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A SYNTHETIC APPROACH TO SEVEN-MEMBERED LACTONES BY THE MICROBIAL TRANSFORMATION OF YNONES HAVING A TRIFLUOROMETHYL GROUP

Tomoya KITAZUME* and Takehiko SATO

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Ookayama, Tokyo 152 (Japan)

SUMMARY

Studies on the microbial transformations of a number of ynones bearing a trifluoromethyl group prepared by the reaction of ethyl trifluoroacetate with a variety of lithium alkynates, have been undertaken. The major products were the corresponding carbinols but microbial carbon-carbon bond degradation and formation occurred also, which proceeded to novel fluorinated seven-membered lactones as significant products.

INTRODUCTION

Research work on the metabolic degradation of halogen-containing compounds which have unique properties as industrial materials, has been extensive in recent years [1-6]. However, it is not easy to transform these halogenated compounds by microorganisms. Especially, in fluorine chemistry, further work is needed to make clear the relation between the molecular structure and the microbial behaviors.

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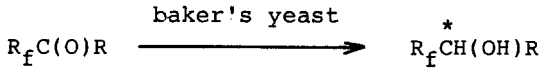
Recently, we have reported that baker's yeast performs a variety of reactions. It can reduce a number of ketones, ketoesters [7,8] and α,β-unsaturated ketones [9] to optically active materials containing a fluorinated group, as shown in Scheme I.



R = alkyl, $CHXCO_2Et$, CH_2CHY

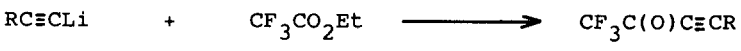
Scheme I

In our continuing study of the microbial behavior of fluorinated compounds, we found a new synthetic approach to seven-membered lactones from ynones possessing trifluoromethyl group, which involved the degradation of carbon-fluorine bonds and the formation of carbon-carbon bonds by active fermenting baker's yeast.

RESULTS AND DISCUSSION

Preparation of trifluoromethyl alkynyl ketones

The preparation of trifluoromethyl alkynyl ketones we used as shown below is simpler than that reported by other workers [10] using the Grignard-type reaction. We found a practical synthetic route to these compounds, which was the reaction of lithium alkynates with ethyl trifluoroacetate.



This method is a simple process involving the dropwise addition of ethyl trifluoroacetate to a solution of the lithium alkynate in tetrahydrofuran as solvent below -50°C. It is suggested that this is a general synthetic method for perfluoroalkyl alkynyl ketones.

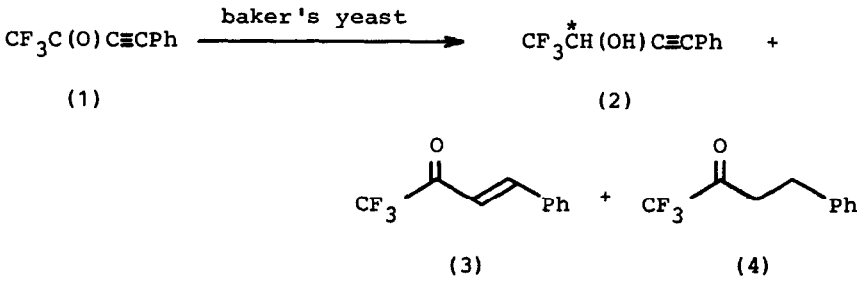
TABLE I

Yields and physical properties of $CF_3C(O)C{\equiv}CR$

Compound No	R	Yield (%)	Bp (°C/mmHg)	IR(cm-1) C=O	IR(cm-1) C≡C
(1)(nc)	Ph	88	93-94/24	1710	2200
(5a)(nc)	$n\text{-}C_3H_7$	50	117-118	1710	2200
(5b)(nc)	$n\text{-}C_4H_9$	74	69-70/65	1710	2200

Microbial reduction of 1,1,1-trifluoro-4-phenyl-3-butyn-2-one(1)

When microbial transformation with active fermenting baker's yeast takes place, the corresponding optically active carbinol is mainly obtained from the title material, along with the compounds based on the selective reduction of the unsaturated carbon-carbon bond.



