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Intramolecular S_N2 reaction α- to a trifluoromethyl group: preparation of 1-cyano-2-trifluoromethylcyclopropane

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Abstract

The first intramolecular S_N2 reaction of α-trifluoromethylated secondary alcohols by a carbanion is described. A stereoselective intramolecular cyclization of 3-substituted-3-cyano-1-trifluoromethylpropyl sulfonate via the cyano stabilized carbanion provides 1-substituted-1-cyano-2-trifluoromethylcyclopropanes in good yields. The product has the opposite configuration to the starting alcohol at the carbon attached to trifluoromethyl group, revealing the reaction takes place in S_N2 manner with Walden inversion at the reaction center.

1. Introduction

A low availability of optically active fluorinated compounds is a long-standing problem in the synthesis of organofluorine compounds.[1] One exception is optically active α-trifluoromethyl alcohols which are a reliable class of fluorinated chiral building blocks due to a wide variety of methods for their preparation.[2] On this basis, the development of stereospecific nucleophilic substitutions of the hydroxyl group of α-trifluoromethylated alcohols with carbanions is needed to extend the utilization of these alcohols.

Displacement of the hydroxyl group of α-trifluoromethylated alcohols by a carbanion is very difficult,[3] although there have been some reports on S_N1-like substitution involving π-conjugation[4] or neighboring group participation of heteroatoms.[5,6] To date, only a single such example of nucleophilic substitution of 2,2,2-trifluoroethanol has been reported.[7] A reaction of hindered α-trifluoromethylated secondary alcohols with organometallic reagents has resulted in recovery of starting alcohols[3] or the unexpected production of tertiary alcohols,[8] and no S_N2 reaction has been reported.

The prevention of nucleophilic substitution by the vicinal fluorine atoms has been attributed to their strong electron-withdrawing effect as well as to electrostatic repulsion between the lone pairs on the fluorine atoms and the negatively charged nucleophile.[9] The former effect results in shortened C–O bond

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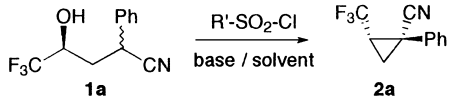
of fluorinated alcohols,[10] and the latter effect hinders an access of the nucleophile toward the carbon in the S_N2 reaction. We considered that the latter effect would be depressed somehow in an intramolecular substitution.[11] We designed an intramolecular cyclization, a cyclopropane synthesis as a model reaction because an electrostatic repulsion between the CF_3 group and the nucleophile would be reduced in such a process. In this report, we describe the first intramolecular S_N2 reaction of α-trifluoromethylated secondary alcohols by a carbanion.

2. Results and discussion

Preparation of the starting materials, 4-substituted-4-cyano-1,1,1-trifluoro-2-butanols **1** by ring opening reaction of 3,3,3-trifluoropropene oxide (TFPO)[12] with substituted acetonitrile carbanions has been described in our previous report.[13] Mixtures of the two diastereomers of secondary alcohols **1** (about 30% de) were subjected to the subsequent cyclization without separation.

Starting compound 4-hydroxy-2-phenyl-5,5,5-trifluoropentanenitrile **1a** was allowed to react with *p*-TsCl in the presence of NaH, affording trifluoromethylated cyclopropane **2a** as a sole product. Optimization results on changing the leaving group, solvent, base, and temperature are summarized in Table 1.

Table 1
Effect of leaving groups, solvents, bases, and temperature



1a **2a**

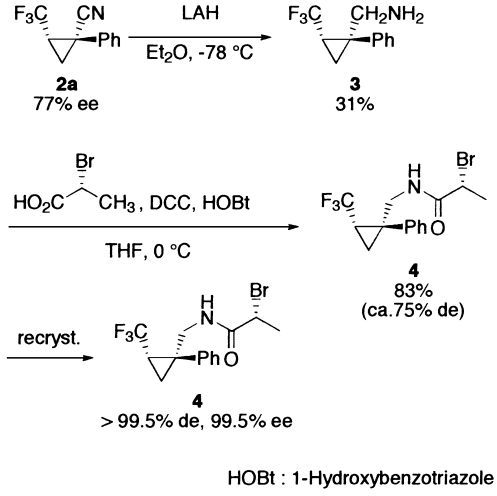
entry	R'-	base	solvent	temp. [°C]	yield [%][a]	de [%][b]
1	*p*-Tol-	NaH	THF	0	75	90
2	Mes-	NaH	THF	0	61	89
3	*p*-MeO-C_6H_4-	NaH	THF	0	61	78
4	CH_3-	NaH	THF	0	61[c]	24[d]
5	CF_3-	NaH	THF	0	78	69
6	*p*-Tol-	*n*-BuLi	THF	0	trace	-
7	*p*-Tol-	MeONa	THF	0	15	84
8	*p*-Tol-	NaH	Et_2O	0	58	82
9	*p*-Tol-	NaH	DME	0	71	82
10	*p*-Tol-	NaH	THF	reflux	43	90
11	*p*-Tol-	NaH	THF	r.t.	68	87
12	*p*-Tol-	NaH	THF	-20	83	92

