Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 17, pp. 2933–2937, 1997
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Printed in Great Britain
PII: S0957-4166(97)00320-0 0957-4166/97 $17.00 + 0.00

Intramolecular S_N2 reaction at α-carbon of trifluoromethyl group: preparation of optically active 2-trifluoromethylaziridine

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Abstract: We have succeeded in *intramolecular* nucleophilic substitution of the hydroxyl group in (*S*)-1-(alkylamino)-3,3,3-trifluoro-2-propanol. The reaction provides an optically pure (*R*)-1-benzyl-2-trifluoromethylaziridine in good yield from optically pure (*S*)-3-(benzylamino)-1,1,1-trifluoro-2-propanol, which was prepared from (*S*)-3,3,3-trifluoropropene oxide (75% ee). © 1997 Published by Elsevier Science Ltd

Fluorinated compounds have received great interest as the candidates for new pharmaceuticals and agrochemicals.[1] Until now, a large number of chiral fluorinated building blocks have been developed and proposed for further synthesis of fluorinated bioactive molecules.[2] Among them, 3,3,3-trifluoropropene oxide has been paid much attention by many chemists[3] and biochemists.[4] The ring opening reactions of this epoxide always gave 3-substituted-1,1,1-trifluoro-2-propanols.[3] Thus, a substitution reaction of the hydroxyl group in this 2-propanol is essential for further utilization of these derivatives.

However, it is notorious in the field of fluorine chemistry that replacement of hydroxyl group with nucleophiles in 1-substituted-3,3,3-trifluoro-2-propanols is difficult; only a few halogenations have been reported.[5] More recently, intermolecular carboxylations, sulfenylations, and aminations of such 2-propanols via sulfonates have been developed; however yield of this amination reaction was moderate.[6]

Prevention of the nucleophilic substitution of the hydroxyl group has been attributed mainly to the strong electron withdrawing effect of the trifluoromethyl group as well as electrostatic repulsion between the trifluoromethyl group and negatively charged nucleophiles.[7] We considered that the latter repulsion effect would be depressed in an intramolecular substitution. We designed the synthesis of trifluoromethylaziridine as a model reaction (Scheme 1).

The starting material, *N*-benzyl aminoalcohol **2**, was prepared by ring opening reaction of (*S*)-3,3,3-trifluoropropene oxide[8] **1** with benzylamine. The reaction gave optically active (75% ee) aminoalcohol **2** in 85% yield. Since aminoalcohol **2** is a crystalline compound, the enantiomeric purity of the product **2** was readily increased by recrystallization. The enantiomeric excess of aminoalcohol **2** was 95% ee in the first recrystallization and comes to >99.5% ee after the second recrystallization from diethyl ether–hexane. Aminoalcohol **2** was converted to aziridine **3** by the ring closure reaction with dichlorotriphenylphosphorane in good yield.[9] We found that the aziridine was the sole product having fluorine in this reaction; also the yield of the aziridine was virtually quantitative (96%) by ^{19}F-NMR. Aziridine **3** was isolated as a colorless liquid in 85% yield. The compound was found to be optically pure (>99.5% ee) (Scheme 1).

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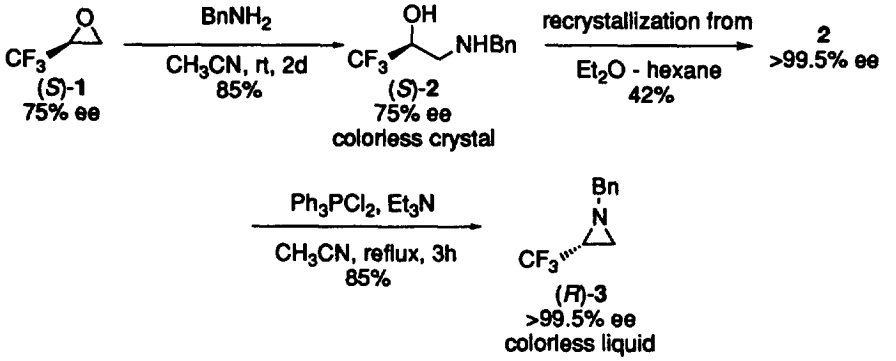
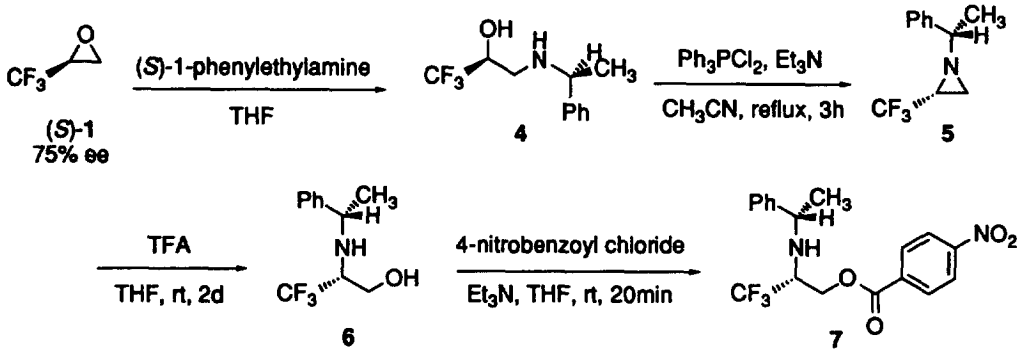