The following conclusions may be drawn from the above results. Although no chemoselective reduction occurs, stereoselective reduction of the carbon-carbon triple bond to a double bond took place to produce a trans-type α,β-unsaturated ketone. The stereochemistry of the α,β-unsaturated ketone was determined by its ^{1}H NMR spectrum, the identification being based on the well-established coupling constants.
In the ^{1}H NMR spectrum, two doublet signals at δ 6.90 and 7.84 assigned to the olefinic protons are split by each other, J_{H-H} = 15 Hz. This fact suggests the trans-isomer.

Furthermore, the optical purity of the carbinols (2) was determined by ^{19}F NMR signal intensities conversion of the carbinol to their diastereomeric esters by optically active α-methoxy-α-trifluoromethylphenylacetic acid (MTPA).
These results show in Table II.

TABLE II

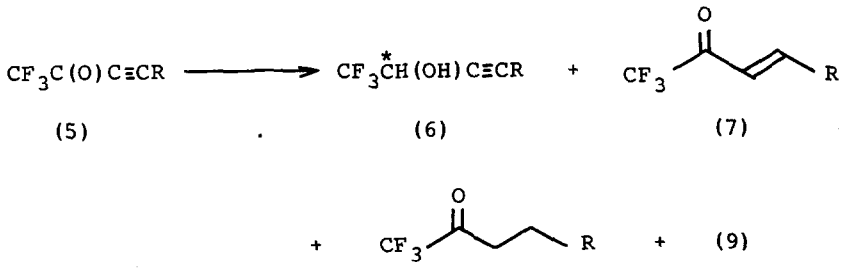
Yields for the compounds (2), (3) and (4)

Yeast from	Yield (%)		
	(2)	(3)	(4)
Oriental Co. Ltd.	40	7	12
Sigma Co. Ltd.	46	8	2
Nisshin Co. Ltd.	5	1	1

Microbial reduction of 1,1,1-trifluoro-4-alkyl-3-butyn-2-ones(5)

The substrates with alkyl groups attached to the carbon-carbon triple bond were also transformed to the corresponding carbinols along with smaller amounts of the corresponding

α, β-unsaturated ketone and saturated ketone. Furthermore, in these cases, we found that the very interesting materials (9) were produced as a result of microbial transformation of compounds (5).



(5) (6) (7)

(8)

R= $C_3H_7{}^n$(a); $C_4H_9{}^n$(b)

As it is well known that the microbial reduction of carbonyl groups [11-13] leads to optically active carbinols, we have attempted to determined the optical purity of carbinols (6) by using the chiral MTPA, as shown in Table III. The facts shown in Table III support the synthetic route to optically active propargylic alcohols possessing perfluoroalkyl groups because the chiral reducing agent gives only the racemic carbinol in these system [9].

TABLE III

Physical properties of $CF_3\overset{*}{C}H(OH)C{\equiv}CR$

Compound No	R	Yield (%)	Bp (°C/mmHg)	α_D/MeOH	Optical purity %ee
(2)(nc)	Ph	46	98-100/5	-5.18 (c 9.09)	46
(6a)(nc)	n-C_3H_7	22	80-83/5	2.26 (c 1.05)	82
(6b)(nc)	n-C_4H_9	19	90-92/4	1.35 (c 2.20)	53

Identification of compound (9)

The most interesting product in the above system is a seven-membered lactone (9) produced as a result of the partial degradation of the carbon-fluorine bond and the formation of a new carbon-carbon bond by the microorganism.

The structure of lactone (9b, R=Bu) was confirmed by several kinds of spectral data. Firstly, the ^{19}F NMR spectrum showed only one singlet signal due to the CF_3 group at δ -9.0 ppm from external CF_3CO_2H. In the ^{1}H NMR spectrum, two characteristic singlet peaks appeared at δ 7.03 and 7.23 ppm, which are assigned to the olefinic protons. Especially, the ^{13}C NMR spectrum showed resonances at δ 12.0, 12.2, 20.7, 20.9, 30.3, 30.9, 33.4, 36.2, 116, 121, 123, 146, 152 and 162, respectively. The resonances at δ 116 and 123 assigned to the carbon-carbon double bond is split by hydrogen atom. Those at δ 146 and 152 are assigned to the other carbon-carbon double bond. The resonance at δ 121 assigned to the CF_3 carbon atom is split by the fluorine atoms, and that at δ 162 to the C=O carbon atom.

