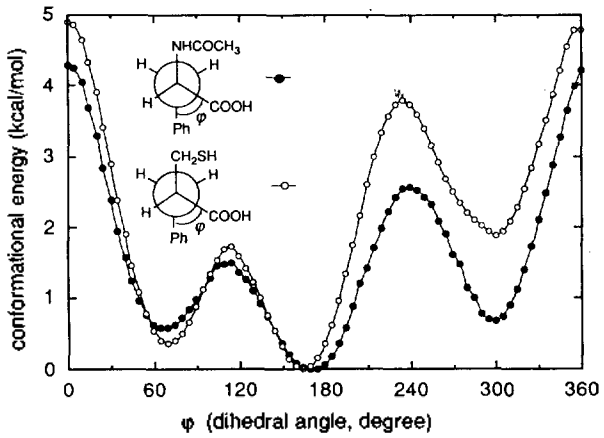

Figure 3. The conformational energy profiles of *N*-acetyl-L-Phe and BMPA calculated by the PM3 method (φ=dihedral angle of C(Ph)-Cβ-Cα-C(CO_2H)).

value for the stereochemical output of the enzymic reaction, and furthermore it serves as a guiding ground for design of chiral inhibitors of not only CPA but also enzymes whose active sites are structurally similar to that of CPA.

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Synthesis of γ,γ,γ-Trifluoro-β-Hydroxy Ketones

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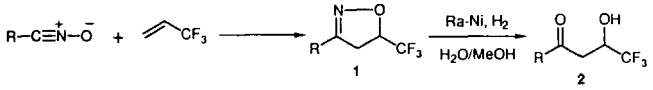
Trifluoromethylated compounds are the subject of renewed interest due to the unique properties of these compounds in the field of medicinal and agricultural chemistry.[1] The influence of the trifluoromethyl group in biologically active molecules is often associated with the increased lipophilicity that this substituent imparts. In addition, its electronegativity and relatively small size are also contributing factors.[2] Development of a general method for trifluoromethylated heterocycles and the related organofluorine compounds would be valuable for the syntheses of many trifluoromethylated target compounds. We wish to report here a very efficient method for the generation of β-trifluoromethyl β-hydroxy ketones.

Our method for the generation of trifluoromethylated heterocycles and the related organofluorine compounds is based on the nitrile oxide cycloaddition with 3,3,3-trifluoropropene[3] followed by the reductive cleavage of corresponding cycloadducts[4] (Eq. 1). Another cycloadditive approach using trifluoroacetonitrile oxide[5] as a source of trifluoromethyl group provided 3-trifluoromethyl 2-isoxazoline cycloadducts in low yield in our hand, probably due to the volatility of trifluoroacetaldehyde oxime intermediate. Thus, we sought the source

of trifluoromethyl group not from the dipole, trifluoroacetonitrile oxide but from the dipolarophile, 3,3,3-trifluoropropene.

Table 1 summerizes the experimental results. Various nitrile oxides were prepared in situ from the corresponding aldehydes by Huisgen's method.[6] We could prepare the cycloadducts either in one-pot procedure (entry 3-9) or two step reaction sequence (entry 1, 2) which involved the isolation of hydroximoyl chloride intermediates. In any case, the reaction yield is usually good (75-95% yield from hydroximoyl chloride, 31-72% two step overall yield from oxime). Chiral amino alkyl substituent derived form L-Phe was successfully attached in the cycloadduct (entry 9). This example indicates that our method can be easily applied to the synthesis of biologically important peptidyl trifluoromethylated compounds.[7]



(Eq. 1)

Our final products, trifluoro carbinol compounds themselves are well known as bioactive molecules such as serine esterase inhibitor[8] and renin inhibitor.[9] Moreover, trifluoro carbinol compounds can be utilized as key intermediates for the synthesis of other trifluoro-methylated compounds like trifluoromethyl ketones,[10] trifluoromethylated β-diketones,[11] γ,γ,γ-trifluorocarbonyl compounds.[12]

In summary, we have developed an efficient synthetic route for the preparation of 5-trifluoromethyl 2-isoxazoline heterocycles and γ-γ-γ-trifluoro-β-hydroxy ketones employing 3,3,3-trifluoropropene as a fluorinated dipolarophile. The trifluoro ketones can be utilized as versatile intermediates for the synthesis of biologically important trifluoromethylated compounds.

