CHEMISTRY LETTERS, pp. 2167-2170, 1994.

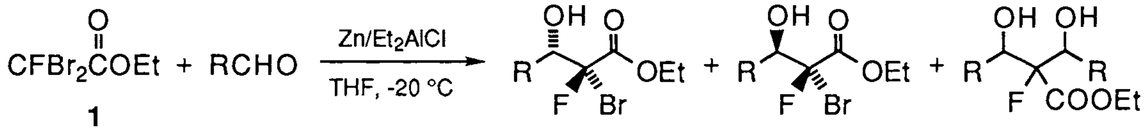
Zinc-Diethylaluminium Chloride Induced Coupling Reaction of Dibromofluoroacetate with Carbonyl Compounds. New Efficient and Selective Synthesis of α-Bromo-α-fluoro-β-hydroxy and α-Fluoro-β,β'-dihydroxy Esters[1)]

Takashi ISHIHARA,* Takayuki MATSUDA, Katsunori IMURA,
Hirofumi MATSUI, and Hiroki YAMANAKA
Department of Chemistry and Materials Technology, Kyoto Institute of Technology,
Matsugasaki, Sakyo-ku, Kyoto 606

Treatment of ethyl dibromofluoroacetate with aldehydes or ketone in the presence of zinc and diethylaluminium chloride at -20 °C gave rise to the corresponding α-bromo-α-fluoro-β-hydroxy alkanoic acid ethyl esters in good yields, while the use of two equivalents each of aldehyde, zinc, and diethylaluminium chloride in the reaction resulted in a double coupling reaction affording the 1:2 adducts, α-fluoro-β,β'-dihydroxy esters in high yields.

The Reformatsky reaction of α-halo esters with carbonyl compounds is one of the most important carbon-carbon bond forming reactions and has widely been applied for the synthesis of β-hydroxy alkanoic acid esters, which serve as a useful building block in constructing a variety of naturally occurring substances. Although a number of methods for the reactions of this type have been reported in the literature,[2)] little is known for the reaction between a di- or trihaloacetate and a carbonyl compound leading respectively to α-halo- or α,α-dihalo-β-hydroxy esters.[3)] To our best knowledge,[4)] there exist only two contributions, made by Castro *et al.*[3a)] and Fürstner,[3b)] that pertain to a classical or modified procedure for effecting successfully the Reformatsky reaction of dichloro-, dibromo-, or trichloroacetate.

This communication describes a new efficient and convenient method for the reductive coupling reaction of dibromofluoroacetate (**1**) with carbonyl compounds induced by zinc and diethylaluminium chloride,[5)] which provides us with the first promising approach for synthesizing selectively α-monofluorinated α-bromo-β-hydroxy (**2**) or β,β'-dihydroxy esters (**3**) in good yields.



1 **2** (erythro) **2** (threo) **3**

When ethyl dibromofluoroacetate (**1**) was allowed to react with butyraldehyde in the presence of zinc and diethylaluminium chloride in tetrahydrofuran (THF) at -20 °C for 1 h, the corresponding 1:1 adduct, α-bromo-α-fluoro-β-hydroxy hexanoic acid ethyl ester (**2b**),[7)] was obtained as a mixture of erythro and threo isomers[8,9)]

Table 1. Synthesis of Hydroxy Esters **2** *via* Coupling Reaction of **1** with Carbonyl Compounds

