Trifluoropropenes as Dipolarophiles

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The cycloaddition of *C*-phenyl-*N*-methylnitrone with 3,3,3-trifluoropropene and methyl 4,4,4-trifluoro-2-butenoate regio- and stereoselectively gave *trans*-2-methyl-3-phenyl-5-trifluoromethylisoxazolidine (**3a**) and methyl 2-methyl-*c*-3-phenyl-*t*-5-trifluoromethyl-*r*-4-isoxazolidinecarboxylate (**3b**), respectively, as major products. The cycloaddition with 3,3,3-trifluoro-1-nitropropene proceeded regiospecifically to give 2-methyl-*c*-4-nitro-*r*-3-phenyl-*t*-5-trifluoromethylisoxazolidine (**3c**) and 2-methyl-*t*-4-nitro-*r*-3-phenyl-*c*-5-trifluoromethylisoxazolidine (**4c**), stereoisomer with 3,4-*cis*-configuration being predominantly produced. This regioselectivity is explained by both the nitrone-HOMO controlled orbital interaction and the steric hindrance in a transition state. Under more drastic conditions *c*-3, *r*-4-isoxazolidine **3b** isomerized to the more stable *c*-3, *t*-4- and regioisomeric isoxazolidines via 1,3-dipolar cycloreversion. The similar treatment of **3c** and **4c** resulted in the formation of *trans*-1-methyl-4-phenyl-3-trifluoromethyl-2-azetidinone.

We have investigated the synthesis of trifluoromethylated heterocycles, which are a class of remarkable compounds from the view point of pharmacological activity,[1] by the cycloadditions of the dipolar compounds such as *C*-trifluoromethylnitrone and trifluoroacetonitrile oxide and imides.[2—4] Cycloadditions with dipolarophiles bearing trifluoromethyl group are another promising route to obtain the trifluoromethylated heterocycles. By this approach the trifluoromethyl group can be fixed to the different positions of the heterocycles from those introduced by the trifluoromethylated dipolar compounds. Regio- and stereoselectivity in the Diels-Alder reactions using trifluoropropenes is well explored,[5—7] however, little information has been available concerning the selectivity of nitrone-dipolar cycloadditions.[8] In this paper, we wish to demonstrate regio- and stereoselectivity in the cycloadditions of *C*-phenyl-*N*-methylnitrone (**1**) with trifluoropropenes and cycloreversion of the initially formed isoxazolidines.[9]

Results and Discussion

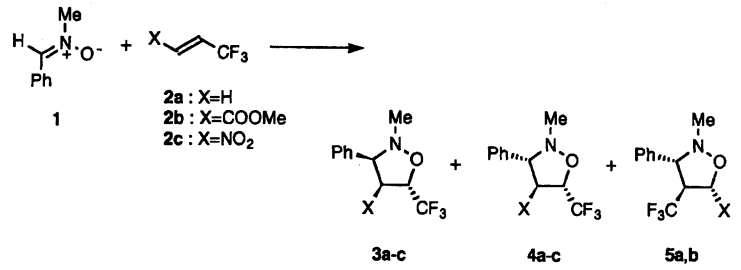
The reaction of nitrone **1** with 3,3,3-trifluoropropene (**2a**) was carried out in a sealed tube at 110°C for 20 h to give a mixture of *trans*- and *cis*-3-phenyl-5-trifluoromethylisoxazolidines (**3a** and **4a**) and their regioisomeric product **5a** in 82% total yield, product ratio 50/23/27 of **3a**/**4a**/**5a** being estimated on the basis of ^{19}F NMR analysis (Scheme 1). Configuration of two 5-trifluoromethylisoxazolidines **3a** and **4a** was specifically determined by ^{13}C NMR analysis of the corresponding 3-amino-1-alcohols derived from **3a** and **4a**. Thus, the reductive N–O cleavage of the isolated **3a** or **4a** with Raney Nickel-hydrogen produced 3-amino-1-alcohol **6a** or **7a** in 74 or 75% yield, respectively. More shielded 4-C and 2-C (62.1 and 69.2 ppm) of **6a** was assigned to be anti-configuration and deshielded ones (64.0 and 71.3 ppm) of **7a** to be *syn*-configuration.[10] These NMR analyses support the stereochemestry of the major 5-trifluoromethylisoxazolidine **3a** as the *trans*-configuration (Scheme 2).

