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Zinc(0)-Copper(I) Chloride Promoted Reaction of Methyl Dichlorofluoroacetate with Carbonyl Compounds. A New Efficient Method for the Synthesis of Methyl (_Z_)-α-Fluoro-α,β-unsaturated Carboxylates

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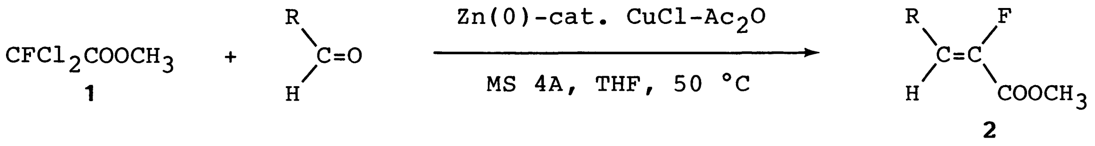
Methyl dichlorofluoroacetate, easily prepared from methyl trichloroacetate and antimony(III) fluoride, underwent the reductive coupling-elimination reaction with carbonyl compounds in the presence of zinc(0), a catalytic amount of copper(I) chloride, acetic anhydride, and molecular sieves to give the corresponding (_Z_)-α-fluoro-α,β-unsaturated carboxylic acid methyl esters in high yields.

α-Fluoro-α,β-unsaturated carboxylic acid esters are one of the most useful intermediates in organic transformations. Three types of methods have generally been employed for the preparation of these compounds: (1) The base-catalyzed condensation reaction of fluorooxalacetate or fluoroacetate with carbonyl compounds followed by dehydration,[1)] (2) the Wittig or Horner-Emmons reaction between alkoxycarbonylfluoromethylides and carbonyl compounds,[2)] and (3) the recently reported reaction of chloromalonic ester with carbonyl compounds using spray-dried potassium fluoride.[3)] In these methods, however, there exist several disadvantages such as the formation of self-condensation products, relatively low yields of the products, or low stereoselectivity.

In this communication is disclosed a zinc(0)-copper(I) chloride promoted reaction of methyl dichlorofluoroacetate, readily obtained by the fluorination of methyl trichloroacetate, with carbonyl compounds and acetic anhydride. The present reaction offers a novel efficient method for the stereoselective synthesis of (_Z_)-α-fluoro-α,β-unsaturated carboxylic acid esters.

$$CCl_3COOCH_3 \quad + \quad SbF_3 \quad \xrightarrow[120\text{-}130\ ^\circ C]{Br_2} \quad \underset{\mathbf{1}}{CFCl_2COOCH_3}$$

Methyl trichloroacetate was treated with finely divided antimony(III) fluoride and bromine at 120-130 °C to afford methyl dichlorofluoroacetate (**1**) in 65% isolated yield, together with a small amount (10% yield) of methyl chlorodifluoroacetate.[4)] When the above-obtained ester **1**[5)] was allowed to react with an aldehyde (1.2 equiv.) and acetic anhydride (1.2 equiv.) in the presence of zinc powder6) (3 equiv.), a catalytic amount (0.3 equiv.) of copper(I) chloride,7) and molecular sieves (MS 4A) in dry tetrahydrofuran (THF) at 50 °C, the corresponding methyl α-fluoro-α,β-unsaturated carboxylate (**2**) was obtained in good to excellent yield.8) Table 1 summarizes the results of the reaction and the coupling constants between a vinylic hydrogen and fluorine in **2**.



