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THE REFORMATSKY REACTION OF BROMODIFLUOROMETHYLACETYLENE DERIVATIVES: APPLICATION TO THE SYNTHESIS OF FLUORINATED BIOACTIVE COMPOUNDS

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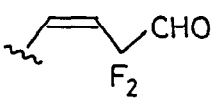
Summary: The Reformatsky reaction of bromodifluoromethylacetylene derivatives with aldehydes gave fluorinated homopropargylic alcohols. The adducts obtained from D-glyceraldehyde acetonide were converted to 2,2-difluoro-2-deoxy-D-ribose and intermediates to fluorinated arachidonic acid and its metabolite.

The introduction of fluorine(s) to biologically active compounds and biological testing of the fluorinated analogs are carried out widely in the fields of organic fluorine and medicinal chemistry.[1] In our recent studies on the fluorinated analogs of unsaturated fatty acids and their metabolites,[2] it was necessary to prepare α,α-difluoro-β,γ-cis-olefinic compound (1) as a key intermediate. In this context, we report the results of Reformatsky reactions of bromodifluoromethylacetylene compounds (2)[3] and how these reactions can be used for the synthesis of fluorinated bioactive compounds. The introduction of a difluoromethylene group using a fluorinated building block has been reported by several research groups.[4] To our knowledge, no paper has been published on a reaction of the fluorinated propargyl system such as 2 with aldehydes. Compounds (2) were prepared by reactions of dibromodifluoromethane with lithium acetylide derivatives following Wakselman's procedure.[5]



1

$RC{\equiv}CCF_2Br$

2

R: Ph[5], nC_5H_{11}, Et_3Si

When bromides (2) were treated with zinc powder in THF, the dimers of 2 were obtained as the sole products in all cases. Each was found to have the structure of a symmetrical diacetylenic compound.[6] Dimers were formed even

when the reaction mixture was quenched at low temperature and none of the reduced product could be isolated. On treating 2 with an aldehyde at higher temperature (40° C-reflux) in the presence of zinc, a complex mixture was obtained. Thus, compound (2) was slowly added to a mixture of zinc and aldehyde at 0°C under argon atmosphere.[7)]

Table I

$$R^1C{\equiv}CCF_2Br \quad (2) \quad + \quad R^2CHO \xrightarrow{Zn^{d)}} R^1C{\equiv}CCF_2\underset{OH}{\underset{|}{CH}}\text{-}R^2 \quad (3)^{e)}$$

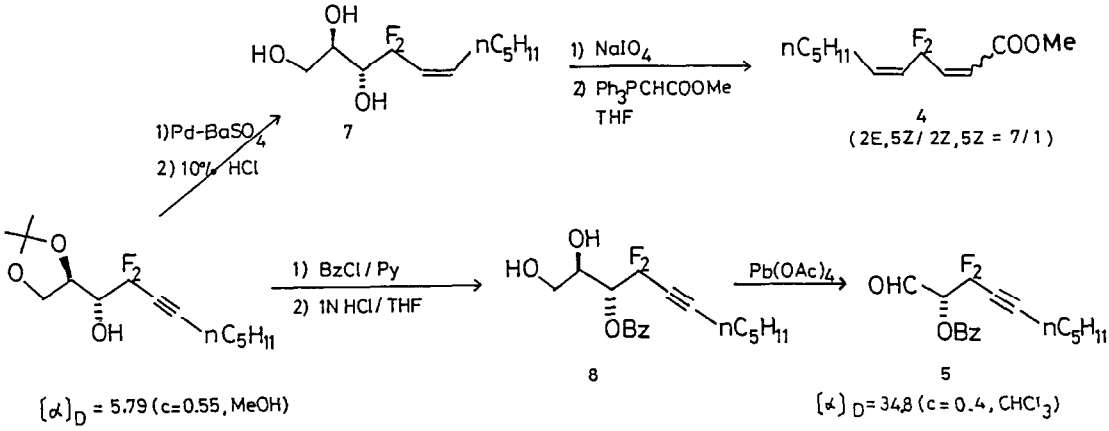
Entry	R^1	R^2CHO	Yield (%)[a)]
1	Ph	PhCHO	78
2	Ph	$PhCH_2CH_2CHO$	82
3	Ph	D-glyceraldehyde acetonide	78[b)]*
4	$n\text{-}C_5H_{11}$	PhCHO	38
5	$n\text{-}C_5H_{11}$	D-glyceraldehyde acetonide	50[c)]*
6	$n\text{-}C_5H_{11}$	$THPOCH_2CH{=}CHCHO$	35
7	Et_3Si	$PhCH_2CH_2CHO$	47

