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SYNTHESIS OF OPTICALLY ACTIVE β-KETO-γ-BUTYROLACTONES HAVING A TRIFLUOROMETHYL GROUP

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SUMMARY

A number of chiral β-keto-γ-butyrolactones and tetronic acids bearing a trifluoromethyl group on an asymmetric carbon were prepared by ultrasound-promoted Reformatsky-type reactions between an optically active O-trimethylsilylated cyanohydrin of trifluoroacetaldehyde and ethyl α-substituted bromoacetates.

INTRODUCTION

A variety of natural products with an unsaturated γ-butyrolactone ring as a common structural feature have been studied for the last two decades [1-3]. However, stereocontrolled syntheses of fluorinated γ-butyrolactone derivatives remain unexplored because the introduction of a center of chirality into fluoroorganic compounds often proves to be quite difficult and limited [4-8].

Recently, we have revealed that new types of technical methods, such as ultrasound irradiation [8-11] and microbial transformation [11-16] can be utilized in fluorine chemistry to open up new avenues for making biologically active compounds containing fluorinated functions. As part of our continuing study of the preparation of new useful fluorinated materials by usage of these new techniques, we have found a practical synthetic method to make optically active trifluoromethylated γ-butyrolactones which are expected with significant biological activities [17,18].

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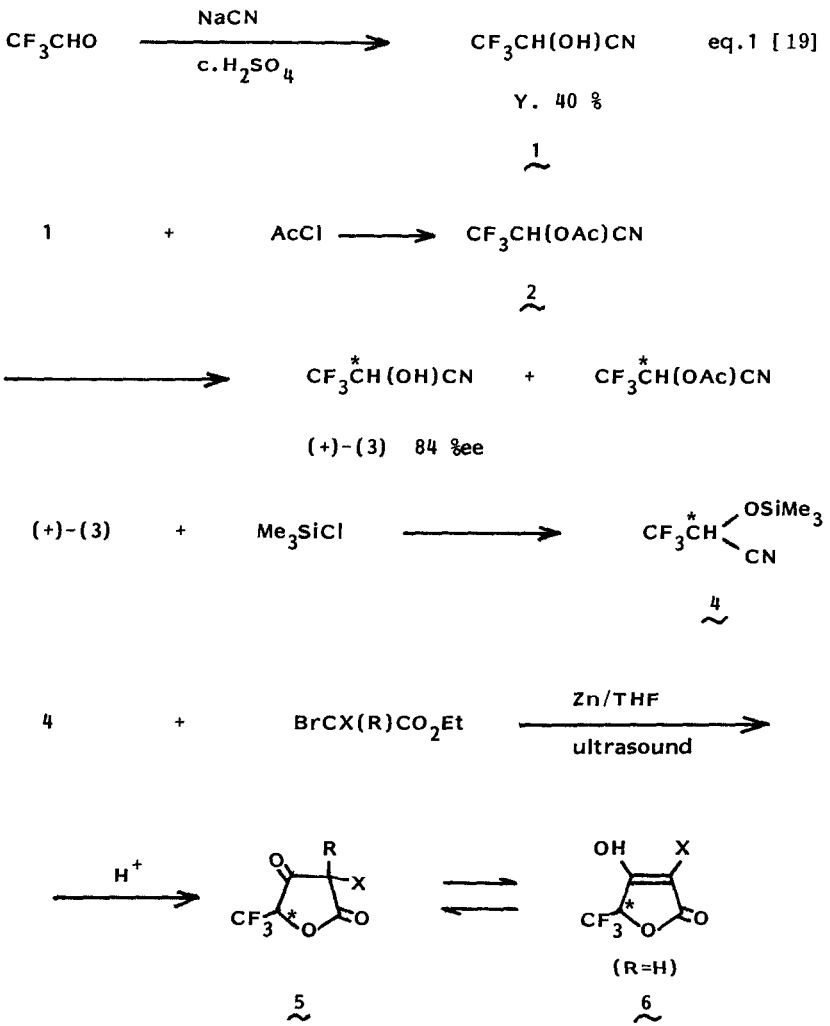
RESULTS AND DISCUSSION

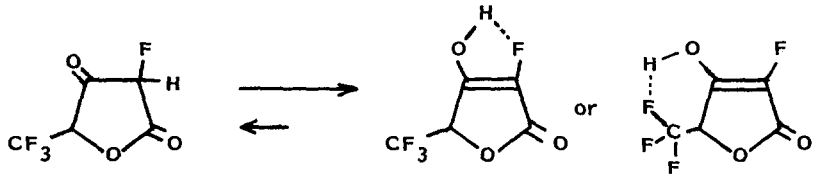
A brief outline of the synthetic strategies employed preparing optically active γ-butyrolactones carrying the trifluoromethyl group is shown in Scheme I.