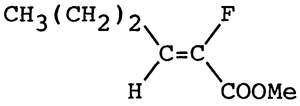
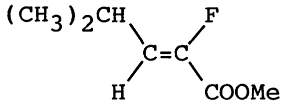
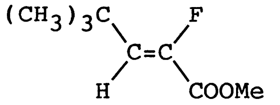
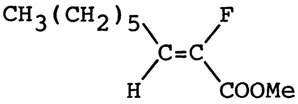
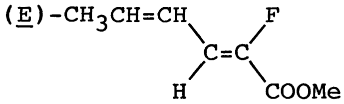
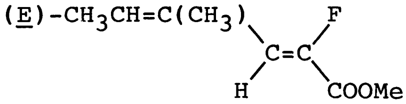
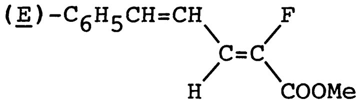
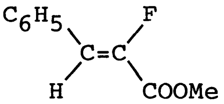
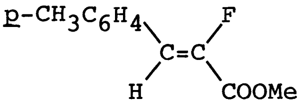
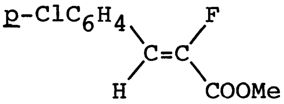
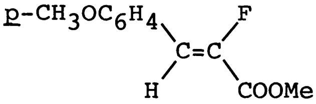
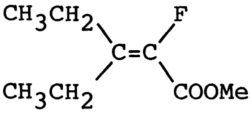
Benzene and *N*,*N*-dimethylformamide were also used as a solvent instead of THF. The absence of MS 4A resulted in the formation of the reduction product, or methyl chlorofluoroacetate, and other unidentified products. The addition of acetic anhydride was essential for making the reaction proceed cleanly:9) When the reaction of ester **1** with butyraldehyde or benzaldehyde was conducted without acetic anhydride in the presence of zinc(0), copper(I) chloride, and MS 4A in THF at 50 °C, a large quantity of β-hydroxy carboxylate was produced and the yield of the desired product **2** was substantially decreased.

As shown in Table 1, a variety of aliphatic and aromatic aldehydes smoothly reacted with **1** to give α-fluoro-α,β-unsaturated esters (**2**) in good yields. α,β-Unsaturated aldehydes, except for cinnamaldehyde, also underwent the reductive coupling-elimination reaction to afford the corresponding dienoic acid esters, no conjugative addition products being detected in the reaction mixture. It should be noted that hindered aldehyde such as pivalaldehyde efficiently reacted with **1**, giving a high yield of **2**. In contrast, the reaction of ketones as well as of cinnamaldehyde gave only low (20-40%) yields of the products, which could not be improved even by use of forced reaction conditions nor by adding a Lewis acid such as trimethyl borate and chlorodiethylaluminium.

Of much significance is that the present reaction preferentially affords (*Z*)-isomers of α-fluoro-α,β-unsaturated carboxylates. In particular, (*Z*)-isomers of **2** were formed exclusively in the case of aromatic aldehydes.

The representative procedure for the reaction is as follows. Acid-washed zinc powder (0.98 g, 15 mmol), copper(I) chloride (0.15 g, 1.5 mmol), MS 4A (ca. 1 g), and dry THF (18 mL) were placed in a flask flushed with argon. To the mixture were added butyraldehyde (0.43 g, 6.0 mmol) and acetic anhydride (0.61 g, 6.0 mmol) by use of a syringe. After this mixture had been heated to 50 °C, methyl ester **1** (0.8 g, 5.0 mmol) was added dropwise to it and the whole mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with diethyl ether (ca. 20 mL) and filtered through a Celite bed. The filtrate was concentrated under reduced pressure. The residual oil was chromatographed on silica gel to give analytically pure methyl 2-fluoro-2-hexenoate (0.65 g, 89%): *Z*/*E* ratio, 93:7; IR (film) 1744, 1678 cm^{-1}; ^1H NMR for (*Z*)-isomer δ = 0.93 (t, *J* = 6.8 Hz, 3H), 1.2-1.8 (m, 2H), 2.21 (br dt, *J* = 7.6, 7.6 Hz, 2H), 3.77 (s, 3H), 6.04 (dt, *J* = 33.0, 7.6 Hz, 1H); ^{19}F NMR ($CFCl_3$ internal standard)

Table 1. Preparation of Methyl α-Fluoro-α,β-unsaturated Carboxylates (2)

