

ALDOL REACTION OF IODODIFLUOROACETATE-Zn AND 2,2-DIFLUOROKETENE SILYL ACETAL¹

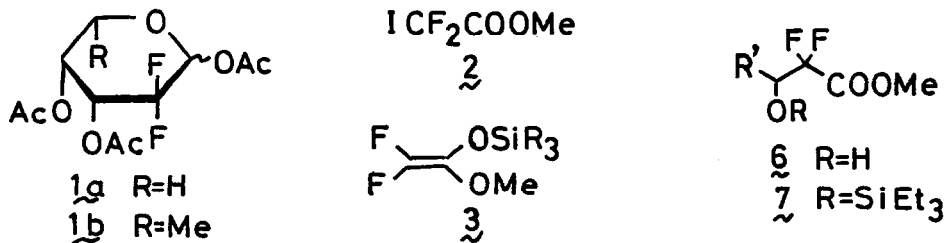
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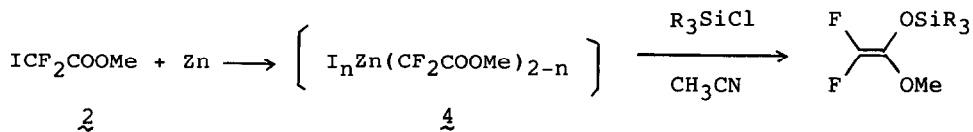
Summary: Generation of the Reformatsky reagent of difluoroacetate from the iodide(2) and the difluoroketene silyl acetal(3), and their aldol reaction are described. High anti-selectivity with chiral aldehyde (5d, 5f) was found in the case of the ketene silyl acetal(3b). 2,2-Difluoro-2-deoxy analogs of D-ribo- and L-galactopyranosides (1a, 1b) were effectively prepared.

Reformatsky reaction of bromodifluoroacetate was firstly reported by Fried² and its applications to the preparations of fluorinated biologically active compounds have been appeared.³⁻⁶ However, the nature of the reactive intermediate has not been fully clarified and the requirement of relatively high temperature for the generation of the reagent and its thermal instability led to the limitation of this reaction with respect to the yield and diastereoselectivity with chiral aldehydes.³⁻⁵

In our continuous efforts⁸ to explore new synthetic methods for the carbon chain extension reaction of difluoroacetate directed to the preparation of fluoro analogs of biologically important sugars, nucleosides and fatty acids, we have investigated aldol reaction using iododifluoroacetate (2). Herein, we report the generation and the nature of the zinc reagent(4) and the ketene silyl acetal(3), and their directed aldol reactions leading to the efficient preparations of 2-deoxy-2,2-difluoro sugar derivatives(1).



Reaction of the iodide (2) with zinc powder was carried out in various solvents to find out the optimized reactions condition for the generation of reactive intermediate by monitoring the ¹⁹F-nmr spectrum of the reaction mixture (Table 1) and the following reaction with benzaldehyde. In each solvent reaction of 2 with Zn completed within 5-10 min at 0°C to form to the reactive species along with the formation of the by-products, tetrafluorosuccinate and/or difluoroacetate. Among these CH₃CN was found the best solvent for the generation of reactive species and the following reaction with aldehydes. The reactive species were gradually decomposed at room temperature (80% of 4 decomposed within 2 h in CH₃CN) and at 80°C within a few minutes. Reaction of 4 formed as above with various aldehydes proceeded at room

Table 1 Reaction of 2 with Zn¹⁰

Solvent	<u>4</u> (%) ^a	(CF ₂ COOMe) ₂ ^a	HCF ₂ COOMe ^a
CH ₃ CN	75-85	10	5-7
THF	50-55	20	trace
Et ₂ O	0	40	—
1,4-dioxane	25	25	—
DMF	55	—	—
DME	21	17	18

3a R₃=Me₃3b R₃=Et₃3c R₃=tBu(Me)₂

a) estimated by ¹⁹F-nmr based on internal benzotrifluoride(BTF)

temperature to give the aldol product in good yields (Table 2). With (D)-glyceraldehyde acetonide anti-selectivity (syn/anti=1/1.8) was observed(run 5).^{3, 10}