The interesting formation of compounds (9) seemed to be caused by the degradation of carbon-fluorine bonds and the formation of new carbon-carbon bonds by microorganism, as shown in Fig I.

In this microbial transformation, the reduction of the carbonyl group leading to the hydrolysis of the CF_3 group and the reduction of the carbon-carbon triple bond must be the initial step (eq. 1 and 2).
It is likely that the next step is the formation of complex (12) which is one of the abilities of active fermenting baker's yeast [14-16]. This would be followed by a nucleophilic attack leading to (13), and then the carbon-carbon bond formation proceeds to the ring-closure leading to the final product.

The present results offer a possibility for the microbial degradation and/or transformation of the fluorinated compounds to versatile bioactive materials.

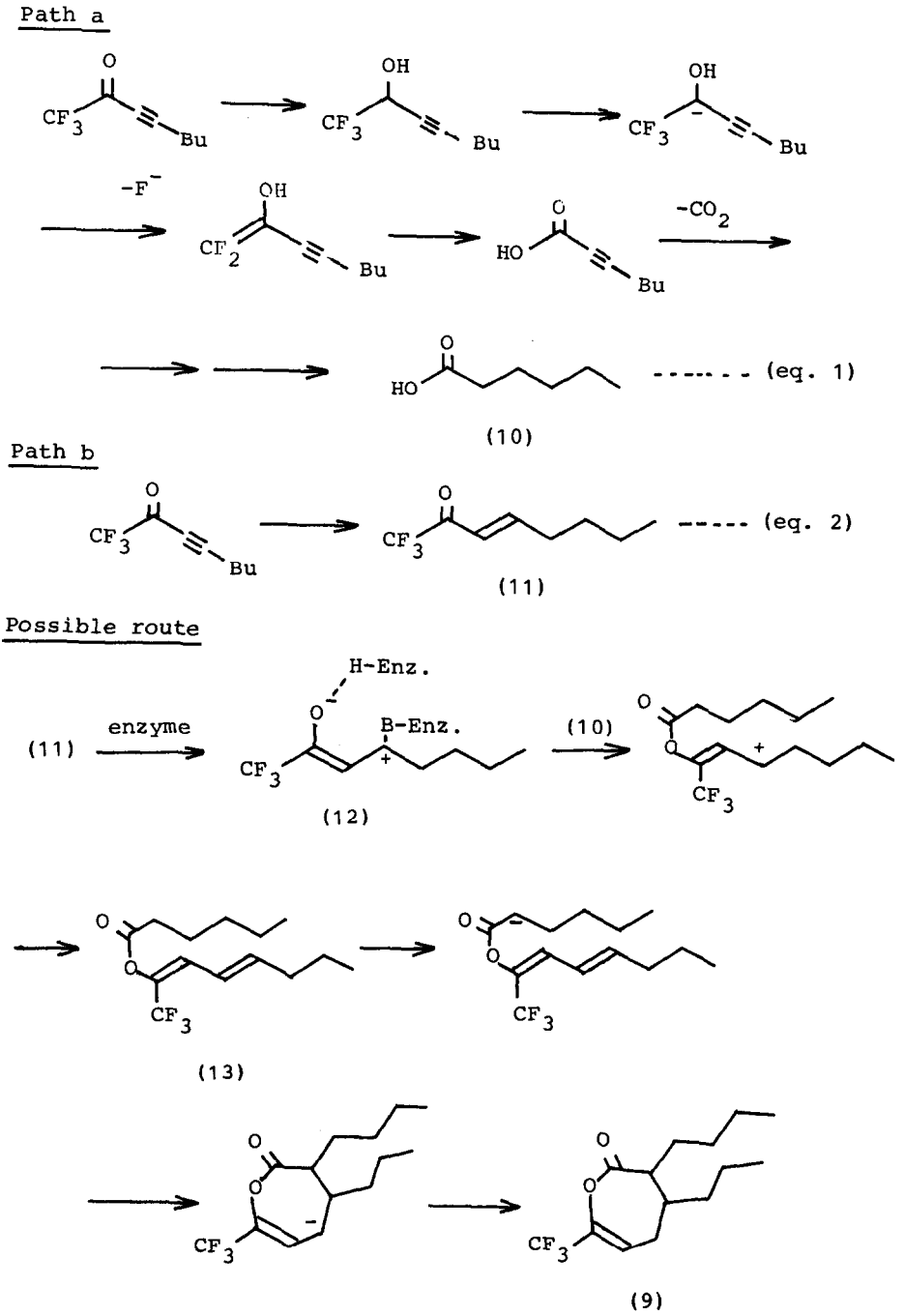


Fig. 1. Representation of bond transformation.

TABLE IV

Reduction of $CF_3C(O)C{\equiv}CR$ (1) or (5)

Compound No	R	Yield (%)[a]			
		$CF_3CH(OH)C{\equiv}CR$[c]	$CF_3C(O)CH{=}CHR$[b]	$CF_3C(O)CH_2CH_2R$[b]	Compound (9)
(1)	Ph	46	8	7	
