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RING OPENING REACTION OF gem-DIFLUOROCYCLOPROPYL KETONES WITH NUCLEOPHILES[1)]

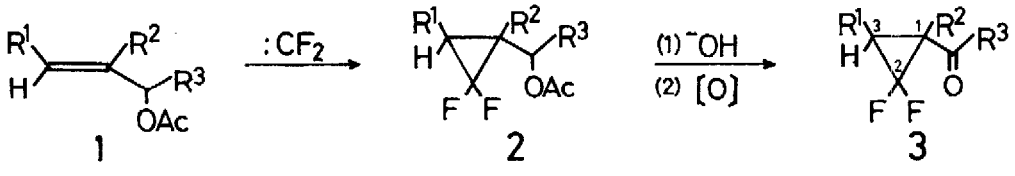
Yoshiro Kobayashi*, Takeo Taguchi, Tsutomu Morikawa, Toyohiko Takase, and Hiroshi Takanashi

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

SUMMARY Syntheses of gem-difluorocyclopropyl ketones (3a-d) and their reactions with nucleophiles are described. Ring opening reactions of 3a,c and d with a methanolate and a thiolate anion took entirely different courses of bond scission of the cyclopropane ring.

Following our recent reports, studies on synthetic reactions utilizing difluorocyclopropane derivatives,[2,3)] we wish to report the reactions of gem-difluorocyclopropyl ketones, having a hydrogen substituent at the C_1 position adjacent to carbonyl group, with a methanolate and a thiolate anion which resulted in an exclusively different course of bond scission of the cyclopropane ring.

The starting materials (3a-d) were synthesized by the addition of difluorocarbene generated by pyrolysis of sodium chlorodifluoroacetate[4)] to the allyl acetates (1) followed by the alkaline hydrolysis and Jones oxidation (Table I). Reactions of the allyl acetates (1a and 1b), which are of E form, with difluorocarbene gave the cyclopropanes (2a and 2b) as a mixture of two racemic diastereoisomers, separable by silica gel column chromatography. Both diastereoisomers were converted to the gem-difluorocyclopropyl ketones (3a and 3b) as an identical single isomer by the subsequent hydrolysis and oxidation. It is well known that addition of difluorocarbene (singlet ground-state) to carbon-carbon double bond proceeds in a stereospecific cis manner;[5)] these results may indicate that the stereochemical relationship between phenyl and acetyl or methoxycarbonyl group of 3a, 3b and 3d is trans, as in the case of the starting allyl acetates.



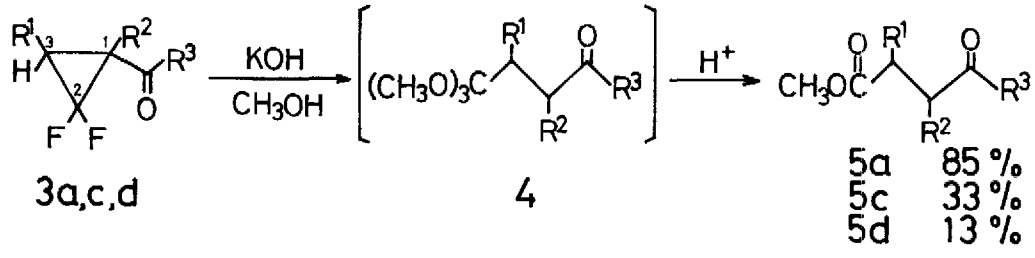
1 2 3

Table I Synthesis of gem-Difluorocyclopropane (3)

	Allyl Acetate (1)			Yield (%)		gem-Difluorocyclopropane (3)	
	R^1	R^2	R^3	1 → 2	2 → 3		bp °C/mmHg
1a	Ph	H	CH_3	70	81	3a	110-113/8
1b	Ph	CH_3	CH_3	64	73	3b	92-93/7
1c	H	H	n-C_4H_9	47	73	3c	70-73/20
1d	Ph	H	H	77	53	3d (R^3=OCH_3)*	70-75/6

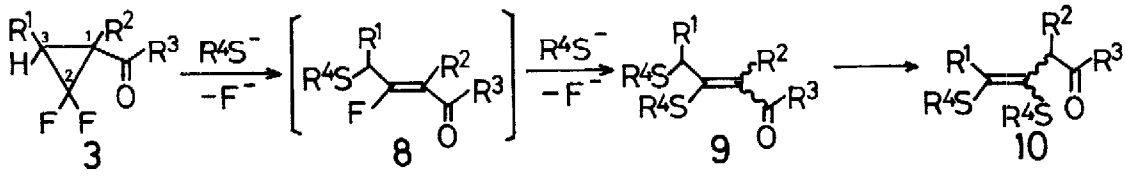
* The resulting carboxylic acid was treated with diazomethane to give 3d.

Reactions of 3a,c and d with methanolic potassium hydroxide was found to afford the corresponding γ-keto esters or the succinic acid derivative via C_1-C_2 bond cleavage of the cyclopropanes. Thus, treatment of 3a with 6 equiv. of potassium hydroxide in methanol and tetrahydrofuran (THF) for 12 hr under reflux followed by acidic work-up gave the γ-keto ester (5a) [85% yield, mp 68-69° (lit.[6] 69.5-70°); IR 1740, 1725 cm^{-1}]. Similarly, 3c (KOH in methanol and THF, reflux, 48 hr) and 3d (sodium methoxide in methanol, reflux, 19 hr followed by acidic work-up and reesterification with diazomethane) afforded 5c and 5d in 33% and 13% yields, respectively, with recovery of the starting cyclopropanes (3d was recovered in 64%). The keto esters (5a and 5c) and dimethyl 2-phenylsuccinate (5d) thus obtained were readily hydrolyzed by methanolic potassium hydroxide to the corresponding acids. Though it is not clear whether the initial step of this reaction is substitution of the fluorine atom with the methoxyl group via successive elimination of the fluoride anion to yield the cyclopropene derivative and addition of the methanolate anion or ring opening by nucleophilic attack of the methanolate anion on C_2 of the cyclopropanes, the above findings may indicate that the intermediary orthoester (4) should be formed.[7]