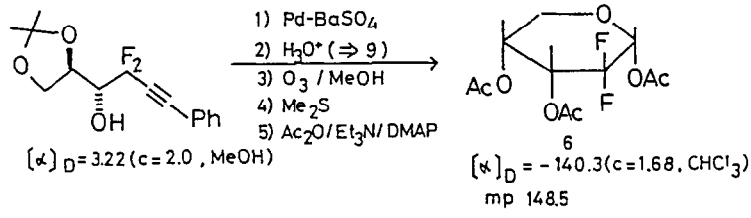
a) Yields refer to the isolated. b) syn/anti ratio = 1/2
c) syn/anti ratio = 1/3 d) activated with $HgCl_2$ (5 mol %)
e) Dimer ($RC{\equiv}CCF_2CF_2C{\equiv}CR$) can be isolated as a minor product.
* Diastereomers were separated by flash column chromatography and the configuration of each isomer was determined by converting to the sugar derivative. See ref. 10.

In a typical reaction, bromodifluoromethylphenylacetylene (1 mmol) in THF (1 ml) was added slowly to a mixture of benzaldehyde (1 mmol) and Zn (3 mmol) activated with $HgCl_2$(5 mol %) in THF (3 ml) at 0°C.[7)] The resulting mixture was stirred for 4 hr at the same temperature. After the usual work-up, the crude product was purified by flash column chromatography on silica gel to give the adduct (78%). ^{1}H-NMR ($CDCl_3$) ; 2.9 (bs, 1H, OH), 4.98 (t, J=9Hz, 1H, CHOH), 7.1-7.6 (m, 10H, Ar-H). ^{19}F-NMR ($CDCl_3$) ppm; 28.7. IR ($CHCl_3$) ; 3300, 2210 cm^{-1}. MS; m/e 258 (M^+).

Using products (3) (entry 3 and 5), we prepared difluoromethylene-containing unsaturated compounds (4 and 5) and 2,2-difluoro-2-deoxy-D-ribose (6).[8)] Partial hydrogenation (Pd-$BaSO_4$ poisoned with quinoline, MeOH) of the triple bond of the syn (or anti) adduct (entry 5) and removal of isopropylidene group (10% HCl, MeOH) gave triol (7) in 73% yield. Treatment of 7 with sodium metaperiodate in aq. methanol followed by reaction of the crude product with Wittig reagent in THF gave 1,4-diene derivatives (4) in 64% yield (2E,5Z/2Z,5Z=7/1). This result confirmed the formation and high reactivity of the aldehyde (1). On the other hand, protection (BzCl/Py, 0°C) of the anti adduct (entry 5) and the following deprotection of the acetonide group (1N HCl/THF, 40°C) gave a protected diol (8), which was converted to α-

hydroxyaldehyde derivative (5) ($PbOAc_4/CH_2Cl_2$, -40°C). The compound (5) is a fluoro analog of the key intermediate to 12-hydroxyeicosatetraenoic acid (12-HETE),[9] one of the metabolites of the arachidonic acid. Triacetate of 2,2-difluoro-2-deoxy-D-ribose (6) was prepared from anti adduct (entry 3)[10] in the following way. Partial reduction of the triple bond and removal of isopropylidene group (10% HCl, MeOH) gave triol (9) in 61 % yield. Successive ozonolysis and reduction by dimethylsulfide of 9 and acetylation (Ac_2O/Et_3N/DMAP) of the crude product gave 6 in 37 % yield.





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6) $RC{\equiv}CCF_2CF_2C{\equiv}CR$
All new compounds were identified by NMR (^1H, ^{13}C, ^{19}F), IR and mass spectra. In ^{19}F-NMR, chemical shifts were presented in ppm upfield from external benzotrifluoride signal.

7) To avoid the formation of the diacetylenic dimer, we used slow-addition method (0.025-0.05ml/min.)

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10) From the syn-isomer (entry 3) 2,2-difluoro-2-deoxy-D-xylose was prepared in triacetate form (54 %, overall yield). ^1H-NMR ($CDCl_3$) : 2.01 (s, 3H, Me), 2.13 (s, 3H, Me), 2.17 (s, 3H, Me), 3.69 (t, 1H, J=11Hz, 5-H), 3.97 (dd, 1H, J=11Hz and 5.7Hz, 5-H), 5.11 (ddd, 1H, J=11Hz, 11Hz and 5.7Hz, 4-H), 5.52 (m, 1H, 3-H), 6.08 (t, 1H, J=3.4Hz, 1-H). ^{13}C-NMR ($CDCl_3$)ppm: 20.34, 20.42, 20.53, 60.8, 67.58, 68.34, 89.04, 114.58, 161.86, 169.37, 169.45. $[\alpha]_D$=89.21 (C=1.81, $CHCl_3$).

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