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A FACILE PREPARATION OF ETHYL α-FLUOROALKANOATES

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Abstract: Alkylation of fluorocarboalkoxymethylene tri-n-butylphosphorane followed by hydrolysis provides the title compounds in moderate to good yields.

Profound changes in the biological activity of an organic compound are often associated with the replacement of a hydrogen atom in the molecule by a fluorine atom.[1,2] Thus, the synthesis of selectively fluorinated building blocks, such as α-fluoroesters, has become an area of active investigation in recent years.[3] Although metathesis reactions,[4] alkylation of fluoroacetate ions,[5] and fluorination of carbanions[6] or trimethylsilyl enol ethers,[7] have been utilized for the preparation of α-fluoroesters, these methods either require extreme reaction conditions or special apparatus, or employ toxic precursors and/or hazardous reagents. Thus the quest for a simple, mild synthesis of these building blocks continues. In this communication we describe such a preparation of α-fluoroalkanoates from commercially available precursors.

Ylide (4) [R = n-Bu][8] smoothly undergoes alkylation at carbon to afford the alkylated salts (5) in good yields (Scheme-I). Subsequent hydrolysis of (5) with aqueous sodium bicarbonate gives the α-fluoroalkanoates (6) in moderate to good yields (Table I). The method is readily adaptable to a one-pot type procedure *via* sequential addition of the requisite precursors and reagents.[10]

Activated alkyl bromides and primary alkyl iodides were employed as alkylating agents. Secondary alkylation agents such as Me_2CHI, Me_2CHOTs, Me(Ph)CHBr, gave little or no alkylation products (5). With crotyl and cinnamyl bromides, the reaction proceeded with retention of stereochemistry, and in the case of substituted allylic bromides alkylation was observed only at the α-carbon.

In a typical experimental procedure, a 200 mL two-necked flask, equipped with a septum port, a Teflon coated magnetic stir bar, and a

Table I Preparation of RCFHCOOEt

$Bu_3P{=}CFCOOEt$ —(1. RX; 2. $NaHCO_3$(aq))→ RCFHCOOEt

No	R	Reaction time (h)	Yield[a]	^{19}F NMR[b]	bp (^{o}C)/ mmHg
1	CH_3	8	59(75)	-184.9(dq)	50/64
2	C_2H_5	66	42(87)	-193.9(dt)	60-61/60
3	n-C_3H_7	166	42(74)	-192.5(dt)	94-95/117
4	n-C_4H_9	138	34(61)	-192.4(dt)	93-94/63
5	n-C_7H_{15}	78	52(72)	-192.3(dt)	93-94/5
6	n-$C_{10}H_{21}$	78	44(50)	-192.5(dt)	115-116/1
7	$CH_2CH{=}CH_2$	20	52(73)	-192.1(dt)	82-83/28
8	$PhCH_2$	21	59(61)	-189.9(dt)	69-70/0.3
9	$PhCH{=}CHCH_2$(E&Z)	22	45(76)	-191.5(dt)	112-13/0.5
10	$CH_3CH{=}CHCH_2$(E&Z)	20	38(72)	-192.0(dt) (E)	
				-191.8(dt) (Z)	84-85/25
11[c]	$CH_3OCOCH{=}CHCH_2$(E)	20	41(45)	-191.6(dt)	72-80/0.6

a) Isolated yields are based on ethyl bromofluoroacetate, and the yields in parentheses are determined by ^{19}F NMR analysis of the reaction mixture using C_6F_6 as an internal standard.

b) Chemical shifts are relative to $CFCl_3$ as internal reference.

c) Isolated *via* flash chromatography on a silica gel (230-400 mesh/Aldrich) column and n-hexane/ethyl acetate (81/19) as eluent. All the products give satisfactory ^{1}H, ^{13}C NMR, IR, and MS data.

reflux water condenser connected to a nitrogen source, was charged sequentially with 25 mL dry THF, 25 mmol (5.06 g) tri-n-butylphosphine,[12] and 25 mmol (4.63 g) ethyl bromofluoroacetate.[13] The resultant homogeneous solution was stirred at RT for 40 hours, cooled to -78°C, and 23.8 mmol of n-butyllithium (hexane) was added dropwise via syringe. The resultant bright yellow mixture was stirred at -78°C for 20 minutes, then 35.5 mmol (6.1 g) of freshly distilled benzyl bromide was slowly added via syringe to produce (5). The reaction mixture was stirred for one hour at -78°C, allowed to warm to RT (five hours), and stirred at that temperature for an additional 16 hours. After addition of 40 mL (47.5 mmol) of a 10% aqueous $NaHCO_3$ solution to the reaction mixture, the solution was stirred at room temperature for 6 hours. After separation of the organic layer, the aqueous layer was extracted with ether (2X30 mL). The combined organic materials were washed successively with saturated brine (2X25 mL) and water (2X25 mL), and dried over anhydrous $MgSO_4$. Removal of the solvents via distillation at atmospheric pressure gave a residue which was distilled through a six-inch Vigreux column to give 2.9 g (59%) of $PhCH_2CFHCOOEt$ (bp 69-70°C/0.3 mmHg, lit.[5] 136-138°C/20 mmHg), 99.8% pure by GLPC analysis.

$$\underset{(1)}{R_3P} + \underset{(2)}{CFHBrCOOR'} \xrightarrow[RT]{THF} \underset{(3)}{[R_3P^+CFHCOOR']Br^-} \xrightarrow[n\text{-BuLi}]{THF/-78^\circ C}$$

R = n-Bu,Ph; R' = Me,Et

$$\underset{(4)}{[R_3P{=}CFCOOR']} \xrightarrow{R''X} \underset{(5)}{[R_3P^+CF(R'')COOR']X^-} \xrightarrow[RT]{HCO_3^-} \underset{(6)}{R''CFHCOOR'}$$

Scheme I

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