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PRELIMINARY NOTE

Synthesis of Optically Pure (R)- or (S)-α-Fluoro-α-Methyl-β-Ketoesters

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SUMMARY

A number of optically pure (R)- or (S)-α-fluoro-α-methyl-β-ketoesters were prepared by the reaction of the optically pure acid chlorides made from the corresponding (R)- or (S)-α-fluoro-α-methylmalonic acid monoethyl esters with alkyl (or aryl) cuprates.

Numerous stereocontrolled syntheses of β-ketoesters have been studied over the years [1-4]. However, the introduction of a center of chirality into α-fluoro-α-methyl-β-ketoesters intended as chiral synthetic tools remains unexplored from a synthetic point of view.

Recently we have reported examples of microbial hydrolyses which proceeded to give the optically pure (R)-(+)- or (S)-(-)-2-fluoro-2-methylmalonic acid monoethyl ester (>98 %ee) [5-8].

As part of our continuing effort to develop stereocontrolled syntheses of fluorinated compounds with high optical purity, we present here some results leading to a practical route to (R)- or (S)-α-fluoro-α-methyl-β-ketoesters.

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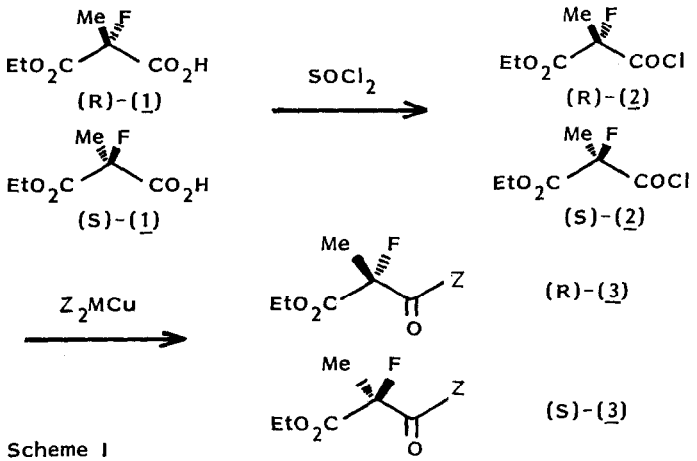
A brief outline of the synthetic strategies employed in preparing optically active α-fluoro-α-methyl-β-ketoesters is shown in Scheme I. The synthetic intermediate is the optically active acid chloride (2) [7], which was prepared from the reaction of the appropriate optically active α-fluoro-α-methylmalonic acid halfester (1) with thionyl chloride. Treatment of the (S)-acid chloride (2) with a variety of alkyl (or aryl) cuprates in diethyl ether gave (S)-α-fluoro-α-methyl-β-ketoesters (3). The analogous (R)-enantiomer (2) was also converted to give (R)-enantiomers of (3). The compounds (3) prepared, and their physical properties, are listed in Table 1, and their nmr spectral data in Table 2.



Scheme I

Acid chloride (2)(nc)

Into a 3-necked flask equipped with reflux condenser, (S)-(-)-α-fluoro-α-methylmalonic acid monoethyl ester (8.2 g, 50 mmol), >98 %ee $[\alpha]_D$ -22.5 (c 2.20, MeOH) and imidazole (220 mg) were placed. Into a mixture, freshly distilled thionyl chloride (13 ml) was added slowly at 0°C, and then the mixture was heated for 6h at 80°C. Distillation gave the corresponding acid chloride (2)(8.4 g) in a yield of 92 %, bp 77-78°C/32 mmHg.
$[\alpha]_D$ +5.24 (c 2.05, $CHCl_3$).
IR (cm^{-1}) : 1795(COCl), 1760(CO_2Et)
^{19}F NMR ($CDCl_3$) : δ 66.7(CF, q, J_{CF-CH_3} = 20 Hz)

TABLE 1

Preparation of α-fluoro-α-methyl-β-ketoesters, $ZC(O)CF(Me)CO_2Et$ (3)