(5a)	n-C_3H_7	22	16	13	18
(5b)	n-C_4H_9	19	12	15	21

[a] Determined by means of ^{19}F NMR using $PhCF_3$ as the internal standard.
[b] See Reference [17]. [c] See Reference [18].

TABLE V

^{1}H and ^{19}F NMR spectral data of $CF_3C(O)C{\equiv}CR$ (1) or (5)

Compound No	R	^{19}F NMR[a] CF_3 δ ppm	^{1}H NMR δ ppm
(1)	Ph	0.50 (s)	7.1 (Ar-H)
(5a)	n-C_3H_7	1.67 (s)	1.07 (CH_3, t, $J_{CH_3-CH_2}$ = 6 Hz) 1.67 (CH_2, hex.) 2.47 (CH_2, t, $J_{CH_2-CH_2}$ = 6 Hz)
(5b)	n-C_4H_9	1.50 (s)	1.03 (CH_3, t, $J_{CH_3-CH_2}$ = 6 Hz) 1.33-1.90 (CH_2 x 2, m) 2.57 (CH_2, t, $J_{CH_2-CH_2}$ = 6 Hz)

[a] From ext. CF_3CO_2H in $CDCl_3$.

TABLE VI

^{1}H and ^{19}F NMR spectral data and elemental analysis of $CF_3CH(OH)C{\equiv}CR$

Compound No	R	^{19}F NMR[a] CF_3 δ ppm	J_{CF_3-H} (Hz)	^{1}H NMR δ ppm	Analysis: Found (Cacld) C	H
(2)	Ph	0.31 (d)	6.6	3.83(OH), 4.87(CH, q)	60.31	3.67
				7.37(Ar-H)	(60.01)	(3.53)
(6a)	$n\text{-}C_3H_7$	1.70 (d)	5.6	1.0, 1.53, 2.20(7H)	50.47	5.67
				3.67(OH), 4.40(CH, q)	(50.61)	(5.46)
(6b)	$n\text{-}C_4H_9$	2.32 (d)	5.6	0.9, 1.50, 2.30(9H)	53.12	6.09
				3.70(OH), 4.73(CH, q)	(53.33)	(6.15)

[a] From ext. CF_3CO_2H in $CDCl_3$.

