Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 981-986, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00128-6

Alkali Metal Fluorides as Efficient Fluorinating Agents. Enantiocontrolled Synthesis of 2-Fluoroalkyl Carboxylates and 1-Fluoroalkyl Benzenes

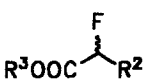
Elke Fritz-Langhals

Consortium für Elektrochemische Industrie GmbH,
Central Research Company of Wacker-Chemie GmbH,
Zielstattstraße 20, D-81379 München, Germany

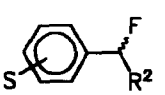
Abstract: Potassium fluoride and cesium fluoride in formamide, N-methylformamide, or acetamide are efficient fluorinating agents. They can be used for the enantiocontrolled synthesis of 2-fluorocarboxylic acids **1a** and 1-fluoroalkyl benzenes **1b** from the corresponding sulfonates which are easily available in high enantiomeric purity. The scope and limitation of the synthetic method is discussed.

Introduction: Optically active compounds **1** bearing fluorine at a stereogenic centre play an important role in various fields of organic chemistry. The introduction of the strongly electronegative fluorine atom causes large electronic effects.[1,2] Sterically however, the fluorine substituent resembles hydrogen.[2] Thus, by the introduction of fluorine into organic molecules non-covalent interactions can be modified.

Optically active compounds bearing fluorine at a stereogenic centre are important in biochemistry, where enzyme/substrate interactions play an important role.[3,4] They are also useful in the development of liquid crystals with new properties, e.g. in the design of chiral dopants for ferroelectric liquid crystal mixtures.[5-7] High values of spontaneous polarization are often due to the presence of fluorine at a stereogenic centre, and it is assumed that best results are obtained when the stereogenic centre is directly bound to an aromatic backbone.[8] Thus, optically active 1-fluoroalkyl benzenes **1b** (R^1 = aryl, R^2 = alkyl)[9] are prospective candidates for such spontaneous polarization. On the other hand, 2-fluorocarboxylic acids **1a** (R^1 = $COOR^3$ with R^3 = H, R^2 = alkyl)[10,11] are versatile synthons in the development of many new chiral dopants.[5-7]



1a



1b

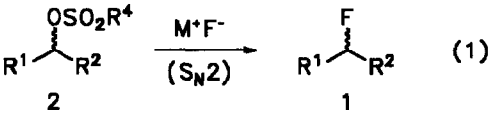
Optically active 2-fluorocarboxylic acids **1a** were originally prepared by deamination of the corresponding 2-aminocarboxylic acids in anhydrous HF/pyridine mixtures[5-7,12,13] in an optical purity of 70% or lower.[10] This method is not suitable for bulk quantities however, because the anhydrous HF/pyridine

reagent which is used in a large excess is difficult to handle. The excess of reagent also hinders the isolation of the very polar and hydrophilic product **1a**, especially when R^2 is CH_3. Other methods also need hydrogen fluoride.[14] For compounds **1b** an analogous procedure does not exist. Therefore, a simple method for the synthesis of the title compounds **1** is desirable.

Results and Discussion

Alkali Metal Fluorides as Nucleophilic Reagents

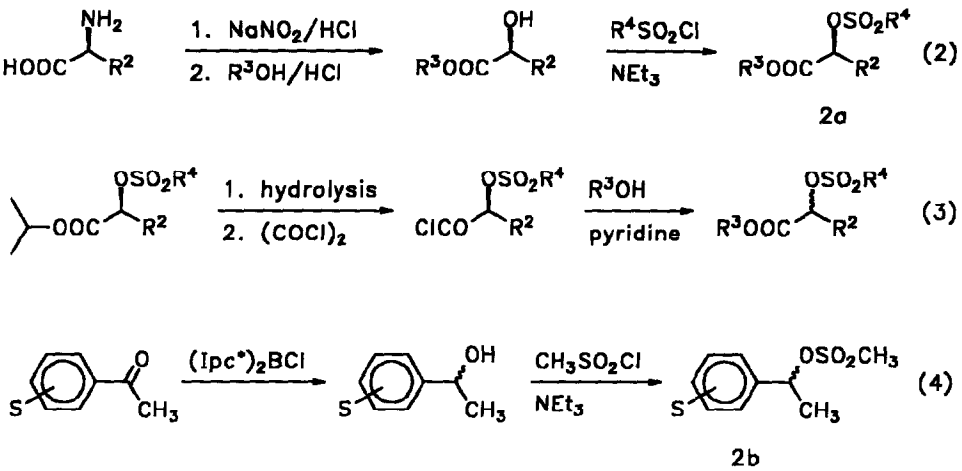
A simple route for the synthesis of the title compounds **1** should be the reaction of the corresponding optically active sulfonates **2** (**2a** : R^1 = COOalkyl, **2b** : R^1 = aryl) in a stereochemically unambiguous S_N2 reaction with fluoride as a nucleophile according to eq. 1. The use of alkali metal fluorides, especially potassium fluoride, should be most attractive because they are easy to handle and cheap, so that the synthesis could be done even on a technical scale.



