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New synthetic approaches to ethyl 3,3-difluoro-2-methylacrylate

Carlo Botteghi,* Stefano Paganelli, Federico Sbrogiò and Camillo Zarantonello

Dipartimento di Chimica, Università Ca' Foscari di Venezia, Calle Larga S. Marta, 2137, I-30123 Venezia, Italy

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Abstract

3,3-Difluoro-2-methylacrylate (DFMA) was synthesized starting from ethyl 2-(trifluoromethyl) propanoate according to two different preparative routes with yields ranging from 70 to 90%. Alternatively, DFMA was obtained from ethyl pyruvate by Wittig reaction using the difluoromethylentriphenyl phosphorane ylide. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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In the last few years, organofluorine compounds have attracted the great interest of chemistry researchers in different areas, such as pharmaceuticals,[1–3] agrochemicals[4] and polymers.[5–7] In particular, fluorine containing α,β-unsaturated acids and their derivatives constitute a valuable class of precursors both for a variety of compounds endowed with outstanding therapeutic activity[8] and macromolecular materials exhibiting special optical properties and high performance coating ability.[9,10] However, the development of these valuable production lines is currently strongly hampered by the difficulty of the preparation of acrylic acid derivatives having one or more fluorine atoms in defined positions of the molecule.[11,12]

In this paper we wish to present new synthetic approaches to 3,3-difluoro-2-methylacrylate (DFMA), the two fluorine atoms of this molecule derive completely from commercially available 3,3,3-trifluoropropene (TFP) or difluorodibromomethane. Only a few reports on the preparation of β,β-difluoroacrylic acids are available in the literature;[13] in particular, the synthesis of DFMA, to our knowledge, has been described only twice.[14,15] According to the first preparative route, DFMA was obtained in 54% yield from 2-(trifluoromethyl)acrylic acid (TFMA) sodium salt by reaction with 0.25 molecular equivalent of $LiAlH_4$ in diethyl ether–THF at −78°C.[14] Some attempts to reproduce this last reaction in our laboratory were unsuccessful.

In the second route, diethyl methylmalonate is alkylated with CF_2Br_2 and the alkylation product treated with KBr in DMSO at 170°C: DFMA was obtained in 59% yield.[15]

Two different synthetic schemes have been employed by us to obtain DFMA, using as a sole starting material ethyl 2-(trifluoromethyl) propanoate **1** (Scheme 1), easily accessible by regioselective rhodium

* Corresponding author. Fax: +39 041 2578517

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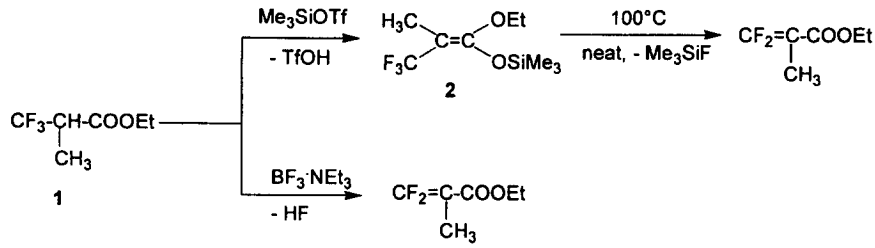
catalyzed hydroformylation of TFP to 3,3,3-trifluoro-2-methylpropanal followed by oxidation with $NaClO_2$ and H_2O_2 in CH_3CN.[12]

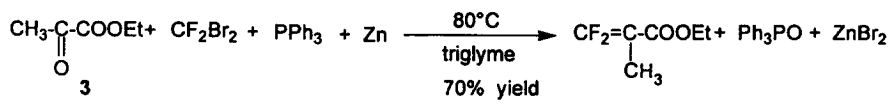


Scheme 1.

In the first synthetic pathway we have exploited the known thermal instability of fluorinated ketene silyl acetals which gradually decompose over 50°C to produce β,β-difluoroacrylic acid esters.[16] Thus, **1** was treated with 1.1 equiv. of Me_3SiOTf and 1.1 equiv. of triethylamine at 100°C: after 5 h the conversion of **1** to **2** was nearly quantitative. Pure DFMA was obtained by distillation (bp 94°C)[17] in 85% yield.

In order to prepare 10–20 g of DFMA for polymerization experiments, we performed the dehydrofluorination of **1** by using the adduct $Et_3N \cdot BF_3$ (Scheme 1) which has proved to be a suitable defluorinating reagent for the conversion of hexafluoroisobutyrate to the corresponding perfluoromethacrylate.[18] Therefore, a mixture consisting of **1** and $Et_3N \cdot BF_3$ (1.5 equiv.) was refluxed for 60 h (97% GC yield); after cooling, distillation at rt at reduced pressure into a trap cooled at –78°C, gave 70% of the desired DFMA.

The two synthetic methods outlined in Scheme 1 present a drawback, consisting in fluorine atom loss during the conversion of the starting material to the final product. Therefore, we decided to explore another preparative approach by which the two fluorine atoms of the source reagent are embodied in the DFMA molecule. As efficient preparative methods of the ylide $Ph_3P^+-{}^-CF_2$ are well described in the literature and it has been successfully employed in Wittig reactions with keto lactons to afford the corresponding difluoro olefins,[19,20] we extended this reaction to ethyl pyruvate **3** (Scheme 2): the use of zinc dust was crucial for the fluorinated ylide formation.[21]



Scheme 2.

We successfully modified the described procedure[20] using only 1.1 equiv. of CF_2Br_2 and triglyme as the solvent, without affecting the chemical yield. Thus, a solution of 10 mmol of **3** in triglyme (5 mL) was cooled to –5°C and 2.3 g (11 mmol) of CF_2Br_2 were added; successively, a solution of PPh_3 (11 mmol) in triglyme (10 mL) was added dropwise maintaining the temperature at 0°C. The reaction mixture was stirred at room temperature for 30 min, then cooled at –5°C and 11 mmol of Zn dust (Aldrich, <10 μ) were added. The mixture was heated at 80°C for 4.5 h to give 87% of DFMA (GC yield). The product was isolated in 70% yield by distillation at reduced pressure using a short-path column (bp 45°C/20 mm Hg).

Among the three preparative methods this last one seems to be the more attractive and convenient for a possible semi-industrial production of DFMA due to the large availability of α-ketoesters and to the feasibility of the synthetic scheme.

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