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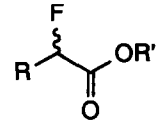
SIMPLE SYNTHESIS OF OPTICALLY ACTIVE 2-FLUOROPROPANOIC ACID AND ANALOGS OF HIGH ENANTIOMERIC PURITY

Elke Fritz-Langhals* and Gabi Schütz

Consortium für Elektrochemische Industrie GmbH, Central Research Company of Wacker-Chemie GmbH, Zielstattstraße 20, D-8000 München 70, Germany

Abstract: A very simple synthesis of optically active 2-fluoropropanoic acid **1** (R=CH_3, R'=H) and analogs of high enantiomeric purity was developed using the sulfonates **2** of the corresponding optically active 2-hydroxycarboxylic esters and potassium fluoride in formamide. Thus methyl (R)-2-fluoropropanoate (**1**, R=CH_3, R'=CH_3) was prepared in an optical purity of 96% from the mesylate of methyl (S)-lactate (ee 97.4 %) and isolated in 83% yield.

Optically active 2-fluorocarboxylic acids **1** and derivatives are an interesting class of compounds. The substitution of hydrogen by the strongly electronegative fluorine atom causes large electronic effects. On the other hand, steric effects due to the introduction of fluorine are small.[1] As a result, fluorine containing carboxylic acids are useful in biochemical studies,[2] e.g. as metabolism slowing agents.[3] More recently, optically active 2-fluorocarboxylic acids were used as building blocks in chiral dopants for ferroelectric liquid crystals[4,5] showing large values of spontaneous polarization.[6]



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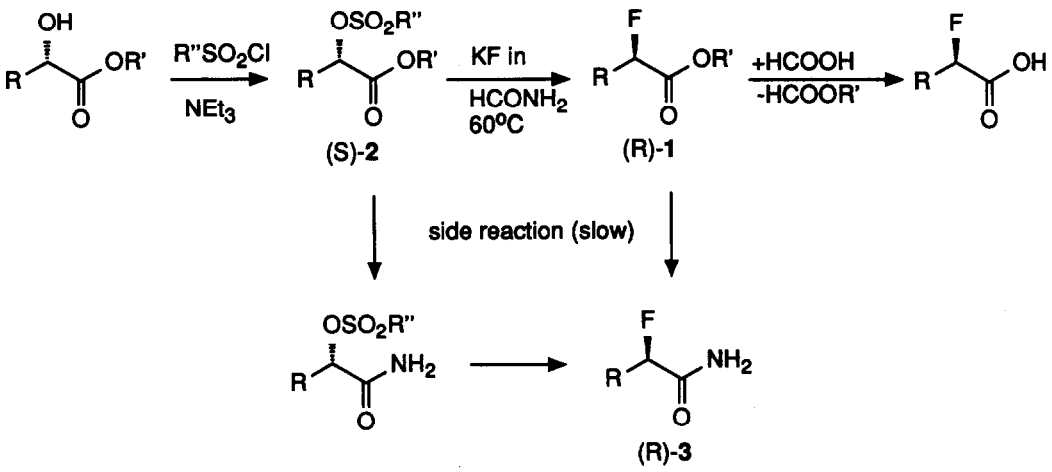
Deamination of an optically active 2-aminocarboxylic acid in anhydrous hydrogen fluoride/pyridine mixtures[4-8] offers a possibility of obtaining the desired 2-fluorocarboxylic acids, the optical purities however are only about 70%[9] or even lower,[10] as was found for 2-fluoropropanoic acid . Moreover, the deamination method is not suitable for the synthesis of bulk quantities because the large excess of HF/pyridine used strongly hinders the isolation of product. Other methods[1b,11] also need hydrogen fluoride.

Because the use of potassium fluoride instead of hydrogen fluoride as fluorinating agent would be an attractive alternative we developed a simple synthesis of optically active 2-fluorocarboxylic acids based on S_N2 reaction of optically active sulfonates **2** and potassium fluoride as nucleophilic reagent.