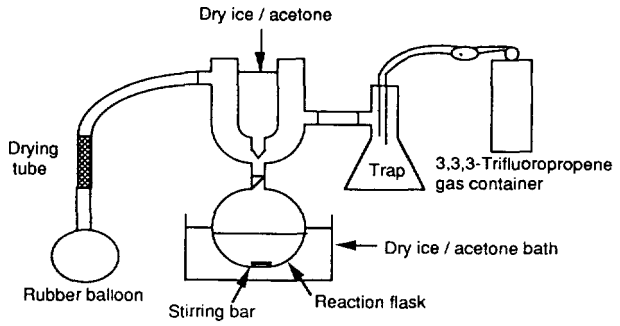


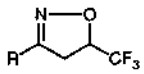
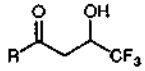
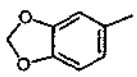
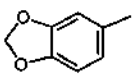
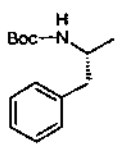
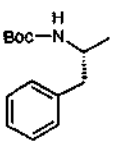
Figure 1. The reaction diagram for the cycloadditions with 3,3,3-trifluoropropene.

Experimental

3,3,3-Trifluoropropene was initially provided by Japan Halon Co., Ltd and additional purchase was made from Aldrich. ^{1}H, ^{13}C, and ^{19}F-NMR spectra were recorded on a Bruker Aspect 3000 (300 MHz for ^{1}H; 75 MHz for ^{13}C; 282 MHz for ^{19}F) or a Bruker AC 80. IR spectra were obtained with a Bomem Model FT-IR M100-C15. Mass spectra were obtained with a Kratos 25 RFA instrument. Measurement of melting points was performed using a Haake Buchler apparatus or Thomas Hoover apparatus. All cycloadditions with 3,3,3-trifluoropropene were carried out based on the reaction diagram (Figure 1).

Procedure for the preparation of 3-*tert*-butyl-5-trifluoromethyl 2-isoxazoline (1a). To a toluene (30 mL) solution of trimethylacetohydroximoyl chloride (1.98 g, 14.6

Table 1. Syntheis of 5-Trifluoromethyl 2-Isoxazolines and γ,γ,γ-Trifluore-β-Hydroxy Ketones

Entry		Yield		Yield
1	R=*t*-Bu (**1a**)	75%[a]	R=*t*-Bu (**2a**)	93%
2	*R*=Ph (**1b**)	95%[a]	*R*=Ph (**2b**)	97%
3	*R*=*n*-Pr (**1c**)	51%[b]	*R*=*n*-Pr (**2c**)	90%
4	*R*=Cyclohexyl (**1d**)	72%[b]	*R*=Cyclohexyl (**2d**)	90%
5	*R*=*p*-Methoxyphenyl (**1e**)	60%[b]	*R*=*p*-Methoxyphenyl (**2e**)	90%
6	*R*=  (**1f**)	43%[b]	*R*=  (**2f**)	90%
7	*R*=*p*-Nitrophenyl (**1g**)	45%[b]	*R*=*p*-Nitrophenyl (**2g**) *R*=*p*-Aminophenyl (**2g'**)	32% 21%[c]
8	*R*=*o*-Trifluoromethyl-phenyl (**1h**)	43%[b]	*R*=*o*-Trifluoromethyl-phenyl (**2h**)	62%
9	*R*=  (**1i**)	31%[b,d]	*R*=  (**2i**)	77%

[a] isolated yield from hydroximoyl chloride. [b] isolated yield (two step overall yield) from oxime. [c] nitro group reduced product. [d] NaOCl was used for the cycloadditon.