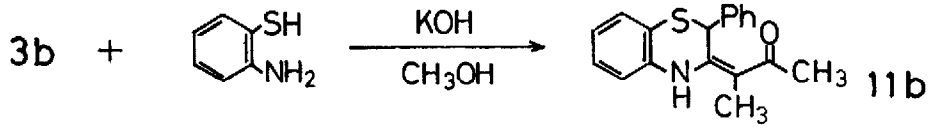


In contrast to the above-mentioned ring cleavage of the difluorocyclopropanes with methoxide, reactions of the difluorocyclopropanes with the thiolate anion gave C_1-C_3 bond cleavage products, exclusively, but no thiol ester,

thioorthoester or γ-keto ester derived from C_1-C_2 bond cleavage was detected. Treatment of 3a with 2.5 equiv. of benzenethiol in the presence of 2.5 equiv. potassium hydroxide in methanol and THF at room temperature for 3 hr afforded 4,5-diphenylthio-5-phenylpentan-2-one (9a-1) [69% yield, MS m/e 376 (M^+)]. Longer reaction time (6 hr) resulted in the formation of the corresponding β,γ-unsaturated ketone (10a-1, 80% yield), which was also obtained by treating of 9a-1 with potassium hydroxide in methanol and THF. Similar ring opening products were obtained by the reaction of 3a,b and c with benzenethiol or toluene-3,4-dithiol as shown in Table II.



Furthermore, reaction of 3b with o-aminobenzenethiol in the presence of potassium hydroxide in methanol and THF was found to give 11b [73% yield, mp 186-187°; MS m/e 295 (M^+); IR 1600, 1580, 1545 cm^{-1}; NMR δ 1.92 (s, 3H), 2.26 (s, 3H), 5.00 (s, 1H), 13.83 (bs, 1H)] which was formed through C_1-C_3 bond cleavage of the cyclopropane ring by nucleophilic attack of the thiolate anion on C_3.



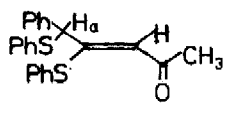
These reactions may proceed in the initial ring opening by nucleophilic attack of the thiolate anion on C_3 to afford the intermediary β-fluoro enone (8) followed by addition of the second thiolate anion or the amino group at the β-carbon of 8 and elimination of the fluoride anion.

In conclusion, ring cleavage of gem-difluorocyclopropyl ketones having a hydrogen substituent at the C_1 adjacent to carbonyl group with a methanolate anion occurred between the carbon atom with the acyl group and the carbon atom with the fluorine substituent to afford the corresponding γ-keto esters or the succinic ester derivative. On the other hand, when a thiolate anion was used as a nucleophile, ring cleavage occurred between the C_1 and the C_3 opposite to the difluoromethylene group. The detailed mechanism of these present reactions and the application to synthetic reaction are now being investigated.

Table II Reaction of Difluorocyclopropane (3) with Thiol

	Thiol	Time	Product	(Yield %)	$\nu_{C=O}$ cm^{-1}	δ ppm
3a	PhSH	3 hr	9a-1	(69)	1665	4.96 (s, Ha)
3a	PhSH	6 hr	10a-1*	(80)	{1730 1730	3.81 (s, Ha) 3.26 (s, Ha)
3a		3 hr	10a-2	(76)	1715	3.48 (s, Ha)
3b	PhSH	4 hr	10b-1*	(72)	{1720-1700 1715	1.15 (d, Ha), 3.48 (q, Hb) 1.47 (d, Ha), 4.30 (q, Hb)
3b		3 hr	10b-2	(90)	1720-1700	1.32 (d, Ha), 3.65 (q, Hb)
3c	PhSH	6 hr	10c-1*	(27)	{1720 1720	3.50 (s, Ha), 6.63 (s, Hb) 3.27 (s, Ha), 6.63 (s, Hb)
3c		6 hr	9c-2	(59)	1665	3.52 (s, Ha), 6.24 (s, Hb)

* Stereoisomeric mixtures, separable by silica gel column chromatography.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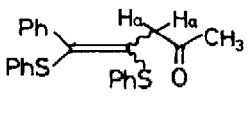
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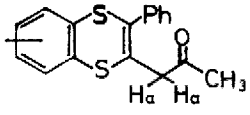
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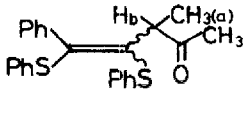
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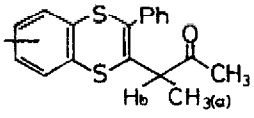
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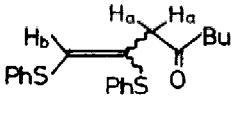
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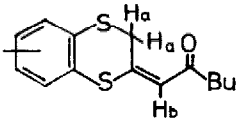
9c-2

References and Notes

1) A part of this work was presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August, 1979.

2) Y. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaki, and N. Ikekawa, Tetrahedron Lett., 2023 (1979).

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7) Reactions of 1,1-dichloro-2-phenylsulfonylcyclopropanes with sodium alkoxide were reported. W. E. Parham, W. D. McKown, V. Nelson, S. Kajigaeshi, and N. Ishikawa, J. Org. Chem., 38, 1361 (1973).

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