The reaction of **1** with methyl 4,4,4-trifluoro-2-butenoate (**1b**) at 80°C for 22 h afforded a mixture of **3b**, **4b**, and **5b** in 98% total yield (**3b**/**4b**/**5b** ratio of 57/29/14). Configuration of **3b** and **4b** was determined by the chemical shifts of 4-ester methyl protons; that is, the shielded chemical shift (δ=3.22) of **3b** is ascribed to the *c*-3,*r*-4-configuration and the chemical shift of δ=3.69 of **4b** to the *t*-3,*r*-4-configuration.[11] This stereochemistry was also supported by the ^{13}C NMR analysis of the chemical shifts of 3-amino-1-alcohols **6b** and **7b**, derived by the reductive cleavage of **3b** and **4b**.[10] Hydrogenolysis of **5b** produced one diastereoisomer, *trans*-5-phenyl-4-trifluoromethyl-2-pyrrolidone **8b**.[12] This result indicates the stereochemistry of the regioisomeric isoxazolidine **5b** is the *t*-4,*r*-3,*c*-5-configuration. It should be noted that these cycloadducts **3b**, **4b**, and **5b** are the primary products because their product ratio did not change under the reaction conditions unless more drastic conditions were applied.

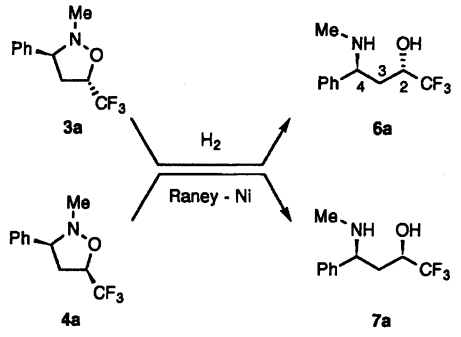
Recyclization of **6b** and **7b** with ethylmagnesium bromide produced the corresponding *trans*-2-azetidinones **9b** and **10b**, respectively (Scheme 3).[13] Epimerization at 3-C of **10b** seems to take place under the basic reaction conditions.

The cycloaddition with 3,3,3-trifluoro-1-nitropropene (**2c**) proceeded regiospecifically at room temperature to give 5-trifluoromethylisoxazolidines **3c** and **4c** in 98% total yield and the ratio of **3c**/**4c** was determined to be 69/31 as the primary product ratio. Under more drastic conditions, **3c** gradually converted into **4c**, which shows that **4c** is thermodynamically more stable than **3c**, suggesting the *t*-4,*r*-3,*c*-5-configuration of **4c**. Product ratios and regioselectivity together with total yields of these cycloadditions are all collected in Table 1.

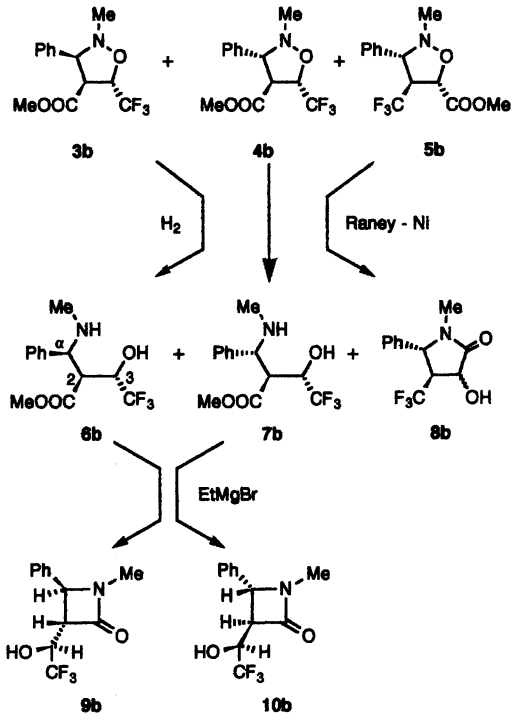
On the basis of AM1 calculation of the energy levels of **1** and trifluoropropenes, these cycloadditions are seen to proceed in the nitrone-HOMO controlled pathways.[14] The predominant formation of 5-trifluoromethylisoxazolidine in the reaction with **2a** is, however, not explained only by the interaction between the ni-



Scheme 1.



Scheme 2.



