Tetrahedron Letters,Vol.30,No.45,pp 6113-6116,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN EXPEDIENT SYNTHESIS OF α-FLUORO-β-KETOESTERS[1]

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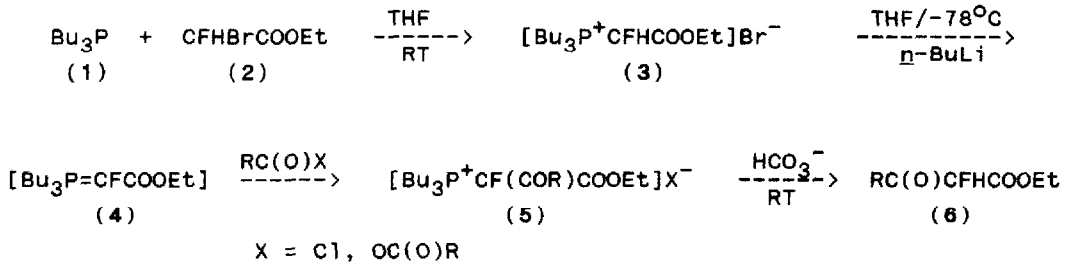
Abstract: Acylation of fluorocarboethoxymethylene tri-n-butylphosphorane (4) followed by hydrolysis under mild basic conditions provides the title compounds (6) in good yields.

α-Fluoro-β-ketoesters are reagents of considerable interest in synthetic organofluorine chemistry, and a number of them have been successfully employed as intermediates in the synthesis of bioactive fluoropyrimidines[2] and fluorine substituted isoprenyl derivatives[3].

Conventional methods for the preparation of the title compounds include Claisen and crossed-Claisen condensation of fluoroacetates,[4] fluorination of active methylene moieties with fluorinating agents such as $FClO_3$[5] and $C_{19}XeF_6$[6], reaction of the enol derived from fluoroacetate[2] and fluorinated ketene silyl acetals[7] with acylating agents, and acylation of trifluoroethene with acid chlorides under Friedel-Crafts conditions[8]. Although numerous syntheses exist for the preparation of α-fluoro-β-ketoesters, these methods suffer from the use of toxic and/or hazardous starting materials, lead to formation of by-products, and require multistep preparations with low yields.

In an earlier communication[9], we described a synthesis of α-fluoroalkanoates *via* alkylation of fluorocarboethoxymethylene tri-n-butylphosphorane (4) and subsequent hydrolysis of the resultant alkylated phosphonium salts. We also reiterated the advantages of this approach over the known methods for the preparation of α-fluoroesters from alkyl halides and $[Bu_3P^+CFHC(O)OEt]Br^-$ (3). In our continuous efforts[9] to explore new synthetic methodologies for the introduction of fluorine adjacent to a carbonyl group, we have also investigated the acylation reaction of the ylid (4). In this communication, we report the formation of the acylated phosphonium salts (5) from (4) and their transformation to α-fluoro-β-ketoesters (6).

Acid chlorides and anhydrides acylate the ylid (4) at carbon to form the corresponding phosphonium salts (5) in good yields. Subsequent hydrolysis of the salts with aqueous sodium bicarbonate solution gives the title compounds (6) in moderate to good yields (Scheme I).

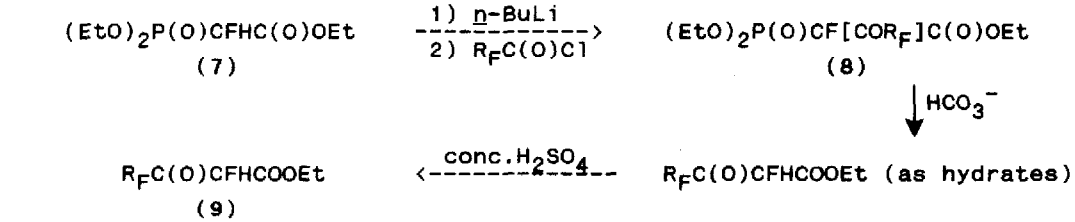


Scheme I

The acylation of the ylid (4) is applicable to aliphatic and aromatic acid chlorides (Table I). Among the aliphatic reagents, primary, secondary, tertiary, and cyclic acid chlorides will undergo acylation to give the corresponding phosphonium salts (5) in good yields. The use of ethyl chloroformate and ethyl chlorothioformate as acylating agents led to the formation of diesters such as $CFH(COOEt)_2$ and EtSC(O)CFHC(O)OEt. Presence of functionalities such as ester and halogen is tolerated under the reaction conditions as illustrated in entry # 12 and # 10 (Table I).

In contrast to other methods,[8] our method provides the convenience of carrying out all the transformations such as formation of salt (3) from phosphine (1) and bromofluoroacetate (2), ylid (4) generation, acylation and hydrolysis in one pot to afford the ketoesters (6).