Entry	Carbonyl compd	Yield/%[a) of 2		Isomer ratio of **2** erythro : threo[b)	Yield/%[a) of **3**	
1	CH_3CH_2CHO	**2a**	63	66 : 34	**3a**	14
2	$CH_3CH_2CH_2CHO$	**2b**	69	67 : 33	**3b**	13
3	$(CH_3)_2CHCHO$	**2c**	70	67 : 33	**3c**	2
4	*c*-$C_6H_{11}CHO$	**2d**	67	63 : 37	**3d**	14
5	$CH_3CH=CHCHO$	**2e**	68	55 : 45	**3e**	19
6	C_6H_5CHO	**2f**	71	59 : 41	**3f**	8
7	*p*-$CH_3C_6H_4CHO$	**2g**	77	51 : 49	**3g**	3
8	*p*-$CH_3OC_6H_4CHO$	**2h**	74	52 : 48	**3h**	2
9	*p*-ClC_6H_4CHO	**2i**	66	63 : 37	**3i**	15
10	2-furaldehyde	**2j**	74	59 : 41	**3j**	10
11	$CH_3CH_2COCH_2CH_3$	**2k**	49	–	**4k**	(15)[c)

a) Yields refer to analytically pure products isolated by column chromatography. b) The isomer ratios were determined by ^{19}F NMR. c) The figure in parentheses stands for the yield of ethyl (*Z*)-3-ethyl-2-fluoro-2-pentenoate (**4k**).

in 69% yield, together with a small amount of the 1:2 adduct, α-fluoro-β,β'-dihydroxy ester **3b**[7) (13%). Diethylaluminium chloride was essential for the reaction to proceed cleanly. The absence of this Lewis acid led to the formation of substantial amounts of by-products including diethyl difluorofumarate and difluoromaleate,[7) and the yield of the adduct **2b** became low (36%). Other Lewis acids, such as triethylaluminium and boron trifluoride diethyl etherate, were much less satisfactory than diethylaluminium chloride. The reaction carried out below -20 °C (at -30 or -50 °C) took place very sluggishly, whereas the reaction at temperatures higher than -20 °C resulted in the formation of **3b** (30%), while **2b** was formed in 32% yield. THF was a favored solvent of the reaction. The use of diethyl ether or benzene caused no reaction, and the starting acetate **1** was recovered unchanged.

The following procedure is representative for the coupling reaction of **1** with carbonyl compounds.[11) Diethylaluminium chloride (1.1 equiv., a 1.0 mol dm^{-3} hexane solution) and a carbonyl compound (1.1 equiv.) were sequentially introduced into a stirred suspension of zinc dust (1.2 equiv.) in THF at -20 °C under argon. To this mixture was added dropwise a solution of **1** in THF at such a rate that the reaction temperature dose not rise above -15 °C. After stirring for 1 h at -20 °C, the reaction mixture was hydrolyzed with cold 10% HCl and saturated NH_4Cl solutions and then was extracted with diethyl ether. The extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel by successive use of hexane-EtOAc (2 : 1) and EtOAc to obtain β-hydroxy ester **2**[7) and β,β'-dihydroxy ester **3**.[7) The results of these reactions are summarized in Table 1.

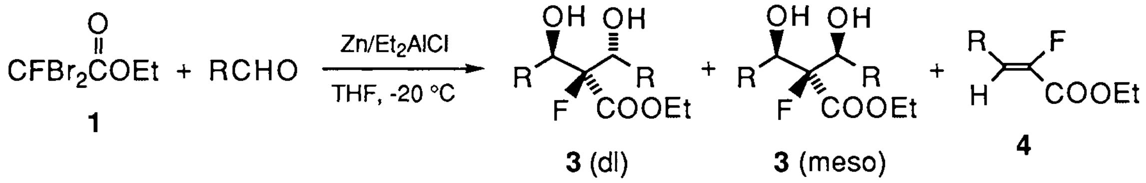
Various aliphatic (Entries 1-4) and aromatic aldehydes (Entries 6-10) including α,β-unsaturated aldehyde (Entry 5) could participate nicely in the reaction to afford the expected adducts, α-bromo-α-fluoro-β-hydroxy esters **2a-j**, in good yields as a diastereomeric mixture. Their erythro to threo ratios range from 51/49 to 67/33.