Scheme 1. Preparation of optically pure (*R*)-1-benzyl-2-trifluoromethylaziridine.

To confirm the absolute configuration of trifluoromethylaziridine **3**, diastereomerically pure 1-phenylethylaziridine **5** was prepared from (*S*)-1-phenylethylamine using a similar procedure. Hydrolysis of aziridine **5** with trifluoroacetic acid (TFA) followed by esterification with 4-nitrobenzoyl chloride produced benzoyl ester **7** (Scheme 2).



Scheme 2. Preparation of benzoyl ester **7** for X-ray analysis.

Recrystallization of benzoyl ester **7** from chloroform gave colorless plates, which were submitted to X-ray crystal structure analysis (Figure 1). The absolute configuration at α-carbon of the trifluoromethyl group in the benzoyl ester **7** was found to be (*R*). Therefore, the inversion of the stereochemistry in the nucleophilic substitution of the hydroxyl group was confirmed.

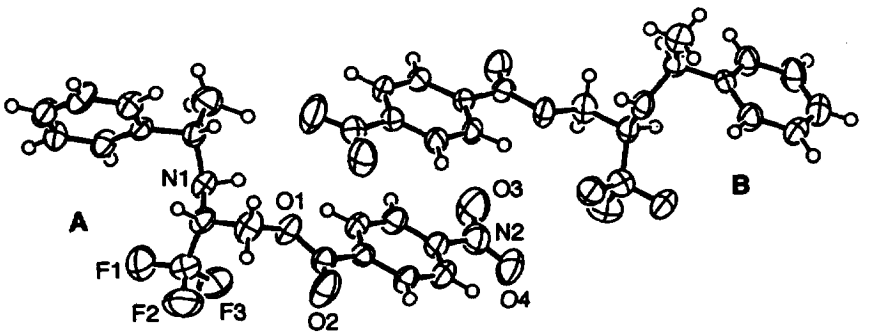


Figure 1. ORTEP drawing of two independent molecules **A** and **B** of the benzoyl ester **7**.

In conclusion, we found that the intramolecular process functioned well for the nucleophilic substitution of the α-trifluoromethyl alcohol. The synthetic applications of the optically pure (*R*)-2-trifluoromethylaziridines are now in progress.

Experimental

Melting points (mp) are uncorrected. Infrared spectra (IR) were measured on a Hitachi Model 270-30 Infrared Spectrometer. ^{1}H- (200 MHz), ^{19}F- (188 MHz), and ^{13}C- (50.3 MHz) nuclear magnetic resonance (NMR) spectra were recorded by Varian VXR apparatus in $CDCl_3$ and the chemical shifts are reported in parts per million (δ ppm) relative to tetramethyl silane (Me_4Si, δ 0.00 ppm for ^{1}H- and ^{13}C-NMR) and hexafluorobenzene(C_6F_6, δ 0.00 ppm for ^{19}F-NMR) as internal standards. For the quantitative analysis by ^{19}F-NMR, 1,3-bis(trifluoromethyl)benzene was used as a standard. Coupling constants (*J*) are reported in Hz. Optical rotations were measured in a cell with 50 mm length and 1 mL capacity using a Horiba High Sensitive Polarimeter SEPA-300. Mass spectra were recorded on a GC/MS instrument under electron impact ionization. Elemental analyses were performed on a Perkin Elmer series II CHNS/O Analyzer 2400. All commercial reagents and solvents were employed without further purification. E. Merck silica gel (kieselgel 60, 230–400 mesh) was employed for the chromatography. Analytical thin layer chromatography (TLC) was performed with 0.2 mm coated commercial plates (E. Merck, kiselgel 60 F254). Enantiomeric excess of the aminoalcohol and aziridine were determined by HPLC analysis on a chiral column (Chiralcel OJ). Intensity measurements were carried out on a Rigaku AFC5R diffractometer at the X-ray Laboratory of Okayama University.

