Pergamon

Tetrahedron Letters, Vol. 35, No. 12, pp. 1851-1854, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0158-T

SYNTHESIS OF OPTICALLY ACTIVE 1-FLUOROALKYL BENZENES

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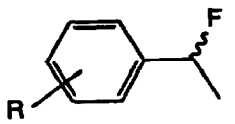
Abstract: A simple synthesis of optically active 1-fluoroalkyl benzenes bearing electron withdrawing substituents is developed. Optically active 1-hydroxyalkyl benzenes are converted into the methanesulfonates and subsequently converted into the optically active 1-fluoroalkyl benzenes **1** by use of the fluorinating agent cesium fluoride/N-methyl-formamide.

In the development of ferroelectric liquid crystals chiral dopants bearing fluorine at a chiral centre play an important role.[1-2] High values of spontaneous polarization are assumed for systems in which the chiral centre is most closely bound to the aromatic backbone.[3-5] Thus optically active 4'-substituted 1-fluoroethyl benzenes **1** and homologs are prospective candidates for that purpose. Furthermore, the introduction of fluorine often causes pronounced biological effects[6], so that the title compounds are also useful in pharmacological studies.[6,7]



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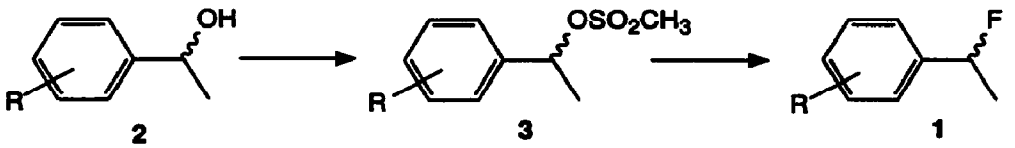
In general, for the synthesis of optically active compounds bearing fluorine at a chiral centre only a few methods are known.[8,9] To date no method is known for the synthesis of the title compounds.[10] Because 1-fluoroalkyl benzenes have no functional group for resolution it is necessary to introduce fluorine by a stereochemically unambiguous route. A stereospecific S_N2 reaction of a 1-phenylalkyl methanesulfonate may be an attractive way, for the corresponding optically active 1-phenylalcanols can easily be obtained by enantioselective reduction of ketones in high chemical and optical yield.[11,12] Two facts, however, restrict the success of this attractive possibility. Firstly, difficulties arise from the fact that in benzylic position S_N1 reactions are favoured. Secondly, the introduction of fluorine by nucleophilic substitution, however, is difficult because the small fluoride anion behaves as a base rather than a nucleophile.[8] As we have shown

previously[13], crown ether in an apolar or dipolar aprotic solvent which is commonly used for S_N2 type reactions is not efficient enough for replacements by fluorine. From the reaction of a 1-(4-phenoxy-carbonyl)phenylethyl methanesulfonate with cesium fluoride/18-crown-6 in THF the 1-(4-phenoxy-carbonyl)phenylethyl fluoride was obtained in only 1% yield.[14]

We report here a new method for the synthesis of title compounds from the corresponding methanesulfonates using cesium fluoride in N-methylformamide as an efficient fluorinating reagent.



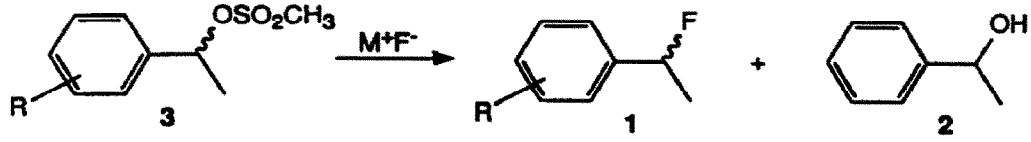
Scheme 1 R = 4-CN, 4-NO_2, 4-COOEt, 4-Br, 2-F, 4-(4'-NO_2-phenyl), 4-H