Scheme 3.

trone-HOMO and the trifluoropropene-LUMO, which rather leads to the reverse regioselectivity (Table 2). The steric hindrance of a trifluoromethyl group,[15] leading to 5-trifluoromethylisoxazolidine, could be considered for this regioselectivity. The regiospecific formation of **3c** and **4c** in the case of **2c** is interpreted by the larger LUMO coefficient of 2-carbon of **2c**, compared with that of 1-carbon, along with the steric consideration. The relaxation of regioselectivity in the case with **2b** is ascribed to decrease in the difference between the LUMO coefficient magnitudes of two olefinic carbons. Stereochemistry of the cycloadditions, leading to the preferential formation of 3,5-*trans*-isoxazolidines, is of interest and now under studying in detail.

As mentioned above, isoxazolidines **3b**, **4b**, and **5b** from butenoate **2b** are all stable under the reaction conditions but heating at 140°C gave rise to isomerization of **3b** into **4b** and **5b**. The changing molar ratio of these isoxazolidines with time was monitored by ^{1}H NMR analysis using toluene as an internal standard. Heating was carried out in a sealed NMR tube containing a mixture of **3b**, **4b**, and **5b** (57/29/14 ratio) in deuteriochloroform and the results being described in Fig. 1. As shown in Fig. 1, the amount of *c*-3,*r*-4-isoxazolidine **3b** was remarkably reduced with increasing amount of **4b** and **5b** along with regeneration of the starting material **2b**. On prolonged heating, these four compounds came to equilibrium. Isomerization of **3b** into the thermodynamically stable **4b** and **5b** seems to be via the 1,3-dipolar cycloreversion, which is suggested by the formation of **2b** and confirmed by the fact that refluxing of a mixture of **3b**, **4b**, and **5b** (61/28/11 ratio) with an excess of styrene in xylene produced 3,5-diphenylisoxazolidine (**11**) in 64% yield.[16] Heating of a mixture of only **4b** and **5b** (66/34 ratio) in the presence of styrene afforded **11** in 56% yield with recovery of **4b** (23%) and **5b** (6%). These results indicate that even more stable **4b** and **5b** also take a 1,3-dipolar cycloreversion path. Therefore, isomerization seems to take place via the 1,3-dipolar cycloreversion of **3b**, **4b**, and **5b**, as depicted in Scheme 4.

A similar isomerization is observed with 4-nitroisoxazolidines **3c** and **4c**; that is, the 92/8 ratio (**3c**/**4c**) changed to the 71/29 ratio on heating at 80°C for 20 h. Heating **3c** at more elevated temperature (170°C) for 4 h, 20% of *trans*-1-methyl-4-phenyl-3-trifluoromethyl-2-azetidinone (**12**) was formed and the yield of **12** increased to 33% when heated in the presence of an equimolar amount of pyridine. Azetidinone **12** will be formed via transformation of the regioisomeric 5-nitro-4-trifluoromethylisoxazolidine **5c** arised from 1,3-dipolar cycloreversion of **3c** and **4c** (Scheme 5).[17]

As a conclusion, the high regioselectivity in the cy-

Table 1. Yields and Regioselectivity in Cycloadditions of Nitrone **1** with Trifluoropropenes **2**

Propene	Conditions Temp/°C	Time/h	Total Yield/% (**3**/**4**/**5** Ratio)	Regioselectivity 5-/4-CF_3-Isoxazolidine
2a	110	20	82 (50/23/27)	73/27
2b	80	22	98 (57/29/14)	86/14
2c	R. T.	23	98 (69/31/0)	100/0

Table 2. AM1-estimated Frontier Orbital Energies and Coefficients for Nitrone **1** and Trifluoropropenes **2**

1 2 3
PhCH=N(Me)-O
1

1 2
X-CH=CH-CF_3
2

Compound		Energy/eV	Coefficient 1	2	3
1	LUMO	−0.301	0.390	−0.499	0.350
	HOMO	−8.448	0.481	0.279	−0.514
2a	LUMO	0.199	0.734	−0.648	
	HOMO	−11.593	0.670	0.723	
2b	LUMO	−0.959	0.564	−0.637	
	HOMO	−11.918	0.604	0.631	
2c	LUMO	−1.787	0.521	−0.621	
	HOMO	−12.748	0.678	0.672	

cloaddition of **1** with **2a**, **2b**, and **2c** is explained by both the steric hindrance of the substituents of **1** and **2**, particularly the trifluoromethyl group, and the difference between the LUMO coefficient magnitudes of the two olefinic carbons of trifluoropropenes. Under more drastic conditions 3,4-*cis*-isoxazolidines isomerize to the thermodynamically more stable 3,4-*trans*- and regioisomeric isoxazolidines via 1,3-dipolar cycloreversion. A similar isomerization to the thermally stable **4c** is also observed with **3c** and, at higher temperature, **3c** and **4c** are converted to *trans*-4-phenyl-3-trifluoromethyl-2-azetidinone (**12**).