Table 2. Synthesis of Dihydroxy Esters **3** through Coupling Reaction of **1** with Aldehydes

Entry	Aldehyde	Time/h	Yield/%[a] of 3		Isomer ratio of 3 dl : meso[b]	Yield/%[a] of 4	
12	CH_3CH_2CHO	3	**3a**	73	63 : 37	**4a**	14
13	$CH_3CH_2CH_2CHO$	3	**3b**	79	64 : 36	**4b**	12
14	$(CH_3)_2CHCHO$	3	**3c**	77	66 : 34	**4c**	10
15	$CH_3CH{=}CHCHO$	2	**3e**	76	56 : 44	**4e**	15
16	C_6H_5CHO	2	**3f**	79	64 : 36	**4f**	20
17	*p*-$CH_3C_6H_4CHO$	2	**3g**	74	61 : 39	**4g**	17
18	*p*-$CH_3OC_6H_4CHO$	2	**3h**	73	66 : 34	**4h**	14
19	*p*-ClC_6H_4CHO	2	**3i**	70	57 : 43	**4i**	20

a) Yields are of pure products isolated by column chromatography. b) The isomer ratios were measured by ^{19}F NMR.

The coupling reaction with a ketone such as 3-pentanone (Entry 11) also occurred to give the corresponding adduct **2k** in moderate yield, along with 15% yield of ethyl (Z)-3-ethyl-2-fluoro-2-pentenoate (**4k**),[7] no dihydroxy ester **3k** being produced at all. It may be noted that, while the present reaction was accompanied by the formation of small portions (2-19%) of dihydroxy esters **3a**-**j** or α-fluoro-α,β-unsaturated ester **4k**, these side products were easily removed by column chromatography.



It was found, moreover, that simple change in a molar ratio of the reagents made it possible to produce dihydroxy esters **3** predominantly. Thus, on treating **1** with aldehydes (2.1 equiv.) in the presence of zinc (2.1 equiv.) and diethylaluminium chloride (2.1 equiv.) at -20 °C for 2 or 3 h, the corresponding 1:2 adducts **3**[7] were given as a mixture of two diastereoisomers (dl : meso = 56/44 to 66/34) in high yields and (Z)-α-fluoro-α,β-unsaturated esters **4**[7] were formed in less than 20% yield as a sole by-product (Table 2).

Interestingly, the monitoring of the reaction between **1** and zinc (1.2 equiv.) without carbonyl compound by ^{19}F NMR indicated that the resonance due to **1** at δ 12.3 (downfield from external trifluoroacetic acid (TFA)) disappeared and a new resonance appeared at δ -61.0. Hydrolysis of this mixture with deuterium oxide (D_2O) offered ethyl deuteriobromofluoroacetate.[7,12] Similarly, treatment of **1** with 2 equiv. of zinc followed by quenching with D_2O gave ethyl dideuteriofluoroacetate.[7,12] These facts strongly suggest that the former and the latter reaction would involve an intermediary monometallated and dimetallated[5a] species, respectively, though their exact structures are unclear at the present stage.

In summary, the Reformatsky-type aldol reaction of dibromofluoroacetate (**1**) with various carbonyl compounds has been shown to proceed efficiently under the influence of zinc and diethylaluminium chloride.

The present reaction will constitute an effective and practical synthetic method for α-fluorinated β-hydroxy **2** or β,β'-dihydroxy esters **3**, which are hard to obtain by other methods.

