Synthesis of α-Trifluoromethylated Carboxylic Acid Esters

Tomoya Kitazume,* Takeshi Ohnogi

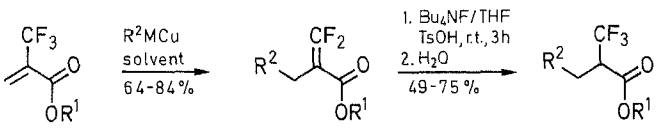
Department of Bioengineering, Tokyo Institute of Technology Ookayama, Meguro-ku, Tokyo 152, Japan

A series of menthyl 2-(trifluoromethyl)alkanoates were prepared by reaction of menthyl 2-(trifluoromethyl)propenoates with dialkyl- or diphenylcuprates and hydrofluorination of the menthyl 2-(difluoromethylene)alkanoates thus obtained by addition of tetrabutylammonium fluoride followed by hydrolysis.

Numerous studies have shown that trifluoromethyl substitution confers interesting properties to important organic materials such as bioactive compounds[1-3] and ferroelectric liquid crystals.[4,5] 2-(Trifluoromethyl)propenoic acid is known to be a useful building block for the synthesis of trifluoromethylated compounds.[6,7] However, the reaction of both 2-(trifluoromethyl) propenoic acid and its ethyl ester with metal reagents produce complex mixtures from further nucleophilic attack on the fluorinated acrylate intermediates. In fact, although postulated as an intermediate in several reports, compounds of the type $CF_2=C(R^1)COR^2$ are difficult to isolate in non-anhydrous or nucleophilic media due to further reactions,[8-10] except for the fluorinated acrylates made from dibromodifluoromethane and malonic acid diesters.[11]

As part of our efforts to develop synthetic routes to trifluoromethylated compounds,[12-14] we describe herein a synthetic approach to α-trifluoromethylated carboxylic acid menthyl esters. We have found *l*- (or *d*-)menthyl 2-(trifluoromethyl)propenoate (**1**) to be a versatile material for the synthesis of menthyl 2-(trifluoromethyl)alkanoates **3** via fluorinated acrylates **2**.

Although various types of nucleophiles such as Grignard reagents, lithium reagents, etc., were examined in this system, only metal dialkyl- and diphenylcuprates[15] effected the formation of the fluorinated acrylates **2** smoothly (Table 1).



1 **2** **3**

To achieve the desired conversion **2** → **3**, we investigated the transformation of *l*-menthyl 2-benzyl-3,3-difluoropropenoate (**2a**) to *l*-menthyl 2-trifluoromethyl-3-phenylpropanoate (**3a**), using a variety of fluorination reagents (Table 2). The results indicate that the tetrabutylammonium fluoride (TBAF) tetrahydrofuran/*p*-toluenesulfonic acid system gave by far the best yield. Therefore, we examined the conversion of acrylates **2** to α-trifluoromethyl esters **3** using the TBAF/*p*-TsOH system (Table 3). The desired products **3** were obtained in moderate to good yields.

l-Menthyl 2-Trifluoromethyl-3-phenylpropanoate (3a); Typical Procedure:

l-Menthyl 2-Benzyl-3,3-difluoropropenoate (**2a**):

A solution of Ph_2LiCu is prepared from CuI (3.8 g, 20 mmol) and PhLi (20 mmol) in freshly dried Et_2O (30 mL) at 0 °C. To this is added, by syringe and with stirring under argon at 0 °C, a mixture of l-menthyl 2-(trifluoromethyl)propenoate (**1**, R^1 = *l*-menthyl; 2.8 g, 10 mmol) and $ClSiMe_3$ (1.0 g), and stirring is continued for 3 h at 0 °C. The mixture is then quenched with saturated NH_4Cl solution (50 mL) and the oily materials are extracted with EtOAc (3 × 100 mL). The extract is dried