Experimental

The IR spectra were recorded on a JASCO A-100 spectrometer and samples were run as film or potassium bromide pellets. The ^1H, ^{19}F, and ^{13}C NMR spectra were measured with a JEOL JNM-GX270 spectrometer (270 MHz) using tetramethylsilane as an internal standard (for ^1H and ^{13}C NMR) and trifluoroacetic acid as an external standard (for ^{19}F NMR), the chemical shifts being given in δ/ppm downfield. Samples were prepared by dissolving in deuteriochloroform. Trifluoropropenes **2a** and **2b** are commercially available and **2b** includes 3% of *cis*-isomer. Preparative method of trifluoronitropropene **2c**, including 2% of *cis*-isomer, will be described in detail in another paper.

Cycloaddition of 1 with Trifluoropropene 2a. A

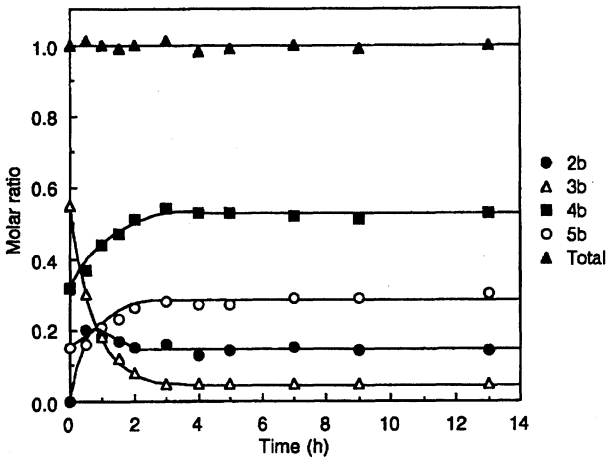
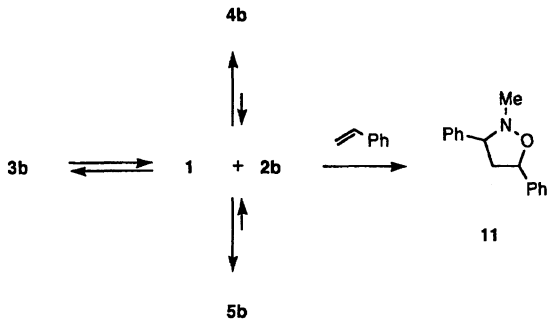
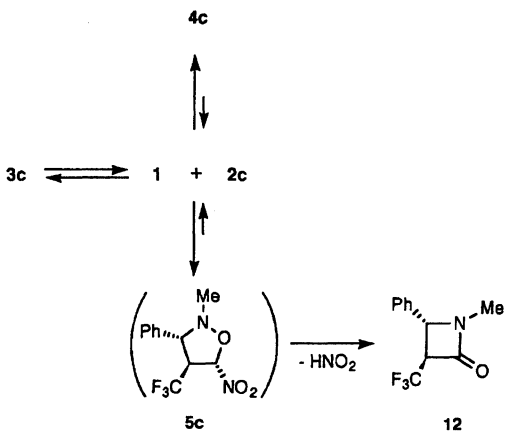


Fig. 1. Thermal isomerization of isoxazolidines **3b**, **4b**, and **5b** at 140°C.



Scheme 4.



Scheme 5.

solution of **1** (1.71 g, 12.7 mmol) and gaseous **2a** (38.1 mmol) in 20 cm^3 of toluene was heated at 110°C for 20 h with stirring in a stainless autoclave. The solvent was evaporated to give a residue which was chromatographed on a silica gel eluting with hexane–ethyl acetate (3/1), affording 2.40 g (82% total yield) of a mixture of *trans*- and *cis*-2-methyl-3-phenyl-5-trifluoromethylisoxazolidines (**3a** and **4a**) and 2-methyl-3-phenyl-4-trifluoromethylisoxazolidine (**5a**) in the ratio of 50/23/27 (by ^{19}F NMR analysis). Each compound was separated by flash chromatography (silica gel, hexane–chloroform–ethyl acetate, 5/2/1).

