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Preliminary Note

Introduction of nitrogen functionalities into (*R*)-1-fluoro-3-(*p*-tolylsulfinyl)propan-2-one

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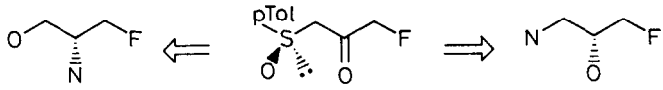
Abstract

Nitrogen functionalities have been introduced on C-2 and C-3 of (*R*)-1-fluoro-3-(*p*-tolylsulfinyl)propan-2-one (**1**) through high yield elaborations of the carbonyl and sulfinyl groups, respectively.

A description has already been given of the use of (+)-(*R*)-1-fluoro-3-(*p*-tolylsulfinyl)propan-2-one (**1**) as a chiral synthon for the preparation of enantiomerically pure fluoro-organic compounds carrying one to four oxygen functionalities [1].

We report here how a nitrogen group can be introduced on carbons 2 and 3 of this chiral 1-fluoropropane unit so that access to the functional systems **2** and **3** becomes available. These elaborations are of particular interest as few methods have been described which afford nitrogen-substituted fluoro-organic compounds in an optically active form (chemical approaches [2], enzymatic approaches [3]).



3 (+)-(R)-1 2

Systems of type **2** may be prepared by reducing the carbonyl group of the fluoropropanone, (*R*)-**1**, diastereoselectively with diisobutylaluminum hydride to the corresponding fluoro alcohol, which was then benzylated to give the fluoro sulfinyl ether, (2*S*, R_S)-**4**, as already described [4]. Overall replacement of the sulfoxide group of **4** with nitrogen functionalities (compounds **5–8**) has been performed by removing the sulfinyl residue through a Pummerer rearrangement, hydrolyzing the so-formed intermediate, and finally elaborating the β-benzyloxy-γ-fluoro-aldehyde obtained.

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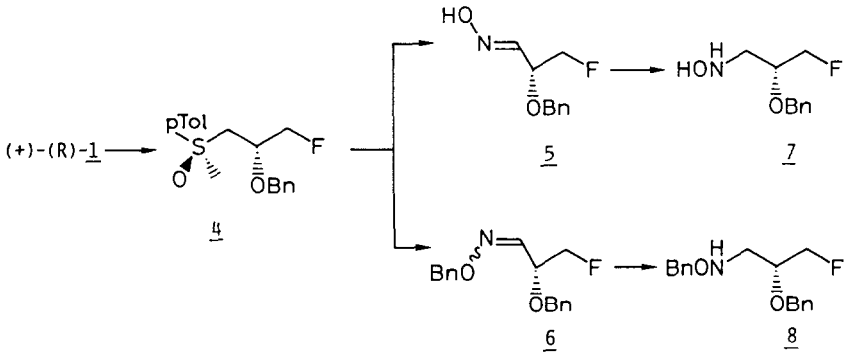


Scheme 1.

Specifically, an acetonitrile solution of trifluoroacetic anhydride (6.0 mmol) was added at 0 °C to a stirred solution of the substrate (2*S*, R_S)-**4** (3.0 mmol) and 2,4,6-trimethylpyridine (6.9 mmol) in the same solvent [5]. After 30 min at room temperature, the starting material had disappeared and a compound having a higher R_f value on TLC (silica gel 60, F_{254}) was formed. This was the 1-trifluoroacetyloxy-1-tolylthio-2-benzyloxy-3-fluoropropane, which was hydrolyzed *in situ* by adding a solution of mercury(II) chloride (2.1 mmol) in water. After 2 h, the precipitate formed was removed by filtration and the residue extracted with ethyl acetate (Scheme 1). The oil remaining after evaporation of the solvent contained the crude 2-benzyloxy-3-fluoropropanal, which was not isolated but was directly dissolved in absolute ethanol. Sodium carbonate (6.0 mmol), hydroxylamine hydrochloride (6.0 mmol) and molecular sieves (4 Å) were added to this solution and the resulting mixture left overnight at room temperature. Filtration, evaporation and flash-chromatographic purification afforded the (*E*,*R*)-2-benzyloxy-3-fluoropropanal oxime (**5**) in 78% yield. Analysis*: $[\alpha]_D^{20}$, −81° (c = 1.1, $CHCl_3$). ^{1}H NMR δ: 4.24 (m, 1H, H-2, J = 4.8, 7.2, 9.7 and 18 Hz); 4.53 and 4.67 (AB system, CH_2O); 4.56 and 4.75 (ddd each, 1H each, H_2-3) ppm. ^{19}F NMR δ: −230.5 (dt, J = 46 and 17 Hz) ppm.

