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Reformatsky Reaction of Methyl 2-Bromo-3,3,3-trifluoropropanoate. A Synthetic Method for α-Trifluoromethyl-β-hydroxy Esters

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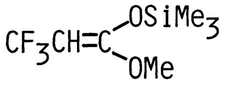
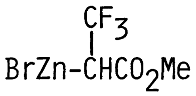
The Reformatsky reagent, prepared from the title bromo-ester and zinc powder in dioxane, is found to be thermally stable enough to undergo addition reactions with aldehydes to afford the α-trifluoromethyl-β-hydroxy esters in high yields. The unique reactivity of the fluorinated zinc reagent is discussed.

In view of the central role of enolate chemistry in organic synthesis, an α-trifluoromethyl(CF_3)-ester enolate should serve as a versatile building block for otherwise difficult preparations of a variety of CF_3-containing compounds which have currently received much interest because of their possible biological activities.[1)] However, such lithium enolates are extremely labile and undergo facile defluorination prior to trapping.[2)] In previous papers[2,3)] we have reported that the ketene silyl acetal (**1**) of methyl 3,3,3-trifluoropropanoate can serve as an α-CF_3-ester enolate equivalent in the Lewis acid-promoted reaction with acetals and acid chlorides and also in the Claisen rearrangement. Unfortunately, however, the reagent **1** is not reactive enough to undergo addition reactions with aldehydes except for benzaldehyde. Herein we wish to report the successful generation of the Reformatsky reagent (**2**) from methyl 2-bromo-3,3,3-trifluoropropanoate (**3**)[4,5)] which is capable of undergoing addition reactions with a variety of aldehydes to afford the corresponding α-CF_3-β-hydroxy esters (**4**) in high yields.



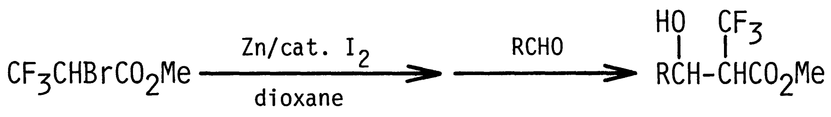
$CF_3CH{=}C(OSiMe_3)(OMe)$

1



$BrZn\text{-}CH(CF_3)CO_2Me$

2



$$CF_3CHBrCO_2Me \xrightarrow[\text{dioxane}]{\text{Zn/cat. } I_2} \xrightarrow{\text{RCHO}} RCH(OH)\text{-}CH(CF_3)CO_2Me$$

3 **4**

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In order to establish the opitimal conditions for generating this particular Reformatsky reagent, we first studied the reaction with benzaldehyde using the various procedures which have currently been recommended for the ordinary (non-fluorinated) Reformatsky reactions. Some of the results thus obtained are shown in Table 1. We found that the fluorinated Reformatsky reagent **2** was best generated using dioxane as the solvent and a catalytic amount of iodine (entry 4). Particularly noteworthy is that use of a mixture of tetrahydrofurane (THF) and trimethylborate as the solvent, which have been claimed as one of the best choice for the ordinary Reformatsky reactions,6) results in a considerable extent of defluorination (entry 2).

Table 1. The Reformatsky Reaction of **3** with Benzaldehyde

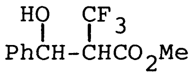
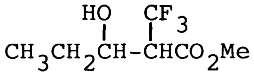
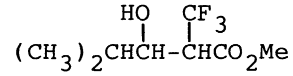
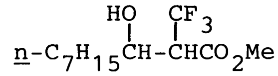
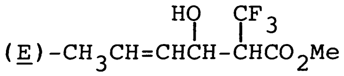
Entry	Conditions	^{19}F NMR Yield of **4** (R=Ph)
1	benzene / r.t., 24 h6)	no reaction
2	THF-$(MeO)_3B$ / r.t., 24 h6)	defluorination
3	dioxane / cat. I_2 - ultrasound / r.t., 1 h7)	62%
4	dioxane / cat. I_2 / r.t., 15 h	71%

Molar ratio of **3** : benzaldehyde : zinc powder = 1 : 1 : 1.8.

With the optimized conditions in hand, we next carried out the Reformatsky reactions of methyl 2-bromo-3,3,3-trifluoropropanoate **3** with a variety of aldehydes. Thus, a solution of **3**, an aldehyde, and iodine (0.2 equiv.) in dioxane was added to zinc powder (activated by aqueous ammonium chloride8)) and stirring was continued for 6 h at ambient temperature. Quenching of the reaction mixture with hydrochloric acid followed by usual workup afforded the corresponding α-CF_3-β-hydroxyesters **4** in good yields (Table 2).

