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). 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-phenylethanamine (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.

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(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-fluorocarboxylic esters 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-fluorocarboxylic esters in pure, unmodified THF, –20 °C.

(E) EDBFA derivative 4 was used in the preparation of dibromo-fluoromethylcarbinyl esters 12 from carbamates. Compound 4 was prepared by reduction of 1 with LiBH₄ in the presence of trimethylborate.⁶,⁷ The dibromo-fluoromethylcarbinyl 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.¹³

References