Tetrahedron Letters, Vol. 33, No. 44, pp. 6579-6582, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

An Expedient Synthesis of α–Fluoro-α,β-Unsaturated Diesters

Hou-Jen Tsai[a], Alagappan Thenappan[b] and Donald J. Burton*[b]
[a]Department of Applied Chemistry, Chung Cheng Institute of Technology, Ta-shi, Taiwan, R.O.C.
[b]Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, USA.

Key Words: β-ketophosphonate; ylid; ethyloxalyl chloride; perfluorinated Grignard reagent; Wadsworth-Emmons reaction

Abstract: *Acylation of $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ (2) with alkyloxalyl chlorides followed by subsequent reaction of the acylated phosphonates with Grignard reagents provides the title compounds in moderate to good yields with high E-stereoselectivity.*

A variety of monofluoro compounds exhibit remarkable biological activities,[1] and medical and biological sciences exert an increasing demand for fluorinated organic compounds. Biologically active molecules containing a vinylic fluorine atom are of special interest,[2] as this moiety is present in a number of enzyme inhibitors.[3]

Literature methods for the preparation of α-fluoro-α,β-unsaturated diesters generally lack stereospecificity and generality. Thus, the reaction of diethyl oxalate with phosphonate carbanion 2 to give diethyl 2-fluoro-3-ethoxyfumarate only allows the introduction of the ethoxy group in the β-position of α-fluoro-α,β-unsaturated diesters.[4] The condensation of carboethoxymethylenetriphenylphosphorane with diethyloxalofluoroacetate in DMF gives a 1:1 mixture of ethylenic triethylesters: $(EtO_2CCFH)(CO_2Et)C{=}CHCO_2Et$ and the isomerization product, $(EtO_2CCH_2)(CO_2Et)C{=}CFCO_2Et$.[5] Alkylation of ethyl phenylsulfinylfluoroacetate followed by subsequent thermal elimination leads to the preparation of α-fluoro-α,β-unsaturated diesters.[6] Herein, we describe a general, one-pot synthesis of α-fluoro-α,β-unsaturated diesters, which permits variation of the group at the β-position *via* an intramolecular Wadsworth-Emmons reaction.

Deprotonation of diethyl carboethoxyfluoromethylphosphonate[7] (1) with *n*-butyl lithium in THF at −78°C gives $[(EtO)_2P(O)CFCO_2Et]^- Li^+$ (2). Addition of a THF solution of 2 to a THF solution of an acid chloride, such as methyloxalyl chloride or ethyloxalyl chloride, forms the corresponding C-acylated phosphonates $(EtO)_2P(O)CF(COCO_2R)CO_2Et$ (3) in 90 to 92% ^{19}F NMR yields relative to $C_6H_5CF_3$ internal standard (eq 1).

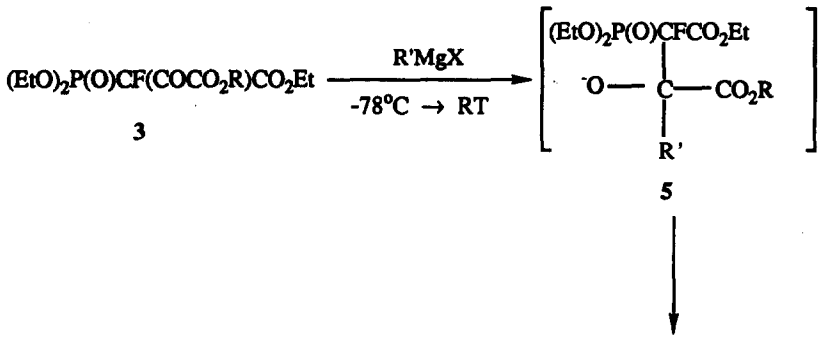
$$(EtO)_2P(O)CFHCO_2Et \xrightarrow[2)\ ClC(O)CO_2R]{1)\ n\text{-}BuLi\ /\ THF\ /\ -78^\circ C} (EtO)_2P(O)CF(COCO_2R)CO_2Et \qquad (1)$$