2 1 (1)

There are two main obstacles however, which hinder the incorporation of fluoride from alkali metal fluorides. Firstly, its small size and low polarizability makes the fluoride anion behave rather as a base than as a nucleophile[2], so that alkali metal fluorides are normally used as bases in organic synthesis[15] and not as nucleophiles. Secondly, potassium fluoride and cesium fluoride are not sufficiently soluble in the commonly used dipolar aprotic S_N2 solvents.[1,2] High temperatures enhance the solubility of the salts but the sulfonates **2b** with R^1 = aryl are thermally unstable.[16] Moreover racemization can occur. As an example, optically active **2a** (R^1 = $COOCH_3$, R^4 = CH_3 or C_6H_5) with e.e. > 99% reacts with a saturated solution of potassium fluoride in HMPT at 85°C slowly to form **1a** (R^1 = $COOCH_3$, R^2 = CH_3) with e.e. = 76 %. No reaction occurs with potassium fluoride in other dipolar aprotic solvents even at 100°C.[10] With stoichometric amounts of 18-crown-6 in DMPU **1a** (R^1 = $COOCH_3$, R^2 = CH_3) was formed slowly at room temperature with some racemization.[10] A further disadvantage is that 18-crown-6 is expensive and difficult to recover from the reaction mixture. The design of special cation complexes leads to the so-called "naked" fluoride ions which prove to be only bases.[17] Similar results were obtained with tetrabutylammonium fluoride. In polar protic solvents, mainly alcohols, glymes and glycols, which are better solvents especially for potassium fluoride the nucleophilicity is greatly diminished.[1,2] Attempts at synthesising **1a** (R^1 = $COOCH_3$, R^2 = CH_3) from **2a** (R^1 = $COOCH_3$, R^4 = CH_3 or C_6H_5) in diethylene glycol, 2,3-butane diol, 1-methoxy-2-propanol or trifluoroethanol have been made. In all cases racemization competes with product formation.

It was found that in formamide (FA) the fluorination potential of alkali metal fluorides is strongly increased.[9-11] Formamide has a high polarizability[18], which favors S_N2 reactions, and a high polarity[19] rendering potassium fluoride and cesium fluoride sufficiently soluble in the reaction mixture. As will be shown below, the less polar solvents N-methylformamide (MFA), acetamide (AA) or N-methylacetamide (MAA) can be used instead of formamide. Although the reaction rate is diminished in these media and therefore higher reaction temperatures are required, they are important in some cases[9], e.g. for lipophilic sulfonates **2** which are only poorly soluble in formamide.[11]

