Communications to the Editor

[Chem. Pharm. Bull. 33(11)5137—5140(1985)]

SYNTHESES OF β,β-DIFLUOROCARBOXYLIC ACID DERIVATIVES THROUGH THE CLAISEN REARRANGEMENT OF 1,1-DIFLUORO-1-ALKEN-3-OLS[1)]

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3,3-Difluoro-4-alkenoic esters (3) were obtained through the Claisen rearrangement of 1,1-difluoro-1-alken-3-ols (1) with ortho ester.

KEYWORDS ——— Claisen rearrangement; 1,1-difluoroethene; dibromodifluoromethane; trimethyl orthoacetate

The Claisen rearrangement is a powerful tool for the preparation of γ,δ-unsaturated carbonyl compounds which are useful intermediates in synthetic chemistry. A number of applications directed to the synthesis of the natural products have been reported.[2)]

Fluorine-modified bioactive compounds have been attracting attention recently because of their biological activities and usefulness in investigating the mechanism of the metabolism of parent compounds.[3)] Fluorinated fatty acids in which the hydrogen is replaced with fluorine to block metabolic oxidation, such as β-oxidation should be of considerable interest.[4)] A few reports have appeared dealing with the preparation of β,β-difluorocarboxylic acids, but these cannot always be considered as general methods for such compounds.[5)] Metcalf and his co-workers have recently reported one example of an ortho ester Claisen rearrangement of the difluoroallyl alcohol derived from 2,2-difluoro-1-tosyloxyvinyllithium and phenylacetaldehyde to give the β,β-difluoro ester.[6,7)] This prompted us to report here an efficient method for the synthesis of β,β-difluoro-γ,δ-unsaturated ester (3) through the ortho ester Claisen rearrangement of 1,1-difluoro-1-alken-3-ol (1) and its conversion to the β,β-difluoro acid (6) and β,β-difluoro-γ-keto acid (7).

1,1-Difluoro-1-alken-3-ols (1) were prepared as follows. Normant and his co-worker reported the generation of 2,2-difluorovinyllithium (CF_2=CH_2/sec-BuLi, THF-Et_2O, -100°C),[8)] which reacted with aldehydes to give the difluoroallyl alcohols (1a, 1b) in moderate yield. The instability of this lithium reagent and its reactivity toward substrates (nucleophilicity vs. basicity) limit its use for the preparation of 1 (Chart 1). In contrast, difluoromethylenation of α-acetoxyaldehydes or ketones with phosphonium ylid[9,10)] to give 2c-2e followed by saponification afforded 1c-1e in high yields. By this method, the 1,1-difluoro-1-alken-3-ols having alkyl substituent at the 2-position (1d and 1e) were also prepared (Chart 1). Alcohols 1 are quite sensitive to acid and heat, but stable in aqueous alkaline solution.

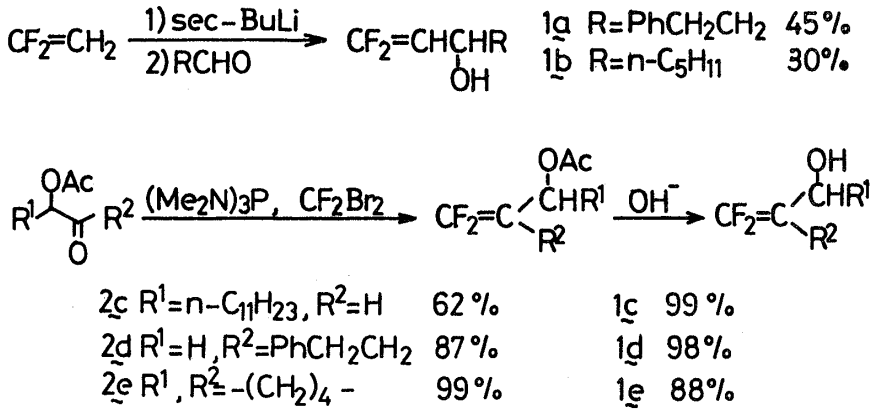


Chart 1

The β,β-difluoro-γ,δ-unsaturated esters (3) were obtained in good yields through the Claisen rearrangement of 1 with ortho esters. For example, the treatment of 1e (6.8 mmol) with trimethyl orthoacetate (10 ml) in the presence of a catalytic amount of propionic acid in boiling toluene for 5 h followed by column chromatography (SiO_2) gave the desired difluoro ester (3e) in 78% yield. In similar manner, the difluoroallyl alcohols (1a-1d) were smoothly rearranged to the corresponding unsaturated esters (3a-3d), as summarized in Table. As expected from the favourable conformation of the transition state for the Claisen rearrangement,[2] the geometry of the olefinic bond in the products (3a-3c) was assigned as the E-form from their NMR spectra.[11]

We attempted to carry out the rearrangement of silyl ketene acetal derived from the acetate or propionate of 1a, so-called Ireland-Claisen rearrangement, but we could not obtain the desired carboxylic acid (3, R^4=H).