Optically active (R)-1-phenylethanols **2** (scheme 1)[15] were prepared from the corresponding ketones using (-)-B-chloro-diisopinocampheyl borane in THF[11] according to Brown[11] and converted into the methanesulfonates **3**.[16] These showed a pronounced substituent effect concerning their thermal stabilities which decreases for the sequence 4-CN, 4-NO_2 > 4-Br, 4-COOEt, 2-F > 4-(4'-NO_2-phenyl) > 4-H. Methanesulfonate **3** with R = H decomposes fast at temperatures below 10°C,[17] whereas the methane-sulfonates **3** with R = 4-CN or 4-NO_2 were stable at 60°C for several hours. The differences in thermal stabilities reflect the diminished tendency of carbenium ion formation in the presence of electron with-drawing substituents. For the conversion into the 1-fluoroethyl benzenes **1** the methanesulfonates **3** were dissolved in a small quantity of methylene chloride at about 0°C and added to a stirred suspension of CsF in N-methylformamide at the reaction temperature. Thermally stable methanesulfonates were added without solvent.[18]

Results are summarized in the table. It shows that the yield of optically active **1** 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 **1** is predominantly an S_N2 process. In all cases we found the alcohol **2** as byproduct. In the absence of electron withdrawing substituents (R = H, phenyl) the conversion into the fluoride failed completely, and the alcohol **2** was formed as the main product. Because we excluded water carefully it is assumed that the alcohol formation is a competing reaction with the solvent probably under formation of iminium ions as intermediates as known for DMF.[19] In the absence of fluoride the formation of alcohol **2** is quantitative. On the other hand, the amount of cesium fluoride - when used in excess - and the temperature did not dramatically affect the ratio between **1** and **2**. The table shows that in contrast to the synthesis of optically active 2-fluorocarboxylic acids[13] potassium fluoride in formamide is not suitable for the synthesis of the title compounds. Addition of tetrabutylammonium fluoride in THF, a commonly used fluorinating reagent[20], to the reaction mixture gave no improvement. The reaction of **3** (R = 4-NO_2) with tetrabutylammonium fluoride in THF, gave a complex mixture. **1** (R = 4-NO_2) was not found. For the synthesis of **1** with R = NO_2 it is possible to use

cesium fluoride in formamide or acetamide. The solubility of the methanesulfonates 3 with R = 4-CN, 4-Br and 2-F, however, is very low in these very polar media. As seen for R = 4-CN, in DMF the reaction is much more slower and the yield of 1 is markedly diminished.

Table 1: Synthesis of 1-fluoroethyl benzenes 1 from methanesulfonates 3



R	ee (%)[a]	solvent[b]	M(equiv.)	T/h[c]	ratio 1 : 2[d]
4-CN	96.2[e]	MFA	Cs(4)	60/4	81 (96.0[e]) : 19 (88[e])
4-CN	96.2	DMF	Cs(4)	60/4	60 : 40[f]
4-NO_2	96.4[g]	MFA	Cs(4)	60/5	75 (91.4[h]) : 25
4-NO_2	96.4	MFA	Cs(2)	100/0.5	73 : 27
4-NO_2	96.4	MFA	Cs(16)	60/1	78 : 22
4-NO_2	96.4	MFA	Cs(8)	100/0.5	75 : 25
4-NO_2	96.4	AA	Cs(4)	90/1	73 : 27
4-NO_2	96.4	FA	Cs(16)	60/1	62 : 38
4-NO_2	96.4	FA	K(8)	60/8	25 : 75
4-COOEt	83.0[i]	MFA	Cs(4)	60/1	46 (73.0[h]) : 54 (20[i])
2-F	rac.	MFA	Cs(4)	60/1	56 : 44
2-F	rac.	AA	Cs(4)	90/1	0 : 100
4-Br	rac.	MFA	Cs(4.5)	65/1	36 : 64
4-Br	rac.	MFA	K(4)[k]	65/1	0 : 100
4'-(4-NO_2Ph)	rac.	MFA	Cs(4)	40/8	0 : 100