a) Isolated yield of a mixture of diastereomers, b) Diastereomeric ratio is determined by GC analysis, c) This yield was determind by ^{19}F NMR, d) Opposite diastereomer was obtained as the major diastereomer

The reactions with tosyl chloride, 2-mesitylenesulfonyl chloride, and trifluoromethanesulfonyl chloride as activating agents for the OH group resulted in production of the *cis*-diastereomer **2a** with moderate to good diastereoselectivities (69–92% des). Meanwhile, the reaction of methanesulfonyl

chloride produced the *trans*-diastereomer, the opposite diastereomer of the **2a**, as the major product with low diastereoselectivity (24% de).

These results clearly revealed that the combination of *p*-TsCl with NaH in THF resulted in high yield (83%) as well as high diastereomeric purity (92% de) in this cyclization.[14] To confirm the configuration of the major product, the trifluoromethylated cyclopropane **2a** was converted to amide **4** having the chiral acid moiety with a known absolute configuration via the reactions illustrated in Scheme 1.



Scheme 1.

Repeating recrystallization of the amide **4** from hexane gave colorless needles whose X-ray analysis revealed the absolute configuration of the amide **4**. Fig. 1 represents the ORTEP drawing of amide **4**.

The geometry of the phenyl group and the trifluoromethyl group was found to be *trans*,[15] and the trifluoromethylated stereogenic carbon had the *S* configuration. These results clearly reveal that the stereochemistry of the carbon attached to a trifluoromethyl group has been inverted during the intramolecular nucleophilic substitution consistent with an S_N2 mechanism.

The range of substituents investigated is summarized in Table 2. Carbanion moieties possessing a π-conjugation system (entries 1–3, 5) could give the desired cyclopropanes in moderate to good yields. Meanwhile, the carbanion moiety lacking such a π-system (entry 4) gave no desired cyclopropane.[16]

In conclusion, it has been found that an intramolecular process functions well for the nucleophilic substitution of the α-trifluoromethyl secondary alcohols. The synthetic applications of (1-substituted-2-trifluoromethyl)cyclopropyl cyanides **2** are now in progress.

3. Experimental

IR spectra were measured on a Hitachi model 270–30 infrared spectrometer. The ^{1}H (200 MHz), ^{19}F (188 MHz), and ^{13}C (50.3 MHz) NMR spectra were recorded by Varian VXR apparatus and the chemical shifts are reported in δ (ppm) values relative to TMS (δ 0.00 ppm for ^{1}H and ^{13}C NMR) and C_6F_6 (δ 0.00 ppm for ^{19}F NMR). For the quantitative analysis by ^{19}F NMR, 1,3-bis(trifluoromethyl)benzene was used as an internal standard. Coupling constants (*J*) are reported in hertz. The NOESY was recorded by a VXR-500 instrument. Optical rotation was measured in a cell with 50 mm length and 1 mL capacity using a Horiba high sensitive polarimeter SEPA-300. Elemental analyses were performed on Perkin–Elmer series II CHNS/O analyzer 2400. The EI-MS was performed on a Hewlett–Packard

