# Regio- and Stereoselectivity of Cycloadditions of *C*-(Trifluoromethyl)nitrone with Olefins



Kiyoshi Tanaka*, Yasuhiko Sugimoto, Yoshiaki Okafuji,
Masahiro Tachikawa and Keiryo Mitsuhashi

Department of Industrial Chemistry, College of Technology, Seikei University,
Musashino-shi, Tokyo 180, Japan

Received September 27, 1988

*N*-Methyl-*C*-(trifluoromethyl)nitrone (**1**) cycloadds with various olefins to give 2-methyl-3-trifluoromethylisoxazolidines. Predominant formation of 5-substituted isoxazolidines in the cycloadditions with monosubstituted olefins is observed and this high regioselectivity is attributed to the dipole-LUMO controlled interaction, being rationalized on the basis of molecular orbital calculation of **1**. 'Anti'-favorable approach of **1** to olefin in the transition state is considered from the configuration of the cycloadducts, pointing out the very weak secondary orbital interaction between trifluoromethyl group and olefin-substituents including phenyl or ester group.

*J. Heterocyclic Chem.*, **26**, 381 (1989).

Nitrones are a class of thoroughly investigated 1,3-dipolar compounds [1-8] and have been proved to be exceedingly useful for the synthesis of alkaloidal natural products [9,10]. In connection with the synthetic utility of nitrone cycloadditions, their regio- and stereoselectivity in the reactions with olefins is a renewed problem [11-14]. On the other hand, it has been reported recently that the introduction of a trifluoromethyl group into biologically active compounds often gives rise to an increase of their activities [15-19]. We have been demonstrating that use of 1,3-dipolar compounds bearing a trifluoromethyl group provides a successful pathway for the introduction into heterocyclic systems [20]. As a part of these studies, we now wish to report regio- and stereoselectivity of cycloadditions of *N*-methyl-*C*-(trifluoromethyl)nitrone (**1**) with various olefins.

Nitrone **1** was generated by dehydration of *N*-methyl-*C*-(trifluoromethyl)nitrone hydrate (**1'**) [21]. Intramolecular nuclear Overhauser enhancement in the $^1$H nmr analysis provides the evidence that nitrone **1** has a configuration of the *C*-trifluoromethyl and *N*-methyl groups in a *trans* relationship.

Cycloadditions of **1** with *cis*-olefins such as *N*-methyl- and *N*-phenylmaleimides, and dimethyl maleate proceeded with high stereoselectivity, giving 4,5-*trans* substituted cycloadducts **2** and **3**, respectively, accompanied by a small amount (5% ratio) of the 4,5-*cis* one in the case of *N*-phenylmaleimide (Scheme I, Table I, entry 1-3) [22]. The 4,5-*trans*-configuration of **2** and **3** was proved by the smaller coupling constants between the 4- and 5-protons in the $^1$H nmr. With dimethyl fumarate as a *trans*-olefin, the high stereoselectivity was relaxed to yield almost equal amounts of 3,4-*trans*- and -*cis*-substituted isoxazolidines **3b** and **3b'**.

The cycloaddition with styrene gave exclusively 5-phenylisoxazolidines consisting of two stereoisomers in the