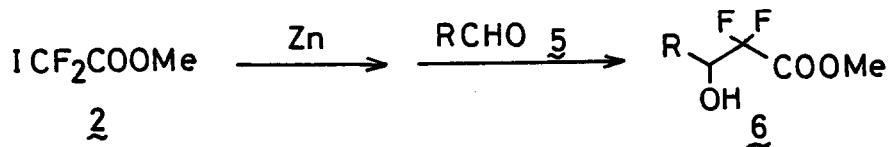
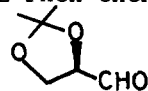


Table 2

Run	RCHO	Solvent	Time	Temp.	Yield (%)
1	PhCHO	THF	4 h	rt	<u>6a</u> 90
2	PhCH ₂ CH ₂ CHO	THF	2 h	rt	<u>6b</u> 68
3	PhCH ₂ CH ₂ CHO	CH ₃ CN	2 h	rt	<u>6b</u> 79
4	E-PhCH=CHCHO	CH ₃ CN	30 min	rt	<u>6c</u> 68
5		CH ₃ CN	2 h	0°C	<u>6d</u> 45 (syn/anti=1/1.8)

The disadvantage in the selectivity with chiral aldehyde was improved by using the ketene silyl acetal(3). The ketene silyl acetal(3) was effectively prepared in situ by the reaction of the zinc reagent(4) mentioned as above with silyl chloride in CH₃CN.¹⁰ The ketene silyl acetal(3) are extremely moisture sensitive and the thermal stability of 3 depends on the alkyl substituents of the silyl group. The TMS derivative(3a) is unstable even at room temperature as it completely decomposed after 24 h,¹³ while the triethyl(3b) or t-butyl dimethyl(3c) derivative is relatively stable. Results of the reactions of 3 with aldehydes are summarized in Table 3. With aldehydes triethylsilyl(TES) derivative (3b) afforded the O-silylated products(7) in good yield after the extractive workup and the subsequent flash column chromatography, while 3a gave the hydroxy compounds(6) in moderate yield. From the tlc analysis of the reaction of 3 with aldehyde, firstly aldehyde was consumed within a few minutes to form the hydroxy derivative(6), then the silylated product(7, 8) was gradually formed. Thus, the slow silyl group transfer was observed in the case of TBDMS derivative(3c,

run 7) and 3b with cyclohexanone giving the tertiary alcohol(run 4).

With both (*D*)-glyceraldehyde acetonide(run 5, 6) and 4-deoxy-*L*-threose acetonide¹⁴(run 8) high anti-selectivity was observed.⁹ The presence of zinc halide in the reaction mixture probably facilitates the aldol reaction and affects the selectivity.¹⁵

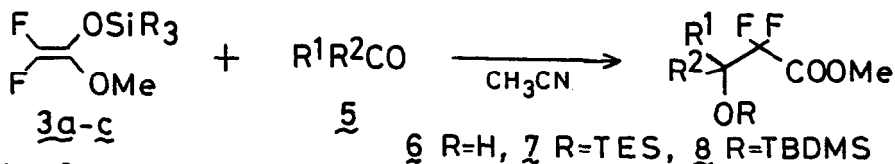

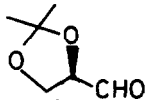
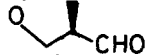
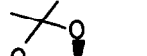
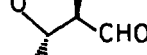
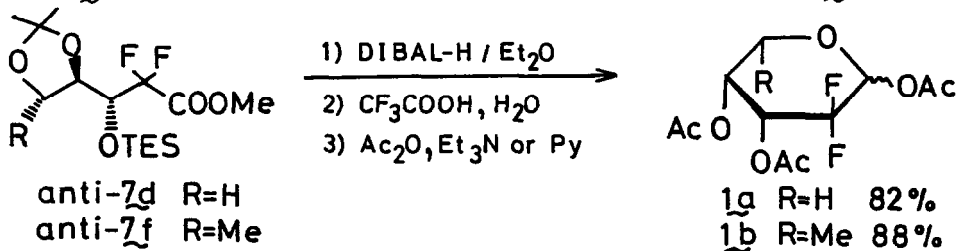


