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)

Compiled by Cátia V. Almeida Santos

Cátia V. Almeida Santos was born in Lisbon, Portugal. She received her degree in biochemistry from the Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa in 2013. Currently, she is carrying out research under the supervision of Professor M. Manuel B. Marques at the Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa on the synthesis of biologically active glycopeptides.

REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal
E-mail: cv.santos@fct.unl.pt

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/cm³.5 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).5,7 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.3
(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.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 zine 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 carboxyl derivative mediated by Et₂Zn occurs by two different pathways depending on the nature of the carbonyl compound. This strategy led to the syntheses of α-fluoroacylates 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-fluoroacylates in pure 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 dibromo-fluoromethylcarbiny esters 12 from carbamates. Compound 4 was prepared by reduction of 1 with LiBH₄ in the presence of triethylborate.¹⁵ The dibromo-fluoromethylcarbiny esters 11 are useful for the preparation of 1-fluro-1-alkenyl carbamates 12 via a [2,3]-sigmatropic rearrangement mediated by CrCl₂ and Mn.¹⁶

References