Scheme I

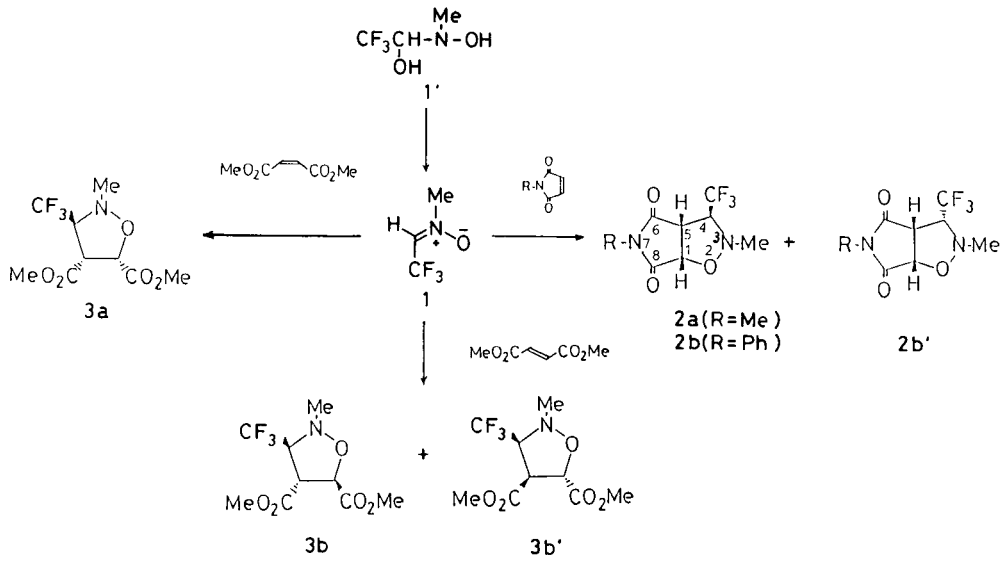

Table I

Synthesis of Trifluoromethylisoxazolidines

| Entry | Product | Total yield, % [a] | Ratio [b] |
|---|---|---|---|
| 1 | **2a** | 27 | |
| 2 | **2b** + **2b'** | 60 | **2b/2b'** = 95/5 |
| 3 | **3a** | 80 | |
| 4 | **3b** + **3b'** | 50 | **3b/3b'** = 48/52 |
| 5 | **4a** + **4a'** | 71 | **4a/4a'** = 83/17 |
| 6 | **4b** + **4b'** | 58 | **4b/4b'** = 70/30 |
| 7 | **4c** + **4c'** | 65 | **4c/4c'** = 68/32 |
| 8 | **4d** + **4d'** | 70 | **4d/4d'** = 86/14 |
| 9 | **4e** + **4e'** | 55 | **4e/4e'** = 69/31 |

[a] Yield after purification by chromatography or distillation. [b] Ratio of stereoisomers was determined by $^1$H nmr (270 MHz) and/or glc analyses.

ratio of 83/17. Thus obtained stereoisomers were subjected to hydrogenolysis, giving two stereoisomers of trifluoromethyl-1,3-aminoalcohols **5a** and **5a'**, from which the oxazinones **6a** and **6a'** were derived, respectively, on treatment with diethyl carbonate (Scheme II). Analysis of the $^{13}$C nmr chemical shift differences, in particular of the C-1 and C-3 signals of aminoalcohols indicates **5a** and **5a'** with *anti*- and *syn*-configuration, respectively (Table II) [23,24]. The smaller coupling constants between the vicinal protons(-NCH-$CH_2$-) of the oxazinone **6a**, compared with those of **6a'**, also supports the *anti*-configuration of **6a** [25,26]. On the basis of these nmr analyses, the stereochemistry of the major 5-phenylisoxazolidine was assigned to be the *trans*-configuration. Similar regiospecific and '*anti*'-favorable cycloadditions were also recognized in the cases with 1-octene, allyl alcohol, methyl acrylate, and acrylonitrile (Table I, entry 6-9). The stereochemistry of the isoxazolidines from 1-octene and allyl alcohol was also determined by the $^{13}$C nmr chemical shift differences of the derived 1,3-aminoalcohols **5** and **5'**: the major stereoisomers with *anti*-configuration were obtained in both cases. Cycloadditions with methyl acrylate and acrylonitrile also proceeded '*anti*' -favorably to give **4d** and **4e**, respectively, as major products, the configuration of which was determined by the conversions of **4c(4c')** on treatment with lithium alminum hydride and of **4e(4e')** into **4d(4d')** by alcoholysis with methanol, respectively.

