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]

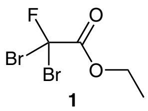

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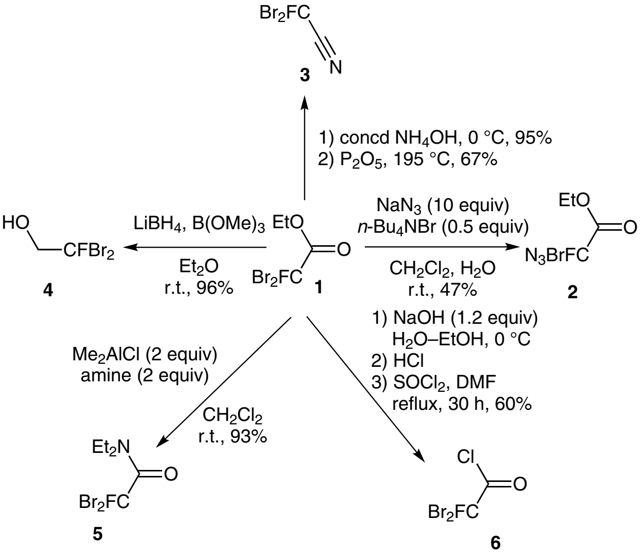
Figure 1 Ethyl dibromofluoroacetate (EDBFA)

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**).

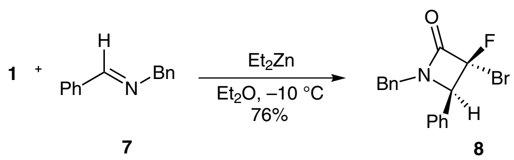


Scheme 1 Synthesis of EDBFA derivatives

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**).

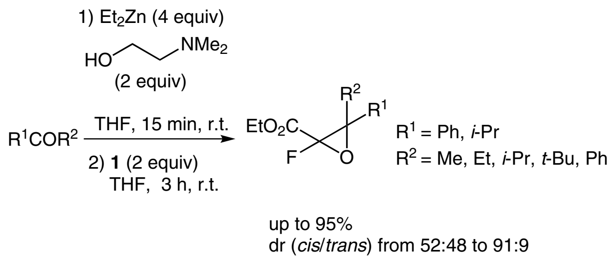
Abstracts

(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-bromo-α-fluoro-β-lactam **8** in 76% yield as a single diastereomer, with *syn* configuration between the hydrogen and fluorine atom.[8]

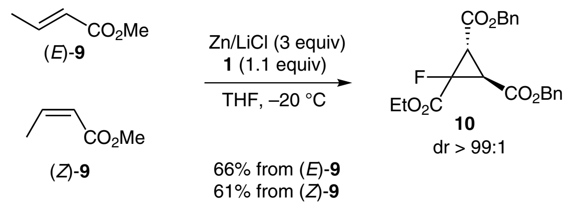


SYNLETT 2014, 25, 1188–1189
Advanced online publication: 07.04.2014
DOI: 10.1055/s-0033-1341111; Art ID: ST-2014-V0476-V

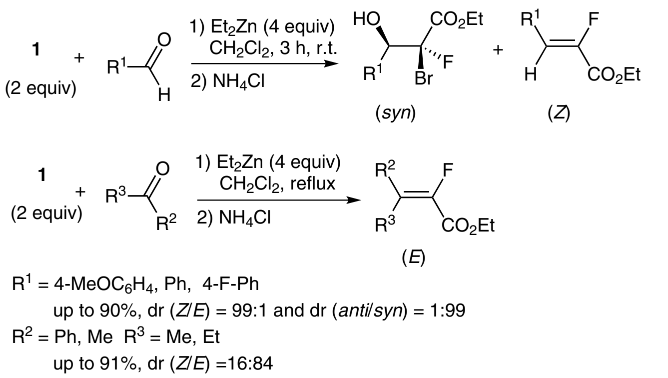
(B) **1** can be used for the formation of fluorinated epoxides. The reaction of **1** with a ketone in the presence of diethylzinc and *N,N*-dimethylaminoethanol gives access to the corresponding fluorinated glycidic ester. The authors have improved a previously reported procedure by replacing triphenylphosphine with *N,N*-dimethylaminoethoxide (prepared in situ from the reaction of Et_2Zn with *N,N*-dimethylaminoethanol). The compounds are obtained with high purity after a very simple isolation procedure.[9,10]



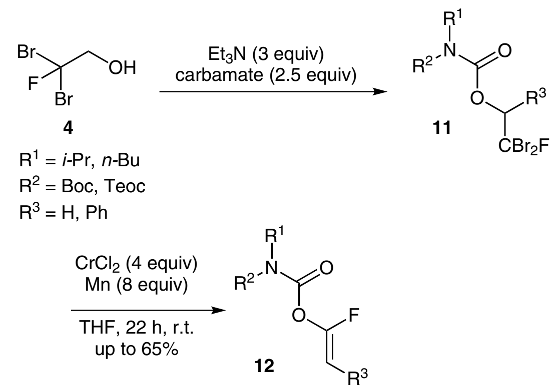
(C) A general and versatile approach for the formation of monofluorinated cyclopropanes using **1** was reported.[11] This procedure consists of a Michael addition of zinc enolates, generated from **1** with Zn and LiCl, to electron-deficient alkenes followed by nucleophilic cyclization. The most reproducible 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-fluoroacrylates 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 $LiBH_4$ 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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