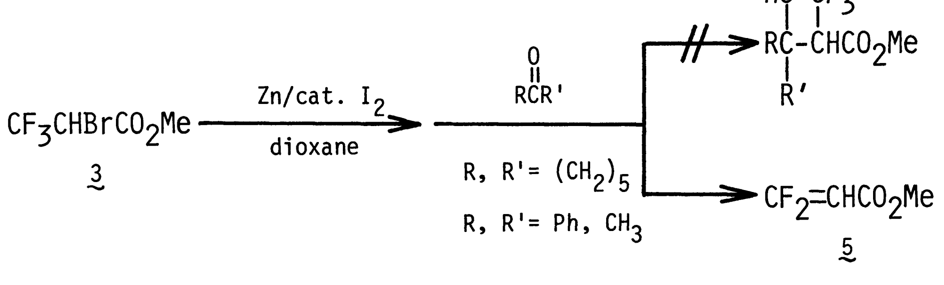
Inspection of results in the table reveals some characteristic features of this Reformatsky reaction. (1) The fluorinated Reformatsky reagent **2** is reactive enough to react with a variety of aldehydes, while the CF_3-ketene silyl acetal **1** does not react with aldehydes except for benzaldehyde.2) (2) The observed levels of diastereoselection are very low in analogy with the low stereoselectivities reported for the ordinary Reformatsky reactions.9) (3) The reaction with α,β-unsaturated aldehyde afforded only the 1,2-adduct in preference to the 1,4-adduct (entry 5).

Table 2. Reformatsky Reactions of 3 with Aldehydes

Entry	Aldehyde	Product[a)]	^{19}F NMR[b)] δ/ppm (J/Hz)	Yield/%[c)] (Diastereomeric ratio)[d)]
1	PhCHO	 $Ph\overset{\mathrm{HO}}{\overset{\mid}{C}}H-\overset{\mathrm{CF_3}}{\overset{\mid}{C}}HCO_2Me$	-13.4 (7.2) -14.0 (7.2)	76 (71 : 29)
2	CH_3CH_2CHO	 $CH_3CH_2\overset{\mathrm{HO}}{\overset{\mid}{C}}H-\overset{\mathrm{CF_3}}{\overset{\mid}{C}}HCO_2Me$	-12.9 (7.5) -14.5 (7.5)	71 (57 : 43)
3	$(CH_3)_2CHCHO$	 $(CH_3)_2CH\overset{\mathrm{HO}}{\overset{\mid}{C}}H-\overset{\mathrm{CF_3}}{\overset{\mid}{C}}HCO_2Me$	-13.0 (7.2) -15.1 (7.2)	66 (77 : 23)
4	n-$C_7H_{15}CHO$	 n-$C_7H_{15}\overset{\mathrm{HO}}{\overset{\mid}{C}}H-\overset{\mathrm{CF_3}}{\overset{\mid}{C}}HCO_2Me$	-10.8 (7.2) -14.8 (7.2)	79 (57 : 43)
5	(E)-$CH_3CH=CHCHO$	 (E)-$CH_3CH=CH\overset{\mathrm{HO}}{\overset{\mid}{C}}H-\overset{\mathrm{CF_3}}{\overset{\mid}{C}}HCO_2Me$	-13.4 (7.2) -14.4 (7.2)	55 (63 : 37)

a) All products exhibited spectral (NMR and IR) data in accord with the assigned structures. b) CF_3CO_2H as external standard; solvent, $CDCl_3$. c) Isolated yields based on aldehydes. d) Determined by ^{19}F NMR analysis.

Further, we attempted the Reformatsky reactions of 3 with ketones instead of aldehydes. Surprisingly, however, ketones did not react with the fluorinated Reformatsky reagent 2 under similar conditions but 2 underwent defluorination to give the methyl difluoroacrylate 5[10)] in *ca.* 55% yield. This fact shows that the reactivity of the fluorinated Reformatsky reagent 2 is much less reactive than the non-fluorinated counterpart which is capable of undergoing addition reactions both with aldehydes and ketones.[11)] Thus, the fluorinated Reformatsky reagent 2 may show a unique chemoselectivity in the competing reaction with aldehyde- and ketone-functionalities.



In summary, we have now described the successful generation of the trifluoromethylated Reformatsky reagent 2 which is capable of undergoing addition reactions with aldehydes without an appreciable extent of defluorination. Thus, this Reformatsky reaction could serve as a complementary synthetic method for a broad variety of α-CF_3-β-hydroxy esters which have not been obtainable via the CF_3-ketene silyl acetal methodology.

References

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4) The bromo-ester 3 was prepared in 82% yield from the ketene silyl acetal 1 and bromine by applying Reuss's procedure: R. H. Reuss and A. Hassner, J. Org. Chem., 39, 1785 (1974).
5) Bp 126 °C; IR (neat), 1760, 1255, 1115 cm^{-1}; ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H), δ -8.7 (d, J=6.6 Hz).
6) M. W. Rathke and A. Lindert, J. Org. Chem., 35, 3966 (1970).
7) B.-H. Han and P. Boudjouk, J. Org. Chem., 47, 5030 (1982).
8) F. A. J. Kerdesky, R. J. Ardecky, M. V. Lakshmikantham, and M. P. Cava, J. Am. Chem. Soc., 103, 1992 (1981).
9) J. Canceill, J. J. Basselier, and J. Jacques, Bull. Soc. Chim. Fr., 1967, 1024; J. Canceill and J. Jacques, ibid., 1970, 2180.
10) ^{19}F NMR (CH_2Cl_2, ext. CF_3CO_2H), δ -13.4 (dd, J=12.6 Hz and 22.5 Hz, 1F), -7.1 (dd, J=2.7 Hz and 12.6 Hz, 1F).
11) For general discussions of the reactivities of the ordinary Reformatsky reagents, see: M. Gaudemar, Organomet. Chem. Rev. Sect. A, 8, 183 (1972); M. W. Rathke, Org. React., 22, 423 (1975).

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