The formation of **1** (R=CH_3, R'=CH_3 or $CH(CH_3)_2$) from optically active **2** (R=CH_3, R'= CH_3 or $CH(CH_3)_2$, R''=CH_3 or C_6H_5,) and KF in commonly used dipolar aprotic S_N2 solvents (e.g. acetonitrile, DMF, sulfolane, DMPU) does not occur even at 100°C due to the low solubility of potassium fluoride.[12] We found that addition of 18-crown-6[13] increases the reaction rate appreciably (cf. lit.[14]) only when used in stoichometric amounts and then gives some racemization.[15] Furthermore, 18-crown-6 is expensive. In alcohols (e.g. diethyleneglycol, c.f. lit.[16]) which are better solvents for potassium fluoride, the reaction was slow, too, due to the diminished nucleophilicity of fluoride ion,[1b] and was accompanied by transesterifications.

We found that in formamide (FA) the reaction rate is increased by several orders of magnitude. This solvent is especially useful for S_N2 reactions with potassium fluoride both because of its high polarizability,[17] which favours S_N2 reactions, and because of its high polarity[18] rendering potassium fluoride sufficiently soluble in the reaction mixture[19]. For formamide, $t_{1/2}$ was about 30 min at 60°C (saturated solution of potassium fluoride). Thus, methyl (S)-2-methanesulfonyloxipropanoate (**2**, R=R'=R''=CH_3)[20] prepared from the commercially available methyl (S)-lactate (ee = 97.4 %) was treated with potassium fluoride in formamide at 60°C for 3 h to give methyl (R)-2-fluoropropanoate with ee = 96 % (scheme 1, table 1)[21].



Scheme 1 R=CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, CH_2-aryl, R'=CH_3, C_2H_5, $CH(CH_3)_2$, R''=CH_3, C_6H_5

Instead of formamide, the less polar solvents N-methylformamide (MFA), acetamide (AA, cf. lit.[22]) or N-methylacetamide (MAA) can be used. The reaction rate, however, is diminished in these media by about one order of magnitude and therefore requires higher reaction temperatures (table 1).

Homologous optically active (S)-2-hydroxycarboxylic acid esters were prepared by deamination of the corresponding optically active (S)-2-aminocarboxylic acids[23] followed by treatment with hydrogen chloride in alcohol[22]. Reaction with methanesulfonyl chloride[20] or phenylsulfonyl chloride gave the sulfonates **2** (R''=CH_3, C_6H_5). The reaction with KF in formamide lead to the (R)-2-fluorocarboxylic esters **1**, see table 1.

For R = alkyl the optical yields are high. In the case of R = C_6H_5, however, some racemization is observed due to the enhanced stability of carbenium ions in homobenzylic position. In this case the optical yield can be improved by use of the less polar solvents MFA or AA (see table 1).

Table 1: Synthesis of (R)- 2-fluorocarboxylic esters **1** from (S)-sulfonates **2**[20,21]

(S)-sulfonate **2**[a] R	R'	ee[b]	solv.[c]	temp. (°C)	p[d] (torr)	time (h)	yield[e] (%)	ee[f] (%)
CH_3	CH_3	98.7	FA	60	20	4	83	96.0[g]
CH_3	CH_3	98.7	MFA	70	25	12	74	87.2
CH_3	CH_3	98.7	AA	80	10	10	78	86.8
CH_3	CH_3	98.7	MAA	80	15	14	88	95.2
CH_3	$CH(CH_3)_2$[h]	99.7	FA	60	15	4	33	96.4
$CH(CH_3)_2$	CH_3	97.0	FA	95	12	4	50	94.4[i]
$CH_2CH(CH_3)_2$	CH_3	95.8	FA	80	10	2.5	60	93.2[k]
CH_2-C_6H_5	CH_3	96.4	FA	87	1	2	51[m]	81.6[n]
CH_2-C_6H_5	$CH(CH_3)_2$	92.6	FA	75	1	13	37	55.5
CH_2-C_6H_5	$CH(CH_3)_2$	92.6	MFA	85	1	5		65.8
CH_2-C_6H_5	$CH(CH_3)_2$	92.6	AA	85	1	5		86.8