Scheme II

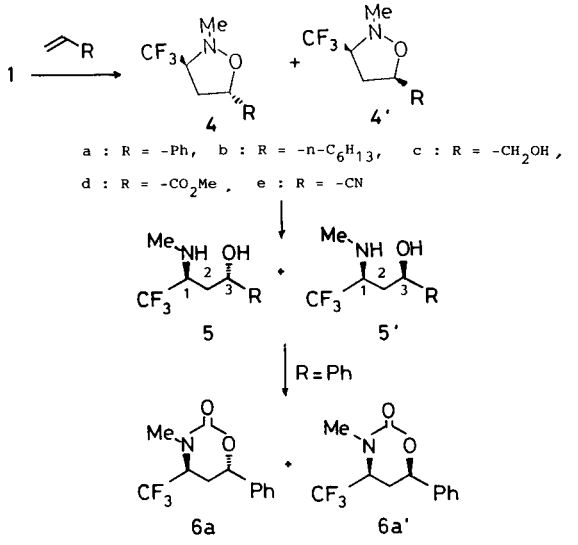


Table II

Selected Chemical Shifts of 1,3-Aminoalcohols in $^{13}$C NMR Spectra [a]

| | C-1 | C-2 | C-3 |
|---|---|---|---|
| **5a** | 57.6 (q, J = 27.4 Hz) | 35.5 | 70.9 |
| **5a'** | 61.3 (q, J = 27.4 Hz) | 36.6 | 74.0 |
| **5b** | 57.7 (q, J = 26.4 Hz) | 37.4 | 68.4 |
| **5b'** | 61.7 (q, J = 26.4 Hz) | 38.0 | 71.9 |
| **5c** | 57.4 (q, J = 27.4 Hz) | 34.1 | 68.9 |
| **5c'** | 60.6 (q, J = 27.4 Hz) | 33.9 | 71.6 |

[a] Measured in deuteriochloroform.

The cycloaddition of **1** with electron deficient olefins to give only 5-substituted isoxazolidines is in sharp contrast to that of *N*-methyl-*C*-phenylnitrone which affords substantial amount of 4-substituted isoxazolidines [11,12,27]. The high regioselectivity of **1** can be rationaliz-

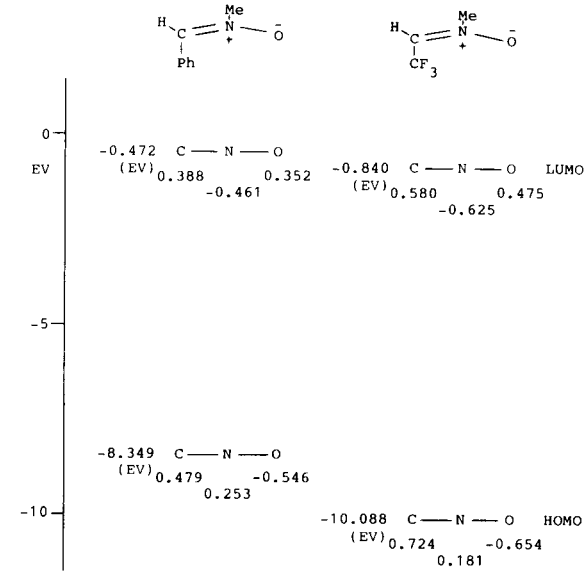


Figure 1. MNDO-calculations of Nitrones

ed by the **1**-LUMO controlled process, giving rise to 5-substituted isoxazolidines. That is attributed to the effect of the trifluoromethyl group lowering the HOMO energy level enough, accompanying with the slight drop in the LUMO level compared with a phenyl group. Such an assumption is fully supported by molecular orbital calculation using MNDO method, as shown in Figure 1.

'*Syn*'-favorable cycloadditions of *C*-phenylnitrone with methyl acrylate and styrene were previously reported [11,28] and this is interpreted by the contribution of secondary orbital interactions between the phenyl group of the nitrone and ester or phenyl group of the dipolarophile, respectively, in an *endo* transition state. The predominant formation of the *trans*-trifluoromethylisoxazolidines in the case of **1** would point out that such secondary orbital interactions between the trifluoromethyl group and the substituents, including a phenyl or an ester group, of the dipolarophiles is very weak and that the steric repulsion between these groups is in preference to the secondary orbital interactions in the transition state.

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-100 or a JEOL JIR-3510 spectrometer. Samples were run as potassium bromide pellets for solid and film for oil. The $^1H$ and $^{13}C$ nmr spectra were measured with JEOL JNM-GX 270 and/or -PMX 60 spectrometers using tetramethylsilane as an internal standard, the chemical shifts being given in $\delta$ ppm downfield. Samples were prepared by dissolving in deuteriochloroform. *N*-Methyl-*C*-(trifluoromethyl)nitrone hydrate (**1'**) was prepared by the method reported in our previous paper [21].