mmol) was added excess (160 drops, *ca.* 17 mmol) of 3,3,3-trifluoropropene (bp. −18 ~ −16℃) through dry ice condenser, and triethylamine (4.07 mL, 29.2 mmol) was added dropwise at −78℃. The reaction mixture was stirred overnight and allowed to warm to room temperature. Solvent extraction and flash chromatography (hexane : ethyl acetate = 9 : 1) gave 2.14 g (75%) of **1a**: mp. 26-27℃; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 4.88-4.67 (1H, m), 3.25-3.12 (2H, m), 1.23 (9H, s); ^{19}F NMR ($CDCl_3$, 282 MHz, external reference: trifluoroacetic acid) δ −5.57 (d, J=7.6 Hz); IR ($CHCl_3$) 2971, 2875, 1618, 1472, 1279, 1190, 1167, 1047, 969, 863, 658 cm^{-1}; Ms m/e 196 (M^++1), 180, 140, 126, 122, 109, 98, 85, 74, 69, 61.

One pot procedure for the preparation of 3-cyclohexyl-5-trifluoromethyl 2-isoxazoline (1d). N-Chlorosuccinimide (1.68 g, 12.6 mmol) was added to a chloroform (12 mL) solution of pyridine (60 μL, 0.74 mmol) and then cyclohexanecarboxaldehyde oxime (1.53 g, 12.0 mmol) was added. To the reaction mixture was added excess (160 drops, *ca.* 17 mmol) of 3,3,3-trifluoropropene through dry ice condenser and triethylamine (3.35 mL, 24.0 mmol) was added dropwise at −78℃. The reaction mixture was stirred overnight and allowed to warm to room temperature. Extraction by ethyl acetate followed by flash chromatography (hexane : ethyl acetate = 8 : 1) provided 1.91 g (72%) of **1e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.85-4.72 (1H, m), 3.21 (1H, dd, J=11.0, 17.6 Hz), 3.07 (1H, dd, J=5.7, 17.6 Hz), 2.49-2.40 (1H, m), 1.89-1.86 (2H, m), 1.81-1.80 (2H, m), 1.72-1.69 (1H, m), 1.44-1.21 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.9 (s), 123.7 (q, J_{CF}=279.5 Hz, coupled with three F nuclei), 75.5 (q, J_{CCF}= 32.5 Hz, coupled with three F nuclei), 36.7 (s), 36.5 (s), 30.1 (s), 25.6 (s), 25.4 (s); ^{19}F NMR ($CDCl_3$, 282 MHz, external reference: trifluoroacetic acid) δ −5.61 (d, J=7.8 Hz); IR ($CHCl_3$) 2932, 2858, 1625, 1448, 1282, 1174, 1128, 971, 868 cm^{-1}; MS m/e 220 (M^+), 166, 153, 140, 122, 108, 94, 81, 71, 67.

Procedure for the preparation of 1,1,1-trifluoro-5,5-dimethyl-2-hydroxyhexan-4-one (2a). To a solution of **1a** (442 mg, 2.26 mmol) in 5/1 methanol/water (7 mL) were added boric acid (279 mg, 4.51 mmol) and a spatula tip of w-2 Raney nickel. The reaction mixture was placed under hydrogen by repeated evacuation and flushing with hydrogen gas by means of a balloon attached to a three-way stopcock. The mixture was stirred vigorously for 4h and then filtered through celite. Extraction by ethyl ether followed by flash chromatography (hexane : ethyl acetate = 3 : 1) provided 417 mg (93%) of **2a**: mp. 44.5-45.5℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.48-4.42 (1H, m), 3.48 (1H, br) 2.90 (1H, dd, J=9.1, 17.8 Hz), 2.76 (1H, dd, J=2.8, 17.8 Hz) 1.15 (9H, s); ^{19}F NMR ($CDCl_3$, 282 MHz, external reference: trifluoracetic acid) δ −4.84 (d, J=7.3 Hz); IR ($CHCl_3$) 3448, 2967, 1706, 1479, 1282, 1170, 1122, 885, 679 cm^{-1}; MS m/e 198 (M^+), 181, 143, 135, 123, 107, 95, 83, 77, 69, 63, 60.

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