SYNLETT Spotlight 469

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Ethyl Dibromofluoroacetate (EDBFA)

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Introduction

Over the last decades, fluorinated organic compounds have increasingly received great attention by the scientific community; in several scientific fields, from material science to medicine. Today, approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine.^{1,2} The unique properties of fluorinated compounds are due to the high electronegativity of fluorine, the small size of fluorine, and the significant electrostatic character of the C–F bond.³ The presence of a fluorine atom in organic compounds imparts several properties (basicity, lipophilicity, and metabolic stability) which in some cases enhance the drug-like properties of the molecule.⁴

A useful and commercially available reagent for fluorination of organic compounds is ethyl dibromofluoroacetate [EDBFA (1), Figure 1].⁵



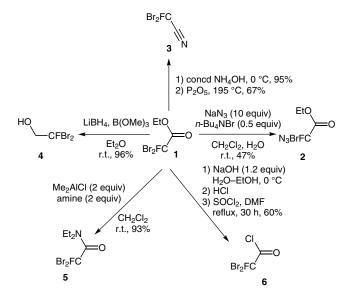
Figure 1 Ethyl dibromofluoroacetate (EDBFA)

Fluoroacetate 1 is a solid with a molecular weight of 263.89 g/mol, a boiling point of 173 °C, and a density of 1.92 g/cm^{3.5} Derivatives of EDBFA such as compounds **2–6** (Scheme 1) are also efficient reagents.⁶ Replacement of one bromine atom in 1 by an azide generates a stereocenter, affording ethyl 2-azido-2-bromo-2-fluoroacetate (**2**). A two-step strategy is used to convert the ester moiety into the corresponding nitrile to give the 2,2-dibromo-2-fluoroacetonitrile (**3**).

Abstracts

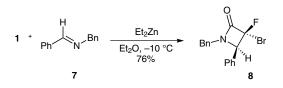
(A) The Reformatsky-type reaction of **1** with (*E*)-*N*-benzyl-1-phenylmethanimine (**7**), mediated by diethylzinc, was performed to achieve a chemo- and diastereoselective synthesis of the α -bro-mo- α -fluoro- β -lactam **8** in 76% yield as a single diastereomer, with *syn* configuration between the hydrogen and fluorine atom.⁸

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Scheme 1 Synthesis of EDBFA derivatives

Using lithium borohydride as the reducing agent and trimethylborate, the ester moiety of 1 can be converted into an alcohol to give 2-azido-2-bromo-2-fluoroethan-1-ol (4).^{6,7} It can also be changed into a tertiary amide in the presence of dimethylaluminium chloride, affording 2-azido-2-bromo-N,N-diethyl-2-fluoroacetamide (5) or be transformed in the corresponding acyl chloride, via a three-step procedure, to afford 2-azido-2-bromo-2-fluoroacetyl chloride (6).



(B) **1** can be used for the formation of fluorinated epoxides. The reaction of **1** with a ketone in the presence of diethylzinc and *N*,*N*-dimethylaminoethanol gives access to the corresponding fluorinated glycidic ester. The authors have improved a previously reported procedure by replacing triphenylphosphine with *N*,*N*-dimethylaminoethoxide (prepared in situ from the reaction of Et₂Zn with *N*,*N*-dimethylaminoethanol). The compounds are obtained with high purity after a very simple isolation procedure.^{9,10}

(C) A general and versatile approach for the formation of monofluorinated cyclopropanes using **1** was reported.¹¹ This procedure consists of a Michael addition of zinc enolates, generated from **1** with Zn and LiCl, to electron-deficient alkenes followed by nucleophilic cyclization. The most reproducible procedure involved previous treatment of Zn and LiCl with 2 mol% DMSO and 2 mol% TMSCl in THF. This also allowed the preparation of spiro-oxindoles fluorinated in a nonaromatic position.

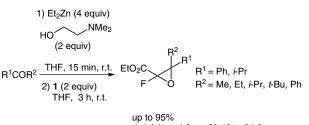
(D) The addition of **1** to a carbonyl derivative mediated by Et_2Zn occurs by two different pathways depending on the nature of the carbonyl compound. This strategy led to the syntheses of α -fluoro-acrylates via a one-pot stereoselective approach. When aldehydes are used, the reaction follows an E2-type mechanism, whereas with ketones the reaction follows an E1cB-type mechanism. This strategy tolerates various functional groups including esters, nitriles, and protected alcohols. Aldehydes were converted into α -fluoroacrylates in pure Z form. However, in most cases, the α -bromo- α -fluoro- β -hydroxy esters afforded the *syn* isomer selectively. Concerning ketones, good stereoselectivity could only be afforded for unsymmetrical ketones possessing one hindered group.¹²

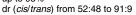
(E) EDBFA derivative 4 was used in the preparation of dibromofluoromethylcarbinyl esters 12 from carbamates. Compound 4 was prepared by reduction of 1 with LiBH₄ in the presence of trimethylborate.^{6,7} The dibromofluoromethylcarbinyl esters 11 are useful for the preparation of 1-fluro-1-alkenyl carbamates 12 via a [2,3]-sigmatropic rearrangement mediated by $CrCl_2$ and $Mn.^{13}$

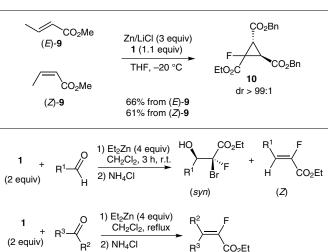


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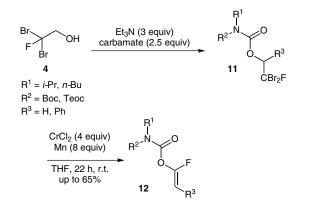
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(*E*) $R^1 = 4\text{-MeOC}_6H_4$, Ph, 4-F-Ph up to 90%, dr (*Z*/*E*) = 99:1 and dr (*anti/syn*) = 1:99 $R^2 = \text{Ph}$, Me $R^3 = \text{Me}$, Et up to 91%, dr (*Z*/*E*) =16:84



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