References

1) Presented in part at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, August 1994, Abstr. No. 1P-49.
2) a) M. W. Rathke, *Org. React.*, **22**, 423 (1975); b) A. Fürstner, *Synthesis*, **1989**, 571.
3) a) B. Castro, J. Villieras, and N. Ferracutti, *Bull. Soc. Chim. Fr.*, **1969**, 3521; b) A. Fürstner, *J. Organomet. Chem.*, **336**, C33 (1987); c) for the reaction of α,α-dibromo ketones, A. Takahashi and M. Shibasaki, *J. Org. Chem.*, **53**, 1227 (1988).
4) Fluorine-containing haloacetates are shown to undergo the Reformatsky reaction giving α-fluorinated β-hydroxy alkanoates. For the reactions of bromofluoroacetates, see: E. T. McBee, O. R. Pierce, and D. L. Christman, *J. Am. Chem. Soc.*, **77**, 1581 (1955); S. Brandänge, O. Dahlman, and L. Mörch, *ibid.*, **103**, 4452 (1981). For the reactions of chloro-, bromo-, or iododifluoroacetates and of related carbonyl compounds, see: E. A. Hallinan and J. Fried, *Tetrahedron Lett.*, **25**, 2301 (1984); T. Yokozawa, N. Ishikawa, and T. Nakai, *Chem. Lett.*, **1987**, 1971; R. W. Lang and B. Schaub, *Tetrahedron Lett.*, **29**, 2943 (1988); O. Kitagawa, T. Taguchi, and Y. Kobayashi, *ibid.*, **29**, 1803 (1988); M. Kuroboshi and T. Ishihara, *Bull. Chem. Soc. Jpn.*, **63**, 428 (1990); T. Tsukamoto and T. Kitazume, *J. Chem. Soc., Chem. Commun.*, **1992**, 540; T. T. Curran, *J. Org. Chem.*, **58**, 6360 (1993), and references cited therein.
5) It has been reported that the coupling reaction of polyhaloacetates with carbonyl compounds in the presence of zinc-diethylaluminium chloride leads to the exclusive formation of α,β-unsaturated esters.[6] See: a) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **53**, 1698 (1980); b) A. R. Daniewski and W. Wojciechowska, *J. Org. Chem.*, **47**, 2993 (1982), and see also Ref. 2b.
6) For the related reactions of polyfluorohalo esters, see: T. Ishihara and M. Kuroboshi, *Chem. Lett.*, **1987**, 1145; T. Allmendinger and R. W. Lang, *Tetrahedron Lett.*, **32**, 339 (1991).
7) Spectroscopic and analytical data of the products were in good accord with the assigned structures.
8) The relative stereochemical nomenclature proposed by Noyori *et al.* is applied in this work. See: R. Noyori, I. Ishida, and J. Sakata, *J. Am. Chem. Soc.*, **105**, 1598 (1983).
9) The configurational assignment of the products **2** or **3** was made on the basis of the relative magnitudes of vicinal hydrogen-fluorine couplings.[10] For instance, ^{1}H NMR ($CDCl_3$) of the acetonide derived from **2f** (erythro : threo = 59 : 41): δ 1.46 (br s, 6H x 2), 3.4-4.4 (m, 2H x 2), 4.77 (d, J = 8.0 Hz, 1H) for the erythro isomer, 4.91 (d, J = 24.0 Hz, 1H) for the threo isomer, 7.1-7.4 (br s, 5H x 2).
10) T. Yamazaki, T. Yamamoto, and T. Kitazume, *J. Org. Chem.*, **54**, 83 (1989); M. Kuroboshi and T. Ishihara, *Bull. Chem. Soc. Jpn.*, **63**, 1191 (1990); T. Ishihara, M. Kuroboshi, K. Yamaguchi, and Y. Okada, *J. Org. Chem.*, **55**, 3107 (1990).
11) The reaction procedure could be applied to a large-scale (10 mmol) preparation. Zinc dust was washed sequentially with 10% HCl, methanol, and diethyl ether, and was dried under vacuum.
12) ^{19}F NMR data (from external TFA): CDFBrCOOEt (47%) δ -73.0 (t, J = 6.8 Hz); $CD_2FCOOEt$ (57%) δ -154.0 (quint, J = 7.5 Hz). For comparison, CHFBrCOOEt δ -72.0 (d, J = 46.9 Hz); $CH_2FCOOEt$ δ -152.5 (t, J = 47.1 Hz).

(Received August 26, 1994)