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2,2-DIFLUORO-3-HYDROXYESTERS BY REFORMATSKII REACTION

E. Ann Hallinan and Josef Fried*
Department of Chemistry, The University of Chicago
Chicago, IL 60637

Summary: Ethyl bromodifluoroacetate undergoes facile Reformatskii addition to aldehydes and ketones to form 2,2-difluoro-3-hydroxyesters.

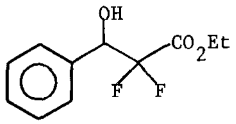
The application of the Reformatskii reaction to prepare α-fluoro-β-hydroxyesters was first described by McBee et al.,[1] Most recently this procedure was successfully applied to a protected carbohydrate ketone.[2] In need of a procedure for the preparation of the presently difficultly accessible 2,2-difluoro-3-hydroxyesters we have successfully extended this reaction to the commercially available ethyl bromodifluoroacetate. Both the classical one step[3] and two step procedures[3,4] could be used with both aldehydes and ketones. Ethyl bromodifluoroacetate reacted vigorously with activated zinc dust[5] in THF or toluene and furnished the desired products in good to excellent yield. We prefer the two step procedure for sensitive and precious substrates, since it requires lower temperature and can be carried out in titrimetric fashion. The following experimental conditions are typical of the two variants of the reaction:

One Step Procedure: To a refluxing suspension of 85 mg (1.3 mg-atom) of freshly activated Zn dust[6] in 1.0 ml of dry THF was added a solution of 223 mg (1.1 mmol) of ethyl bromodifluoroacetate[7] and 1 mmol of the aldehyde or ketone in 1.0 ml THF at a rate so as to maintain vigorous reflux. After 30 min the reaction mixture was cooled, quenched by the addition of ethyl acetate, brine and 1 M $KHSO_4$, and the organic layer dried, evaporated and purified by flash chromatography.

Ethyl 2,2-difluoro-3-hydroxy-3-phenylpropionate (1): oil; Rf 0.20 (20% EtOAc/hexane); yield 57%; ^{1}H-NMR: δ 7.76 (m), 5.19 (oct, J=15,9,6 CHOH), 2.82 (d, J=6, OH), 4.13 (q), 1.33 (t) (OC_2H_5); ^{19}F-NMR: $\delta CFCl_3$ 112.4[8] (dd, J_{FF}=262.2, J_{HF}=8.7), 121.0 (dd, J_{HF}=16.3); m/z: 230 (3%, M^+), 213 (1.5%, M-OH), 185 (1.0%, M-OC_2H_5); Anal. C, 57.64; H, 5.53; F, 15.81.

Ethyl 2,2-difluoro-2-(1'-hydroxy-1'-cyclohexyl) acetate (2): oil; Rf 0.38 (CH_2Cl_2); yield 72%, ^{1}H-NMR: δ 2.03 (broad d), 1,72 (m) 1.65 (m) 1.56 (m) $(CH_2)_5$, 4.34 (q) 1.34 (t) OC_2H_5; ^{19}F-NMR: $\delta CFCl_3$ 119.3 (s); m/z: 222 (1%, M^+), 223 (3%, M+1), 205 (6%, M-OH). 177 (2%, M-OC_2H_5).

Ethyl 2,2-difluoro-3-hydroxyoctanoate (3): oil, Rf 0.42 (CH_2Cl_2), yield 35%; ^{1}H-NMR: δ 4.03 (m, CHOH), 1.67 (m) (CH_2), 0.90 (t, CH_3), 4.46 (q) 1.36 (t) OC_2H_5; ^{19}F-NMR: $\delta CFCl_3$ 113.6 (dd, J_{FF}=262.2, J_{HF}=5.8), 123.0 (dd, J_{HF}=15.4; m/z: 224 (14%, M^+), 225 (25%, M+1, 206 (2%, M-H_2O).



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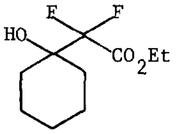

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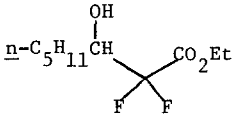

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Two Step Procedure: Freshly etched zinc dust (1.2 mg-atom) was allowed to react with 1.2 mmole of ethyl bromodifluoroacetate in 2 ml of dry THF at reflux. After the reaction had started (ca 1 to 2 min) the aldehyde or ketone (1 mmole) was added by addition funnel.[9] After 15 min of reflux the mixture was checked for completeness of reaction. If incomplete, additional zinc bromoester adduct was added. Yield of 1, 78%.

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References:

1. McBee, E. T.; Pierce, O. R.; Christman, D. L. J. Am. Chem. Soc. 1955, 77, 1581.
2. Brandänge, S.; Dahlman, D.; Mörch, L. J. Am. Chem. Soc. 1981, 103, 4452.
3. M. W. Rathke. Org. React. 1975, 22, 423.
4. Siegel, A.; Keckeis, H. Monatsh. 1953, 84, 901.
5. It is interesting to note that perfluoroalkyl bromides and iodides readily form alkyl zinc halides in donor solvents, which are powerfully stabilized by solvation. Cf. Miller, Jr., W. T.; Bergman, E.; Fainberg, A. H. J. Am. Chem. Soc. 1957, 79, 4159. and references cited therein.
6. Frankenfeld, J. W.; Werner, J. J. J. Org. Chem. 1969, 34, 3689.
7. Purchased from PCR Inc.
8. Upfield from $CFCl_3$.
9. The early addition of the carbonyl compound is essential since 15 min reflux is sufficient to decompose the organometallic reagent.

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