(S)-1-(Benzylamino)-3,3,3-trifluoro-2-propanol **2**

To an ice cooled solution of benzylamine (48 mmol) in 12 mL of acetonitrile, (*S*)-3,3,3-trifluoropropene oxide **1** (49 mmol, 75% ee) was added dropwise. The reaction mixture was stirred at room temperature for 2 days. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel. The amino alcohol **2** (75% ee) was obtained in 85% yield. Enantiomerically pure aminoalcohol (>99.5% ee) was obtained by twice recrystallizing from ether–hexane. mp 103°C. $[\alpha]_D^{28} = -9.24$ (*c* 0.50, $CHCl_3$). IR (KBr) ν 3316, 3092, 1434, 1376, 1280, 1268, 1144, 1084, 1068, 1030, 922, 844, 754, 706, 692 cm^{-1}. Anal. Calcd for $C_{10}H_{12}F_3N_1O_1$: C, 54.79; H, 5.52; N, 6.39. Found C, 55.17; H, 6.07; N, 6.23. ^{1}H-NMR δ 2.88 (1 H, dd, *J*=12.6, 5.0 Hz), 2.98 (1H, dd, *J*=13.0, 6.0), 3.82 (2H, s), 3.95 (1H, m), 7.31 (5H, m). ^{13}C-NMR δ 46.9, 53.6, 66.9, 67.5, 68.1, 68.7, 116.5, 122.1, 127.5, 127.7, 128.1, 128.6, 133.3, 138.7. ^{19}F-NMR δ 83.2 (d, *J*=7.1) EI MS m/z (relative intensity) 219 (M+, 4), 120 (50), 91 (100).

(R)-1-Benzyl-2-trifluoromethylaziridine **3**

To a solution of dichlorotriphenylphosphorane (14 mmol) in 10 mL of acetonitrile, aminoalcohol **2** was added. Then triethylamine (52 mmol) was dropped into the above mixture with ice cooling. The reaction mixture was stirred for 3 h at reflux. Aziridine **3** was isolated as a colorless liquid in 85% yield by distillation (110°C/20 mm Hg) of filtrate from the precipitated triethylamine hydrochloride and triphenylphosphine oxide. The compound was found to be optically pure (>99.5% ee). $[\alpha]_D^{24} = +20.1$ (*c* 0.139, $CHCl_3$). IR (neat) ν 1498, 1432, 1364, 1280, 1156, 1070, 1028, 848, 736, 698, 658 cm^{-1}. ^{1}H-NMR δ 1.68 (1 H, d, *J*=5.9), 2.17 (2H, m), 3.56 (2H, s), 7.34 (5H, m). ^{19}F-NMR δ 90.7 (d, *J*=5.3). EI MS m/z (relative intensity) 201 (M+, 7), 91 (100), 65 (13).

(S)-1-((S)-1-Phenylethylamino)-3,3,3-trifluoro-2-propanol **4**

4 was prepared from (*S*)-1-phenylethylamine in accordance with a procedure similar to that for **2** in 67% yield, where hexane was used as recrystallization solvent. Diastereomeric excess of **4** was determined by ^{19}F-NMR analysis. mp 91°C. $[\alpha]_D^{28} = -38.8$ (*c* 1.10, $CHCl_3$). IR (KBr) ν 3112, 2876, 1270, 1176, 1156, 1122, 834, 764, 702, 692 cm^{-1}. Anal. Calcd for $C_{11}H_{14}F_3N_1O_1$: C, 56.65; H, 6.06; N, 6.01. Found C, 56.75; H, 6.32; N, 5.97. ^{1}H-NMR δ 1.40 (d, 3H, *J*=6.6 Hz), 2.67–2.85 (m, 2H),

3.75 (q, 1H, *J*=6.6), 3.87–4.03 (m, 1H), 7.23–7.36 (m, 5H). ^{19}F-NMR δ 83.4 (d, *J*=6.8). EI MS m/z (relative intensity) 233 (M+, 1), 218 (32), 134 (30), 105 (100).