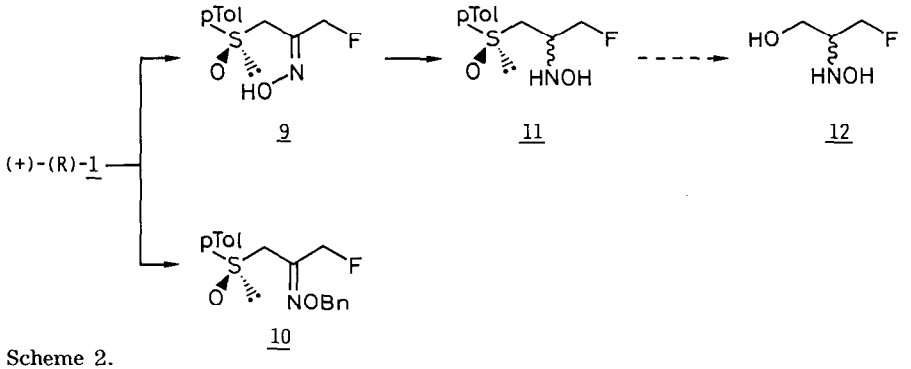
Similarly, by using the procedure described above and by employing O-benzylhydroxylamine instead of hydroxylamine, the O-benzyloximes **6** having *E* and *Z* configurations were isolated in pure form as single isomers (82% yield, *E*:*Z* ratio 4:1). Structural assignment of the stereoisomeric aldoximes was based on their ^{1}H NMR spectra, the formyl proton *syn* to the lone pair of electrons on the nitrogen resonating at higher fields than the corresponding *anti* proton. Analyses: (*E*,*R*)-**6**: $[\alpha]_D^{20}$ −56.0° (c = 1.1, $CHCl_3$). ^{1}H NMR δ: 4.22 (m, 1H, H-2, J = 4.2, 5.5, 7.2 and 18.5 Hz); 4.47 and 4.62 (AB system, 2H, CH_2O); 4.54 and 4.56 (ddd each, 1H each, H_2-3); 5.11 (s, 2H, CH_2ON)

*^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker CPX-300 or a Bruker AC 250L spectrometer. $CDCl_3$ was used as a solvent. $SiMe_4$ was used as an internal standard (δ_H and δ_C, 0.00 ppm) for ^{1}H and ^{13}C nuclei while C_6F_6 was used as the internal standard (δ_F, −162.90 ppm) for ^{19}F nucleus. Values of $[\alpha]_D^{20}$ were obtained on a Iasco DIP-181 polarimeter. Melting points are reported uncorrected and were obtained on a capillary apparatus.

ppm. ^{19}F NMR δ: −230.9 (dt, J=46.5 and 18.0 Hz) ppm. (*Z*,*R*)-**6**: ^{1}H NMR δ: 4.55 (ddd, 1H, H-3, J=2.5, 10 and 47 Hz); 4.54 and 4.62 (AB system, 2H, 2H, CH_2O); 4.89 (ddt, 1H, H-2, J=2.5, 5.5 and 21.2 Hz); 5.11 (s, 2H, CH_2ON); 6.79 (dd, 1H, H-1, J=6 and 2 Hz) ppm. ^{19}F NMR δ: −229.0 (dt, J=47.0 and 21.6 Hz) ppm.

Aldoximes are highly versatile intermediates and can be used in alkylation, oxidation, reduction and cycloaddition reactions. As a typical example of these elaborations, the high-yield reduction of (*Z*,*R*)-**5** and (*Z*,*R*)-**6** is reported here. The oximes (1.0 mmol) were treated with sodium cyanoborohydride (2.0 mmol) at room temperature in methanol solution and the reaction mixtures were maintained at a pH value of 3–4 (methyl orange indicator) by adding a 12 N aqueous hydrochloric acid solution dropwise [6]. Enantiomerically pure (*R*)-*N*-(2-benzyloxy-3-fluoro)-1-propyl hydroxylamine (**7**) and (R)-O-benzyl-*N*-(2-benzyloxy-3-fluoro)-1-propyl hydroxylamine (**8**) were isolated in 76% and 84% yield, respectively, after flash chromatography. Analyses: (*R*)-**7**: $[\alpha]_D^{20}$, +44° (c=1.2, $CHCl_3$). ^{1}H NMR δ: 3.00 and 3.08 (dd each, 2H, H_2-1); 4.02 (m, 1H, H-2); 4.52 (m, 2H, H_2-3); 4.61 and 4.77 (AB system, 2H, CH_2O) ppm. ^{19}F NMR δ: −229.2 (dt, J=46 and 21 Hz). (*R*)-**8**: $[\alpha]_D^{20}$, +46.5° (c=1.0, $CHCl_3$). ^{1}H NMR δ: 2.96 (dd, 1H, H-1, J=13 and 7.5 Hz); 3.08 (dd, 1H, H-1, J=13 and 4.5 Hz); 3.95 (m, 1H, H-2); 4.40 (ddd, 1H, H-3, J=5.5, 10.0 and 47.5 Hz); 4.59 (ddd, 1H, H-3); 4.67 (s, 2H, CH_2ON); 4.61 and 4.71 (AB system, 2H, CH_2O) ppm. ^{19}F NMR δ: −228.8 (dt, J=20 and 48 Hz).