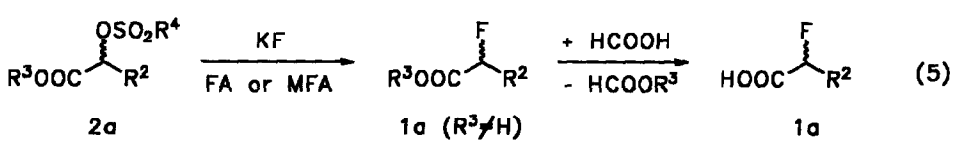


Scheme 1

Synthesis of Optically Active Sulfonates 2

Optically active 2-hydroxycarboxylic acids were prepared by deamination of the corresponding 2-aminocarboxylic acids under retention of configuration[20] and transformed into their esters by treatment with hydrogen chloride in alcohol[21,22] (scheme 1, eq. 2). (S)-Lactate esters ($R^2 = CH_3$) with R^3 = methyl, ethyl or isopropyl (see scheme 1) are commercially available in high optical yield (see table). Optically active sulfonates **2a** were prepared from the alcohols and methanesulfonyl chloride or phenylsulfonyl chloride in high yield.[9-11] For the synthesis of methanesulfonyl (S)-lactate esters of long chain alcohols the corresponding isopropylester was hydrolized to the free carboxylic acid, conversion into the acid chloride was accomplished by oxalyl chloride (scheme 1, eq. 3).[23] Reaction with the long chain alcohols gave the esters. (S) and (R)-alcohols with R^1 = aryl can be prepared from the corresponding ketones in high chemical and optical yield (see table) using (+) or (-)-B-chloro-diisopinocampheyl borane [$(Ipc^*)_2BCl$] in THF according to Brown[24] (scheme 1, eq. 4). Another possibility is the enantioselective reduction with chiral oxazaborolidines according to Corey.[25] The aryl-substituted sulfonates **2b**[10] were prepared at temperatures below 0°C because of some thermal instability which decreases with the electron withdrawing effect of the substituent S. When S is 4-CN or 4-NO_2 **2b** is stable at 60°C for several hours.

Optically Active 2-Fluorocarboxylic Acids 1a



Methyl (S)-2-methanesulfonyloxipropanoate (**2a**, $R^2 = R^3 = R^4 = CH_3$, e.e. = 98.7%) was treated with anhydrous potassium fluoride in formamide at 60°C for 3 h to give methyl (R)-2-fluoropropanoate with e.e. = 96% in 83% yield[10] (see table 1). Good optical yields were also obtained for $R^2 = CH(CH_3)_2$ or $CH_2CH(CH_3)_2$. As can be seen from table 1 the less polar solvents N-methylformamide (MFA), acet-

amide (AA) or N-methylacetamide (MAA) can be used instead of formamide. The reaction rate however is diminished so that temperature and time of the reaction have to be increased. For $R^2 = CH_2\text{-}C_6H_5$ some racemization is observed in formamide because the formation of carbenium ions is favoured in the homobenzylic position. The S_N1 reaction can be repressed by use of the less polar solvents AA or MAA. Finally, lipophilic substrates as **2a** with $R^3 = n\text{-}C_{12}H_{25}$ or $n\text{-}C_{20}H_{41}$ can be converted into the fluoro compounds in MFA, because they are only poorly soluble in FA.

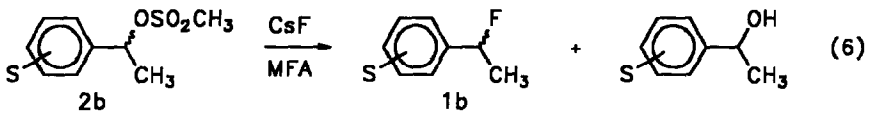
Table 1: Synthesis of optically active fluoro compounds **1** from sulfonates **2**