[a]R''=CH_3, [b]optical purity of the parent (S)-2-hydroxycarboxylic ester, determined by gaschromatographic analysis of the corresponding isopropyl urethane on the chiral stationary phase 'Chiral-XE-60-S-Val' (50 m capillary, Chrompak, Munich/Germany) or Chiraldex G-TA (20 m capillary, Astec, Wippany/USA), [c] FA: formamide, MFA: N-methylformamide, AA: acetamide, MAA: N-methylacetamide, [d]pressure, [e]isolated yield of **1**, [f]optical purity of isolated **1**, determined by gaschromatographic analysis on the chiral stationary phases 'Lipodex A' and 'C' (Macherey-Nagel, Düren/Germany), [g]b.p. 80-82°C/300 Torr, 35°C/13 Torr (lit.[24]: 106.5-108.5°C, lit.[25]: 106-106.5°C) ^{1}H-NMR ($CDCl_3$): δ = 1.58 (dd,J_{HF}= 23 Hz, J_{HH}= 7 Hz, CH_3), 3.80 (s, OCH_3), 5.03 (qd, J_{HF}= 49 Hz, J_{HH}= 7 Hz, CH) - IR (Film): 2955w (CH); 1765s, 1748s (CO), 1450m, 1220m cm^{-1}, [h]R''=4-CH_3-C_6H_5, [i]b.p. 40°C/12 Torr, ^{1}H-NMR ($CDCl_3$) : δ = 0.97, 1.06 (2d, J= 8 Hz, 2 CH_3), 2.30 (mc, CH), 3.80 (s, OCH_3), 4.73 (dd, J_{HF}= 50 Hz, J_{HH}= 5 Hz, CH), IR (Film): 2962 m (CH), 1760s, 1745s (CO) cm^{-1}, [k]b.p. 66°C/12 Torr, ^{1}H-NMR ($CDCl_3$) : δ = 0.97 (mc, 2 CH_3), 1.55-1.93 (m, CH_2, CH), 3.78 (s, OCH_3), 4.97 (ddd, J_{HF}=50 Hz, CH), [l]isolated by ether extraction, [m] 20 % of the amide **3** (R=$CH_2C_6H_5$) were found, [n] ^{1}H-NMR ($CDCl_3$) : δ = 3.17 (mc, CH_2), 3.76 (s, OCH_3), 5.10 (ddd, J_{HF}= 50 Hz, CH)), 7.17-7.40 (m, 5 H), amide **3** (R=$CH_2C_6H_5$): ^{1}H-NMR ($CDCl_3$) : δ = 3.25 (mc, CH_2), 5.12 (ddd, J_{HF}= 50 Hz, CH), 5.50 and 6.15 (2s, broad, NH_2), 7.17-7.40 (m, 5H),

In formamide, however, we observed a comparably slow side reaction with the methyl esters (R'=CH_3) leading to (R)-2-fluorocarboxamides **3** and methyl formiate (see scheme 1, cf. lit.[26]). As we found, this reaction is catalyzed by fluoride. This problem was overcome by distilling off the volatile esters **1** in situ from the reaction mixture under reduced pressure. Alternatively, the amide formation can be completely suppressed by using the isopropyl esters, as was found for **2** (R=$CH_2C_6H_5$, R'=$CH(CH_3)_2$, table 1).

The 2-fluorocarboxylic acids were prepared from the esters by transesterification with formic acid (Scheme 1). This method is especially useful for the preparation of the strongly hydrophilic 2-fluoropropanoic acid which is difficult to separate from aqueous solutions.

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21 **2-Fluorocarboxylic acids (1) - general procedure** (see also table 1): In a round-bottom flask 90 ml of the amide solvent were heated to the reaction temp. (see table 1). Anhydrous potassium fluoride (37.2 g, 0.64 mol) was digested with stirring. The flask was connected with a trap cooled with dry ice. 0.16 mol sulfonate **2** were added slowly and the product **1** distilled from the reaction mixture into the trap in vacuo during the reaction. The contents of the cooling trap was redistilled to give the pure 2-fluorocarboxylic esters **2** (yields see table 1). The isolated yield is improved by 10-15% by ether extraction of the reaction mixture after dilution with 50 ml water.
The ester **2** was heated with 1.1 eq. formic acid and the alkyl formiate formed was distilled off. Distillation of the residue in vacuo gave the pure 2-fluorocarboxylic acids. Yield: 80-90%.

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