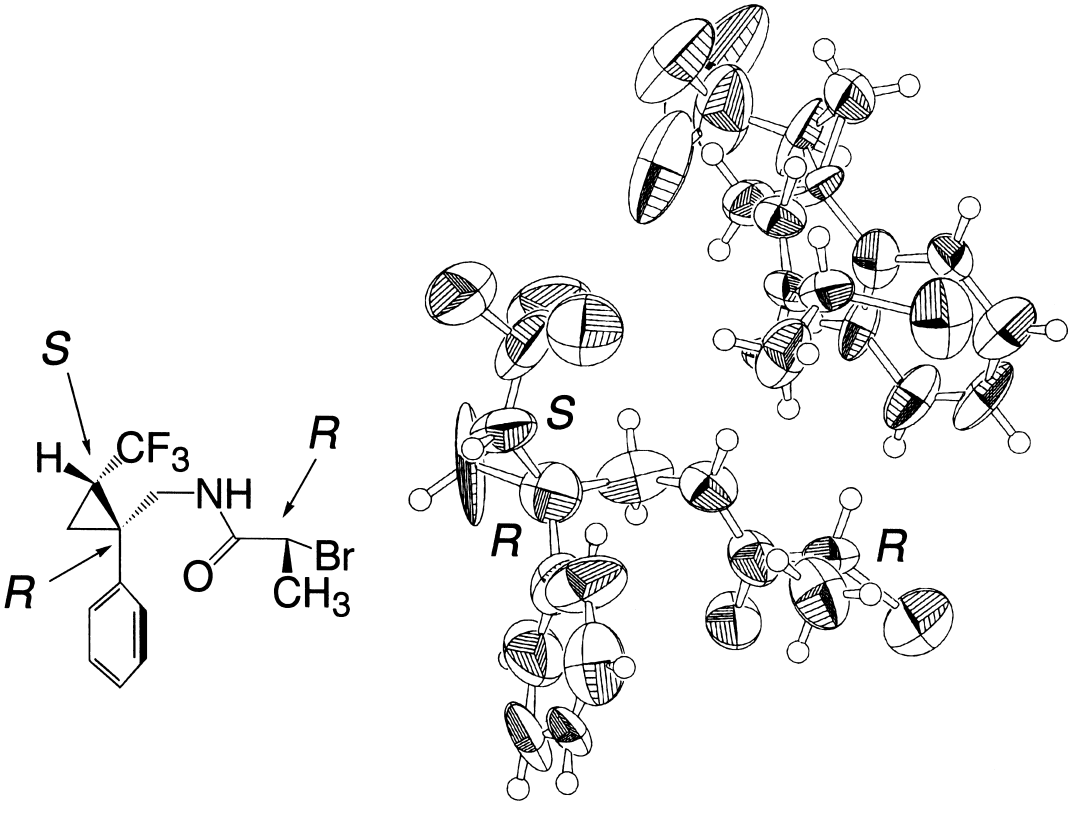
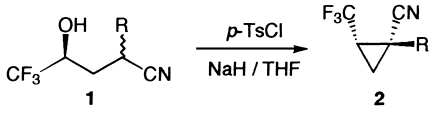


Figure 1. ORTEP depiction of *N*-[(1*R*,2*S*)-(2-trifluoromethyl-1-phenyl)cyclopropyl]methyl-(*R*)-2-bromo-propionamide **4**

Table 2
Effect of substituents



entry	R-	Product (yield [%][a])	de [%][b]
1	Ph-	**2a** (75)	90
2	*p*-MeO-C_6H_4-	**2b** (64)	89
3	*p*-Cl-C_6H_4-	**2c** (85)	89
4	H-	trace[c]	-
5	Ph_2C=N-	**2d** (52)	32

a) Isolated yield of a mixture of diastereomers, b) Diastereomeric ratios were determined by GC analysis, c) 70% recovery of tosyl ester.

HP5971A. All commercially available reagents were employed without further purification. THF and Et_2O were freshly distilled from Na and benzophenone, and CH_3CN was distilled from CaH_2 and stored under nitrogen over molecular sieves. E. Merck silica gel (Kieselgel 60, 230–400 mesh) was employed for chromatography. Enantiomeric excesses of 1-cyano-1-aryl-2-trifluoromethyl-cyclopropanes were determined by GC analysis equipped with a chiral column (CP-Cyclodex-β-256M) on Shimadzu GC-12A. Intensity measurements were carried out on a Rigaku RAXIS-IV imaging plate area detector.

3.1. (2-Trifluoromethyl-1-phenyl)cyclopropyl cyanide **2a**

A THF solution (2 mL) of **1a** (0.5 mmol, 0.115 g: starting from (*S*)-3,3,3-trifluoropropene oxide (75% ee)) was added to a solution of TsCl (0.6 mmol, 0.114 g) and NaH (50–60% in liquid paraffin, 2.0 mmol, 0.076 g) in THF (3 mL). The mixture was stirred for 24 h at 0°C, and then treated with a saturated solution of NH_4Cl (2 mL, 3×). The organic layer was separated, and the aqueous layer was extracted with Et_2O (5 mL, 3×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification on silica gel chromatography gave 0.079 g (75% yield (mixture of major and minor diastereomers, 90% de), major diastereomer: 76.8% ee) of **2a** as a yellowish oil. IR (neat, mixture of major and minor diastereomers): 2260 cm^{-1}; ^1H NMR ($CDCl_3$, major diastereomer): δ 1.86 (ddq, *J*=6.2, 9.2, 1.4, 1H), 2.08 (dd, *J*=6.4, 6.9, 1H), 2.28 (ddq, *J*=6.9, 9.2, 6.2, 1H), 7.3–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$, major diastereomer): δ 14.3, 18.1, 29.7 (q, *J*=38), 117.7, 123.7 (q, *J*=271), 126.7, 129.0, 129.3, 133.5; ^{19}F NMR ($CDCl_3$): δ 97.4 (d, *J*=6.4, major diastereomer), 99.3 (d, *J*=6.4, minor diastereomer); EI-MS (rel. int.) major diastereomer: 211 (27, M^+), 142 (100), 115 (100). Anal. calcd mixture of major and minor diastereomers for $C_{11}H_8F_3N$: C, 62.56; H, 3.82; N, 6.63. Found: C, 62.54; H, 4.12; N, 6.38.