Table 1. *l*- and *d*-Methyl 2-Alkyl-3,3-difluoropropenoates **2** Prepared

2	R^1	R^2M in R^2M/CuI	Yield (%)	bp (°C)/Torr	$[\alpha]_D$ (MeOH)	Molecular Formula[a]
a	*l*-menthyl	C_6H_5Li	64	138/0.34	−62.41 (c = 1.13)	$C_{20}H_{26}F_2O_2$ (336.4)
b	*l*-menthyl	*n*-C_4H_9Li	72	117–121/1	−56.90 (c = 1.02)	$C_{18}H_{30}F_2O_2$ (316.4)
c	*l*-menthyl	*n*-$C_6H_{13}MgBr$	82	121/0.30	−48.46 (c = 1.06)	$C_{20}H_{34}F_2O_2$ (344.5)
d	*l*-menthyl	*n*-$C_8H_{17}MgBr$	84	153/0.50	−47.42 (c = 0.96)	$C_{22}H_{38}F_2O_2$ (372.5)
e	*d*-menthyl	C_6H_5Li	72	121/0.68	+62.25 (c = 1.06)	$C_{20}H_{26}F_2O_2$ (336.4)

[a] Satisfactory microanalyses obtained: C ±0.33, H ±0.27.

Table 2. Preparation of *l*-Menthyl 2-Trifluoromethyl-3-phenylpropanoate **(3a)** under Various Conditions

MF (source of F)	Solvent	Reaction Temperature and Time	Yield (%)
CsF	diethylene glycol	r.t., 3 h	37
CsF	diethylene glycol	0°C, 3 h	28
CsF	THF	r.t., 12 h	45
TBAF	diethylene glycol	0°C, 4 h	47
TBAF	THF	r.t., 42 h	22
TBAF	THF/TsOH	0°C, 3 h	71

Table 3. *l*- and *d*-Menthyl 2-(Trifluoromethyl)alkanoates **(3)** Prepared

3	R^1	R^2	Yield (%)	bp (°C)/Torr [mp (°C)]	Molecular Formula[a]
a	*l*-menthyl	C_6H_5	71	[72–75]	$C_{20}H_{27}F_3O_2$ (356.4)
b	*l*-menthyl	*n*-C_4H_9	55	95–97/2	$C_{18}H_{31}F_3O_2$ (336.4)
c	*l*-menthyl	*n*-C_6H_{13}	49	115–121/0.18	$C_{20}H_{35}F_3O_2$ (364.5)
d	*l*-menthyl	*n*-C_8H_{17}	74	136–138/0.38	$C_{22}H_{39}F_3O_2$ (392.6)
e	*d*-menthyl	C_6H_5	75	[73]	$C_{20}H_{27}F_3O_2$ (356.4)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.34.

Table 4. NMR-Spectral Data of Compounds **2** and **3**

Compound	^{1}H-NMR ($CDCl_3$), δ	^{19}F-NMR, ($CDCl_3$/CF_3CO_2H), δ, J(Hz)
2a	0.30–2.10 (m, 18H); 3.50 (m, 2H); 4.70 (m, 1H); 7.20 (H_{arom})	−3.2 (m); −8.1 (m)
2b	0.70–2.40 (m, 29H); 4.70 (m, 1H)	−0.7 (m); −6.4 (m)
2c	0.60–2.40 (m, 33H); 4.80 (m, 1H)	−1.8 (m); −7.6 (m)
2d	0.60–2.30 (m, 37H); 4.70 (m, 1H)	−0.8 (m); −6.6 (m)
2e	0.50–2.10 (m, 18H); 3.50 (m, 2H); 4.70 (m, 1H); 7.10 (H_{arom})	−3.2 (m); −8.2 (m)
3a	0.50–2.10 (m, 18H); 2.90–3.60 (m, 3H); 4.60 (m, 1H); 7.30 (H_{arom})	−1.9 (d, J_{CF_3-CH} = 7.0); 9.7 (d, J_{CF_3-CH} = 6.6)
3b	0.60–2.20 (m, 29H); 3.00 (m, 1H); 4.80 (m, 1H)	−9.9 (d, J_{CF_3-CH} = 9.4); −9.8 (d, J_{CF_3-CH} = 7.6)
3c	0.70–2.40 (m, 33H); 2.40 (m, 1H); 4.80 (m, 1H)	−9.7 (d, J_{CF_3-CH} = 8.1); −9.8 (d, J_{CF_3-CH} = 8.4)
3d	0.70–2.20 (m, 37H); 3.00 (m, 1H); 4.70 (m, 1H)	9.7 (d, J_{CF_3-CH} = 7.5); 9.8 (d, J_{CF_3-CH} = 7.5)
3e	0.70–2.00 (m, 18H); 2.90–3.60 (m, 3H); 4.60 (m, 1H); 7.30 (H_{arom})	−1.9 (d, J_{CF_3-CH} = 7.0); 9.7 (d, J_{CF_3-CH} = 6.6)

(MgSO$_4$), the solvent removed, and the residue distilled at reduced pressure to give product **2a**; yield: 2.15 g (64%); bp 138°C/0.34 Torr; $[\alpha]_D$ −62.41° (*c* = 1.13; MeOH).

