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FLUORINE CHEMISTRY SYNTHESIS

PREPARATION OF ETHYL 2-FLUOROACRYLATE, CH_2=CFCOOEt* [8]

$$(EtO)_2P(O)CFHC(O)OEt \xrightarrow[\substack{1)\ \underline{n}\text{-BuLi} \\ 2)\ HCOOEt \\ 3)\ DIBAL \\ -78^{o}C\ \text{to r.t.}}]{Et_2O/-78^{o}C} CH_2{=}C(F)COOEt$$

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A 500 mL three-necked flask equipped with a Teflon coated magnetic stirbar, a rubber septum, a 250 mL constant pressure addition funnel and a reflux condenser connected to a source of nitrogen and mineral oil bubbler was charged sequentially with 100 mL of anhydrous diethyl ether① and 24.2 g (100 mmol) of $(EtO)_2P(O)CFHC(O)OEt$②. The resultant homogeneous solution was

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* The title compound has previously been prepared in 45% yield via reaction of the enolate of diethylfluoro-oxaloacetate with paraformaldehyde [1].
The analogous phenyl ester has been prepared in three steps from 2-fluoroacrolein in 46% overall yield [2], in four steps from vinyl ethyl ether in 40% overall yield [3], and in three steps from 2,2,3,3-tetrafluoro-1-propanol in 40% overall yield[6].

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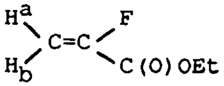
stirred vigorously and cooled to -78° C via a Dry ice/isopropyl alcohol slush bath. To the cooled solution 10.0 mL (101 mmol) of a 10.1 M n-hexane solution③ of n-BuLi④ was added dropwise via syringe. The resultant bright yellow solution was stirred at -78° C for 30 minutes and then 8.1 g (110 mmol) of freshly distilled ethyl formate⑤ was added dropwise via syringe. After equilibration of the bath temperature to -78° C, 110 mL (110 mmol) of a 1.0 M dichloromethane solution of diisobutylaluminum hydride (DIBAL)⑥ was added dropwise via the constant pressure addition funnel over 30 minutes. During the addition of DIBAL a mild exotherm was observed and the temperature of the cold bath was maintained below -70° C. The resultant mixture was stirred at -78° C for one hour, then allowed to warm up to room temperature (6 hours), and stirred at that temperature overnight. The reaction mixture was transferred into a one-litre flask, then cooled with an ice-water bath and quenched⑦ with 200 mL of 6.0 M hydrochloric acid. The organic layer⑧ was separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic phase was washed with brine (2 x 25 mL), dried over anhydrous $MgSO_4$ and filtered. Removal of the solvents under a nitrogen atmosphere via an efficient distillation apparatus⑨ provided a pale yellow liquid. Redistillation of the liquid through a short path distillation apparatus at 102-104° C and atmospheric pressure gave 7.3 g (62%) of $CH_2=C(F)COOEt$⑩, 98% pure by GLPC analysis.

^{19}F NMR [$CDCl_3$, $CFCl_3$]: -117.6 ppm (dd); $^{3}{}_{H(a),F}$ = 12 Hz
$^{3}J_{H(b),F}$ = 44 Hz



^{1}H NMR [$CDCl_3$, TMS]:

H_a = 5.31 ppm (dd) $^3J_{H(a),F}$ = 13 Hz

$^2J_{H(a),H(b)}$ = 3 Hz

H_b = 5.67 ppm (dd) $^3J_{H(b),F}$ = 44 Hz

$C(O)O\underline{CH_2}CH_3$ = 4.3 ppm (q) $^3J_{H,H}$ = 7 Hz

$C(O)OCH_2\underline{CH_3}$ = 1.34 ppm (t)

^{13}C NMR {^{1}H} [$CDCl_3$, TMS]:

$\underset{a}{CH_2}=\underset{b}{C}F\underset{c}{C}(O)O\underset{d}{CH_2}\underset{e}{CH_3}$

C_a = 102.4 (d) $^2J_{F,C(a)}$ = 15 Hz

C_b = 153.7 (d) $^1J_{F,C(b)}$ = 262 Hz

C_c = 160.4 (d) $^2J_{F,C(c)}$ = 36 Hz

C_d = 62.0 (s)

C_e = 14.1 (s)

FT IR [CCl_4 solution]: 896(m), 907(w), 941(w), 949)w), 1024(m), 1161(s), 1167(s), 1171(s), 1176(s), 1183(s), 1320(s), 1323(s), 1374(m), 1397(m), 1466(w), 1658(m), 1737(s), 1740(s), 1742(s), 1747(s), 2932(w), 2964(w) and 2985(w).

GC-MS: 119 ($M+1^+$, 1.1), 118 (M^+, 7.5), 117 ($M-1^+$, 1.8), 103 ($M-15^+$, 6.0), 100 (6.0), 91 (15.9), 90 (7.2), 74 (11.0), 73 ($M-C_2H_2F^+$ = $COOEt^+$, 100), 59 (12.2), and 54 (8.4).

High resolution mass spectral data: Observed: 118.0422

Calculated: 118.0430

NOTES

1. Anhydrous diethyl ether (Mallinckrodt) was dried over 4Å molecular sieves.
2. $(EtO)_2P(O)CFHC(O)OEt$ was prepared from $(EtO)_3P$ and CFHBrCOOEt via the literature procedure [5].
3. Removal of *n*-hexane from the reaction mixture was tedious and a concentrated solution of *n*-BuLi (10.1 M) minimizes the amount of hexane present in the reaction mixture.

4. Hexane solution of n-BuLi (Aldrich) was used directly without any further purification.
5. Ethyl formate (Aldrich) was distilled at 52-54^{O} C (atmospheric pressure) and used immediately.
6. Dichloromethane solution of DIBAL (Aldrich) was used directly without any further purification.
7. Quenching the reaction mixture with 6 M hydrochloric acid is an exothermic reaction with vigorous gas evolution. Care must be taken not to add the acid rapidly and the addition was accomplished dropwise over a period of 30 minutes. Alternatively, the reaction can be carried out in a one -litre flask.
8. Sufficient time must be allowed (60 minutes) for the two layers to separate and the top organic layer was used for further purification.
9. Spinning Band distillation apparatus [model # B/R 24T; 8 mm bore X 36" long, 100 plate Teflon Spinning Band Column, operated between 3000-4000 rpm] was used for removal of solvents.
10. Reported NMR and IR data for $CH_2=CFC(O)OC_6H_5$ [2]
    ^{1}HNMR [$CDCl_3$, TMS]: 5.55 (dd), 6.05(dd), 7.1-7.75(m); $^3J_{FH}$ = 13 Hz, $^2J_{HH}$ = 3.3 Hz, $^3J_{FH}$ = 42 Hz.
    ^{19}F NMR [$CDCl_3$, $CFCl_3$]: -117.0 ppm (dd) $^3J_{FH}$ = 13 Hz, 42 Hz.
    IR ($CHCl_3$): 1755, 1652, and 1590 cm^{-1}.

ACKNOWLEDGEMENT

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6 For additional examples of the methodology and principles illustrated in this preparation, *cf*. A. Thenappan, D.J. Burton, Tetrahedron Lett., 30 (1989) 5571.