3.2. [2-Trifluoromethyl-1-(4-methoxyphenyl)]cyclopropyl cyanide **2b**

Yellowish oil, 64% yield (mixture of major and minor diastereomers, 89% de). IR (neat, mixture of major and minor diastereomers): 2244 cm^{-1}; ^1H NMR ($CDCl_3$, major diastereomer): δ 1.78 (ddq, *J*=6.2, 9.1, 1.3, 1H), 2.00 (dd, *J*=6.2, 6.9, 1H), 2.21 (ddq, *J*=6.8, 9.1, 6.6, 1H), 3.79 (s, 3H), 6.89 (d, *J*=8.9, 2H), 7.26 (d, *J*=8.9, 2H); ^{13}C NMR ($CDCl_3$, major diastereomer): δ 15.0, 18.3, 29.9 (q, *J*=38), 55.8, 115.2, 121.7, 128.6 (q, *J*=247), 128.9, 131.2, 160.5; ^{19}F NMR ($CDCl_3$): δ 97.6 (d, *J*=6.8, major diastereomer), 99.6 (*J*=7.6, minor diastereomer); EI-MS (rel. int.) major diastereomer: 241 (10, M^+), 172 (30), 102 (43), 69 (100), 29 (92). Anal. calcd mixture of major and minor diastereomers for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.88; H, 4.40; N, 6.00.

3.3. [1-(4-Chlorophenyl)-2-trifluoromethyl]cyclopropyl cyanide **2c**

Yellowish oil, 82% yield (mixture of major and minor diastereomers, 89% de). IR (neat, mixture of major and minor diastereomers): 2251 cm^{-1}; ^1H NMR ($CDCl_3$, major diastereomer): δ 1.73 (ddq, *J*=6.3, 9.1, 1.3, 1H), 1.99 (dd, *J*=6.3, 7.1, 1H), 2.14 (ddq, *J*=7.0, 9.1, 1.4, 1H), 7.1–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$, major diastereomer): δ 15.0, 18.7, 30.4 (q, *J*=40), 117.8, 124.0 (q, *J*=271), 128.7, 129.9, 130.1, 135.7; ^{19}F NMR ($CDCl_3$): δ 97.5 (d, *J*=6.0, major diastereomer), 99.5 (d, *J*=6.2, minor diastereomer); EI-MS (rel. int.) major diastereomer: 247 (4, M^+), 245 (17, M^+), 210 (100), 190 (56), 176 (22), 149 (20), 140 (67), 114 (33). Anal. calcd mixture of major and minor diastereomers for $C_{11}H_7ClF_3N$: C, 53.79; H, 2.87; N, 5.70. Found: C, 54.07; H, 3.17; N, 5.68.

3.4. [2-Trifluoromethyl-1-(1,1-diphenylmethylideneamino)]cyclopropyl cyanide **2d**

Yellowish oil, 52%, (mixture of major and minor diastereomers, 32% de). IR (neat, mixture of major and minor diastereomers): 2240 cm^{-1}; ^1H NMR ($CDCl_3$; major diastereomer): δ 1.82 (m, 2H), 2.35 (m, 1H), 7.2–7.7 (m, 10H); ^{19}F NMR ($CDCl_3$): δ 101.4 (d, *J*=6.8, major diastereomer), 98.2 (d, *J*=6.0, minor diastereomer); EI-MS (rel. int.) major diastereomer: 314 (3, M^+), 218 (50), 165 (100). Anal. calcd

mixture of major and minor diastereomers for $C_{18}H_{13}F_3N_2$: C, 68.79; H, 4.17; N, 8.91. Found: C, 68.66; H, 4.51; N, 9.09.