Scheme I

In Scheme I, the synthetic intermediate is the optically active cyanohydrin of trifluoroacetaldehyde (1), which was produced by the asymmetric hydrolysis of the corresponding acetate with lipase-MY. A Reformatsky-type reaction between the O-trimethylsilylated cyanohydrin and ethyl α-substituted bromoacetates proceeded at room temperature by the assistance of ultrasonic irradiation. Without the aid of ultrasonic irradiation, the reaction did not proceed at all at room temperature. Commercially available zinc powder without any activation was used and the solvent, tetrahydrofuran, was dried over molecular sieve 4A. The corresponding β-keto-γ-butyrolactones were thus obtained after hydrolysis of reaction intermediates as shown in the Scheme I, and listed in Table 1.

The structures of the trifluorinated β-keto-γ-butyrolactones obtained were confirmed from their IR, NMR and mass spectra. When X=F, the ^{19}F NMR spectra in DMSO-d_6 solution revealed a signal at about δ +110(CF) ppm from external CF_3CO_2H. When R=H, in the ^{1}H NMR spectra one broad signal due to the OH proton appeared at δ 11 as well as the other signals due to alkyl protons (Table 2). In addition, no infrared absorption band due to a carbonyl group except the lactone carbonyl group was observed in the spectra of these γ-butyrolactones(R=H). These results suggest that these compounds (R=H) prefer the tetronic acid type structure (6) to the β-keto-γ-butyrolactone type one (5). This may be ascribed to hydrogen bond formation between the oxygen atom and the fluorine atom, which stabilizes the enol form (8) or (9) rather than the keto form (7).



7 8 9

TABLE 1

Preparation of β-keto-γ-butyrolactones (5) or tetronic acids (6)

Product No	Product[a] R	X	Yield[b] (%)	bp(°C(mmHg)) (mp °C)	$[\alpha]_D$/MeOH[c]	Analysis Found C	(Calcd) H
6a	H	H	44 (47)	76-79(27)	+18.4 (c 1.47) (-17.9 (c 1.23))	35.64 (35.73)	1.91 (1.80)
6b	H	Me	63 (43)	91-93(21)	+15.3 (c 1.73) (-15.9 (c 0.78))	39.74 (39.58)	2.54 (2.77)
5a	Me	Me	57 (51)	(96-97)	+20.1 (c 1.45) (-21.4 (c 1.18))	42.59 (42.87)	3.57 (3.60)
6c	H	F	45 (34)	75-77(26)	+14.5 (c 0.76) (-13.9 (c 1.38))	32.57 (32.28)	1.35 (1.08)
5b	Me	F	58 (62)	81-83(14)	+13.5 (c 1.65) (-14.2 (c 1.03))	35.86 (36.02)	1.84 (2.02)

[a] Each structure was determined by means of IR, NMR and mass spectral data.

[b] The figures in parentheses give the yields obtained by using (-)-(3).

[c] The figures in parentheses give the specific rotations obtained by using (-)-(3).

TABLE 2

Spectral data of compounds (5) or (6)

Compound No	^{19}F NMR[a] δ ppm	^{1}H NMR δ ppm (DMSO-d_6)	IR (cm^{-1}) C=O
6a	+4.0(CF_3, d)	5.13(s, 1H), 5.76(CH, q, 1H, J_{CH-CF_3} = 8.5 Hz), 10.6(br, 1H)	1725
6b	+4.2(CF_3, d)	1.86(CH_3, s), 5.81(CH, q, 1H, J_{CH-CF_3} = 8.4 Hz), 10.8(br, 1H)	1730
5a	+3.8(CF_3, d)	1.26-1.31(6xH), 5.74(CH, q, 1H, J_{CH-CF_3} = 8.5 Hz),	1755, 1725
6c	+4.2(CF_3, d) +109(CF, s)	5.83(CH, q, 1H, J_{CH-CF_3} = 8.4 Hz), 10.9(br, 1H)	1730
5b	+4.1(CF_3, d) +112(CF, s)	1.29(CH_3, d, J_{CH_3-CF} = 5.6 Hz), 5.79(CH, q, 1H, J_{CH-CF_3} = 8.5 Hz)	1750, 1725

[a] From CF_3CO_2H as an external standard.