Table 3a

Run	R ¹ R ² CO	<u>3</u>	Time	Temp.	Product,	Yield(%)
1	PhCHO	<u>3b</u>	20 min	0 °C	<u>7a</u> R=TES	81
2	PhCH ₂ CH ₂ CHO	<u>3b</u>	20 min	0 °C	<u>7b</u> R=TES	77
3	PhCH ₂ CH ₂ CHO	<u>3a</u>	20 min	0 °C	<u>6b</u> R=H	59
4		<u>3b</u>	4 h	rt	<u>7e</u> R=TES 21, <u>6e</u> R=H 28	
5		<u>3a</u>	30 min	-20 °C	<u>6d</u> ^b R=H	46
6		<u>3b</u>	20 min	0 °C	<u>7d</u> ^c R=TES	74
7		<u>3c</u>	20 min	0 °C	<u>8d</u> R=TBDMS 8.5, <u>6d</u> R=H 58	
8		<u>3b</u>	40 min	0 °C	<u>7f</u> ^d R=TES	90

a) molar ratio, 2:Zn:R₃SiCl:R¹R²CO=2.2:2.4:2.2:1 b) syn/anti ratio=1/9 c) syn/anti ratio=1/9 d) syn/anti ratio=1/17

Triacetate form of 2,2-difluoro-2-deoxy-*D*-ribofuranoside(1a)⁷ was prepared by the following procedure. Reduction of anti-7d with DIBAL-H(Et₂O, -78 °C) followed by the deprotection(CF₃COOH-H₂O, rt, 2.5 h) and acetylation(Et₃N, Ac₂O, DMAP, 30 min) gave 1a in 82% yield(α/β ratio=4/1).⁹ In a similar way, triacetate of 2,2-difluoro-2,6-dideoxy-*L*-galactopyranoside(1b), an oxygen analog of daunosamine¹⁶ was obtained from anti-7f in 88% yield.¹⁷



In conclusion, an efficient preparation of the Reformatsky reagent(4) and difluoroketene silyl acetal(3) was achieved using the iodide(2) and their reaction with aldehyde or ketone gave the aldol product in good yield. High diastereoselectivity was found in the reaction of 3 with chiral aldehydes(5d, 5f).

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References and Notes

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- 8) T. Taguchi, O. Kitagawa, T. Morikawa, T. Nishiwaki, H. Uehara, H. Endo, and Y. Kobayashi, *Tetrahedron Lett.*, 27, 6103(1986).
- 9) Diastereomers were separated by flash column chromatography and the configuration of the aldol product was determined by converting to the sugar derivative. The structural determination of 1a was carried out by comparing the spectral data of 1a with those of the authentic sample.⁶
- 10) To Zn powder(4.8 mmol) in CH_3CN (3 ml) was added 2(4 mmol) in the same solvent(3 ml) dropwise during 5 min at 0°C. ¹⁹F-nmr spectrum of the reaction mixture showed two broad singlet peaks at -55.1 and -55.4 ppm in a ratio of ca 1:2 corresponding to the zinc reagent (4).^{11, 12} After being stirred for 10 min, the reaction mixture was treated with chlorotriethylsilane(4.4 mmol) for 5 min to form 3b(¹⁹F-nmr: -64.5 and -66.5 ppm, AB quartet, $J_{\text{F-F}}=103$ Hz) in 85-90% yield based on 2. When the three components(2, Zn and R_3SiCl) were stirred in acetonitrile, the dimer, tetrafluorosuccinate was the main product.
- 11) In ¹⁹F-nmr benzotrifluoride was used as internal standard.
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- 16) Chemical modification of anthracycline antibiotics with 2-fluoro-2,6-dideoxy-L-talose was reported; T. Tsuchiya, Y. Takagi, K. D. Ok, S. Umezawa, T. Takeuchi, N. Wako, H. Umezawa, *J. Antibiotics*, 29, 731(1986).
- 17) The major α -anomer of 1b was isolated as crystalline form, mp 128 C. $[\alpha]_{\text{D}} -127^\circ$ ($c=0.87$, CHCl_3), ¹H-nmr(400 MHz, CDCl_3) : 1.20(3H, d, $J=6.5$ Hz, 6-H), 2.10(3H, s), 2.17(3H, s), 2.18(3H, s), 4.31(1H, dq, $J=0.9$ and 6.5 Hz, 5-H), 5.3(1H, m, 4-H), 5.42(1H, ddd, $J=4$, 5.2 and 22.8 Hz, 3-H), 6.20(1H, d, $J=7.2$ Hz, 1-H); ¹⁹F-nmr(CDCl_3) -56.7(dd, $J=5.2$ and 22.8 Hz, axial-F) and -57.2(d, $J=7.2$ Hz, eq.-F).

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