3a: Colorless oil, ^1H NMR δ=7.45—7.23 (5H, m), 4.48 (1H, ddq, J=9.2, 4.2, 6.8 Hz, 5-H), 3.60 (1H, dd, J=9.2, 7.0 Hz, 3-H), 2.69 (1H, ddd, J=13.0, 7.0, 4.2 Hz, 4-H), 2.56 (1H, dt, J=13.0, 9.2 Hz, 4-H), 2.62 (3H, s). ^{19}F NMR δ=−1.21 (d, J=6.8 Hz). IR 1605 (Ph), 1170, 1145, 1125 (CF_3) cm^{-1}.

4a: Colorless oil, ^1H NMR δ=7.43—7.23 (5H, m), 4.41 (1H, ddq, J=9.0, 6.7, 6.7 Hz, 5-H), 3.51 (1H, dd, J=10.3, 7.1 Hz, 3-H), 2.84 (1H, ddd, J=13.0, 9.0, 7.1 Hz, 4-H), 2.49 (1H, ddd, J=13.0, 10.3, 6.7 Hz, 4-H), 2.58 (3H, s). ^{19}F NMR δ=−1.04 (d, J=6.7 Hz). IR 1605 (Ph), 1160, 1140, 1120 (CF_3) cm^{-1}.

5a: Colorless oil, ^1H NMR δ=7.45—7.26 (5H, m), 4.19 (1H, dd, J=9.2, 9.2 Hz, 5-H), 4.09 (1H, dd, J=9.2, 3.5 Hz, 5-H), 3.53 (1H, d, J=7.4 Hz, 3-H), 3.21 (1H, dddq, J=9.2, 7.4, 3.5, 9.2 Hz, 4-H), 2.59 (3H, s). ^{19}F NMR δ=6.71 (d, J=9.2 Hz). IR 1605 (Ph), 1165, 1140, 1125 (CF_3) cm^{-1}.

Found: C, 56.94; H, 5.22; N, 6.04%. Calcd for $C_{11}H_{12}NF_3O$: C, 57.14; H, 5.23; N, 6.06% (for a mixture of **3a**, **4a**, and **5a**).

Reductive Cleavage of 3a and 4a with Raney Nickel-Hydrogen. The inside pressure of a stainless autoclave, including a solution of **3a** (0.35 g, 1.51 mmol) and 20 mg of Raney Nickel in 10 cm^3 of methanol, was fixed at 3 kgw cm^{-2} with hydrogen. After stirring at room temperature for 4 d, Raney Nickel was filtered off and the filtrate was evaporated to leave a residue which was recrystallized from hexane–ethyl acetate, affording 0.26 g (74%) of 1,1,1-trifluoro-4-methylamino-4-phenyl-2-butanol (**6a**), mp 105.5—107°C, ^1H NMR δ=7.45—7.23 (5H, m), 4.13 (1H, ddq, J=6.0, 4.4, 7.4 Hz, 2-H), 4.03 (1H, dd, J=8.7, 3.5 Hz, 4-H), 2.37 (3H, s), 2.09 (1H, ddd, J=14.9, 6.0, 3.5 Hz, 3-H), 1.98 (1H, ddd, J=14.9, 8.7, 4.4 Hz, 3-H). ^{13}C NMR δ=140.9, 128.9, 127.9, 126.3, 125.5 (q, J=282.7 Hz), 69.2 (q, J=30.3 Hz, 2-C), 62.1 (4-C), 33.7, 33.2. IR 3300—2400 (OH), 3275 (NH), 1170, 1120, 1100 (CF_3) cm^{-1}.

Found: C, 56.42; H, 5.88; N, 5.96%. Calcd for $C_{11}H_{14}NF_3O$: C, 56.65; H, 6.05; N, 6.01%.

A similar procedure to the above afforded 75% of 1,1,1-trifluoro-4-methylamino-4-phenyl-2-butanol (**7a**), mp 96—97°C (recrystallized from hexane–ethyl acetate), ^1H NMR δ=7.45—7.18 (5H, m), 4.31 (1H, ddq, J=10.3, 4.0, 6.6 Hz, 2-H), 3.68 (1H, dd, J=10.3, 4.0 Hz, 4-H), 2.27 (3H, s), 1.95 (1H, t, J=10.3 Hz, 3-H), 1.93 (1H, t, J=4.0 Hz, 3-H). ^{13}C NMR δ=141.3, 129.0, 128.0, 126.2, 124.6, (q, J=280.7 Hz), 71.3 (q, J=31.3 Hz, 2-C), 64.0 (4-C), 34.5, 33.1. IR 3400—2300 (OH), 3275 (NH), 1165, 1120, 1100 (CF_3) cm^{-1}.