General Procedures for Cycloadditon of *N*-Methyl-*C*-(trifluoromethyl)nitrone (**1**) with Olefin.

Nitrone hydrate **1'** (10 mmoles) was converted into nitrone **1** by boiling with 50 ml of benzene in a flask fitted with an azeotropic distillation apparatus to remove water. To the mixture was added olefin (12 mmoles for *N*-methyl maleimide, *N*-phenyl maleimide, dimethyl maleate, or dimethyl fumarate; 30 mmoles for other olefins) and the mixture was stirred under the conditions such as: entry 1, 2, and 3, room temperature for 24 hours; entry 4, room temperature for 72 hours, entry 5 and 6, 80° for 12 hours; entry 7, 80° for 7 hours; entry 8, 50° for 3 hours; entry 9, 50° for 48 hours. After removal of the solvent, the products were isolated by column chromatography (silica gel) or distillation and purified further by recrystallization for solid or by preparative glc for oil.

$H_4$,$H_5$-*trans*-3,7-Dimethyl-6,8-dioxo-4-trifluoromethyl-2,3,7-oxadiazabicyclo[3.3.0]octane (**2a**).

This compound had mp 115-117° (hexane-ethyl acetate); $^1H$ nmr: $\delta$ 2.81 (s, 3H), 3.06 (s, 3H), 3.82 (dd, J = 2.1 and 6.8 Hz, 1H), 3.83 (dq, J = 2.1 and 7.1 Hz, 1H), 4.85 (d, J = 6.8 Hz, 1H); ir: ($cm^{-1}$) 1700 (C=O), 1170, 1150, 1130 ($CF_3$).

*Anal.* Calcd. for $C_8H_9N_2F_3O_3$: C, 40.35; H, 3.81; N, 11.76. Found: C, 40.44; H, 3.72; N, 11.64.

$H_4$,$H_5$-*trans*-3-Methyl-6,8-dioxo-7-phenyl-4-trifluoromethyl-2,3,7-oxadiazabicyclo[3.3.0]octane (**2b**).

This compound had mp 137-139° (hexane-chloroform); $^1H$ nmr: $\delta$ 2.92 (s, 3H), 3.97 (dq, J = 2.1 and 7.6 Hz, 1H), 3.98 (dd, J = 2.1 and 7.4 Hz, 1H), 4.95 (d, J = 7.4 Hz, 1H), 7.2-7.6 (m, 5H); ir: ($cm^{-1}$) 1720 (C=O), 1195, 1170 ($CF_3$).

*Anal.* Calcd. for $C_{13}H_{11}N_2F_3O_3$: C, 52.01; H, 3.69; N, 9.33. Found: C, 52.00; H, 3.69; N, 9.23.

$H_4$,$H_5$-*cis*-3-Methyl-6,8-dioxo-7-phenyl-4-trifluoromethyl-2,3,7-oxadiazabicyclo[3.3.0]octane (**2b'**).

This compound had mp 135-137° (hexane-chloroform); $^1H$ nmr: $\delta$ 2.89 (s, 3H), 3.45 (dq, J = 8.6 and 6.2 Hz, 1H), 3.90 (dd, J = 8.6 and 7.8 Hz, 1H), 5.01 (d, J = 7.8 Hz, 1H), 7.2-7.6 (m, 5H); ir: ($cm^{-1}$) 1720 (C=O), 1180, 1160, 1130 ($CF_3$).

*Anal.* Calcd. for $C_{13}H_{11}N_2F_3O_3$: C, 52.01; H, 3.69; N, 9.33. Found: C, 51.97; H, 3.45; N, 9.29.

$H_3$,$H_4$-*trans*-$H_4$,$H_5$-*cis*-Dimethyl 2-Methyl-3-trifluoromethylisoxazolidine-4,5-dicarboxylate (**3a**).

This compound had bp 97-100°/4 mm Hg; $^1H$ nmr: $\delta$ 3.00 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 3.79 (dd, J = 1.7 and 7.1 Hz, 1H), 3.85 (dq, J = 1.7 and 6.6 Hz, 1H), 4.75 (d, J = 7.1 Hz, 1H); ir: ($cm^{-1}$) 1740 (C=O), 1170 ($CF_3$).