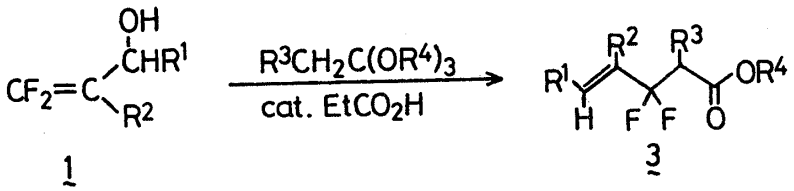
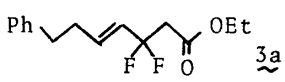
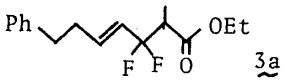
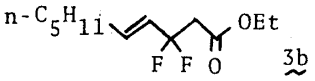
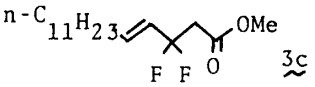
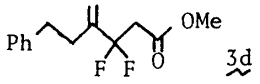
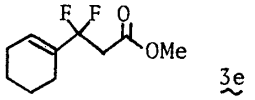


Chart 2

Table. Synthesis of β,β-Difluoro-γ,δ-unsaturated Ester (3) through the Claisen Rearrangement of 1 with Ortho Esters

Entry	Alcohol (1)	Ortho ester	Product (3)	Yield (%)
1	1a	$CH_3C(OEt)_3$	 3a	76
2	1a	$CH_3CH_2C(OEt)_3$	 3a'	69
3	1b	$CH_3C(OEt)_3$	 3b	37
4	1c	$CH_3C(OMe)_3$	 3c	60
5	1d	$CH_3C(OMe)_3$	 3d	72
6	1e	$CH_3C(OMe)_3$	 3e	78

Next, the potential utility of the unsaturated difluoro esters (3) for the preparation of β,β-difluoro acid (6) and β,β-difluoro-γ-keto acid (7) was investigated. Because of the facility of dehydrofluorination of 3,[14] this was achieved by the following procedure.

The saturated difluoro esters (4c and 4e) obtained in excellent yields by hydrogenation of 3c and 3e (H_2-10% Pd-C, EtOH, 2-3 atm) could be converted to the corresponding carboxylic acids (6c and 6e) via transesterification with benzyl alcohol (cat. p-TsOH, Benzene, reflux, 5h) followed by debenzylation (H_2-10% Pd-C, EtOH, 2-3 atm) as shown in Chart 3.

Conversion of 3d to the corresponding γ-keto acid (7d) was achieved by the same method as above after ozonolysis of the double bond. Thus, ozonolysis of 3d [O_3, CH_2Cl_2 at -78°C, then excess $(CH_3)_2S$] afforded the γ-keto ester (94% yield), which was in turn, transesterified with benzyl alcohol (cat. p-TsOH, benzene, reflux, 6h) followed by debenzylation (H_2-10% Pd-C, EtOH, 2-3 atm) in 85% yield (Chart 3).

In conclusion, the Claisen rearrangement of 1,1-difluoro-1-alken-3-ols (1) smoothly proceeded to give the unsaturated difluoro ester (3) in a good yield. This provides a new entry for the synthesis of fluorinated compounds owing to its functionality.

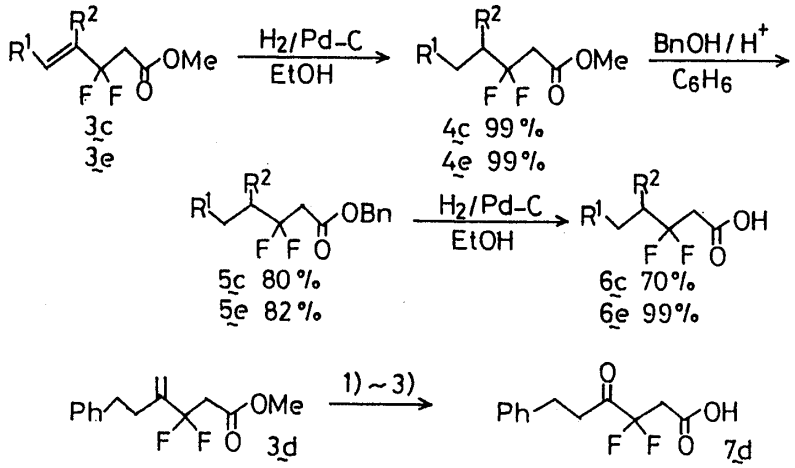


Chart 3

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2) P. A. Bartlett, Tetrahedron, 36, 2 (1980).
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11) 2a: ^{1}H-NMR(CCl_4) δ: 1.23 (3H, t, J=7 Hz), 2.17-2.90 (4H, m), 2.87 (2H, t, J_{H-F}=15 Hz), 4.10(2H, q, J=7 Hz), 5.70(1H, dt, J=16 and 10 Hz, -CH=CHCF$_2$-), 6.15 (1H, dtt, J=16, 6 and 2 Hz, -CH=CHCF$_2$). ^{19}F-NMR(CCl_4) +28.3 ppm (dt, J=10 and 15 Hz).[12]
12) Benzotrifluoride was used as the internal standard. + means high field.
13) R. E. Ireland and R. H. Mueller, J. Am. Chem. Soc., 94, 5897 (1972).
14) Under basic conditions (K_2CO_3-MeOH or DBU-benzene e.g.) dehydrofluorination of 3 occurred easily to give the 3-fluoro-2,4-dienoate. Hydrolysis of 3 under acidic conditions or treatment of 3 with trimethylsilyl iodide gave a complex mixture.

(Received September 3, 1985)