TABLE VII

^{1}H and ^{19}F NMR spectral data and elemental analysis of compound (9)

Compound No	^{19}F NMR[a] CF_3 δ ppm	^{1}H NMR δ ppm	Mass M^+	Analysis: Found (Calcd) C	H
(9a)	-10.0 (s)	0.83-1.93(9H), 2.67(4H) 7.00(1H, s), 7.23(1H, s)	248	58.24 (58.07)	6.30 (6.05)
(9b)	-9.0 (s)	0.80-1.81(11H), 2.71(4H) 7.03(1H, s), 7.23(1H, s)	276	60.57 (60.87)	6.58 (6.88)

[a] From ext. CF_3CO_2H in $CDCl_3$.

EXPERIMENTAL

4,4,4-Trifluoro-1-phenylbutyn-3-one (1)(nc)

n-Butyl lithium (162 mmol, 1.65 M in hexane) was added to a mixture of phenyl acetylene (16.5 g, 162 mmol) and freshly dried tetrahydrofuran (120 ml) at 0°C. After 30 min of stirring, ethyl trifluoroacetate (12.8 g, 90 mmol) was added dropwise at a temperature below -50°C. After a further 1h of stirring below -50°C, the reaction mixture was quenched with saturated NH_4Cl. An oily material was extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave 4,4,4-trifluoro-1-phenylbutyn-3-one in a yield of 88%, bp 93-94°C/24 mmHg.

Analysis. Found : C, 60.98 ; H, 2.35 %.
Calcd for $C_{10}H_5OF_3$: C, 60.66 ; H, 2.53 %.

1,1,1-Trifluoro-3-heptyn-2-one (5a)(nc)

1-Pentyne (2.4 g, 30 mmol), ethyl trifluoroacetate (2.8 g, 20 mmol) and n-butyl lithium (30 mmol, 1.65 M in hexane) were used in the same manner, and worked up similarly. Distillation gave 1,1,1-trifluoro-3-heptyn-2-one in a yield of 50 %, bp 117-118°C.

Analysis. Found : C, 51.45 ; H, 4.56 %.
Calcd for $C_7H_7OF_3$: C, 51.22 ; H, 4.27 %.

1,1,1-Trifluoro-3-octyn-2-one (5b)(nc)

1-Hexyne (2.5 g, 30 mmol), ethyl trifluoroacetate (2.8 g, 20 mmol) and n-butyl lithium (30 mmol, 1.65 M in hexane) were used in the same manner, and worked up similarly. Distillation gave 1,1,1-trifluoro-3-octyn-2-one in a yield of 74%, bp 69-70°C/65 mmHg.

Analysis. Found : C, 53.75 ; H, 5.25 %.
Calcd for $C_8H_9OF_3$: C, 53.93 ; H, 5.06 %.

Microbial transformation of 4,4,4-trifluoro-1-phenylbutyn-3-one(1)

A suspension of baker's yeast (50 g), starch (75 g) in buffer solution (600 ml, PH 7.3), which is prepared from 1/15 M aq. KH_2PO_4 solution (139.2 ml) and 1/15 M Na_2HPO_4 solution (460.8 ml), was stirred for 1h at 35-36°C in Jarfermentor (M-100, Tokyo Rikakikai Co. Ltd.). Into the mixture, 4,4,4-trifluoro-1-phenylbutyn-3-one (5 g) was added, and then the whole mixture was stirred at 35-36°C. After 5 days of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 100 ml) was added into the stirring mixture for a few minutes. After 1h of stirring, the mixture was acidified with 1N HCl and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. The products were seperated by column chromatography on silica gel using n-hexane as an eluent.

Microbial transformation of 1,1,1-trifluoro-3-heptyn-2-one

Baker's yeast (50 g), starch (75 g) and 1,1,1-trifluoro-3-heptyn-2-one (5 g) were used in the above reaction, and worked up similarly. The products were seperated by column chromatography on silica gel using the mixture solution of n-hexane-diethyl ether (5:1) as an eluent.

Microbial transformation of 1,1,1-trifluoro-3-octyn-2-one

In the above reaction, 1,1,1-trifluoro-3-octyn-2-one (5 g), baker's yeast (50 g) and starch (75 g) were used, and then worked up as usual. The products were seperated by column chromatography on silica gel using the mixture solution of n-hexane-diethyl ether (5:1) as an eluent.

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