Carbonyl compd	Reaction time/h	Product 2	Yield[a]/% (*Z*/*E*)[c]	$J_{\text{H-F}}$[b] /Hz
$CH_3(CH_2)_2CHO$	4		89(93/7)	33.0
$(CH_3)_2CHCHO$	3		69(99/1)	34.2
$(CH_3)_3CCHO$	4		69(100/0)	39.1
$CH_3(CH_2)_5CHO$	4		79(93/7)	33.0
(*E*)-$CH_3CH{=}CHCHO$	4		83(93/7)	30.5
(*E*)-$CH_3CH{=}C(CH_3)CHO$	4		76(99/1)	35.4
(*E*)-$C_6H_5CH{=}CHCHO$	4		40[d]	
C_6H_5CHO	1.5		78(100/0)	35.4
p-$CH_3C_6H_4CHO$	2		83(100/0)	35.4
p-ClC_6H_4CHO	2		75(100/0)	34.2
p-$CH_3OC_6H_4CHO$	2		76(100/0)	35.4
$(CH_3CH_2)_2CO$	4		20[d]	

a) The yields refer to pure isolated products, unless otherwise noted. b) The values present the vinylic hydrogen-fluorine coupling constants in (*Z*)-isomers. These were determined by ^1H and ^{19}F NMR. c) Determined by ^1H and ^{19}F NMR. d) Determined by ^{19}F NMR.

δ = -85.7 (d, J = 33.0 Hz) for (Z)-isomer, -77.6 (d, J = 22.0 Hz) for (E)-isomer; MS m/z 146 (M^+).

References

1) H. Gault, D. Rouge, and E. Gordon, Compt. Rend., 250, 1073 (1960); E. D. Bergmann and I. Shahak, J. Chem. Soc., 1961, 4033; E. Elkik, Bull. Soc. Chim. Fr., 1964, 2558; 1967, 1569; E. D. Bergmann, I. Shahak, E. Sali, and Z. Aizenshtat, J. Chem. Soc., C, 1968, 1232; M. Hudlicky, "Chemistry of Organic Fluorine Compounds," Halsted Press, John-Wiley & Sons, New York (1976), p. 347.
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3) T. Kitazume and N. Ishikawa, Chem. Lett., 1981, 1259.
4) E. Gryszkiewicz-Trochimowski, A. Sporzyñski, and J. Wnuk, Recl. Trav. Chim. Pays-Bas, 66, 419 (1947). The improved procedure is as follows: In a flask equipped with a distillation apparatus and mechanical stirrer were placed methyl trichloroacetate (0.15 mol) and antimony(III) fluoride (0.1 mol). Bromine (0.16 mol) was slowly added to the well-stirred mixture under heating. Crude products were distilled at such a rate that the boiling point of the distillate did not exceed 120 °C. A usual treatment of the distillate followed by fractional distillation gave pure 1 (bp 117.0-118.5 °C) and methyl chlorodifluoroacetate (bp 80-82 °C).
5) Zinc(0)-mediated Reformatsky reaction of other halofluoroacetates has been reported. See, M. W. Rathke, Org. React., 22, 423 (1975); S. Brandage, O. Dahlman, and L. Morch, J. Am. Chem. Soc., 103, 4452 (1981); N. Ishikawa, M. G. Koh, T. Kitazume, and S. K. Choi, J. Fluorine Chem., 24, 419 (1984); E. A. Hallinan and J. Fried, Tetrahedron Lett., 25, 2301 (1984); J. Fried, E. A. Hallinan, and M. J. Szwedo, Jr., J. Am. Chem. Soc., 106, 3871 (1984).
6) Commercially available zinc powder was washed successively with dilute HCl, methanol, and diethyl ether, and was dried under vacuum.
7) For a zinc-copper couple reagent, H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, Org. React., 20, 75 (1973); R. M. Blankenship, K. A. Burdett, and J. S. Swenton, J. Org. Chem., 39, 2300 (1974).
8) All isolated products exhibited spectroscopic (IR, MS, ^{1}H and ^{19}F NMR) and analytical data which are fully consistent with the assigned structures including the stereochemistry.
9) The effectiveness of acetic anhydride for the reductive elimination has been observed. See, M. Fujita, T. Hiyama, and K. Kondo, Tetrahedron Lett., 27, 2139 (1986); M. Fujita and T. Hiyama, ibid., 27, 3655 (1986).

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