1 → 3

3a: R = C_2H_5

b: R = CH_3

Treatment of the acylated phosphonate **3** with one equivalent of a Grignard reagent (R'MgX) gives an E/Z mixture of α-fluoro-α,β-unsaturated diesters R'(CO_2R)C=C(F)CO_2Et **4** in 48-68% isolated yields. The initial step in the synthesis of olefin **4** is nucleophilic attack of the Grignard reagent at the carbonyl carbon of **3** to form **5**, followed by intramolecular elimination of diethylphosphate to afford **4** (eq 2).



$$R'(CO_2R)C{=}CFCO_2Et + (EtO)_2P(O)OMgX \qquad (2)$$

4 (E, Z)

The results for the preparation of several α-fluoro-α,β-unsaturated diesters R'(CO_2R)C=C(F)CO_2Et **4** (a-h) are summarized in Table 1.

In general, for compounds having the formula R'(CO_2R)C=C(F)CO_2Et, the vinyl fluorine of the Z-isomer exhibits an upfield signal compared to the vinyl fluorine resonance of the E-isomer. This assignment was confirmed by a Nuclear Overhauser Effect (N.O.E.) experiment.

An alternative approach to the title compounds is *via* the condensation of **2** with α-ketoesters. The stereochemical preference, however, for our current approach is superior to the α-ketoester condensation as

$$2 + CH_3C(O)CO_2Et \longrightarrow 4a \qquad (3)$$

65% (E/Z = 45/55)

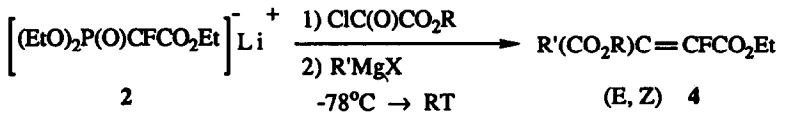
indicated in eq. 3. In addition, the current approach avoids the preparation of the requisite α-ketoester.

The stereoselectivity of the product (E,Z)-(CH_2=CH)(CO_2Et)C=C(F)CO_2Et (**4e**) in the current approach was unaffected when the solvent was changed from THF to diethyl ether. The stereochemistry of **4e** did, however, vary when HMPA or DMPU were added to the reaction mixture. The use of a lithium base in THF with HMPA or DMPU in the preparation of **4e** gave 98-99% E-stereoselectivity. Additional work is in progress to explore this effect.

In a typical experimental procedure, a 100 mL three-necked flask equipped with a septum port, a glass stopper, a magnetic stirbar, and a reflux water condenser topped with a nitrogen tee tube leading to a source of nitrogen and a mineral oil bubbler was charged sequentially with 30 mL of dry THF and 16.0 mmol (3.90 g)

of $(EtO)_2P(O)CFHCO_2Et$. The contents of the flask were cooled to -78°C in a Dry Ice/IPA slush bath. To the cooled solution, 16.0 mmol (6.4 mL) of a 2.5 M *n*-hexane solution of *n*-butyllithium was added dropwise *via* syringe. The resultant bright yellow solution was stirred at -78°C and maintained at that temperature. Into another 250 mL three-necked flask equipped as above (the standard assembly) was placed 20 mL of dry THF and 16.0 mmol (2.18 g) of ethyloxalyl chloride. The contents of the flask were stirred and cooled to -78°C and

Table 1. Preparation of $R'(CO_2R)C{=}CFCO_2Et$



no.	R	R'	X	E/Z[b]	N.O.E. (%)	Isolated yields (%)[a]
4a	C_2H_5	CH_3	I	100/0	+6.2/0	52
4b	CH_3	CH_3	I	100/0	+8.0/0	51
4c	C_2H_5	i-C_3H_7	Cl	100/0		54
4d	CH_3	t-Bu	Cl	100/0		49
4e	C_2H_5	$H_2C{=}CH$	Br	85/15[c]	+17.2/0	50
4f	CH_3	$H_2C{=}CH$	Br	87/13[c]	+9.2/0	50
4g	CH_3	C_6H_{11}	Cl	100/0		48
4h	C_2H_5	C_6F_5	Br	90/10		68

[a] Isolated yields are based on $(C_2H_5O)_2P(O)CFHCO_2C_2H_5$. [b] E/Z ratio was obtained by ^{19}F NMR integration of the vinyl fluorine signals. [c] E and Z isomers were separated by flash chromatography. All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR, FT-IR and GC/MS data.