[a] enantiomer excess in percent of educt alcohol 2, [b] MFA : N-methylformamide, AA : acetamide, FA : formamide, concentration of 3 was 2-3M, [c] temperature in °C and reaction time in hours, [d] at full conversion, enantiomer excess in brackets, [e] determined by gas chromatographic analysis on Chiraldex B-PH (20 m capillary, Astec, Wippany/USA), [f] conversion 60 %, [g] determined by gas chromatographic analysis of the corresponding trifluoroacetate on Chiraldex G-TA (20 m capillary, Astec, Wippany/USA), [h] determined by gas chromatographic analysis on Lipodex C (50 m glass capillary, Macherey-Nagel, Düren/Germany), [i] determined by gas chromatographic analysis of the corresponding trifluoroacetate as in [h], [k] addition of 0.3 equiv. 1.1 M tetrabutylammonium fluoride in THF.

Summarizing the results the new synthetic method is useful for the synthesis of 1-fluoroalkyl benzenes with electron withdrawing substituents such as cyano, nitro, carboxy, bromine or fluorine. The formation of the alcohol **2** as a byproduct is tolerable because it can be easily removed by distillation or chromatography. The aromatic substituents are useful functional groups for further conversions.

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15. We thank Dr. R. Hirsenkorn for a sample of (R)-1-(4-carboxyethyl)phenylethanol.
16. To a solution of alcohol **2** and 1.5 equiv. triethylamine in methylene chloride were added 1.2 equiv. methanesulfonyl chloride in methylene chloride at -20 to -10°C. After 1-2 hours reaction time excess triethylamine was removed by extraction with 2N HCl. After drying methylene chloride was removed in vacuo. For the thermally instable methanesulfonates **3** the workup was performed at low temperature. Structures were verified by ^{1}H-NMR spectroscopy.
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18. **1-Fluoroethyl benzenes (1) - general procedure** (see also table): cesium fluoride was added to freshly distilled N-methylformamide at the reaction temperature under argon and stirring. In the case of R = 4-CN or 4-NO_2 the methanesulfonate **3** was added crystalline without solvent. In the case of the thermally instable methanesulfonates **3** [R = 4-Br, 4-COOEt, 2-F, 4-(4'-NO_2-phenyl), H] a 5-7M solution in methylene chloride cooled to -20°C was added slowly so that the reaction temperature remains constant. For workup the mixture was diluted with water and extracted with diethyl ether or methyl tert.butylether. The ether extract was washed with water, dried ($MgSO_4$) and evaporated to dryness. The ratio of **1** and **2** was determined by ^{1}H-NMR spectroscopy using the α-protons. Pure **1** (R = 4-CN) was obtained by fractionated distillation (bp. 85-86°C/1.7 Torr), yield 61%, $[\alpha]_D^{20}$ = +27.1 (c = 1.00 / methylene chloride), ^{1}H-NMR ($CDCl_3$): δ = 1.53 (dd, J_{HF} = 23 Hz, J_{HH} = 8 Hz, CH_3), 5.68 (dq, J_{HF} = 48 Hz, J_{HH} = 8 Hz, CHF), 7.45 and 7.70 (AA'XX', 4 aromat. H). Pure **1** (R = 4-NO_2) was obtained by chromatography on silica gel (petroleum ether / ethyl acetate 9 : 1. yield 38%. $[\alpha]_D^{22}$ = +18.3 (c = 1.00 / methylene chloride), ^{1}H-NMR ($CDCl_3$): δ = 1.67 (dd, J_{HF} = 23 Hz, J_{HH} = 8 Hz, CH_3), 5.73 (dq, J_{HF} = 48 Hz, J_{HH} = 8 Hz, CHF), 7.50 and 8.24 (AA'XX', 4 aromat. H).
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(*Received in Germany* 7 *December* 1993; *accepted* 15 *January* 1994)