sulfonate 2[a]						fluoro compound 1	
		e.e.[b]	solv.[c]	M	T/time	yield	e.e.[b]
R^1	R^2	(%)		(equ.)	(°C/h)	(%)	(%)
$COOCH_3$	CH_3	98.7(S)[d]	FA	K(4)	60/4	83	96.0(R)[e]
$COOCH_3$	CH_3	98.7(S)[d]	MFA	K(4)	70/12	74	87.2(R)[e]
$COOCH_3$	CH_3	98.7(S)[d]	AA	K(4)	80/10	78	86.8(R)[e]
$COOCH_3$	CH_3	98.7(S)[d]	MAA	K(4)	80/14	88	95.2(R)[e]
$COOCH(CH_3)_2$	CH_3[f]	99.7(S)[d]	FA	K(4)	60/4	33	96.4(R)[e]
$COOCH_3$	$CH(CH_3)_2$	97.0(S)[d]	FA	K(4)	95/4	50	94.4(R)[e]
$COOCH_3$	$CH_2CH(CH_3)_2$	95.8(S)[d]	FA	K(4)	80/2.5	60	93.2(R)[e]
$COOCH_3$	$CH_2\text{-}C_6H_5$	96.4(S)[d]	FA	K(4)	87/2	51	81.6(R)[e]
$COOCH(CH_3)_2$	$CH_2\text{-}C_6H_5$	92.6(S)[d]	FA	K(4)	75/13	37	55.5(R)[e]
$COOCH(CH_3)_2$	$CH_2\text{-}C_6H_5$	92.6(S)[d]	MFA	K(4)	85/5		65.8(R)[e]
$COOCH(CH_3)_2$	$CH_2\text{-}C_6H_5$	92.6(S)[d]	AA	K(4)	85/5		86.8(R)[e]
$COOCH(CH_3)_2$	$CH_2\text{-}C_6H_5$	92.6(S)[d]	MAA	K(4)	85/7		86.8(R)[e]
$COOn\text{-}C_{20}H_{41}$	CH_3		MFA	K(4)	80/4	39	86(R)[g]
$COOn\text{-}C_{12}H_{23}$	CH_3		MFA	K(4)	80/4	70	
$4\text{-}CN\text{-}C_6H_5$	CH_3	96.2(R)[h]	MFA	Cs(4)	60/4	81	96.0(S)[hi]
$4\text{-}CN\text{-}C_6H_5$	CH_3	96.2(R)[h]	DMF	Cs(4)	60/4	60	
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	MFA	Cs(4)	60/5	75	91.4(S)[hk]
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	MFA	Cs(2)	100/0.5	73	
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	MFA	Cs(16)	60/1	78	
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	MFA	Cs(8)	100/0.5	75	
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	AA	Cs(4)	90/1	73	
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	FA	Cs(16)	60/1	62	
$4\text{-}NO_2\text{-}C_6H_5$	CH_3	96.4(R)[h]	FA	K(8)	60/8	25	
$4\text{-}COOEt\text{-}C_6H_5$	CH_3	83.0(R)[h]	MFA	Cs(4)	60/1	46	73.0(S)[h]
$2\text{-}F\text{-}C_6H_5$	CH_3		MFA	Cs(4)	60/1	56	
$4\text{-}Br\text{-}C_6H_5$	CH_3		MFA	Cs(4.5)	65/1	36	
$4\text{-}Br\text{-}C_6H_5$	CH_3		MFA	K(4)[l]	65/1	0	
4'-NO_2-Biph.	CH_3		MFA	Cs(4)	40/8	0	
C_6H_5	$COOC_2H_5$	99.9(R)[m]	MFA	Cs(4)	20/24	88	0[n]

[a] $R^4 = CH_3$, [b] absolute configuration in brackets, [c] FA : formamide, MFA : N-methylformamide, AA : acetamide, MAA : N-methylacetamide, the concentration of 2 was 2-3M, [d] optical purity of the parent optically active (S)-2-hydroxycarboxylic ester, determined by GC analysis of the corresponding isopropyl urethane as described in lit.[10,11], [e] optical purity determined by GC analysis as described in lit.[10], [f] $R^4 = 4\text{-}CH_3\text{-}C_6H_5$, [g] optical purity of the parent methylester which was prepared by transesterification, determined by GC analysis as described in lit.[10,11], [h] optical purity determined by GC analysis as described in lit.[9], [i] $[\alpha]_D^{20} = +27.1$ (c 1.00, CH_2Cl_2), [k] $[\alpha]_D^{22} = +18.3$ (c 1.00, CH_2Cl_2), [l] addition of 0.3 equiv. 1.1M tetrabutylammmonium fluoride in THF, [m] enantiomeric excess of (R)-ethylmandelate, determined by GC analysis of the corresponding trifluoroacetate on Chiraldex G-TA (20m capillary, Astec, Wippany,USA), [n] determined ^{1}H-NMR-spectroscopically.[30]

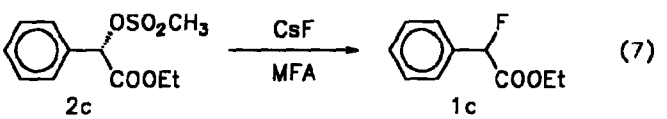
The free carboxylic acids **1a** (R^3 = H) can be prepared from the methyl esters by transesterification with formic acid (eq. 5).[27] Treatment with thionyl chloride gives the acid chlorides. Thus (R)-2-fluoropropanoyl chloride with e.e.=92.4 % can be prepared from methyl (R)-2-fluoropropanoate with e.e.=96.0 %.