*Anal.* Calcd. for $C_9H_{12}NF_3O_5$: C, 39.86; H, 4.46; N, 5.16. Found: C, 39.74; H, 4.24; N, 5.13.

$H_3$,$H_4$-*trans*-$H_4$,$H_5$-*trans*-Dimethyl 2-Methyl-3-trifluoromethylisoxazolidine-4,5-dicarboxylate (**3b**).

This compound was obtained as a colorless oil; $^1H$ nmr: $\delta$ 2.90 (s, 3H), 3.77 (dq, J = 4.9 and 6.9 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.04 (dd, J = 4.9 and 3.9 Hz, 1H), 4.95 (d, J = 3.9 Hz, 1H); ir: ($cm^{-1}$) 1740 (C=O), 1180, 1140 ($CF_3$).

*Anal.* Calcd. for $C_9H_{12}NF_3O_5$: C, 39.86; H, 4.46; N, 5.16. Found: C, 39.59; H, 4.23; N, 5.12.

$H_3$,$H_4$-*cis*-$H_4$,$H_5$-*trans*-Dimethyl 2-Methyl-3-trifluoromethylisoxazolidine-4,5-dicarboxylate (**3b'**).

This compound had mp 55-57° (hexane); $^1H$ nmr: $\delta$ 2.86 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.89 (dq, J = 8.8 and 8.8 Hz, 1H), 4.13 (t, J = 8.8 Hz, 1H), 5.01 (d, J = 8.8 Hz, 1H); ir: ($cm^{-1}$) 1720 (C=O), 1180, 1130 ($CF_3$).

*Anal.* Calcd. for $C_9H_{12}NF_3O_5$: C, 39.86; H, 4.46; N, 5.16. Found: C, 39.64; H, 4.20; N, 5.16.

*trans*-2-Methyl-5-phenyl-3-trifluoromethylisoxazolidine (**4a**).

This compound was obtained as a colorless oil; $^1H$ nmr: $\delta$ 2.36 (dt, J = 13.0 and 10.0 Hz, 1H), 2.73 (ddd, J = 13.0, 6.0, and 4.0 Hz, 1H), 2.93 (s, 3H), 3.30 (ddq, J = 10.0, 4.0, and 6.6 Hz, 1H), 5.03 (dd, J = 10.0 and 6.0 Hz, 1H), 7.3 (s, 5H); ir: ($cm^{-1}$) 1160, 1140, 1120 ($CF_3$).

*cis*-2-Methyl-5-phenyl-3-trifluoromethylisoxazolidine (**4a'**).

This compound was obtained as a colorless oil; $^1H$ nmr: $\delta$ 2.0-2.8 (m, 2H), 2.80 (s, 3H), 3.0-3.6 (m, 1H), 5.1 (dd, J = 9.0 and 7.0 Hz, 1H), 7.1-7.5 (m, 5H); ir: ($cm^{-1}$) 1160, 1130, 1120 ($CF_3$).

*Anal.* Calcd. for $C_{11}H_{12}NF_3O$: C, 57.14; H, 5.23; N, 6.06. Found: (as a mixture of **4a** and **4a'**): C, 56.94; H, 5.22; N, 6.04.

*trans*-5-Hexyl-2-methyl-3-trifluoromethylisoxazolidine (**4b**).

This compound was obtained as a colorless oil; $^1H$ nmr: $\delta$ 0.9 (t, 3H), 1.0-1.7 (m, 10H), 1.9-2.6 (m, 2H), 2.80 (s, 3H), 2.9-3.4 (m, 1H), 3.7-4.2 (m, 1H); ir: ($cm^{-1}$) 1160, 1120 ($CF_3$).

*cis*-5-Hexyl-2-methyl-3-trifluoromethylisoxazolidine (**4b'**).

This compound was obtained as a colorless oil; $^1$H nmr: $\delta$ 0.9 (t, 3H), 1.1-1.7 (m, 10H), 1.8-2.7 (m, 2H), 2.78 (s, 3H), 3.0-3.6 (m, 1H), 4.0-4.5 (m, 1H); ir: ($cm^{-1}$) 1150, 1120, 1100 ($CF_3$).