Found: C, 56.54; H, 5.95; N, 5.97%. Calcd for $C_{11}H_{14}NF_3O$: C, 56.65; H, 6.05; N, 6.01%.

Cycloaddition of 1 with Butenoate 2b. A solution of **1** (0.90 g, 6.67 mmol) and **2b** (1.20 g, 7.79 mmol) in 30 cm^3 of toluene was stirred at 80°C for 22 h and the solvent was removed. The resulting oil was chromatographed on silica gel (hexane–ethyl acetate, 3/1) to give 1.89 g (98% total yield) of a mixture of methyl 2-methyl-*c*-3-phenyl-*t*-5-trifluoromethyl-*r*-4-isoxazolidinecarboxylate (**3b**) and methyl 2-methyl-*t*-3-phenyl-*t*-5-trifluoromethyl-*r*-4-isoxazolidinecarboxylate (**4b**) and methyl 2-methyl-*c*-3-phenyl-*t*-4-trifluoromethyl-*r*-5-isoxazolidinecarboxylate (**5b**) in the ratio of 57/29/14 (by ^1H NMR analysis). Each compound could not be separated by further chromatography. The distinguished NMR data are as follows.

3b: ^1H NMR δ=5.01 (1H, dq, J=6.2, 6.2 Hz, 5-H), 3.22 (3H, s, OMe), 2.66 (3H, s, NMe). ^{19}F NMR δ=0.03 (b).

4b: ^1H NMR δ=4.73 (1H, dq, J=5.3, 7.4 Hz, 5-H), 3.69 (3H, s, OMe), 2.58 (3H, s, NMe). ^{19}F NMR δ=−0.17 (d, J=7.5 Hz).

5b: ^1H NMR δ=4.64 (1H, d, J=3.3 Hz, 5-H), 3.88 (3H, s, OMe), 2.60 (3H, s, NMe). ^{19}F NMR δ=7.04 (d, J=9.0 Hz).

Found: C, 53.80; H, 4.84; N, 4.88%. Calcd for $C_{13}H_{14}NF_3O_3$: C, 53.98; H, 4.88; N, 4.84% (for a mixture of **3b**, **4b**, and **5b**).

Reductive Cleavage of 3b, 4b, and 5b with Raney Nickel-Hydrogen. A mixture of **4b** and **5b** (0.80 g, 2.77 mmol, **4b**/**5b**=71/29) and 20 mg of Raney Nickel in 10 cm^3 of methanol was stirred at room temperature for 15 d in an atmosphere of hydrogen. After filtration of the catalyst, the filtrate was evaporated under reduced pressure to give an oil. The resulting oil was chromatographed on silica gel (hexane–chloroform–ethyl acetate, 4/2/1) to give 0.26 g (32%) of methyl 4,4,4-trifluoro-3-hydroxy-2-(α-methylaminobenzyl)-butanoate (**7b**) and 0.18 g (25%) of 3-hydroxy-1-methyl-5-phenyl-4-trifluoromethyl-2-pyrrolidone (**8b**), both of which were purified by recrystallization from hexane–chloroform.

7b: Mp 102—102.5°C, ^1H NMR δ=7.43—7.19 (5H, m), 4.62 (1H, dq, J=9.7, 5.9 Hz, 3-H), 3.88 (1H, d, J=11.0 Hz, α-H), 3.25 (3H, s), 2.98 (1H, dd, J=11.0, 9.7 Hz, 2-H), 2.28 (3H, s). ^{13}C NMR δ=170.1, 137.7, 128.8, 128.6, 127.3, 124.3 (q, J=281.7 Hz), 72.9 (q, J=31.3 Hz, 3-C), 66.3 (α-C), 51.8, 49.9 (2-C), 32.9. IR 3315 (NH), 3200—2500 (OH), 1720 (C=O), 1160, 1120, 1100 (CF_3) cm^{-1}.

Found: C, 53.84; H, 5.47; N, 4.81%. Calcd for $C_{13}H_{16}NF_3O_3$: C, 53.61; H, 5.54: N, 4.81%.