Optically Active 1-Fluoralkyl Benzenes 1b



The table shows that potassium fluoride is not suitable for the synthesis of **1b** in contrast to the synthesis of optically active **1a**. No improvement is obtained by the addition of tetrabutylammonium fluoride in THF, a commonly used fluorinating reagent.[28] When potassium fluoride is replaced by cesium fluoride, the 1-fluoroalkyl benzenes **1b** are formed (equ. 6). The results are summarized in table 1. It shows that the yield of optically active **1b** is good in the presence of the strongly electron withdrawing substituents 4-NO_2 and 4-CN and moderate for 4-COOEt, 4-Br and 2-F. The optical purities indicate that the formation of **1b** is predominantly an S_N2 process, although in benzylic position S_N1 is normally favoured. For the synthesis of **1b** with S = 4-NO_2 it is possible to use formamide or acetamide as solvent. The solubility of the methanesulfonates **2b** with S = 4-CN, 4-Br and 2-F, however, is very low in these very polar media, so that N-methylformamide is used preferentially. As it is shown for S = 4-CN, in DMF the reaction is much slower and gave **1b** in a lower yield. In all cases we found the corresponding alcohol as a byproduct (eq.6).[29] In the absence of electron withdrawing substituents only the alcohol formation is observed.

Ethyl 2-Fluorophenylacetate



When ethyl (S)-2-methanesulfonyloxiphenylacetate (**2c**, R^1 = $COOC_2H_5$, R^2 = phenyl, R^3 = C_2H_5, R^4 = CH_3)[30] is treated with 4 equiv. of cesium fluoride in N-methylformamide at room temperature (table 1) ethyl 2-fluorophenylacetate **1c** is formed in 88 % yield (eq.7). As determined by ^{1}H-NMR-spectroscopy[31] the product is completely racemic. It is supposed that the racemization occurs during deprotonation by the basic fluoride anion. This is indicated by the fact that **2c** (but not **1c**) undergoes H/D-exchange in α-position in the presence of fluoride.[32] The method might be useful, however, for the synthesis of racemic **1c**, since it is very simple, and a method of resolution of **1c** is known.[33]

Summary: Alkali metal fluorides are good nucleophiles in formamide and its C-and/or N-monomethylated analogs. The new fluorination system is useful for the stereospecific introduction of fluorine in α-position of carboxyl groups and in benzylic position when the aromatic ring is electronically deficient. 2-Fluorophenyl acetic acid however can be prepared in only racemic form because of α-deprotonation by fluoride ion.

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22. In the case of $R^2 = CH_2\text{-}C_6H_5$ and $R^3 = CH(CH_3)_2$ about 20% isopropyl phenylacetate and about 10% of isopropyl 2-chloro-3-phenylacetate were found as side products.
23. 30 g (0.14 mole) Isopropyl (S)-2-methanesulfonyloxipropanoate were dissolved in a mixture of 100 ml methanol and 105 ml (0.21 mole) 2N NaOH. After 16 h at room temperature the mixture was acidified with 2N HCl and extracted with ether. Evaporation of the organic layer gave 15 g (64%) (S)-2-methanesulfonyloxipropanoic acid as colourless crystals. They were dissolved in 40 ml methylene chloride, oxalyl chloride (42 g) was added and the mixture was heated under reflux for 8 h. Evaporation in vacuo (10 torr) gave 16.1 g (98%) (S)-2-methanesulfonyloxipropanoyl chloride as colourless liquid.
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26. For experimental details see lit.[10].
27. A mixture of 148 g (1.39 mol) **1a** ($R^2 = COOCH_3$, e.e. = 96.0), 70 g (1.53 mol) formic acid and catalytic amounts of 4-toluenesulfonic acid were heated slowly and the methyl formiate (bp 34°C) formed was distilled off. The residue was fractionated in vacuo and gave 79 g (62%) of **1a** (R^2 = COOH), bp. 64-68°C /15 Torr, $[\alpha]_D^{23} = -0.320$ (neat). The acid was treated with thionyl chloride (1.2 equiv.) and catalytic amounts of DMF at 50°C for 15 h. Fractionated distillation gave (R)-2-fluoropropanoyl chloride, bp. 79°C, yield 88 %. E.e. = 92.4 % (GC analysis on Chiraldex G-TA, 20 m capillary, Astec, Wippany, USA)
28. See for example: Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, 110, 7538-7539.
29. Discussion of the mechanism of the alcohol formation see lit.[9]
30. Ethyl (R)-2-methanesulfonyloxiphenylacetate was prepared from (R)-ethylmandelate (e.e. > 99.9%) using CH_3SO_2Cl/NEt_3 in diethyl ether. $[\alpha]_D^{22} = -85.5$ (c 1.0, methylene chloride).
31. The splitting of the α-H signal with 0.7-1.0 equiv. tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]praseodym in CD_2Cl_2 was monitored.
32. The α-NMR signal of **2c** in d_7-DMF/D_2O disappeared on addition of CsF at room temperature.
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(*Received* 17 *March* 1994)