In our hands, acylation of the ylid (4) with perfluorinated and partially fluorinated acid chlorides did not proceed cleanly to give the corresponding ketoesters in good isolated yields. However, the anion derived from the phosphonate (7) undergoes acylation with fluorine substituted acid chlorides to form the corresponding acylated phosphonates (8). Hydrolysis of (8) under mild basic conditions provides the respective ketoesters (9) in good yields (Scheme II) as hydrates. Distillation of these hydrates in the presence of concentrated H_2SO_4 gives the ketoesters (9).



Scheme II

Table I: Preparation of RC(O)CFHCOOEt

$Bu_3P{=}CFC(O)OEt$ —(1) RC(O)Cl, (2) $NaHCO_3$ (aq)→ RC(O)CFHCOOEt (Method A)

$(EtO)_2P(O)CFHC(O)OEt$ —(1) n-BuLi, (2) RC(O)Cl, (3) $NaHCO_3$ (aq)→ RC(O)CFHCOOEt (Method B)

No	R	Method	Isolated[a] yield(%)	Boiling point (^{o} C/ mm Hg)	^{19}F NMR[b] (ppm)
1	CH_3	A	60	60-62/4.0	-193.7(dq)
2	CH_3CH_2	A	50	48-52/2.2	-195.8(dt)
3	$(CH_3)_2CH$	A	58	62-63/2.5	-196.3(d)
4	$(CH_3)_3C$	A	56	56-61/2.0	-191.1(d)
5	C_6H_{11}	A	68	76-84/0.5	-196.2(d)
6	EtO	A	50	72-74/3.5	-195.6(d)
7	EtS	B	57	74-77/0.5	-192.2(d)
8	n-C_3F_7	B	77	45-47/5.0	-199.7(dt)
9	CF_3	B	60	42-43/43	-199.5(dq)
10	CF_2Cl	B	67	60-65/38	-198.6(dt)
11	C_6H_5	A	70	112-114/0.4	-191.4(d)
12	$CH_3OC(O)CH_2CH_2$	A	38	92-97/0.45	-195.9(d)

a) Isolated yields are based on acid chloride. All the isolated compounds give satisfactory ^{1}H, ^{13}C NMR, IR and GC-MS data. b) ^{19}F NMR chemical shifts are relative to $CFCl_3$ as an internal reference.

In a typical experimental procedure, a 300 mL two-necked flask equipped with a septum port, a Teflon coated magnetic stir bar, and a reflux condenser connected to a nitrogen source, was charged sequentially with 50 mL dry THF, 35 mmol (7.1 g) tri-n-butylphosphine, and 35 mmol (6.5 g) ethyl bromofluoroacetate. The resultant homogeneous solution was stirred at RT for 40 hours, cooled to -78^{o} C, and 35 mmol (14 mL) of 2.5 M n-BuLi (hexane) was added dropwise via syringe. The resulting bright yellow solution was stirred at -78^{o} C for 20 minutes followed by dropwise addition of 35 mmol (4.9 g) of freshly distilled benzoyl chloride. The reaction mixture was stirred at -78^{o} C for one hour, allowed to warm to RT (5 hours), and stirred at that temperature for an additional 16 hours. After addition of 50 mL of a 5% aqueous sodium bicarbonate solution to the reaction mixture, the solution was stirred at RT for 6 hours to give (6).

The reaction mixture was diluted with 100 mL cold water and the organic layer was separated, washed sequentially with brine (25 mL) and water (25 mL), and dried over anhydrous $MgSO_4$. Concentration of the dried material on a rotary evaporator gave a dark brown residue which was flash chromatographed on a silica gel (200-425 mesh, Fischer Scientific) column with 8:2 hexane/ethyl acetate as eluent. Distillation of the chromatographed material through a short path distillation apparatus at 112-114° C and 0.4 mm Hg (lit.[8] 125-128° C and 4 mm Hg) gave 5.1 g (70%) of PhC(O)CFHCOOEt, 100% pure by GLPC analysis.

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

References and Notes

1. Presented in part at the 23rd Midwest Regional Meeting of the American Chemical Society, Iowa City, Iowa, November 1988, Abstract # 157.
2. Bergman, E.D.; Cohen, S.; Shahak, I. J. Chem. Soc. **1959**, 3278.
3. Montellano, P.R.O.; Vinson, W.A. J. Org. Chem. **1977**, 42, 2013.
4. McBee, E.T.; Pierce, O.R.; Kilbourne, H.W.; Wilson, E.R. J. Am. Chem. Soc. **1953**, 75, 3152.
5. Gershon, H.; Renwick, J.A.A.; Wynn, W.K.; D'Ascoli, R. J. Org. Chem. **1966**, 81, 916.
6. Yemul, S.S.; Kagan, H.B. Tetrahedron Lett. **1980**, 21, 277.
7. Easdon, J.C. Ph.D. Thesis, University of Iowa, **1987**.
8. Ishikawa, N.; Takaoka, A.; Iwakiri, H.; Kubota, S.; Kagaruki, S.R.F. Chem. Lett. **1980**, 1107.; Ishikawa, N.; Takaoka, A.; Ibrahim, K. J. Fluorine Chem. **1984**, 25, 203.
9. Thenappan, A.; Burton, D.J. Tetrahedron Lett. **1989**, 30, 3641.

(Received in USA 23 August 1989)