8b: Mp 133—134°C, ^1H NMR δ=7.49—7.12 (5H, m), 4.79 (1H, dd, J=8.5, 3.9 Hz, 3-H), 4.77 (1H, d, J=3.6 Hz, 5-H), 4.63 (1H, d, J=3.9 Hz, OH), 3.06 (1H, ddq, J=8.5, 3.6, 9.1 Hz, 4-H), 2.80 (3H, s). ^{13}C NMR δ=172.9, 137.3, 129.5, 129.0, 126.1, 125.2 (q, J=279.7 Hz), 67.5 (3-C), 62.3 (q, J=2.9 Hz, 5-C), 49.9 (q, J=25.4 Hz, 4-C), 28.7. IR 3205 (OH), 1675 (C=O), 1160, 1105 (CF_3) cm^{-1}.

Found: C, 55.50; H, 4.64; N, 5.40%. Calcd for $C_{12}H_{12}NF_3O_2$: C, 55.60; H, 4.67; N, 5.40%.

A similar reduction of a mixture of **3b**, **4b**, and **5b** (1.01 g, 3.49 mmol, **3b**/**4b**/**5b**=61/28/11) afforded 43% of methyl 4,4,4-trifluoro-3-hydroxy-2-(α-methylaminobenzyl)butanoate (**6b**), together with 24% of **7b** and 10% of **8b**.

6b: Colorless oil, ^1H NMR δ=7.43—7.20 (5H, m), 4.50 (1H, dq, J=3.3, 7.4 Hz, 3-H), 4.23 (1H, d, J=3.3 Hz, α-H), 3.59 (3H, s), 3.06 (1H, dd, J=3.3, 3.3 Hz, 2-H), 2.35 (3H, s). ^{13}C NMR δ=170.8, 138.0, 128.7, 127.8, 126.9, 125.2 (q, J=283.7 Hz), 72.4 (q, J=31.3 Hz, 3-C), 62.5 (α-C), 52.1, 48.4 (2-C), 33.5. IR 3600—2400 (OH), 3330 (NH), 1730 (C=O), 1170, 1125 (CF_3) cm^{-1}.

Found: C, 54.00; H, 5.30; N, 4.74%. Calcd for $C_{13}H_{16}NF_3O_3$: C, 53.61; H, 5.54; N, 4.81%.

Cyclization of 6b and 7b into 2-Azetidinones 9b and 10b. A solution of 3 M (1 M=1 mol dm^{-3}) ethylmagnesium bromide (0.53 cm^3, 1.59 mmol) in diethyl ether was added dropwise to a solution of **7b** (0.15 g, 0.52 mmol) in 5 cm^3 of dried tetrahydrofuran below 0°C under an atmosphere of nitrogen and the mixture was stirred at room temperature for 25 h. After adding ammonium chloride saturated aqueous solution, the mixture was extracted with chloroform and the extracts were dried over magnesium sulfate and evaporated to leave a residue. The residue was chromatographed on silica gel (hexane–ethyl acetate, 1/1) to give 0.06 g (45%) of *trans*-1-methyl-4-phenyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-2-azetidinone (**10b**), which was recrystallized from hexane-chloroform, mp 129—131°C, ^{1}H NMR δ=7.50—7.25 (5H, m), 4.49 (1H, bs, 4-H), 4.44 (1H, dq, J=8.2, 6.7 Hz, C<u>H</u>(OH)), 3.32 (1H, dq, J=8.2, 1.1 Hz, 3-H), 2.80 (3H, bs). IR 3330 (OH), 1740 (C=O), 1170, 1125 (CF_3) cm^{-1}.

Found: C, 55.30; H, 4.38; N, 5.30%. Calcd for $C_{12}H_{12}NF_3O_2$: C, 55.60; H, 4.67; N, 5.40%.

A similar procedure to the above using a mixture of **6b** and **7b** (**6b**/**7b**=65/35) produced 45 and 13% of the diastereoisomers **9b** and **10b**.

9b: Mp 136—138°C (recrystallized from hexane–chloroform), ^{1}H NMR δ=7.50—7.20 (5H, m), 4.84 (1H, s, 4-H), 4.50 (1H, dq, J=1.8, 7.1 Hz, C<u>H</u>(OH)), 3.30 (1H, d, J=1.8 Hz, 3-H), 2.80 (3H, s). IR 3250 (OH), 1740 (C=O), 1170, 1120 (CF_3) cm^{-1}.

