

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

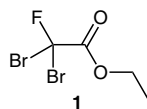
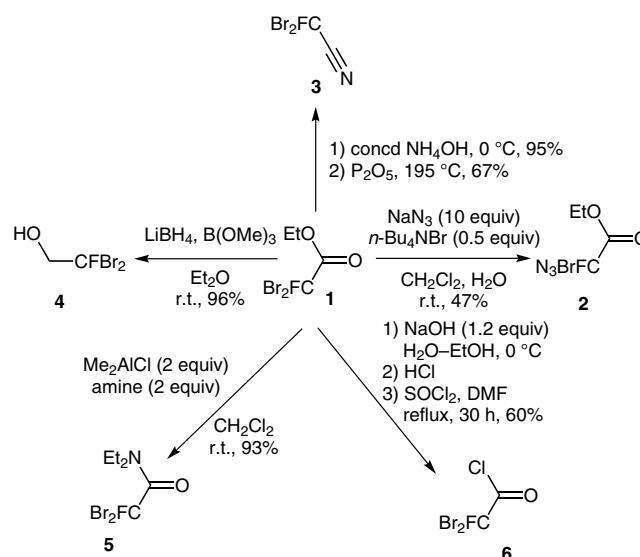


Figure 1 Ethyl dibromofluoroacetate (EDBFA)

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/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**).

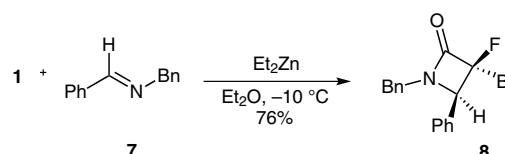
Abstracts

(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

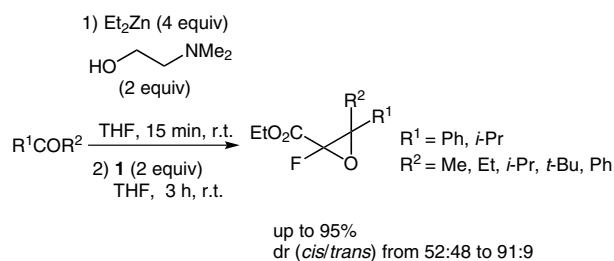


Scheme 1 Synthesis of EDBFA derivatives

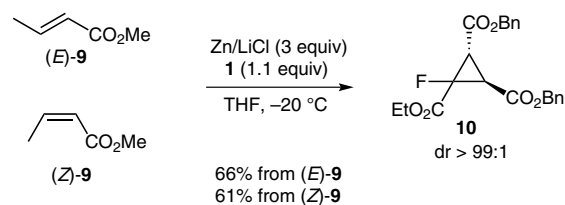
Using lithium borohydride as the reducing agent and trimethylborate, the ester moiety of **1** can be converted into an alcohol to give 2-azido-2-bromo-2-fluoroethan-1-ol (**4**).^{6,7} It can also be changed into a tertiary amide in the presence of dimethylaluminium chloride, affording 2-azido-2-bromo-*N,N*-diethyl-2-fluoroacetamide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



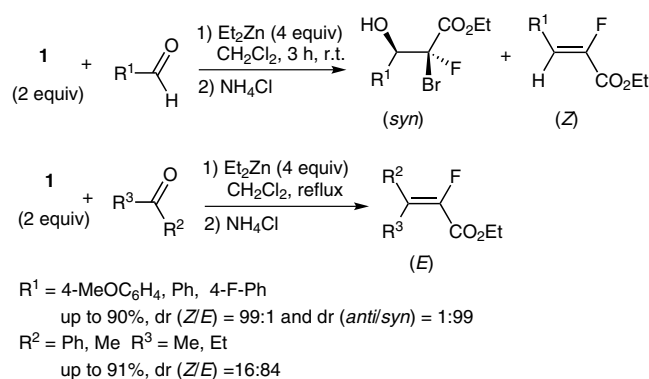
(B) **1** can be used for the formation of fluorinated epoxides. The reaction of **1** with a ketone in the presence of diethylzinc and *N,N*-dimethylaminoethanol gives access to the corresponding fluorinated glycidic ester. The authors have improved a previously reported procedure by replacing triphenylphosphine 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}



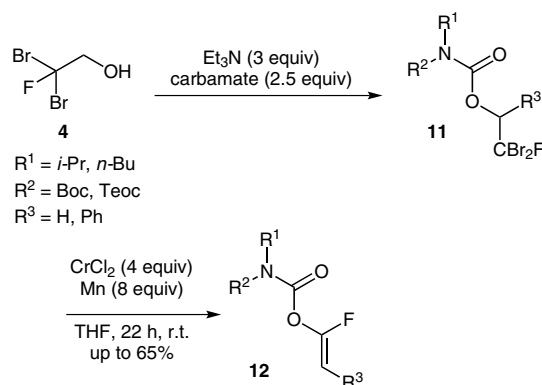
(C) A general and versatile approach for the formation of monofluorinated cyclopropanes using **1** was reported.¹¹ This procedure consists of a Michael addition of zinc enolates, generated from **1** with Zn and LiCl, to electron-deficient alkenes followed by nucleophilic cyclization. The most reproducible 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 Et₂Zn 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 dibromofluoromethylcarbonyl esters **12** from carbamates. Compound **4** was prepared by reduction of **1** with LiBH₄ in the presence of trimethylborate.^{6,7} The dibromofluoromethylcarbonyl esters **11** are useful for the preparation of 1-fluoro-1-alkenyl carbamates **12** via a [2,3]-sigmatropic rearrangement mediated by CrCl₂ and Mn.¹³



References

- (1) Ami, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119; and references cited therein.
- (2) Estevão, M. S.; Duarte, F. J. S.; Fernandes, E.; Santos, A. G.; Marques, M. M. B. *Tetrahedron Lett.* **2012**, *53*, 2132.
- (3) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
- (4) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
- (5) Data taken from the EUROPE Catalog, TCI Fine Chemicals **2012–2013**.
- (6) David, E.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Tetrahedron* **2013**, *69*, 11039.
- (7) (a) Nakagawa, M.; Saito, A.; Soga, A.; Yamamoto, N.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 5257. (b) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *82*, 1604.
- (8) (a) Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Miwa, Y.; Minami, H.; Ando, A. *Tetrahedron Lett.* **2010**, *51*, 2000. (b) Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Ando, A. *Tetrahedron Lett.* **2010**, *51*, 4246.
- (9) Lemonnier, G.; Zoute, L.; Quirion, J.; Jubault, P. *Org. Lett.* **2010**, *12*, 844.
- (10) Zoute, L.; Lemonnier, G.; Nguyen, T. M.; Quirion, J.; Jubault, P. *Tetrahedron Lett.* **2011**, *52*, 2475.
- (11) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270.
- (12) Lemonnier, G.; Zoute, L.; Dupas, G.; Quirion, J.-C.; Jubault, P. *J. Org. Chem.* **2009**, *74*, 4124.
- (13) Saito, A.; Tojo, M.; Yanai, H.; Wada, F.; Nakagawa, M.; Okada, M.; Sato, A.; Okatani, R.; Taguchi, T. *J. Fluorine Chem.* **2012**, *133*, 38.