*Anal.* Calcd. for $C_{11}H_{20}NF_3O$: C, 55.22; H, 8.42; N, 5.85. Found: (as a mixture of **4b** and **4b'**): C, 55.15; H, 8.41; N, 5.82.

*trans*-5-Hydroxymethyl-2-methyl-3-trifluoromethylisoxazolidine (**4c**).

This compound was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.2-2.5 (m, 2H), 2.83 (s, 3H), 3.25 (m, 1H), 3.62 (dd, J = 4.8 and 12.0 Hz, 1H), 3.83 (dd, J = 2.9 and 12.0 Hz, 1H), 4.2 (m, 1H); ir: ($cm^{-1}$) 3320 (OH), 1170, 1130 ($CF_3$).

*cis*-5-Hydroxymethyl-2-methyl-3-trifluoromethylisoxazolidine (**4c'**).

This compound was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.4-2.7 (m, 2H), 2.79 (s, 3H), 3.36 (m, 1H), 3.69 (dd, J = 5.3 and 12.6 Hz, 1H), 3.75 (dd, J = 3.7 and 12.6 Hz, 1H), 4.4 (m, 1H); ir: ($cm^{-1}$) 3370 (OH), 1170, 1140, 1130 ($CF_3$).

*Anal.* Calcd. for $C_6H_{10}NF_3O_2$: C, 38.92; H, 5.44; N, 7.57. Found: (as a mixture of **4c** and **4c'**): C, 38.98; H, 5.48; N, 7.54.

*trans*- and *cis*-Methyl 2-Methyl-3-trifluoromethylisoxazolidine-5-carboxylates (**4d** and **4d'**).

A mixture was collected at the boiling range of 63-65°/5 mm Hg.

Compound **4d** was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.65-2.85 (m, 2H), 2.88 (s, 3H), 3.48 (ddq, J = 6.5, 11.0, and 9.0 Hz, 1H), 3.80 (s, 3H), 4.60 (t, J = 7.7 Hz, 1H); ir: ($cm^{-1}$) 1761 (C=O), 1180, 1150 ($CF_3$).

Compound **4d'** was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.65-2.85 (m, 2H), 2.86 (s, 3H), 3.28 (ddq, J = 5.5, 9.0, and 7.0 Hz, 1H), 3.80 (s, 3H), 4.70 (dd, J = 4.9 and 8.8 Hz, 1H); ir: ($cm^{-1}$) 1780, 1757 (C=O), 1176, 1148 ($CF_3$).

*Anal.* Calcd. for $C_7H_{10}NF_3O_3$: C, 39.44; H, 4.73; N, 6.57. Found (as a mixture of **4d** and **4d'**): C, 39.57; H, 4.65; N, 6.40.

*trans*- and *cis*-5-Cyano-2-methyl-3-trifluoromethylisoxazolidines (**4e** and **4e'**).

A mixture was collected at the boiling range of 38-42°/3 mm Hg.

Compound **4e** was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.87 (ddd, J = 13.6, 4.9, and 5.3 (or 8.6) Hz, 1H), 2.94 (ddd, J = 13.6, 8.5, and 8.6 (or 5.3) Hz, 1H), 3.01 (s, 3H), 3.70 (ddq, J = 4.9, 8.5, and 7.3 Hz, 1H), 4.80 (dd, J = 5.3 and 8.6 Hz, 1H).

Compound **4e'** was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.72 (ddd, J = 13.4, 10.1, and 9.1 Hz, 1H), 2.85-3.0 (m, 1H), 2.89 (s, 3H), 3.26 (ddq, J = 10.1, 5.4, and 6.6 Hz, 1H), 4.87 (dd, J = 9.1 and 2.9 Hz, 1H).

*Anal.* Calcd. for $C_6H_7N_2F_3O$: C, 40.01; H, 3.92; N, 15.55. Found: (as a mixture of **4e** and **4e'**): C, 39.80; H, 3.60; N, 15.61.

Conversion of **4d** (**4d'**) into **4c** (**4c'**).