then the cold ylid solution generated in the first flask was added dropwise *via* syringe. The resulting mixture was stirred at -78°C for one hour and then allowed to warm to -10°C over 5 hours. ^{19}F NMR analysis of the reaction mixture revealed the complete consumption of the ylid and the presence of the product $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$ (δ -177.9 ppm d, J = 73.3 Hz). The reaction mixture was cooled again to -78°C then 16 mmol (5.4 mL) of a 3.0 M diethyl ether solution of methylmagnesium iodide was added dropwise *via* syringe. The resultant mixture was allowed to warm to room temperature over 6 hours and stirred at that temperature overnight. ^{19}F NMR analysis of the reaction mixture indicated the absence of 3 and the formation of (E)-$CH_3(CO_2Et)C{=}CFCO_2Et$. The reaction mixture was poured into water (60 mL), the organic layer was separated, and the water layer extracted with ether (3 x 50 mL). The ether extracts were combined with the organic layer and the combined fractions washed with dilute hydrochloric acid until the

washings were neutral to litmus paper. The resulting solution was washed successively with saturated brine solution (30 mL) and water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was loaded onto a flash chromatography column (120 g silica gel, 200-425 mesh/Fisher Scientific) and eluted with a *n*-hexane/ethyl acetate (24/1) mixture to give 1.69 g (52%) of (E)-$CH_3(CO_2Et)C{=}CFCO_2Et$ (98% pure by GLPC analysis). ^{19}F NMR ($CDCl_3$): -125.5 (q, $^4J_{FH}$ = 3.8 Hz); ^1H NMR ($CDCl_3$): 1.32 (t, CH_3), 1.33 (t, CH_3), 2.05 (d, CH_3), 4.27 (q, OCH_2), 4.29 (q, OCH_2); ^{13}C NMR ($CDCl_3$): 13.9 (d, $CH_3C{=}$, J = 5 Hz), 13.9 (s, CH_3), 14.0 (s, CH_3), 61.8 (s, OCH_2), 62.1 (s, OCH_2), 121.7 (d, C=CF, J = 18 Hz), 147.9 (d, C=CF, J = 266 Hz), 159.7 (d, $=CFCO_2$, J = 35 Hz), 169.9 (d, $O_2CC{=}CF$, J = 13 Hz). GC/MS: 204 (M^+, 0.37), 131 (M^+-CO_2Et, 100); FT-IR (CCl_4): 1739 vs (C=O), 1675 m (C=C), 1287 s (C-F); HRMS: Calc'd. 204.0798, Found 204.0813.

ACKNOWLEDGEMENT

We thank the National Science Foundation for support of this work.

REFERENCES

1. Welch, J.T. *Tetrahedron* **1987**, *43*, 3123.
2. Thenappan, A.; Burton, D.J. *J. Org. Chem.* **1990**, *55*, 4639. Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871. McCarthy, J.R.; Matthews, D.P.; Edwards, M.L.; Stemerick, D.M.; Jarvi, E.T. *Tetrahedron Lett.* **1990**, *38*, 5449. Patrick, T.B.; Nadji, S. *J. Fluorine Chem.* **1990**, *49*, 147.
3. McDonald, I.A.; Lacoste, J.M.; Bey, P.; Wagner, J.; Zreika, M.; Palfreyman, M.G. *J. Am. Chem. Soc.* **1984**, *106*, 3354. McCarthy, J.R.; Jarvi, E.T.; Matthews, D.P.; Edwards, M.L.; Prakash, N.J.; Bowlin, T.L.; Mehdi, S.; Sunkara, P.S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127.
4. Grell, W.; Machleidt, H. *Lieb. Ann. Chem.* **1966**, *693*, 134.
5. Cantacuzene, D.; Wakselman, C.; Massoudi, H. *Synth. Commun.* **1984**, *14*, 1067.
6. Allmendinger, T. *Tetrahedron* **1991**, *47*, 4905.
7. Burri, K.F.; Cardone, R.A.; Chen, W.Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.

(Received in USA 30 June 1992; accepted 6 August 1992)