(R)-1-((S)-1-Phenylethylamino)-2-trifluoromethylaziridine **5**

5 was prepared from aminoalcohol **4** in accordance with a procedure similar to that for **3** in 24% yield. $[\alpha]_D^{28} = -70.6$ (*c* 1.37, $CHCl_3$). IR ($CHCl_3$) ν 2980, 1496, 1452, 1430, 1356, 1286, 1236, 1150, 1088, 948, 758, 702, 656 cm^{-1}. ^{1}H-NMR δ 1.46 (d, 3H, *J*=6.6 Hz), 1.68 (d, 1H, *J*=5.9), 1.99–2.07 (m, 1H), 2.25 (d, 1H, *J*=3.1), 2.56 (q, 1H, *J*=6.4), 7.30–7.36 (m, 5H). ^{19}F-NMR δ 91.0 (d, *J*=6.0). EI MS m/z (relative intensity) 215 (M+, 5), 200 (12), 105 (100), 77 (19).

(R)-2-((S)-1-Phenylethylamino)-3,3,3-trifluoro-1-propanol **6**

To a solution of **5** (0.519 g, 2.41 mmol) in THF (5 ml) was added trifluoroacetic acid (0.549 g, 4.82 mmol) at 0°C. After being stirred for 2 days at room temperature, the mixture was poured into sat. aq. $NaHCO_3$, and the products were extracted with ether. The ether extracts were dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography gave the colorless solid in 99% yield. mp 91°C. $[\alpha]_D^{28} = -14.8$ (*c* 1.04, $CHCl_3$). IR (KBr) ν 3360, 1646, 1440, 1362, 1280, 1258, 1202, 1140, 1066, 1016, 704 cm^{-1}. ^{1}H-NMR δ 1.68 (d, 3H, *J*=6.8 Hz), 3.35–3.48 (m, 1H), 3.96–4.01 (m, 2H), 4.55 (q, 1H, *J*=6.3), 7.34–7.49 (m, 5H). ^{19}F-NMR δ 88.5 (d, *J*=8.5). EI MS m/z (relative intensity) 218 (M+, 4), 105 (100), 77 (49).

(R)-2-((S)-1-Phenylethylamino)-3,3,3-trifluoropropyl 4-nitrobenzoate **7**

To a solution of **6** (0.441 g, 1.89 mmol) and 4-nitrobenzoyl chloride (0.351 g, 1.89 mmol) in THF (5 ml) was added triethylamine (0.190 g, 1.88 mmol) at 0°C. After being stirred for 20 min at room temperature, the mixture was poured into H_2O, and the products were extracted with AcOEt. The AcOEt extracts were dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography to give benzoyl ester **7** in 21% yield. mp 114°C. $[\alpha]_D^{28} = -63.7$ (*c* 1.07, $CHCl_3$). IR (KBr) ν 2972, 1732, 1612, 1532, 1494, 1456, 1390, 1346, 1322, 1286, 1240, 1214, 1140, 1066, 1040, 1010, 956, 912, 872, 848, 786, 762, 724, 714, 546 cm^{-1}. Anal. Calcd for $C_{18}H_{17}F_3N_2O_4$: C, 56.55; H, 4.48; N, 7.33. Found C, 56.76; H, 4.67; N, 7.51. ^{1}H-NMR δ 1.36 (d, 1H, *J*=6.5), 3.34–3.36 (m, 1H), 4.08 (q, 1H, *J*=6.4), 4.49 (dd, 1H, *J*=12.2, 3.6), 4.68 (dd, 1H, *J*=12.1, 5.1), 7.30–7.37 (m, 5H), 8.21 (d, 2H, *J*=8.9), 8.33 (d, 2H, *J*=9.1). ^{19}F-NMR δ 88.0 (d, *J*=7.1). EI MS m/z (relative intensity) 150 (M+,23), 105 (100), 77 (25).

Absolute configuration of the chiral center was based on the known absolute configuration of the α-carbon atom in (*S*)-1-phenylethylamino moiety of benzoyl ester **7**.

Crystal data for benzoyl ester **7**; $C_{18}H_{17}N_2O_4F_3$, *Mr*=764.68, triclinic, *P*1, *a*=7.970(3), *b*=19.759(6), *c*=5.683(3) Å, α=96.63(3), β=91.13(4), γ=93.03(2)°, V=887(1)Å^3, *Z*=2, *Dx*=1.431 g/cm^3, μ=0.12 mm^{-1} for Mo Kα radiation (λ=0.71073 Å). The structure was solved by a direct method, and refined by a full-matrix least-squares method. Final R was 0.052 and Rw was 0.032 for 3235 reflections with $I_0 > 1.5\sigma(I_0)$.

Acknowledgements

We thank SC-NMR Laboratory of Okayama University for ^{19}F-NMR analyses. The financial support by Okayama Foundation for Science and Technology is also gratefully acknowledged.

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(Received in Japan 7 July 1997)