A solution of **4d** and **4d'** (2.00 g, 9.4 mmoles, **4d**/**4d'** = 77/23) in 20 ml of diethyl ether was added dropwise below 3° to a suspension of lithium aluminum hydride (0.73 g, 19.2 mmoles) in 30 ml of diethyl ether. The mixture was stirred at 0° for 2.5 hours and further at room temperature for 14 hours. Aqueous sodium hydroxide solution (20%) was added to the mixture and ether layer was separated. The resulting residue was further extracted twice with 30 ml of diethyl ether. The combined extracts were washed with brine and dried over magnesium sulfate. Usual workup afforded 1.58 g (61%) of a mixture of **4c** and **4c'** in the ratio of 81/19. Each isomer was separated by flash chromatography over silica gel (200-300 mesh) and each spectral data were consistent with those obtained above.

Conversion of **4e** (**4e'**) into **4d** (**4d'**).

A mixture of 100 mg of **4e** and **4e'** (**4e**/**4e'** = 69/31) and a catalytic amount of *p*-toluenesufonic acid in 10 ml of methanol was refluxed for 16 hours. The $^1$H nmr analysis of the reaction mixture showed the presence of **4e**, **4e'**, **4d**, and **4d'** in the ratio of 42/16/28/14 without any by-products.

Reductive Cleavage of Trifluoromethylisoxazolidines.

A mixture of **4a** and **4a'** (1.20 g, **4a**/**4a'** = 79/21) and a spatula of Raney Nickel in 60 ml of methanol was stirred at room temperature for 7 days in an atmosphere of hydrogen (1 kg/cm$^2$). Glc analysis of the reaction mixture then showed the entire disappearance of the starting material. After filtration of the catalyst, the filtrate was evaporated under reduced pressure to give an oily substance which was chromatographed over silica gel, giving 1.09 g (79%) of a mixture consisting of *anti*- and *syn*-4,4,4-trifluoro-3-methylamino-1-phenyl-1-butanols **5a** and **5a'** in the ratio of 81/19. Aminoalcohol **5a** was further purified by flash chromatography over silica gel (200-300 mesh), and, however, **5a'** was always contaminated by a small amount of **5a**.

Compound **5a** was obtained as a colorless oil; $^1$H nmr: $\delta$ 2.0 (m, 2H), 2.50 (q, J = 1.5 Hz, 3H), 3.05 (m, 1H), 5.08 (t, J = 4.9 Hz, 1H), 7.4 (s, 5H); ir: ($cm^{-1}$) 3400 (OH, NH), 1175, 1122 ($CF_3$).

Compound **5a'** had $^1$H nmr: $\delta$ 1.7-2.0 (m, 2H), 2.61 (q, J = 1.5 Hz, 1H), 3.3 (m, 1H), 4.90 (dd, J = 9.8 and 2.8 Hz, 1H), 7.3 (m, 5H).

*Anal.* Calcd. for $C_{11}H_{14}NF_3O$: C, 56.65; H, 6.05; N, 6.01. Found: (as a mixture of **5a** and **5a'**): C, 56.57; H, 5.95; N, 5.98.

Similarly a mixture of **4b** and **4b'** (**4b**/**4b'** = 70/30) was subjected to hydrogenolysis in an atmosphere of hydrogen (1 kg/cm$^2$) at room temperature for 2 days to give a mixture of *anti*- and *syn*-1,1,1-trifluoro-2-methylamino-4-decanols **5b** and **5b'** (73%, **5b**/**5b'** = 67/33). Each aminoalcohol was separated by flash chromatography.

Compound **5b** was obtained as a colorless oil; $^1$H nmr: $\delta$ 0.9 (t, 3H), 1.3-1.6 (m, 13H), 1.7 (m, 2H), 2.55 (q, J = 1.4 Hz, 3H), 3.30 (tq, J = 7.4 and 7.4 Hz, 1H), 3.8 (m, 1H); ir: ($cm^{-1}$) 3500 (OH, NH), 1165, 1116 ($CF_3$).