$C_{20}H_{26}F_2O_2$ (336.4) calc. C 71.40 H 7.79 found 71.29 7.84

Exact Mass: calc. 336.422, found 336.457.

IR (KBr): ν = 1740 (C=O); 1715 (C=C) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.3–2.1 (m, 18H); 3.5 (m, 2H); 4.7 (m, 1H); 7.2 (5 H_{arom}).

^{19}F-NMR ($CDCl_3$/$CF_3CO_2H_{ext}$): δ = −8.1 (m, F[a]); −3.2 (m, F[b]).

1-Methyl 2-Trifluoromethyl-3-phenylpropanoate **(3a)**: A solution of ester **2a** (3.36 g, 10 mmol), $Bu_4N^+F^-$ (3.92 g, 15 mmol), and TsOH (50 mg) in freshly dried THF (30 mL) is stirred under argon for 3 h at room temperature. The mixture is then quenched with saturated NH_4Cl solution (30 mL), and extracted with EtOAc (3 × 100 mL). The extract is dried ($MgSO_4$) and evaporated and the residue is column-chromatographed on silica gel using hexane/EtOAc (10:1) as eluent. The product is recrystallized from benzene to give analytically pure **3a**; yield: 2.52 g (71%); mp 72–75°C.

The ratio of diastereoisomers (1:1) is determined using the intensities of the ^{19}F-NMR signal.

$C_{20}H_{27}F_3O_2$ (356.4) calc. C 67.40 H 7.64 found 67.68 7.49

Exact Mass: calc. 356.428, found 356.464.

IR (KBr): ν = 1740 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.5–2.0 (m, 18H); 2.9–3.6 (m, 3H); 4.6 (m, 1H); 7.3 (H_{arom}).

^{19}F-NMR ($CDCl_3$/$CF_3CO_2H_{ext}$): δ = −1.9 (d, CF_3, J_{F-CH} = 7.0 Hz); −9.7 (d, CF_3, J_{F-CH} = 6.6 Hz).

Received: 13 January 1988; revised: 28 March 1988

(1) Filler, R., Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha, Tokyo, and Elsevier Biomedical, Amsterdam, 1983.
(2) Walsh, C. *Tetrahedron* **1982**, *38*, 357.
(3) Tsushima, T. *Kagaku To Seibutsu* **1982**, *20*, 770; *C.A.* **1983**, *98*, 85179.
(4) Fuchikami, T., Yatabe, M., Ojima, I. *Synthesis* **1981**, 365.
(5) Fuchikami, T. *J. Syn. Org. Chem. Jpn.* **1984**, *42*, 775.
(6) Yoshino, K., Ozaki, M., Taniguchi, H., Ito, M., Satoh, K., Yamasaki, N., Kitazume, T. *Chemistry Express* **1987**, *2*, 53.
(7) Yoshino, K., Ozaki, M., Taniguchi, H., Ito, M., Satoh, K., Yamasaki, N., Kitazume, T. *Jpn. J. Appl. Phys.* **1987**, *26*, L77.
(8) Suda, M. *Tetrahedron Lett.* **1981**, *22*, 1421.
(9) Rico, I., Cantacuzene, D., Wakselman, C. *Tetrahedron Lett.* **1981**, *22*, 3405.
(10) Buxton, M.W., Stacey, M., Tatlow, J.C. *J. Chem. Soc.* **1954**, 366.
(11) Everett, T.S., Purrington, S.T., Bumgardner, C.L. *J. Org. Chem.* **1984**, *49*, 3702.
(12) Lin, J.T., Yamazaki, T., Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211.
(13) Kitazume, T., Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186.
(14) Kitazume, T., Ikeya, T. *J. Org. Chem.*, **1988**, *53*, 2350.
(15) Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, John Wiley & Sons, New York, 1980.