Product[a] No	Absolute configuration	Z	Yield (%)	bp (°C/mmHg)	$[\alpha]_D$/MeOH[b]
3a (nc)	(R)	Me	57	66-68/27	-45.4 (c 2.07)
	(S)	Me	66		+45.8 (c 2.10)
3b (nc)	(R)	Et	85	80-82/24	-52.9 (c 1.28)
	(S)	Et	88		+53.5 (c 1.19)
3c (nc)	(R)	Pr	73	65-67/19	-42.6 (c 2.04)
	(S)	Pr	83		+42.3 (c 1.69)
3d (nc)	(R)	Bu	76	92-94/19	-40.3 (c 1.70)
	(S)	Bu	74		+40.0 (c 1.50)
3e (nc)	(R)	Ph	48	102-104/4	-84.8 (c 1.79)
	(S)	Ph	60		+85.4 (c 1.97)

[a] Structures were confirmed by means of IR, NMR and mass spectra. For each of the new compounds, the microanalysis was in satisfactory agreement with the calculated value (C,H,N; ± 0.5 %).

[b] The optical purities were determined by glc and/or ^{19}F NMR after conversion of the α-fluoro-α-methyl-β-ketocarboxylic acids derived from the hydrolysis of α-fluoro-α-methyl-β-ketoesters to their diastereomeric amides by optically active α-methylbenzylamine.

TABLE 2

^{1}H and ^{19}F NMR spectral data for $ZC(O)CF(Me)CO_2Et$ (3)

Product No	Z	Chemical shift (δ ppm)	
		^{19}F NMR (from ext.CF_3CO_2H)	^{1}H NMR (in $CDCl_3$)
3a	Me	77(q.q, J_{F-CH_3} = 21.5 Hz J_{F-CH_3} = 5.0 Hz)	1.29(t,CH_3, $J_{CH_3-CH_2}$ = 7.0 Hz), 1.57 (d,CH_3), 2.26(d,CH_3), 4.16(q,CH_2)
3b	Et	79(q.t, J_{F-CH_3} = 21.5 Hz J_{F-CH_2} = 3.0 Hz)	1.06(t,CH_3, $J_{CH_3-CH_2}$ = 7.5 Hz), 1.30 (t,CH_3, $J_{CH_3-CH_2}$ = 7.3 Hz), 1.60(d,CH_3), 2.63(d,q.CH_2), 4.07(q,CH_2)
3c	Pr	79(q.t, J_{F-CH_3} = 22.2 Hz J_{F-CH_2} = 7.2 Hz)	0.92(t,CH_3, $J_{CH_3-CH_2}$ = 7.7 Hz), 1.29 (t,CH_3, $J_{CH_3-CH_2CH_2}$ = 7.2 Hz), 1.43-1.88 (m,2xH), 1.58(d,CH_3), 2.59(d.t,2xH)
3d	Bu	79(q.t, J_{F-CH_3} = 22.0 Hz J_{F-CH_2} = 6.9 Hz)	0.91(t,CH_3, $J_{CH_3-CH_2}$ = 6.5 Hz), 1.29(t, CH_3, $J_{CH_3-CH_2}$ = 7.3 Hz), 1.19-1.73(m, 4xH), 1.58(d,CH_3), 2.59(d.q,CH_2, $J_{CH_2-CH_2}$ = 3.0 Hz), 4.19(q,CH_2)
3e	Ph	72(q, J_{F-CH_3} = 22.3 Hz)	1.18(t,CH_3, $J_{CH_3-CH_2}$=7.1 Hz), 1.79(d, CH_3), 4.18(q,CH_2), 7.16-7.98(Ar-H)

from ext. CF_3CO_2H
^1H NMR ($CDCl_3$) :δ 1.40(CH_2CH_3, t, $J_{CH_3-CH_2}$ = 6.8 Hz), 1.84($CFCH_3$, d), 4.33(CH_2CH_3, q)
Anal. Found : C, 39.62 ; H, 4.63 %
Calcd for $C_6H_8ClFO_3$: C, 39.47 ; H, 4.42 %

Preparation of α-fluoro-α-methyl-β-ketoesters

(R)-Ethyl α-fluoro-α-methylacetoacetate.

Methyl cuprate (15 mmol) was added to a mixture of (R)-acid chloride (2)(10 mmol) and freshly dried diethyl ether (30 ml) at -60°C. After 5h of stirring, the reaction mixture was poured into 1N HCl solution, oily materials were extracted with diethyl ether. The ethereal extract was dried over magnesium sulfate, and the solvent removed. Distillation gave (R)-ethyl α-fluoro-α-methylacetoacetate in a yield of 57 %, bp 66-68°C/27 mmHg.

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