EXPERIMENTAL

(+)-Cyanohydrin of trifluoroacetaldehyde

A suspension of lipase-MY (*Candida cylindracea*, Meito Sangyo Co. Ltd., 3 g) in buffer solution (60 ml, pH=7.3), prepared from 1/15 M aq Na_2HPO_4 solution (46.1 ml) and 1/15 M aq KH_2PO_4 solution (13.9 ml), was stirred for 15 min at 40-41°C in "CULSTIR" flask for suspension culture with double arms and jacket (300 ml. Sibata Scientific Technology Ltd.).
Into the mixture, the acetate of cyanohydrin of trifluoroacetaldehyde (1.7 g, 10 mmol) [19] was added, and then the whole was stirred at 40-41°C. After 5h of stirring, the reaction mixture was worked up in the usual manner, and then the hydrolysis ratio was determined by ^{19}F NMR. The cyanohydrin was purified by column chromatography on Silica gel using of n-hexane-diethyl ether (10:1) as an eluent. The optical purity was determined by ^{19}F NMR using a diastereomeric ester of MTPA. $[\alpha]_D$/MeOH +24.1(c 1.86) ; 84 %ee.

Determination of optical purity

A mixture solution of (R)- -methoxy- -trifluoromethylphenylacetic acid chloride (MTPA-Cl)(1.1 mmol), (+)-cyanohydrin of trifluoroacetaldehyde (1 mmol) in pyridine (1 ml) was stirred at room temperature. After 24h of stirring, the whole mixture was poured into water, and then oily materials were extracted with diethyl ether. The ethereal layer was washed with 1N HCl, 5% $NaHSO_4$, sat. $Na_2S_2O_3$ solution and then brine. After removing the solvent, the diastereomeric ratio was determined by ^{19}F NMR signal intensities.

(-)-Cyanohydrin of trifluoroacetaldehyde

A suspension of cellulase (*Trichoderma viride* , Yakult Pharmaceutical Industry Co. Ltd., 3 g) in distilled water

(75 ml) was stirred for 15 min at 40-41°C in "CULSTIR" flask. Into the mixture solution, the acetate of cyanohydrin of trifluoroacetaldehyde (10 mmol) which was recovered from the above asymmetric hydrolysis (hydrolysis ratio 55 % : (+)-3 , 71 %ee), was added and then the mixture was stirred at 40-41°C. After 6h of stirring, the reaction mixture was worked up in the usual manner. $[\alpha]_D$/MeOH -24.7(c 1.57); 86 %ee.

Silylation

A mixture of (+)-cyanohydrin of trifluoroacetaldehyde (2.5 g, 20 ml), chlorotrimethylsilane (3.3 g, 30 mmol), triethylamine (2.5 g, 25 mmol) in dichloromethane (30 ml) was stirred for 24h at room temperature. On removal of the solvent, distillation gave O-trimethylsilylated cyanohydrin of trifluoroacetaldehyde in a 76 % yield, bp 94-97°C/19 mmHg.
^{19}F NMR ($CDCl_3$) : δ 1.6(d, J_{CF_3-CH}= 8.5 Hz) ppm from external CF_3CO_2H.
^1H NMR ($CDCl_3$) : δ 0.05(CH_3, s), 4.86(CH, q, 1H).
IR (cm^{-1}) : 2245(CN).

γ-Trifluoromethyl-α-fluorotetronic acid (6c)(nc)

Into a 100 ml 3-necked flask equipped with a dry-ice condenser, were placed commercially available zinc powder (3.9 g, 0.06 g-atom), O-trimethylsilylated cyanohydrin of trifluoroacetaldehyde (2.0 g, 10 mmol) and tetrahydrofuran (30 ml). Ethyl α-fluorobromoacetate (2.8 g, 15 mmol) in tetrahydrofuran (5 ml) was added to the mixture, and irradiated in the water bath of an ultrasonic laboratory cleaner (44 KHz, 50 W). After 2h of irradiation, the reaction mixture was poured into a mixture of ice (300 g) and conc. H_2SO_4 (20 ml), and then allowed to stand at room temperature overnight. The organic layer was extracted with several portions of ethyl acetate, and dried over anhydrous magnesium sulfate. After removing the solvent, distillation gave γ-trifluoromethyl-α-fluorotetronic acid (6c).

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