For the preparation of systems of type **3**, a tetrahydrofuran solution of the fluorosulfinyl ketone (*R*)-**1** (4.0 mmol) was treated with sodium carbonate (3.0 mmol) and either hydroxylamine hydrochloride or O-benzyl hydroxylamine hydrochloride (5.0 mmol) were added. Hydroxylamine gave the oxime **9** having the *Z* configuration (88% yield) exclusively while O-benzyl hydroxylamine afforded a mixture of the *Z* and E isomers **10** (91% yield) (Scheme 2). The configurations of the oximes were derived from the fact that in the ^{13}C NMR spectra the carbon atom *cis* to the oximino-O atom is known [7] to be more shielded than the corresponding *trans* carbon atom. Analyses: (*Z*,*R*)-**9**: $[\alpha]_D^{20}$, +283° (c=1.5, $CHCl_3$). ^{1}H NMR δ:2.41 (s, 3H, CH_3); 3.78



Scheme 2.

and 3.85 (dd each, 1H each, H_2-1); 5.22 (dq, 2H, H_2-3, $J=47$ and 15 Hz); 7.32 and 7.54 (4H, CH ar.) ppm. ^{19}F NMR δ: -236.5 (t) ppm. ^{13}C NMR δ: 57.09 (C-1); 78.08 (C-3, $J=168$ Hz); 148.9 (C-2, $J=22$ Hz); 21.5; 124.3; 130.1; 139.4; 142.2 ppm. (*Z,R*)-**10**: $[\alpha]_D^{20}$, $-30.5°$ ($c=1.1$, $CHCl_3$). ^1H NMR δ: 2.39 (s, 3H, CH_3); 3.81 and 3.99 (dd each, 1H each, H_2-1); 4.58 and 4.82 (dd, each, 1H each, H_2-3, $J=44.0$ and 10.4 Hz); 5.07 and 5.09 (AB system, 2H, CH_2O) ppm. ^{19}F NMR δ: -224.0 (t) ppm. ^{13}C NMR δ: 53.4 (C-1); 82.5 (C-3), $J=168.6$ Hz); 147.3 (C-2, $J=19.5$ Hz); 21.39; 76.85; 129.87; 128.39; 128.23; 128.17; 123.96; 136.49; 140.41; 142.08 ppm. (*E,R*)-**10**: ^1H NMR δ: 2.40 (s, 3H, CH_3); 3.80 (m, 2H, H_2-1); 5.11 (dd, 2H, H_2-3); 5.07 (s, 2H, CH_2O) ppm. ^{19}F NMR δ: -234.6 (t) ppm. ^{13}C NMR δ: 57.19 (C-1); 81.02 (C-3), $J=202$ Hz); 21.45; 76.72 ppm.

Several reagents commonly employed for the reduction of oximes (e.g. lithium aluminium hydride) failed to saturate the carbon–nitrogen double bond of the (*Z,R*)-oxime **9** selectively, since they deoxygenated the auxiliary sulfinyl residue preferentially. However, when sodium cyanoborohydride was employed under the reaction conditions described above, the fluorosulfinyl hydroxylamine **11** was formed in 84% yield as a 7:3 mixture of the two isomers at the carbon stereocentre. Analyses: major diastereoisomer: ^{13}C NMR δ: 55.3 (C-1); 81.6 (C-3, $J=170$ Hz); 21.4; 124.0; 130.1; 141.7; 139.9 ppm. ^{19}F NMR δ: -230.3 (dd, $J=46$ and 18 Hz) ppm. Minor diastereoisomer: ^{13}C NMR δ: 55.4 (C-1); 81.4 (C-3, $J=170$ Hz); 21.4; 124.3; 130.1; 142.0; 140 ppm. ^{19}F NMR δ: -230.7 (dd, $J=46$ and 19 Hz) ppm.

The removal of the auxiliary sulfinyl group through a Pummerer rearrangement followed by a reduction allows the final 2-hydroxylamino-3-fluoro-1-propanol (**12**) to be obtained.

The introduction of nitrogen on other α-fluoro-α'-sulfinyl ketones [1] using the above procedures is under present study.

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