3.5. *[(1*R*,2*R*)-(2-Trifluoromethyl-1-phenyl)cyclopropyl]methylamine **3***

To an Et_2O solution (100 mL) of $LiAlH_4$ (23.08 mmol, 1.84 g) was added **2a** (75% ee, 23.1 mmol, 4.87 g) at −78°C under a nitrogen atmosphere. After the mixture was stirred for 3 h, 10% HCl aq. (15 mL) was added and the mixture was extracted with Et_2O (100 mL). The extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford 1.52 g (7.1 mmol, 31%) of **3** (diastereomerically pure) as a yellowish oil. IR (neat): 3400 cm^{-1}; $[\alpha]_D^{20}$ +27.9 (*c* 2.03, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.24–1.40 (m, 2H), 1.67 (br, 2H), 1.75–1.95 (m, 1H), 3.01 (s, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 25.1 (q, *J*=36), 34.2, 45.8, 126.4 (q, *J*=271), 127.0, 128.3, 128.9, 141.2; ^{19}F NMR ($CDCl_3$): δ 102.7 (d, *J*=8.5); EI-MS (rel. int.) 215 (33, M^+), 118 (57), 30 (100). Anal. calcd for $C_{11}H_{12}F_3N$: C, 61.39; H, 5.62; N, 6.51. Found: C, 61.21; H, 5.75; N, 6.48.

3.6. N-*[(1*R*,2*S*)-(2-Trifluoromethyl-1-phenyl)cyclopropyl]methyl-(*R*)-2-bromo-propionamide **4***

A THF solution (20 mL) of DCC (4.7 mmol, 0.96 g) was added to a solution of **3** (2.3 mmol, 0.50 g) and (*R*)-(+)-2-bromopropionic acid (2.8 mmol, 0.25 mL) and HOBt (3.5 mmol, 0.47 g) in THF (20 mL). The mixture was stirred for 1 h at 0°C, and then warmed to room temperature, filtered and washed with Et_2O. The organic layer was separated, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography gave 0.68 g (83%) of **4** as a colorless powder. The compound **4** thus obtained was recrystallized from hexane (3 mL, 5×), and diastereomeric purity was increased to >99.5% de, >99.5% ee (7% yield). Mp: 72°C; IR (KBr): 3280, 1670 cm^{-1}; $[\alpha]_D^{20}$ +24.1 (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.38–1.52 (m, 2H), 1.77 (d, *J*=7.2, 3H), 1.82–2.02 (m, 1H), 3.47 (dd, *J*=14.3, 4.8, 1H), 3.92 (dd, *J*=6.9, 14.2, 1H), 4.30 (q, *J*=7.0, 1H), 6.46 (br, 1H), 7.2–7.4 (m, 5H); ^{19}F NMR ($CDCl_3$): δ 102.3 (d, *J*=8.1); EI-MS (rel. int.) 350 (2, M^+), 270 (95), 198 (100), 174 (100), 119 (95). Anal. calcd for $C_{14}H_{15}BrF_3NO$: C, 48.02; H, 4.32; N, 4.00. Found: C, 48.03; H, 4.53; N, 4.20.

3.7. *Absolute configuration of the stereogenic centers were determined on the basis of the (*R*)-(+)-2-bromopropionic acid moiety of amide **4***

Crystal data for amide **4**: $C_{28}H_{30}Br_2F_6N_2O_2$ for a pair of molecules having the same chemical structure $C_{14}H_{15}BrF_3NO$ with different conformations. M_r=700.36 (for a pair of two molecules 350.18×2); orthorhombic; $P2_12_12_1$; *a*=9.524(0), *b*=33.19(7), *c*=9.561(7) Å, *V*=3023.(1) $Å^3$, *Z*=4, *D*x=1.539 g/cm^3; μ=27.54 cm^{-1} for Mo K_α radiation (λ=0.7107 Å). The structure was solved by a direct method (SIR 92), and refined by a full-matrix least-squares method. Final *R* was 0.066 and R_w was 0.061 for 1256 reflection with $I_0 > 3.00\sigma(I_0)$.

Acknowledgements

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14. Semiempirical molecular orbital calculation (PM3) of the two diastereomeric products showed that the difference in energy between two diastereomers is only 0.1 kcal/mol. Thus, the present cyclization would be a kinetic stereocontrolled process.
15. This X-ray crystallographic analysis result agrees well with the NOESY result. The NOESY correlation between the *ortho* proton of a phenyl group and two protons on the three-membered ring of trifluoromethylated cyclopropane **2a** suggested that the CF_3 and phenyl groups would have a *trans* relationship.
16. Major product (>70%) of this reaction was 4-cyano-1,1,1-trifluoro-2-butyl tosylate, tosyl ester of the starting compound, together with small amounts (<5%) of compounds of undefined structure.