5/95[c]	56-59/52
11	$-(CH_2)_3C(O)O-$	-	A	76	95/5	75-80/0.7
12	$\underline{E}$-$C_6H_5CH{=}CF$	C_2H_5	B	45	100/0[c]	80-86/0.3

a) Isolated yields are based on RCOOR'. b) E/Z ratios were determined by integration of the vinyl fluorine signals in ^{19}F NMR spectra. c) EE/EZ ratio. All the products give satisfactory ^{19}F, ^1H, ^{13}C NMR, IR, and MS data.

In a typical experimental procedure, a 250 mL two-necked flask equipped with a septum port, a Teflon coated magnetic stir bar, and a water condenser connected to a nitrogen source was charged sequentially with 35 mL dry THF, and 33.5 mmol (8.1 g) $(EtO)_2P(O)CFHC(O)OEt$. The resulting homogeneous solution was stirred and cooled to -78^{o}C and then 33.5 mmol (13.4 mL) of 2.5 M $\underline{n}$-butyllithium (hexane) was added dropwise $\underline{via}$ syringe. Into another 250 mL two necked flask equipped with the same assembly were introduced 20 mL THF and 30 mmol (4.3 g) CF_3COOEt. The contents of the flask were stirred and cooled to -78^{o}C, and then 30 mmol (30 mL) of 1.0 M DIBAL (dichloromethane) was added dropwise $\underline{via}$ syringe. The resulting solution was stirred at -78^{o}C for 30 minutes and then the cold anion solution (THF) generated in the first flask was added dropwise $\underline{via}$ syringe to the pre-generated aldehyde. The resultant mixture was stirred at -78°C for one hour, allowed to warm to RT (six hours) and then quenched with 60 mL of 6M hydrochloric acid. The organic layer was separated and washed successively with saturated brine solution (2X25 mL), and water (25 mL) and subjected to steam distillation. After separation of the organic layer of the steam distillate, the water layer was extracted with diethyl ether (2X25 mL) and the combined organic materials were dried over anhydrous $MgSO_4$. Removal of the solvents via distillation at atmospheric pressure gave a yellow residue which was distilled again through a six-inch Vigreux column to give 3.5 g (63%) of an E and Z mixture of $CF_3CH=CFCOOEt$ (bp 60-63°C/144 mmHg), 100% pure by GLPC analysis. The E/Z ratio of $CF_3CH=CFCOOEt$ as determined by ^{19}F NMR analysis is 83/17.

Acknowledgement We thank the National Science Foundation and the Air Force Office of Scientific Research for financial support of this work.

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(Received in USA 7 July 1989)