Compound **5b'** was obtained as a colorless oil; $^1$H nmr: $\delta$ 0.9 (t, 3H), 1.3-1.6 (m, 13H), 1.7-1.8 (m, 2H), 2.57 (q, J = 1.4 Hz, 3H), 3.17 (ddq, J = 11.5, 2.8, and 7.4 Hz, 1H), 3.8 (m, 1H); ir: ($cm^{-1}$) 3400 (OH, NH), 1167, 1116 ($CF_3$).

*Anal.* Calcd. for $C_{11}H_{22}NF_3O$: C, 54.75; H, 9.19; N, 5.80. Found: (as a mixture of **5b** and **5b'**): C, 54.45; H, 8.79; N, 5.79.

*anti*- and *syn*-1,1,1-Trifluoro-2-methylamino-4,5-pentanediols **5c** and **5c'** were also obtained by hydrogenolysis (4 kg/cm$^2$, room temperature, 7 days) of a mixture of **4c** and **4c'** (**4c**/**4c'** = 80/20). The $^1$H nmr analysis of the reaction mixture showed the presence of **4c**, **4c'**, **5c**, and **5c'** in the ratio of 40/3/42/15, from which **5c** was separated by flash chromatography. Isomer **5c'** was contaminated by traces of **5c**.

Compound **5c** was obtained as a colorless oil; $^1$H nmr: $\delta$ 1.6-1.9

(m, 2H), 2.56 (q, J = 1.4 Hz, 3H), 2.8 (br s, 3H), 3.36 (m, 1H), 3.5-3.7 (m, 2H), 4.0 (m, 1H); ir: ($cm^{-1}$) 3600 (OH, NH), 1173, 1124 ($CF_3$).

Compound **5c'** had $^1H$ nmr: δ 1.6-1.9 (m, 2H), 2.59 (q, J = 1.4 Hz, 3H), 2.8 (br s, 3H), 3.25 (m, 1H), 3.5-3.7 (m, 2H), 4.0 (m, 1H).

*Anal.* Calcd. for $C_6H_{12}NF_3O_2$: C, 38.50; H, 6.46; N, 7.48. Found: (as a mixture of **5c** and **5c'**): C, 38.74; H, 6.17; N, 7.56.

Cyclization of **5a** (**5a'**) with Diethyl Carbonate.

A solution of 0.8 g (3.4 mmoles) of **5a** and **5a'** (**5a**/**5a'** = 81/19) and 1.22 g (10.3 mmoles) of diethyl carbonate in 10 ml of benzene was subjected to azeotropic distillation. After removal of benzene, 50 mg of potassium *t*-butoxide was added and the mixture was heated at 130° for 3 days. Excess of chloroform was added to the mixture and the precipitate was filtered off and the filtrate was evaporated under reduced pressure to give a residue which was chromatographed (silica gel, hexane-ethyl acetate, 3/1) to give 330 mg (30%) of a mixture of *trans*- and *cis*-3-methyl-6-phenyl-4-trifluoromethyltetrahydro-1,3-oxazin-2-ones **6a** and **6a'** in the ratio of 85/15. Each product was separated by flash chromatography.

Compound **6a** had mp 112-114° (hexane-ethyl acetate); $^1H$ nmr: δ 2.2-2.6 (m, 2H), 3.20 (q, J = 0.8 Hz, 3H), 3.88 (ddq, J = 6.7, 1.8, and 6.7 Hz, 1H), 5.50 (dd, J = 12.2 and 3.0 Hz, 1H), 7.4 (s, 5H); ir: ($cm^{-1}$) 1757 (C=O), 1176, 1139 ($CF_3$).

*Anal.* Calcd. for $C_{12}H_{12}NF_3O_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.50; H, 4.61; N, 5.33.

Compound **6a'** was obtained as a colorless oil; $^1H$ nmr: δ 2.2-2.6 (m, 2H), 3.10 (q, J = 1.7 Hz, 3H), 4.10 (ddq, J = 9.5, 8.3, and 5.8 Hz, 1H), 5.15 (dd, J = 12.0 and 2.5 Hz, 1H), 7.4 (s, 5H); ir: ($cm^{-1}$) 1767 (C=O), 1178, 1146 ($CF_3$).

*Anal.* Calcd. for $C_{12}H_{12}NF_3O_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.63; H, 4.38; N, 5.37.

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