Found: C, 55.53; H, 4.67; N, 5.40%. Calcd for $C_{12}H_{12}NF_3O_2$: C, 55.60; H, 4.67; N, 5.40%.

Cycloaddition of 1 with Nitropropene 2c. A solution of **1** (0.91 g, 6.74 mmol) and **2c** (1.12 g, 7.94 mmol) in 15 cm^3 of toluene was stirred at room temperature for 23 h. After removing the solvent, the residue was chromatographed on silica gel (hexane–chloroform, 1/1) to give 1.82 g (98% total yield) of 2-methyl-*c*-4-nitro-*r*-3-phenyl-*t*-5-trifluoromethylisoxazolidine (**3c**) and 2-methyl-*t*-4-nitro-*r*-3-phenyl-*c*-5-trifluoromethylisoxazolidine (**4c**) (**3c**/**4c**=69/31). The isoxazolidine **3c** was purified by recrystallization from hexane–chloroform and **4c** by distillation.

3c: Mp 59—61°C, ^{1}H NMR δ=7.45—7.25 (5H, m), 5.43 (1H, dd, J=7.5, 4.3 Hz, 4-H), 5.29 (1H, dq, J=4.3, 6.2 Hz, 5-H), 4.04 (1H, d, J=7.5 Hz, 3-H), 2.71 (3H, s). IR 1565, 1385 (NO_2), 1185, 1140 (CF_3) cm^{-1}.

4c: Colorless oil, ^{1}H NMR δ=7.45—7.25 (5H, m), 5.33 (1H, dd, J=7.9, 3.8 Hz, 4-H), 5.01 (1H, dq, J=3.8, 7.5 Hz, 5-H), 4.06 (1H, d, J=7.9 Hz, 3-H), 2.68 (3H, s). IR 1560, 1370 (NO_2), 1180, 1140 (CF_3) cm^{-1}.

Found: C, 47.84; H, 4.01; N, 10.08%. Calcd for $C_{11}H_{11}N_2F_3O_3$: C, 47.83; H, 4.01; N, 10.14% (for a mixture of **3c** and **4c**).

Heating of 3b, 4b, and 5b in the Presence of Excess Styrene. A mixture of **3b**, **4b**, and **5b** (0.71 g, 2.46 mmol, **3b**/**4b**/**5b**=61/28/11) was refluxed in 6 cm^3 of xylene for 25 h in the presence of 3 cm^3 of styrene. After removing the solvent, the residue was chromatographed on silica gel (hexane–ethyl acetate, 6/1) to give 0.38 g (65%) of 1-methyl-3,5-diphenylisoxazolidine (**11**), 19% of **4b** and 8% of **5b** being recovered.

11: ^{1}H NMR δ=5.26 (1H, dd), 3.8—3.7 (1H, m), 3.09 (1H, ddd), 2.70 (3H, s), 2.43 (1H, ddd).

These ^{1}H NMR data were consistent with the reported ones.[16]

A similar reaction using 0.29 g (1 mmol) of **4b** and **5b** (**4b**/**5b**=66/34) produced 56% of **11**, 23% of **4b** and 6% of **5b** being recovered.

Conversion of 3c and 4c into 2-Azetidinone 12. A mixture of 0.40 g (1.45 mmol) of **3c** and **4c** (**3c**/**4c**=1/1), pyridine (0.11 g, 1.39 mmol), and toluene (4 cm^3) was heated at 170°C for 4 h in a sealed tube. The mixture was extracted with toluene and the extracts were washed with water, dried over magnesium sulfate, and evaporated. The resulting oil was chromatographed on silica gel (hexane–ethyl acetate, 3/1) to give 0.11 g (33%) of *trans*-1-methyl-4-phenyl-3-trifluoromethyl-2-azetidinone (**12**) which was further purified by GLC, yellow oil, ^{1}H NMR δ=7.50—7.24 (5H, m), 4.61 (1H, d, J=2.5 Hz, 4-H), 3.65 (1H, qm, J=9.0 Hz, 3-H), 2.85 (3H, d, J=0.8 Hz). IR 1775 (C=O), 1170, 1120 (CF_3) cm^{-1}.

Found: C, 57.47; H, 4.11; N, 6.22%. Calcd for $C_{11}H_{10}NF_3O$: C, 57.64; H, 4.40; N, 6.11%.

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